SIOPEL 4

Intensified pre-operative chemotherapy and radical surgery for HIGH RISK HEPATOBLASTOMA

International Childhood Liver Tumours Strategy Group - SIOPEL

EUDRACT Number: 2004-001828-20

FINAL VERSION
Final Version July 2004
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1. CONFIDENTIALITY STATEMENT

This document describes a non-randomised, open, phase II clinical trial in children with high risk hepatoblastoma and provides information for entering patients into it. It is not intended for use as an aide-memoire or guide for the treatment of non-registered patients. Although every care was taken in its drafting, amendments may be necessary. These will be circulated to known participants in the trial, but centres entering patients for the first time are advised to contact the Data Centre to confirm the correctness of the protocol in their possession and to obtain the necessary authorization to enter patients into the trial. Participants are requested to maintain confidentiality regarding the contents of this protocol. Responsibility for the administration of the protocol treatments lies with the participants.

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Principal investigator
(Study chair)
Principal investigator
(Study chair)
Responsible statistician

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<th>Statistician:</th>
<th>Transplant Co-ordinator:</th>
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*SIOPeL 4 final version_July 2004*
For a complete list of all *SIOPEL 4 trial committee* members see section 22.

### 3. LIST OF ABBREVIATIONS

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>AFP</td>
<td>Alpha-Fetoprotein</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute Neutrophil count</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Aminotransferase</td>
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<tr>
<td>Beta-HCG</td>
<td>Beta-Human Chorionic Gonadrotrophin</td>
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<tr>
<td>CDDP</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>CR</td>
<td>Complete Remission</td>
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<tr>
<td>CRR</td>
<td>Complete Resection Rate</td>
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<tr>
<td>CT</td>
<td>Computer Tomography</td>
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<tr>
<td>CTC</td>
<td>Common Terminology Criteria</td>
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<tr>
<td>EFS</td>
<td>Event Free Survival</td>
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<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>HACE</td>
<td>Hepatic Artery Chemoembolisation</td>
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<tr>
<td>HB</td>
<td>Hepatoblastoma</td>
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<tr>
<td>HCC</td>
<td>Hepatocellular Carcinoma</td>
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<tr>
<td>HR-HB</td>
<td>High Risk Hepatoblastoma</td>
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<tr>
<td>LTX</td>
<td>Liver Transplantation</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>OS</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>PA</td>
<td>Posterior-Anterior</td>
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<tr>
<td>PD</td>
<td>Progressive Disease</td>
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<td>PET</td>
<td>Positron Emission Tomography</td>
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<td>PR</td>
<td>Partial Response</td>
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<td>PRETEXT</td>
<td>Pre-treatment Tumour Extension</td>
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<td>RECIST</td>
<td>Response Criteria In Solid Tumours</td>
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<td>RR</td>
<td>Response Rate</td>
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<td>RRR</td>
<td>Rapid Radiology Review</td>
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<td>SAE</td>
<td>Severe Adverse Event</td>
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<td>Stable Disease</td>
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<td>SIAK</td>
<td>Swiss Institute for Applied Cancer Research</td>
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<td>SIOP</td>
<td>International Society of Paediatric Oncology</td>
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<td>SIOPEL</td>
<td>International Paediatric Liver Tumour Strategy Group</td>
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<tr>
<td>SF</td>
<td>Shortening Fraction</td>
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<td>SR-HB</td>
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<td>UKCCSG</td>
<td>United Kingdom Children’s Cancer Study Group</td>
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<td>VCR</td>
<td>Vincristine</td>
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<td>VP-16</td>
<td>Etoposide</td>
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<td>5-FU</td>
<td>5-Fluorouracil</td>
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4. SYNOPSIS

Title: Intensified pre-operative chemotherapy and radical surgery for high risk hepatoblastoma

Primary objectives:
- To determine the effectiveness and short term toxicity of an intensified new chemotherapy regime in children with high risk hepatoblastoma.
- To increase the rate of complete surgical resection by using liver transplantation in children with otherwise unresectable tumour.
To evaluate prospectively the role of pre-operative chemotherapy in rendering unresectable tumours, resectable.
- To assess the accuracy of initial imaging in predicting surgical resectability after pre-operative chemotherapy in children presenting with unresectable disease.

Trial design:
- Open, uncontrolled phase II clinical trial.
- End-points:
  - Primary: Complete remission (CR), defined as the lack of evidence of residual disease and a normal alpha-fetoprotein (AFP) at the end of trial treatment.
  - Secondary: Complete resection rate (CRR)
    - Overall and event free survival (OS, EFS)
    - Response rate (RR) to pre-operative chemotherapy
    - Rate of grade 3 and 4 toxicity during and at the end of trial treatment
- Projected accrual: 25-30 patients/year.
- Projected total accrual: 57 evaluable patients
- Expected duration of the trial: ca. 2 years.

Selection of patients (for detailed information see section 9):
- Definition of high-risk hepatoblastoma: At least one of the following criteria:
  - Tumour involving all 4 hepatic sections - PRETEXT IV
  - Abdominal extra-hepatic disease (any of V, P or E)
  - Presence of metastases (M+)
  - Alpha-fetoprotein (AFP) < 100 ng/ml
  - Tumour rupture at diagnosis irrespective of PRETEXT
- Inclusion criteria
  - Histologically confirmed hepatoblastoma
  - < 18 years of age
  - Risk category: high-risk patient
  - Written informed consent and national/local ethical committee approval
  - Ability to comply with requirements for submission of material for central review
- Exclusion criteria
  - Diagnosis not confirmed by histology.
  - Abnormal renal function defined as GFR < 60 ml/min/1,73 m² at diagnosis.
  - Patient unable to follow the protocol for any reason.

Trial treatment
Trial treatment consists of the following phases (see figure 4.1):
- Pre-operative chemotherapy (blocks A1, A2, A3) for all patients, consisting of Cisplatin (administered weekly) and Doxorubicin (one cycle per block).
- Additional pre-operative chemotherapy (block B) for patients whose tumour is still unresectable. It consists of two cycles of medium high dose Carboplatin and Doxorubicin.
- Surgical removal of all remaining tumour lesions (where feasible) including liver transplantation and metastectomy.
- Post-operative chemotherapy (block C) for eligible patients.

**Toxicity monitoring:**
The trial treatment is potentially toxic and children are at risk of developing myelo-, mucosal- or other reversible toxicity as well as oto-, renal- and cardiac-, irreversible toxicity. Children with severe impairment of renal function at diagnosis are excluded from the trial.
- Frequent toxicity monitoring will be required for each child throughout the trial.
- Reporting of specific renal, cardiac and grade 3 ototoxicity will be required as an adverse event. Reporting of unexpected non haematological grade 4 toxicity or any death will be required as a Severe Adverse Event (SAE) to be sent to the data centre 24 hours after the knowledge of the event. The steering committee will evaluate toxicity reports on a regular basis and may stop the trial if an unacceptable rate of severe toxicity is recognized.
- Dose and treatment modifications due to toxicity are specified in the protocol.
- Long-term follow up of the toxicity of patients in this trial will be pursued by the SIOPEL group.

**Central radiological and pathological review**
In order to ensure that high quality data is acquired in this trial, central review of pathology slides and films (radiological images) will be mandatory. The Data Centre will request the necessary material once the patient has been registered.

**Statistical analysis:**
We consider a CR rate, achieved with or without LTX, of 50% or less to be unsatisfactory, whereas a CR rate of 70% would be considered promising for further development. Statistical analysis will be performed using Simon’s two stage optimal design, with 5% significance level and 90% power.

**Trial conduct:**
This trial will be carried out according to the Declaration of Helsinki and the principles of Good Clinical Practice.
Figure 4.1  SIOPEL 4 – TRIAL DESIGN

- **C** = Cisplatin 80mg/m²
- **C** = Cisplatin 70mg/m²
- **D** = Doxorubicin 60mg/m²
- **CA** = higher dose Carboplatin AUC 10.6 mg/ml.min
- **D** = higher dose Doxorubicin 75mgs/m²
- **CA** = Carboplatin AUC 6.6 mg/ml.min
- **D** = Doxorubicin 40mg/m²
  (Cumulative dose/cycle)
5. PREAMBLE

The SIOPEL 4 trial is part of a comprehensive research strategy developed by the International Childhood Liver Tumour Strategy Group (SIOPEL) (for membership list see section 22.2), which among others presently includes:

- a prospective randomised clinical trial of “standard risk” hepatoblastoma (SIOPEL 3)
- a phase II trial for relapsing and/or resistant hepatoblastoma (with Irinotecan)
- a clinical trial on childhood hepatocellular carcinoma (HCC) (in preparation)
- an international childhood liver tumour tissue banking program

The SIOPEL 4 trial represents the fourth generation of clinical trials run by the SIOPEL group.

The SIOPEL 4 trial is a prospective co-operative international single arm trial directed to a sub-set of hepatoblastoma identified for the purpose of the trial as "high risk". It includes those hepatoblastomas that involve the four hepatic sections, classified according to the ‘pre-treatment extent of disease’ system, adopted for the trial, as PRETEXT IV and/or presenting with evidence of extra-hepatic disease and/or with a low alpha-fetoprotein value at diagnosis (< 100 ng/L). The small number of patients expected to be recruited means that it is not possible to design a randomised trial. In fact, while waiting for a larger inter-group cooperation the SIOPEL group is planning to run a series of consecutive, phase II-like single arm trials on newly diagnosed HR-HB patients. The present trial is based on the hypothesis that the intensification of the most effective agent so far known for hepatoblastomas, Cisplatin, will result in an improvement of survival with an acceptable toxicity.
6. BACKGROUND AND RATIONALE FOR THE TRIAL

6.1. BACKGROUND
The SIOPEL group has decided to design the future trials according to the risk adapted treatment approach philosophy initiated with the SIOPEL 2 trial. This implies a clear understanding of the consolidated prognostic factors for childhood HB and of the biological and clinical behaviour of the subsets of tumours identified by those prognostic factors.

Previous SIOPEL experience
SIOPEL 1
The first prospective international clinical trial on childhood hepatoblastoma – SIOPEL1 - run by the SIOPEL group aimed, inter alia, to investigate the prognostic significance of several pre-treatment patient and tumour characteristics (7,27,32). In the SIOPEL 1 trial no therapeutic stratifications by any clinical or histopathological characteristics were planned. All patients were supposed to receive the same therapy. The treatment strategy of the SIOPEL1 trial was based on the use of pre-operative chemotherapy utilizing the combination Cisplatin/Doxorubicin (PLADO) regimen. The extent of pre-treatment intra-hepatic disease, as defined by the PRETEXT system and the presence of lung metastases were identified as important prognostic factors for 5-year event-free survival (EFS). In multivariate analysis, however, the PRETEXT category was the only statistically significant prognostic factor for 5-year overall survival (OS) (7). In the SIOPEL 1 trial PRETEXT IV patients had a 5-year EFS and OS of 46% (95%CI 12-44%) and 57% (95%CI 41-73%) respectively (Fig 6.1); the corresponding figures for patients presenting with metastases were 28% (95% CI 12-44%) and 57% (95%CI 39-75%) (fig 6.2 and 6.3).

![Graph](image)

**Figure 6.1** 5 year EFS by PRETEXT category in the SIOPEL 1 trial
These results brought the group to formulate the hypothesis that within the HB patients at least two risk clusters for treatment failure exist: a) a “standard risk” (SR) group, comprising those patients with an HB completely confined to the liver, with up to 3 hepatic sectors involved (PRETEXT groups I, II and III) and b) a “high risk” (HR) one comprising those children with an HB extending to all 4 hepatic sectors (PRETEXT IV) or with extra-hepatic spread, such as vascular invasion, intra-abdominal extra-hepatic involvement or metastases.

**SIOPEL 2**

The treatment strategy of the SIOPEL 2 trial was “intentionally” based on the concept of patient stratification by these two risk groups of patients with the aims of: examining further the question of whether the notion of clustering patients into 2 risk groups was valid and helpful and if a more intensive chemotherapy regimen could improve the prognosis of children with high risk disease (30,31).

For HR-HB patients, in the SIOPEL 2 trial treatment was intensified by adding Carboplatin to the Cisplatin/Doxorubicin regimen used in the SIOPEL1 trial, in a rapidly alternating sequence of administration (42). Data indicating that Carboplatin was an “active” agent in HB were available at the time the trial was launched (8,11). Fifty-eight HR-HB children were enrolled into the trial (19 females and 39 males) with an age range of 4 to 169 months.
(median 18 months). The distribution by PRETEXT category was as follows: PRETEXT II 6 patients, III 19, IV 33; 17 patients had major vessel involvement identified on imaging or evidence of intra-abdominal extra-hepatic disease; 25 had metastases.

As a whole 45 HR-HB children (78% with 95%CI 65-87%) had a partial response to pre-operative chemotherapy. Thirty-two achieved a complete macroscopical resection by conventional hepatectomy (leaving microscopical residual disease in 6) yielding a complete resection rate of 55% (95%CI 42-68%). In 7 children, complete tumour removal was achieved by total hepatectomy and LTX, for an overall resection rate of 67% (95%CI 54-79%). In 15 patients the tumour was never considered resectable while in 4 cases delayed surgery was attempted but macroscopical residual disease was left behind. One child died of surgical complications. Microscopical residual disease was documented in 6 children; all had post-operative CT as per protocol but one patient had 1 extra-course of Cisplatin and Carboplatin/Doxorubicin. At the last follow-up 2 had died of disease (one presenting with metastases) and 4 are alive with no evidence of disease. At three years the EFS was 48% (±13%) and the OS 53% (±13%) (Figure 6.4). The median follow-up time was 3 years and 10 months.

**Figure 6.4** Overall and progression free survival in 58 HR-HB in SIOPEL 2

Of the 7 HR patients who relapsed after being disease-free, 5 developed metastases (in the lung and one also in the brain and skeleton; 2 of them presented with lung metastases) and 2 local recurrences. Only 1 of these children survives disease-free while 5 have died and 1 is alive but with persistent tumour. The 10 patients, whose tumours remained stable or progressed during therapy, died of uncontrollable disease, despite alternative treatments.
In order to assess the relevance of the risk group assignment adopted for the trial response and resection rates as well as the survival rates were investigated according to the 4 PRETEXT categories, the presence of metastases and of intra-abdominal extra-hepatic disease (V/P/E). The data are reported in Table 6.1.

**Table 6.1**  Response, resection rates and 3 year survival rate by PRETEXT category and extrahepatic disease in the SIOPEL 2 trial

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of patients</th>
<th>No of positive responses (%)</th>
<th>No. of patients with a radical tumour resection incl OLT (%)</th>
<th>No. patients who died of surgical complications</th>
<th>No. of patients who died of disease</th>
<th>OS at 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRETEXT I</td>
<td>6</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
<td>-</td>
<td>-</td>
<td>100%</td>
</tr>
<tr>
<td>PRETEXT II</td>
<td>39</td>
<td>37 (95%)</td>
<td>39 (100%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>95%</td>
</tr>
<tr>
<td>PRETEXT III</td>
<td>32</td>
<td>26 (81%)</td>
<td>30 (94%)</td>
<td>1 (3%)</td>
<td>4 (13%)</td>
<td>84%</td>
</tr>
<tr>
<td><strong>High risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRETEXT IV only (no mets)</td>
<td>21</td>
<td>17 (81%)</td>
<td>16 (76%)</td>
<td>-</td>
<td>8 (38%)</td>
<td>61%</td>
</tr>
<tr>
<td>E/V/P patients, no mets</td>
<td>12</td>
<td>10 (83%)</td>
<td>8 (67%)</td>
<td>1 (8%)</td>
<td>4 (33%)</td>
<td>58%</td>
</tr>
<tr>
<td>M+ patients</td>
<td>25</td>
<td>18 (72%)</td>
<td>15 (60%)</td>
<td>1 (4%)</td>
<td>13 (52%)</td>
<td>44%</td>
</tr>
</tbody>
</table>

Legend: *Positive response rate* = complete and partial responses; *Complete resection rate* = including patients having microscopical residuals after surgery. *Standard risk patients* include also those who were treated with HR regimen (n=11)

The association of OS with PRETEXT categories, presence of metastases (M) and of intra-abdominal extra-hepatic disease (V/P/E), and AFP dichotomized as < 100 ng/ml vs. ≥100 ng/ml were further evaluated in a multivariate analysis by Cox regression within the HR-group of patients. An AFP < 100 ng/ml at diagnosis was significantly associated with reduced OS (hazard ratio 4.8, 95% CI 1.5-15.3, p=0.0089). The presence of metastases also resulted in lower OS (hazard ratio 2.5, 95% CI 1.1-6.0, p=0.037), whereas PRETEXT category IV vs I,II and III and the presence of extrahepatic disease (V, P or E) showed no association with OS. The 3-year OS by PRETEXT IV alone, presence of metastases (M), intra-abdominal extrahepatic disease (V/P/E) and AFP < 100 ng/ml (considered separately) are reported in Figure 6.5. The OS and PFS of all SR patients, a few of whom received high risk treatment, and of the HR ones are reported in Figure 6.6 and 6.7 together with 95% CIs at yearly intervals.
Figure 6.5  Overall survival in 58 HR-HB, by PRETEXT 4 (IV) alone vs intra-abdominal extrahepatic disease (V/P/E) vs metastatic disease vs AFP < 100 ng/ml (SIOPEL 2)

Figure 6.6  Overall survival by risk category with 95% confidence interval at years 1, 2 and 3 (SIOPEL 2)
In conclusion: The SIOPEL2 trial supported the findings derived from the previous trial regarding the existence, within the HB population, of at least two risk groups for treatment failure, conventionally called SR and HR group. The difference in the 3-year OS and EFS observed between these two prognostic groups is striking (Figures 6.6 & 6.7).

The treatment results achieved in the HR group - 48% (±13%) 3-year EFS and 53% (±7%) 3-year OS - are far from satisfying. In SIOPEL2, treatment intensity for HR patients was increased, compared with SIOPEL1, by rapidly alternating the administration of Cisplatin (every 14 days) with Carboplatin and Doxorubicin. Longer follow-up is needed but it is doubtful whether significant improvements in OS will have been achieved although EFS may have improved.

*Other study reports on “high risk” hepatoblastoma*

To some extent PRETEXT IV HB represent a comparable group of tumours to those HB that in the North American and German Co-operative Liver Tumour Trials, based on primary surgery, are considered in Stage III, meaning unresectable or tumour for which macroscopical residual disease was left after an initial attempt at surgical resection. Thus, some comparisons between different experiences, using modern series all based on platinum derived drugs, in this sub-set of HB can be attempted. The most relevant results achieved for stage III HB patients in trials using primary surgery are reported in the Table 6.2. The summaries of the results achieved in our previous trials – SIOPEL 2 and 3 are reported in Table 6.3. The summary of the treatment results of metastatic HB is listed in Table 6.4.
### Table 6.2  Treatment results achieved in Stage III hepatoblastoma in trials adopting a primary surgery strategy

<table>
<thead>
<tr>
<th></th>
<th>Response Rate</th>
<th>Complete resection rate</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCG-823GF (24)</td>
<td>Estimated survival ~ 60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POG 8697 (15)</td>
<td>30/31</td>
<td>24/31</td>
<td>4-years EFS% 67± 10.8%</td>
</tr>
<tr>
<td>INT-0089 (23)</td>
<td>Not reported</td>
<td>40/83</td>
<td>5-year survival 69% (SD=5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-years EFS 64% (SD=5%)</td>
</tr>
<tr>
<td>POG 9345 (20)</td>
<td>19/22</td>
<td>15/22</td>
<td>5-years EFS 59± 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-years OS 73 ± 10%</td>
</tr>
<tr>
<td>HB-94 (17)</td>
<td></td>
<td></td>
<td>DFS 76% (19/25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median survival time of the entire population 58 months (range 32-93)</td>
</tr>
</tbody>
</table>

### Table 6.3  Summary of the treatment results of the SIOPEL 1 and 2 studies on PRETEXT IV – Hepatoblastoma

<table>
<thead>
<tr>
<th></th>
<th>Response Rate</th>
<th>Complete resection rate</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIOPEL1 (ref 32) (including M+ pts)</td>
<td>-</td>
<td>-</td>
<td>5-years EFS 46% (95%CI 12-44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-years OS 57% (95%CI 41-73%)</td>
</tr>
<tr>
<td>SIOPEL 2 (42)</td>
<td>81%</td>
<td>76%</td>
<td>3-years OS  61%</td>
</tr>
</tbody>
</table>

### Table 6.4.  Treatment results achieved in metastatic hepatoblastoma

<table>
<thead>
<tr>
<th></th>
<th>Response Rate</th>
<th>Complete resection rate</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCG-823GF (24)</td>
<td>Estimated survival ~ 25-30%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POG 8697 (15)</td>
<td>6/8</td>
<td>1/8</td>
<td>4-years EFS% 12± 11.7%</td>
</tr>
<tr>
<td>INT-0089 (23)</td>
<td>Not Reported</td>
<td>7/40</td>
<td>5-year survival 37% (SD=8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-years EFS 25% (SD=7%)</td>
</tr>
<tr>
<td>POG 9345 (20)</td>
<td>8/11</td>
<td>4/11</td>
<td>5-years EFS 27%± 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-years OS 27 % ± 16</td>
</tr>
<tr>
<td>HB-94 (17)</td>
<td></td>
<td></td>
<td>DFS 21% (3/14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median survival time of the entire population 58 months (r.32-93)</td>
</tr>
<tr>
<td>SIOPEL1 (27)</td>
<td>-</td>
<td>-</td>
<td>5-years EFS 28% (95%CI 12-44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-years OS 57% (95%CI 39-75%)</td>
</tr>
<tr>
<td>SIOPEL2 (42)</td>
<td>72%</td>
<td>60%</td>
<td>3-years OS 44%</td>
</tr>
</tbody>
</table>
Different strategies have been recently adopted to improve the survival of unresectable or metastatic HBs.

The POG group in North America adopted a novel treatment strategy based on intensification of pre-operative chemotherapy determined by tumour response, in order to improve the overall survival and decrease long term sequelae (POG 9345) (20). Therapy was started with Carboplatin, followed by Carboplatin/VCR/5-FU and also by high dose Cisplatin and VP16 only for those patients whose tumours were not resectable after the fourth course of chemotherapy with Carboplatin/VCR/5-FU or who experienced no response (NR), or who had progressive disease (PD) at any time after course 2. Therapy consisted of high dose Cisplatin HDDP (40 mg/m\(^2\)/d) over 1 hour, followed by IV hydration on days 1 to 5, and Etoposide (100 mg/m\(^2\)/d and 3.3 mg/kg/d for patients < 10 kg) over 1 hour on days 2 to 4 immediately before HDDP for a total of two courses.

Twenty-four patients (80%) had at least a PR to Carboplatin/VCR/5-FU and 10 of those (71%) had a complete remission with chemotherapy and surgery; the 5 year EFS in this group of children is 71% ± 14%. Twelve patients were than treated with HD-Cisplatin/VP16. Nine (75%) of 12 assessable patients (six stage III and three stage IV) had responses to HDDP-ETOP, with two patients experiencing PD. Each of the five patients who had a CR after HDDP-ETOP and resection has remained free of disease, with a minimum follow-up period of at least 5.5 years. Among the 12 patients who received HDDP-ETOP, 5-year EFS was 42% ± 14%. The 5-year event-free survival (EFS) for the entire cohort was 48% ± 9% with a 5-year overall survival of 57% ± 9% and a median follow-up period of 6.2 years for the surviving patients (range, 1.3 to 7.0 years). Superior survival was observed in patients without metastatic disease, with 5-year EFS of 59% ± 11% and 27% ± 16% in stage III and IV patients, respectively \( (P = .037) \). Overall estimates of survival at 5 years were similar, with 73% ± 10% in stage III and 27% ± 16% in stage IV, respectively \( (P = .012) \). The main results are reported in Figures 6.8 & 6.9 describing the 5 year EFS by stage at diagnosis and by entirety of surgical resection.

Figure 6.8  5 years EFS by stage at diagnosis in the POG 9345 trial (20)
The treatment results of the POG trial, considering the entire cohort of patients and the two subgroups of children included (the unresectable and the metastatic ones, assuming similarities between the POG Stage III HB and the SIOPEL PRETEXT IV tumours) seem to be almost superimposable to ones achieved in the SIOPEL studies (SIOPEL HR group: 3-year EFS 48% (±13%), 3-year OS 53% (±7%); POG data on unresectable/metastatic HB: 5-year EFS 48% ± 9%; 5-years OS 57% ± 9%; for the different subgroups see Tables 6.2, 6.3 & 6.4).

The German group adopted a similar strategy to the one used by the POG group, based also on primary surgery. All children started with Ifosfamide/Cisplatin/Doxorubicin and then the ones not achieving a response to the first 2 cycles and/or with metastatic and advanced disease switched to Carboplatin/VP16 (17). In their report responses by stage are not available. It is only said that 85% children responded after the first two courses of chemotherapy and that 18 children ended-up being treated with CARBO/VP16. Twelve children responded, and, in one child with stage IV HB, complete disappearance of lung metastases was registered. Six patients were non-responders: Five of them had an undifferentiated or embryonal HB with anaplastic components. All children who did not have a tumour response died (p = 0.0013). There was a minor difference in response to Carboplatin/VP16 in patients who had metastatic HB compared with patients who had advanced HB. The DFS of patients with stage III HB and of the ones presenting with metastases are 76% (19/25) and 21% (3/14) respectively with a median survival time of the entire population of 58 months (range 32-93). Based on this experience, the German group is now recommending high dose VP16/Carboplatin chemotherapy with stem cell rescue for all children with stage III HB, with vascular invasion and/or multifocal, spreading tumour and stage IV HB.

North American investigators tried to intensify therapy by increasing the dose intensity of platinum derived agents, alternating the use of Carboplatin (700 mg/m²) and Cisplatin (100mg/ m²) every 14 days (25). It appears that despite the initial promising results of the pilot trial (2 CR, 8 PR out of the first 13 patients with 9 patients alive with no evidence of disease for greater than 21 months) this regimen when tested prospectively versus the Carboplatin/VCR/5-FU brought such unsatisfactory results that the trial was prematurely closed (M. Malogolowkin, personal information).
The role of prognostic factors

A number of the above mentioned studies revealed that some clinical and pathological features of the patient and the tumour are associated with a bad outcome or, for a few, with a good outcome. Some of these prognostic factors are widely accepted, and used in past and current trials for treatment stratification, the role of others remains to be confirmed.

The consolidated independent pre-treatment prognostic factors (at diagnosis) seem to be the so-called static prognostic factors (7,17,28,30):

- tumour extension as defined by the PRETEXT system
- presence of metastases
- the low α-fetoprotein (AFP) at diagnosis
- resectability at diagnosis

Other clinical and tumour characteristics that reflect the response to therapy – dynamic prognostic factors - have also been outlined with solid evidence for their possible prognostic role (7,34,39,40)

- magnitude of the decrease of the α-fetoprotein
- resectability

Beside the above mentioned established (at least in some settings) prognostic factors other characteristics are also described as possible indicators of ultimate patients’ outcome (7,12,16,19,23):

- radiolocally visible or microscopic vascular invasion
- growth pattern within the liver (meaning the multifocality)
- undifferentiated cell HB histology and the pure fetal HB in case of primary complete resection
- histologically documented complete response to chemotherapy (in the INT-0098, no events have been documented in those Stage III and IV HB patients who at the post-induction surgery were found to be tumour free)

The predictive value of many of these factors, remains, however, unclear: whether they are prognostic for the whole group or only for specific subsets of patients with HB, which one could be used for tailoring therapy etc. Given the low number of HB patients, only large international, inter-group co-operative studies will be able to address these issues. The SIOPEL group is committed to design and run clinical trials - in co-operation with other groups - that can answer these important questions.

6.2. WHICH DIRECTION TO GO TO IMPROVE TREATMENT OUTCOME?

Which challenges do we face?

The major issue of both present and future research on liver tumours is to understand which are the actual therapeutic challenges posed by the different subgroups and risk categories of HB.

Are all the PRETEXT IV tumours bad players? Do they present a chemotherapeutic or a surgical challenge or both? Is there any evidence that pretext IV tumours can be shrunk by chemotherapy to become operable or should they all receive LTX? Should we make a distinction between unifocal and multifocal PRETEXT IV when deciding upon treatment strategy?
Are there prognostic factors which could define which metastatic HB patients would be expected to fail therapy? Does the presence of a single metastasis predict a better outcome? Can well timed single or multiple metastectomy improve the outcome? Can complete metastatic response to therapy be better defined?

HB presenting with a low AFP seems to represent one of the most unfavourable groups of HB. However, the clinical and pathological profile of these neoplasms is far from fully described. Are they all metastatic and/or unresectable? Do they respond to chemotherapy or not at all? Also the striking correlation between a low AFP value and the “undifferentiated” histology deserves further confirmation.

Although many of the questions will remain unanswered, a number of these particular issues will be addressed by the present and forthcoming SIOPEL trials.

The heterogeneity of the ‘high risk’ HBs and the different therapeutic challenges they pose make it rather difficult to design a single, common therapeutic strategy for the whole group. E.g., for those HB presenting with low AFP and metastases and/or with multiple negative prognostic factors experimental aggressive approaches could be considered. However, the relatively promising results achieved in isolated PRETEXT IV HB prevent us from adopting a completely experimental approach. On the other hand, the rarity of this malignancy, makes it unreasonable to apply different treatment plans for the different subgroups and would only lead to a ‘collection of case reports’ rather than solid evidence obtained in an appropriate manner on a particular issue. The SIOPEL 4 Committee has therefore decided to design a single treatment strategy for all ‘high risk’ patients and, although it realises the limitations and drawbacks of such an approach, is convinced that in this way the most can be learned on the treatment of HR hepatoblastomas.

Which chemotherapy to choose?
The combination Cisplatin/Doxorubicin, at least in the SIOPEL experience, seems to represent the cornerstone of treatment of HB. Interestingly, in the INT-0098 trial despite the fact that the difference was not significant, a trend towards better survival in the Cisplatin/Doxorubicin combination (Regimen B) was observed compared to that of the Cisplatin/VCR/5-FU combination (Regimen A) (23). This was true for any tumour stage (see Figure 6.10 below ). Based on the SIOPEL 2 data of the 15-day schedule of administering Cisplatin it was felt that there was a margin to allow intensification of the use of this drug in combination with Doxorubicin.
The evidence base for the addition of other chemotherapeutic agents in HB is quite scanty. The combination Etoposide - Carboplatin seems to be an effective regimen against childhood HB. As previously reported by POG investigators, nine (75%) of 12 assessable patients (six stage III and three stage IV) had responses to Cisplatin-VP16, with two patients experiencing PD (2,20). The German group reported that twelve out of 18 children responded to Carboplatin/VP16, with actually a CR in one child with stage IV HB. The activity and efficacy of Carboplatin as single agent is clearly confirmed in different studies, although it may be less effective than Cisplatin (18). However, VP-16 has never been tested in a classical Phase II setting or as a single agent in HB patients and it remains completely unclear whether it has any additional value when administered with platinum derivates. Also for other drugs, currently used in different non-SIOP trials (Ifosfamide, VCR, 5-FU), there is insufficient evidence that these drugs have a specific additional value when used on a Cisplatin (+Doxorubicin) backbone (41). Adding those drugs to the principal and crucial agents in HB treatment (Cisplatin and Doxorubicin) could significantly increase the toxicity of the regimen and could thereby even jeopardize the current results. The SIOP committee did not feel justified, therefore, in adding a new drug to the current combination. It is hoped that the consecutive Phase II trials launched by the SIOP group will in the near future reveal novel active agents in HB that can be incorporated successfully into the front line therapy.

A summary of modern treatment regimens used for childhood hepatoblastoma is detailed in Table 6.5.

**Considerations on weekly Cisplatin**

Since Cisplatin is the most effective drug in HB (1,9,14,25,29,32) it seems reasonable to exploit its full potential by increasing the dose density and intensity in the pre-operative
phase. Given the mild toxicity seen in the previous SIOPEL trials it is felt that there is room for giving an intensified Cisplatin regimen safely. Since this specific issue is not addressed yet, no direct or indirect evidence exists in HB whether dose intensity and/or density of Cisplatin plays a major role in the treatment. As mentioned earlier, preliminary results seem to confirm, however, the importance of using Cisplatin vs Carboplatin. These observations supported our intention to focus on the single most effective agent in HB and try to use it in the most effective way.

In the adult setting the dose density of Cisplatin has been gradually increased over the past 2 decades. This has been done in 2 entirely different contexts. The first was to enable palliative chemotherapy to be given in an outpatient setting with mild toxicity in order to increase the quality of life, particularly of older patients. The dose of weekly Cisplatin ranges from 20-40 mg/m². The second is to intensify treatment by increasing the dose density of already medium to high dose Cisplatin in order to improve response. In this setting a number of studies have shown that weekly Cisplatin at a dose of 70-80 mg/m² is tolerable and is a feasible treatment option (10,13,21,37). Giving Cisplatin weekly in this way does increase the bone marrow toxicity of the Cisplatin and whereas blood transfusion is rarely required in patients receiving Cisplatin monotherapy it becomes standard when weekly Cisplatin is administered in these doses. In the adult setting phase II studies are now looking at the feasibility of administering weekly Cisplatin in combination with particularly the taxanes and anthracyclines. In a randomised trial of standard regimen Cisplatin comparing it to dose dense Cisplatin efficacy has been shown to be statistically significantly better in the dose dense group in patients with ovarian cancer (10,38).

Paediatric data on weekly (intensive) Cisplatin are very scanty and study results are not available. A concurrent trial in relapsing Ewing sarcoma (EORTC-62993) with weekly Cisplatin and oral Etoposide is presently underway in the UK and in France.

Considerations on liver transplantation.
In SIOPEL-1, 12 patients underwent LTX (8% of all patients), as the first-line surgical option in 7 children and as the second-line salvage procedure in 5 patients who had undergone a previous partial hepatectomy (26). The median follow-up at December 2001 was 127 (10-135) months since diagnosis and 117 (52 – 125) months since LTX for patients who were alive. The overall patient survival was 75 % after 5 and 66 % after 10 years since LTX. The review of the world experience collected 147 cases operated in 24 centres. LTX was performed as the first-line surgery in 106 cases (72 %) and as the rescue surgery in 41 cases (28 %). Twenty-eight patients (19 %) received a live related liver transplant and 119 (81 %) received a post-mortem liver graft. Additional chemotherapy was given post-LTX in 65 (44 %) cases. The patient survival beyond 6 years post-transplant was 82 % (95 % CI 72-92%) for the primary LTX and 30 % (95 % CI 14 % - 46 %) for the rescue LTX (26).

Incomplete tumour resection and intrahepatic recurrence after partial hepatectomy were considered potential indications for rescue LTX. However significantly better survival rates obtained in patients who received a primary transplantation, after good response to chemotherapy, support the strategy of avoiding any attempt at partial hepatectomy when radical resection seems difficult and unlikely, as is the case in a PRETEXT III tumour in close proximity to the main vessels, because peeling the tumour off the vessels is likely to leave microscopic malignant residue at the resection line. Moreover, multivariate analysis of the world review material showed that no independent factor can explain the low survival after rescue LTX.
In the case of *hepatocellular carcinoma*, which is often chemoresistant, macroscopic venous invasion and lung metastases are very dismal prognostic factors and are recognized as absolute contraindications to LTX. These features do not hold true for HB because of its usually high chemosensitivity.

Should patients with lung metastases at presentation be excluded from LTX? Such is the policy in some centres but not in others, if the lung deposits clear after chemotherapy. Of the 12 patients who received a liver transplant in the SIOPEL 1 trial, five had lung metastases at presentation. Their lungs cleared after chemotherapy. Four of the 5 (80%) were alive and disease-free with a follow-up of 52 to 99 months since LTX.

The value of post-LTX chemotherapy is controversial, at least in patients who have had a good response to primary chemotherapy. Indeed, many resected tumours show extensive necrosis on pathologic examination and metastatic relapse was unusual in SIOPEL 1 (only 5 patients of 115 who had delayed surgery relapsed in the lungs), suggesting that micrometastases were effectively eradicated by chemotherapy. In the review of the world experience, 65 patients received post-LTX chemotherapy while 82 did not; the corresponding overall survival rates (77 % and 70 %, respectively) were not statistically different. There is a real concern that post-LTX chemotherapy may simply add morbidity in conjunction with immunosuppressive agents. This issue can only be evaluated in a large international randomised trial.

Transplant is clearly not the solution for all the therapeutic challenges that PRETEXT IV HB poses. In the recent POG experience with Stage III (n=22) and metastatic (n=11) HB, only three of the 14 children who were never considered to have a resectable tumour had a transplant. Liver transplantation was not performed in the others because of either early progression (n=9) or metastatic disease (n=1). Unfortunately it is not clear from the manuscript how many of the 9 who had an early progression were Stage III-HB.

*Considerations regarding lung metastases*

In the SIOPEL 1 trial all 4 of the 31 patients with pulmonary metastases at diagnosis, in whom a metastasectomy was performed, survived without residual disease (33). However in the SIOPEL 2 trial 8 patients out of 25 had surgery for lung metastases and only 3 of these patients are alive. No further details are available at the moment but thorough follow-up will continue. Even when there was a relapse, surgical treatment seemed to be a curative procedure, so long as there was local control of the primary tumour.

*Considerations on microscopic residual disease:*

Interestingly, unpublished SIOPEL 1 and 2 experience has shown that microscopic tumour residuum does not necessarily carry an adverse prognosis. In the SIOPEL 1 trial of 11 patients with a positive resection margin, only 2 died, but neither of the 2 had a local relapse. None of the 11 had a second resection, and all but 1 (radiotherapy) were treated only with postoperative chemotherapy. No relapse occurred and all survivors were in complete remission at their last follow-up (mean 5.5 years). It shows that a re-resection of the positive margin may not necessarily have to be performed. Possibly these favorable and quite unexpected results can be explained by the use of the CUSA device (ultrasonic dissection and aspiration) during surgery. The resection margin is ‘vacuum cleaned’, and therefore ablated. One could hypothesize that, despite the positive margin at the specimen site, there may have been a negative margin at the patient’s site. Alternatively or in addition, residual tumour may
not be ‘viable’ because of the lethal cell damage from pre-operative chemotherapy. However these data require further studies and should be interpreted with caution.

In spite of the above considerations it has to be stressed once more that in all hepatoblastoma cases a surgeon should aim at complete tumour resection.
<table>
<thead>
<tr>
<th>Regimen Used for Childhood Hepatoblastoma in Modern Series</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table 6.5</strong></td>
</tr>
<tr>
<td><strong>Regimen used for childhood hepatoblastoma in modern series</strong></td>
</tr>
<tr>
<td><strong>Carboplatin</strong></td>
</tr>
<tr>
<td>CCG-823GF (24)</td>
</tr>
<tr>
<td># of courses</td>
</tr>
<tr>
<td>Cumulative dose</td>
</tr>
<tr>
<td>POG 8697 (15)</td>
</tr>
<tr>
<td># of courses</td>
</tr>
<tr>
<td>Cumulative dose</td>
</tr>
<tr>
<td>INT-0098 (23)</td>
</tr>
<tr>
<td>Regimen a</td>
</tr>
<tr>
<td>Cumulative dose</td>
</tr>
<tr>
<td>Regimen b</td>
</tr>
<tr>
<td>Cumulative dose</td>
</tr>
<tr>
<td>POG 9345 (20)</td>
</tr>
<tr>
<td># of courses</td>
</tr>
<tr>
<td>Cumulative dose</td>
</tr>
<tr>
<td>For no responders</td>
</tr>
<tr>
<td># of courses</td>
</tr>
<tr>
<td>Cumulative dose</td>
</tr>
<tr>
<td>SIOPEL1 (32)</td>
</tr>
<tr>
<td># of courses</td>
</tr>
<tr>
<td>Cumulative dose</td>
</tr>
<tr>
<td>SIOPEL2 (42)</td>
</tr>
<tr>
<td># of courses</td>
</tr>
<tr>
<td>Cumulative dose</td>
</tr>
<tr>
<td>German HB – 94 (17)</td>
</tr>
<tr>
<td># of courses</td>
</tr>
<tr>
<td>Cumulative dose</td>
</tr>
<tr>
<td>For non responders</td>
</tr>
<tr>
<td># of courses</td>
</tr>
<tr>
<td>Cumulative dose</td>
</tr>
<tr>
<td>CCG pilot</td>
</tr>
<tr>
<td># course</td>
</tr>
</tbody>
</table>

*The first cycle consisted of Cisplatin alone; ** 2 cycles if complete resection at post-induction surgery or + 4 in incomplete resection*
7. OBJECTIVES OF THE TRIAL

7.1. PRIMARY OBJECTIVES:

- To determine the effectiveness and short-term toxicity of an intensified new chemotherapy regime in children with high risk hepatoblastoma.
- To increase the rate of complete surgical resection by full implementation of liver transplantation in the treatment strategy as a valid option for tumour removal when partial liver resection or other surgical options remain unfeasible even after extensive pre-operative chemotherapy.
- To evaluate prospectively the role of pre-operative chemotherapy in rendering unresectable tumours, resectable.
- To assess the accuracy of initial imaging in predicting the surgical options after pre-operative chemotherapy in children presenting with unresectable disease.

7.2. SECONDARY OBJECTIVES

- To improve overall and event-free survival with an acceptable overall toxicity
- To assess toxicity of this Cisplatin intensive regimen
- To assess response rate to pre-operative chemotherapy
- To assess whether the response to chemotherapy defined by the modified RECIST criteria can be used for better monitoring of response
- To assess whether the fall of AFP during pre-operative chemotherapy can be used as a prognostic factor
- To further evaluate the feasibility of rapid central review of pre-treatment tumour extent of disease and resectability for 'difficult' patients, by a panel of experts
- To prospectively collect data on radiological, surgical and pathological characteristics of the tumour in order to identify possible novel factors that might influence treatment choice and disease outcome
- To continue collecting biological materials derived from HB patients in order to improve knowledge of the pathology and biology of HB and to facilitate basic research on this rare tumour
- To improve clinical care for children with HB by giving guidelines for the diagnostic, therapeutic and follow-up management of these patients
8. TRIAL DESIGN

This is a prospective, international, multi-centre, open, single arm, phase II clinical trial for patients with ‘high-risk’ hepatoblastoma.

8.1. END-POINTS

**Primary end-point:**
- The primary endpoint of the trial is the rate of complete remission (CR) after the end of trial treatment (chemotherapy and partial resection or liver transplant), defined as a normal serum AFP level and absence of disease on imaging (abdominal ultrasound/CT and lung CT). Complete remission, as defined above, coincides with disease-free status. Total hepatectomy followed by liver transplantation will be considered as complete tumour resection and will be counted – if accompanied by no remaining tumour lesion on imaging and normal AFP - as complete resection and not failure of chemotherapy (for detailed definition see section 15).

**Secondary end-points:**
- Complete resection rate is considered as a surrogate marker of overall and progression free survival and, for the purpose of early monitoring of outcome, will also be evaluated in this trial.
- Response rate (RR) to pre-operative chemotherapy
- Rate of grade 2 cardiac and renal, grade 3 oto and grade 4 non haematological toxicity during and at the end of trial treatment
- Overall and event free survival (OS, EFS)

8.2. PATIENT ACCRUAL:
- Projected accrual: 25-30 patients/year.
- Projected total accrual: 57 evaluable patients.
- Expected duration of the trial: ca. 2 years.

8.3. TREATMENT PLAN

The treatment strategy is based on the use of intensified neo-adjuvant chemotherapy and complete surgical removal of the tumour (including metastatic lesions). After entering into the trial patients receive three blocks of Cisplatin-intensive pre-operative chemotherapy followed by assessment of resectability. If the tumour is considered resectable at this stage definitive surgery will be performed including the option of liver transplantation and/or metastectomy. Patients with an unresectable but responding primary tumour will continue chemotherapy and receive two courses of medium/high dose chemotherapy before definitive surgery is reconsidered. After complete tumour removal eligible patients will receive a short post-operative chemotherapy cycle (Figure 4.1).

Tumour response and resectability status will be evaluated according to the SIOPEL criteria (see section 15). A CR rate, achieved with or without LTX, of 50% or less would be considered to be unsatisfactory, whereas a CR rate of 70% would be considered promising for further development. Regular toxicity monitoring is required throughout the whole trial and results will be evaluated regularly to highlight unacceptable toxicity.

In the case of unresectable stable disease or disease progression at any time during the trial considered not amenable to radical surgery, the patient should be considered for the current
SIOPEL Phase II trial (*see* separate Phase II protocol, available from the UKCCSG Data Centre).

### 9. PATIENT SELECTION CRITERIA

#### 9.1. DEFINITION OF HIGH-RISK HEPATOBlastOMA

Patients with a hepatoblastoma fulfilling at least one of the following criteria are considered as high-risk patients (*see* for detailed definitions and description of the ‘pre-treatment extent of tumour’ system see section 10.3):

- **Tumour involving all 4 hepatic** sections - PRETEXT IV
- **Evidence of abdominal extra-hepatic disease** (ie. any of V, P, E), regardless of the PRETEXT category (NB: All non vascular extra-hepatic disease should be biopsied)
- **Presence of metastases** (M+):
  - **Lung metastases**: Pulmonary lesions documented by chest X-ray and lung CT scan will be considered to be unequivocal metastatic tumour deposits if there is one nodule larger than 10 mm or several nodules with at least one larger than 5 mm. In the other cases, the metastases will be considered as doubtful and a surgical biopsy of one of the nodules should be discussed if the general condition of the child permits it. If biopsy in a doubtful case is not feasible or not conclusive, rapid radiology review is mandatory before the patient can definitively be entered into the trial.
  - **Other sites of metastases**: mainly bone or brain metastases
- **Low level of AFP** defined as: **AFP < 100 ng/ml** at diagnosis. Please be aware that occasionally a very high level of AFP can give a false negative result. Thus, the negative value should be confirmed with at least two consecutive measurements and appropriate dilutions.
- **Tumour rupture at diagnosis, irrespective of PRETEXT**

#### 9.2. INCLUSION CRITERIA

- Histologically confirmed hepatoblastoma
- Risk category: high-risk (as defined above)
- Written informed consent and national/local ethical committee approval
- Ability to comply with requirements for submission of materials for central review
- Age < 18 years

#### 9.3. EXCLUSION CRITERIA

All patients who do not fulfill the eligibility criteria of the protocol are excluded from the trial. Additional exclusion criteria are:

- Diagnosis not confirmed by histology
- Age ≥ 18 years
- Any previous chemotherapy or any previous treatment for hepatoblastoma
- Interval between date of diagnostic biopsy and start of chemotherapy > 15 days
- Abnormal renal function at diagnosis defined as GFR < 75-50% of the lower limit of normal for age which over 2 years of age is < 60 ml/min/1.73 m²
- Patient unable to follow the protocol for any reason.
- Patients referred for recurrent disease
- No written informed consent or no ethical committee approval
10. DIAGNOSTIC AND PRE-TREATMENT INVESTIGATIONS

10.1. GENERAL NOTES
All children with a suspected primary liver tumour should undergo a diagnostic workup including physical examination, laboratory tests, imaging studies and tumour biopsy to establish a correct diagnosis. At the same time, an accurate pre-treatment tumour extension evaluation should be performed and a definitive PRETEXT category assigned. Subsequently, each patient should be allocated to one of the two risk categories: standard risk or high-risk. Only patients with ‘high-risk’ features are eligible for this trial (for definition of ‘high risk’ hepatoblastoma see section 9.1). Patients with standard risk hepatoblastoma are eligible for the ‘standard-risk arm’ of the SIOPEL 3 trial. For registration arrangements see section 19.

In addition to the diagnostic procedures, pre-treatment toxicity evaluation must also be done in order obtain appropriate base line values for on-treatment toxicity monitoring.

IMPORTANT REMARK:
To assist local physicians in the diagnostic workup and entry of a patient into one of the SIOPEL trials an internet-based online registration system has been developed. After pre-registration of a child with a suspected primary malignant hepatic tumour, the system will guide you through the required pre-treatment investigations and the registration procedure. In order to satisfy all the necessary procedures for adequate diagnostic and pre-treatment work-up and centralisation of trial material, if appropriate, please pre-register patients on this system or notify the SIOPEL Data Centre as soon as possible, preferably before biopsy, when a malignant hepatic mass is suspected in a child. For further details on pre-registration and patient entry please consult section 19.

10.2. HOW TO ESTABLISH DIAGNOSIS?
The diagnosis of hepatoblastoma will be based on histological examination. Although in some cases imaging studies and elevated APF level give a high certainty of this diagnosis, histological confirmation and, even more importantly, histological classification of the disease is required for this trial. A central review of the pathology slides of each patient will take place during the trial. Tumour biopsy is, therefore, mandatory for entry into the trial for all children regardless of their age and serum AFP level. For pathological guidelines regarding classification and central review please consult section 16. For further details and guidelines on how to perform biopsy please consult section 14.1.

Please note, that SIOPEL has launched a Childhood Liver Tumour Tissue Storage Program to facilitate biological and translational research on primary malignant liver tumours of children. We strongly recommend participation in this project by sending material to the Central Tissue Bank. For further details regarding tissue sampling, preparation and transportation please consult Appendix 9.

10.3. PRE-TREATMENT EXTENSION OF TUMOUR (PRETEXT)
General considerations
Consistent with the previous SIOPEL trials the SIOPEL 4 trial will continue using the ‘pre-treatment extent of disease’ (PRETEXT) system for the assessment of initial tumour extension. Risk allocation in the current SIOPEL studies is mainly based on these criteria. As outlined earlier, this system has been conceived to describe tumour extension before any therapeutic intervention. As such, it is purely descriptive and is based on radiological findings at diagnosis. Since surgical resection is a crucial prognostic factor and the healthy sectors,
that can be left in place, determine the outcome, the PRETEXT system aims to predict the anatomical configuration of the healthy liver tissue remaining after resection.

Surgical anatomy of the liver
Anatomically and functionally, the right and the left part of the liver are separate (called right hemiliver and left hemiliver). Each part is divided into two sectors. The left hemiliver consists of a left lateral sector (Couinaud segments 2 and 3) and a left medial sector (Couinaud segments 4 and left part of 1). The right hemiliver consists of a right posterior sector (Couinaud segments 6 and 7) and right anterior sector (Couinaud segments 5 and 8 and right part of 1).
**Figure 10.1**

**SIOPEN**

**PRETEXT**

**PRE - TREATMENT EXTENT OF DISEASE**

---

**Invasion (III)** — **Displacement (II)**

- **V** = Vena Cava and / or Main Tributaries (Caval Attachements)
- **P** = Portal Vein and / or Main Tributaries (Hilar)
- **E** = Extrahepatic excluding extrahepatic V or P (rare)
- **M** = Distant Metastases (mostly Lungs - otherwise specify)
**PRETEXT categories**

**Involvement of liver sections**

**PRETEXT I**  One section is involved and three adjoining sections are free

**PRETEXT II**  Two sections are involved and two adjoining sections are free

**PRETEXT III**  Three sections or two non-adjoining sections are involved, and either one or two non-adjoining sections are free

**PRETEXT IV**  All four sections are involved, with no free section

See Figure for possible variations.

**Please note!**

**PRETEXT system has been slightly modified by introduction of V1-3 and P1-2 categories in comparison with former SIOPEL 1-3 studies. However, this does not change the definition of standard risk and high risk, but clarifies it - V1+, V2+ and P1+ are standard risk, V3+, P2+ are high risk.**

**Extension of the tumour beyond the liver***

**V**  indicates extension into the vena cava and/or into any of the three hepatic veins

- **V1+**  one hepatic vein is involved

- **V2+**  two hepatic veins are involved

- **V3+**  all three hepatic veins and/or vena cava are involved

**P**  indicates extension into the main portal vein and/or its left or right branches of the portal vein

- **P1+**  one portal branch is involved

- **P2+**  both portal branches or main portal trunk are involved

**E**  extra-hepatic disease in the abdomen (which includes involvement of lymph nodes in the hepato-duodenal ligament)

**M**  indicates presence of distant metastases

* Although strictly speaking only the vena cava and main portal vein are beyond the liver, their main tributaries and branches within the liver are also included in V and P

Thus the definitive PRETEXT group will be expressed as, for example, PRETEXT IV, V3+, P1+, E+, M+

**Note:**

A. It is important to try to distinguish between actual involvement of the section and compression of the section by tumour.

B. The same distinction applies to "extension" into vessels. This is only present if there is tumour within the vein or complete encasement of the vein by tumour.

C. Pedunculated tumours are considered to be confined to the liver and to occupy only the section from which they originate.
D. Tumour rupture does not automatically indicate E+. Peritoneal metastases must be proved by biopsy.

The assignment of the PRETEXT category should be by consensus of the treating oncologist, radiologist and surgeon at the individual centre. Accurate assessment of PRETEXT category is required at diagnosis and will be compared to the ‘post treatment extent of disease’, assessed just before surgery. Pre-operative tumour extension evaluation is primarily aimed at predicting the probable extent of hepatic resection.

**PRETEXT categories:**

**Involvement of liver sections:**

**PRETEXT I**  
One sector involved, three adjoining sections free

**PRETEXT II**  
Two sections involved, two adjoining sections free

**PRETEXT III**  
Three sections or two non adjoining sections are involved, just one or two non adjoining sections free

**PRETEXT IV**  
All four sections involved, no free sector

The PRETEXT number reflects the numbers of sections that are involved by tumour. See Figure 10.2 for possible variations.

**Extension of the tumour beyond the liver:**

"V" : indicates "extension" into the vena cava and/or all three hepatic veins

"P" : indicates "extension" into the main and/or both left and right branches of portal vein

"E" : extra-hepatic disease except for P and V is rare and must be biopsy-proven. (NB: enlarged lymph nodes on radiological investigation without histological confirmation are not considered a reason for entering the patient on to the high risk trial.)

"M" : indicates presence of distant metastases

Although strictly speaking only the vena cava and portal vein are beyond the liver, the main tributaries within the liver are also included in "VP" since the resection consequences are the same.

**Important remarks:**

- It is important to try to distinguish between actual involvement of the section and only compression of the section. The same distinction applies to "extension" into vessels.
- Pedunculated tumours are considered to be confined to the liver and to occupy only the section from which they originate.
- Tumour rupture at diagnosis automatically makes a patient high risk.
- The assignment of the PRETEXT category should be by consensus of the treating oncologist, radiologist and surgeon at the individual centre.
- Accurate assessment of PRETEXT category is required at diagnosis and will be compared to the ‘post-treatment extent of disease’, assessed just before surgery. Pre-operative tumour extension evaluation is primarily aimed at predicting the probable extent of hepatic resection.

### 10.4. RADIOLOGICAL INVESTIGATIONS

Local radiologists are kindly requested to perform the following procedures:

- To assess the extent of disease (PRETEXT category) from pre-treatment imaging according to the PRETEXT system (☞ for details see section 10.3).
To determine the maximum diameters of the primary tumour in three dimensions and calculate the tumour volume. Tumour volume will be used to monitor response to chemotherapy and should be calculated as accurately as possible. ‘Volume’ will be defined as the actual product of the 3 maximum perpendicular diameters.

To measure the maximal diameter (in one dimension) of all target lesions according to the RECIST criteria (for details see Appendix 3).

To assess (together with the local surgeon) resectability of both the primary tumour and the metastases based on the diagnostic and pre-surgery imaging.

**Required investigations:**
- Abdominal ultrasound and contrast enhanced abdominal CT scan or MRI with gadolinium
- Chest X-ray (in two projections PA & lateral) and chest CT scan

Please note, that, based on experience from previous studies, both chest radiography and CT of the thorax are mandatory to determine the presence and extent of pulmonary metastases

**Important remarks:**
- To assist local physicians a panel of radiologists will be available, on request, for rapid consultation (see section 10.5).
- In all cases of suspected PRETEXT IV tumour rapid radiological review is strongly recommended with regard to a potential liver transplantation.
- Please note, that a central review of initial and pre-surgery imaging studies will take place for all children entered into the trial. Relevant images will be requested by the Data Centre and can be sent preferably electronically by using the internet-based Remote Data Entry system.

**Technical guidelines for radiological investigations**

**Ultrasound:** In general, the hepatic vasculature is best assessed by ultrasound (with and without colour or power Doppler imaging and pulsed wave Doppler). Ultrasound is useful to confirm the hepatic origin of the mass and is also very accurate for measuring the size of small masses. Ultrasound is ideal for follow-up of the child during treatment (although other modalities will also be used in the immediate pre-operative assessment). Different types of transducer may be helpful but in small children high-frequency probes are most useful.

**Computed tomography:** CT may require sedation or general anaesthesia in young children. Evaluation of a liver mass is one of the few occasions in paediatric abdominal CT in which it is justifiable to perform images both before and after intravenous contrast. The pre-contrast images should be restricted to the liver. The timing of scanning after contrast injection will depend on the age of the child and the type of scanner used. Images should be displayed with careful attention to detail. In particular: the maximum picture area allowed by the film format should be used; window width and level should be carefully selected by the reporting radiologist; the images should always carry a calibration ruler, to allow for later measurements. Interpretation of chest CT may be hampered by collapse (atelectasis) of the lungs, usually at the bases. This may be related to sedation or anaesthesia and/or to compression by a large liver mass. In doubtful cases, discuss with your paediatric anaesthetist the possibility of repeating the examination in the prone position. If there is still doubt about the presence of lung metastases, rapid radiological review is recommended.

**Magnetic resonance imaging:** MRI may require sedation or general anaesthesia in young children. Various techniques may be used to try to minimize motion artefacts.
Coronal and transverse sequences are usually most helpful for evaluation of liver tumours in children.

**Other imaging:** Angiography, scintigraphy (nuclear medicine) and intravenous urography are not used in the routine assessment of a child with a presumptive liver tumour. Angiography is occasionally helpful to evaluate the hepatic vasculature when complicated surgery is anticipated or as part of hepatic artery chemoembolization (see surgical section).

### 10.5. RAPID CENTRAL REVIEW OF THE RADIOLOGICAL FINDINGS

It is acknowledged that there may be difficulties in correctly assigning some cases to the 'high risk' or 'standard risk' group. The problem can be illustrated by those cases for which it is difficult to judge if a large PRETEXT III tumour compresses or infiltrates the remaining hepatic section. **In order to assist local physicians in the assessment of tumour extent and to minimize the risk of misallocating patients to risk categories, a panel of radiologists, lead by Dr Derek Roebuck, is available, on request, for rapid consultation (rapid radiological review = RRR).** This means that, if requested, an urgent central review of films will be performed and a final opinion on a specific tumour (extent, PRETEXT category) will be formulated and forwarded rapidly (by fax or email) to the referring centre. This service is also available for pre-surgery assessment.

To submit a case, a preliminary registration of the patient is required using the computer (web) based on-line registration system. On preliminary entry of a patient this system will assist you in arranging RRR and all the necessary steps required for definitive registration of the patient. For further details on (pre-) registration please, consult section 19.

If electronic transport of the pertinent radiological studies is not feasible films should be sent using FEDERAL EXPRESS ACCOUNT NUMBER 207776319 by international overnight service to:

**Dr Derek Roebuck**
Consultant Interventional Radiologist
Department of Radiology
Great Ormond Street Hospital NHS Trust
& Institute of Child Health
Great Ormond Street
London WC1N 3JH, United Kingdom

Tel: +44-20-7829-7856
Tel Home: +44-20-7837-7375
Air Call: +44-20-7405-9200
Fax: +44-20-7242-1607
Email: RoebuD@gosh.nhs.uk

Also colleagues sending material for this rapid central review by mail, are kindly requested to use the on-line registration system to pre-register the patient. The system will then forewarn Dr. Roebuck and Margaret Childs, Trial Co-ordinator, and assist you in arranging all the necessary steps required for definitive registration of the patient. The accuracy of allocating patients to risk categories depends strongly on the quality of the imaging available. To submit a case for RRR, as many images as possible should be submitted.

**IMPORTANT REMARK:**
Please note that RRR must be completed by day 7 of the treatment. This means that participants are urged to pre-register patients and seek RRR immediately after diagnosis of hepatoblastoma is suspected so as not to cause delay to the patient’s treatment.
10.6. INITIAL PATIENT EVALUATION
In addition to diagnostic imaging studies, the following investigations are required before start of treatment in order to assess tumour characteristics or to obtain appropriate base line values for on-treatment toxicity monitoring. Please note that some of these data are required for definitive entry of the patient into the trial. For an overview of all investigations required in the protocol see Appendix 4.

Physical examination
Anthropometric measurements (weight, height and body surface area) and nutritional status assessment (percentiles).

Laboratory tests
Blood: Full blood cell count
Liver function including: bilirubin, ALT & AST, Alkaline Phosphatase; gamma GT
Serum Creatinine, Urea, Na⁺, K⁺, Cl⁻, Ca²⁺, Mg²⁺, Phosphate
Partial Thromboplastin Time, Prothrombin time or equivalent, fibrinogen and Factor V
Serum alpha-fetoprotein and β-human chorionic gonadotrophin hormone (β-HCG) levels. N.B. In cases of normal serum AFP - ensure that appropriate dilutions have been carried out. Beware of false negative result.
Hepatitis B and C serology;
Urine: Creatinine and electrolytes (Na⁺, K⁺, Cl⁻, Ca²⁺, Mg²⁺, Phosphate) so that, using fractionated excretion, tubular function can be measured

Other investigations
- Glomerular filtration rate as measured by ⁵¹Cr-EDTA clearance or other clearly stated clearance method
- Audiogram - pure tone where possible age 3 years +, otherwise free field testing or distortion product otoacoustic emissions
- Cardiac function at diagnosis should be measured by 2d-derived echocardiogram - measurement of shortening fraction (ejection fraction) - and stored on tape for central review. If the initial SF is <29% (or ejection fraction < 40%) the child will not be ineligible for the study and may receive the first dose of cisplatin. However the echocardiogram must be repeated and stored on tape for central review, prior to any administration of Doxorubicin. The toxicity monitoring guidelines should be carefully followed and advice from the chemotherapy co-ordinators is recommended.
11. TREATMENT PLAN

11.1. GENERAL NOTES
The therapeutic strategy for high-risk hepatoblastoma is based on the use of two equally important treatment modalities: surgery and chemotherapy. The ultimate goal of the treatment is to achieve complete surgical removal of the tumour, which is a pre-requisite for cure in HB. Pre-operative chemotherapy is, however, essential in children with advanced disease to render the tumour resectable. Chemotherapy is also indispensable to control microscopic and/or macroscopic metastatic disease.

The treatment plan consists of the following phases (see also Figure 11.1):
- Pre-operative chemotherapy (for all patients)
- Additional pre-operative chemotherapy (for selected patients)
- Definitive surgery
- Post-operative chemotherapy (for eligible patients)

The different phases are followed by assessment of tumour response, resectability and/or remission status according to the guidelines given in section 15.

11.2. PRE-OPERATIVE CHEMOTHERAPY (BLOCKS A1, A2, A3)
After diagnosis, all patients will receive pre-operative chemotherapy consisting of three blocks: A1, A2 and A3, administered every four weeks (week 1, 5 and 9 respectively). The first block (A1) should be started within 15 days from diagnosis. In order to achieve sufficient tumour control, all patients should receive all three courses even if the tumour becomes resectable earlier. Please note, that blocks A1-A2-A3 are very similar but not identical (for details of chemotherapy see section 12).

During pre-operative chemotherapy, tumour response will be evaluated after each course by measurement of AFP and imaging studies (section 15). If unequivocal progression occurs after adequate initial chemotherapy (at least block A1) patient should stop trial treatment and proceed to salvage therapy (SIOPEL phase II trial).

Assessment of tumour response and resectability at the end of pre-operative chemotherapy
After blocks A1 through A3 have been completed, tumour response and resectability must be evaluated. Based on these assessments, patients can proceed to one of the following three options:

- Additional pre-operative chemotherapy (block B) section 11.3
  When complete resection of the remaining tumour lesions deemed not feasible
- Definitive surgery section 11.4
  When complete resection of all remaining tumour lesions is feasible
- Treatment failure >> salvage therapy section 11.9
  When no objective response to chemotherapy observed in a child with unresectable tumour

11.3. ADDITIONAL PRE-OPERATIVE CHEMOTHERAPY (BLOCK B)
Block B consists of the combination of medium/high dose Carboplatin and Doxorubicin administered three weekly times two (for details see section 12). Block B should be started
as soon as the patient has recovered from the toxicity of the last chemotherapy course. At the end of block B tumour response and resectability will be assessed again and patients will proceed to one of the following options:

- **Definitive surgery**  
  When complete resection of all remaining tumour lesions is feasible

- **Treatment failure >> salvage therapy**  
  When complete resection of the remaining tumour lesions deemed not feasible

### 11.4. DEFINITIVE SURGERY

#### General notes

The ultimate goal of hepatoblastoma treatment is to achieve complete surgical resection of all tumour lesions (both of the primary tumour and the metastases) that remain visible after pre-operative chemotherapy. As emphasised earlier, only complete tumour resection gives realistic hope of cure for children with hepatoblastoma. This implies that all options should be explored before declaring a tumour unresectable. In this regard, for selected cases, **liver transplantation** and **pulmonary metastectomy** must be considered a real option.

In the very rare case that a complete response to pre-operative chemotherapy of both metastatic disease and the primary tumour occurs a complete resection of the initially involved liver **sections** is strongly recommended. Please contact the study chair in these cases.

#### Timing of definitive surgery

Definitive surgery should preferably take place after three blocks of pre-operative chemotherapy (blocks A1-A3). At this point every attempt should be made to remove the tumour completely (without microscopic residual disease) through partial or total hepatectomy. However, if complete resection (including liver transplant) is deemed not feasible at this point (e.g. because of persistence of abdominal extra-hepatic disease or unresectable pulmonary metastases) patients should first proceed to additional chemotherapy. After block B, resectability must be reassessed and definitive surgery, if feasible, should then take place.

Tumour resection should be performed as soon as the patient has recovered from the last chemotherapy course. For more details on surgery (incl. liver transplant) see section 14.

#### Surgery in patients with initial lung metastases

In general, the presence of lung metastases at diagnosis is not a contraindication for partial liver resection or liver transplantation. Some lung metastases respond very well to chemotherapy and can disappear completely or become resectable by the end of the pre-operative chemotherapy. Removal of pulmonary residual disease with subsequent resection of the primary tumour is then considered a valid and curative option. We must, however, emphasize that the role of liver transplant in this setting is still to be established. Accordingly,

- **if metastases have disappeared** by the end of pre-operative chemotherapy (blocks A1-A3), all attempts should be made to resect the primary tumour completely either by partial hepatectomy or by LTX. The disappearance of the metastases must, however, be confirmed by appropriate imaging studies (CT scan).
- **if metastases are not (yet) resectable** after blocks A1-A3, the patient should receive additional pre-operative chemotherapy (block B). Resectability should then be reassessed and an attempt at complete tumour removal should be made if deemed feasible.
if metastases become resectable by the end of pre-operative chemotherapy, ‘aggressive
multiple surgery’ is recommended to resect both pulmonary metastases and the primary
tumour. The complete removal of pulmonary metastases must be confirmed with
appropriate imaging studies (CT scan) prior to resection of the primary tumour.
Please note: It is believed, that there may be critical biological differences in achieving
lung CR (= no more lung lesions on chest CT scan) by chemotherapy only or by
chemotherapy and surgery. In the latter case there is more concern that microscopic
residual lung disease remains. We recommend, therefore, that in the case of continuous
tumour response to the first three blocks of pre-operative chemotherapy (A1-A3), the
use of block B can be considered before surgery in the hope that further chemotherapy
may induce the complete disappearance of lung lesions. However, in this case the tumour
volume of the primary and lung lesions and the serum AFP value should be carefully
monitored to document a continuous tumour response to chemotherapy and avoid
progression. Definitive surgery should than be performed after block B.

In patients who undergo both pulmonary and abdominal surgery, administration of
chemotherapy can be considered between the two operations to guarantee continuous
chemotherapeutic control of tumour growth until all tumour lesions have been removed. For
this purpose (a part of ) the post-operative chemotherapy block (block C) is recommended
(Carboplatin+Doxorubicin). The number of courses (1-3) should be individually chosen,
depending on the tumour situation, recovery time and waiting time for surgery. The remaining
courses (0-2) should be given post-operatively.

Post-surgical evaluation
When complete surgical resection is achieved after pre-operative blocks A1-A3, the patient
will proceed to

- post-operative chemotherapy (block C) see section 11.5

When complete surgical resection is achieved after pre-operative blocks A1-A3 and
additional pre-operative chemotherapy (block B) the patient will receive

- no post-operative chemotherapy see section 11.5

Patients with incomplete surgical resection will be off trial (treatment failure) and should be
considered for:

- Phase II (salvage) therapy see section 11.9

11.5. POST-OPERATIVE CHEMOTHERAPY (BLOCK C)
Patients who undergo complete surgical tumour resection after blocks A1, A2 and A3 will
receive post-operatively 3 courses of Carboplatin/Doxorubicin administered every three
weeks. Post-operative chemotherapy should be started as soon as the patient has recovered
from surgery. Patients who receive LTX after blocks A1-A3 are also eligible for post-
operative chemotherapy unless clear surgical or immunological contraindications are present.

In order to avoid excessive toxicity, patients who undergo complete surgical tumour resection
after pre-operative blocks A1-A3 and additional chemotherapy (block B) receive no post-
operative chemotherapy.

11.6. END OF TREATMENT
Trial treatment will be stopped after completion of pre-operative chemotherapy, complete
tumour resection and post-operative chemotherapy (if appropriate) as described in the
protocol. At the end of treatment tumour/remission status must be evaluated see section 15.
11.7. FOLLOW UP
Patients who achieved complete remission should be followed according to the recommendations in Appendix 5. For the estimation of audiology the best results will be obtained around the age of 4 years. Renal function may initially improve during the first two years after stopping treatment. Projected long-term cardiac toxicity is best estimated by the echocardiogram performed within 6 months from the last dose of Doxorubicin. Evaluating these permanent late effects is an important part of this study, if the survival data is to be put into perspective, and for the design of future studies.

11.8. RECOMMENDATIONS FOR MICROSCOPIC RESIDUAL DISEASE
In the case of microscopic residual disease, as reported by the histo-pathological examination, with no macroscopic disease and normal or adequately declining AFP, no change in the trial treatment should be made. However, discussion with the study chairs of the individual situation and possible alternative options is strongly recommended.

11.9. TREATMENT FAILURE - PHASE II (SALVAGE) THERAPY
Patients who experience treatment failure must stop trial treatment and will be eligible for SIOPEL Phase II salvage therapy:
- Patients with no response to chemotherapy (stable disease or progression) at the end of pre-operative blocks A1-A3 and unresectable tumour.
- Patients who fail to achieve complete tumour resection or complete remission with trial treatment
Figure 11.1 HIGH RISK HEPATOBLASTOMA TREATMENT OVERVIEW

Assessment of response

Assessment of response and resectability

Block A1  Block A2  Block A3

PD  PD  PD or SD

days 1 29 57

SURGERY incl. LTX  Block C  STOP therapy

unresectable

SURGERY incl. LTX  Block B  STOP therapy

PHASE II TRIAL
12. CHEMOTHERAPY

12.1. TREATMENT SCHEDULE:

**Block A1** (Figure 12.1):

<table>
<thead>
<tr>
<th>Days:</th>
<th>1</th>
<th>8, 9</th>
<th>15</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
<td>•</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cisplatin: 80 mg/m²/day D1
*in continuous I.V. infusion for 24 hours*

Doxorubicin: 30 mg/m²/day D8, D9
*in a 1 hour IV infusion with Dexrazoxane or I.V. infusion for 24 hours*

Please note that the **first dose of Cisplatin (D1)** is 80 mg/m²/day so that definitive risk allocation and registration on SIOPEL 3 (for standard risk) or SIOPEL 4 (for high risk) would be possible even after the first Cisplatin course, up to day 7.

When the block has started it should be completed regardless of the blood cell count during the course. The only reason for stopping treatment would be grade 4 or life threatening toxicity during the course.

**Block A2** (Figure 12.1):

<table>
<thead>
<tr>
<th>Days:</th>
<th>29</th>
<th>36, 37</th>
<th>43</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td></td>
<td>•</td>
<td>•</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
<td>•</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cisplatin: 70 mg/m²/day D29, D36, D43
*in continuous I.V. infusion for 24 hours*

Doxorubicin: 30 mg/m²/day D36, D37
*in a 1 hour IV infusion with Dexrazoxane or I.V. infusion for 24 hours*

Before starting the block patients should have recovered from the previous course and must not have signs of active infection. Absolute neutrophil count (ANC) and platelet count should have recovered to above 1x10⁹/l and 100x10⁹/l, respectively. It is better to delay chemotherapy (with a maximum delay of two weeks) until these criteria are met, rather than decrease the dose. If the block has been started it should be completed regardless of the blood cell count during the block. The only reason for stopping treatment would be CTC grade 1 GFR, grade 2 cardiac or grade 3 ototoxicity and grade 4 or life threatening non haematological toxicity.
**Block A3 (Figure 12.1):**

<table>
<thead>
<tr>
<th>Days:</th>
<th>57, 58</th>
<th>64</th>
<th>71</th>
<th>78</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin:</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin:</td>
<td>•</td>
<td>•</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Cisplatin:**  70 mg/m²/day  D57, D64  
*in continuous I.V. infusion for 24 hours*

**Doxorubicin:**  30 mg/m²/day  D57, D58  
*in a 1 hour IV infusion with Dexrazoxane or I.V. infusion for 24 hours*

Please note that Block A3 is modified (number of Cisplatin doses and timing of Doxorubicin) in order to avoid delay in surgery due to the bone marrow toxicity of this course.

**Dexrazoxane:**  Cardioxane: Doxorubicin  20:1 dose limitation 1000mg/m² per cycle  
Zinecard : Doxorubicin 10:1

**The actual dose for block A will be Cardioxane 500mg/m² x 2 or Zinecard 300mg/m² x 2**

Before starting the block patients should have recovered from the previous course and must not have signs of active infection. Absolute neutrophil count (ANC) and platelet count should have recovered to above 1x10⁹/l and 100x10⁹/l, respectively. It is better to delay chemotherapy (with a maximum delay of two weeks) until these criteria are met, rather than decrease the dose. If the block has been started it should be completed regardless of the blood cell count during the block. The only reason for stopping treatment would be CTC grade 1 GFR, grade 2 cardiac or grade 3 ototoxicity and grade 4 or life threatening non haematological toxicity.

**Block B (Figure 12.2):**

<table>
<thead>
<tr>
<th>Days:</th>
<th>1,2,3</th>
<th>22,23,24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin:</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Doxorubicin:</td>
<td>• • •</td>
<td>• • •</td>
</tr>
</tbody>
</table>

**Carboplatin:**  AUC  10.6 mg/ml.min  
*in I.V. infusion for 1 hour*

**Doxorubicin:**  25mg/m²/day  D1, D2, D3, D22, D23, D24  
*in a 1 hour IV infusion with Dexrazoxane or IV infusion for 24 hours*

Block B is given for selected patients (see section 11) as soon as the patient has recovered from the last chemotherapy course. Patients must not have signs of active infection and absoluteneutrophil count (ANC) and platelet count should have recovered to above 1x10⁹/l and 100x10⁹/l respectively. It is better to delay chemotherapy (with a maximum delay of two weeks) until these criteria are met, rather than decrease the dose.

**Dexrazoxane:**  Cardioxane: Doxorubicin  20:1 dose limitation 1000mg/m² per cycle  
Zinecard : Doxorubicin 10:1

**The actual dose for block B will be Cardioxane 330mg/m² x 3 or Zinecard 250mg/m² x 3**
**Block C (Figure 12.3):**

<table>
<thead>
<tr>
<th>Days</th>
<th>1,2</th>
<th>22,23</th>
<th>43,44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>●●</td>
<td>●●</td>
<td>●●</td>
</tr>
</tbody>
</table>

**Carboplatin:**  
AUC 6.6 mg/ml.min  
D1, D22, D43  
in I.V. infusion for 1 hour

**Doxorubicin:**  
20 mg/m²/day  
D1, D2, D22, D23, D43, D44  
in a 1 hour IV infusion with Dexrazoxane or IV infusion for 24 hours

Block C is given post-operatively for eligible patients (see section 11) as soon as the patient has recovered from surgery. Patients must not have signs of active infection. An absolute neutrophil count (ANC) greater than 1x10⁹/l and a platelet count greater than 100x10⁹/l are necessary before starting chemotherapy. It is better to delay chemotherapy (with a maximum delay of two weeks) until these criteria are met, rather than decrease the dose.

**Dexrazoxane:**  
Cardioxane: Doxorubicin 20:1 dose limitation 1000mg/m² per cycle  
Zinecard: Doxorubicin 10:1

The actual dose for block C will be Cardioxane 400mg/m² x 2 or Zinecard 200mg/m² x 2

**12.2. DETAILS OF ADMINISTRATION**

**Cisplatin:**
- Pre-Cisplatin hydration  
  200 ml/m²/hour for 3 consecutive hours of Glucose/dextrose 2.5%/sodium chloride 0.45% +  
  - KCl 10 mmol (10 mEq) /500ml  
  - Mg Sulphate 2 mmol (4 mEq) /500 ml  
  - CaGluconate 1.5 mmol (3 mEq)/500ml
- Cisplatin infusion  
  a) Cisplatin made up to 120 ml (for doses ≤120 mg) [or 240 ml (for doses >120 mg)] with sodium chloride 0.9% infused at 5 ml/hour for 24 hours, run concurrently with:  
  b) 120 ml/m²/hour for 24 hours of a solution of Glucose/dextrose 2.5%/sodium chloride 0.45% +  
  - 30 ml Mannitol 20% ≡ 6g Mannitol/500 ml  
  - KCl 10 mmol (10 mEq) /500ml  
  - Mg Sulphate 2 mmol (4 mEq) /500 ml  
  - CaGluconate 1.5 mmol (3 mEq)/500ml
- Post-Cisplatin hydration  
  125 ml/m²/hour for 24 consecutive hours of Glucose/dextrose 2.5%/sodium chloride 0.45% +  
  - KCl 10 mmol (10 mEq) /500ml  
  - Mg Sulphate 2 mmol (4 mEq) /500 ml  
  - CaGluconate 1.5 mmol (3 mEq)/500ml
**Doxorubicin**
Infusion of Doxorubicin in a 0.9% sodium chloride solution is recommended. Protect the drug from sunlight during infusion. In exceptional circumstances, if a central venous catheter is not available for young children, the daily dose of Doxorubicin can be administered through a peripheral catheter over one hour. Deep veins should be avoided since extravasation of the drug is dangerous and is not readily appreciated at these sites.

Consensus has been reached in the SIOPEL 4 Trial Committee to recommend the use of Dexrazoxane along with the administration of Doxorubicin. However, it is acknowledged that Dexrazoxane may not be universally available.

**Dexrazoxane Cardioxane: Doxorubicin 20:1 dose limitation 1000mg/m² per cycle**
**Zinecard : Doxorubicin 10:1**

Dexrazoxane is administered in a 15 minute infusion 30 minutes prior to the infusion of Doxorubicin. The dose is **20:1 Cardioxane : Doxorubicin** or **10:1 Zinecard : Doxorubicin**, however the Cardioxane dose needs to be capped at a maximum of 1000 mg/m² per cycle. This means the dose of **Cardioxane will be 500 mg/m²/day** on day 1 and day 2 or **Zinecard 300 mg/m²/day** day 1 and day 2. The Doxorubicin dose is 30 mg/m² IV given over 1 hour on day 1 and day 2. The 24 hour infusion of Cisplatin will be given in between the 2 doses of Doxorubicin so that the time of hospitalisation is shorter for those getting the cardioprotectant.

Alternatively Doxorubicin can be administered by intravenous infusion via a central venous catheter for 24 hours on day 1 and day 3. The 24 hour infusion of Cisplatin will be given in between the 2 doses of Doxorubicin to allow comparison of the 2 groups and to shorten the hospitalisation time. The second Doxorubicin will be given during the 24 hours of Cisplatin post hydration.

Administer the combination **Cisplatin + Doxorubicin (in blocks A1, A2, A3)** as follows:

- **h. 0** Start pre-Cisplatin hydration over 3 hours
- **h 0.5** Start Dexrazoxane infusion over 15 minutes
- **h. 3** Start Cisplatin infusion over 24 hours
- **h. 27** Stop Cisplatin infusion
- **h 27.5** Start Doxorubicin(2) infusion over 1 hour
- **h. 51** Stop post-Cisplatin hydration

Alternatively administer the combination **Cisplatin + Doxorubicin (in blocks A1, A2, A3)** as follows:

- **h. 0** Start Doxorubicin(1) infusion over 24 hours
- **h 24** Stop Doxorubicin (1) infusion
- **h 24** Start pre-Cisplatin hydration over 3 hours
- **h. 27** Start Cisplatin infusion over 24 hours
- **h. 51** Stop Cisplatin infusion
- **h 51** Start post-Cisplatin hydration over 24 hours
- **h. 51** Start Doxorubicin (2) infusion over 24 hours
h 75 Stop post-Cisplatin hydration
h 75 Stop Doxorubicin (2) infusion

**General measurements**
A careful record of fluid input and output should be kept during the administration of each course. If diuresis falls below 400 ml/m² per 6 hrs, Frusemide 0.5-1 mg/kg intravenously should be given. Careful monitoring of fluid intake and output is essential to prevent renal toxicity and fluid overload. Any fluid lost through vomiting should be replaced intravenously.

Nephrotoxic antibiotics such as aminoglycosides should preferably be avoided during and immediately after the Cisplatin infusion. If used, serum levels should be monitored with extreme care.

Magnesium gluconate, 3g/m²/day orally, is to be given to all patients, for the entire duration of chemotherapy, beginning with the first course.

Cisplatin is a strong emetogenic drug, thus it is recommended to give an anti-emetic cocktail beforehand. The 5-HT3 receptor antagonists are the drugs of first choice.

**Carboplatin**
Due to the fact that the dose intensity of Cisplatin will be high in these patients subsequent Carboplatin dosing should be carried out according to renal function. Target AUCs will be: **10.6 mg/ml.min in Block B and 6.6 mg/ml.min in Block C.**

The daily dose of **Carboplatin, given in mg, not in mg/m²**, can be calculated from the $^{51}$Cr-EDTA half-life ($t_{1/2}$) value and patient’s body weight using the Newell formula and are shown in tables 1a-d for target AUC 6.6 mg/ml.min and tables 2a-d for target AUC 10.6 mg/ml.min (Appendix 6). The tables are based on calculation using the formula shown below (22):

$$Dose(mg) = Target \text{ AUC} \times \left[ \frac{0.693}{t_{1/2}} \times \frac{843x BW (kg)^{0.891}}{51 \text{Cr EDTA}} \right] + [0.36 \times BW (kg)]$$

Carboplatin is administered as an intravenous infusion via a central venous catheter over 1 hour.

Administer **Carboplatin-Doxorubicin (in block B)** as follows:

- h. 0 Start Dexrazoxane infusion over 15 minutes
- h. 0.5 Start Doxorubicin (1) infusion over 1 hour
- h. 2 Start Carboplatin infusion over 1 hour
- h. 24 Start Dexrazoxane infusion over 15 minutes
- h. 24.5 Start Doxorubicin (2) infusion over 1 hour
- h. 48 Start Dexrazoxane infusion over 15 minutes
- h. 48.5 Start Doxorubicin (3) infusion over 1 hour

Alternatively Doxorubicin may be administered over 24 hours:

Administer **Carboplatin-Doxorubicin (in block B)** as follows:

- h. 0 Start Doxorubicin (1) infusion over 24 hours
- h. 24 Stop Doxorubicin (1) infusion
- h. 24 Start Carboplatin infusion over 1 hour
- h. 25 Start Doxorubicin (2) infusion over 24 hours
- h. 49 Stop Doxorubicin (2) infusion
h. 49 Start Doxorubicin (3) infusion over 24 hours
h. 73 Stop Doxorubicin (3) infusion

Administer Carboplatin-Doxorubicin (in block C) as follows:

h. 0 Start Dexrazoxane infusion over 15 minutes
h. 0.5 Start Doxorubicin (1) infusion over 1 hour
h. 2 Start Carboplatin infusion over 1 hour
h. 24 Start Dexrazoxane infusion over 15 minutes
h. 24.5 Start Doxorubicin (2) infusion over 1 hour

Alternatively Doxorubicin may be administered over 24 hours:

Administer Carboplatin-Doxorubicin (in block C) as follows:

h. 0 Start Doxorubicin (1) infusion over 24 hours
h. 24 Stop Doxorubicin (1) infusion
h. 24 Start Carboplatin infusion over 1 hour
h. 25 Start Doxorubicin (2) infusion over 24 hours
h. 49 Stop Doxorubicin (2) infusion

12.3. DOSE MODIFICATIONS BY AGE

For infants and children with body weight between 5 and 10 Kg:

Cisplatin and Doxorubicin doses should be calculated per Kg, assuming that $1m^2 \equiv 30Kg$.

For infants with body weight less than 5 Kg:

Cisplatin and Doxorubicin doses should be calculated per Kg, assuming that $1m^2 \equiv 30Kg$, and a further 1/3 dose reduction should be applied.

<table>
<thead>
<tr>
<th>Drug</th>
<th>children &gt; 10 Kg</th>
<th>children 5-10 Kg</th>
<th>children &lt; 5 Kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin:</td>
<td>70 mg/m²/day</td>
<td>2.3 mg/Kg/day</td>
<td>1.5 mg/Kg/day</td>
</tr>
<tr>
<td>Cisplatin:</td>
<td>80 mg/m² day 1</td>
<td>2.7 mg/Kg day 1</td>
<td>1.8 mg/Kg day 1</td>
</tr>
<tr>
<td>Doxorubicin:</td>
<td>20 mg/m²/day</td>
<td>0.67 mg/Kg/day</td>
<td>0.44 mg/Kg/day</td>
</tr>
<tr>
<td>Doxorubicin:</td>
<td>25 mg/m²/day</td>
<td>0.83 mg/Kg/day</td>
<td>0.56 mg/Kg/day</td>
</tr>
<tr>
<td>Doxorubicin:</td>
<td>30 mg/m²/day</td>
<td>1.0 mg/Kg/day</td>
<td>0.67 mg/Kg/day</td>
</tr>
</tbody>
</table>
HIGH RISK HEPATOBLASTOMA
PRE-OPERATIVE CHEMOTHERAPY

**CISPLATIN**

*80 mg/m²/day*  Day 1
70 mg/m²/day
Days 8, 15, 29, 36, 43, 57 and 64
_in I.V. infusion for 1 hour_

**DOXORUBICIN**

30 mg/m²/day
Days 8, 9, 36, 37, 57 and 58
_in a 1 hour IV infusion with Dexrazoxane_
_or IV infusion for 24 hours_

<table>
<thead>
<tr>
<th>Days</th>
<th>1</th>
<th>8</th>
<th>15</th>
<th>22</th>
<th>29</th>
<th>36</th>
<th>43</th>
<th>50</th>
<th>57</th>
<th>64</th>
<th>71</th>
<th>78</th>
</tr>
</thead>
</table>

Dexrazoxane: Cardioxane: Doxorubicin  20:1 dose limitation 1000mg/m² per cycle
Zinecard : Doxorubicin 10:1

Figure 12.1
HIGH RISK HEPATOBLASTOMA
ADDITIONAL PRE-OPERATIVE CHEMOTHERAPY

Block B

**CARBOPLATIN**

\[ \text{AUC 10.6 mg/ml.min} \]
Days 1 and 22
in I.V. infusion for 1 hour

**DOXORUBICIN**

\[ 25 \text{ mg/m}^2/\text{day} \]
Days 1, 2, 3, 22, 23 and 24
in a 1 hour IV infusion with Dexrazoxane
or IV infusion for 24 hours

<table>
<thead>
<tr>
<th>Days</th>
<th>1</th>
<th>8</th>
<th>15</th>
<th>22</th>
<th>29</th>
<th>36</th>
<th>43</th>
</tr>
</thead>
</table>

Dexrazoxane: Cardioxane: Doxorubicin 20:1 dose limitation 1000mg/m² per cycle
Zinecard : Doxorubicin 10:1

Figure 12.2
HIGH RISK HEPATOBLASTOMA
POST-OPERATIVE CHEMOTHERAPY

Block C

**CARBOPLATIN**

AUC 6.6 mg/ml.min

Days 1, 22 and 43

*in I.V. infusion for 1 hour*

**DOXORUBICIN**

20 mg/m²/day

Days 1, 2, 22, 23, 43 and 44

*in a 1 hour IV infusion with Dexrazoxane or IV infusion for 24 hours*

<table>
<thead>
<tr>
<th>Days</th>
<th>1</th>
<th>8</th>
<th>15</th>
<th>22</th>
<th>29</th>
<th>36</th>
<th>43</th>
<th>50</th>
<th>57</th>
<th>64</th>
</tr>
</thead>
</table>

**Dexrazoxane:**

Cardioxane: Doxorubicin 20:1

Dose limitation 1000mg/m² per cycle

Zinecard: Doxorubicin 10:1

Figure 12.3
13. TOXICITY MONITORING

13.1. TOXICITY MONITORING

General remarks

The importance of toxicity monitoring in this trial cannot be highlighted enough. This is a very high risk group of young patients being treated in a uniform manner by a large number of diverse centres throughout the world. It is crucial to the safe conduct of this trial that any centre entering patients is able to comply with the toxicity monitoring in a prompt manner. The increase in the dose density of the Cisplatin and the ensuing potential toxicity will be monitored closely. This will be by GFR for kidney function and pure tone audiometry wherever possible for ototoxicity. Otoacoustic emissions with distortion products are very useful for prospectively monitoring ototoxicity in the young child and should be used if available. Due to the increased risk of renal toxicity in this protocol Carboplatin will be dosed by AUC according to GFR. Due to the dose intensity and expected myelosuppression of the treatment Carboplatin may not be simply substituted for Cisplatin in the case of reduced GFR.

The potential cardiotoxicity will be monitored by prospective central review of the taped echocardiograms at key points during the treatment and at follow-up. The model for reviewing these echocardiograms will be taken from the ongoing long-term follow up study. The committee appreciates that this is an increased work load for all colleagues at the treating centres however this will be a very small number of patients for any particular group of physicians.

Contact the chemotherapy panel co-ordinator for any life threatening, lethal, unexpected or unusual toxicity. (See also Serious Adverse Events – Section 17)

Ototoxicity

The grading system for hearing loss proposed by Brock et al (4,5) will be used in SIOPEL 4 (see table 13.1). Careful monitoring of children by an expert audiologist and by serial audiometry throughout the treatment with Cisplatin is essential. To monitor ototoxicity in infants distortion product otoacoustic emissions (DPOAE’s), when available, are useful as a prospective method and are a preferable technique to BEAR (brainstem evoked auditory response). Pure tone audiometry is the method of choice in children older than 3 years of age. Pure-tone audiometry by freefield/distraction technique is also an excellent method in experienced hands. If a child starts to show signs of high frequency hearing loss then he/she should be followed more carefully than the minimum requirement of this protocol. Due to the fact that pure-tone audiometry is the most reliable technique for assessing actual hearing ability it will be necessary to follow all children to the age of 4-5 to be sure of being able to appreciate the permanent damage caused by the Cisplatin in this population.

However it should be noted that neither pure-tone audiometry nor oto-acoustic emissions give a good measure of Carboplatin induced ototoxicity. It should also be noted and the parents informed that Carboplatin in itself at standard doses does not produce significant hearing loss however the combination of Carboplatin and Cisplatin can produce the worst ototoxicity as both the inner and the outer hair cells of the cochlear are affected. The full extent of the damage is very difficult to assess in young children and will only be fully appreciated at follow-up when the children are functioning in a normal environment with background noise. The trial committee are aware that the prognosis of the children in this trial is poor and that there is a balance to be achieved between quality of life and survival. The higher doses of Carboplatin have been reserved for the poor responders. It is also of note that there have been considerable advances
made in the care of children with hearing impairments over the last decade and that a number of potential aids or even cochlear implant may need to be discussed with the family.

Table 13.1  Brock grading system for Cisplatin-induced bilateral high-frequency hearing loss

<table>
<thead>
<tr>
<th>BILATERAL HEARING LOSS</th>
<th>GRADE</th>
<th>Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 dB at all frequencies</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>=/&gt; 40 dB at 8,000 Hz only</td>
<td>1</td>
<td>Mild</td>
</tr>
<tr>
<td>=/&gt; 40 dB at 4,000 Hz and above</td>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>=/&gt; 40 dB at 2,000 Hz and above</td>
<td>3</td>
<td>Marked</td>
</tr>
<tr>
<td>=/&gt; 40 dB at 1,000 Hz and above</td>
<td>4</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Brock grade 3 should be considered as a AE

Renal toxicity

a) Glomerular toxicity - Nephrotoxicity of Cisplatin in children (as in adults) is dose-related and sometimes severe (3,6). Although Carboplatin is less nephrotoxic, when given after Cisplatin it can cause more severe nephrotoxicity than alone. Renal monitoring should be carried out carefully during and at the end of treatment and at follow-up.

Plasma creatinine measurements and creatinine clearances are not reliable guides to the degree of Cisplatin-induced renal damage, particularly in children. Careful measurement of Glomerular Filtration Rate (GFR) by isotope clearance or other clearance method is essential for accurate monitoring of renal status. The GFR monitoring in this trial will be requested prior to each block. However as the Cisplatin will be being administered weekly three times in each block it is advisable to watch the creatinine carefully prior to each dose and if necessary repeat the GFR. The GFR should not be done when a child is receiving IV hydration. Please use the same technique on the same child at every time point. Cr$^{51}$ EDTA GFR is the preferred technique and involves obtaining the isotope, injecting it into the child and taking 4 blood samples at hourly intervals (the simplified version with 2 blood samples is also acceptable) from an indwelling catheter. It entails less irradiation to the child than daily natural sources. Other clearance methods for example Iohexol clearance are also acceptable. If, for financial reasons this is not available at your hospital, then do a standard endogenous creatinine clearance with a 24 hr urine collection. If the urine collection is not complete, then please repeat it. DTPA and other scans are useful for gathering information on a child’s renal function but are not helpful in a multi-national trial, so please do not send us these results instead of a GFR.

A GFR of  CTC grade 1: < 75-50% of the lower limit of normal, which over the age of 2 years is < 60 ml/min/1.73 m$^2$ should be reported as an AE

b) Tubular toxicity  Renal loss of Magnesium and consequent hypomagnesemia is expected in nearly all children on this trial and oral Magnesium supplementation is recommended for all children entered into the trial. Hypomagnesemia is not a reason to stop Cisplatin. Children can develop other manifestations of renal tubulopathy at the same time as the GFR is improving. Thus, careful electrolyte monitoring is essential in all children exposed to Cisplatin treatment. Hypomagnesemia may persist years after stopping therapy. Infants are at higher risk of Cisplatin induced electrolyte imbalance and consequently the need for regular electrolyte monitoring is particularly important in this age group. However, Cisplatin does not seem to be more nephrotoxic in infants than in older children.
Cardiotoxicity
The SIOPEL Committee is concerned about cardiotoxicity in this very young population of children. The long term cardiac follow-up study of SIOPEL 1 is not yet ready for analysis. In the meantime the Committee is suggesting that where possible Doxorubicin be administered with a cardioprotectant. To date there are no randomised studies in children using cardioprotectants so the group has agreed to recommend the product which has the best evidence base and safety profile in the adult setting which is dexrazoxane. Dexrazoxane is commercially available in 2 forms Cardioxane and Zinecard. The 2 medications need to be given at different dose ratios to Doxorubicin. Both forms are being allowed as in some parts of the world one is more readily available than the other.

CTC grade 2 left ventricular dysfunction which is defined as asymptomatic, resting ejection fraction EF < 50-40% or shortening fraction SF < 24-15% should be reported as an AE
Cardioxane: Doxorubicin  20:1 dose limitation 1000mg/m² per cycle
Zinecard : Doxorubicin 10:1

In this protocol a total cumulative dose of Doxorubicin of 300/330 mg/m² will be administered mainly to very young patients. Due to the risk of acute or long-term cardiotoxicity careful monitoring for possible cardiotoxicity is essential during and after treatment.

The recommended investigation is 2D and M mode echocardiogram, with measurement of shortening fraction (SF). Echocardiogram should be performed when the patient is normothermic, has normal haemoglobin, and is not being hyperhydrated. True baseline measurements should be obtained prior to administration of Doxorubicin to provide a meaningful reference for comparison with future tests.

In addition to the normal monitoring there will be central review of the echocardiogram at diagnosis, 1-6 months after the last Doxorubicin administration, and at 5 and 10 year follow-up. The first two investigations should be recorded on tape and sent together for central review to Dr Gill Levitt at Great Ormond Street Hospital NHS Trust & Institute of Child Health, as should the follow up tapes. The tapes need to be sent together with the cardiac form and clearly marked with the child’s initials, date of birth, time of assessment and trial number (see Appendix 8).

Anaphylaxis
Carboplatin can give allergic reactions but anaphylaxis is rare. It is sometimes necessary to slow the infusion if the child develops erythema. It may be necessary to stop the infusion if the child becomes dyspnœic or develops bronchospasm. The administration of I.V. steroids is occasionally necessary. In the case of a severe reaction further administration of the drug should be discussed with the chemotherapy panel co-ordinators. It is not suggested that desensitisation programs are used.

Mucositis
It is a concern that mucositis will be more severe in this protocol than previous SIOPEL protocols. This is due to the increased dose density of the Cisplatin together with Doxorubicin. It is expected to be particularly marked in the patients receiving the long infusion of Doxorubicin. This is another reason why Dexrazoxane should be used wherever possible. Some patients may need naso-gastric feeding. Please monitor the grade of mucositis carefully.

Anorexia
It is likely that the three weekly Cisplatin will cause marked anorexia. It is essential that nutritional status is monitored and naso-gastric feeding be implemented where necessary. It is
advised that naso-gastric feeding is implemented immediately for patients presenting in a poor nutritional state.

13.2. REQUIRED INVESTIGATIONS FOR TOXICITY MONITORING
For an overview of all investigations required in the protocol see Appendix 4.

**During chemotherapy**

Physical examination including weight, height, body surface area and nutritional status assessment - **before starting each block**

**Laboratory tests**

Blood: Full blood cell count, ALT & AST, serum creatinine, urea, Na⁺, K⁺, Cl, Ca++, Mg++, Phosphate - **weekly**

Bilirubin - **before starting each course**

Urine: creatinine and electrolytes (Na⁺, K⁺, Cl, Ca++, Mg++, Phosphate) so that, using fractionated excretion, tubular function can be measured – **before starting each block**

**Other investigations (for frequency see Appendix 4)**

- Glomerular filtration rate as measured by ⁵¹Cr-EDTA or other valid clearance method
- Audiogram - pure tone if age 3 years +, otherwise free field testing and/or distortion product otoacoustic emissions
- 2d-derived Echocardiogram measurement of shortening fraction **on tape for central review**

**Before surgery**

Physical examination including weight and nutritional status assessment. Please note, that surgical complications are more common in children with a poor nutritional status.

**Laboratory tests**

Blood: Full blood cell count; Bilirubin, ALT & AST; creatinine, urea, Na⁺, K⁺, Cl, Ca++, Mg++, Phosphate; Partial Thromboplastin Time, Prothrombin time or equivalent;

Urine: creatinine and electrolytes (Na⁺, K⁺, Cl, Ca++, Mg++, Phosphate) so that, using fractionated excretion, tubular function can be measured.

**Other investigations**

- Glomerular filtration rate as measured by ⁵¹Cr-EDTA or other valid clearance method
- Audiogram - pure tone if age 3 years +, otherwise free field testing and/or distortion product otoacoustic emissions
- 2d-derived Echocardiogram measurement of shortening fraction

**NB:** ECHOCARDIOGRAM IS MANDATORY PRE-SURGERY AND MUST BE SEEN BY PAEDIATRIC ONCOLOGIST AND/OR ANAESTHETIST

**At the end of therapy**

Physical examination including weight, height and nutritional status assessment

**Laboratory tests**

Blood: Full blood cell count; Bilirubin, ALT & AST; creatinine, urea, Na⁺, K⁺, Cl, Ca++, Mg++, Phosphate

Urine: creatinine and electrolytes (Na⁺, K⁺, Cl, Ca++, Mg++, Phosphate) so that, using fractionated excretion, tubular function can be evaluated

**Other investigations**

- Glomerular filtration rate as measured by ⁵¹Cr-EDTA or other valid clearance method
- Audiogram - pure tone if age 3 years +, otherwise free field testing and/or distortion product otoacoustic emissions
- 2d-derived Echocardiogram measurement of shortening fraction (on tape) 1-6 months after final dose of Doxorubicin **on tape for central review**
13.3. Dose and/or Treatment Modifications Due to Toxicity

Bone marrow toxicity
An absolute neutrophil count (ANC) greater than $1 \times 10^9/l$ and a platelet count greater than $100 \times 10^9/l$ are necessary before starting each course. It is better to delay chemotherapy until these criteria are met (for a maximum delay of two weeks), rather than decrease the dose. If a delay of two weeks is necessary, decrease dosage by 25% for the next course.

If a course of chemotherapy results in severe neutropenia (ANC < $0.5 \times 10^9/l$) associated with fever and sepsis or severe infection and/or severe thrombocytopenia associated with bleeding, decrease dosage by 25% for the next course. If the subsequent course is not complicated by these events resume the full dosage of the drugs.

Growth factor support: The use of G-CSF between the cycles of chemotherapy is recommended where available. G-CSF should not be given during chemotherapy or 24 hours prior to or following chemotherapy. The most useful time for the administration of G-CSF will be between cycles. The recommended dose is $5 \mu g/kg/day$ given subcutaneously or IV.

Ototoxicity
If grade 3 ototoxicity is documented this should be reported as an Adverse Event AE

Renal toxicity
In cases of severe reduction in $^{51}$CrEDTA GFR (<60 ml/min/1.73 m$^2$), discontinue Cisplatin and contact the chemotherapy panel co-ordinators. In infants refer to Appendix 10 for the curve of expected GFR according to age. If GFR falls 2 SD below the expected GFR contact the chemotherapy panel co-ordinators.

Hypomagnesemia is not a reason to stop Cisplatin. However in infants electrolyte disturbances are to be expected and can lead to fitting particularly if there are multiple abnormalities. The infusion guidelines are standard, however, in some children the electrolyte substitution may need to be increased. Please monitor electrolytes carefully.

Hepatotoxicity
No standardised criteria exist for the adjustment of Doxorubicin dosage in the presence of hepatic dysfunction. It seems reasonable to recommend a 50% reduction of Doxorubicin dosage if total serum bilirubin concentration > 3 mg/100 ml or/and if serum liver enzymes (AST, ALT) are >5 times the normal value. Cisplatin dose need not be modified.

NB. Since Doxorubicin hepatotoxicity is actually very rare, elevated AST, ALT should lead to a vigorous search for other causes of liver dysfunction, eg. viral hepatitis.

Cardiotoxicity
Significant deterioration in function is indicated by a shortening fraction <29%. In this event, temporarily withdraw Doxorubicin. If subsequent testing shows an improvement in shortening fraction, consider reintroducing Doxorubicin.

A fall in shortening fraction by an absolute value of > 10 percentile units but with an actual SF value > 29% (eg SF 42% → SF 31%) may also represent a significant deterioration in function. In this event contact the chemotherapy panel coordinators.
13.4. REPORTING OF ADVERSE AND SEVERE ADVERSE EVENTS

The reporting of adverse events needs to be done as soon as possible and severe adverse events within 24 hrs of knowledge of the event. Severe adverse events will be divided into expected and unexpected by the study co-ordinators and reported to the necessary authorities. It is the unexpected which are of the most concern.

Expected events will be alopecia, nausea and vomiting, grade 4 haematological toxicity, grade 3 infection and mucositis with prolonged hospitalisation.

Adverse events which must be reported as soon as possible are grade 1 metabolic GFR, grade 2 cardiotoxicity and Brock grade 3 ototoxicity as these form an important part of the secondary end points of the study.

The immediate reporting of severe adverse events within 24 hrs of knowledge of the event does not need to include the expected events outlined above.

A summary of Common Terminology Criteria for Adverse Events v3.0 (CTCAE) can be found in Appendix 11. The full version can be found on the internet at http://ctep.cancer.gov. Brock ototoxicity grading can be found in Table 13.1.
14. SURGICAL GUIDELINES

14.1. PRE-TREATMENT BIOPSY

Please note: Diagnostic tumour biopsy is mandatory for all patients regardless of their age and serum AFP level (see section 10.2).

The aim of biopsy is to obtain adequate tumour material for:
- Histological diagnosis and classification of hepatoblastoma
- Central pathological review
- Biological and translational research facilitated by the SIOPEL Liver Tumour Tissue Bank

**Technique:**
Biopsy can be performed either through minilaparotomy subcostal incision or percutaneously in a closed way according to local center preference. Alternatively a laparoscopic biopsy may be chosen, during which a sampling needle can be introduced percutaneously under camera control, combining both approaches. Otherwise the whole procedure can be done endoscopically. Diagnostic material can be obtained with a “Tru-cut” needle but at least 3-5 cores of tissue should be collected. Additionally one core of normal liver parenchyma should be obtained, too. Otherwise a wedge biopsy may be performed, which results in a larger tissue sample allowing for future genetic and other biological studies. **Fine needle biopsy is not acceptable as it generally provides insufficient material.** Often, particularly in the case of very large and necrotic tumours, it is worthwhile to confirm adequacy and viability of the pathologic material sampled by immediate frozen section.

No attempt should be made at this time to perform radical tumour removal. At the time of the surgical biopsy, placement of a long-term central venous catheter should be considered.

In SIOPEL 1 and 2 trials no life threatening complications of biopsy were recorded. Other complications occurred in 7% of cases (7/96) and were generally minor events including bleeding from the biopsy site in 4 patients (1 open, 3 closed), abdominal pain in 2 (1 open, 1 closed), and a wound infection in 1 child who had an open biopsy. All 7 patients recovered completely within hours or a few days.

Please note, that SIOPEL has launched a Childhood Liver Tumour Tissue Storage Program to facilitate biological and translational research on primary malignant liver tumours of children. Participating centres are kindly requested to send material to the SIOPEL Tissue Bank. For further details regarding tissue sampling, preparation and transportation please, consult Appendix 9.

14.2. DEFINITIVE TUMOUR RESECTION

**General notes**
The ultimate goal of hepatoblastoma treatment is to achieve complete surgical resection of all tumour lesions (both of the primary tumour and the metastases) that remain visible after intensive pre-operative chemotherapy. As emphasised earlier, only complete tumour resection gives realistic hope of cure for children with hepatoblastoma. This implies that all options should be explored before declaring a tumour unresectable. In this regard, for selected cases, orthotopic liver transplantation must be considered a real option.
**Technical considerations**

Due to the fact that several techniques are applied in hepatic resections it is very difficult to give detailed surgical guidelines in this field.

Radical resection of the primary tumour can be achieved either with conventional hepatic surgery (partial hepatectomy) or with total hepatectomy followed by orthotopic liver transplantation, which is a real and valid therapeutic option.

Generally, in most cases of malignant liver tumour, hemihepatectomy is a standard minimal resection procedure. Application of the Pringle manoeuvre (compression of the hepato-duodenal ligament) during the parenchymal phase of hepatic resection helps to minimize blood loss. It can be applied safely for up to 30-45 minutes except in the smallest children, in whom one must consider the risk of eventual intestinal necrosis. However, to control bleeding in the case of difficult major resections a total vascular exclusion should be used, with cross-clamping of the liver pedicle (Pringle) as well as of the vena cava, both below the liver paying attention to exclude the right adrenal vein which joins the vena cava behind the liver, and above the liver.

Because of the rarity of liver tumours surgery should be performed in selected centres with adequate experience and modern equipment suitable for hepatic surgery (ultrasonic or water-jet dissector, infrared beam or argon coagulator, portable ultrasonograph with an intra-operative transducer). Appropriate postoperative care facilities and experienced anesthesiologists are of utmost importance. Even if all conditions mentioned above have been met, extensive personal experience in the field of hepatic surgery, as well as a sound knowledge of hepatic anatomy and different resection techniques, remains most important.

Before the operation the patient’s nutritional status should be estimated and corrected, if necessary. Also cardiac function must be assessed by echocardiography to avoid unexpected cardiac complications during surgery.

**Assessment of resectability**

Accurate assessment of tumour resectability at diagnosis (before treatment) and after neo-adjuvant chemotherapy (before the planned definitive surgery) is the most crucial element of the treatment strategy. An accurate assessment requires optimal imaging studies: spiral CT followed by contrast administration (including angio-CT reconstruction of hepatic vessels, when necessary) and/or magnetic resonance imaging with Gadolinium administration. Ultrasonographic Doppler examination is of particular value allowing real-time investigation of the tumour and its relation to hepatic vessels including assessment of their patency or eventual invasion. The surgeon is encouraged to be present during US Doppler evaluation to enable an immediate discussion with the radiologist and the real-time visualisation of important structures, particularly if there are doubts regarding their involvement. However, distinction between real invasion beyond the anatomic border of a given sector and displacement can be very difficult indeed.

Tumour resectability also depends on surgical expertise; for instance, some tumours involving both liver lobes can still be radically resected by trisegmentectomy, when one lateral sector is disease-free. Even tumour encasement or ingrowth into the retrohepatic vena cava does not preclude a radical excision since it can be resected “en-bloc” and replaced by either a “Goretex” prosthetic graft, or a venous allograft.

In selected and rare cases declaration of the tumour’s inoperability may require a diagnostic laparotomy, which should be performed at the transplant centre, if at all. In the majority of cases
it should be discouraged because it is usually more difficult to assess resectability intra-operatively than before the operation by an experienced radiologist with the surgeon sitting by.

**Issue of “difficult” liver resections**

Generally, very difficult liver resections carrying a high probability of leaving tumour residue should be avoided, whenever possible. This rule applies mainly to the tumours located in close proximity to the major hepatic vessels, which in order to be preserved would have to be peeled off the tumour. In such children first line liver transplantation should be considered (for details see section 14.3).

In cases, when difficult hepatic resection is planned or when liver transplantation has to be delayed, hepatic artery chemoembolization (HACE) may be considered. In most cases this can achieve a decrease in the tumour size and significant necrosis, even when the tumour has not responded to former systemic chemotherapy. It also results in the formation of a thick fibrous capsule around the mass, as well as its calcification, which further facilitates the resection, particularly in the vicinity of the vessels.

Completeness of the tumour resection should be assured during hepatectomy by all possible means. If there are any doubts frozen sections of the resection margin should be obtained. Also the resection margin on the patient’s side should be sampled and immediately inspected by a pathologist, when possible and applicable.

When microscopic residue is found, the surgeon should explore the possibility of immediate re-resection of the margin taking an “extra slice” of the liver, when technically applicable and reasonable. However, the final judgement of the completeness of resection is dependent on the final pathology report.

For more detailed advice regarding difficult liver resections and specific surgical techniques, including HACE, please contact the surgical co-ordinator or members of the surgical panel (see below).

**Rapid surgical consultation**

To assist centres in taking the final decision on tumour resectability and issues of operative techniques, the possibility of a rapid consultation with a panel of experts (including a liver transplant expert) is available. To obtain this consultation please send clinical summary of the patient and the pertinent radiological findings to either:

**Dr. Daniel Aronson**, Pediatric Surgical Center of Amsterdam, Emma Children’s Hospital AMC, PO BOX 22700, 1100 DE Amsterdam, The Netherlands. Phone: +31 (020) 566-5693 / Fax: +31 (020) 566-9287 / E-mail: d.caronson@amc.uva.nl

or

**Dr. Piotr Czauderna**, Department of Pediatric Surgery, Medical University of Gdansk, ul. Nowe Ogrody 1-6, 80-803 Gdansk, Poland. Phone: +48-609 060 774 / Fax: +48-58 302 64 27, E-mail: pczaud@amg.gda.pl; czauderna2@wp.pl.

or

**Mr. Gordon MacKinlay**, Director of Surgery, Royal Hospital for Sick Children, Sciennes Road, Edinburgh EH9 1 LF, United Kingdom. Phone: +44-131-536-0660 / Fax: +44-131-536-0455 / E-mail: mackinlays@msn.com; g.a.mackinlay@ed.ac.uk
Colleagues taking advantage of this service are requested to forewarn the doctors concerned via e-mail, phone or fax.

In those cases, where liver transplantation is a probable therapeutic option, e.g. all initial PRETEXT IV tumours, advice of a liver transplant surgeon must be sought as early as possible, preferably directly at the beginning of treatment, to facilitate timely and accurate decision on the required surgical technique and the necessity of liver transplantation. For details on liver transplant please, see section 14.3.

14.3. LIVER TRANSPLANTATION

General notes
As outlined in section 6, recent data from the SIOPEL studies and other world wide experience provide sufficient evidence to state that liver transplantation is a valid, curative and necessary option for definitive tumour resection in children with hepatoblastoma, when partial hepatectomy is not feasible. Accordingly, in this trial we encourage the use of total hepatectomy followed by liver transplantation in those cases when, after extensive pre-operative chemotherapy, the primary hepatic tumour is still unresectable. Below we provide some considerations that will hopefully help in selecting the most appropriate cases and patients for transplantation.

Possible indications for liver transplantation
In the following cases total hepatectomy with liver transplantation must be considered very seriously. Accurate assessment of resectability, facilitated by optimal imaging studies, must take place both at the diagnosis and after neo-adjuvant chemotherapy. Because of the increased likelihood of liver transplant, advice of a paediatric liver transplant surgeon should be sought as early as possible, i.e. directly at the beginning of treatment. Close contact between the surgeons, radiologist and oncologist should be maintained throughout the pre-operative chemotherapy in order not to miss optimal timing for transplantation. The definitive decision on the surgical technique to be used and the necessity of liver transplantation must be taken in a comprehensive discussion by a transplant surgeon, liver surgeon, radiologist and paediatric oncologist.

- Large, solitary PRETEXT IV tumour (involving all four sections of the liver at presentation, as confirmed by state-of-the art imaging): unless tumour “down-staging” is clearly demonstrated after pre-operative chemotherapy (as could be the case when the anatomic border of a normal liver sector is compressed without true malignant invasion), primary liver transplantation seems to be the best option.

- Multifocal PRETEXT IV tumour: even in the case of good response to chemotherapy accompanied by down-staging of the tumour (disappearance of tumour lesions from at least one hepatic sector), it is recommended to perform total hepatectomy followed by liver transplantation in order to guarantee resection of all (remaining) lesions, including the microscopic ones that could not be visible (any more) on imaging studies.

- Unifocal centrally located tumours involving main hilar structures or main hepatic veins, as can be the case for some PRETEXT II or III V+/P+ tumours: it is highly probable that these tumours will not become resectable with partial hepatectomy even after good response to chemotherapy because of the localisation of the tumour.

N.B.: Initial portal (P) or hepatic veins/vena cava (V) involvement is not a contraindication for eventual liver transplantation. Even if the vascular involvement persists after chemotherapy, it should not be considered as an absolute contraindication for transplant. However in these patients retro hepatic VC and as much portal vein as possible should be removed with en bloc liver. Such
cases should be individually discussed with the transplant surgeon and/or transplant protocol co-
ordinator.

In any case when a surgeon has doubts as to the feasibility of surgical resection it is strongly
recommended that the advice of a paediatric liver transplant surgeon and/or of the
transplant/surgical co-ordinator of the trial is sought.

Contraindications

- Persistence of viable extra-hepatic deposits, not amenable to surgical excision, is an absolute
  contraindication to LTX.
- Poor tumour response (stable disease or progression as defined in section 15.1) to pre-
  operative chemotherapy is also a contraindication to liver transplantation.

Timing of LTX

The timing of definitive surgery, including liver transplantation, is crucial for achieving adequate
local tumour control. LTX should not be delayed in excess of four weeks after the last course of
chemotherapy. Entry on the cadaveric waiting list is a good option if the access to a donor graft
can be expected within this time. Otherwise intra-familial live donor liver transplant must be
considered.

Technical considerations

For the sake of complete tumour excision, it is advocated that total hepatectomy for primary
malignancies in children should include removal of the retrohepatic inferior vena cava. This
approach does not preclude a cadaveric transplant provided with retrohepatic vena cava. In a live
related liver transplant not provided with vena cava, reconstruction can be achieved either with a
preserved allogeneic iliac vein procured from a cadaveric donor or, preferentially, with the
internal jugular vein procured from the parental donor. The first choice, however, should be IVC
replacement with the left internal jugular vein of the patient (alternatively with the external iliac
vein). In this case, the patient should be treated with low molecular weight heparin and wear
elastic socks. Autologous vein is superior to venous allograft, which will often get sclerosed and
obstructed, while a Goretex graft will become too small with growth of the patient and will
thrombose with time.

Liver transplant in children with initial lung metastasis

Based on currently available data (see section 6 for details) it appears that liver transplant is a
viable option for children presenting with lung metastases. However, all metastatic lesions must
be either eradicated by chemotherapy alone or (post-chemotherapy remnants) must be removed
by surgical resection, beforehand. Tumour-free condition of the lungs must be confirmed
with advanced imaging studies.

Second line liver transplantation

Since the results of primary LTX are by far superior, in terms of patient survival, to those of
rescue LTX, heroic attempts at partial hepatectomy with risk of incomplete resection, should be
avoided. When tumour resection by partial hepatectomy has been macroscopically incomplete or
when intrahepatic recurrence is observed after a previous partial resection, the indication for
rescue LTX is controversial, because of the disappointing results observed both in the SIOPEL-1
trial and in the world experience. In addition, post-mortem organ shortage necessitates strict
selection of these cases.

Liver transplant consultation

Colleagues seeking advice or consultation on LTX related issues are kindly asked to contact:
14.4. SURGERY OF LUNG METASTASES

Recent data (described in detail in section 6) confirm that in patients with hepatoblastoma, presenting with initial lung metastasis and locally resectable hepatic tumour, reasonable survival can be achieved with Cisplatin-based chemotherapy and aggressive surgery of the metastatic lesions. Lung metastases generally respond sufficiently to initial chemotherapy leading in few cases to complete disappearance of the lung disease. In most cases, however, some residual disease remains visible in the lungs making surgical removal necessary. Evidence from SIOPEL and other studies strongly support the assumption that surgical resection of such remnants of pulmonary metastases is a good treatment option. Subsequent to the successful pulmonary metastectomy hepatic tumour resection must be completed.

The prognosis of patients presenting with both lung metastases and a locally unresectable tumour is much worse than that of the group mentioned above. In these children liver transplantation is often necessary to achieve radical removal of the hepatic tumour. Even in these patients, however, surgical resection of residual lung metastases is justified and strongly recommended if considered feasible and a good response to pre-operative chemotherapy was observed, in order to make removal of the local tumour, including liver transplantation, possible. If complete resection of the lung metastases is achieved, confirmed by advanced imaging studies including appropriate CT scans and, if available, PET-scans, resection of the primary tumour (including total hepatectomy with liver transplant) should be performed.

**Technical considerations**

There is no clear limit to the number of metastases that it is reasonable and justified to attempt to resect. The anticipated result of the operation, however, has to be clear lungs (macroscopic disease-free). Despite adequate imaging manual lung palpation is indispensable for detection of metastases during the operation. Not infrequently the number of metastases detected manually can be higher than shown by imaging studies.

Exploration of both lungs should be encouraged, either via median sternotomy or postero-lateral thoracotomies. Wedge resection is a preferred technique for the removal of pulmonary deposits for the sake of preserving as much pulmonary reserve as possible. Specific pre-operative lung function assessment should be advocated in centres, where it is available. In difficult or controversial cases individual advice should be sought from the surgical co-ordinators.
15. EVALUATION OF TUMOUR RESPONSE

In order to achieve optimal comparability with previous SIOPEL trials, the same criteria as used in the SIOPEL 1, 2 and 3 trials will be applied in the present trial for evaluation of response to pre-operative chemotherapy and tumour status at the end of trial treatment (‘SIOPEL criteria’). The SIOPEL 4 trial intends, however, to assess also the accuracy and feasibility of using modified ‘RECIST’ criteria in the context of a childhood liver tumour (36). Accordingly, patient data required for the RECIST system will also be collected.

15.1. SIOPEL CRITERIA FOR ASSESSMENT OF TUMOUR RESPONSE

Complete response (CR): no evidence of disease and normal serum AFP value (for age).
Partial response (PR): any tumour volume shrinkage associated with a decreasing serum AFP value, > 1 log below the original measurement.
Stable disease (SD): no tumour volume change and no change, or < 1 log fall of the serum AFP concentration.
Progressive disease (PD): unequivocal increase in 1 or more dimensions and/or any unequivocal increase of the serum AFP concentration (three successive 1-2 weekly determinations) even without clinical (physical and/or radiological) evidence of tumour re-growth.

Please note:
- Tumour dimensions, especially the primary, must be recorded in 3 planes.
- Bear in mind that "no change" or even an increase in "tumour" volume, especially during the first few weeks of chemotherapy, may be the consequence of intra-tumoural haemorrhage/oedema. If serum AFP is falling, continue the same chemotherapy for at least one more course.
- ‘Tumour lysis syndrome’ may lead to an initial rise in AFP before the level falls.
- Sometimes the actual tumour volume does not change in response to therapy, but the AFP decreases; these are 'responses' not cases of stable disease.

15.2. SIOPEL DEFINITION OF COMPLETE (SURGICAL) RESECTION:
‘Total macroscopic removal of the tumour as reported by the surgeon and pathologist’. In case of any doubt the lack of residual tumour must be confirmed with imaging studies performed within 2 weeks after surgery. This definition holds for both the primary and the metastatic lesions.

Please note:
- Total hepatectomy followed by liver transplantation will be considered – if accompanied by complete removal of the primary tumour - as complete resection and not as treatment failure.
- Pulmonary metastectomy will be considered – if accompanied by complete removal of the metastatic lesion(s) - as complete resection and not as failure of treatment.
- Tumour removal with microscopical residual disease (confirmed by pathological investigation) but no macroscopical residue (as defined above) will be considered as complete resection.

15.3. SIOPEL DEFINITION OF COMPLETE REMISSION:
‘Lack of evidence of residual disease and normal (for age) AFP at the end of trial treatment’

To establish a complete remission all of the following requirements must be fulfilled:
No evidence of tumour intra-abdominally: negative abdominal (including hepatic) ultrasound or CT scan or MRI.

No evidence of metastases: clear chest X-ray (PA and lateral) for non metastatic patients; normal lung CT scan for patients with lung metastasis at diagnosis.

Serum AFP level either normal or compatible with age for at least 4 weeks after normalisation. For normal ranges at various ages see Appendix 2.

Please note:

- A disease free status achieved by total hepatectomy followed by liver transplantation will be considered – if accompanied by no remaining tumour lesion on imaging and normal AFP - as complete remission and not failure of chemotherapy.
- Patients who have microscopical residual disease (confirmed by pathological investigation) after tumour resection but no macroscopical residue and a normal serum AFP will be considered as being in complete remission.
- It can take several weeks until high AFP level returns to normal. If no residual tumour left, AFP should decrease continually until normal level is reached.
- A minimal rise of AFP value shortly after surgery may be a sign of liver regeneration.
- A persistently elevated serum AFP level usually indicates persistence of active disease until proven otherwise. It is not uncommon to find a slowly rising AFP level (particularly for AFP level < 100 ng/ml), before actual residual tumour can be identified. In this case abdominal and chest radiological investigations should be repeated until the site of relapse is identified. Occasionally, especially in infants, the AFP level eventually declines spontaneously to normal, without any cause having been identified.

15.4. SIOPEL RELAPSE CRITERIA
Relapse is defined as one of the following situations:

- Recurrent tumour lesion(s) (local or metastatic) detected by imaging techniques and serial elevation of serum AFP (at least 3 consecutive rising values, taken at weekly intervals). In these patients biopsy of the tumour is recommended but not compulsory.
- Recurrent tumour lesion(s) (local or metastatic) with normal AFP, histologically confirmed by biopsy.

In case of elevated serum AFP only, without detectable tumour lesions, repeated measurement of the AFP level is recommended. If it continues to increase, imaging studies must be performed (ultrasound, CT, MRI, PET–scan, bone scan etc.) to detect recurrent tumour mass. Past experience indicates that an elevated AFP can precede by many weeks the actual documentation of tumour recurrence. One should, however, wait until the site of recurrence is clear so that local treatment can be performed.

15.5. REQUESTED INVESTIGATIONS DURING TREATMENT
For an overview of all investigations required in the protocol see Appendix 4.

During pre-operative chemotherapy response and tumour status must be evaluated at the end of each block to exclude progression. Evaluation must take place in the fourth week of each block. Additionally, during the first block (A1) weekly measurement of serum AFP is requested (if was elevated initially) to exclude rapid progression on treatment. If a clear response is documented after the first block (A1), the frequency of measurement of serum AFP can be reduced to once in 4 weeks. At the end of pre-operative therapy (after block A3) tumour resectability must also be assessed. Serial measurement of AFP (if still elevated) must be continued until normalization.
**Measurement of serum AFP (if elevated initially):**

- During the first block(s) (but minimally for 4 weeks) until clear response has been documented: *weekly*.
- After a clear response has been documented (starting not earlier than 4 weeks from diagnosis) until end of therapy: *four weekly*.
- For further follow-up see Appendix 5.

**Radiological investigations:**

**Response evaluation after pre-operative blocks:**

- abdominal ultrasound
- chest X-ray in patients with initial lung metastasis (PA and lateral)

**Assessment of resectability after block A3 and/or block B (pre-surgery):**

- abdominal ultrasound and abdominal CT scan with contrast or MRI with gadolinium
- chest X-ray in patients with no initial lung metastasis (PA & lateral); chest CT scan in patients with initial lung metastasis
- other imaging studies (angiography, PET-scan etc.) if indicated

Please note: Careful assessment of the relationship of the tumour to adjacent vital structures and demonstration of the segmental/vascular anatomy of the remaining liver will be required. This may be done by any combination of ultrasound, CT and MR studies. The presence or absence of lung metastases is best assessed by CT.

**Tumour/resection status evaluation after definitive surgery:**

In case of any doubt the lack of residual tumour must be confirmed with imaging studies performed within 2 weeks after surgery:

- abdominal ultrasound or abdominal CT scan with contrast or MRI with gadolinium
- other imaging studies if indicated

**Tumour/remission status evaluation at the end of treatment:**

- abdominal ultrasound and abdominal CT scan with contrast or MRI with gadolinium
- chest X-ray in patients with no initial lung metastasis (PA & lateral); chest CT scan in patients with initial lung metastasis
- other imaging studies if indicated

15.6. **RECIST CRITERA**

These criteria are described in Appendix 3
16. PATHOLOGICAL GUIDELINES

16.1. CLASSIFICATION OF HEPATOBLASTOMA

Hepatoblastoma is an embryonal tumour containing hepatic epithelial parenchyma and/or mesenchymal components (epithelial types and mixed epithelial and mesenchymal types). Based on the epithelial components, four major histological sub-types exist, whereas the two mixed sub-types are distinguished by the presence or absence of teratoid features. Epithelial sub-types are frequently intermixed, but each may exclusively comprise a tumour.

I - Epithelial morphology: sub-types

A - Fetal - Tumour cells are smaller than hepatocytes in adjacent liver, have a low nucleus-cytoplasm ratio, minimal nuclear pleomorphism and small nucleoli. Mitoses are infrequent. Fetal cells may form either slender cords which often contain canaliculi and definite sinusoids or compact mosaic sheets. Fetal cells may contain abundant lipid or glycogen or have granular eosinophilic or amphophilic cytoplasm. When 100% of the tumour is composed of this epithelial cell type, the term, pure fetal histology, has been proposed. Central vein-like vessels may be present but biliary ducts are not a feature of fetal HB.

B - Embryonal - Tumour cells have a higher nucleus-cytoplasm ratio and sparse basophilic cytoplasm in contrast to those of fetal HB. The nuclei have coarser chromatin and prominent nucleoli. Mitoses are frequent. Embryonal cells occur in sheets or trabeculae of various thicknesses. They sometimes lose cohesiveness and all architectural features of epithelium. They may form acini, tubules or pseudorosettes, resembling the early ducts of the liver of a 6 week gestation embryo.

C - Macrotrabecular - is a term that indicates a repetitive arrangement of fetal and/or embryonal tumour cells in cords or plates. The tumour cell size may exceed that of the normal liver cells and may resemble the malignant cells of HCC.

D - Small cell undifferentiated HB - was previously designated anaplastic HB. It consists of sheets of loosely cohesive, almost monotypic cells with scanty cytoplasm and high mitotic rate. The tumour cells are typically round to oval but in some areas they may be spindle shaped.

In addition to HB exclusively composed of small undifferentiated cells, small cells of poor differentiation may also occur as a minor component in other sub-types of HB (‘focal anaplasia’).

II - Mixed epithelial and mesenchymal morphology: sub-types

A - Mixed pattern without teratoid features - HB characterised by a combination of fetal or embryonal epithelial patterns intermixed with immature mesenchymal components. Osteoid-like tissue is a common feature of these tumours.

B - Mixed pattern with teratoid features - This pattern refers to HB containing, in addition to epithelial and immature mesenchymal components, various combinations of heterologous tissues such as cartilage, skeletal muscle, intestinal-type and squamous epithelium and melanin-producing cells.

III - HB NOS (not otherwise specified)

This category comprises rare HB that, owing to their unusual histological presentation, cannot be classified as representing one of the standard sub-types. It is also proposed to classify HB as NOS in situations where, owing to suboptimal sampling, only a diagnosis of HB as such, but no further sub-typing is possible.
BIOPSIES AND RESECTIONS
As immunohistochemistry is an important method in evaluating HB, a sufficient number of unstained sections (if possible at least 10; preferably more) should initially be prepared (on Superfrost Plus slides) in addition to the standard stain (i.e. hematoxylin and eosin).

For the resection specimens, the standard workup should take into account that these specimens may be greatly altered by chemotherapy (extensive necrosis) so that the most 'viable' looking areas should be sampled. It is proposed to macroscopically estimate, on the cut surfaces of the tumour, the area occupied by necrosis (in percent), as this may be relevant for prognosis. A gross photo or digital image of the most representative tumour sector would be very helpful, if feasible.

16.2. CENTRALISATION OF THE HISTOLOGICAL MATERIAL
Please note that slides of both the diagnostic biopsy and representative sections of the resected tumour should be referred for central review.

Central review of the histological material is crucial to produce relevant clinical information. We still do not know if there is an entity such as an 'unfavourable histology HB'. The anaplastic and the macrotrabecular variants may have a more aggressive clinical course and pure fetal histology a more favourable outcome but the evidence is not yet substantive. Only central review of this material will allow us to address this issue seriously.

To unify the centralisation process of the histological and biological material, all the material will be processed via the UKCCSG Data Centre. On receipt of the pathology Registration Form, two stained and two unstained tumour sections will be requested by letter from the Data Centre. Please note that the unstained sections should be on slides allowing immunohistochemistry (e.g. Superfrost Plus). Two unstained sections are the minimum requirement. In order to act in the best way, the Review group would be grateful to have more unstained sections, if it is feasible for this to be done. The specimens should be sent along with clinical data to the Data Centre, from where they will be dispatched for panel review. After review, a formal letter specifying the results of the pathology review for each case will be sent to the pathologist submitting the material.

16.3. ‘PAEDIATRIC LIVER TUMOUR’ TISSUE BANK
Please note, that SIOPEL has launched a TUMOUR BANKING PROGRAM for translational investigations. Full details of this program are circulated with the SIOPEL 4 protocol, for details of tissue sampling, preparation and transportation see section 19 and Appendix 9, details are also available from the web site.
17. SAFETY ARRANGEMENTS

Details on individual safety measures (toxicity monitoring and treatment & dose modifications) are given in section 13. The trial will be monitored for excessive toxicity by regular evaluation of toxicity data by the trial committee during the trial and will be closed prematurely if the treatment leads to unacceptable toxicity. Toxicities will be classified according to the National Cancer Institute Common Toxicity Criteria (version 3.0). The full text version can be downloaded from http://ctep.cancer.gov/reporting/ctc.html.

Serious Adverse Events (SAE), occurring both during therapy and follow up, must be reported within 24 hours of knowledge of the event, using the remote data entry system and by fax, to the UKCCSG Trial Office, using the Serious Adverse Event Form:

Ms Margaret Childs trial co-ordinator
UKCCSG Data Centre
3rd Floor, Hearts of Oak House
9 Princess Road West
LEICESTER, LE1 6TH
United Kingdom
Tel: +44-116-2494465
Tel: +44-116-2494460 (switchboard)
Fax: +44-116-2549504
Email: msc8@le.ac.uk

A serious adverse event is defined – in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice definitions - as any unexpected or untoward medical occurrence that:
- results in death (Death by tumour progression is not considered an SAE for these high risk patients).
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation, for treatment of that event
- results in persistent or significant disability/incapacity
- any unexpected grade 3 and 4 toxicity

SAEs will be immediately directed to the study chairs, the members of the trial committee (incl. national co-ordinators), the local principal investigators and local ethics committees. The trial chairs will be responsible for further assessment of SAEs with regard to their impact on trial treatment. The Data Centre will regularly circulate a summary of SAEs to all participating centres for information.

For the purposes of this study expected toxicity will include grade 3 or 4 haematological toxicity (blood/bone marrow), infection and gastrointestinal.

However the study committee would like to include in the SAE’s Brock grade 3 or 4 ototoxicity, grade 2+ cardiotoxicity which is defined as left ventricular systolic dysfunction asymptomatic, resting ejection fraction EF < 50-40% or shortening fraction SF < 24-15% and grade 1+ metabolic glomerular filtration rate GFR toxicity defined as < 75-50% lower limit of normal which is < 60 ml/min/1.73m² - 40 ml/1.73m²
18. STATISTICAL CONSIDERATIONS

18.1. INTRODUCTION
The primary endpoint of this trial is the complete remission (CR) rate after chemotherapy and resection, defined as a normal serum alphafetoprotein level and absence of disease on imaging (abdominal ultrasound/CT and lung CT). The treatment with ‘SuperPLADO’ chemotherapy (CDDP+CARBO+DOXO) and hepatectomy in the SIOPEL 3 trial yielded in an interim analysis of the first 58 patients a complete resection rate of around 41% and 66% when including patients who received a transplant. Complete remission is however not assessed in SIOPEL 3, because radiology is not a requirement after surgery. Due to the fact that no patients in SIOPEL 3 go to surgery unless they are in radiologically metastatic remission, the rate of complete resections is a good surrogate for complete remission rate. An improvement in the CR rate (achieved with or without LTX) from 60% to 80% would be considered promising for further development. We require that the trial has a probability not greater than 0.05 of accepting the treatment strategy for further development if its true CR rate is below 60%, and a probability no greater than 0.1 of failing to make such a recommendation if its true CR rate is above 80%. We also require that the trial terminate early if there is evidence that a sufficient CR rate is unlikely.

18.2. SAMPLE SIZE ESTIMATION
The sample size was estimated using Simon’s two-stage optimal design (35) with 5% significance level and 90% power for the null hypothesis of CR <60% and the alternative hypothesis of CR >80%. The sample size is \( n_1 = 19 \) for stage 1 and \( n_2 = 34 \) for stage 2, resulting in a maximum sample size of 53 if the trial is not stopped after stage-1 analysis.

18.3. CRITERIA FOR EARLY STOPPING
In the first stage, 19 patients will be treated. If 12 or fewer patients have a CR, the trial will be closed and the treatment rejected as being of little interest. Otherwise 34 more patients will be treated. If 38 or more of these 53 patients have a CR we shall accept the treatment as promising for further investigation, if 37 or less have a CR then the treatment strategy would again be considered as being of little interest. It is anticipated that a total of around 25-30 patients per year will be recruited; this rate of accrual will achieve the required sample size in around 2 years.

If the efficacy criteria specified for early stopping cannot yet be assessed after inclusion of the first 19 patients, recruitment will not be suspended. This can be justified by the fact that the chemotherapy is incorporating agents which have led to a rate of complete resection of 41% in SIOPEL 3 and is therefore expected to be efficacious.

If a high proportion of Serious Adverse Events or deaths is observed, the trial can be suspended or stopped based on the results of continuous safety monitoring.

18.4. EVALUATION
The primary endpoint CR will be documented as a rate with an exact 95% confidence interval. Continuous and discrete variables will be described respectively by descriptive statistics and frequency tables. Logistic regression will be performed to explore the effects of covariates on some binary endpoints. Efficacy evaluations will be analysed for the whole group as well as stratified by patients with PRETEXT 4 tumours confined to the liver, patients with metastatic disease, extrahepatic intra-abdominal disease, and the combination of these factors. Event-free and overall survival will be estimated by the Kaplan-Meier method and analysed in a multivariate fashion using proportional hazards regression.

18.5. DEFINITION OF END OF TRIAL
The last cycle of chemotherapy given to the last patient entered onto the trial, will define the end point of this trial.
19. PATIENT ENTRY AND DATA MANAGEMENT

19.1. GENERAL NOTES
Patients will be accepted for registration into the trial from any centre recognised for the treatment of children with cancer that are able to comply with the requirements of the protocol and the particular requests listed below. Participating centres are kindly requested to complete a Form of Participation, which should be submitted to the UKCCSG Data Centre prior to entry of the first patient.

Whenever possible centres contributing to the trial should do so as a member of a participating national group for whom a national co-ordinator will be identified and for whom representation on the trial committee will be assured. Centres participating outside the framework of a collaborating national group will be requested to provide a name of a local clinician who will be responsible for communication with the Data Centre.

Participating centres are expected to:

- register all eligible patients with high risk hepatoblastoma according to the trial protocol
- provide adequate material for central reviews (pathology, radiology and cardiotoxicity) and, if feasible, for the tissue storage program
- provide required data for analysis by using the Remote Data Entry system
- obtain written informed consent for the treatment from the patients and/or their parents

Prior to registering the first patient, all centres must seek approval for the trial by their Local Ethics Committee, according to local practice. Confirmation of local ethics approval must be sent to the UKCCSG Data Centre prior to entry of the first patient from the centre.

19.2. REGISTRATION PROCEDURE
To assist local physicians in the diagnostic workup and entry of a patient into one of the SIOPEL trials an internet-based online pre-registration system has been developed. After pre-registration of a child with a suspected primary malignant hepatic tumour, the system will guide you through the required pre-treatment investigations and the registration procedure. In order to satisfy all the necessary procedures for adequate diagnostic and pre-treatment work-up and centralisation of trial material, if appropriate, please pre-register patients on this system or notify the SIOPEL Data Centre as soon as possible, preferably before biopsy, when a malignant hepatic mass is suspected in a child.

If on-line pre-registration is not available patients with suspected high risk hepatoblastoma should be notified to the UKCCSG Data Centre as soon as possible, and preferably before biopsy. The contact person for patient (pre-) registration, and all queries relating to trial administration, is Ms Margaret Childs, Trial Coordinator at the UKCCSG Data Centre. (Note that the Data Centre is open from 8.30 am - 5.00 pm, Monday to Friday).
The **Data Centre** of the SIOPEL 4 trial is:

**UKCCSG Data Centre**  
University of Leicester  
3rd Floor Hearts of Oak House  
9 Princess Road West  
Leicester LE1 6TH  
UNITED KINGDOM  
Tel: +44-116-2494465 Fax: +44-116-2549504  
General Number +44-116-2494460

Definitive registration can only be done when definitive risk assessment and allocation has been completed but must occur within 15 days of written biopsy report confirming diagnosis. Please note, that risk assignment can be difficult in some cases. We strongly recommend taking advantage of **rapid radiology review** (RRR) in all patients with suspected high-risk hepatoblastoma but particularly in patients with suspected PRETEXT IV tumour and/or doubtful metastases. The trial radiologist will help you to assign a correct risk group (for details see section 10.5).

In order to make definitive risk assignment (including review process) possible, start of chemotherapy can be delayed for maximally 15 days after diagnosis (date of biopsy report) if the patient’s condition permits. Patients may also start with chemotherapy (first dose of CDDP) while waiting for definitive decision, since the first course of the SIOPEL 3 Standard risk and SIOPEL 4 trials are identical (80 mg/m$^2$). A definitive risk allocation must, however, be completed by day 7 following the first course of Cisplatin in order to avoid delay in further chemotherapy (see Figure 19.1).

**19.3. DATA MANAGEMENT**

For the SIOPEL 4 trial a remote data entry (RDE) system will be implemented through co-operation with a European non-profit inter-university organisation called CINECA. Details of the system are now under construction. Data quality control procedures (common range, logical checks, cross checks etc.) will be applied within the RDE system. Further details will be provided direct to participating centres.
ALL HEPATOBLASTOMAS

Diagnostic procedures + pre-treatment extent evaluation

Pre-registration

Start chemotherapy
1st course: Cisplatin (80 mg/m²)

Definitive risk assessment/allocation
Rapid Radiology Review

Max. 15 days

Standard risk HB

High risk HB

2nd course: Cisplatin (80 mg/m²)

2nd course: PLADO

2nd course: Cisplatin (70 mg/m²) Doxorubicin

SIOPEL 3 SR-HB

SIOPEL 4 HR-HB

Definitive registration

Figure 19.1
20. QUALITY ASSURANCE, CENTRAL REVIEWS

*Pathology review* of diagnostic biopsy material by the trial pathology panel will be undertaken for all patients.

A central *review of diagnostic and pre-surgery imaging studies (films)* will also take place for all children entered into the trial by the trial radiology panel in conjunction with the surgery panel. In this review abdominal and chest CT or MRI and other digitally made images will be studied. Chest X-rays and ultrasound images will also be reviewed if available and appropriate. **Please note that this central review will take place in all patients.**

The **Data Centre** will require relevant material from the participants.

Cardiotoxicity assessment will also be reviewed centrally as a part of a long-term cardiac assessment research project (see Appendix 8).

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21. TRIAL MONITORING  IDMC

Reports on available data will be prepared yearly, describing accrual of the patients, treatment modalities and toxicity. These reports will be circulated to the participating centres. The trial committee will meet regularly to consider patient accrual, eligibility, treatment, outcome and toxicity to ensure the good conduct of the trial.

An independent Data Monitoring Committee (IDMC) composed of three international experts will monitor the progress of the trial on ethical and scientific grounds. Reports of the interim analysis of accrual rate, outcome and toxicity will be reported to the IDMC. The IDMC may recommend to the trial committee early stopping, continuation or extension of the trial.
22. TRIAL ORGANIZATION

22.1. SIOPEN 4 TRIAL COMMITTEE:

☞ See Appendix 1 for detailed contact addresses.

STUDY CHAIRS:
Dr. József Zsíros
Dr. Penelope Brock (also UK co-ordinator)

CHEMOTHERAPY PANEL:
Dr. Penelope Brock (Co-ordinator)
Dr. Laurence Brugieres (Co-ordinator)
Dr. Michela Casanova
Dr. Giorgio Perilongo
Dr. Jon Pritchard
Dr. József Zsíros

SURGERY PANEL:
Dr. Daniel Aronson
Dr. Piotr Czauderna (Co-ordinator)
Dr. Patrizia Dall’Igna
Dr. Frederic Gauthier
Mr. Gordon MacKinlay
Dr. Jean B. Otte (Transplant co-ordinator)
Dr. Jack Plaschkes
Dr. Jean de Ville de Goyet

RADIOLOGY PANEL:
Dr. Daniele Pariente
Dr. Derek Roebuck (Co-ordinator)
Dr. Anne Smet

PATHOLOGY PANEL:
Dr. Arthur Zimmerman (Co-ordinator)

BIOLOGY AND BASIC RESEARCH
A.M. BUENDIA

STATISTICS/TRIAL CO-ORDINATOR
Dr. Sue Ablett (Head of Data Centre)
Ms. Margaret Childs (Trial co-ordinator)
Dr. Rudolf Maibach (Statistician)
23. TRIAL CONDUCT

The trial will be conducted in accordance with the principles of Good Clinical Practice, the EU Directive on Good Clinical Practice and Clinical Trials and the Declaration of Helsinki. Before entering into the trial, clinicians must ensure that they have ethical approval to participate in the trial according to their national guidelines. Written informed consent should be obtained from the patient/and or parent after they have received full explanation of the trial and the treatment options.

The right of the patient/and or parent to withdraw from the trial at any time, without giving reasons, must be respected.
24. PUBLICATION POLICY

A final report of SIOPEL 4 will be written by the trial committee and published with authors on behalf of the SIOPEL group. Additional publications on trial results will be authorized by the trial committee and published with authors on behalf of the SIOPEL group. Participating centres, with the number of patients entered into the trial, will be listed and acknowledged for their contribution.

Participating centres are authorized to publish their own cases of hepatoblastoma after prior consultation with the study chairmen. Data, relating to the SIOPEL 4 trial, may, however, only be published by the trial committee.
25. REFERENCES


9. Champion J, Green AA, Pratt CB. Cisplatin (DDP) an effective therapy for unresectable or recurrent hepatoblastoma. Proceedings American Society of Clinical Oncology (ASCO); # 173, page 671, 1982


# APPENDIX 1: ADDRESSES & CONTACT DETAILS

**ADDRESSES AND CONTACT DETAILS OF THE SIOPEL 4 TRIAL COMMITTEE AND THE INTERNATIONAL LIVER TUMOURS STRATEGY GROUP MEMBERS**

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<th>J.B. Otte</th>
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<th>Jon Pritchard</th>
<th>Derek Roebuck</th>
</tr>
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<tbody>
<tr>
<td>Consultant Paediatric Oncologist</td>
<td>Consultant Interventional Radiologist</td>
</tr>
<tr>
<td>Royal Hospital for Sick Children</td>
<td>Department of Radiology</td>
</tr>
<tr>
<td>Millerfield Place</td>
<td>Great Ormond Street Hospital</td>
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<tr>
<td>Edinburgh EH9 1LF</td>
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<td>London WC1N 3JH</td>
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<tr>
<td>Tel: 0131 536 0451</td>
<td>UK</td>
</tr>
<tr>
<td>Fax: 0131 536 0430</td>
<td>Tel: +44-207-354-2165</td>
</tr>
<tr>
<td>Email: <a href="mailto:drjpritchard@hotmail.com">drjpritchard@hotmail.com</a></td>
<td>Fax: +44-207-242-1607</td>
</tr>
<tr>
<td></td>
<td>Air call: +44-207-405-9200</td>
</tr>
<tr>
<td></td>
<td>Email: <a href="mailto:RoebuD@gosh.nhs.uk">RoebuD@gosh.nhs.uk</a></td>
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<table>
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<tr>
<th>Anne Smets</th>
<th>Arthur Zimmermann</th>
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<td>Emma Children’s Hospital</td>
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<tr>
<td>Meibergdreef 9</td>
<td>3010 Bern</td>
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<tr>
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<td>The Netherlands</td>
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<td>☎: +31-20-566 9111</td>
<td>Fax: +41.31.632.9938</td>
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<tr>
<td>Fax: +31-20-691 7735</td>
<td>email: <a href="mailto:zimmerma@patho.unibe.ch">zimmerma@patho.unibe.ch</a></td>
</tr>
<tr>
<td>Email: <a href="mailto:a.smets@amc.uva.nl">a.smets@amc.uva.nl</a></td>
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</table>
APPENDIX 2: AFP TABLE

AVERAGE NORMAL SERUM ALPHA-FETOPROTEIN OF INFANTS AT VARIOUS AGES

<table>
<thead>
<tr>
<th>AGE</th>
<th>Number of patients</th>
<th>MEAN ± S. D. (ng/ml)</th>
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<tbody>
<tr>
<td>Premature</td>
<td>11</td>
<td>134,734 ± 41,444</td>
</tr>
<tr>
<td>Newborn</td>
<td>55</td>
<td>48,406 ± 34,718</td>
</tr>
<tr>
<td>Newborn -2 weeks</td>
<td>16</td>
<td>33,113 ± 32,503</td>
</tr>
<tr>
<td>2 wk.-1 month</td>
<td>43</td>
<td>9,452 ± 12,610</td>
</tr>
<tr>
<td>1 month</td>
<td>12</td>
<td>2,654 ± 3,080</td>
</tr>
<tr>
<td>2 months</td>
<td>40</td>
<td>323 ± 278</td>
</tr>
<tr>
<td>3 months</td>
<td>5</td>
<td>88 ± 87</td>
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<tr>
<td>4 months</td>
<td>31</td>
<td>74 ± 56</td>
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<tr>
<td>5 months</td>
<td>6</td>
<td>46.5 ± 19</td>
</tr>
<tr>
<td>6 months</td>
<td>9</td>
<td>12.5 ± 9.8</td>
</tr>
<tr>
<td>7 months</td>
<td>5</td>
<td>9.7 ± 7.1</td>
</tr>
<tr>
<td>8 months</td>
<td>3</td>
<td>8.5 ± 5.5</td>
</tr>
<tr>
<td>&gt; 8 months</td>
<td>-</td>
<td>8.5 ± 5.5</td>
</tr>
</tbody>
</table>

*From: Wu, Book and Sudar Serum α-Fetoprotein (AFP) Levels in Normal Infants Paediatric Research 15: 50-52 (1981)*
APPENDIX 3: RECIST CRITERIA

RECIST CRITERIA FOR EVALUATION OF TUMOUR RESPONSE

A new system of response evaluation in solid tumours, the RECIST system has recently been described. However, this system has limited use in paediatric patients and has never been used in children with hepatoblastoma. It might be difficult to apply to patients with group IV hepatoblastoma whose tumour may be difficult to measure precisely or to patients with multiple small lung metastases. Moreover, it does not take into account certain important points about AFP level to define progressive disease, which might lead to difficulties in decision making. Thus, in order to be able to compare this new system to the classic criteria used in previous SIOPEL studies, both methods will be applied in SIOPEL 4. However, treatment decision must only be based on classical SIOPEL criteria. To be able to assess precisely response, all measurable lesions should be measured in 3 dimensions.

**Measurability of tumour lesions**
At baseline, tumour lesions will be categorised as follows:
*Measurable lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques (PET, CT, MRI, x-ray) or as >10 mm with spiral CT scan.

All other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan) and truly non-measurable lesions (pleural or pericardial effusion, ascites, bone lesions, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions) are considered *non-measurable disease*.

All tumour measurements must be taken and recorded in millimetres by use of a ruler or callipers.

**Note:** Lesions are either measurable or non-measurable using the criteria provided above. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

**Baseline documentation of “target” and “non-target” lesions**

**Target Lesions**
All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as *target lesions* and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as reference by, which to characterize the objective tumour response.

**Non-target lesions**
All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

**Tumour marker**
The level of serum *alpha-foetoprotein* (AFP) will also be used to determine response.
**Tumour response evaluation**

**Evaluation of target lesions**

- **Complete Response (CR):** Disappearance of all target lesions
- **Partial Response (PR):** At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum LD
- **Progressive Disease (PD):** At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

**Note:** Changes in only the largest diameter (one-dimensional measurement) of the tumour lesions are used in the RECIST criteria

**Evaluation of non-target lesions and tumour marker level**

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumour marker level
- **Incomplete Response/Stable Disease (SD):** Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits
- **Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions and/or increase of tumour marker level by 1 log or more.

**Overall response**

The patient's overall response assignment will depend on the assessment of both target and non target lesions.

<table>
<thead>
<tr>
<th>Target lesions</th>
<th>Non-Target lesions</th>
<th>New Lesions</th>
<th>Overall response</th>
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</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Incomplete response/SD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD</td>
<td>No</td>
<td>SD</td>
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<td>PD</td>
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<td>Yes or No</td>
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<td>PD</td>
<td>Yes or No</td>
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<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
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</tbody>
</table>

The **best overall response** is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.
## APPENDIX 4: PATIENT INVESTIGATIONS

### REQUIRED INVESTIGATIONS AND PATIENT INFORMATION

<table>
<thead>
<tr>
<th></th>
<th>Pre-operative chemotherapy</th>
<th>Postoperative chemotherapy</th>
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<tr>
<td></td>
<td>A1</td>
<td>A2</td>
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<tr>
<td><strong>Weeks:</strong></td>
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<tr>
<td>Baseline</td>
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<tr>
<td>Cisplatin</td>
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<td>Carboplatin</td>
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<td>Physical exam</td>
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<td>Lab tests C</td>
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<tr>
<td>AFP</td>
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<td>Chest X-ray</td>
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<td>Abdominal US</td>
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<tr>
<td>CT chest</td>
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<td>Abdom CT/MR</td>
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<tr>
<td>Audiogram</td>
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<tr>
<td>GFR</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Echocardiogram on tape</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

### Pre-operative assessment

- **Pre-operative assessment**

### Pre-operative

- **Pre-operative**

### Post-operative

- **Post-operative**

### End of treatment

**Serious Adverse Event**

- Record throughout treatment period and report within 24 hours

1: Biopsy mandatory for all
2: Rapid radiology review - at diagnosis
3: Including anthropometric measurements and (at diagnosis) nutritional status assessment
4: Laboratory tests A: Full Blood Cells, U&Es, Creatinine, Mg, Ca, phosphate, ALT & AST,
5: Laboratory tests B: Urine creatinine and electrolytes (Na⁺, K⁺, Ca²⁺, Phosphate) so that fractionated excretion tubular function can be measured, Serum bilirubin,
6: Laboratory tests C: Partial Thromboplastin time, Prothrombin time
7: If indicated (see section 15.2)
8: In patients with initial lung metastasis

---

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### APPENDIX 5: FOLLOW-UP INVESTIGATIONS

#### FOLLOW-UP INVESTIGATIONS

<table>
<thead>
<tr>
<th>Time from diagnosis: Relevant Exams</th>
<th>First and second year</th>
<th>Third year</th>
<th>From the 4th to the 5th year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>Every 2-3 months</td>
<td>Every 3 months</td>
<td>Twice yearly</td>
</tr>
<tr>
<td>Alpha-fetoprotein*</td>
<td>1st year: every month 2nd year every 3 mo</td>
<td>Every 6 months</td>
<td>Every 6 months</td>
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<tr>
<td>Chest-X ray*</td>
<td>Every 3 months</td>
<td>Every 6 months</td>
<td>Yearly</td>
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<tr>
<td>Abdominal ultrasound*</td>
<td>Every 2-3 months</td>
<td>Every 6 months</td>
<td>Yearly</td>
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<tr>
<td>Serum magnesium</td>
<td>Yearly</td>
<td>Yearly</td>
<td>Yearly</td>
</tr>
<tr>
<td>51Cr EDTA -GFR</td>
<td>One year off treatment - to be repeated yearly if &lt;80ml/min/1.73 m²</td>
<td>Yearly if &lt; 80 ml/min/1.73 m²</td>
<td>Yearly if &lt; 80 ml/min/1.73 m²²</td>
</tr>
<tr>
<td>Audiogram</td>
<td>Yearly until reliable result obtained with pure tone audiometry (age 3 years +)</td>
<td>Yearly until reliable result obtained with pure tone audiometry (age 3 years +)</td>
<td>Yearly until reliable result obtained with pure tone audiometry (age 3+ years) then every 3 years</td>
</tr>
<tr>
<td>Echocardiogram - measurement of shortening fraction</td>
<td>1-6 months after final dose of Doxorubicin; further echos to be done yearly if SF=&lt;/29%; if SF &gt;29% then every 5 years</td>
<td></td>
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</tr>
</tbody>
</table>

* Abnormal findings should be further investigated with MRI/CT abdomen and/or spiral lung CT scan.
APPENDIX 6: CARBOPLATIN DOSING

CALCULATION OF DAILY DOSE OF CARBOPLATIN

Table 1a  Carboneplatin 500 mg/m²  AUC 6.6 mg/ml.min

<table>
<thead>
<tr>
<th>Body Wt (kg)</th>
<th>Half life EDTA(min)</th>
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<tbody>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>546</td>
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<tr>
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</table>

BW: 10 – 40 kg  EDTA t½: 30 – 105 min

To calculate the daily dose (given in mg, NOT mg/m²) required for renal function-based dosing, use the value in the cell given by the intersect of the body weight row and the EDTA half-life (t½) column.
Table 1b  Carboplatin 500 mg/m²  AUC 6.6 mg/ml.min

<table>
<thead>
<tr>
<th>BW: 41 – 70 kg</th>
<th>EDTA t₁/₂: 30 – 105 min</th>
</tr>
</thead>
</table>

To calculate the daily dose (given in mg, NOT mg/m²) required for renal function-based dosing, use the value in the cell given by the intersect of the body weight row and the EDTA half-life (t₁/₂) column.
Table 1c  Carboplatin 500 mg/m²  

<table>
<thead>
<tr>
<th>Body Wt (kg)</th>
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AUC 6.6 mg/ml.min  

BW: 10 – 40 kg  

EDTA t½: 110 – 185 min  

To calculate the daily dose (given in mg, NOT mg/m²) required for renal function-based dosing, use the value in the cell given by the intersect of the body weight row and the EDTA half-life (t½) column.
Table 1d  Carboplatin 500 mg/m²  AUC 6.6 mg/ml.min

BW: 41 – 70 kg  EDTA t₁/₂: 110 – 185 min

To calculate the daily dose (given in mg, NOT mg/m²) required for renal function-based dosing, use the value in the cell given by the intersect of the body weight row and the EDTA half-life (t₁/₂) column.
Table 2a  Carboplatin 800 mg/m\textsuperscript{2}  AUC 10.6 mg/ml.min  

BW: 10 – 40 kg  EDTA t\textsubscript{1/2}: 30 – 105 min

To calculate the daily dose (given in mg, NOT mg/m\textsuperscript{2}) required for renal function-based dosing, use the value in the cell given by the intersect of the body weight row and the EDTA half-life (t\textsubscript{1/2}) column

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Table 2b  Carboplatin 800 mg/m²  AUC 10.6 mg/ml.min

BW: 41 – 70 kg  EDTA t₁/₂: 30 – 105 min

To calculate the daily dose (given in mg, NOT mg/m²) required for renal function-based dosing, use the value in the cell given by the intersect of the body weight row and the EDTA half-life (t₁/₂) column.
To calculate the daily dose (given in mg, NOT mg/m²) required for renal function-based dosing, use the value in the cell given by the intersect of the body weight row and the EDTA half-life (t₁/₂) column.
Table 2d  Carboplatin 800 mg/m²  AUC 10.6 mg/ml.min  

BW: 41 – 70 kg  EDTA t_{1/2}: 110 – 185 min

To calculate the daily dose (given in mg, NOT mg/m²) required for renal function-based dosing, use the value in the cell given by the intersect of the body weight row and the EDTA half-life (t_{1/2}) column.
APPENDIX 7 : DRUG INFORMATION

DRUG INFORMATION

CISPLATIN
Alternative Names:
- Cis DDP
- Cis diaminedichloro-platinum

Mechanisms of action:
- Produces interstrand and intrastrand DNA crosslinks.

Considerations prior to chemotherapy
- Renal function
- Audiology
- Adequate hydration and diuresis must be established prior to administration
- FBC

Adverse Effects
Common
- Nausea/vomiting (may be delayed)
- Nephrotoxicity (dose limiting)
- Myelosuppression
- Hypokalaemia
- Hypomagnesaemia
- Hyperuricaemia
- Alopecia
- Ototoxicity

Occasional
- Peripheral neuropathy
- Taste disturbance

Rare
- Anaphylaxis
- Other neurotoxicity
- Ocular

Recommended schedule of administration:
Intravenous

CAUTION:
- Must establish adequate hydration and diuresis prior to administration
- Prolonged electrolyte losses are seen in some cases (especially magnesium & potassium)

Administration
- Hydration is necessary to ameliorate the renal damage caused by Cisplatin.
- All protocols require hydration, and an adequate urine output to be established before administration of Cisplatin.
Mannitol is also used and has advantages over Frusemide (which can itself cause renal damage).

• Mannitol should be given during the Cisplatin infusion, and in some cases after the infusion.
• Hydration needs to continue for at least 24 hours after the end of the Cisplatin infusion
• Cisplatin should be given as a continuous infusion over 24 hours as dose rate can affect both acute and late toxicities.
• There is some evidence to suggest that a continuous infusion may be as/or more effective with decreased emesis.

**Recommended hydration protocol:**

**Pre-Cisplatin hydration**
- 200 ml/m²/hour for 3 consecutive hours of Glucose/dextrose 2.5%/sodium chloride 0.45% +
  - KCl 10 mmol (10 mEq) /500ml
  - Mg Sulphate 2 mmol (4 mEq) /500 ml
  - CaGluconate 1.5 mmol (3 mEq)/500ml

**Cisplatin infusion**
- Cisplatin made up to 120 ml (for doses ≤120 mg) [or 240 ml (for doses >120 mg)] with sodium chloride 0.9% infused at 5 ml/hour for 24 hours, run concurrently with:
  - 120 ml/m²/hour for 24 hours of a solution of Glucose/dextrose 2.5%/sodium chloride 0.45% +
    - 30 ml Mannitol 20% = 6g Mannitol/500 ml
    - KCl 10 mmol (10 mEq) /500ml
    - Mg Sulphate 2 mmol (4 mEq) /500 ml
    - CaGluconate 1.5 mmol (3 mEq)/500ml

**Post-Cisplatin hydration**
- 125 ml/m²/hour for 24 consecutive hours of Glucose/dextrose 2.5%/sodium chloride 0.45% +
  - KCl 10 mmol (10 mEq) /500ml
  - Mg Sulphate 2 mmol (4 mEq) /500 ml
  - CaGluconate 1.5 mmol (3 mEq)/500ml

**Interactions**
- Co-administration with potentially nephrotoxic agents should be avoided due to the risk of acute reductions in GFR and hence decreased clearance, as well as additive renal toxicity.
- Concomitant administration of Cisplatin and Etoposide may reduce Etoposide clearance.

**Overdosage**
- Full supportive measures should be considered
- Plasmapheresis may be of use in Cisplatin overdosage

**Dilution specification and stability:**
- Cisplatin is stable in Sodium Chloride 0.9% for 7 days
- It remains stable in Sodium Chloride 0.9% in the presence of magnesium sulphate & potassium chloride for up to 24 hours
- Do not refrigerate
- No need to protect from light
NB. The minimum concentration of sodium chloride providing an acceptable level of stability is approximately 0.3% w/v.

**Pharmacokinetics**
Median (range) Pharmacokinetic Parameters:
- Clearance: 394 (213-931) ml/min/1.73m^2
- Half-life: 48 (38-139) min
- AUC: 0.48 (0.13-0.8) mg/ml.min/100mg/m^2

**Pharmacodynamics**
In adults, Cisplatin toxicity has been related to free Cisplatin concentrations, either AUC or peak levels, i.e. renal toxicity, myelosuppression and emesis. In children, ototoxicity has been related to plasma total Pt concentrations. These observations support the use of a 24h infusion for Cisplatin administration to minimise peak concentrations and non-antiproliferative toxicities.

**DOXORUBICIN**

**Alternative Names**
- Adriamycin hydrochloride,
- 14- hydroxydaunorubicin
- 3- Hydroxyacetyldaunorubicin

**Mechanism of action**
Doxorubicin is an anthracycline antibiotic active in all phases of the cell cycle with maximal activity in S phase. It has several modes of action including intercalation to DNA double helix, topoisomerase II mediated DNA damage, production of oxygen- free radicals which cause damage to DNA and cell membranes, and complex formation with iron or copper via the hydroquinone moieties. Iron doxorubicin complexes may contribute to cardiotoxicity by toxic free radical generation.

**Considerations prior to administration**
- Well-established robust venous access. A central venous catheter or indwelling vascular access port is recommended for prolonged infusions to reduce the risk of extravasation.
- Full blood count
- Liver function tests
- Cardiac function
- Creatinine, urea, electrolytes

**Adverse effects**

**Common**
- Nausea and Vomiting
- Myelosuppression
- Alopecia
- Mucositis
- Red urine
- Diarrhoea
- Severe tissue damage if extravasated

**Occasional**
- Increased bilirubin
- Cardiomyopathy
Rare

- Hepatocellular necrosis
- Hyperpigmentation of skin, mucous membranes, nails
- Anaphylaxis, chills, fever
- Renal damage
- Drowsiness
- Conjunctivitis

Recommended routes:
Intravenous

Caution

A baseline echocardiogram must be done prior to treatment. This should be repeated prior to alternate courses of doxorubicin up to a total cumulative dose of 300mg/ m², and before each course thereafter. If the left ventricular shortening fraction (SF) is < 29% to 30% (depending on precise echocardiographic methodology) temporary withdrawal of doxorubicin therapy should be considered. If subsequent testing shows an improvement in SF consider reintroducing doxorubicin. A fall in SF by an absolute value of > 10 percentile units, or a rate of fall of > 2 to 3 percentile units per 100mg/ m², despite an SF > 29% to 30%, may also represent significant deterioration. If the patient’s hepatic function is significantly impaired, doxorubicin dosage reduction should be considered.

Dose /schedule

Due to the vesicant properties of doxorubicin it is strongly recommended that doxorubicin be given through a central venous line. For ease of administration, to reduce cardiotoxicity, and allow haematological recovery the following schedule is recommended: administration of doxorubicin together with Dexrazoxane or as a 24 hour infusion (in Glucose/dextrose 5% or sodium chloride 0.9%). Administration: as a single daily dose or divided doses fractionated over several days. Cumulative dose of 450 mg/m² to 550 mg/m², exceeded with extreme caution.

Interactions

Doxorubicin may interact with the following:
- Dexrazoxane- reduce cardiotoxicity
- Cardiac irradiation - increased cardiac damage
- Actinomycin, mithramycin- cardiomyopathy
- Mercaptopurine- increased hepatotoxicity
- Mitomycin-increased incidence of late congestive heart failure
- Barbiturates - increased Doxorubicin elimination
- Verapamil- increased Doxorubicin serum levels, reversal of Doxorubicin resistance, reduced absorption of verapamil
- Propranolol- increased cardiotoxicity
- Tamoxifen- reduced Doxorubicin clearance, modulation of doxorubicin resistance
- Cyclosporin- increased Doxorubicin serum levels and myelotoxicity, modulation of Doxorubicin resistance
- Carbamazepine, phenytoin, sodium valproate- altered anticonvulsant serum levels
- Warfarin- increased warfarin effect
- Cimetidine, Ranitidine- increased Doxorubicin toxicity
• Interferon alfa-altered Doxorubicin disposition, Doxorubicin dose reduction
• Paclitaxel-increased toxicity of Doxorubicin, if administered after Paclitaxel
• Cyclophosphamide - increases AUC and reduces clearance of parent drug and active metabolite

The clinical relevance of many of these interactions is unclear.

Overdose
Doxorubicin overdosage can prove fatal. Manifestations of overdose may include acute myocardial degeneration, severe myelosuppression and delayed cardiac failure. There is no specific antidote. Symptomatic supportive measures should be implemented.

Dilution specification
Preparation
Doxorubicin supplied in:
(i) Vials containing 10 mg and 50 mg freeze dried powder. Reconstitute with water for injection or sodium chloride 0.9 % injection adding 5ml to the 10mg vial and 25 ml to the 50 mg vial to give a 2 mg/ml solution.
(ii) Vials containing 10mg and 50mg as a 2mg/ml solution in sodium chloride 0.9 %.

Dilution
Doxorubicin is compatible with sodium chloride 0.9% and Glucose/dextrose 5%.

Stability
A large body of information is available on the stability of Doxorubicin in solution.
Doxorubicin is compatible with polypropylene polyvinyl chloride (PVC) glass, ethylene vinylacetate (EVA) and polyisoprene containers. Solutions should be protected from light during storage and administration unless the solution is freshly prepared and the concentration is greater than or equal to 0.5mg/ml. In addition, Doxorubicin appears to be chemically stable in polypropylene, PVC, or EVA containers for at least 7 days, when refrigerated or stored at room temperature, protected from light, and diluted in the following: sodium chloride 0.9% at concentrations of 0.1 mg/ml to 2mg/ml: dextrose 5% at concentrations of 0.1mg/ml to 1.25 mg/ml adsorptive losses which may be pronounced at low concentrations can be prevented by storage in polypropylene or when Doxorubicin is used at concentrations of at least 0.5mg/ml. In addition, at least a 7-day expiry can be given to Doxorubicin reconstituted with water for injection to a concentration of 2mg/ml, stored in polypropylene syringes at 4oC.

Pharmacokinetics
The pharmacokinetics of Doxorubicin in paediatric patients have been characterised in children, but the large number of protocols and different disease types make it difficult to produce representative summaries. Volume of distribution varies from 20-28 l/kg (approx 609 l/ m²). Anthracyclines are ionised and have low lipid solubility and so do not easily cross the blood-brain barrier. Doxorubicin is metabolised to doxorubicinol, an active metabolite, which may occur at higher concentrations than parent drug in plasma. Excretion of drug and metabolites is via further metabolism and/or biliary excretion, with only 5 to 15% excreted by the kidney. Elimination is triphasic, with no effect of age on clearance when normalised for surface area. Terminal half-life is 14 to 50 hours, with clearance varying from 267 to 1443 ml/min/m². Relatively little difference in pharmacokinetics has been observed in infants, but there was a trend to lower systemic clearance than in older children (790 vs. 1500 ml/min/m², p=0.07).
Dosage adjustment has been recommended in patients with impaired hepatic function, although this has not been validated in paediatric patients.

**Pharmacodynamics**
Although some data exists regarding the influence of plasma concentrations on the therapeutic and toxic effects of Doxorubicin, little of this has been obtained in paediatric patients.

Additional Information
A number of ways to reduce cardiotoxicity have been suggested but the use of an alternative dosage schedule of weekly rather than 3 weekly, prolonged infusion schedules, adjuvant cardioprotective agents (e.g. ICRF-187) or the administration of Doxorubicin in a liposome formulation, whilst increasingly advocated are not yet of proven utility. Due to the risk of cardiac abnormalities developing many years after Doxorubicin therapy, long term cardiac follow up is recommended.

**CARBOPLATIN**

**Alternative names**
- JM8
- Paraplatin (Proprietary Name)
- CBCDA

**Mechanism of action**
Produces interstrand and intrastrand DNA crosslinks

**Considerations prior to administration**
- Renal function
- FBC

**Adverse effects**

**Common**
- Nausea + vomiting
- Myelosuppression
- Persisting thrombocytopenia

**Occasional**
- Ototoxicity
- Raised LFT's (Alk Phos)
- Nephrotoxicity

**Rare**
- Neurotoxicity
- Rash
- Anaphylaxis + anaphylactoid reactions
- Ocular, transient visual disturbances
- Alopecia

**Recommended routes**
Intravenous
CAUTION
If treatment is aiming for Area Under Curve (AUC’s) over 10mg/ml.min consideration should be
given to growth factor and stem cell support. Dose tolerability depends upon pre treatment
chemotherapy/radiotherapy and renal function. Therapeutic Drug Monitoring mandatory for AUC
> 20 mg/ml.min and should be considered for AUC > 10mg/ml.min.

Administration:
Administered as an intravenous infusion over 1 hour or greater if dictated by fluid volume

Dose/schedule
If renal function is poor, dose should be calculated using one of the formulas below.
In some cases it may be desirable to calculate the dose to deliver a specific AUC.
Paediatric regimens aim to deliver a carboplatin AUC 6 - 10mg/ml.min.

Interactions
Co administration with potentially nephrotoxic agents should be avoided due to the risk of acute
reductions in GFR and hence decreased drug clearance.

Overdose
Full supportive measures, including the use of growth factors should be considered.
Carboplatin is removed by haemodialysis. Although there are no publications on its use following
overdosage, haemodialysis would be a reasonable management option.

Dilution specification & stability
• Glucose/dextrose 5%
• Concentration is not critical and should be adjusted to the child’s fluid requirements
• Carboplatin can be diluted as low as 500 micrograms/ml
• Hydration is not required
• Once reconstituted, carboplatin is stable for 8 hours at room temperature, or 24 hours if
  refrigerated

Pharmacokinetics
Carboplatin is eliminated primarily by urinary excretion. Dosing of Carboplatin on the basis of
GFR. (see below) produces more consistent exposure (AUC) than surface area based dosing

Medium (Range) pharmacokinetic parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Clearance</td>
<td>75 (42-130) ml/min/m²</td>
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<tr>
<td>t½</td>
<td>82 (45 - 258) mins</td>
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<tr>
<td>AUC</td>
<td>5.3 (3.1 - 9.6) mg/ml.min/400mg/m²</td>
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Pharmacodynamics
Studies in adults have shown relationships between haematological toxicity and AUC and have
suggested AUC/response relationships

Adult equation
Dose (mg) = Target AUC x (GFR ml/min + 25)

25 is a constant to allow for non renal clearance in adults
Paediatric equation  
Dose (mg) = Target AUC x (GFR ml/min + [0.36 x wt in kg])

GFR is uncorrected for surface area and is best estimated as

\[
\left[ \frac{0.693}{t_{1/2\text{EDTA}}} \right] \times \left(0.52 \times 843 \times BW^{0.891}\right)
\]

where \(t_{1/2\text{EDTA}}\) is the half-life of the elimination of \(^{51}\text{Cr-EDTA}\) and BW is wt in kg.

DEXRAZOXANE

Alternative Names
Cardioxane
Zinecard

There is insufficient evidence to date to make guidelines for the use of Dexrazoxane in the treatment of paediatric malignancies. However, the SIOPEL Group is particularly concerned about the average low age of patients with hepatoblastoma and the long term cardiotoxic risks. The SIOPEL Group is aware of the results of the POG 9426 study showing an increased incidence of second malignancies with patients with paediatric Hodgkin disease who received Dexrazoxane. Therefore, there is the option of using a cardioprotectant within this study.\(^{43}\)

Mechanism of action
Chelates metal ions. It is thought that the uptake and subsequent hydrolysis of dexrazoxane in the myocardium protects against anthracycline induced cardiotoxicity by the scavenging of metal ions from their potentially damaging complexes with doxorubicin and by preventing the Fe \(^{3+}\) doxorubicin complex from redox cycling and forming reactive radicals.

Considerations prior to administration
- Liver function
- Renal function

Adverse Effects
- Increased incidence of chemotherapy induced leukopenia and thrombocytopenia
- Pain at the site of injection
- Skin reactions following direct contact with dexrazoxane
- Rarely liver dysfunction
- A recent study in Hodgkin patients\(^{43}\) has shown a possible link with increased risk of second malignancies, however, Hodgkin’s patients have a known higher incidence of second malignancy.

Recommended routes
Intravenous

Administration
Over 15 minutes, 30 minutes before Doxorubicin infusion. An infusion of sodium chloride 0.9% is recommended for 10-15 minutes before the Doxorubicin. Doxorubicin should be administered over 60 minutes.

Cardioxane Dose/schedule
20 x the dose of Doxorubicin but not exceeding a maximum of 1000mg/m\(^2\)/course
Interactions
May potentiate the toxicity induced by chemotherapy or radiotherapy

Dilution specification & stability
- Reconstitute 500mg vial with 25ml water for injection.
- This solution has a pH of approximately 1.6 therefore must be further diluted to avoid the risk of thrombophlebitis.
- Dilute in Hartmann’s Solution for central line administration to concentration range of between 4-8mg/ml –to be confirmed.
- If administering peripherally a phosphate buffer should be used taking care to calculate the concentration and rate of administration of the potassium and phosphate in the final solution.
- Administer within 4 hours of dilution.

Zincard Dose/schedule
10 x the dose of Doxorubicin

Interactions
May potentiate the toxicity induced by chemotherapy

Dilution specification & stability
- Reconstitute in buffer provided to give concentration of 10mgs/ml.
- Further dilute with 0.9% sodium chloride or 5% glucose to a concentration range of 1.3-5mgs/ml.
- Administer within 6 hours of dilution.
APPENDIX 8: CARDIAC ASSESSMENT

CARDIOTOXICITY ASSESSMENT

Background
The risk of anthracycline cardiotoxicity is associated with cumulative dose, total single dosage, age and gender. The effective treatment for hepatoblastoma is high anthracycline dose per course (60mg/m$^2$) and total doses in excess of 300mg/m$^2$ in very young children. In theory, therefore, this group of patients is at significant risk of cardiac dysfunction. Certainly paediatric patients surviving primary hepatic malignancies have been reported with irreversible cardiac failure and requiring heart transplantation. The SIOPEL studies have addressed this problem by giving the anthracyclines over 48 hours but there has been no formal trial to document the clinical impression of reduced cardiac problems. Various studies have been published on the effect of lengthening anthracycline administration on early cardiac function. There are only two studies on paediatric patients both involving treatment for hepatoblastoma who received anthracyclines via 96 hr infusion. Neglia suggests that anthracycline doses up to 750mg/m$^2$ can safely be given but Ortega reports cardiac failure at lower doses. Late anthracycline cardiotoxicity is now documented, as the incidence of early cardiotoxicity in the paediatric population declines. There are no long term studies published on patients treated with long infusions (>48hr). It will therefore be very informative to conduct a study to formally assess cardiac function in this potentially vulnerable group.

Noninvasive echocardiography is the recognised method of assessing cardiac function in children. To achieve useful, uniform, blinded and optimal information on cardiac function in this group of patients compared to already established healthy controls, locally acquired standardised echocardiograms will be recorded on videotape and centrally reviewed to secure quality and uniform analysis.

Cardiac assessment
Cardiac assessment must be carried out locally according to the following recommendations: (The tape recordings will be assessed centrally).

- Patients must be afebrile and clinically not anaemic at time of echocardiography
- Complete cardiac form (see next pages). Keep a copy of form in patient’s notes in centre.
- Please note which type of echocardiography machine (company, type) was used.
- Collect all patients on one tape (preferred) or send a tape on each patient.
- Copy the tape before sending it
- Record on VHS/S-VHS tape
- Remember to put patient identification on recording
- Record height in cm and weight in Kg on cardiac form
- Attach blood pressure cuff on right arm
- Record blood pressure – minimum 3 values, preferably obtained during last part of echocardiogram or immediately after.
- Make all recordings with the highest sweep speed possible (usually 50 mm/sec)
- Please use the following mode of sequence when making the recordings
- Record a minimum of 10 consecutive cardiac cycles of each of the following sequences

2D echo:
- Apical four chamber view
- Apical 5 chamber view (with aorta)
• Short axis left ventricle (papillary muscle level)
• Short axis left ventricle (aortic valve/pulmonary artery level)
• Parasternal long axis

**Colour echo:**
• Apical four chamber (mitral, tricuspid, aortic flows)

**Pulsed Doppler echo:**
• Left ventricular outflow (apical four chamber view, for LV ejection time)
• Mitral valve inflow (at the tips of mitral valve leaflets)

**M-mode echo:**
• Left ventricle – parasternal long axis
  
  *Note that the M-mode cursor must be perpendicular to the interventricular septum and immediately below the tips of the mitral leaflets in a plane where the mitral valve and aorta valve are visible. Confirm on tape that the M-mode cursor is positioned correctly.

• Aortic valve opening time (for LVET) if aortic Doppler not obtained

**Echocardiographic measurements and calculations**
From the M-mode echocardiograms, the following indices will be measured using standard techniques (American Society of Echocardiography):
• Left ventricular internal diameter in systole (LVIDs) and diastole (LVIDd).
• Interventricular septal thickness in systole (IVSs) and diastole (IVSd)
• Posterior wall thickness in systole (LVPWs) and diastole (LVPWd).
• Left ventricular ejection time (LVET) – optional if aortic Doppler is acquired.

From the Doppler interrogation the following measurements will be done:
• Left ventricular ejection time (LVET)
• Mitral E-velocity
• Mitral A-velocity
• Mitral E-deceleration time

Based on all measurements and blood pressure recordings, the following parameters will be calculated:
• Left ventricular fractional shortening (FS)
• Mean velocity of circumferential shortening (Vcf)
• Heart rate corrected Vcf (Vcfc)
• Left ventricular end-systolic wall stress (ESWS)
• Stroke-velocity index (SVI)

**Statistical analysis**

_a. Study population_
All patients entered onto the Siopel 4 trial will be eligible
Patient demographic data will be expressed as mean values and standard deviations.

_b. Assessment of cardiac performance_
Cardiac measurements from our normal cohort (previously reported) will be used to provide a normal range within which the measurements from the SIOPEL patients can be expressed in SD
units (z scores). The mean z scores for the normal group and the treatment group will be contrasted using two-sample t-tests.

**Organisation:**

**Principal Investigator**  
**Dr. Gill Levitt**  
Consultant Paediatrician in Oncology & Late Effects  
Great Ormond Street Children’s Hospital NHS Trust  
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London WC1N 3JH UK  
Phone + 44 020 7829 0073/8832  
Fax + 44 020 7813 8588  
Email levitg@gosh.nhs.uk

**Study Cardiologist**  
**Dr. Keld Sorensen**  
Consultant Cardiologist  
Department of Cardiology  
Skejby University Hospital  
DK-8200 Aarhus N Denmark  
Phone + 45 8949 6115  
Fax + 45 8949 6025  
Email kes@dadlnet.dk

For further information please contact Dr. Gill Levitt or the SIOPEL 4 chemotherapy panel co-ordinators.
# HEPATOBLASTOMA / CARDIAC STUDY
## Case History Form

## 1. HOSPITAL DETAILS

| Centre: |  |
| Consultant: | Contact Person: |
| Address: |  |
| Phone: | Fax: |
| Email: |  |

## 2. PATIENT’S PERSONAL DETAILS

Patient Name: **First 3 letters of surname + first 2 letters of first name**

| Study Number: |  |
| Date of Birth: | dd/mm/yy |
| Sex (tick): | MALE | FEMALE |
| Race (tick): | CAUCASIAN | ASIAN | AFRO/CARRIBEAN | OTHER |

## 3. TREATMENT DETAILS

| Total Doxorubicin dose (mg / m²): |  |
| Infusion Time (hours): |  |
| Last dose of Doxorubicin: DAY | MONTH | YEAR |
| Lung Radiation (tick): | YES | NO |
| Lung Radiation dose (Gy): |  |

## 4. ELIGIBILITY CRITERIA

| Treated on SIOPEL 4 (tick): | YES | NO |
| Infusional Doxorubicin (tick): | YES | NO |
| Doxorubicin + dexrazoxane (tick): | YES | NO |
| No other Cardiotoxic drug: | YES | NO |
| Apyrexial: | YES | NO |
| No clinical anaemia: | YES | NO |
HEPATOBLASTOMA / CARDIAC STUDY
Cardiac Form

1. HOSPITAL DETAILS

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2. PATIENT'S PERSONAL DETAILS

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<tr>
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3. PATIENTS EXAMINATION DETAILS

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<tr>
<td>Echo Machine Company:</td>
<td>Echo Machine Type:</td>
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</tbody>
</table>

4. COMMENTS

If any queries re echocardiograms please contact:
Dr Keld Sorensen - Department of Cardiology, Skejby University Hospital, DK-8200 Aarhus N, Denmark
Phone +45 8949 5566 (switchboard - ask for bleep 6115)  Phone (direct line) + 45 8949 6115

Please send completed forms and tape/s to Dr Gill Levitt
Consultant Paediatrician in Oncology & Late Effects
Great Ormond Street Children’s Hospital NHS Trust
Great Ormond Street
London WC1N 3JH. UK

111  SIOPEL 4_final version_July 2004
APPENDIX 9: TISSUE STORAGE PROGRAM

CHILDHOOD LIVER TUMOUR TISSUE STORAGE PROGRAM

Objectives:
The primary objective of the SIOPEL Liver Tumour Tissue Storage Program is to facilitate basic and translational research aimed at a better understanding of the biology of childhood liver tumours.

To reach this objective the SIOPEL group decided to:

- Collect and store a significant number of childhood liver tumour specimens and tumour-derived DNA, RNA and cDNA for future molecular analyses. For comparison, we will also store patient derived (normal liver or blood) normal DNA.
- Establish, characterize and store primary cell cultures of childhood liver tumours and derived immortalized cell lines.
- Provide childhood liver tumour material for approved research projects conducted by investigators affiliated with the SIOP.

It is hoped that, with the help of the SIOPEL Tumour Tissue Bank, it will become possible to study molecular changes, occurring in hepatoblastoma and hepatocellular carcinoma, in large and homogeneously treated groups of patients and to correlate the biologic findings to the clinical features and outcome: to see whether these changes are of any diagnostic or prognostic relevance and/or whether they can be used for the development of novel treatment approaches.

Eligibility:
All paediatric patients with a suspected primary malignant liver tumour are eligible, irrespective of whether he/she will definitively be registered on one of the SIOPEL studies, since the definitive diagnosis and/or risk assignment is not (yet) known, in most cases, at the time of biopsy. Prior to obtaining tumour sample (biopsy), informed consent with appropriate information about the storage program must be signed by the patient and/or the parents.

Obtaining tumour tissue, sample processing:
Local surgeons, pathologists and oncologists are kindly requested to obtain tumour material from all eligible patients both at diagnostic biopsy and definitive tumour resection.

Initial diagnosis in liver tumours is made by histological examination. The required tumour material can be obtained by core tissue biopsy (true cut technique) or wedge resection through a small laparotomy or laparoscopic surgery. Basically, all these approaches allow the surgeon to, besides providing adequate material for accurate diagnosis and classification (by the local pathologist), collect sufficient tumour material to satisfy the requirements of the Childhood Liver Tumour Storage Program without any additional risk for the patient.

Tumour resection provides, almost always, abundant amount of tumour tissue making collection of the required samples more than easy. Surgeons / pathologist are encouraged to store the tumour material in the operation room immediately after surgical removal to guarantee good RNA quality.

Tumour tissue should be put in a sterile container immediately after sampling in order to maintain good RNA quality. The tumour tissue will be collected in three tubes all containing different preservatives (see figure below).
One tumour fragment (approx. 5x10x10 mm) or a biopsy cylinder have to be collected and stored aseptically in *RNA*later for future RNA- and DNA analyses.

Another tumour fragment (approx. 5x10x10 mm) or a biopsy cylinder have to be collected and stored aseptically in *F*-10 medium for cytogenetic/FISH analysis and cell cultures.

Another tumour fragment (approx. 5x10x10 mm) or a biopsy cylinder have to be collected and stored aseptically in *formalin* for histological examination/quality assurance.

If normal tissue is available, this can be stored in the same way as the tumour. If normal tissue is not available, 5-10 ml Citrate blood should be taken during the surgery.

*RNA*later (Ambion, Cat. No. 7020 & 7021) is a colorless non-toxic tissue- and RNA stabilization solution. *RNA*later permeates tissues and protects cellular RNA in situ. *RNA*later-treated tissue can be stored for at least 7 days at 20 °C without significant RNA-degradation.

Ham's *F*-10 Medium (Life Technologies, Cat. No. 41550-013) is a pink culture medium for the propagation of cell lines that - in contrast to other culture media - contains also Fe, Cu, Zn and fatty acids. Tumour cells stay vital in the *F*-10 transport medium at 20 °C for up to 48h and they can be cultured.

**TRANSPORT ARRANGEMENTS**

The transport tubes with the tumour samples have to be labelled with initials and birth date of the patient. They have to be sent together with the appropriate form acknowledging that the centre has obtained and filed written informed consent by international priority mail (e.g. FedEx, DHL) to the Oncology Laboratory of the University Children's Hospital of Zurich. Because the tumour sample must be handled right after arrival, colleagues sending material are kindly requested to forewarn the oncology lab in Zurich by phone or email.

Contact persons are:

**David Betts**

David.Betts@ksipi.unizh.ch

Tel. +411 266 71 11

**Dr. Michael Grotzer**

Michael.Grotzer@kispi.unizh.ch

Tel. +411 266 71 11 or

**Dr. Felix Niggli**

Felix.Niggli@kispi.unizh.ch

Tel. +411 266 71 11
After arrival at the Oncology laboratory in Zurich, each sample will be anonymized by giving a unique identifying number. As soon as the SIOPEL Tumour Tissue Bank confirms the arrival of correctly processed tumour material along with the adequately filled in form, the sender will be credited 50 Euro as compensation.

Kits with the transport tubes will be distributed free every 6 months to the participating centres. They can be stored at 4°C. Participating centres are kindly requested to identify a local contact person (surgeon, oncologist, pathologist or research nurse etc) who will be responsible for communication with the tissue bank.

Tumour samples should be sent along with the adequately filled in transportation form:

**SPECIMEN INFORMATION, TRANSPORT FORM**

**Sender**
Physician: _______________________________________________________
Institution: _______________________________________________________

**Patient**
Initials: First 3 Letters of Patient’s Surname  
First 2 Letters of Patient’s Forename:

Date of birth: ___________________________________________________

Gender:    ☐ F    ☐ M

Clinical diagnosis:  
Diagnostic biopsy     Definitive surgery     Recurrence

Remarks (e.g. 2. recurrence, secondary tumour, hepatitis B infection...):

Tumour material
☐ Tumour in RNAlater  ☐ Tumour in F-10  ☐ Tumour in formalin  ☐ 5-10ml citrate blood  
☐ normal liver in RNAlater

Date and time of biopsy/tumour removal: _______________________________

Tumour localization: _______________________________________________

☐ Please send me transport kits with tubes containing RNA later, F-10

**Procedure for providing material for approved research projects**
The tumour material, isolated DNA and RNA, cell cultures and cell lines will be distributed free of charge to investigators, affiliated with SIOP, for approved research projects. A specific committee of the SIOPEL group, the SIOPEL Childhood Liver Tumour Tissue Bank Committee, with at least one paediatric oncologist, one paediatric surgeon, one pathologist and one basic researcher, will review and approve, if appropriate, all requests for the use of tissue bank material. Written applications must be submitted to this committee and should provide sufficient
information on the objectives of the planned study, the quantity and kind of requested material and the expected biological and clinical relevance of the planned research project.

Only the following data will be available with the requested tissue to investigators:

- SIOPEL Tumourbank sample identifier number
- Pathological diagnosis (central review diagnosis, where applicable)
- Whether specimen is from primary tumour or a metastatic site
- If matching normal tissue has been requested, the type of tissue will be specified (e.g. blood, adjacent normal liver etc).

It is expected that the molecular analysis will be done “blind”, without any knowledge of the status of the patients, other than diagnosis, on the part of the researcher. Under no circumstances will specific patient identifiers be released to investigators nor will results of research studies on specific specimens be released to clinicians or patients.

Once the molecular analysis is completed on the cohort of tumour samples, the principal researcher must contact the SIOPEL Study Group to discuss the procedure for further analysis (correlation of the findings with clinical data). Studies, which require additional clinical information for correlation of molecular genetic findings with clinical parameters, have to be approved by the SIOPEL Study Group as part of the procedure for release of biological material.

All manuscripts and abstracts resulting from analysis of biological specimens of the SIOPEL Liver Tumour Tissue Bank should be sent to the relevant SIOPEL Manuscript Committee for final approval prior to submission to a conference or journal. Reports of such research projects must be presented and/or published with author(s) and on behalf of the International Childhood Liver Tumours Strategy Group (SIOPEL).

**Organisation**

The Childhood Liver Tumour Tissue Storage Program is a common project of the International Childhood Liver Tumours Strategy Group (SIOPEL) and the Swiss Paediatric Oncology Group (SPOG).

**Project Co-ordinator:** Dr. Michael A. Grotzer  
University Children's Hospital  
Steinwiesstrasse 75  
CH-8032 Zurich  
Switzerland

**Location of Tissue Bank:** Oncology Laboratory  
University Children's Hospital  
Steinwiesstrasse 75  
CH-8032 Zurich  
Switzerland

Initial financing of appliances (hood, freezers), supplies and personnel will be undertaken by the Department of Oncology of the University Children's Hospital of Zurich, Switzerland, and by contributions from the Swiss Paediatric Oncology Group (SPOG).
### APPENDIX 10: GFR

**NORMAL GFR IN CHILDREN AND YOUNG ADULTS**

<table>
<thead>
<tr>
<th>Age (Sex)</th>
<th>Mean GFR ± SD (mL/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week (males and females)</td>
<td>40.6 ± 14.8</td>
</tr>
<tr>
<td>2-8 weeks (males and females)</td>
<td>65.8 ± 24.8</td>
</tr>
<tr>
<td>&gt; 8 weeks (males and females)</td>
<td>95.7 ± 21.7</td>
</tr>
<tr>
<td>2-12 years (males and females)</td>
<td>133.0 ± 27.0</td>
</tr>
<tr>
<td>13-21 years (males)</td>
<td>140.0 ± 30.0</td>
</tr>
<tr>
<td>13-21 years (females)</td>
<td>126.0 ± 22.0</td>
</tr>
</tbody>
</table>

*Data based on three studies [44, 45, 46].

Abbreviation: SD, standard deviation

http://www.kidney.org/professionals
APPENDIX 11: CTCAE CRITERIA

COMMON TOXICITY CRITERIA

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: December 12, 2003

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The ‘SHORT NAME’ column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word ‘Select’ and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A ‘REMARK’ is a clarification of an AE.

ALSO CONSIDER

An ‘ALSO CONSIDER’ indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A ‘NAVIGATION NOTE’ indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the ‘NAVIGATION NOTE’ states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild AE
Grade 2 Moderate AE
Grade 3 Severe AE
Grade 4 Life-threatening or disabling AE
Grade 5 Death related to AE

A Semi-colon indicates ‘or’ within the description of the grade.
An ‘Em dash’ (—) indicates a grade not available.

Grades 1-4 are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: ‘Death not associated with CTCAE term – Select’ with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.

Important:

☐ Grade 5 is the only appropriate Grade
☐ This AE is to be used in the situation where a death cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  1. cannot be reported within a CTCAE CATEGORY as ‘Other (Specify)’
  2. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  3. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
## ALLERGY / IMMUNOLOGY

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Short Name</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reaction/hypersensitivity (including drug fever)</td>
<td></td>
<td>Allergic reaction</td>
<td>Transient flushing or rash; drug fever &lt;38°C (&lt;100.4°F)</td>
<td>Rash; flushing; urticaria; dyspnea; drug fever =38°C (=100.4°F)</td>
<td>Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension</td>
<td>Anaphylaxis</td>
<td>Death</td>
</tr>
</tbody>
</table>

## BLOOD / BONE MARROW

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Short Name</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td></td>
<td>Hemoglobin</td>
<td>&lt;LLN – 10.0 g/dL</td>
<td>&lt;10.0 – 8.0 g/dL</td>
<td>&lt;8.0 – 6.5 g/dL</td>
<td>&lt;6.5 g/dL</td>
<td>Death</td>
</tr>
<tr>
<td>Leukocytes (total WBC)</td>
<td></td>
<td>Leukocytes</td>
<td>&lt;LLN – 3000/mm³</td>
<td>&lt;3000 – 2000/mm³</td>
<td>&lt;2000 – 1000/mm³</td>
<td>&lt;1000/mm³</td>
<td>Death</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td></td>
<td>Lymphopenia</td>
<td>&lt;LLN – 800/mm³</td>
<td>&lt;800 – 500/mm³</td>
<td>&lt;500 – 200/mm³</td>
<td>&lt;200/mm³</td>
<td>Death</td>
</tr>
<tr>
<td>Neutrophils/granulocytes (ANC/AGC)</td>
<td></td>
<td>Neutrophils</td>
<td>&lt;LLN – 1500/mm³</td>
<td>&lt;1500 – 1000/mm³</td>
<td>&lt;1000 – 500/mm³</td>
<td>&lt;500/mm³</td>
<td>Death</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td>Platelets</td>
<td>&lt;LLN – 75,000/mm³</td>
<td>&lt;75,000 – 50,000/mm³</td>
<td>&lt;50,000 – 25,000/mm³</td>
<td>&lt;25,000/mm³</td>
<td>Death</td>
</tr>
</tbody>
</table>

## CARDIAC GENERAL

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Short Name</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular diastolic dysfunction</td>
<td></td>
<td>Left ventricular diastolic dysfunction</td>
<td>Asymptomatic diagnostic finding; intervention not indicated</td>
<td>Asymptomatic, intervention indicated</td>
<td>Symptomatic CHF responsive to intervention</td>
<td>Refractory CHF, poorly controlled; intervention such as ventricular assist</td>
<td>Death</td>
</tr>
</tbody>
</table>
### Left ventricular systolic dysfunction

<table>
<thead>
<tr>
<th>Device or heart transplant indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic, resting ejection fraction (EF) &lt;60 – 50%; shortening fraction (SF) &lt;30 – 24%</td>
</tr>
<tr>
<td>Asymptomatic, resting EF &lt;50 – 40%; SF &lt;24 – 15%</td>
</tr>
<tr>
<td>Symptomatic CHF responsive to intervention EF &lt;40 – 20% SF &lt;15%</td>
</tr>
<tr>
<td>Refractory CHF or poorly controlled; EF &lt;20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated</td>
</tr>
<tr>
<td>Death</td>
</tr>
</tbody>
</table>

### GASTROINTESTINAL

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Symptomatic, able to eat regular diet</td>
</tr>
<tr>
<td>Mucositis/stomatitis (clinical exam) – Select: Anus, Esophagus, Large bowel, Larynx, Oral cavity, Pharynx, Rectum, Small bowel, Stomach, Trachea</td>
<td>Erythema of the mucosa, Patchy ulcerations or pseudomembranes, Confluent ulcerations or pseudomembranes, bleeding with minor trauma, Tissue necrosis, significant spontaneous bleeding, life-threatening consequences</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
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<tbody>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Increase of 4 – 6 stools per day over baseline; IV fluids indicated &lt;24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated &lt;24 hrs</td>
</tr>
<tr>
<td>Mucositis/stomatitis (clinical exam) – Select: Anus, Esophagus, Large bowel, Larynx, Oral cavity, Pharynx, Rectum, Small bowel, Stomach, Trachea</td>
<td>Erythema of the mucosa, Patchy ulcerations or pseudomembranes, Confluent ulcerations or pseudomembranes, bleeding with minor trauma, Tissue necrosis, significant spontaneous bleeding, life-threatening consequences</td>
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<th>Grade</th>
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<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Increase of = 7 stools per day over baseline; incontinence; IV fluids = 24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated = 24 hrs</td>
</tr>
<tr>
<td>Mucositis/stomatitis (clinical exam) – Select: Anus, Esophagus, Large bowel, Larynx, Oral cavity, Pharynx, Rectum, Small bowel, Stomach, Trachea</td>
<td>Erythema of the mucosa, Patchy ulcerations or pseudomembranes, Confluent ulcerations or pseudomembranes, bleeding with minor trauma, Tissue necrosis, significant spontaneous bleeding, life-threatening consequences</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Life-threatening consequences (e.g., hemodynamic collapse)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Life-threatening consequences (e.g., obstruction, perforation)</td>
</tr>
<tr>
<td>Mucositis/stomatitis (clinical exam) – Select: Anus, Esophagus, Large bowel, Larynx, Oral cavity, Pharynx, Rectum, Small bowel, Stomach, Trachea</td>
<td>Life-threatening consequences (e.g., obstruction, perforation)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
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<tbody>
<tr>
<td>1</td>
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<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Death</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Death</td>
</tr>
<tr>
<td>Mucositis/stomatitis (clinical exam) – Select: Anus, Esophagus, Large bowel, Larynx, Oral cavity, Pharynx, Rectum, Small bowel, Stomach, Trachea</td>
<td>Death</td>
</tr>
</tbody>
</table>
**REMARK:** Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.

<table>
<thead>
<tr>
<th>Mucositis/stomatitis (functional/symptomatic) – Select:</th>
<th>Mucositis (functional/symptomatic) – Select</th>
<th>Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function</th>
<th>Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL</th>
<th>Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL</th>
<th>Upper aerodigestive tract sites: Symptomatic, medical intervention indicated but not interfering with ADL</th>
<th>Lower GI sites: Stool incontinence or other symptoms interfering with ADL</th>
<th>Symptoms associated with life-threatening consequences</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anus</td>
<td>–</td>
<td>Lower GI sites: Minimal discomfort, intervention not indicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Esophagus</td>
<td>–</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Large bowel</td>
<td>–</td>
<td></td>
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<tr>
<td>Larynx</td>
<td>–</td>
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<tr>
<td>Oral cavity</td>
<td>–</td>
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<td></td>
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<tr>
<td>Pharynx</td>
<td>–</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trachea</td>
<td>–</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

| Nausea | Nausea | Loss of appetite without alteration in eating habits | Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs | Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated = 24 hrs | Life-threatening consequences | Death |

**ALSO CONSIDER:** Anorexia; Vomiting.

### GASTROINTESTINAL

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>Vomiting</td>
<td>1 episode in 24 hrs</td>
</tr>
</tbody>
</table>

### INFECTION

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC &lt; 1.0 x 10^9/L, fever = 38.5°C)</td>
<td>Febrile neutropenia</td>
<td>—</td>
</tr>
</tbody>
</table>

**ALSO CONSIDER:** Neutrophils/granulocytes (ANC/AGC).
| Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC < 1.0 x 10^9/L) | Infection (documented clinically) – *Select* | — | Localized, local intervention indicated | IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated | Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis) | Death |

**Remark:** Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection).

**Also Consider:** Neutrophils/granulocytes (ANC/AGC).

<p>| Infection with normal ANC or Grade 1 or 2 neutrophils | Infection with normal ANC – <em>Select</em> | — | Localized, local intervention indicated | IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated | Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis) | Death |</p>
<table>
<thead>
<tr>
<th>INFECTION – SELECT</th>
<th>GENERAL</th>
<th>PULMONARY/UPPER RESPIRATORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUDITORY/EAR</td>
<td>– External ear (otitis externa)</td>
<td>– Bronchus</td>
</tr>
<tr>
<td>– Middle ear (otitis media)</td>
<td>CARDIOVASCULAR</td>
<td>– Larynx</td>
</tr>
<tr>
<td>– Artery</td>
<td></td>
<td>– Lung (pneumonia)</td>
</tr>
<tr>
<td>– Heart (endocarditis)</td>
<td></td>
<td>– Mediastinum NOS</td>
</tr>
<tr>
<td>– Spleen</td>
<td></td>
<td>– Mucosa</td>
</tr>
<tr>
<td>– Vein</td>
<td></td>
<td>– Neck NOS</td>
</tr>
<tr>
<td>DERMATOLOGY/SKIN</td>
<td></td>
<td>– Nose</td>
</tr>
<tr>
<td>– Lip/perioral</td>
<td></td>
<td>– Paranasal</td>
</tr>
<tr>
<td>– Peristomal</td>
<td>DERMATOLOGY/SKIN</td>
<td>– Pharynx</td>
</tr>
<tr>
<td>– Skin (cellulitis)</td>
<td>– Ungual (nails)</td>
<td>– Pleura (empyema)</td>
</tr>
<tr>
<td>– Biliary tree</td>
<td>GASTROINTESTINAL</td>
<td>– Sinus</td>
</tr>
<tr>
<td>– Gallbladder (cholecystitis)</td>
<td>– Brain (encephalitis, infectious)</td>
<td></td>
</tr>
<tr>
<td>– Liver</td>
<td>– Brain + Spinal cord (encephalomyelitis)</td>
<td></td>
</tr>
<tr>
<td>– Pancreas</td>
<td>– Meninges (meningitis)</td>
<td></td>
</tr>
<tr>
<td>LYMPHATIC</td>
<td>– Nerve-cranial</td>
<td></td>
</tr>
<tr>
<td>– Lymphatic</td>
<td>– Nerve-peripheral</td>
<td></td>
</tr>
<tr>
<td>MUSCULOSKELETAL</td>
<td>– Spinal cord (myelitis) OCULAR</td>
<td></td>
</tr>
<tr>
<td>– Bone (osteomyelitis)</td>
<td>– Conjunctiva</td>
<td></td>
</tr>
<tr>
<td>– Joint</td>
<td>– Cornea</td>
<td></td>
</tr>
<tr>
<td>– Muscle (infection myositis)</td>
<td>– Eye NOS</td>
<td></td>
</tr>
<tr>
<td>– Soft tissue NOS</td>
<td>– Lens</td>
<td></td>
</tr>
<tr>
<td>NEUROLOGY</td>
<td>– Brain (encephalitis, infectious)</td>
<td></td>
</tr>
<tr>
<td>– Brain + Spinal cord</td>
<td>– Brain + Spinal cord (encephalomyelitis)</td>
<td></td>
</tr>
<tr>
<td>– Meninges (meningitis)</td>
<td>– Nerve-cranial</td>
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</tr>
<tr>
<td>– Nerve-peripheral</td>
<td>– Nerve-peripheral</td>
<td></td>
</tr>
<tr>
<td>– Spinal cord (myelitis) OCULAR</td>
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<td></td>
</tr>
<tr>
<td>– Conjunctiva</td>
<td>– Eye NOS</td>
<td></td>
</tr>
<tr>
<td>– Cornea</td>
<td>– Lens</td>
<td></td>
</tr>
<tr>
<td>– Uterus</td>
<td>– Sexual/Reproductive FUNCTION</td>
<td></td>
</tr>
<tr>
<td>– Vagina</td>
<td>– Cervix</td>
<td></td>
</tr>
<tr>
<td>– Vulva</td>
<td>– Fallopian tube</td>
<td></td>
</tr>
<tr>
<td>– Uterus</td>
<td>– Pelvis NOS</td>
<td></td>
</tr>
<tr>
<td>– Vagina</td>
<td>– Penis</td>
<td></td>
</tr>
<tr>
<td>– Scrotum</td>
<td>– Scrotum</td>
<td></td>
</tr>
<tr>
<td>– Uterus</td>
<td>– Uterus</td>
<td></td>
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<tr>
<td>– Vagina</td>
<td>– Vulva</td>
<td></td>
</tr>
<tr>
<td>– Cervix</td>
<td>– Fallopian tube</td>
<td></td>
</tr>
<tr>
<td>– Pelvis NOS</td>
<td>– Penis</td>
<td></td>
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<tr>
<td>– Uterus</td>
<td>– Scrotum</td>
<td></td>
</tr>
<tr>
<td>– Vagina</td>
<td>– Uterus</td>
<td></td>
</tr>
<tr>
<td>– Vulva</td>
<td>– Sexual/Reproductive FUNCTION</td>
<td></td>
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</table>
## METABOLIC / LABORATORY

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (hyperbilirubinemia)</td>
<td>Bilirubin</td>
<td>&gt;ULN – 1.5 x ULN</td>
<td>&gt;1.5 – 3.0 x ULN</td>
<td>&gt;3.0 – 10.0 x ULN</td>
<td>&gt;10.0 x ULN</td>
<td>—</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Creatinine</td>
<td>&gt;ULN – 1.5 x ULN</td>
<td>&gt;1.5 – 3.0 x ULN</td>
<td>&gt;3.0 – 6.0 x ULN</td>
<td>&gt;6.0 x ULN</td>
<td>Death</td>
</tr>
</tbody>
</table>

**Remark:** Adjust to age-appropriate levels for pediatric patients.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Glomerular filtration rate</th>
<th>Magnesium, serum-low (hypomagnesemia)</th>
<th>Calcium, serum-low (hypocalcemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GFR</td>
<td>Hypomagnesemia</td>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>2</td>
<td>&lt;75 – 50% LLN</td>
<td>&lt;LLN – 1.2 mg/dL</td>
<td>&lt;LLN – 8.0 mg/dL</td>
</tr>
<tr>
<td>3</td>
<td>&lt;50 – 25% LLN</td>
<td>&lt;1.2 – 0.9 mg/dL</td>
<td>&lt;LLN – 2.0 mmol/L</td>
</tr>
<tr>
<td>4</td>
<td>&lt;25% LLN, chronic dialysis not indicated</td>
<td>&lt;0.9 – 0.7 mg/dL</td>
<td>&lt;2.0 – 1.75 mmol/L</td>
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<tr>
<td>5</td>
<td>Chronic dialysis or renal transplant indicated</td>
<td>&lt;0.7 mg/dL</td>
<td>&lt;1.75 – 1.5 mmol/L</td>
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<tr>
<td>6</td>
<td>Death</td>
<td>&lt;0.3 mmol/L</td>
<td>&lt;6.0 mg/dL</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Death</td>
<td>&lt;1.5 mmol/L</td>
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</tbody>
</table>

## NEUROLOGY

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>Encephalopathy</td>
<td>—</td>
<td>—</td>
<td>Mild signs or symptoms; not interfering with ADL</td>
<td>Signs or symptoms interfering with ADL; hospitalization indicated</td>
<td>Life-threatening; disabling</td>
<td>Death</td>
</tr>
<tr>
<td>Seizure</td>
<td>Seizure</td>
<td>—</td>
<td>—</td>
<td>One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL</td>
<td>Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention</td>
<td>Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)</td>
<td>Death</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>Short Name</td>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death not associated with CTCAE term</td>
<td>Death not associated with CTCAE term</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Select</td>
<td>– Select</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Death NOS</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>– Disease progression NOS</td>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Multi-organ failure</td>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>– Sudden death</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Remark:** Grade 5 is the only appropriate grade. ‘Death not associated with CTCAE term – Select’ is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE ‘Other (Specify, __)’.
## SURGERY / INTRA-OPERATIVE INJURY

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-operative injury – Select Organ or Structure</td>
<td>Primary repair of injured organ/structure indicated</td>
<td>Partial resection of injured organ/structure indicated</td>
<td>Complete resection or reconstruction of injured organ/structure indicated</td>
<td>Life threatening consequences; disabling</td>
<td></td>
</tr>
<tr>
<td>Intraop injury – ‘Select’</td>
<td>Life threatening consequences; disabling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Remark:** The ‘Select’ AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.

| Intra-operative Injury – Other (Specify, __) | Intraop Injury – Other (Specify) | Primary repair of injured organ/structure indicated | Partial resection of injured organ/structure indicated | Complete resection or reconstruction of injured organ/structure indicated | Life threatening consequences; disabling |

**Remark:** Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the ‘Select’ AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.

**Navigation Note:** Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.
<table>
<thead>
<tr>
<th>AUDITORY/EAR</th>
<th>ENDOCRINE (continued)</th>
<th>GASTROINTESTINAL (continued)</th>
<th>NEUROLOGY (continued)</th>
<th>PULMONARY/UPPER RESPIRATORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner ear</td>
<td>Thyroid</td>
<td>Stoma (GI)</td>
<td>CN V (trigeminal) motor</td>
<td>Bronchus</td>
</tr>
<tr>
<td>Middle ear</td>
<td>Larynx</td>
<td>Stomach</td>
<td>CN V (trigeminal) sensory</td>
<td>Lung</td>
</tr>
<tr>
<td>Outer ear NOS</td>
<td>Nasal cavity</td>
<td>Gallbladder</td>
<td>CN VI (abducens)</td>
<td>Mediastinum</td>
</tr>
<tr>
<td>Outer ear-Pinna</td>
<td>Nasopharynx</td>
<td>Gall bladder</td>
<td>CN VII (facial) motor-face</td>
<td>Pleura</td>
</tr>
<tr>
<td></td>
<td>Neck NOS</td>
<td>Gall bladder</td>
<td>CN VII (facial) sensory- taste</td>
<td>Thoracic duct</td>
</tr>
<tr>
<td></td>
<td>Nose</td>
<td>Gall bladder</td>
<td>CN VIII (vestibulocochlear)</td>
<td>Trachea</td>
</tr>
<tr>
<td></td>
<td>Oral cavity NOS</td>
<td>Gall bladder</td>
<td>CN IX (glossopharyngeal) motor pharynx</td>
<td>Upper airway NOS</td>
</tr>
<tr>
<td></td>
<td>Parotid gland</td>
<td>Gall bladder</td>
<td>CN IX (glossopharyngeal) sensory ear-pharynx- tongue</td>
<td>Bladder</td>
</tr>
<tr>
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<td>Pharynx</td>
<td>Gall bladder</td>
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<td>Cervix</td>
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<tr>
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<td>Salivary duct</td>
<td>Gall bladder</td>
<td></td>
<td>Fallopian tube</td>
</tr>
<tr>
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<td>Salivary gland</td>
<td>Gall bladder</td>
<td></td>
<td>Kidney</td>
</tr>
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<td>Sinus</td>
<td>Gall bladder</td>
<td></td>
<td>Ovary</td>
</tr>
<tr>
<td></td>
<td>Teeth</td>
<td>Gall bladder</td>
<td></td>
<td>Pelvis NOS</td>
</tr>
<tr>
<td></td>
<td>Tongue</td>
<td>Gall bladder</td>
<td></td>
<td>Penis</td>
</tr>
<tr>
<td></td>
<td>Upper aerodigestive NOS</td>
<td>Gall bladder</td>
<td></td>
<td>Prostate</td>
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<td></td>
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<td>Gall bladder</td>
<td></td>
<td>Scrotum</td>
</tr>
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<td></td>
<td>Gall bladder</td>
<td></td>
<td>Testis</td>
</tr>
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<td></td>
<td>Gall bladder</td>
<td></td>
<td>Ureter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gall bladder</td>
<td></td>
<td>Urethra</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gall bladder</td>
<td></td>
<td>Urinary conduit</td>
</tr>
<tr>
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<td></td>
<td>Gall bladder</td>
<td></td>
<td>Urinary tract NOS</td>
</tr>
<tr>
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<td></td>
<td>Gall bladder</td>
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<td>Uterus</td>
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<td></td>
<td>Gall bladder</td>
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<td>Vagina</td>
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<td>Gall bladder</td>
<td></td>
<td>Vulva</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gall bladder</td>
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</tr>
</tbody>
</table>
APPENDIX 12: PIS SHEETS

PARENT/PATIENT INFORMATION SHEETS AND CONSENT FORM

Parent information sheet
Information sheet for patients 16+ in Scotland
Information sheet for patients aged 14+
Information sheet for patients aged 8-14
Information sheet for patients less than 8 years
Information sheet for General Practitioners
Parent/child consent form
Patient consent form
Dear Parent/Guardian.

We are inviting you to allow your child to take part in a research study looking at the treatment of high-risk hepatoblastoma. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please do not hesitate to ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish your child to take part.

1. What is the purpose of the study?

You already know that your child has hepatoblastoma. Hepatoblastoma is a rare malignant tumour (cancer) of the liver. Experts who make up the International Society of Paediatric Oncology (SIOP) Liver Group have developed major initiatives to improve the cure rate of children with hepatoblastoma. They have now run a series of treatment ‘trials’ known as the ‘SIOPEL (SIOP Epithelial Liver Tumour) studies’ to test different forms of chemotherapy. In the first trial all patients with hepatoblastoma were treated with the same chemotherapy (drugs) regardless of the extent of their disease at diagnosis. From the results of that first study it has been possible to identify a group of patients with so called ‘high risk’ hepatoblastoma who have more extensive disease at diagnosis and have a worse prognosis than those patients with more localised disease. The purpose of this study is to try and improve the survival of patients with ‘high risk’ hepatoblastoma by using the drugs that we believe to be most effective in a new way.

2. Why has my child been chosen?

The study is a clinical trial (a research study involving human patients). Clinical trials involve only patients who choose to take part. You are being asked to allow your child to take part because he/she has been diagnosed with a high-risk hepatoblastoma.

3. Does my child have to take part?

It is up to you to decide whether or not to allow your child to take part in the study. You will need to make this decision by the end of the first week of treatment (day 8). If you do decide to allow your child to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to let your child take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care your child receives.
4. What will happen to my child if he/she takes part?

If your child takes part in the trial he/she will be treated according to the fourth study of the SIOPEL group. The treatment on this trial consists of pre-operative (before operation) chemotherapy, with 2 drugs - Cisplatin given weekly for 3 weeks out of 4 and Doxorubicin given once in each 4 week block of chemotherapy. Chemotherapy will be started within 15 days of the diagnosis being made and 3 blocks of this chemotherapy will be given before surgery is considered. This chemotherapy is extremely intensive and your child may be hospitalised more often than not. The treatment will increase the risk of infection and will reduce your child’s appetite. It is likely that your child will need antibiotics regularly and extra nutrition. If your child’s tumour has shrunk in response to chemotherapy and it is felt that it can be completely removed at operation, surgery will take place. This may be removal of part of the liver or if the tumour can only be removed by taking out all of the liver your child will also have a liver transplant. If your child had tumour in the lungs as well as the liver at diagnosis it may be necessary for your child to have lung surgery as well.

If your child has responded to chemotherapy but it is thought that the liver tumour cannot be completely removed at operation your child will be given additional chemotherapy consisting of relatively high dose Carboplatin and Doxorubicin. Two courses will be given before your child is assessed again for surgery as above. Children who have surgery after the first 3 blocks of chemotherapy will receive further chemotherapy when they have recovered from their operation. Three courses of standard dose Carboplatin and Doxorubicin will be given at 3 weekly intervals. Children who have the two additional courses of chemotherapy prior to surgery will not have any further chemotherapy after surgery.

If your child’s tumour cannot be removed by operation after pre-operative chemotherapy or their disease progresses at any time point alternative treatment will be discussed with you.

5. What do I have to do?

During the whole of the treatment period you will be guided by the team treating your child as to what precautions need to be taken. Most of the time you will need to be aware of the increased risk of infection and other side effects of treatment. These are discussed in more detail in section 8.

6. What is the drug or procedure that is being tested?

We believe that Cisplatin is the most effective drug in the treatment of hepatoblastoma. In this study the total dose of Cisplatin will be more than in previous studies. The total dose, which in previous studies was given over a period of 22 weeks, both before and after surgery, will be given in just 12 weeks before an attempt is made to remove the tumour at operation. It is hoped that increasing the dose and intensity of Cisplatin chemotherapy will increase the number of patients who can have their tumour removed at surgery, which in turn will increase the survival rate. We are testing the effectiveness of this new intensive chemotherapy regime and assessing the short-term toxic effects of this treatment.

7. What are the treatment alternatives?

If you decide not to take part in this study your child will be treated with the chemotherapy used in the previous study - SIOPEL 3. This treatment consists of chemotherapy every 10 days alternating Cisplatin with two other drugs Carboplatin and Doxorubicin. The side effects of these drugs are detailed within this sheet. Your doctor will discuss this with you.
8. What are the side effects of any treatment received when taking part?

Chemotherapy can cause both immediate side effects and more long-term effects. Surgery carries the risks of complications. Not all side effects can be predicted. Occasionally side effects can become life threatening or even fatal. There is also a very small risk that the treatment itself increases the chance of your child developing a second cancer. You need to discuss the potential risks with your doctor. Medication can be given to reduce some side effects. Your child will be carefully monitored and where possible treatment altered if serious side effects develop.

Reproductive risks: It is unknown what effect(s) these treatments may have on an unborn child. For this reason, if your child is of childbearing age, your child will, if appropriate, be asked to practice an effective method of birth control while participating in this study.

General side effects of chemotherapy: -
- Nausea, and vomiting can usually be controlled by medication,
- Bone marrow production is affected. This may result in a reduction in red blood cells (anaemia) which means your child may require a blood transfusion. A lowering of white blood cells can make your child more susceptible to infections and they may need admission to hospital. Bleeding and bruising caused by a reduction in platelets (cells that help blood clot) which may result in your child having a platelet transfusion.
- Loss of appetite and mouth ulcers if this occurs you child may need nutritional support. This will be discussed in more detail if necessary.
- Hair loss

Specific side effects:
Cisplatin may result in deterioration in kidney function – tests of kidney function will be done before each block of Cisplatin and the dose of Cisplatin altered if necessary. Your child may be given additional magnesium medication as children having Cisplatin can lose magnesium in their urine. Cisplatin may also cause a high tone hearing loss. Your child’s hearing will be monitored and the results discussed with you. Assessment of very young children is difficult and the full extent of the hearing loss may not be apparent until the child is around 4 years old.
Doxorubicin is known to cause damage to heart muscle. This effect is related to the total dose - the higher the dose the more likely damage is to occur. This damage may become evident whilst your child is being treated or not until many years later. To minimise this effect your child will be given an additional drug – Dexrazoxane which protects the heart from this damage. Your child will also have regular tests of the function of their heart – echocardiograms both during and after treatment. Dexrazoxane is known to increase the risk of infection by lowering the bone marrow production.
Carboplatin – the main side effect of this drug is poor bone marrow production, particularly of the platelets. Although carboplatin on its own does not cause significant hearing loss when used in combination with cisplatin the effects are increased. Carboplatin also increases the effect of Cisplatin on kidney function.

Complications of surgery: Bleeding of the tumour or liver edge can occur.

9. What are the possible disadvantages and risks of taking part?

The main disadvantages and risks will be from the side effects of the treatment which have been outlined above. By taking part in this study your child’s treatment will not be delayed. For the duration of the trial, however, there are no funds for travel purposes. If your child is eligible for NHS transport this will continue.
10. What are the possible benefits of taking part?

While the hope is that more children with high-risk hepatoblastoma will be cured on this study than on previous studies, there may not be any direct medical benefit to your child if he/she participates. It is hoped that the information learned from this study may be of help to future patients with high-risk hepatoblastoma.

11. What if new information becomes available?

Sometimes during the course of a research project new information becomes available about the treatment/drug that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your child your doctor will make arrangements for your child’s care to continue. If you decide to continue in the study you will be asked to sign an updated consent form. Also, on receiving new information your doctor might consider it to be in your child’s best interest to withdraw him/her from the study. Your doctor will explain the reasons and make arrangements for your child’s care to continue.

12. What happens when the research study stops?

Once the research study finishes, unless the study stops for reasons mentioned in section 11, if your child is still receiving treatment he/she should be able to continue with that treatment for the agreed duration or stop if clinically indicated.

13. What if something goes wrong?

If your child is harmed by taking part in this research project, there are no special compensation arrangements. If however your child is harmed due to someone’s negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

14. Will my child’s participation in this study be kept confidential?

All information that is collected about your child during the course of the research will be kept strictly confidential. This study will involve use of remote data entry, which means that participating centres will enter data directly onto a computer. The data will be sent electronically to an organisation in Italy, called CINECA. CINECA is an organisation supported by a number of Italian universities, and has considerable experience of holding large amounts of patient data so that it is completely secure. While the data are being transferred electronically they will be encrypted. Members of the study committee and relevant staff in the UK Children’s Cancer Study Group Data Centre in Leicester, and the statistical centre in Switzerland, will be able to access the data online. The management of patient data is subject to very strict controls. All of the information that can be traced to your child will remain confidential.

To ensure accurate assessment of the extent of your child’s tumour, x-rays and CT scans will be reviewed by the study radiologist in London. Biopsy material and liver tumour removed at operation will be sent to the study pathologist in Switzerland.

15. What will happen to the results of the research study?

The results of the study will be published in medical journals and presented at medical conferences. Your child’s name will not be used when the research results are published. The
publication will happen a few years after the study has closed so that we know what happened to the patients after ending their treatment.

16. Who is organising and funding the research?

The study is being organised by International Society of Paediatric Oncology (SIOP) Liver Tumour Group in conjunction with the United Kingdom Children’s Cancer Study Group. Financial support for the coordination of the study is being provided by Cancer Research UK. No one will receive payments for taking part in this study.

17. What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator (name, tel. etc.), or you may contact the hospital/Primary Care Trust/health authority (name etc.) complaints department.

If you agree for your child to take part in this study we will need you to sign a consent form. You will be given a copy of the consent form and this information sheet to keep. Also with your consent we will be informing your GP about your child’s participation in this study.

Thank you so much for taking the time to read this information.
Dear Patient

We are inviting you to take part in a research study looking at the treatment of high-risk hepatoblastoma. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please do not hesitate to ask us if there is anything that is not clear or if you would like more information. Take time in deciding whether or not you wish to take part. Thank you for reading this.

1. **What is the purpose of the study?**

You already know that you have hepatoblastoma. Hepatoblastoma is a rare tumour. It is a form of liver cancer. Experts who make up the International Society of Paediatric Oncology (SIOP) Liver Group have developed major initiatives to improve the cure rate of patients with hepatoblastoma. They have now run a series of treatment ‘trials’ known as the ‘SIOPEL (SIOP Epithelial Liver Tumour) studies’ to test different forms of chemotherapy. In the first trial all patients with hepatoblastoma were treated with the same chemotherapy regardless of the extent of their disease at diagnosis. From the results of that first study it has been possible to identify a group of patients with hepatoblastoma who have more extensive disease at diagnosis and have a worse outcome than those patients with more localised disease. The purpose of this study is to try and improve the cure rate of patients with hepatoblastoma by using the drugs that we believe to be most effective in a new way.

2. **Why have you been chosen?**

The study is a clinical trial (a research study involving human patients). Clinical trials involve only patients who choose to take part. You are being asked to take part because you have been diagnosed with hepatoblastoma.

3. **Do I have to take part?**

Although you need treatment for your liver cancer it is up to you to decide whether or not to take part in this study. You will need to make this decision by the end of the first week of treatment (day 8). If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. You will however still need to have treatment with both medication and surgery.
4. What will happen to me if I take part?

If you take part in the trial you will be treated according to the fourth study of the SIOPEL group. The treatment on this trial consists of medication, chemotherapy, with 2 drugs - Cisplatin given weekly for 3 weeks out of 4 and Doxorubicin given once in each 4 week block of chemotherapy. Chemotherapy will be started within 15 days of the diagnosis being made and 3 blocks of this chemotherapy will be given before surgery is considered. This chemotherapy is extremely intensive and you may be hospitalised more often than not. The treatment will increase the risk of infection and will reduce your appetite. It is likely that you will need antibiotics regularly and extra nutrition. If your tumour has shrunk in response to chemotherapy and it is felt that it can be completely removed at operation, surgery will take place. This may be removal of part of the liver or if the tumour can only be removed by taking out all of the liver you will also have a liver transplant.

If you had disease in the lungs as well as the liver at diagnosis it may be necessary for you to have lung surgery as well.

If you have responded to chemotherapy but it is thought that the liver tumour can not be completely removed at operation you will be given additional chemotherapy consisting of higher dose Carboplatin and Doxorubicin. Two courses will be given before you are assessed again for surgery as above. Patients who have surgery after the first 3 blocks of chemotherapy will receive further chemotherapy when they have recovered from their operation. Three courses of standard dose Carboplatin and Doxorubicin will be given at 3-week intervals. Patients who have the two additional courses of chemotherapy prior to surgery will not have any further chemotherapy after surgery.

If your tumour cannot be removed by an operation after chemotherapy or your disease progresses at any time point, alternative treatment will be discussed with you.

5. What do I have to do?

During the whole of the your treatment period you will be guided by the team treating you as to what precautions need to be taken. Most of the time you will need to be aware of the increased risk of infection and other side effects of treatment. These are discussed in more detail in section 8.

6. What is the drug or procedure that is being tested?

We believe that Cisplatin is the most effective drug in the treatment of hepatoblastoma. In this study the total dose of Cisplatin, which in previous studies was given over a period of 22 weeks both before and after surgery, will be given in just 12 weeks before an attempt is made to remove the tumour at operation. It is hoped that increasing the intensity of Cisplatin chemotherapy will increase the number of patients who can have their tumour removed at surgery, which in turn will increase the survival rate. We are testing the effectiveness of a new intensive chemotherapy regime and assessing the short- and long-term toxic effects of this treatment.

7. What are the treatment alternatives?

If you decide not to take part in this study you will be treated with the chemotherapy used in the previous study of the SIOPEL group (SIOPEL 3). This treatment consists of chemotherapy every 10 days alternating Cisplatin with two other drugs Carboplatin and Doxorubicin. The side effects of these drugs are detailed within this sheet. Your doctor will discuss this with you.
8. **What are the side effects of any treatment received when taking part?**

Chemotherapy can cause both immediate side effects and more long-term effects. Surgery carries the risks of complications. Not all side effects can be predicted. Some side effects can become life threatening. There is also a very small risk that the treatment itself increases the chance of you developing a second cancer. You need to discuss the potential risks with your doctor. Medication can be given to reduce some side effects. You will be carefully monitored and where possible, treatment altered if serious side effects develop.

**Reproductive risks:** It is unknown what effect(s) these treatments may have on an unborn child. For this reason you will, if appropriate, be asked to practice an effective method of birth control while participating in this study.

**General side effects of chemotherapy:**

- Nausea and vomiting can usually be controlled by medication
- Bone marrow production is affected. This may result in a reduction in red blood cells (anaemia) which means you may require a blood transfusion. A lowering of white blood cells can make you more susceptible to infections and you may need admission to hospital. Bleeding and bruising caused by a reduction in platelets (cells that help blood clot) which may result in you having a platelet transfusion.
- Loss of appetite and mouth ulcers. If this occurs you may need nutritional support. This will be discussed in more detail if necessary.
- Hair loss – this should grow back after treatment.

**Specific side effects:**

- **Cisplatin** may result in deterioration of kidney function – tests of kidney function will be done before each course of Cisplatin and the dose of Cisplatin altered if necessary. You may be given additional magnesium medication as patients having Cisplatin can lose magnesium in their urine. Cisplatin may also cause hearing loss. Your hearing will be monitored regularly and the results discussed with you.
- **Doxorubicin** is known to cause damage to the heart muscle. This effect is dose related - the higher the dose the more likely damage is to occur. This damage may become evident whilst you are being treated or many years later. To minimise this effect you will be given an additional drug – Dextrazoxane - which protects the heart from this damage. You will also have regular tests of the function of your heart- echocardiograms- both during and after treatment. Dextrazoxane is known to increase the risk of infection by lowering the bone marrow production
- **Carboplatin** – the main side effect of this drug is bone marrow suppression particularly of the platelets.
  Although Carboplatin on its own does not cause significant hearing loss when used in combination with Cisplatin, the effects are increased. Carboplatin also increases the effect of Cisplatin on kidney function.

**Complications of surgery:** Bleeding of the tumour or liver edge can occur.

9. **What are the possible disadvantages and risks of taking part?**

The main disadvantages and risks of will be from the side effects of the treatment which have been outlined above. By taking part in this study your treatment will not be delayed. For the duration of the trial, however, there are no funds for travel purposes. If you are eligible for NHS transport this will continue.
10. What are the possible benefits of taking part?

While the hope is that more patients with high-risk hepatoblastoma will be cured on this study than on previous studies, there may not be any direct medical benefit to you if you participate. It is hoped that the information learned from this study may be of help to future patients with high-risk hepatoblastoma.

11. What if new information becomes available?

Sometimes during the course of a research project new information becomes available about the treatment/drug that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your doctor will make arrangements for your care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form. Also, on receiving new information, your doctor might consider it to be in your best interest to withdraw from the study. Your doctor will explain the reasons and make arrangements for your care to continue.

12. What happens when the research study stops?

Once the research study finishes, unless the study stops for reasons mentioned above, if you are still receiving treatment you should be able to continue with that treatment for the agreed duration or stop if your doctor suggests it.

13. What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If however you are harmed due to someone’s negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

14. Will my participation in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. This study will involve use of remote data entry, which means that participating centres will enter data directly onto a computer. The data will be sent electronically to an organisation in Italy, called CINECA. CINECA is an organisation supported by a number of Italian universities, and has considerable experience of holding large amounts of patient data so that it is completely secure. While the data are being transferred electronically they will be encrypted. Members of the study committee and relevant staff in the UK Children’s Cancer Study Group Data Centre in Leicester, and the statistical centre in Switzerland, will be able to access the data on line. The management of patient data is subject to very strict controls. All of the information that can be traced to you will remain confidential.

To ensure accurate assessment of the extent of your tumour, x-rays and scans will be reviewed by the study radiologist in London. Samples of liver tumour tissue removed at diagnosis or at operation will be sent to the study pathologist in Switzerland to be analysed together with the tissue from all the other patients on the study.
15. **What will happen to the results of the research study?**

The results of the study will be published in medical journals and presented at medical conferences. Your name will not be used when the research results are published. The publication will happen a few years after the study has closed so that we know what happened to the patients after ending their treatment.

16. **Who is organising and funding the research?**

The study is being organised by International Society of Paediatric Oncology (SIOP) Liver Tumour Group in conjunction with the United Kingdom Children’s Cancer Study Group. Financial support for the co-ordination of the study is being provided by Cancer Research UK. No one will receive payments for taking part in this study.

17. **What if I have any concerns?**

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator (name, tel. etc.), or you may contact the hospital/Primary Care Trust/health authority (name etc.) complaints department.

If you agree to take part in this study we will need you to sign a consent form. You will be given a copy of the consent form and this information sheet to keep. Also with your consent we will be informing your GP about your participation in this study.

*Thank you so much for taking the time to read this information.*
Dear Patient

We are inviting you to take part in a research study looking at the treatment of high-risk hepatoblastoma. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please do not hesitate to ask us if there is anything that is not clear or if you would like more information. Take time in deciding whether or not you wish to take part. Thank you for reading this.

1. What is the purpose of the study?

You will have been told that you have hepatoblastoma. Hepatoblastoma is a rare malignant tumour (cancer) of the liver. Experts who make up the International Society of Paediatric Oncology (SIOP) Liver Group have developed new treatments for children with hepatoblastoma. They have now run a series of treatment trials to test different forms of chemotherapy. In the first trial all patients with hepatoblastoma were treated with the same chemotherapy regardless of the amount of disease at diagnosis. From the results of that first study it has been possible to identify a group of patients with so called ‘high risk’ hepatoblastoma who have more extensive disease at diagnosis. The purpose of this study is to try and improve the treatment for patients with ‘high risk’ hepatoblastoma by using the drugs that we believe to be most effective in a new way.

2. Why have you been chosen?

The study is a clinical trial (a research study involving human patients). Clinical trials involve only patients who choose to take part. You are being asked to take part because you have been diagnosed with hepatoblastoma.

3. Do I have to take part?

Although you need treatment for your liver cancer it is up to you and your parents to decide whether or not to take part in this study. You will need to make this decision by the end of the first week of treatment (day 8) If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. You will, however, still need to have treatment with both medication and surgery.
4. What will happen to me if I take part?

The treatment on this trial consists initially of chemotherapy, with two drugs, Cisplatin and Doxorubicin. This chemotherapy is intensive and you may be hospitalised more often than not. The treatment will increase the risk of infection and will reduce your appetite. It is likely that you will need antibiotics regularly and extra nutrition.

If your tumour has shrunk after chemotherapy, and it is felt that it can be completely removed at operation surgery will then take place. This may involve removal of part of the liver or, if the tumour can only be removed by taking out all of the liver, you will also have a liver transplant. This means removing your liver and replacing it with half of an adult liver from a donor. Following surgery you will have more chemotherapy.

If you had tumour in the lungs as well as the liver at diagnosis it may be necessary for you to have lung surgery as well.

If you have responded to chemotherapy but it is thought that the liver tumour cannot be completely removed at operation you will be given two further courses of different chemotherapy and assessed again for surgery. Patients who have this extra chemotherapy will not have any further chemotherapy after surgery.

If your tumour cannot be removed by an operation after all, or your disease progresses at any time point, alternative treatment will be discussed with you.

5. What do I have to do?

During the whole of the your treatment period you will be guided by the team treating you. Most of the time you will need to be aware of the risk of infection and other side effects of treatment. These are discussed in more detail in section 8.

6. What is the drug or procedure that is being tested?

We are testing the effectiveness of a new intensive chemotherapy regime and assessing the short and long-term effects of this treatment. We believe that Cisplatin is the most effective drug in the treatment of hepatoblastoma. In this study the total dose of Cisplatin will be given over 12 weeks instead of 22 weeks. It is hoped that by making this change more patients will be able to have their tumour removed at surgery.

7. What are the treatment alternatives?

If you decide not to take part in this study you will be treated with the chemotherapy used in the previous study - SIOPEL 3. This treatment consists of chemotherapy every 10 days alternating Cisplatin with two other drugs Carboplatin and Doxorubicin. The side effects of these drugs are detailed within this sheet. Your doctor will discuss this with you.
8. What are the side effects of any treatment received when taking part?

Chemotherapy can cause both immediate and more long-term side effects. Not all side effects can be predicted. There is also a very small risk that the treatment itself increases the chance of you developing a second cancer. Medication can be given to reduce some side effects. You will be carefully monitored and where possible treatment altered if serious side effects develop.

Reproductive risks: It is unknown what effect(s) these treatments may have on an unborn child. If you are sexually active, you will be asked to practice an effective method of birth control while participating in this study.

General side effects of chemotherapy:
- Nausea and vomiting can usually be controlled by medication
- Bone marrow production is affected. The bone marrow produces blood cells. This may result in a reduction in red blood cells (anaemia) which means you may require a blood transfusion. A lowering of white blood cells can make you more susceptible to infections and you may need admission to hospital for antibiotics. Bleeding and bruising caused by a reduction in platelets (cells that help blood clot) which may result in you having a platelet transfusion.
- Loss of appetite and mouth ulcers, if this occurs you may need extra support with feeding. This will be discussed in more detail if necessary.
- Hair loss, this should grow back after treatment.

Specific side effects.
Cisplatin can affect how well your kidneys work – tests of kidney function will be done before each course of Cisplatin and the dose of Cisplatin reduced if necessary.
Cisplatin may also cause hearing loss. Your hearing will be tested regularly and the results discussed with you. Doxorubicin is known to cause damage to heart muscle. To lessen this damage you will be given another drug – Dexrazoxane, this protects the heart. You will have regular heart tests, (echocardiograms) both during and after treatment.
Dexrazoxane is known to increase the risk of infection by lowering the bone marrow production

Carboplatin – this mainly affects bone marrow production (see above), particularly of the platelets which may cause easy bruising and bleeding e.g. nose bleeds.
Although Carboplatin on its own does not cause significant hearing loss when used in combination with Cisplatin the effects are increased. Carboplatin also increases the effect of Cisplatin on kidney function.

Complications of surgery: Bleeding of the tumour or liver edge can occur.

9. What are the possible disadvantages and risks of taking part?

The main disadvantages and risks of will be from the side effects of the treatment, which have been outlined above. By taking part in this study your treatment will not be delayed. For the duration of the trial, however, there are no funds for travel purposes. If you are eligible for NHS transport this will continue.
10. **What are the possible benefits of taking part?**

Although we hope that this study will improve the treatment of high risk hepatoblastoma, we cannot guarantee that there will be any direct medical benefit to you. The information learned from this study may also benefit patients in the future.

11. **What if new information becomes available?**

Sometimes during the course of a research project new information becomes available about the treatment/drug that is being studied. If this happens, your doctor will tell you and your parents about it and discuss with you whether you want to continue in the study. If you decide to stop your doctor will make arrangements for other treatment. If you decide to continue in the study you and your parents will be asked to sign an updated consent form. Also, on receiving new information your doctor might consider it to be in your best interests to withdraw from the study. Your doctor will explain the reasons and make arrangements for your new treatment.

12. **What happens when the research study stops?**

Once the research study finishes, unless the study stops for reasons mentioned above, if you are still receiving treatment you should be able to continue with that treatment for the agreed time or stop if your doctor thinks that is best.

13. **What if something goes wrong?**

If you are harmed by taking part in this research project, there are no special compensation arrangements. If however you are harmed due to someone making a mistake, then you may have grounds for legal action but you may have to pay for it. Whatever happens, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

14. **Will my participation in this study be kept confidential?**

All information, which is collected, about you during the course of the research will be kept strictly private. This study will involve use of remote data entry, which means that information will be entered directly onto a computer. The data will be sent electronically to a university based organisation in Italy, called CINECA. The information will be coded in a special way (encrypted) Members of the study committee and relevant staff in the UK Children’s Cancer Study Group Data Centre in Leicester, and the statistical centre in Switzerland, will be able to access this coded information. All of the information that can be traced to you will remain confidential.

15. **What will happen to the results of the research study?**

The results of the study will be published in medical journals and presented at medical conferences. Your name will not be used when the research results are published. The publication will happen a few years after the study has closed so that we know what happened to the patients after ending their treatment.
16. **Who is organising and funding the research?**

The study is being organised by International Society of Paediatric Oncology (SIOP) Liver Tumour Group in conjunction with the United Kingdom Children’s Cancer Study Group. Financial support for the coordination of the study is being provided by Cancer Research UK. No one will receive payments for taking part in this study.

17. **What if I have any concerns?**

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator Dr ……………………………..(local details here) or you may contact the hospital/GP/health authority (name etc.) complaints department.

If you agree to take part in this study we will need you and/or your parents to sign a consent form. You will be given a copy of the consent form and this information sheet to keep. Also with your consent we will be informing your GP about your participation in this study.

**Thank you so much for taking the time to read this information.**
(form to be printed on Institution headed paper)

Study Title: Intensified pre-operative chemotherapy and radical surgery for the treatment of high risk Hepatoblastoma (SIOPEL 4) (TBA)

INFORMATION SHEET for PATIENTS aged 8-14
(Version 2.0, November 2003)

Dear Patient

You are being invited to take part in a research study. Although we have to have your parents permission for you to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read this sheet and talk to others about it if you wish. Ask us if there is anything that is not clear or if you would like more information.

1. What is research?

Research means finding out more about something.

2. What is this research study about?

You will probably have been told that you have a lump or tumour in your tummy. This lump has a special name, hepatoblastoma and it is in a part of your tummy called the Liver. If we leave the hepatoblastoma alone it will make you very poorly so the doctors need to try and get rid of it, this is called treatment. We already know a lot about treatment for hepatoblastomas but we would like to find out more about how to make the treatments better. When we study a treatment we call it a Clinical Trial.

3. Why have you been chosen?

Because you have a hepatoblastoma.

4. Do I have to take part?

Your parents have to make the decision about you taking part but they may also like to know how you feel about it. They do not have to say yes they can say no and this will not affect the way the doctors treat you. If they do say yes they can always change their mind later on.
5. **What will happen to me if I take part?**

The treatment will be medicines called chemotherapy and an operation. We use the three best medicines that we have used before for getting rid of hepatoblastomas. They are called Cisplatin, Carboplatin and Doxorubicin. This chemotherapy is strong and you may be in hospital quite a lot. Whilst on the treatment you may get infections and need antibiotics, also you probably won’t feel very hungry.

In this trial we will give you three lots of chemotherapy to try and shrink the tumour and then the doctors will decide if the tumour can be taken out with an operation. After the operation you will get three more lots of chemotherapy.

If your tumour has not shrunk enough for an operation you will get two more lots of chemotherapy and then the doctors will do the operation to remove the tumour.

If your tumour does not shrink the doctors will talk to you and your parents about other types of treatment.

6. **What do I have to do?**

You will need to come into hospital to get the treatment. Sometimes you may feel poorly between treatments and need to be in hospital until you are feeling better. The doctors and nurses looking after you will tell you more about this.

From time to time you may need scans and blood tests to help the doctors find out how you are.

7. **What is the treatment being tested in the trial?**

We know that the Cisplatin is a very good treatment for hepatoblastomas and so in this trial we are going to give Cisplatin treatments closer together than in the last trial to try and see if it will work better. If you feel you don’t want this new treatment, then we will suggest treating you on the previous treatment. Ask your doctor to talk to you about it.

8. **What if I don’t join the study?**

You will be treated with the chemotherapy that has been used in the previous study. Your doctor will talk to you about it.

9. **Can the treatment cause me any harm?**

All chemotherapy medicines have side effects and your doctor will tell you more about them.

Here are some of the side effects that you may have:

*Feeling sick* - you will be given medicine to try and stop this.
**Lose your hair** - Unfortunately this happens with all chemotherapy. When the treatment is finished though your hair will grow back again.

**Anaemia** (reduction in amount of red blood cells) - which can be treated with a blood transfusion.

**Reduction in white blood cells** - this will reduce your body's ability to fight infection. This may require admission to hospital to treat the infection.

**Reduction in platelets** - (cells in the blood that help blood to clot) making you more likely to bleed and get bruises. This can be treated with a platelet transfusion.

*Cisplatin and Carboplatin can affect your hearing and how well your kidneys work. You will have your hearing checked and your kidneys tested regularly.*

*Doxorubicin can affect the muscles in your heart so we will test your heart regularly to check for any problems.*

**Side effects of surgery:** The tumour can bleed during the surgery but the doctors will take care of this. Also your tummy will hurt after the operation but we can give you medicine to help with this.

**10. What are the risks of taking part in the study?**

These will be all the side effects that we have already talked about. Sometimes some children need a bigger operation to give them a completely new liver, this is called a liver transplant. After a liver transplant children need to take extra medicines.

**11. What could be good about taking part in the study?**

We hope that more children with hepatoblastoma will get better on this study, but this may not happen. We also hope that the information learned from this study may help other children in the future.

**12. What if you learn more about the treatment during the study?**

Sometimes during a clinical trial we learn more about the treatment as the study goes along and may need to make changes. If this happens, your doctor will tell you and your parents about it and discuss whether you want to continue in the study. Whatever happens you will still have treatment.

**13. Will the information collected about me be kept private?**

All information that is collected about you during the course of the study is kept confidential (private). We will send the information by computer to Italy where it will be collected together with that of children treated in other countries and looked at only by the doctors and researchers dealing with the study.
14. What will happen to the results of the research study?

The results of the research will be made into a report, published in a Medical Journal and presented at medical conferences however nobody will be able to tell from this information that you took part in this study. The information from the study may help in the development of further treatments in the future.

15. What if I am worried about the study?

If you are worried or have questions about the study, you should talk to your doctor or nurse, or ask your parents to talk to them. We are there to help and are happy to answer any questions.

If you and your parents agree for you to join the study we will need you and your parents to sign a consent form. You will be given a copy of the consent form and this letter to keep.

Thank you so much for reading this letter.
You will probably have been told that you have a lump or tumour in your tummy. This lump has a special name, hepatoblastoma and it is in a part of your tummy called the Liver. If we leave the hepatoblastoma alone it will make you very poorly so the doctors need to try and get rid of it, this is called treatment. We already know a lot about treatment for hepatoblastoma but we would like to find out more about how to make the treatments better. When we study a treatment we call it a Clinical Trial.

For the first part of your treatment we will give you some medicine to try and make your lump shrink. This medicine is called chemotherapy and you may hear people calling it "chemo". There are different types of chemotherapy and they all have different names, the ones you will get are called Cisplatin, Carboplatin and Doxorubicin.

Although it is good at shrinking hepatoblastoma, chemo can do some bad things too, called side effects but we can do some things to help. Here are some of the side effects that you may have:

**Feeling sick** - you will be given medicine to try and stop this.

**Lose your hair** - Unfortunately this happens with all chemotherapy. When the treatment is finished though your hair will grow back again.
Makes you have less red cells in your blood - which can be treated with a blood transfusion.

Makes you have less white cells in your blood - this will make you more likely to get poorly and you will need to come into hospital to get better.

Makes you have less cells in your blood to stop you from bleeding - If you get a nose bleed or lots of bruises we can give you a platelet transfusion.

Cisplatin and Carboplatin can affect your hearing and how well your kidneys work. You will have your hearing checked and your kidneys tested regularly.

Doxorubicin can affect the muscles in your heart so we will test your heart regularly to check for any problems.

After the chemotherapy, by taking some special pictures of your tummy (called scans) the doctors will be able to tell if your lump has shrunk enough to have it taken away. We will ask a special doctor called a surgeon to do this.

After the lump has been taken away you may need to have some more chemo.

You will need to come into hospital to get the treatment. Sometimes you may feel poorly between treatments and need to be in hospital until you are feeling better. The doctors and nurses looking after you will talk to you more about this.

We know you may have some worries about having your treatment, we want to help you, please ask us about anything you want to know.
Dear Colleague

Your patient…………………………………………………………..is being invited to take part in a research study looking into the treatment of high-risk hepatoblastoma. The following information is to help you to understand the purpose of the study, how it may help your patient, any risks to your patient, and what is expected of your patient if they agree to enter the study.

1. What is the purpose of the study?

Your patient has high-risk hepatoblastoma. This International study aims to treat patients with high-risk hepatoblastoma on the SIOPEL 4 protocol. Information will be collected on approximately 60 patients worldwide over a 2-year period.

2. Why has your patient been chosen?

All children with high-risk hepatoblastoma in the UK are eligible for this clinical trial.

3. Does my patients have to take part?

No, their decision is entirely voluntary and they are free to withdraw at any time, without giving a reason and this will not affect the care they receive from our team. They will need to make this decision by the end of the first week of treatment (day 8).

4. What will happen to my patient if they take part?

If your patient takes part in the trial he/she will be treated according to the SIOPEL 4 protocol. The treatment on this trial consists of pre-operative chemotherapy, with 2 drugs - Cisplatin given weekly for 3 weeks out of 4 and Doxorubicin given once in each 4 week block of chemotherapy. Chemotherapy will be started within 15 days of the diagnosis being made and 3 blocks of this chemotherapy will be given before surgery is considered. This chemotherapy is extremely intensive and your patient may be hospitalised more often than not. The treatment will increase the risk of infection and will reduce your patient’s appetite. It is likely that your patient will need antibiotics regularly and extra nutrition. If your patient's tumour has shrunk in response to chemotherapy and it is felt that it can be completely removed at operation, surgery will take place. This may be removal of part of the liver or, if the tumour can only be removed by taking out all of the liver, your patient will also
have a liver transplant. If there is tumour in the lungs as well as the liver at diagnosis it may be necessary for them to have lung surgery also.

If they respond to chemotherapy but it is thought that the liver tumour cannot be completely removed at operation your patient will be given additional chemotherapy consisting of carboplatin and doxorubicin. Two relatively high dose courses will be given before your patient is assessed again for surgery as above. Patients who have surgery after the first 3 blocks of chemotherapy will receive further chemotherapy when they have recovered from their operation. Three courses of standard dose Carboplatin and Doxorubicin will be given at 3 weekly intervals. Patients who have the two additional courses of chemotherapy prior to surgery will not have any further chemotherapy after surgery.

5. **What do I have to do?**

The Paediatric Oncology liaison team will supply you with more detailed guidance on the care of children undergoing chemotherapy treatment

6. **What is the drug or procedure that is being tested?**

We are testing the effectiveness of a new intensive chemotherapy regime and assessing the short and medium-term toxic effects of this treatment. It is believed that Cisplatin is the most effective drug in the treatment of hepatoblastoma. In this study the total dose of Cisplatin will be increased. Whereas in previous studies the Cisplatin was given over a period of 22 weeks, both before and after surgery, it will now be given in just 12 weeks before an attempt is made to remove the tumour at operation. It is hoped that increasing the dose intensity of Cisplatin chemotherapy will increase the number of patients who can have their tumour removed at surgery. This in turn should increase the survival rate.

7. **What are the alternatives for diagnosis or treatment?**

If your patient decides not to take part in this study he/she will be treated with the chemotherapy used in the previous study - SIOPEL 3. This treatment consists of chemotherapy every 10 days alternating Cisplatin with two other drugs Carboplatin and Doxorubicin. The side effects of these drugs are detailed within this sheet.

Are there any other options?

The Americans, Germans and Japanese currently run different liver tumour trials. To date the results of the SIOPEL studies have equalled or improved on other national study results.

8. **What are the side effects of any treatment received when taking part?**

**General side effects of chemotherapy:**

- Nausea and vomiting
- Bone marrow suppression resulting in anaemia, neutropenia (increasing their susceptibility to infections) and thrombocytopenia
- Loss of appetite
- Mouth ulcers
- Hair loss
- A risk of developing a second cancer.
Specific side effects:

**Cisplatin** may result in deterioration in kidney function – tests of kidney function will be done before each cycle of Cisplatin and the dose of Cisplatin reduced if serious deterioration in kidney function is noted. All patients on Cisplatin lose magnesium in the urine whilst on treatment and this may continue once chemotherapy is completed so your patient will be prescribed magnesium supplements to counteract this. In order to prevent osteoporosis later in life these supplements may need to be continued long-term. Cisplatin may also cause permanent bilateral high tone hearing loss. In those patients old enough to co-operate, hearing will be monitored regularly.

**Doxorubicin** is known to cause damage to heart muscle. This effect is dose related - the higher the dose the more likely damage is to occur. This damage may become evident whilst your patient is being treated or many years later. To minimise this effect a cardioprotectant named Dexrazoxane, will be given with the Doxorubicin. Your patient will also have regular echocardiograms both during and after treatment and thereafter yearly lifelong.

It is wise to avoid all other renal- and ototoxic medication whenever possible. Dexrazoxane is known to increase the risk of infection by lowering the bone marrow production **Carboplatin** – the main side effect of this drug is bone marrow suppression particularly of the platelets, which may cause bruising, and bleeding. Although Carboplatin on its own does not cause significant hearing loss when used in combination with Cisplatin the effects are additive. Carboplatin also exacerbates the effect of Cisplatin on kidney function.

**Complications of surgery:** bleeding. In the case of liver transplant: rejection or more rarely lymphoproliferative disease.

9. **What are the possible disadvantages and risks of taking part?**

**Reproductive risks:** It is unknown what effect(s) these treatments may have on an unborn child. For this reason, if your patient is of childbearing age, they will, if appropriate, be asked to practice an effective method of birth control while participating in this study. **Fertility:** The long-term effects of Cisplatin are only just becoming known. Although fertility may be reduced, your patient is unlikely to become infertile due to the treatment.

By taking part in this study your patient’s treatment will not be delayed. For the duration of the trial, however, there are no funds for travel purposes. If your patient is eligible for NHS transport this will continue.

10. **What are the possible benefits of taking part?**

To date, the event-free survival of high-risk hepatoblastoma at 5 years is around 45%. While the hope is that more patients with high-risk hepatoblastoma will be cured on this study than on previous studies, there may not be any direct medical benefit to your patient. It is hoped that the information learned from this study may help future patients with high-risk hepatoblastoma.
11. **What if new information becomes available?**

Sometimes during the course of a research project new information becomes available about the treatment that is being studied requiring changes to be made. If this occurs it will be discussed with the family, if they decide to withdraw from the study their care will continue. If they decide to continue in the study they or their parents will be asked to sign an updated consent form. If this happens you will be informed.

12. **What happens when the research study stops?**

The study will run for about 2 years during which time we hope to recruit about 60 patients. This number of patients will allow us to determine whether this treatment is effective for high-risk hepatoblastoma. At this point no more patients will be entered into the study. This should not affect the treatment your patient is receiving. In time the data will be analysed and published.

13. **What if something goes wrong?**

If your patient is harmed by taking part in this research project there are no special compensation arrangements. If however your patient is harmed due to someone’s negligence, then your patient may have grounds for legal action but may have to pay for it. Regardless of this, if they wish to complain, or have any concerns about any aspect of the way they have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to them.

14. **Will my patient’s participation in this study be kept confidential?**

All information that is collected about your patient during the course of the research will be kept strictly confidential. This study will involve use of electronic remote data entry. The encrypted data will be sent to an organisation in Italy, called CINECA. CINECA is supported by a number of Italian universities, and has considerable experience of holding large amounts of patient data so that it is completely secure. Members of the study committee and relevant staff in the UK Children’s Cancer Study Group Data Centre in Leicester, and the statistical centre in Switzerland, will be able to access the data on line. The management of patient data is subject to very strict controls. All of the information that can be traced to your patient will remain confidential. To ensure accurate assessment of the extent of your patients tumour, x-rays and CT scans will be reviewed by the study radiologist in London. Biopsy material and liver tumour removed at operation will be sent to the study pathologist in Switzerland.

15. **What will happen to the results of the research study?**

The results of the study will be published in medical journals, which are available via the internet. Your patient’s name will not be used when the research results are published. The study is expected to run for two years, however the results will only be published after a few years follow-up.
16. **Who is organising and funding the research?**

The study is being organised by International Society of Paediatric Oncology (SIOP) Liver Tumour Group in conjunction with the United Kingdom Children’s Cancer Study Group. Financial support for the coordination of the study is being provided by Cancer Research UK. No one will receive payments for taking part in this study.

Yours sincerely,

Dr. ...................... (local investigator)

Dr Penelope Brock. UK Study Co-ordinator
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(Form to be on headed paper)

Centre Number:
Study Number:
Patient Identification Number for this trial:

Title of Project: Intensified Preoperative chemotherapy and radical surgery for High Risk Hepatoblastoma / SIOPEL 4 (TBA)

PARENT/CHILD CONSENT FORM
Version 1.0 October 2003

Name of Local Researcher:
UK Co-ordinator: Dr. Penelope Brock

Please initial box

1. I confirm that I have read and understand the information sheet(s) dated November 2003 for the above study and have had the opportunity to ask questions.

2. I understand that my/my child’s participation is voluntary and that I am/he/she is free to withdraw at any time, without giving any reason, without my/his/her medical care or legal rights being affected.

3. I understand that sections of any of my/my child’s medical notes, imaging, blood and/or tissue specimens may be looked at by responsible individuals from the International Society of Paediatric Oncology Liver Tumour Group, UK Children’s Cancer Study Group or from regulatory authorities where it is relevant to my/my child’s taking part in research. I give permission for these individuals to have access to my/my child’s records and/or material.

4. I agree that data about me/my child relating to this study may be sent to countries that do not have data protection laws that are similar to those in the UK.

5. I agree/agree for my child to take part in the above study.

________________________ ________________ ____________________
Name of patient Date Signature

________________________ ________________ ____________________
Name of parent/guardian Date Signature

_________________________ _________________ ___________________
Name of person taking consent Date Signature (if different from researcher)

_________________________ _________________ ___________________
Researcher Date Signature

1 for child/parents; 1 for researcher; 1 to be kept with hospital notes
(Form to be on headed paper)

Centre Number:
Study Number:
Patient Identification Number for this trial:

Title of Project: Intensified Preoperative chemotherapy and radical surgery for High Risk Hepatoblastoma / SIOPEL 4 (TBA)

PATIENT CONSENT FORM
For patients aged 16+ in Scotland
Version 1.0 October 2003

Name of Local Researcher:

UK Co-ordinator: Dr. Penelope Brock

1. I confirm that I have read and understand the information sheet(s) dated November 2003 for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes, imaging, blood and/or tissue specimens may be looked at by responsible individuals from the International Society of Paediatric Oncology Liver Tumour Group, UK Children’s Cancer Study Group or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records and/or material.

4. I agree that data about me relating to this study may be sent to countries that do not have data protection laws that are similar to those

5. I agree to take part in the above study.

__________________________ ________________ ____________________
Name of patient Date Signature

_________________________ _________________ ___________________
Name of person taking consent Date Signature
(if different from researcher)

__________________________ ________________ ____________________
Researcher Date Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes