SIOP

INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

SIOPEL - 3
LIVER TUMOUR STUDIES

HEPATOBLASTOMA
AND
HEPATOCELLULAR CARCINOMA

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0.0 PREMISE

This SIOP Liver Tumour Study - SIOPEL 3 - represents the 3rd generation of clinical trials launched by the SIOP Liver Tumour Study Group. The first study - SIOPEL 1 (1/1990 - 2/1994) - was designed to evaluate, within the framework of a non-randomised trial, the effectiveness of the combination Cisplatin (CDDP) Doxorubicin (DOXO), abbreviated to 'PLADO', in a pre-operative setting, and was also a feasibility study, aimed at evaluating the possibility of conducting an international cooperative clinical trial of such rare tumours as hepatoblastoma (HB) and childhood hepatocellular carcinoma (HCC).

Hepatoblastoma

The second trial - SIOPEL 2 (opened 10/1995) - was a combination of two pilot studies and was launched to test the feasibility and efficacy of 2 new chemotherapy regimens upon which SIOPEL 3 is based. In the SIOPEL 2 study the concept of stratifying children with HB into two risk categories ('standard risk' and 'high risk' HB), based on the results of SIOPEL 1, was introduced. Different treatment strategies were designed for these two risk categories. SIOPEL 3 also uses these two different therapeutic strategies - one for 'standard risk' HB (the larger group) and one for 'high risk' tumours. The 'standard risk' HB study is a prospective randomised trial which aims to test a specific clinical hypothesis (see objective). The 'high risk' protocol, due to the expected small sample size, is a single arm trial.

The rarity of hepatoblastoma means that at present it is not realistic to conceive clinical trials with sophisticated questions. However, considering the success of the previous studies (in terms both of recruitment and survival rates) and their widespread use by the international paediatric oncology community, it was decided to proceed further with clinical research in this field. Furthermore, on the principle that it is preferable to run a randomised rather than a single arm study, the 'SIOPEL' group decided to launch a randomised trial for the so-called 'standard risk' patients. Participation by a number of additional nations, from within and outside Europe, and including several South American countries, as well as Australia and New Zealand, is expected. Germany and Austria are about to complete a joint national trial of HB and it is hoped that both countries will also join SIOPEL 3 in the future. The study committee is confident that the patient recruitment rate will be sufficient to run the randomised trial, albeit with limited statistical power.
Hepatocellular Carcinoma

The SIOPEL 3 treatment protocol is designed primarily for hepatoblastoma (HB). However, as with the previous SIOPEL trials, hepatocellular carcinoma (HCC) cases should also be registered and treatment guidelines for HCC, using the ‘high risk’ chemotherapy regime, are provided in this protocol. Given the extreme rarity of childhood HCC (only 10 cases per year recruited into SIOPEL 1 from throughout Europe), collaboration with adult oncologists may be the only way forward in achieving a trial protocol designed with HCC specifically in mind.

This protocol has been designed and written to provide comprehensive diagnostic and therapeutic guidelines for the treatment of HB and HCC, thereby giving children affected by these diseases the best chance of cure.

1.0 BACKGROUND AND RATIONALE

The prognosis of children with HB has dramatically improved in the last decade

During the late eighties a quite dramatic change in the prognosis of childhood HB was observed because effective chemotherapy, capable of reducing tumour volume and making unresectable tumours resectable, became available. The use of CDDP, in association with other agents (mainly Doxorubicin - DOXO), seems to have been the key factor. (8,9,25,29). The response to chemotherapy and the resectability rates at delayed surgery of the major series of HB treated with CDDP based regimens so far published varies from 80 - 100% and from 67 - 80%, respectively (10,19,20,30). For these patients the 3-year overall survival (OS) has improved dramatically from 25% (11,12,22) to roughly 70%.

The SIOPEL 1 study contributed to this progress and the 154 children enrolled into the study are enjoying a 79% 3-year OS (CI 73-85%) and 67% (CI 60-75%) event-free survival (EFS), comparable (if not superior) to the results achieved by other cooperative study groups (24). In contrast to all other concurrent studies, SIOPEL 1 used pre-operative chemotherapy for all children, regardless of apparent initial tumour ‘resectability’ (14,15,21,30). It was hoped and expected that, due to shrinkage of the tumour, the primary resection rate would be higher, the operation easier, the likelihood of residual disease less and that there would be fewer unnecessary exploratory operations to determine resectability. A novel pre-operative (pre-treatment tumour extension - ‘PRETEXT’) classification, based on the anatomy of the liver, was introduced for this purpose. The excellent results confirm the feasibility of this overall approach and pre-operative chemotherapy is advocated for all patients in SIOPEL 3. On the other hand there is evidence from SIOPEL 1 that prognostic risk groups can be
identified at diagnosis (see next section) raising the possibility of future improvements in management by (a) reducing chemotherapy for patients with a relatively good prognosis (‘standard risk’ patients) and (b) intensifying chemotherapy for those anticipated to have a less favourable overall outcome (‘high risk’ patients).

**Prognostic factors in childhood hepatoblastoma - SIOPEL I data**

For the SIOPEL 1 HB population both (lung) metastases at presentation and the pre-treatment tumour extension (PRETEXT) (see Section 5.0) at diagnosis were statistically significant factors associated with 2-year OS (logrank $\chi^2=4.2$ degrees of freedom= 1, $p=0.04$ - logrank $\chi^2=13.4$; degrees of freedom= 3, $p=0.004$ respectively) and EFS (logrank $\chi^2=32.0$ degrees of freedom= 1, $p<0.001$ - Logrank $\chi^2=21$; degrees of freedom= 3, $p=0.001$ respectively). The 2-year OS and EFS for children without and with (lung) metastases were 83% vs 66% and 77% vs 32%, respectively. Among the four PRETEXT categories, the PRETEXT IV group (ie tumour involving all 4 hepatic sections at diagnosis) had the worst 2-year OS and EFS, (68% and 44%, respectively). All other recent HB studies indicate a worse outcome for children with HB presenting with lung metastases, with 3-year EFS varying from 0 to 33% (10,13,20,21,30). No other clinical or tumour characteristic has been clearly and consistently identified as a potential prognostic factor for OS in our study. However, for EFS, multi-focality of tumour and extra-hepatic (usually inferior vena cava, or portal vein involvement) were both identified as poor prognostic factors (40% and 44%, $\chi^2 = 10.5$, df = 1, $p = 0.001$ and $\chi^2 = 8.99$, df = 1, $p = 0.003$ respectively), though this was not confirmed on multivariate analysis.

In the SIOPEL 1 study, tumour multifocality and extra-hepatic tumour extension (inferior vena cava and hepatic vein involvement) were so uncommon as to preclude meaningful statistical analysis of these findings. Despite the statistics, however, it was decided to consider patients presenting with extra-hepatic tumour extension as ‘high risk’ patients as it was thought that this finding highly compromises the possibility of complete tumour resection, which is the ultimate goal of the whole treatment strategy. The prognostic importance of tumour multifocality is still under study.

Thus, based on the SIOP Liver Tumour Study Group experience gained from the previous studies, and in accord with other data emerging from the literature, two different HB ‘risk groups’ can now be identified:

**The group with the more favourable prognosis - ‘standard (previously called ‘low’) risk’ HB** - includes those HB involving 1, 2 or 3 hepatic sections PRETEXT I, II & III - (see
Pre-treatment tumour extension system - Section 5.0) and entirely confined to the liver (no metastases - no extra-hepatic extension). These patients will be randomised to receive either single agent CDDP (as piloted in SIOPEL 2) or the PLADO regimen used in SIOPEL 1. (Note that for SIOPEL 3 ‘standard risk’ is used instead of ‘low risk’ to give a more accurate reflection of prognosis.)

**The group with the less favourable prognosis - 'high risk' HB** - includes those HB involving all 4 hepatic sections PRETEXT IV - (See Pre-treatment tumour extension system - Section 5.0) and/or with evidence of extra-hepatic disease (metastases and/or extra-hepatic abdominal disease). For these patients a single arm study of an intensive chemotherapy regimen including CARBOPLATIN, CDDP and DOXO, will be evaluated.

From the SIOPEL-1 experience, we acknowledge possible difficulties in the precise determination of pre-treatment extent of disease, e.g large PRETEXT III tumour for which one has to decide whether the possible remaining free section is (a) displaced or (b) infiltrated. Generally, a tendency to over-estimate tumour extension has been noted in the ‘difficult’ cases. In the SIOPEL 2 study, for instance, more ‘low risk’ HBs have been classified as ‘high risk’ than vice versa. To minimise this problem and reduce the number of cases requiring a change in PRETEXT classification, and since it is not feasible to ask for central review of the initial radiological findings of all patients entering the SIOPEL 3 study, it was decided to offer rapid evaluation of these difficult cases by a panel of experts from the SIOP Liver Tumour Study Group, if the referring centre requests it.

In the SIOPEL 1 study PRETEXT I, II and III patients had a 2-year OS of 100%, 94% and 70% respectively; the corresponding figures for EFS were 100%, 83% and 62%. For PRETEXT IV the figures were 0S - 68%, EFS - 44%. Thus, PRETEXT III patients have an intermediate survival rate and a case could be made for allocating them to 'high' or 'low' risk categories. In the SIOPEL 2 pilot study PRETEXT III patients responded as well as PRETEXT I and II patients to CDDP alone. Furthermore, unifocal PRETEXT III HB, without inferior vena cava and/or hepatic vein involvement (conditions which by themselves allocate a child to the 'high risk' category - see above), should almost by definition be ‘resectable’ tumours. Thus, though we strongly recommend that centres seek advice in the case of questionable PRETEXT III HB (see rapid central evaluation of tumour extension - Section 6.6), it was elected to leave these patients within the 'standard risk' category, as in the SIOPEL 2 pilot study.
In summary, the 'standard risk' category should identify those HB which should be resectable at diagnosis (the exception of those small or large HB centrally located is acknowledged), while the 'high risk' category is for those tumours which are not amenable to radical surgery at presentation. In the SIOPEL 1 study the ratio between the so called 'standard risk' and 'high risk' HB patients is approximately 1.8/1.

**Why Cisplatin alone as one arm of the randomised study for 'low risk' HB?**

The PLADO regime was remarkably successful but, although the incidence of documented cardiotoxicity is at present low, there is a real risk of late cardiomyopathy, especially as children with HB have a very young (mean 20 months) median age at diagnosis - a known risk factor for cardiac damage. An effective anthracycline-free regime would eliminate the risk of cardiomyopathy in a population of children with an otherwise full life expectancy.

What is the evidence that doxorubicin 'adds' to cisplatin in HB treatment? In 1994, the Intergroup HB study published the preliminary results of their prospective randomised study, launched in 1989 designed to test the curability of these tumours with an anthracycline-free regimen (21). The combination CDDP-DOXO was tested against a regimen containing CDDP, 5-FU and Vincristine (VCR). The end-points of the comparison were the OS and disease-free survival (DFS), and the toxicity of these regimens. They achieved 71% and 63% 3-year OS and DFS with no differences between the two arms and with no cardiac toxicity in the anthracycline-free regimen. There were several major cardiotoxicities and 7 toxic deaths in the CDDP-DOXO arm of the study. Thus, they claimed that

"The regimen CDDP, 5-FU and VCR was associated with minimal toxicity, was equally effective as the CDDP, DOXO iv c.i. regimen and should presently be considered the treatment of choice for childhood HB".(21)

One decade before this report, Evans et al published the results of the first two cooperative prospective single-arm studies run by the CCSG in the 1970s on childhood "hepatoma" (mostly hepatoblastoma) (11). The chemotherapy they used for all patients consisted of two different pulses of chemotherapy delivered alternately at intervals of three weeks. The first pulse consisted of VCR 1.5 mg/m\(^2\)/day 1, Cyclophosphamide (CPM) 600 mg/m\(^2\)/day 2, and DOXO 25 mg/m\(^2\)/days 1, 2 and 3. The second pulse at three weeks consisted of VCR 1.5 mg/m\(^2\)/day 22, CPM 600 mg/m\(^2\)/day 23, and 5-FU 500 mg/m\(^2\) orally days 24, and 30. The 3
year OS of children affected by HB was of the order of 30%, with only a few survivors reported among children with unresectable tumours at diagnosis and with metastases.

Why did these two quite similar regimens - the "VCR, CDDP, 5-FU" of the Intergroup HB Trial and the "VCR, CPM, 5-FU/DOXO" of the old CCSG study - give such different results? A likely explanation is the use of CDDP in the former regimen, but improvement in surgical techniques and supportive procedures during the period may also be relevant.

**What single agent data is there for Cisplatin?**

In 1985, Douglass reported 4 significant responses in 5 children affected by recurrent or progressive HB treated with CDDP alone (9). More recently, in 1991, Black published a series of 7 consecutive newly-diagnosed children with HB treated pre-operatively with CDDP 150 mg/m² alone (1). Each had a bi-lobar tumour, with lung metastases in 3 and bone marrow seeding in one. Six of the seven patients had volumetric tumour reduction documented on CT scan. Six had surgery and the histologic assessment of the surgical specimens revealed no viable tumour in 1, more than 95% necrosis in 3, more than 75% necrosis in 1 and 20% necrosis in the remaining patient. Lung metastases disappeared in two patients and in the third they reduced in size. However 5/7 patients died (3 of tumour, 2 of surgical complications). At the time of publication two children survived without evidence of disease at 22 and 14 months respectively (one of these had presented with lung metastases). The tumour response rate of this series is quite impressive despite the poor survival rate. However, it should be noted that all the patients of this series had unfavourable clinical characteristics at presentation and, by the risk criteria set for SIOPEL 3, would have been treated with the 'high risk' regime and not cisplatin alone.

**Why CDDP and not CARBO?**

CDDP is not a "friendly" drug. It requires hospital admission for its administration and careful monitoring during infusion.

The nephro- and ototoxicity of CDDP are a matter of concern. However, its toxicity in the SIOPEL 1 study, in which CDDP was used at 80 mg/m² as a 24 hour continuous infusion, was low. Tables 1 & 2 show the reported oto- and nephrotoxicity data:
Table 1 OTOTOXICITY - Detailed information on 96 patients enrolled into the SIOPEL 1 study.

<table>
<thead>
<tr>
<th>Hearing loss *</th>
<th>&lt;4 years</th>
<th>&gt;4 years</th>
<th>Total n. = 96</th>
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<tr>
<td>Grade 1</td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Grade 2</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Grade 3</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Grade 4</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>8</td>
<td>19</td>
<td>27</td>
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* Graded by the Brock system (3)

Table 2 NEPHROTOXICITY - Data on 57 patients from the SIOPEL 1 study.

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<th>GFR reduction measured by</th>
<th>N. pts studied</th>
<th>N. pts with low GFR</th>
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<tr>
<td>51Cr EDTA</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Creatinine clearance**</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>TOTAL</td>
<td>57</td>
<td>10</td>
</tr>
</tbody>
</table>

** The data related to creatinine clearance should be interpreted bearing in mind the greater overall accuracy of GFR measurement, especially in infants.

It is worthwhile noting that the glomerular toxicity of CDDP often improves after stopping therapy (4).

Due to the concurrent use of DOXO we cannot make any comments on the contribution of CDDP to myelotoxicity in the SIOPEL 1 study (see Table 3). However, it is worthwhile remembering that CDDP by itself has relatively little myelotoxicity.
CARBOPLATIN, a platin analogue of CDDP, is neither nephro- nor ototoxic but neutropenia and particularly thrombocytopenia are very common. Consequently blood products, and possible admissions for broad spectrum antibiotic cover in case of fever and neutropenia, are part of the supportive therapy for all patients treated with this drug. On the other hand, CARBO is a "friendly" drug which is easy to administer on an out-patient basis, with relatively little fluid throughput during infusion.

There is, as yet, no head-to-head comparison of CDDP and CARBO in childhood HB. Single arm pilot studies of CARBOPLATIN-containing regimens demonstrate that some patients respond but there is concern that CARBO may be less effective than CDDP.(7)

Considering the high efficacy of CDDP in childhood HB and its low toxicity experienced in SIOPEL I, when CDDP was used at a relatively low dose and in continuous infusion, and the uncertain anti-tumour efficacy of CARBO, we favoured the use of CDDP instead of CARBO.

Why still PLADO for the second arm of the randomised study instead of the CDDP, Vincristine and 5-FU combination?

As already mentioned, in 1994, the Intergroup HB study published an abstract regarding a prospective randomised study launched in 1989 comparing the combinations CDDP-DOXO and CDDP, 5-FU and VCR. They claimed in their preliminary report that: "the regimen CDDP, 5-FU and VCR was associated with minimal toxicity and was equally effective as the CDDP, DOXO iv c.i. regimen "(21). In contrast to their experience, PLADO as used in SIOPEL 1 study did not cause the toxicity problems reported for this arm of the Intergroup Study. The single dose as well as the cumulative dose of DOXO were significantly less in the SIOPEL 1 study than in the American CDDP/DOXO combination (60 vs 80 mg/m² single dose and 360 vs 480 mg/m² total). The total cumulative dose of DOXO in the SIOPEL 3 PLADO arm will also be slightly lower than that used in the SIOPEL 1 study because the

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<td>N. courses complicated by</td>
<td>%</td>
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<tr>
<td>Septicaemia</td>
<td>17</td>
<td>3%</td>
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<td>Grade 3 infection</td>
<td>13</td>
<td>2%</td>
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<tr>
<td>Febrile Neutropenia</td>
<td>147</td>
<td>26%</td>
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Table 3  TOXICITY - Data from the SIOPEL 1 study - Infections and neutropenia -
no. of courses = 569
first course is replaced by CDDP alone. (See treatment strategy). Furthermore, the "equal effectiveness" of the two regimens used in the Intergroup study must be tempered by the low statistical power of the study. Thus, the SIOP Liver Tumour Study Committee thought it more appropriate to continue with its own experience of PLADO and to run a randomised study comparing PLADO with CDDP alone.

**What to do for 'high risk' hepatoblastoma?**

The main objective of the present clinical research for 'high risk' HB is to improve the EFS and OS. The cure rate of these children (as discussed in the Section 'Prognostic Factors in Childhood HB') is quite unsatisfactory. The main therapeutic problem is represented by the difficulties in reaching a complete resection. In fact, these tumours are unresectable by definition, because of the local tumour extension, or because of the presence of lung metastases. Thus, one should rely on the use of systemic chemotherapy in the hope of reaching a tumour status amenable to surgical resection. Consequently, the way to improve the EFS/OS of these patients is to intensify and improve the systemic treatment. The possible research strategies which can be conceived for achieving this goal are: i) to intensify the present regimens (using and combining the drugs presently known to be effective against these tumours), or: ii) to look for new effective drugs to be incorporated in future phase III trials, adopting the so-called "pre-treatment phase II research window" in untreated patients. The less favourable outcome of these patients could justify the latter approach. No research group has so far been able to run satisfactory classical phase II studies on relapsing HB.

Due to the small number of 'high risk' HB patients who are expected to be recruited into the SIOPEL 3 study, neither of these two research strategies can be incorporated into prospective randomised trials. Thus, only a series of consecutive prospective single arm studies, designed to be suitable for comparison with a historical control, can be conceived.

For now, the SIOPEL 3 Committee has elected, for the 'high risk' HB group, to intensify therapy using drugs currently available. The use of the "pre-treatment phase II research window" to test, up front, new drugs will be considered for the future generation of 'high risk' studies.

In SIOPEL 1, in which cisplatin containing pre-operative chemotherapy was used, the treatment results obtained for these patients are among the best so far reported by the various national and international Study Groups. Thus, there was a consensus for moving forward in research on these subjects by maintaining, as a backbone of the treatment
strategy, the combination CDDP/DOXO. There was also agreement to intensify the use of the platinum derived agents according to the philosophy already used for other malignant solid tumours, which sees the alternating use of myelotoxic and non-myelotoxic agents. Because CDDP is minimally myelotoxic, it was thought to be a suitable drug to be incorporated into such a schema. Other potentially effective drugs, such as VCR and 5-FU do not seem very promising. In this regard, it is worth noting that the Intergroup Hepatoma Study (combining the CCSG and POG Liver Study Groups) is planning to launch a randomised study for those HB which cannot be resected straightaway and/or presenting with metastases (the SIOPEL 3 'high risk' group), comparing their historical regimen (VCR/CDDP/5-FU) with an alternating fifteen day regimen including CDDP and CARBO only (very similar to that designed for the SIOPEL 3 study), and dropping 5-FU. A recent update of the treatment results achieved in the previous Intergroup Hepatoblastoma Study in children with HB and lung metastases with the CDDP, VCR, 5-FU regimen, projects a 3-year OS on the 30% range (while in the SIOPEL 1 study the 2-year OS stands at 66%). The alternating administration of CDDP and CARBO has the theoretical advantage of giving to a single patient more platinum-derived drugs, more intensively. The different toxic profile of these drugs should not expose the patient to excessive toxicity.

**Main data derived from the SIOPEL 2 Pilot Study**

Before launching a comprehensive prospective randomised trial of PLADO vs CDDP alone and recommending the use of the intensive regimen designed for the 'high risk' HB it seemed reasonable to have first a pilot phase in order: 1) to substantiate the data which already exist on the use of CDDP alone in childhood HB; 2) to allay the possible concerns about the use of 'monotherapy' for a human malignancy; and 3) to test the effectiveness and toxicity of the combination CARBO, CDDP, DOXO.

The SIOPEL 2 Pilot study opened to patient registration in October 1995. As of 31st October 1997, 86 HB patients - 47 'low risk' and 39 'high risk' patients - have been enrolled in the trial, with an average recruitment rate of 41 new cases per year. The "responses" to the main questions the pilot study aimed to answer were as follows. The preliminary response rate obtained in the "CDDP alone" arm is 77.8% ± 6.9, with a resection rate of 79%. The resection rate turned out to be high and the response rate to CDDP is gratifying but possibly lower than expected. This was perhaps because in SIOPEL 2 the treating physicians were asked to pay special attention to monitoring of tumour response. A careful retrospective review of every patient entered into the trial by the SIOPEL committee revealed a very conservative attitude by the treating physicians in attributing tumour response to CDDP.
This was particularly true of some of the early cases enrolled. For instance, 2 patients considered to have 'stable disease' (and moved to the 'high risk' protocol) could more accurately be described as having a 'slowly-responding' tumour (stable tumour volume with a consecutively decreasing $\alpha$-FP). Two other patients, who seemed to have stable disease on CDDP alone, gained, both in terms of tumour volume reduction and decreasing $\alpha$-FP, from moving to the 'high risk' regimen, while two others did not. Furthermore, it was because of this attention to monitoring tumour response that it was noted that 5 'low risk' patients whose $\alpha$-FP level initially fell in response to chemotherapy, with an associated decrease in tumour volume, had a rise in $\alpha$-FP level just prior to definitive surgery. In at least 2 patients the response was coded as PD rather than PR because of the rise in $\alpha$-FP alone but there was no mention of an increase in tumour volume in these children. These are the only 2 patients whose response to CDDP has been reported as progressive disease (PD). Four of the 5 patients who had a rising $\alpha$-FP just before surgery, for whom data on definitive surgery is available, had complete tumour resection. Only one of them relapsed subsequently. Retrospective review of the SIOPEL 1 data reveals 8 children whose tumour response was coded as PR but actually had a rising $\alpha$-FP just before surgery. All these patients had a complete resection and only one subsequently relapsed.

The CDDP regimen in SIOPEL 2 - exactly the same as proposed for SIOPEL 3 - was very well tolerated. Two week intervals were scheduled between courses and the median time interval between courses 1 to 2, 2 to 3 and 3 to 4 was exactly 14 days. Myelotoxicity was minimal and no episodes of oto- or nephrotoxicity have been reported.

As expected the chemotherapy regimen designed for the 'high risk' HB was more toxic. The time interval between the first four drug administrations varied from 14 to 16.5 days and then increased for the next two courses to 20.5 and 21 days respectively. Almost 47% of the courses of chemotherapy were complicated by fever and neutropenia. Thirty-eight packed red blood cell and 22 platelet transfusions were required in the 93 courses for which we have toxicity data. No oto- or nephrotoxicity or cardiotoxic events have been reported. For the 22 evaluable patients, the tumour response rate has been 77.3% + 8.9 with a complete resection rate of 50%.

In summary, the preliminary data of the SIOPEL 2 pilot study indicate that:

- for 'low risk', now called 'standard risk', HB monotherapy with CDDP is feasible and effective, and
- that for this tumour a randomisation comparing the historical PLADO with the "CDDP alone" arm can be conducted with little likelihood of prejudicing the survival of children in the single agent arm, and the advantage of avoiding anthracycline therapy;
that the chemotherapy regimen designed for the 'high risk' HB is feasible. It remains to be shown in a larger patient population whether the "price" (in terms of hospitalisation, discomfort and 'late effects') is justified.

2.0 MAIN OBJECTIVES

'STANDARD RISK' HB  To determine whether or not Cisplatin (CDDP) alone is as effective as the cisplatin (CDDP)/ Doxorubicin (DOXO) combination PLADO in terms of both tumour response to chemotherapy and complete resection rate, and less toxic for 'standard risk' childhood HB. (The comparison between the two regimens in terms of effectiveness will be based on resection rate (primary end-point) and also response rate, overall survival and event-free survival (secondary end-point - see also SR 6.1 and SR 6.2).

'HIGH RISK' HB AND ALL HCC  Using an historical control, to evaluate whether an intensive multi-agent chemotherapy regimen including CARBO, CDDP and DOXO improves the response rate to chemotherapy and subsequent resection rate of children affected by a 'high risk' HB or HCC.

All HB  To continue to collect biological materials derived from HB patients and their families in order to facilitate basic research on this rare tumour.

OTHER OBJECTIVES

Other objectives of this study include: (a) an improvement in knowledge of the biology of HB; (b) better clinical care; and (c) a better quality of life for long term-HB survivors.

The SIOPEL 3 study will also serve to further validate the pre-treatment tumour extension system (PRETEXT) adopted for the previous SIOPEL studies.

The study also aims to evaluate the feasibility of rapid central review for 'difficult' patients, by a panel of experts, of tumour extent and resectability.

For relapsed HB patients, the study also aims to evaluate a series of salvage therapies (initially high dose cyclophosphamide, with mesna).
For HB patients, whose primary tumour remains unresectable after chemotherapy, the study also aims to expand on the role of liver transplantation, which, from the preliminary results from SIOPEL 1, is a realistic option for carefully selected patients.

3.0 OVERALL STUDY DESIGN - HEPATOBLASTOMA STUDY CONCEPTS (FIG 1) AND FLOW DIAGRAM (FIG 2)

3.1 STUDY DESIGN

3.1.1 Diagnostic procedures. All children aged less than 16 years with a suspected primary liver tumour will undergo a diagnostic biopsy (see surgical guidelines, Section 7.0). The biopsy is mandatory for children aged less than 6 months or over 3 years, or if presenting with a normal serum $\alpha$-FP level. In case of unequivocal clinical findings (e.g. age between 6 months and 3 years, with a solid hepatic mass, associated with elevated serum alpha fetoprotein ($\alpha$-FP) value and maybe with thrombocytosis) the decision about performing the initial, diagnostic surgical biopsy is left to the individual centre. However, biopsy is strongly recommended if there is doubt about the diagnosis. If no biopsy is performed compatible imaging and a raised serum $\alpha$-FP level (for age) are mandatory for entering patients into the study. 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.

3.1.2 Pre-treatment tumour extension evaluation - At the same time as or soon after the diagnostic procedures an accurate pre-treatment tumour extension evaluation should be performed and a definitive PRETEXT category assigned. (see Section 5.0). All patients must have a lung CT scan to document the presence or absence of metastatic disease and ensure allocation to the correct 'risk' category. In case of discrepancy between chest X-ray and lung CT (ie negative chest x-Ray and positive lung CT, a review panel can be consulted for a rapid definitive opinion (see Section 6.6)). Subsequently, each patient will be allocated to one of the two risk categories.

3.1.3 First course of chemotherapy - The entire treatment strategy is based on pre-operative chemotherapy. All patients, regardless of the risk category to which they are allocated, will start therapy with a single dose of CDDP. In the time interval between the first dose of CDDP and the subsequent course of chemotherapy (15
days) central review by a panel of experts of the initial pre-treatment tumour extension findings can take place, if required. The course of CDDP should be started within 15 days of diagnosis.

3.1.4 Further treatment - Additional treatment will depend upon the risk category. 'Standard risk' HB patients will be randomised to receive either "PLADO" or the "CDDP alone" arm. 'High risk' HB patients will proceed with the chemotherapy regimen called "Super PLADO".

3.1.5 Delayed surgery - At the end of pre-operative chemotherapy the feasibility of definitive tumour resection will be considered. In case of a 'responding' (to chemotherapy) HB which remains unresectable at the end of preoperative chemotherapy, surgery can be postponed until completion of the whole chemotherapeutic programme.

3.1.6 Post-operative chemotherapy - After delayed surgery, all patients will continue with the same chemotherapy as that given pre-operatively, unless the entire course has already been completed, eg in the case of a ‘slow responder’ (see 3.1.5).

3.2 Study concepts

The importance of complete tumour resection - Only complete tumour resection gives realistic hope of cure for children with HB. No long-term complete tumour disappearances (complete remission) with chemotherapy alone were seen in SIOPEL 1. Thus, the ultimate goal of the treatment in SIOPEL 3 is to aim to achieve a high complete tumour resection rate. This implies also 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. For centres which require assistance in making the final decision on tumour resectability and of the techniques to use, the option of a rapid consultation with a panel of experts (including a liver transplant expert) is available. (see section 7.3)

Not too much chemotherapy! - Past experience has taught that there is little to be gained from prolonging conventional chemotherapy beyond the planned treatment regimen. In other words, delayed surgery should be carried out according to the timing laid out in the protocol. Prolonging chemotherapy beyond the total number of
courses recommended is unlikely to result in an unresectable tumour becoming resectable, so other options, including liver transplant, should be considered.

**Radiotherapy** - Radiotherapy has not yet found a definitive role in the treatment of HB. Thus, its use is limited to very selected cases (but see Addendum V).
SIOPEL 3 Study
Overall Study Design
(Hepatoblastoma)

* Under certain circumstances surgery can be delayed until all chemotherapy has been completed (See 3.1.5)
**SIOPEL 3 study - Hepatoblastoma Flow Diagram**

All eligible HB patients

- Tumour extent
- PRETEXT category

\[ \downarrow \]

Initial CDDP alone
(all patients)

- PRETEXT I, II & III
  - NO V; P; E*; M,

  \[ \downarrow \]

Randomisation

- PLADO
- CDDP ALONE

- PRETEXT IV
  - +/- V; P; E*, M,
  - or PRETEXT I, II, III
  - + V; P; E*; M

\[ \downarrow \]

Super PLADO

* NB Enlarged lymph nodes on radiological investigation are not considered a reason for entering the patient onto the high risk study.
4.0 DEFINITION OF RISK CATEGORIES

'Standard risk' HB - Patients with single, or apparently multifocal, tumours involving at the most 3 hepatic sections - PRETEXT I, II & III, entirely confined to the liver (no metastases (ie negative lung CT) - and with no extra-hepatic abdominal disease, ie no V,P,E,M) - (see pre-treatment tumour extension system - Section 5.0).

'High risk' HB - Tumours involving: a) all 4 hepatic sections - PRETEXT IV, and/or (b) evidence of extra-hepatic disease (metastases and/or extra-hepatic abdominal disease, ie with any of V,P,E or M) (see pre-treatment tumour extension system - Section 5.0).

Lung metastases - All "unequivocal" (See Section 5.3 'Chest') pulmonary lesions documented on the chest X-Ray and/or lung CT scan considered to be metastatic tumour deposits. To assure a more consistent assessment of cases where there is a discrepancy between chest X-ray and lung CT, or other difficulties, rapid central radiology review is recommended.

NB: For any unusual clinical findings, which do not easily fit the above categories, please contact the study coordinator(s).

5.0 PRE-TREATMENT TUMOUR EXTENSION (PRETEXT) SYSTEM

5.1 GENERAL CONSIDERATIONS

The system adopted to describe pre-treatment tumour extension has been called PRETEXT. It has been conceived to describe tumour extension before any therapeutic intervention. Such a system is essential for a study such as SIOP-EL 3, which is based on pre-operative chemotherapy. It also serves to assign patients to risk categories ('standard' and 'high'). (For Background and Rationale see Section 1.0).

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 sections. The left hemiliver consists of a left lateral section (Couinaud segments 2 and 3) and a left medial section (Couinaud segments 4 and left part of 1). The right hemiliver consists of a right posterior section (Couinaud segments 6 and 7) and right medial section (Couinaud segments 5 and 8 and
right part of 1). (Note that there is now international agreement that the term ‘sector’ used in SIOPEL 2 should be replaced by ‘section’).

Since surgical resection is a crucial prognostic factor, the healthy sections that can be left in place determine the outcome. PRETEXT aims to predict the anatomical configuration of the healthy liver tissue remaining after resection. It is purely descriptive and is derived as follows:

- **PRETEXT** (depicted in Figure 3)
  The PRETEXT number reflects the numbers of sections that are free of tumour (or involved):

  - **PRETEXT I** Three adjoining sections free, one section involved
  - **PRETEXT II** Two adjoining sections free, two sections involved
  - **PRETEXT III** Two non adjoining sections or just one section free, in the latter case three sections are involved
  - **PRETEXT IV** No free section, all four sections involved

  (See Fig. 3 for possible variations).

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 (next section - Extent).

- **Extent**
  Extension of the tumour beyond the liver should also be indicated *:

  "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 braches 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 are not considered a reason for entering the patient on to the high risk study.)
  "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.

- **Volume** Calculation of the actual tumour volume will not influence the final allocation of a tumour into one of the four PRETEXT categories. However,
this data will be collected to evaluate the possible impact on patient outcome and to try to monitor, as accurately as possible, tumour response to therapy. In SIOPEL 3 the “volume” will be defined, for ease of calculation, as the actual product of the 3 maximum perpendicular diameters.

Thus the definitive tumour group will be expressed in terms of:

* PRETEXT category I - IV
* Extent V, P, E and M
* Volume The “volume” will be calculated as the actual product of the 3 maximum perpendicular diameters.

When is tumour extension assessed?

During therapy tumour response monitoring can be assessed, with some accuracy, by routine physical examination, serial serum α-FP assessments and possibly abdominal ultrasound. However, definitive evaluations of tumour extent are required at diagnosis and before delayed surgery.

Pre-operative tumour extension evaluation is primarily to try to predict the surgical findings and the probable extent of necessary hepatic resection.

Note:

i) Pedunculated tumours are considered to be confined to the liver and to occupy only the section from which they originate.

ii) Tumour rupture does not automatically assign a patient to the ‘high risk’ regimen. Patients should be classified according to the PRETEXT category.
INVASION (III)  DISPLACEMENT (II)

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

For further clarifications see detailed text Section 5.0
5.2 RADIOLOGICAL INVESTIGATIONS REQUIRED TO STAGE PATIENTS APPROPRIATELY

The extent of disease (PRETEXT) is assessed from pre-treatment imaging, preferably ultrasound, with contrast enhanced abdominal CT scan or MRI with Gadolinium. The imaging radiologist must also determine the three maximum diameters of the lesion.

Both a chest X-ray (PA and lateral) and a CT scan of the thorax will be used to determine the presence of pulmonary metastases. To overcome the problem of atelectasis on CT scan of the chest, in doubtful cases, discuss with your paediatric anaesthetist the possibility of repeating the examination in the prone position.

No central review of the diagnostic images is required to enter patients into the trial but central review may become possible, in the future, when digital image transmission has further developed. However, as outlined in Section 6.6 there is the possibility of a rapid review of difficult cases, if required.

The assignment of the PRETEXT category should be by collaborative consent between the treating oncologist, radiologist and surgeon at the individual centre. The appropriate form should be returned by the data manager or other person responsible for returning all the trial forms.

5.3 GUIDELINES FOR RADIOLOGICAL INVESTIGATIONS

What to do?

To improve the reliability and confidence of diagnostic imaging in children with liver tumours the following points should be taken into consideration.

1. The most important is not to ask for routine CT examinations of chest and abdomen just 'because of the protocol', but to ask the radiologist in every individual (rare) case of a hepatic mass to provide an answer on specific questions (eg about the vascular anatomy), and to leave it to the discretion of the local doctors to decide on the imaging technique by which this information should be obtained (eg by combining CT with ultrasound (US) including Doppler studies, or by MRI).

Abdomen
2. Technical CT aspects, which are often neglected, include:
   - series both without and with contrast enhancement (tumour may be partly obscured by liver enhancement);
   - appropriate timing of CT exam after intravenous contrast injection (often too early, or too late);
- use maximum picture area allowed by film format;
- always put calibration on film, to allow post-process measurements.

3. Medical CT aspects include:
- improve skills in both looking at the tumour and its extension, and looking at the remaining part of the liver and its vascular anatomy;
- improve quality of films by taking care of proper window/centre setting for each series, by the radiologist in person.

4. Improve skills in performing US and Doppler studies, alone, or in addition to CT to assess the condition/patency of hepatic vessels (hepatic and portal veins, inferior vena cava).

5. Cooperation between radiologist and surgeon, especially in the pre-operative assessment, may considerably increase the reliability of the anatomical information.

6. Angiography, intravenous urography and nuclear studies have no place in the routine assessment of a child with a presumptive liver tumour. Angiography may be indicated in rare cases to exclude vascular anomalies when complicated surgery is anticipated.

Chest
7. A correctly performed chest CT in the initial phase (with often very large abdominal tumour) is hampered by elevation of the diaphragm, giving rise to compression atelectasis of the basal and posterior portions of the lungs. Also movement artefacts (breathing) play a role in disturbing the CT image. Therefore, in most cases CT of the chest provides no more reliable information than plain radiography, in combination with fluoroscopy, if necessary. However, until more data are collected regarding the comparison between chest X-ray and chest CT in staging childhood HB, chest CT scan at diagnosis is still mandatory.

8. In case of a normal chest X-ray, the demonstration by CT of small lung metastases is of value. For very young children the chest CT may need to be performed under general anaesthetic. In case of posterior atelectasis one should be prepared to turn the patient in prone position and to make an additional series of CT images. Where there is a discrepancy between the
chest X-ray and CT findings, rapid central radiological review is recommended for a confirmatory opinion prior to randomisation (see Section 6.6).

**Technical difficulties**

**CT**
- inadequate W/C setting
- inadequate timing of contrast enhancement
- non contiguous slices and movement artefacts
- pulsating heart apex may cause blurring in segments II and IVb

**US**
- improper selection of transducers
- inadequate gain setting
- under-estimation of extent of tumour in case of extensive calcification

**MRI**
- movement artefacts
- omitting of transverse cuts
- inadequate sequences

**Imaging Advice**

1. Analysis at diagnosis
   
   **US** - To demonstrate the hepatic origin of the mass
   - To assess the vascular anatomy of the remaining liver (-/+ Doppler)
   - To allow initial assessment of PRETEXT category

   **Abdominal CT** - (standard or spiral)

   **Chest X-ray** (possibly combined with fluoroscopy)

2. Assessment during pre-operative chemotherapy
   
   **Abdominal US**
   **Chest X-ray**

3. Pre-operative assessment
   
   **Abdomen:**
   - assessment of relationships of tumour with adjacent vital structures
- demonstration of segmental/vascular anatomy of the remaining liver
  Both may be done by CT in combination with US/Doppler, or by precise MR imaging.

Chest:
- assessment of presence/absence of lung metastases.
  This is best done by CT.

6.0 ELIGIBILITY CRITERIA AND PATIENT REGISTRATION

6.1 GENERAL NOTES

All Centres, having completed a Form of Participation for the study, are required:

- to register with the Trial Office, within 3 working days of diagnosis, all patients affected by HB and HCC;
- to randomise all eligible ‘standard risk’ patients;
- to provide histological material for central review;
- to send to the Trial Office the data collection forms according to the outlined Schedule of Form Return (See Addendum X)

Prior to registering the first patient, all centres must seek approval for the study by their Local Ethical Committee, according to local practice. Written notification of local ethical approval should be sent to the UKCCSG Data Centre.

6.2 ELIGIBILITY CRITERIA

6.2.1 GENERAL CRITERIA FOR PATIENT ELIGIBILITY

Age: Children less than 16 years of age at the time of diagnosis.

Previous treatment:
None. All patients including those having had, or requiring, primary tumour resection (complete or incomplete), for whatever reason, should be entered into the study. The reason for primary surgery should be specified. Patients who have had primary surgery will be analysed separately.

Diagnosis:
Hepatoblastoma (see also histological considerations - Section 8.0).

**Diagnostic surgical biopsy is strongly recommended for all patients and is mandatory in the following:**

- children under six months of age because of the wide range of possible tumours presenting at this age and the possible confounding effect of an elevated $\alpha$-FP level just because of the age of the child (see Addendum VIII);
- children older than 3 years of age to distinguish HB from hepatocellular carcinoma;
- all patients with a normal serum $\alpha$-FP.

In other cases, if clinical findings are unequivocal (e.g. age between 6 months and 3 years, with a solid hepatic mass, associated with elevated serum $\alpha$-FP value and maybe with thrombocytosis) the decision to perform the initial, diagnostic surgical biopsy is left to each individual centre (31). **If no biopsy is performed, compatible imaging and raised serum $\alpha$-FP level are mandatory for entering patients into the study.**

- **Time to start therapy:** children must begin chemotherapy within 15 days of diagnosis.

It is strongly recommended that the Trial Office is notified also of all patients treated with primary surgery. These patients should be registered using the study forms and, following review of the reasons why they were treated with primary surgery, will be analysed separately. It is recommended that these patients should be treated according to the historical arm, ie with 4 courses of PLADO.

### 6.2.2 ELIGIBILITY CRITERIA FOR PATIENT RANDOMISATION

All patients with a ‘standard risk’ HB are eligible for the randomised trial. For detailed eligibility criteria see SR 2.0.

All 'standard risk' HB patients eligible for randomisation but not randomised because of parental refusal, or any other reason, will be registered in the study but analysed separately.
See Figure 4 for Flow Sheet of Registration and Randomisation Procedures for All Liver Tumours and Figure 5 for Registration and Randomisation Procedures - Hepatoblastoma.
Figure 4

SIOPEL 3
Registration and Randomisation Procedures
All Liver Tumours

Register within 3 working days of diagnosis:
All children with liver tumours

Trial Number assigned at registration

- HB
  - See next flow sheet

- HCC
  - Enter trial?
    - Yes
      - If resectable - primary surgery followed by chemotherapy according to High Risk protocol (up to day 85)
      - If not resectable - chemotherapy according to High Risk protocol and monitor response
      - Notify use and outcome of any other therapeutic strategies
    - No
      - Record reasons for not entering trial e.g. parental refusal or previous surgery.
      - Notify use and outcome of any other therapeutic strategies
      - These patients will be analysed separately

- Non HB, Non HCC Liver Tumours
  - Register and send details of therapy and follow-up

If relapsing and/or resistant
PHASE II STUDY
(see Addendum VI)

(Siopel 3 (final) May 98)
SIOPEL 3
Registration and Randomisation Procedures
Hepatoblastoma

Figure 5

HB

Unknown Risk

Standard Risk

High Risk

Rapid Review

Enter trial?

Yes

No

RANDOMISE BEFORE DAY 15 FOLLOWING START OF FIRST CDDP COURSE between the two treatments according to Standard Risk protocol.

Record reasons for not entering trial e.g. parental refusal or previous surgery. These patients will be analysed separately.

Record reasons for not entering trial e.g. parental refusal or previous surgery. These patients will be analysed separately.

Enter trial?

Yes

No

If relapsing and/or resistant

PHASE II STUDY
(see Addendum VI)
6.3 PATIENT REGISTRATION

The Trial Office of the SIOP EL 3 study is:

UKCCSG Data Centre
University of Leicester University
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

The contact person for patient registration/randomisation, and all queries relating to trial form return for SIOP EL 3, 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).

All liver tumour patients should, within 3 working days of diagnosis and preferably before starting therapy, be notified to the UKCCSG Data Centre by sending the Registration Form by FAX. Receipt of the Registration Form will be acknowledged by return fax, giving the trial number, and reminding the referring centre that the patient may be eligible for subsequent randomisation. Further trial forms will be sent out on receipt of the Registration Form. (Note that the Registration Form should still be sent within 3 working days of diagnosis, even if central radiology review is being sought). All patients should be registered and then reasons for not entering the study should be notified (e.g. parental refusal, previous treatment, etc.).

Subsequently two unstained and two stained slides of the tumour biopsy specimen should be sent to the Trial Office for central review. (On receipt of the Pathology Registration Form - A (Form 2.1) in the UKCCSG Data Centre, the specimens will be requested from the referring centre by letter, outlining material required. Once received, specimens will then be forwarded to the panel chairman for review).

Please, remember to notify the tissue bank as soon as possible when a malignant hepatic mass is suspected in a child, and before biopsy, in order to satisfy all the necessary procedures for the centralisation of the biological material. (See Addendum III).
Non HB, non HCC Liver Tumours in Children
As in SIOPEL I and 2 we would like to continue to keep a record of other rare liver tumours in children (non HB, non HCC) and ask you to register these as well and also supply details of therapy and follow up.

6.4 Randomisation Procedures ('Standard Risk' Patients Only)
All patients affected by HB considered to be 'standard risk' and eligible for randomisation must be randomised not more than 15 days after starting therapy since all patients, regardless of the risk category, will start therapy with a single dose of CDDP. This "common" initial drug treatment has been introduced to allow, where necessary, a rapid central review of the initial diagnostic radiological findings (on which the risk group allocation is based - see Section 6.6), without delaying institution of therapy.

Thus, for those patients for whom no central review of the initial diagnostic radiological findings is required, randomisation may take place at the same time as registration of the patient to the study. The Randomisation Form should be faxed to the UKCCSG Data Centre. Acknowledgement of the randomisation, and patient assignment to one of the 2 treatment regimens will be notified by a return FAX. Similarly for those patients for whom a central review of the initial diagnostic radiological findings is required, assignment to one of the 2 randomisation arms will be notified by a return FAX within one or two days of receipt of the results of the rapid review (see Section 6.6). Randomisation must take place no more than 15 days from the start of the initial course of CDDP.

Please note that for randomising a patient the following information is essential:
- patient's name, sex and date of birth
- date of diagnosis
- initial α-FP value
- initial platelet count
- histologic diagnosis*
- PRETEXT category
- tumour extent assessment, including normal lung CT scan
- Name, telephone and FAX number and e-mail address, if available, of the contacting physician
- confirmation of parental or legal guardian's acceptance of patient randomisation.
*Exceptions are accepted according to the general criteria for patient eligibility (See Section 6.2.1).

The randomisation will be stratified by PRETEXT I/II and III, and by country.

6.5 Material Necessary for Final Patient Evaluation
Tumour histology (obtained at the time of the diagnostic biopsy or at the time of delayed surgery) should be confirmed by the pathology panel of the study before considering a patient evaluable for final analysis.

6.6 PROCEDURES FOR RAPID CENTRAL REVIEW OF THE RADIOLOGICAL FINDINGS

It is acknowledged that there may be difficulties in correctly assigning some cases to the 'high' 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 minimize the risk of mis-allocating patients to risk categories, our radiological colleague, Dr Derek Roebuck has agreed to provide a service for a rapid central review of the radiological findings. This means that upon review of the films, a final opinion on a specific tumour will be formulated and forwarded urgently (by fax) to the referring centre by these experts. (A further copy of the results will be sent by fax to the UKCCSG Data Centre). A special form (Radiology Rapid Review Request - Form 3.0) has been devised for this review. The completed form and all the pertinent radiological findings must be sent by international overnight delivery, or if possible, electronically to:

Dr Derek Roebuck  
Consultant Interventional Radiologist  
Department of Radiology  
Great Ormond Street Hospital  
Great Ormond Street  
London WC1N 3JH  
UK  
Tel: +44-207-354-2165/Tel Home: +44-207-354-4324  
Air Call: +44-207-405-9200  
Fax: +44-207-242-1607  
Email: RoebuD@gosh.nhs.uk

Colleagues sending material for this rapid central review are requested to forewarn Dr. Roebuck by email (above) and also Margaret Childs, Trial Co-ordinator msc8@le.ac.uk.

Once centres have received the results of the rapid radiological review, they should consider the patient’s eligibility for randomisation.
7.0 SURGICAL GUIDELINES

7.1 PRE-TREATMENT BIOPSY

Diagnostic surgical biopsy is strongly recommended for all patients and is mandatory for the following:

- children under six months of age because of the wide range of possible tumours presenting at this age and the possible confounding effect of an elevated $\alpha$-FP level just because of the age of the child (see Addendum VII);
- children older than 3 years of age to distinguish hepatoblastoma from hepatocellular carcinoma;
- all patients with a normal serum $\alpha$-FP.

In all other cases, in the face of unequivocal clinical findings (e.g. age between 6 months and 3 years; a solid hepatic mass, associated with elevated serum alpha-fetoprotein ($\alpha$-FP) value and maybe with thrombocytosis) the decision to perform the initial, diagnostic surgical biopsy is left to each individual centre (31). In this case compatible imaging and raised serum $\alpha$-FP level are mandatory for entering patients into the study.

The reasons for recommending a biopsy are:
- to try to establish the nature of the tumour
- to collect material which may retrospectively yield prognostic information.

In SIOPEL I there were no life threatening events after biopsy. Biopsy should be obtained either by core tissue biopsy (Tru cut technique) or wedge resection through "a small laparotomy", taking at least 3 cores of tissue from different sites. The latter approach allows the surgeon to collect more material, to sample different areas and to control bleeding better. Fine needle biopsy is not recommended by the SIOPEL 3 Committee.

Laparoscopic biopsy: Laparoscopic techniques are on the increase and the procedure can also be considered in appropriately sized children. The question of assessing resectability during laparoscopic biopsy is being considered and evaluated, but not as a formal part of SIOPEL 3.

If a biopsy is to be performed, the tissue bank should be contacted as far in advance as possible to obtain the correct kit and instructions for handling the tissue. (Addendum III).

7.2 DELAYED SURGERY - GENERAL GUIDELINES
Because of the many techniques used in liver resection, it is not practical to provide comprehensive guidelines. However, some recommendations are given below:

- complete surgical removal of the tumour is the ultimate goal. When this seems impossible, it is better to refrain from attempts to do so and to opt for another strategy;
- the surgical team, including the anaesthetist, should ideally have extensive experience in paediatric liver surgery;
- advanced modern equipment for liver surgery should be readily available;
- facilities for post-operative intensive care should be optimal;
- the nutritional status of the patient should be evaluated and improved if necessary. (27)

**Microscopical Complete Surgical Resection**

As stated above, the aim of definitive surgery is the microscopical complete (margins free of tumour) resection of the tumour. This means that if, during the operation, the surgeon has any doubts about being microscopically radical, frozen sections of the resection margins should be obtained before proceeding. If positive, the surgeon should try, as long as it is reasonable and possible, to achieve a resection whose margins are tumour free. Thus the final judgement of the surgical act (if macro or microscopically complete) will depend on the final pathology report.

Please note that all possibilities should be explored before declaring a tumour unresectable. Only complete resection gives a realistic hope of cure. In this regard, for selected cases (see below), orthotopic liver transplantation must be considered a real option. Furthermore, to assist centres in taking the final decision on tumour resectability and on which techniques to use the possibility of a rapid consultation with a panel of experts (including a liver transplant expert) is made available. To obtain this consultation, please send the clinical summary of the patient and the pertinent radiological findings to:

<table>
<thead>
<tr>
<th>Dr Gordon MacKinlay</th>
<th>Dr Piotr Czauderna</th>
<th>Professor Otte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Director of Surgery</td>
<td>Department of Pediatric Surgery</td>
<td>Director of Transplant Surgery</td>
</tr>
<tr>
<td>Royal Hospital for Sick Children</td>
<td>Medical University of Gdansk</td>
<td>AZ Kinderen VUB</td>
</tr>
<tr>
<td>Sciennes Road</td>
<td>Ul Nowe Ogrody 1-6</td>
<td>Laarbeeklaan 101</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>80-803 Gdansk</td>
<td>1090 Brussels</td>
</tr>
<tr>
<td>EH9 1LF</td>
<td>Pland</td>
<td>Belgium</td>
</tr>
</tbody>
</table>

For direct contact details please see Addendum II of Protocol

**NB:**
• Patients treated with DOXO must have an echocardiogram after completion of pre-operative chemotherapy and prior to surgery, and the results must be reviewed by the paediatric oncologist and/or the anaesthetist.

• Contact the surgical coordinator or study chairman immediately to report any unusual/unexpected surgical complications or perioperative deaths.

• For suggestions on treatment of patients with lung metastases, see HR3.2.

7.3 ORTHOTOPIC LIVER TRANSPLANTATION (OLT)

Data from SIOPEL 1 (see Tables 4 and 5) and other smaller studies support the use of orthotopic liver transplantation (OLT) as a potentially curative treatment option in carefully selected patients with hepatoblastoma. The underlying rationale is based upon (a) the excellent (100%) control of micrometastases in 123 SIOPEL 1 patients with negative lung CT scans and (b) the very low (4%) local recurrence rate in SIOPEL 1 after successful tumour resection by partial hepatectomy, implying that histopathological tumour margins are not subject to "sampling error". Most paediatric liver transplant surgeons now accept these children on to their transplant programmes.

Children should be referred for an opinion from a transplant surgeon if:

(a) despite a standard course of chemotherapy, the tumour cannot, in the surgeon's view, be resected except by total hepatectomy;

(b) there is no conclusive evidence of extra-hepatic "local" tumour extension (bearing in mind that imaging can sometimes be misleading in this respect), and

(c) the lung CT scan is negative for metastases. (Bone and brain scans are optional, according to the policy of the centre concerned).

The commonest reasons for a tumour being deemed "unresectable" (except via total hepatectomy) are: (a) tumour clearly involving all four sections of the liver as judged by MRI scan ± angiography, ± at laparatomy or (b) location so close to the main vessels at the hilum of the liver that it is unlikely that a tumour-free excision plane will be achieved. These patients should be identified at diagnosis and their clinical course and imaging followed closely throughout their initial chemotherapy, in conjunction with a liver transplant surgeon.

Note 1.
No 'second-line' chemotherapy is known to be superior to PLADO or its variants in hepatoblastoma and a variety of drug combinations were used in SIOPEL 1 (See Table 4). Clinicians therefore have the option, whilst a donor liver is awaited, either to continue PLADO, single agent cisplatin or 'SuperPLADO' or to introduce new agents. The chemotherapy coordinator will be happy to provide recent information on the relative merits of 'other' agents, via up-to-date contacts with other collaborative groups and the latest SIOPEL data.

Note 2
Patients with lung metastases visible on CT scan or chest X-ray at diagnosis who achieve, or can achieve, "lung CR" but still have an "inoperable" tumour may be curable by OLT (see Table 4). (But see also Section 7.5 - Surgery of lung metastases).

Note 3
In some cases, 'quarternary' referral to a specialist paediatric liver transplant specialist may raise surgical options other than OLT, using new techniques, eg liver revascularisation.

IF IN DOUBT, REFER YOUR PATIENT TO A PAEDIATRIC LIVER TRANSPLANT SPECIALIST. Professor Jean-Bernard Otte, transplant surgeon to the SIOPEL group, is available for advice at Service de Chirurgie Pediatrique - General et Abdominal, Université Catholique de Louvain, Cliniques Universitaires Saint-Luc, Avenue Hippocrate 10, UCK 10/1401 - 1200 Bruxelles, Belgium. Fax: +32.2.762.3680.

For South American countries, the paediatric liver transplant specialist is Dr. Paulo Chapchap, R. Dona Adma Jafet, 60-6º andar, CEP O1308-050, Sao Paulo - SP, Brazil. Tel: +55.11.214.4184; Fax: +55.11.255.9397; email: mchapcha@ibm.net.
<table>
<thead>
<tr>
<th>Phase of Treatment</th>
<th>No. of patients</th>
<th>No. of pts NED (mo. from diagnosis) (data at 9/97)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>A. No recurrent disease (n=10</em>)</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Group 4</td>
<td>7**</td>
<td>7 (31-54, median 46 mo.)</td>
</tr>
<tr>
<td>(b) Group 2 or 3 but 'unresectable' (close proximity to major vessels, at hilum)</td>
<td>2</td>
<td>2 (28 &amp; 36 mo.)</td>
</tr>
<tr>
<td>(c) Failed partial hepatectomy and HVOD</td>
<td>1</td>
<td>0 (Died &lt; 1 mo. due to &quot;vascular complications&quot;)</td>
</tr>
<tr>
<td><strong>B. After local recurrence (n=1)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After second-line chemotherapy</td>
<td>1</td>
<td>0 (Died 24 mo. further local recurrence)</td>
</tr>
</tbody>
</table>

* Six of these 10 patients received only PLADO (median 5 courses) prior to OLT; the other 4 patients received PLADO (median 6 courses) and additional treatments, as follows: cisplatin (1pt), carboplatin (3), etoposide (2) and local radiotherapy (2). (All received more than 1 agent). No patient received post-transplant chemotherapy or RT.

**NB 4 of these patients also had lung secondaries visible on chest X-ray/CT scan at diagnosis. All cleared with "PLADO" chemotherapy alone; none had lung RT.
Table 5

Orthotopic Liver Transplantation in SIOPEL 1 (Hepatocellular carcinoma)

<table>
<thead>
<tr>
<th>Phase of Treatment</th>
<th>No. of patients</th>
<th>No. of pts NED (mo. from diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No recurrent disease (n=2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Group 4</td>
<td>1</td>
<td>1 (55 mo.)</td>
</tr>
<tr>
<td>(b) Underlying metabolic liver disease (tyrosinaemia) (Group 2) tumour</td>
<td>1</td>
<td>1 (40 mo.)</td>
</tr>
</tbody>
</table>

7.4 Microscopic Residual Disease

The prognostic significance of the presence of microscopic residual disease along the surgical margins is at least controversial. In general, the feeling is that the presence of microscopic residual disease does not imply a negative prognosis. However, it is also felt that occasionally microscopic residuals can be the sign of a diffuse multifocal intra-hepatic HB growth. Furthermore, it is felt that it is quite different if the surgeon is aware of leaving microscopic residual disease, or if the findings of having left tumour along the resection margins comes as an “unexpected finding” at the time of the final written pathologic report. No specific guidelines are available in the event of microscopic residual disease. In such a situation a collective review of the case by the radiologist, the surgeon and the pathologist is indicated. The following issues should be addressed: Has artefact (eg ‘knife carry’) been excluded? Is the tumour actually multifocal rather than unifocal and, consequently, are what the pathologist has called ‘positive’ margins actually independent microscopic tumour nodules? Are there other nodules in the liver? Does the surgeon have a feeling of having cut too close to the tumour margins? Were there good reasons for that? Are the microscopic residuals along the margins of the resected main tumour specimen or along the margins of the healthy remaining liver? How much are those microscopic residuals? Was the
resected tumour all/mostly necrotic? Is the post-surgical α-FP back to normal or continuously decreasing?

Once these issues have been addressed, bearing in mind that the presence of microscopic residual tumour is potentially a very serious problem, the following therapeutic options are suggested:

i) no evidence that the resected specimen is part of a multifocal HB and particularly if the finding comes as an “unexpected finding”, proceed with the scheduled chemotherapy, following very closely the α-FP serum level. The α-FP level must go back to normal after the operation. Be aware that: a) the continuous decrease of the serum α-FP value can take some weeks before reaching the normal value and b) a minimal rise of the α-FP value may occur immediately after the operation as a sign of liver regeneration. To slice some more remaining liver is not usually a practical option, but it could be considered and should be discussed with the national study representative or study coordinator.

ii) no evidence that the resected specimen is part of a multifocal HB and the surgeon is aware of leaving minimal measurable (= miniscopic) disease or microscopic residues along the resection margins. In these cases it is suggested that the surgeon should identify the region of the residual disease with a surgical clip and contact the Radiotherapy Coordinator to discuss the possibility of delivering stamp-like field of radiotherapy.

iii) (possible) evidence of multifocal HB. In this case it is expected that the α-FP never returns to normal. Bear in mind that HB is a surgical disease and that no further or alternative chemotherapy (to the one used) is likely to cure the remaining tumour. Thus, for these rare cases, if no evidence of extra-hepatic disease becomes evident aggressive liver surgery should be considered. The feeling for these cases is that one is likely to be dealing with a “intra-hepatic systemic disease”, thus it is also thought unlikely that any other conservative hepatic resection can be curative. Thus orthotopic liver transplantation can be considered a reasonable therapeutic option. Please contact the study coordinator about such cases.

Moving the child to a different chemotherapy is obviously an option, but is not recommended until the case has been discussed with one of the chemotherapy coordinators.

7.5 SURGERY OF LUNG METASTASES
Persistent lung metastases after chemotherapy can and should be considered for surgery (resection), if at all possible. There is no clear answer as to the upper limit of the number of metastases which it is reasonable and justified to attempt to resect.
The anticipated result of the operation, however, has to be clear lungs (macroscopic
disease-free). Bilateral thoracotomies are allowed. Advice can be sought from the
surgical coordinator.

8.0 HISTOLOGICAL CONSIDERATIONS

8.1 GENERAL NOTES

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 - Macrotubular - 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.

8.2 CENTRALISATION OF THE HISTOLOGICAL MATERIAL

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.

Note that slides of both the diagnostic biopsy and representative sections of the resected tumour must be referred for central review. Post-chemotherapy specimens may be greatly altered by chemotherapy (up to 100% necrosis) so the most ‘viable’ looking areas should be sampled. (26)

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 (Form A for Biopsy or B for Surgery), two stained and two unstained tumour slides will be requested by letter from the Data Centre, and specimens should be sent along with clinical data to the Data Centre, from where they will be despatched for panel review.

9.0 RESPONSE AND RELAPSE CRITERIA

The same criteria used in the SIOPEL 1 and 2 studies for judging tumour response will be used for this study. They are the following:

Complete response (CR): no evidence of disease and normal serum $\alpha$-FP value (for age).
Partial response (PR): any tumour volume shrinkage associated with a decreasing serum $\alpha$-FP value, > 1 log below the original measurement.
Stable disease (SD): no tumour volume change and no change, or <1 log fall of the serum $\alpha$-FP concentration. **N.B. Sometimes the actual volume does not change in response to therapy, but the $\alpha$-FP decreases. These are responses not cases of stable disease.**
Progressive disease (PD): unequivocal increase in 1 or more dimensions and/or any unequivocal increase of the serum $\alpha$-FP concentration (three successive 1-2 weekly determinations) even without clinical (physical and/or radiological) evidence of tumour re-growth.

The patient's overall response status is given by the "worst" response for primary tumour and metastases,

eg if primary tumour = PR
metastases = SD
then the patient's overall response = SD

Disease-free status/Recurrence Criteria

**Disease Free Status**

a) no evidence of tumour in the liver; (negative hepatic ultrasound and CT scan or MR)

b) clear chest X-ray (PA and lateral) - if any doubt, do CT scan which must be negative

c) serum $\alpha$-FP level either normal or compatible with age and/or recent liver resection (in latter case range is up to about 200 ng/ml).
**Recurrence**

Biopsy confirmation of recurrence is *strongly recommended*. However, UNEQUIVOCAL imaging plus unequivocal serial elevation (3 consecutive rising values, taken at weekly intervals) of serum $\alpha$-FP would be an acceptable alternative. If serum $\alpha$-FP is normal, biopsy proof is MANDATORY.

Past experience indicates that an elevated $\alpha$-FP can precede by many weeks the actual documentation of tumour recurrence and that a constantly elevated or rising $\alpha$-FP is always very suggestive of tumour recurrence until proven otherwise.

**Note**  

i  Tumour dimensions, especially the primary, MUST be recorded in 3 planes.  

ii  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 $\alpha$-FP is falling, consider continuing the same chemotherapy for at least one more course.  

iii ‘Tumour lysis syndrome’ may lead to an initial rise in $\alpha$-FP before the level falls.  

iv To qualify for CR serum $\alpha$-FP must be normal; to qualify for PR there must have been a one log fall of $\alpha$-FP from the initial elevated value. CR or PR is precluded if $\alpha$-FP is rising.

**10.0 SERIOUS ADVERSE EVENTS/REPORTING**

All serious adverse events, occurring both during therapy and follow up, must be reported **immediately, by fax**, to the Trial Office, using the Serious Adverse Event Form (Form 13.0).

A serious adverse event is defined as any unexpected or untoward medical occurrence that:  
- results in death  
- is life-threatening  
- requires inpatient hospitalisation or prolongation of existing hospitalisation, for treatment of that event, or  
- results in persistent or significant disability/incapacity.
In addition any grade 4 toxicity (see NCIC Common Toxicity Criteria attached) will be regarded as a Serious Adverse Event, and should also be reported using the Serious Adverse Event Form.

The Study Coordinators will be responsible for further reporting of Serious Adverse Events.
'STANDARD RISK' HEPATOBLASTOMA
Therapeutic Guidelines
‘STANDARD RISK’ HEPATOBLASTOMA

SR.1.0 Definition - ‘STANDARD RISK’ HB - TUMOURS INVOLVING AT THE MOST 3 HEPATIC SECTIONS (PRETEXT I, II & III), ENTIRELY CONFINED TO THE LIVER (NO EXTRA-HEPATIC ABDOMINAL DISEASE, AND NO METASTASES, IE NO V, P, E OR M) (SEE PRE-TREATMENT TUMOUR EXTENSION EVALUATION SYSTEM, SECTION 5.0).

SR.2.0 CRITERIA FOR PATIENT ELIGIBILITY

Age

Less than 16 years of age at diagnosis.

Previous treatment

None. All patients including those having had, or requiring, primary tumour resection (complete or incomplete) should be entered into the study. Patients who have had primary surgery will be analysed separately.

Histology

Hepatoblastoma (see also pathology guidelines - Section 8.0). Diagnostic surgical biopsy is strongly recommended for all patients and is mandatory for the following:

- children under six months of age because of the wide range of possible tumours presenting at this age and the possible confounding effect of a physiologically elevated $\alpha$-FP level because of the age (see Addendum VIII);
- children older than 3 years of age to distinguish hepatoblastoma from hepatocellular carcinoma;
- all patients with a normal serum $\alpha$-FP.

In all other cases, in the face of unequivocal clinical findings (e.g age between 6 months and 3 years; a solid hepatic mass, associated with elevated serum $\alpha$-FP value and maybe with thrombocytosis) initial, diagnostic surgical biopsy is strongly recommended but the final decision is left to each individual centre (31). In this case compatible imaging and raised serum $\alpha$-FP level are mandatory for entering patients into the study.

- Time to start therapy: children must begin chemotherapy within 15 days of diagnosis.
**Tumour extension**

Tumours involving at the most 3 hepatic sections (PRETEXT I, II & III), entirely confined to the liver (no extra-hepatic abdominal disease and no metastases, ie no V, P, E or M) (see Pre-treatment tumour extension system - Section 5.0). **All patients must have a lung CT scan to exclude metastatic disease.**

**SR.2.1 ELIGIBILITY CRITERIA FOR PATIENT RANDOMISATION**

- **Risk category** - All patients with a ‘standard risk’ HB are eligible for the randomised trial.

- **Informed consent** - The patient's family are legally the authorized guardians and must acknowledge in writing that consent to enter the study has been given, in accordance with local institutional policy. (See Appendix VII for a framework information sheet/informed consent form. Each participating institution/country should adapt this as required locally).

All ‘standard risk’ HB patients eligible for randomisation, but not randomised because of parental refusal, or any other reason, will be registered in the study but analysed separately.

**SR. 3.0 - STUDY DESIGN - RANDOMISATION**

After diagnosis, all patients will receive **a single dose of CDDP alone**. Subsequently, 15 days from the date of administration of this initial dose of CDDP, treatment will vary according to the randomisation arm (see Fig. 6):

Regimen A - the PLADO regimen;
Regimen B - the CDDP alone regimen.

Please proceed with the assigned randomisation arm regardless of the patient and tumour status after the first dose of CDDP. In rare cases where genuine tumour progression is suspected, one of the coordinators must be consulted. Hepatoblastomas are ‘slow responding’ cancers and, unless there is an unequivocal new site of disease, response cannot be judged until at least 6 weeks into chemotherapy. Also, clinicians should be aware that ‘tumour lysis syndrome’ may lead to an initial **rise** of α-FP, before the level falls.

See Section 6.4 for details of patient randomisation procedure.
SR. 3.1 REGIMEN A - PLADO - OVERVIEW OF REGIMEN A TREATMENT PLAN.

Preoperative phase
At day 15 after the initial dose of CDDP, the patient will start regimen A which consists of a total of 5 courses of the combination CDDP/DOXO (called PLADO), administered every 21 days. Initial tumour response is evaluated before the 2nd PLADO (= before day 36). If stable (no tumour volume change and no fall of α-FP) or progressive disease consider radical surgery or move to phase II chemotherapy. **Please, note that sometimes the actual tumour volume does not change in response to therapy, but the α-FP decreases; these are 'responses' not cases of stable disease, and the original chemotherapy should be continued.** Patients who are responding continue to receive the remaining two courses of PLADO of the pre-operative phase, after which resectability is determined.

Delayed surgery
If the tumour is now thought to be "resectable" the patient undergoes delayed primary surgery. If the tumour is still "unresectable", but the patient is responding to chemotherapy, the patient continues with two more courses of PLADO. If, after five courses of PLADO (plus the initial single dose of CDDP), the tumour is still "unresectable" the patient is eligible for liver transplant or Phase II chemotherapy (see Addendum VI). If after the first three courses of PLADO (plus the initial single dose of CDDP), the tumour is unresectable and no longer responding to PLADO, (see comment on stable disease above) the patient is then eligible for Phase II chemotherapy.

Post operative phase
Patients who received three courses of pre-operative PLADO, and who had the tumour successfully resected, receive two post-operative courses of PLADO, but if the patient has received five courses of PLADO before successful resection (plus the initial single dose of CDDP alone), they receive no further therapy.

Stopping therapy
Therapy will be stopped after administration of the initial dose of CDDP alone and 5 courses of PLADO.

SR. 3.2 REGIMEN B - CDDP ALONE - OVERVIEW OF REGIMEN B TREATMENT PLAN.
Preoperative phase
At day 15 after the initial dose of CDDP, patients will start regimen B which consists of 3 pre-operative courses of CDDP alone (i.e. patients in Regimen B receive a total of 4 doses of CDDP pre-operatively), administered every 15 days. Initial tumour response is evaluated before the 2nd dose of CDDP of the regimen (before day 29 which is, for this regimen before the 3rd of the 4 pre-operative doses of CDDP).

Administer the second dose of CDDP of regimen B, (the 3rd actual dose) unless there is stable (= no tumour volume change and no fall in $\alpha$-FP) or progressive disease. Please, note that sometimes the actual tumour volume does not change in response to therapy but the $\alpha$-FP decreases; these are 'responses' not cases of stable disease, and the original therapy should be continued. For a patient with genuinely unresponsive stable disease (SD) consider radical surgery or move to the 'high risk' HB regimen (see HR 4.0); in the case of progressive disease (PD) consider radical surgery or move to the Phase II study with high dose cyclophosphamide (See Addendum VI). In case of either SD or PD please contact the study co-ordinator(s) or chemotherapy co-ordinator before commencing alternative therapy. Patients who are responding continue to receive a total of 4 doses of CDDP alone, after which resectability is determined. (See Fig. 6).

The final judgement on tumour response and tumour resectability will be formulated only after the third course of Regimen B (= 4th dose of CDDP) (after day 44). (For tumour response definition see Section 9.0).

Delayed surgery - Delayed surgery will be considered after the 3rd (in total 4) course of pre-operative CDDP (after day 44). If surgery is not feasible at this time, but the tumour is responding to chemotherapy, the patient will be treated with, at the most, 2 more courses of CDDP. Definitive surgery will be re-considered at the end of these 2 further courses of chemotherapy. All patients will receive at the most 6 (including the dose given prior to randomisation) courses of CDDP (assuming that the tumour continues to respond to CDDP), before considering alternative therapy.

Post-operative chemotherapy - If the patient received only four doses of CDDP before delayed surgery he/she will receive two post-operative courses of CDDP at the same dose and schedule used for the pre-operative phase. If 6 courses of CDDP were given pre-operatively, no chemotherapy will be given post-operatively.

Stopping therapy - The therapy will be stopped after a total of 6 courses of CDDP.
SIOPEL 3 Study
"Standard Risk" Hepatoblastoma protocol - therapeutic strategy

REGIMEN A: NB. 21 day interval between courses of PLADO on this arm.

REGIMEN B: NB 14 day interval between courses of CDDP on this arm.

Regimen A: Cisplatin (CDDP) 80mg/m² continuous 24 hours I.V. continuous infusion
or
Doxorubicin (DOXO) 60mg/m² continuous 48 hours I.V. continuous infusion

Regimen B: Cisplatin (CDDP) 80mg/m² alone

▼ Assessment of hearing, kidney function and heart function (see protocol)
▲ * RE = response evaluation
** See Protocol
SR. 3.3 RESIDUAL DISEASE AFTER STOPPING THERAPY

If there is still evidence of disease and/or an elevated serum $\alpha$-FP level at the scheduled end of therapy, alternative therapy must be considered. However, in the case of disease which is apparently still responding at the end of the scheduled therapy, experience has taught that there is little to gain by proceeding with the same drug regimen.

Note that a persistently elevated serum $\alpha$-FP level usually indicates persistence of active disease until otherwise proven. It is not uncommon to find a slowly rising $\alpha$-FP level (particularly for $\alpha$-FP 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 the $\alpha$-FP level eventually declines spontaneously to normal, no cause having been identified.

There is the possibility of considering “postage stamp” fields of radiotherapy in case of persistent small volume macroscopic residual disease, if the surgeon thinks that a further surgical attempt of tumour removal is not feasible. In this case please refer to the radiotherapy guidelines (See Addendum V) and contact the radiotherapy coordinator (See Addendum II).

SR. 4.0 - CHEMOTHERAPY GUIDELINES

SR. 4.1 Initial dose CDDP
The first dose of CDDP, common to both treatment arms, is:

- Cisplatin (PLA) 80mg/m$^2$/day in continuous I.V. infusion for 24 hours

For modality of administration and therapy modification see SR 4.2.1.

SR. 4.2 Regimen A - PLADO
PLADO chemotherapy consists of:

- Day 1 Cisplatin (PLA) 80mg/m$^2$/day in continuous I.V. infusion for 24 hours
- Day 2 Doxorubicin (DO) 30mg/m$^2$/day in continuous I.V. infusion for 48 hours, ie. total of 60mg/m$^2$/course.

This combination is to be administered in 3-day courses at 21-day intervals, for a maximum of five courses.
Administer PLADO as follows (dose adjustments for children of body weight less than 10 kg follow).

Day 1  h. 0  Pre-Cisplatin hydration
       h. 12  Start Cisplatin infusion

Day 2  h. 36  Stop Cisplatin infusion
       Start post-Cisplatin hydration
       Start Doxorubicin infusion

Day 3  h. 60  Stop post-Cisplatin hydration

Day 4  h. 84  Stop Doxorubicin infusion

**SR 4.2.1. Dose, modality and timing of administration**
Cisplatin 80 mg/m²/day in continuous I.V. infusion for 24 hours (dose calculated per Kg if body weight < 10 Kg see following page).

**Administration**

*Pre-Cisplatin hydration*
125 ml/m²/hour for 12 consecutive hours of
   - Glucose 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 80 mg/m² made up to 120 ml with Glucose 2.5%/sodium chloride 0.45% infused at 5 ml/hour for 24 hours, run concurrently with:

b) 120 ml/m²/hour for 24 hours of a solution of
   - Glucose 2.5%/sodium chloride 0.45% +
   - 30 ml Mannitol 20%/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

a) 125 ml/m²/hour for 24 consecutive hours of
   Glucose 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

   A careful record of fluid input and output should be kept. If diuresis falls below 400 ml/m² per 6 hrs, frusemide 0.5-1mg/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 Gentamycin should preferably be avoided during and immediately after CDDP infusion. If used, serum levels should be monitored with extreme care.

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

   CDDP 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.

   **Doxorubicin Infusion**, 30 mg/m²/24 hrs Day 2, and 30 mg/m²/24hrs Day 3 (total dose/course 60 mg/m²/48 hrs).
   DOXO 30 mg/m²/24 hrs is administered in continuous intravenous infusion via a central venous catheter for 48 consecutive hours, immediately after completion of CDDP infusion. The infusion rate of DOXO should be kept constant throughout the 48-hour infusion. For this reason, infusion of DOXO through a separate i.v. line, in a 5% glucose solution, is recommended (smallest possible volume). 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 DOXO can be administered during a few hours intravenous infusion. **Deep veins should be avoided since extravasation of the drug is dangerous and is not readily appreciated at these sites.**

**SR 4.2.2. Therapy modification:**
**By age**

**In infants with body weight less than 5 Kg** administer the first dose of CDDP at 1.7 mg/kg; if well tolerated, increase the dose to 2.6 mg/Kg. Similarly, administer the first dose of DOXO at 0.7mg/kg; if well tolerated increase the dose to 1mg/kg. This is because for body weight less than 10 Kg, drug doses should be calculated per Kg, assuming that 1 m² ≡ 30 Kg, and that in very young and small children it is wiser to start with a further 1/3 dose reduction.

**For infants and children with body weight between 5 and 10 Kg** administer CDDP at 2.6 mg/Kg and DOXO at 1mg/kg, on the basis that for body weight less than 10 Kg drug dose must be calculated per Kg, assuming that: 1 m² ≡ 30 Kg.

Remember also to adjust the amount of hydration fluids according to infant's weight and age.

Please note that infants are at higher risk of CDDP-induced electrolyte imbalance than older children and consequently the need for regular electrolyte monitoring is particularly important in this age group. However, CDDP does not seem to be more toxic, overall, in infants than in older children. (5)

**For toxicity**

Try to avoid indiscriminate dose-reduction and unnecessary delay of chemotherapy. Give each patient the maximum recommended and tolerable dose of the drugs at the appropriate time.

**Contact the chemotherapy panel coordinator (Addendum II) for any life threatening, lethal, unexpected or unusual toxicity. (See also Serious Adverse Events - Section 10.0)**

*Bone marrow toxicity* - An absolute neutrophil count (ANC) greater than 1000/mm³ and a platelet count greater than 100.000/mm³ are necessary before starting chemotherapy. It is better to delay chemotherapy until these criteria are met, rather than decrease the dose. If a delay of one or more weeks is necessary, decrease dosage by 25% for the next course only.

If a course of chemotherapy results in severe neutropenia (ANC < 500 /mm³), 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.

(Siopel 3\final\May 98)
**Ototoxicity** - The grading system for hearing loss proposed by P R Brock et al (3) will be used in SIOPEL 3 (Table 6). Careful monitoring of children by an expert audiologist and by serial audiometry throughout the treatment with CDDP is recommended. To monitor ototoxicity in infants otoacoustic emissions, when available, 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. 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. If grade 3 or 4 ototoxicity is documented CDDP should be withdrawn and replaced by CARBO.

Table 6: 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>

**Renal toxicity** - a) **Glomerular toxicity** - Nephrotoxicity of CDDP in children (as in adults) is dose-related and sometimes severe. Plasma creatinine measurements and creatinine clearances are not reliable guides to the degree of CDDP-induced renal damage, particularly in children. Careful measurement of Glomerular Filtration Rate (GFR) by isotope clearance is essential for accurate monitoring of renal status. The GFR monitoring in this study will be requested less frequently than previously but it is essential that it be carried out on all patients at the time-points that it is asked for. It 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 from an indwelling catheter. It entails less irradiation to the child than daily natural sources. The technique is well described by Chantler et al. Clin Sci 1969; 37: 169-180 and Arch Dis Child 1972; 47: 613-617. If any centre requires further practical information or cannot obtain the literature this can be sent on request. 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 comparative randomised study, so please do not send us these results instead of a GFR. In cases of severe reduction in $^{51}$CrEDTA GFR (≤60 ml/min/1.73 m$^2$), discontinue CDDP and use CARBO. In infants refer to Addendum IX for a table of expected GFR according to age and if GFR falls below 2 SD below the expected GFR then CARBO should be substituted for CDDP.

b) Tubular toxicity Renal loss of Magnesium and consequent Hypomagnesemia is expected in nearly all children on this study and oral Magnesium supplementation is recommended for all children entered into the study. Hypomagnesemia is not a reason to stop CDDP. 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 CDDP treatment. Hypomagnesemia may persist years after stopping therapy.

Infants are at higher risk of CDDP induced electrolyte imbalance and consequently the need for regular electrolyte monitoring is particularly important in this age group (5). However, CDDP does not seem to be more nephrotoxic in infants than in older children.

Hepatotoxicity - No standardised criteria exist for the adjustment of DOXO dosage in the presence of hepatic dysfunction. It seems reasonable to recommend a 50% reduction of DOXO dosage if total serum bilirubin concentration > 3 mg/100 ml or/and if serum liver enzymes (AST, ALT) are >5 times the normal value.

NB. Since DOXO hepatotoxicity is actually very rare, elevated AST, ALT should lead to an energetic search for other causes of liver dysfunction, eg viral hepatitis. CDDP dose need not be modified.

Cardiotoxicity - Regular monitoring for possible cardiotoxicity is essential. (28). 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 a normal haemoglobin, and is not being hyperhydrated. True baseline measurements should be obtained prior to administration of DOXO to provide a meaningful reference for comparison with future tests.

N.B. An echocardiogram must be performed prior to surgery.
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 DOXO.

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 chemotherapy panel coordinator. (See Addendum II).

**SR 4.3 Regimen B - CDDP alone**

Regimen B consists of:

Cisplatin 80mg/m²/day in continuous i.v. infusion over 24 hours (dose calculated per kg if body weight < 10 kg) on day 1, 15, 29 and 44 pre-surgery (NB: day 1 = course given pre-randomisation) and on day 1 and 15 post surgery.

**SR 4.3.1. Dose, modality and timing of administration**

*Pre-Cisplatin hydration*

125 ml/m²/hour for 12 consecutive hours of

- Glucose 2.5%/sodium chloride 0.45%
- KCl 10 mmol (10mEq)/500 ml
- Mg Sulphate 2 mmol (4 mEq)/500 ml
- CaGluconate 1.5 mmol (3mEq)/500 ml

*Cisplatin infusion*

a) Cisplatin 80 mg/m² made up to 120 ml with Glucose 2.5%/sodium chloride 0.45% infused at 5 ml/hour for 24 hours, run concurrently with:

b) 120 ml/m²/hour for 24 hours of a solution of:

- Glucose 2.5%/sodium chloride 0.45%
- 30 ml Mannitol 20%/500 ml
- KCl 10 mmol (10 mEq)/500 ml
- Mg Sulphate 2 mmol (4 mEq)/500 ml
- CaGluconate 1.5 mmol (3mEq)/500 ml

*Post-Cisplatin hydration*

a) 125 ml/m²/hour for 24 consecutive hours of:

- Glucose 2.5%/sodium chloride 0.45%
- KCl 10 mmol (10 mEq)/500 ml
- Mg Sulphate 2 mmol (4 mEq)/500 ml
- CaGluconate 1.5 mmol (3 mEq)/500 ml
A careful record of fluid input and output should be kept. If diuresis falls below 400 ml/m² per 6 hrs, frusemide 0.5 - 1mg/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 Gentamycin should preferably be avoided during and immediately after CDDP infusion. If used, serum levels should be monitored with extreme care.

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

CDDP is a strongly emetogenic drug; thus it is recommended to precede its infusion with an anti-emetic cocktail. The 5-HT3 receptor antagonists are the drugs of first choice.

**SR 4.3.2 Therapy modification:**

**By age**

**In infants with body weight less than 5 Kg** administer the first dose of CDDP at 1.7 mg/kg. If well tolerated, increase the dose to 2.6 mg/Kg; this is because for body weight less than 10 Kg, drug dose should be calculated per Kg, assuming that 1 m² = 30 Kg, and that in very young and small children it is wiser to start with a further 1/3 dose reduction.

**For infants and children with body weight between 5 and 10 Kg** administer CDDP at 2.6 mg/Kg, on the basis that for body weight less than 10 Kg drug dose must be calculated per Kg, assuming that 1 m² = 30 Kg. Remember also to adjust the amount of hydration fluids according to infant's weight and age.

Please note that infants are at higher risk of CDDP-induced electrolyte imbalance than older children and consequently the need for regular electrolyte monitoring is particularly important in this age group. However, CDDP does not seem to be more toxic, overall, in infants than in older children. (5)

**For toxicity**
Try to avoid indiscriminate dose-reduction and unnecessary delay of chemotherapy. Give each patient the maximum recommended and tolerable dose of the drugs at the appropriate time.

Contact the chemotherapy panel coordinator (Addendum II) for any life threatening, lethal, unexpected or unusual toxicity. (See also Serious Adverse Events - Section 10.0)

Bone marrow toxicity - CDDP is only mildly myelotoxic. Thus, lower levels of absolute neutrophil count can be accepted for commencing chemotherapy, if the general condition of the patient is good and there is no evidence of infection. Thus an absolute neutrophil count (ANC) greater than 750/mm$^3$ and a platelet count greater than 75,000/mm$^3$ are necessary before starting chemotherapy. It is better to delay chemotherapy until these criteria are met, rather than decreasing the dose. If a delay of one or more weeks is necessary, decrease dosage by 25% for the next course only.

If a course of chemotherapy results in severe neutropenia (ANC < 500 /mm$^3$), 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 those events resume the full dosage of the drug.

Ototoxicity - The grading system for hearing loss proposed by P R Brock et al (3) will be used in SIOPEL 3 (Table 6). Careful monitoring of children by an expert audiologist and by serial audiometry throughout the treatment with CDDP is recommended. To monitor ototoxicity in infants otoacoustic emissions, when available, 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. 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. If grade 3 or 4 ototoxicity is documented CDDP should be withdrawn and replaced by CARBO.

Renal toxicity -

a) **Glomerular toxicity** - Nephrotoxicity of CDDP in children (as in adults) is dose-related and sometimes severe. Plasma creatinine measurements and creatinine clearances are not reliable guides to the degree of CDDP-induced renal damage, particularly in children. Careful measurement of Glomerular...
Filtration Rate (GFR) by isotope clearance is essential for accurate monitoring of renal status. The GFR monitoring in this study will be requested less frequently than previously but it is essential that it be carried out on all patients at the time-points that it is asked for. It 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 from an indwelling catheter. It entails less irradiation to the child than daily natural sources. The technique is well described by Chantler et al. Clin Sci 1969; 37: 169-180 and Arch Dis Child 1972; 47: 613-617. If any centre requires further practical information or cannot obtain the literature this can be sent on request. 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 comparative randomised study, so please do not send us these results instead of a GFR. In cases of severe reduction in Cr$^{51}$ EDTA GFR (<60 ml/min/1.73 m$^2$), discontinue CDDP and use CARBO. In infants refer to Addendum IX for a table of GFR according to age, and if the GFR falls below 2 SD below the expected GFR then CARBO should be substituted for CDDP.

b) Tubular toxicity - Renal loss of Magnesium and consequent Hypomagnesemia is expected in nearly all children who will be treated and oral Magnesium supplementation is recommended for all children entered into the study. (See SR 4.2). Hypomagnesemia is not a reason to drop CDDP. 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 CDDP treatment. In children hypomagnesemia may persist years after stopping therapy.

Infants are at higher risk of CDDP induced electrolyte imbalance and consequently the need for regular electrolyte monitoring is particularly important in this age group (5). However, CDDP does not seem to be more toxic in infants than in older children.
SR.5.0 - REQUIRED PATIENT INFORMATION

**At diagnosis**

*Physical examination including also -*
- Anthropometric measurements and nutritional status assessment;
- Determination of the liver/abdominal mass size measured from the costal margin in the right and left mid-clavicular line and from the xiphisternum

*Laboratory tests*
- Full blood cell count
- Bilirubin, ALT & AST; Creatinine, Urea, Electrolytes, Mg**,Ca**, Fibrinogen and Factor V
- Partial Thromboplastin Time, Thrombin time - Prothrombin time or equivalent
- Serum \( \alpha \)-FP and \( \beta \)-human chorionic gonadotrophin hormone levels;
- Hepatitis A,B and C serology;

*N.B. In cases of normal serum \( \alpha \)-FP - ensure that appropriate dilutions have been carried out. Beware false negative result.*

*Imaging investigations*
- For pre-treatment tumour extension (PRETEXT) (see also Section 5.0)
- Abdominal ultrasound + abdominal CT scan with contrast or MRI with Gadolinium;
- Chest X-ray (in two projections PA & Lateral) and **chest CT scan**;

*Chemotherapy toxicity monitoring*
- Glomerular filtration rate as measured by \(^{51}\text{Cr-EDTA} \) clearance;
- Audiogram - pure tone where possible age 3 years +, otherwise free field testing or otoacoustic emissions

2d-derived echocardiogram - measurement of shortening fraction - for patients on Regimen A - PLADO.

**During chemotherapy** - Weekly serum \( \alpha \)-FP level if initially elevated.

*Physical examination including also - Before starting each course*
- Anthropometric measurements and nutritional status assessment;
- Determination of the liver/abdominal mass size measured from the costal margin in the right and left mid-clavicular line and from the xiphisternum
**Laboratory tests - Before starting each course**

Full blood cell count  
Bilirubin, ALT & AST; Creatinine, Urea, Electrolytes, Mg**, Ca**  
Partial Thromboplastin Time, Thrombin time; Prothrombin time or equivalent  
Serum α-FP and β-human chorionic gonadotropin hormone levels (if initially elevated);  
Urine creatinine and electrolytes (Na+, K+, Cl, Ca**, Mg**, Phosph) so that, using fractionated excretion, tubular function can be measured.

**Imaging investigations**

For tumour response monitoring (see also below "Before surgery")  
Abdominal ultrasound before each course of chemotherapy. Please, note that pre-operative tumour response evaluation is required after 1 CDDP + 3 PLADO for Regimen A and a total of 4 CDDP for Regimen B.

**Chemotherapy toxicity monitoring**

Glomerular filtration rate as measured by $^{51}$Cr-EDTA clearance should be obtained prior to surgery, and at the end of chemotherapy unless the plasma creatinine level has risen unexpectedly prior to courses 2, 3, 4, 5 or 6.

Audiogram prior to surgery and at the end of chemotherapy.

For patients on Regimen A, echocardiogram should be carried out prior to surgery, and at the end of treatment, and at other times if there is clinical concern.

**Before surgery (other than "the pre-surgery routine")**

Physical examination including also nutritional status assessment;  
Please note that surgical complications are more common in children with a poor nutritional status (27).  
Determination of the liver/abdominal mass size measured from the costal margin in the right and left mid-clavicular line and from the xiphisternum

**Laboratory tests**

Full blood cell count  
Bilirubin, ALT & AST; Creatinine, Urea, Electrolytes, Mg**, Ca**  
Partial Thromboplastin Time, Thrombin time, Prothrombin time;  
Serum α-FP and β-human chorionic gonadotrophin hormone levels (if initially elevated);  
Urine creatinine and electrolytes (Na+, K+, Cl, Ca**, Mg**, Phosph) so that, using fractionated excretion, tubular function can be measured

**Imaging investigations**
For the evaluation of tumour response and extent
Abdominal ultrasound and CT scan with contrast or MRI with gadolinium
Chest X-ray (in two projections PA & Lateral); chest CT scan. (See Radiology
recommendations - section 5.3).

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

**At the end of therapy**

*Physical examination including also -*
- Anthropometric measurements and nutritional status assessment;

*Laboratory tests*
- Full blood cell count
- Bilirubin, ALT & AST; Creatinine, Urea, Electrolytes, Mg**+** and Ca**++**
- Partial Thromboplastin Time, Thrombin time, Prothrombin time;
- Serum α-FP and β-human chorionic gonadotrophin hormone levels (if initially
elevated);
- Urine creatinine and electrolytes (Na**, K**, Cl, Ca**++, Mg**+, Phosph) so that, using
fractionated excretion, tubular function can be evaluated

*Imaging investigations*

*For tumour status evaluation*
- Abdominal ultrasound - abdominal CT scan with contrast or MRI with Gadolinium;
- Chest X-ray (in two projections PA & Lateral) and chest CT scan

*For end of chemotherapy toxicity evaluation*
- Glomerular filtration rate as measured by **5**1Cr-EDTA clearance;
- Audiogram - pure tone if age 3 years +, otherwise free field testing or otoacoustic
emissions.
- 2d-derived Echocardiogram measurement of shortening fraction for Regimen A
patients.
**Table 7: Follow up investigations after stopping therapy**

<table>
<thead>
<tr>
<th>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 6 months</td>
<td>yearly</td>
</tr>
<tr>
<td>Alpha-fetoprotein</td>
<td>every 2-3 months</td>
<td>every 6 months</td>
<td>yearly</td>
</tr>
<tr>
<td>Chest-X ray</td>
<td>every 3 months</td>
<td>every 6 months</td>
<td>yearly</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>every 2-3 months</td>
<td>every 6 months</td>
<td>yearly</td>
</tr>
<tr>
<td>Serum magnesium</td>
<td>yearly</td>
<td>yearly</td>
<td>yearly</td>
</tr>
<tr>
<td>$^{51}$Cr EDTA -GFR</td>
<td>one year off treatment - to be repeated yearly if &lt; 80 ml/min/1.73 m$^2$</td>
<td>yearly if &lt; 80 ml/min/1.73 m$^2$</td>
<td>yearly if &lt; 80 ml/min/1.73 m$^2$</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 +</td>
</tr>
<tr>
<td>Echocardiogram - measurement of shortening fraction (for patients on Regimen A only)</td>
<td>1 year off treatment and yearly</td>
<td>yearly</td>
<td>yearly</td>
</tr>
</tbody>
</table>
SR.6.0 STATISTICAL CONSIDERATIONS

SR. 6.1 OUTCOME MEASURES/END-POINTS

The primary outcome measure for the trial will be toxicity, as defined by febrile neutropenia, mucositis (grade 3/4) or infection and complete resection rate. Secondary outcome measures will be response, survival and event-free survival.

SR. 6.2 SAMPLE SIZE AND STATISTICAL METHODS

The principal comparison will be to show differential toxicity between the two pre-operative chemotherapy arms whilst preserving equivalence in terms of resection rate.

Toxicity

64% of evaluable patients (27% of courses) experienced febrile neutropenia and 20% of evaluable patients (7% of courses) suffered mucositis (grade 3/4) during chemotherapy on SIOPEL1 [PLADO] (J Brown, personal communication). Similarly on SIOPEL 2 [CDDP] 45% of evaluable patients (16% of courses) experienced febrile neutropenia, and no evaluable patients suffered mucositis (grade 3/4). In addition, in SIOPEL 2 55% of evaluable patients (21% of courses) experienced infections during chemotherapy. The inclusion and evaluation of 170 patients for toxicity (85 CDDP: 85 PLADO) would provide approximately 80% power to demonstrate a reduction in the rate of febrile neutropenia from 64% to 45% with a 1-sided test ($\alpha=0.05$), and similarly a reduction in mucositis from 20% to 2% would be able to be detected with a 1-sided test ($\alpha=0.05$) with approximately 98% power. In addition 170 patients would also enable a reduction in the infection rate from 75% to 55% to be detected with a 1-sided test ($\alpha=0.05$) with approximately 83% statistical power.

The reason for eliminating doxorubicin is to avoid the associated long-term cardiotoxicity. Only long-term follow up will allow such toxicity to be assessed. In the absence of such information from SIOPEL 1, it is currently not possible to use this endpoint in sample size determination.

Resection Rate

Strict equivalence cannot be shown in any trial. The ultimate goal of the trial is to find a regimen which is less toxic yet with similar resection rate as the PLADO regimen developed in SIOPEL 1. A similar rate may be expressed in terms of the maximally acceptable difference between rates. If a reduction from 90% to 80% in resection rate is considered to be an acceptable difference, then a total sample size of 244 would be required to rule this out with a significance level of 5% and 80% power. By
contrast 170 patients would yield a power of 65%, assuming the same size difference and significance level.

Accrual
The accrual of these patients onto SIOPEL2 was approximately 30 per year, and such an accrual rate would allow 170 patients to be recruited in approximately 5½ years. Whilst this would be sufficient to meet the sample size requirements with respect to toxicity, it would be desirable for further patients to be recruited in order to address the question of equivalence in resection rate. This could be achieved either by securing the participation of additional centres, or by the continuation of the trial beyond 5½ years.

Secondary End-Points
Response rate, survival and event-free survival will be secondary end-points of the study. A total of 170 patients would be sufficient to rule out a reduction from 95% (SIOPEL 1) to 85% in response rate at the 5% significance level and with over 80% power. After a minimum of 3 years follow up the width of the 90% CI for a difference in OS from 85% on PLADO to 75% on CDDP would have expected width approximately ± 10%.

Analysis
The main analysis will be according to the intention to treat principle, so all patients randomised onto CDDP alone, regardless of whether or not they also subsequently receive doxorubicin, will be compared to all patients randomised to PLADO, in turn regardless of whether or not they subsequently only receive CDDP. Further analyses will explore the role of treatment compliance. Chi squared or Fisher’s exact test will be used to compare toxicity, response and complete resection rates per patient between treatment arms. Log rank tests will be used to compare survival and event-free survival.

SR 6.3 INTERIM ANALYSIS AND INDEPENDENT DATA MONITORING COMMITTEE (IDMC)
An early interim analysis will be performed on randomised patients 18 months from the start of the trial when median follow up is approximately 9 months and 38 patients would be evaluable for toxicity. An Independent Data Monitoring Committee will be formed to review the data in particular with regard to toxicity and complete resection rate, and advise on further recruitment.

A group sequential approach will be used in order to preserve the overall level of significance. A conservative spending function in the spirit of O’Brien and Fleming will be chosen. If recruitment continues, the timing of further reviews will be decided by the IDMC.
'HIGH RISK' HEPATOBLASTOMA
Therapeutic Guidelines
'HIGH RISK' HEPATOBLASTOMA

HR.1.0 DEFINITION

'High risk' HB - Tumours involving: (a) all 4 hepatic sections (PRETEXT IV) and/or (b) with evidence of extra-hepatic disease (metastases and/or extra-hepatic abdominal disease) (see pre-treatment tumour extension system - Section 5.0).

Lung metastases - All "unequivocal" (See Section 5.3 'Chest') pulmonary lesions documented on the chest X-Ray and/or CT scan considered to be metastatic tumour deposits. For equivocal cases, rapid central radiology review is recommended - see Section 6.6).

HR.2.0 CRITERIA FOR PATIENT ELIGIBILITY

Age
Less than 16 years of age at diagnosis.

Previous treatment
None. All patients including those having had, or requiring, primary tumour resection (complete or incomplete), for whatever reason, should be entered into the study. Patients who have had primary surgery will be analysed separately. The reason for primary surgery should be specified.

Histology
Hepatoblastoma (see also pathology guidelines). Diagnostic surgical biopsy is strongly recommended for all patients and is mandatory for the following:
- children under six months of age because of the wide range of possible tumours presenting at this age and the possible confounding effect of a physiologically elevated α-FP level because of the age (see Addendum VIII).
- children older than 3 years of age, to distinguish hepatoblastoma from hepatocellular carcinoma;
- all patients with a normal serum α-FP.

In all other cases, in the face of unequivocal clinical findings (e.g age between 6 months and 3 years; a solid hepatic mass, associated with elevated serum alpha-fetoprotein (α-FP) value and maybe with thrombocytosis) initial, diagnostic surgical biopsy is strongly recommended but the final decision is left...
to each individual centre (31). In this case compatible imaging and raised serum α-FP level are mandatory for entering patients into the study.

- Time to start therapy: children must begin chemotherapy within 15 days of diagnosis.

Important notes -
No central review of the initial diagnostic images is required to enter patients into the trial.
Due to the international nature of the present trial, and time and cost constraints, it is unrealistic to expect to obtain central review of the radiological films in order to validate the PRETEXT category assigned to each patient by the participating centres, but for difficult cases a rapid review of radiological findings at diagnosis is available on request (See Section 6.6).

Tumour extension
Tumours involving all 4 hepatic sections (PRETEXT IV) and/or with evidence of extra-hepatic disease (distant metastases and/or extra-hepatic abdominal disease) (see pre-treatment tumour extension system - Section 5.0). Note that enlarged lymph nodes on imaging are not a criteria for considering a patient high risk.

Note:
- All patients must have a lung CT scan and chest X-ray.
- All unequivocal (See Section 5.3 'Chest') pulmonary lesions documented on the chest X-ray and/or CT scan considered to be metastatic tumour deposits. For equivocal cases rapid central radiology review is recommended - see Section 6.6.

HR 3.0 Study Design

After diagnosis, all patients will receive pre-operative chemotherapy. Children classified as having a 'high risk' HB, will be treated with the intensive multi-agent regimen including CARBO, CDDP and DOXO, preceded by a single dose of CDDP.

Pre-operative phase - Pre-operatively, this regimen will consist of alternating administration of CDDP at days 1, 29, 57 & 85 and of the combination CARBO/DOXO at days 15, 43 & 71. CDDP will be administered regardless of the blood cell count. Tumour response will be evaluated before days 29, 57 and 85, and just before surgery. (For tumour response definition see Section 9.0).
Delayed surgery - Delayed surgery should be performed within three weeks of day 85 of the pre-operative chemotherapy. However, if feasible, definitive surgery could be considered also after the second administration of the combination CARBO/DOXO (after day 43). If surgery, is not feasible after the 85th day of the pre-operative phase, but the tumour is responding to chemotherapy, the patient will be treated with, at the most, another 2 doses of CARBO/DOXO alternating with one dose of CDDP. Definitive surgery will be re-considered at the end of these further courses of chemotherapy. All patients will receive at the most 5 courses of CARBO/DOXO and 5 of CDDP alone if the tumour continues to respond to chemotherapy).

Note that if at day 43 there is stable disease (please read response definitions, Section 9.0, carefully) contact the Study Coordinator with a view to considering orthotopic liver transplantation for a patient with localised disease. Alternatively, it is suggested that the patient may be entered into the phase II study with high dose cyclophosphamide. (See Addendum VI)

Post-operative chemotherapy - After delayed surgery patients will receive another 2 courses of CARBO/DOXO at day 1 and 29 post-surgery alternating with one dose of CDDP at day 15 post-surgery at the same dose and schedule used for the pre-operative phase.

Stopping therapy - The therapy will be stopped after 5 courses of CARBO/DOXO and 5 of CDDP. Please note: regardless of the time of delayed surgery all patients will receive the same number of courses and therefore the same total cumulative doses of chemotherapy.

HR 3.1 RESIDUAL DISEASE AFTER STOPPING THERAPY

If there is still evidence of non responding disease and/or persistently elevated serum α-FP level at the scheduled end of therapy, alternative therapy should be considered. Please, contact the chemotherapy panel co-ordinator (Addendum II) if this occurs.

Note that a persistently elevated serum α-FP level usually indicates persistence of active disease until otherwise proven. It is not uncommon to find a slowly rising α-FP level, particularly for α-FP 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 the α-FP level eventually declines spontaneously to normal, no cause having been identified.
There is the possibility of considering "postage stamp" fields of radiotherapy in case of persistent small volume macroscopic residual disease, if the surgeon thinks that a further surgical attempt at tumour removal is not feasible. In this case please refer to the radiotherapy guidelines (Addendum V) and contact the radiotherapy coordinator (Addendum II).

**HR. 3.2 SUGGESTIONS FOR TREATMENT OF PATIENTS WITH LUNG METASTASES**

Chemotherapy is the first line treatment for control of metastases. However, surgery should be considered for patients with lung metastases which do not disappear with chemotherapy. (2) (Contact Study Coordinator). In these cases tumour response should be monitored very carefully in order to document chemotherapy failure as soon as possible. There are no data on the role of high dose chemotherapy with peripheral stem cells or autologous bone marrow rescue for these children (see also Addendum VI on Phase II chemotherapy).

**HR.4.0 CHEMOTHERAPY GUIDELINES**

Every effort should be made to keep to the chemotherapy guidelines and report carefully all adverse events.

**HR.4.1 GENERAL INDICATIONS FOR SUPPORTIVE THERAPY**

The chemotherapy regimen designed for "high risk" HB is quite intensive (see Fig. 7) and includes the intentional administration of CDDP during the myelotoxic phase, following CARBO/DOXO pulses. The following guidelines must be respected in order to avoid excessive toxicity and to keep to the time schedule of drug administration:

- all children should have a central venous line inserted;
- **If the body weight is less than 10 Kg, drug dosage should be calculated per Kg as indicated in Section HR 4.4:**
  - all children with a body weight equal to or less than the 3rd percentile at the time of starting therapy must have total parenteral nutritional (TPN) support;
  - In case of renal dysfunction, **CARBO actual dosage** must be calculated using the modified Calvert’s formula (see below); if it is not possible to measure the GFR by $^{51}$Cr EDTA clearance, the first dose of CARBO must be reduced by 25%; if no episodes of fever and neutropenia or of severe thrombocytopenia associated with external bleeding occur the next dose can be administered at 100%.

Consider using **Granulocyte colony stimulating factor (G-CSF)** if the first course of CARBO/DOXO has been complicated by severe and protracted
neutropenia (regardless of the occurrence of fever) which delayed the institution of the subsequent course of CARBO/DXO. G-CSF is administered subcutaneously at the dosage of 5 μg/kg, 24 hours after the administration of CDDP; it should be administered until the absolute neutrophil count is >500/mm³ for at least two consecutive days. G-CSF must be stopped 48 hours before the next dose of carbo/doxo is given. However, note that G-CSF support is not mandatory in this protocol.

Pneumocystis carinii prophylaxis with trimethoprin-sulfamethoxazole must be instituted for all patients on 3 days a week - TMP 150 mg/m²/d of TMP and SMX-750 mg/m²/day (1994 Red Book - American Academy of Pediatrics);

- Haematologic support should be provided as needed.

HR.4.2 Doses, Schedules and Timing of Administration

Cisplatin 80 mg/m² over 24 hours as a continuous i.v. infusion on days 1, 29, 57, 85 of the pre-operative phase and then after surgery at day 15. Please, note that Cisplatin should be administered regardless of the peripheral blood cell count.

Carboplatin 500 mg/m² as an i.v. infusion from hours 0-1 on days 15, 43, 71 of the pre-operative course; after surgery, as soon as the child has recovered from surgery; CARBO will be administered at days 0 and 29. In case of renal dysfunction, the actual dose of CARBO to be administered will be calculated according to the modified Calvert's formula as proposed by Newell et al. (18):

\[
\text{Dose (mg)} = \text{target AUC (mg/ml.min) \times [GFR (ml/min) + (0.36 \times BW (Kg))]}
\]

where target AUC is 6.25 mg/mL.min

\[
(AUC = \text{area under the curve})
\]

\[
(BW = \text{body weight})
\]

Doxorubicin 60 mg/m² as a 48 hours continuous i.v. infusion starting soon after the end of the CARBO infusion at days 15, 43, 71 of the pre-operative course and after surgery, as soon as the child has recovered from surgery at days 1 and 29.
HR.4.3 ADMINISTRATION

Cisplatin administration

*Pre-Cisplatin hydration*
125 ml/m²/hour for 12 consecutive hours of
Glucose 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 80 mg/m² made up to 120 cc with Glucose 2.5%/sodium chloride 0.45% infused at 5 ml/hour for 24 hours, run concurrently with:

b) 120 ml/m²/hour for 24 hours of a solution of
Glucose 2.5%/sodium chloride 0.45% +
30ml Mannitol 20%/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*

a) 125 ml/m²/hour for 24 consecutive hours of
Glucose 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

A careful record of fluid input and output should be kept. If diuresis falls below 400 ml/m² per 6 hrs, frusemide 0.5-1mg/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 Gentamycin should preferably be avoided during and immediately after CDDP infusion. If used, serum levels should be monitored with extreme care.

**Magnesium gluconate**, 3 g/m²/day orally, is to be given to all patients, for the entire duration of chemotherapy, beginning with the first cycle.
**Carboplatin** is infused in a 5% glucose solution, 80 ml/m², or 4 ml/kg for infants and children weighing less than 10 kg, over 60 minutes. Immediately after the end of CARBO infusion, start **Doxorubicin** administration. No pre- or post-CARBO infusion hyper-hydration is recommended, but good hydration status is recommended before starting therapy. DOXO is administered in continuous infusion, via a central venous catheter, for 48 consecutive hours. The infusion rate of DOXO should be constant throughout the 48 hour infusion. For this reason infusion of DOXO through a separate i.v. line, in a 5% glucose solution is recommended, using the smallest volume of fluid possible. **If central lines are not available, deep veins should be avoided since extravasation of the drug is dangerous and is not readily appreciated at these sites.** After reconstitution and throughout infusion, all drugs should be protected from the light.

Before each dose of CARBO/DOXO the absolute neutrophil count (ANC) should be greater than 1000/mm³ and the platelet count greater than 100.000/mm³.

CDDP and CARBO are strong emetogenic drugs. Thus, it is recommended to precede the infusions of these two drugs with an anti-emetic cocktail. The 5-HT3 receptor antagonists are the drugs of first choice.

**HR.4.4 THERAPY MODIFICATION:**

**By age**

**In infants with body weight less than 5 Kg** administer drugs at the following dosages

Cisplatin 1.7 mg/kg: if well tolerated increase the dose to 2.6 mg/Kg;  
This is because for body weight less than 10 Kg drug dose must be calculated per Kg, assuming that 1 m² = 30 Kg - and that in very young and small children it is wiser to start with a further 1/3 dose dose reduction.

Carboplatin 11.5 mg/kg: if well tolerated increase the subsequent dose to 16.6 mg/Kg;  
Doxorubicin 1.34 mg/Kg in 48 hours continuous infusion: if well tolerated increase the subsequent dose to 2.0 mg/Kg/48 hours

**For infants and children with body weight between 5 and 10 Kg** administer drugs at the following dosages:  

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>2.6 mg/kg</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>16,6 mg/kg</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>1 mg/kg/day x 2 days, ie 2 mg/kg over 48 hours</td>
</tr>
</tbody>
</table>
This is because for body weight less than 10 Kg drug dose must be calculated per Kg, assuming that 1 m² = 30 Kg.

Please, note that infants are at higher risk of CDDP induced electrolyte imbalance and consequently the need for regular electrolyte monitoring is particularly important in this age group (5). Remember also to adjust the amount of hydration fluids according to infant's weight and age.

**For toxicity**

Try to avoid indiscriminate dose-reduction and unnecessary delay of chemotherapy. Give each patient the maximum recommended and tolerable dose of the drugs at the appropriate time.

**Contact the chemotherapy panel coordinator (Addendum II) for any life threatening, lethal, unexpected or unusual toxicity.** (See also Section 10.0 - Serious Adverse Events).

*Ototoxicity* - The grading system for hearing loss proposed by P R Brock et al will be used in SIOPEL 3 (Table 8) (3). Careful monitoring of children by an expert audiologist and by serial audiometry throughout the treatment with CDDP is recommended. To monitor ototoxicity in infants otoacoustic emissions, when available, 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. If a child starts to show signs of high frequency hearing loss he/she should be followed more carefully than the minimum requirement of this protocol. If grade 3 or 4 ototoxicity is documented, CDDP should be withdrawn. In this event contact chemotherapy panel coordinator (Addendum II).

Table 8 - 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>
Data from the literature seem to indicate a possible increase of ototoxicity in patients treated with CARBO and CDDP. Therefore, the hearing should be carefully monitored, (by whatever method is compatible with the child’s age) throughout treatment and thereafter.

Renal toxicity -

a) Glomerular toxicity - Nephrotoxicity of CDDP in children (as in adults) is dose-related and sometimes severe. Plasma creatinine measurements and creatinine clearances are not reliable guides to the degree of CDDP-induced renal damage, particularly in children. Careful measurement of Glomerular Filtration Rate (GFR) by isotope clearance is essential for accurate monitoring of renal status. The GFR monitoring in this study will be requested less frequently than previously but it is essential that it be carried out on all patients at the time-points that it is asked for. It 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\textsuperscript{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 from an indwelling catheter. It entails less irradiation to the child than daily natural sources. The technique is well described by Chantler et al. Clin Sci 1969; 37: 169-180 and Arch Dis Child 1972; 47: 613-617. If any centre requires further practical information or cannot obtain the literature this can be sent on request. 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 comparative randomised study, so please do not send us these results instead of a GFR. In cases of severe reduction in Cr\textsuperscript{51} EDTA GFR (<60 ml/min/1.73 m\textsuperscript{2}), discontinue CDDP and contact chemotherapy panel coordinator (Addendum II).

In infants refer to Addendum IX for a table of GFR according to age and if the GFR falls below 2 SD below the expected GFR, then discontinue CDDP and contact chemotherapy panel coordinator (Addendum II).

b) Tubular toxicity - Renal loss of Magnesium and consequent Hypomagnesemia is expected in nearly all children on this study and oral Magnesium supplementation is recommended for all children who will be entered into the study. (See HR 4.3). Hypomagnesemia is not a reason to stop CDDP. Children can develop other manifestations of renal tubulopathy at the same time as the GFR is improving. Thus, careful monitoring of electrolytes is essential in all children exposed to CDDP treatment. Hypomagnesemia may persist years after stopping therapy.
Infants are at higher risk of CDDP induced electrolyte imbalance and consequently the need for regular electrolyte monitoring is particularly important in this age group (5). However, CDDP seems no more nephrotoxic in infants than in older children.

*Bone marrow toxicity* - An absolute neutrophil count (ANC) greater than 1000/mm³ and a platelet count greater than 100,000/mm³ are necessary before starting chemotherapy with Carboplatin and Doxorubicin. It is better to delay slightly the institution of chemotherapy until these criteria are met, rather than decreasing the dose. If a delay of one or more additional weeks is required, decrease dosage by 25% for the next course only, and use GCSF (See HR 4.1).

If a course of chemotherapy results in *severe* neutropenia (ANC < 500/mm³) associated with fever and sepsis or severe infection and/or severe thrombocytopenia (< 10,000/mm³ lasting more than 5 days) associated with bleeding, decrease dosage by 25% for the next course. If the subsequent course is not complicated by those events resume the full dosage of the drugs.

*Hepatic toxicity* - No standardised criteria exist for the adjustment of DOXO dosage in the presence of hepatic dysfunction. It seems reasonable to recommend a 50% reduction of DOXO dosage if total serum bilirubin concentration is > 3 mg/100 ml, and/or if serum liver enzymes (AST, ALT) are >5 times the normal value. NB Since DOXO hepatotoxicity is actually very rare, elevated AST, ALT should lead to an energetic search for other causes of liver dysfunction, eg viral hepatitis. *Neither CARBO nor CDDP doses need to be modified.*

*Cardiotoxicity* - Regular monitoring for possible cardiotoxicity is essential. (28). 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 a normal haemoglobin, and is not being hyperhydrated. True baseline measurements should be obtained prior to administration of DOXO to provide a meaningful reference for comparison with future tests.

**An echocardiogram must be performed prior to surgery.**

Significant deterioration in function is indicated by a shortening fraction < 29%. In this event, temporarily withdraw DOXO. 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 chemotherapy panel coordinator (Addendum II).
Cisplatin (CDDP) 80mg/m² 24 hours continuous infusion
Doxorubicin (DOXO) 60mg/m² 48 hours continuous infusion
Carboplatin (CARBO) 500mg/m² 1 hour infusion (Modified Calvert's formula)

Assessment of hearing, kidney function and heart function (see protocol)

RE = response
See Protocol
HR.5.0 REQUIRED PATIENT INFORMATION

At diagnosis

Physical examination including also -
  Anthropometric measurements and nutritional status assessment;
  Determination of the liver/abdominal mass size measured from the costal margin in
  the right and left mid-clavicular line and from the xiphisternum

Laboratory tests
  Full blood cell count
  Bilirubin, ALT & AST; Creatinine, Urea, Electrolytes, Mg"/+Ca"+, Fibrinogen,
  Factor V
  Partial Thromboplastin Time, Thrombin time, Prothrombin time or equivalent;
  Serum α-FP and β-human chorionic gonadotrophin hormone levels;
  Hepatitis A,B and C serology;

NB In case of normal serum α-FP level, ensure that appropriate dilutions have
been carried out. Beware false negative result.

Imaging investigations
  For Pre-treatment tumour extension (PRETEXT) (see also Section 5.0)
  Abdominal ultrasound + abdominal CT scan with contrast or MRI with Gadolinium;
  Chest X-ray (in two projections PA & Lateral) and chest CT scan;

  For chemotherapy toxicity monitoring
  Glomerular filtration rate as measured by $^{51}$Cr-EDTA clearance;
  Audiogram - pure tone in children age 3 years +, or free field or otoacoustic
  emissions
  2-d derived Echocardiogram - measurement of shortening fraction.

During chemotherapy - weekly serum α-FP level - if initial level elevated.

Physical examination including also - Before starting each course
  Anthropometric measurements and nutritional status assessment;
  Determination of the liver/abdominal mass size measured from the costal margin in
  the right and left mid-clavicular line and from the xiphisternum
**Laboratory tests- Before administering chemotherapy**

Full blood cell count
Bilirubin, ALT & AST; Creatinine, Urea, Electrolytes, Mg**+/Ca**, Fibrinogen, Factor V
Partial Thromboplastin Tllme, Thrombin time, Prothrombin time;
Serum alphafetoprotein and ß-human chorionic gonadotrophin hormone levels (if initially elevated);
Urine, creatinine and electrolytes (Na**, K**, Cl, Ca**, Mg**, Phosph) so that, using fractionated excretion, tubular function can be measured.

**Imaging investigations**

For tumour response monitoring
Abdominal ultrasound at days 29, 50 and 90
Chest X-ray (in two projections PA & Lateral) and chest CT scan (if needed at day 50 and 90);

**Chemotherapy toxicity monitoring.**

Glomerular filtration rate as measured by $^{51}$Cr-EDTA clearance should be obtained prior to surgery, and at the end of chemotherapy, unless the plasma creatinine level has risen unexpectedly prior to any course of chemotherapy.
Audiogram prior to surgery and at the end of chemotherapy.
Echocardiogram should be carried out, prior to surgery and at the end of treatment, and at other times if there is clinical concern.

**Before surgery (other than "the pre-surgery routine")**

**Physical examination including also** nutritional status assessment;
Please note that surgical complications are more common in children with a poor nutritional status (27)
Determination of the liver/abdominal mass size measured from the costal margin in the right and left mid-clavicular line and from the xiphisternum

**Laboratory tests**

Full blood cell count
Bilirubin, ALT & AST; Creatinine, Urea, Electrolytes, Mg**+/Ca**, Fibrinogen, Factor V.
Partial Thromboplastin Tllme, Thrombin time, Prothrombin time;
Serum alphafetoprotein and ß-human chorionic gonadotrophin hormone levels (if initially elevated);
Urine creatinine and electrolytes (Na\(^+\), K\(^+\), Cl, Ca\(^{++}\), Mg\(^{++}\), Phosph) so that, using fractionated excretion, tubular function can be measured.

**Imaging investigations**

*For the evaluation of tumour response and extension*
- Abdominal ultrasound and CT scan with contrast or MRI with gadolinium
- Chest X-ray (in two projections PA & Lateral) and chest CT scan

**At the end of therapy**

*Physical examination including also -*
- Anthropometric measurements and nutritional status assessment;

**Laboratory tests**

- Full blood cell count
- Bilirubin, ALT & AST; Creatinine, Urea, Electrolytes, Mg\(^{++}\)/Ca\(^{++}\), Fibrinogen Factor V
- Partial Thromboplastin Time, Thrombin time, Prothrombin time;
- Serum alphafetoprotein and β-human chorionic gonadotrophin hormone levels (if initially elevated);
- Urine creatinine and electrolytes (Na\(^+\), K\(^+\), Cl, Ca\(^{++}\), Mg\(^{++}\), Phosph) so that, using fractionated excretion, tubular function can be measured.

**Imaging investigations**

*For tumour status evaluation*
- Abdominal ultrasound + abdominal CT scan with contrast or MRI with Gadolinium;
- Chest X-ray (in two projections PA & Lateral) and chest CT scan;

*For end of chemotherapy toxicity evaluation*
- Glomerular filtration rate as measured by \( ^{51}\text{Cr}-\text{EDTA} \) clearance;
- Audiogram - pure tone if age 3 years +, otherwise free field testing or otoacoustic emissions

- 2d derived Echocardiogram measurement of shortening fraction
Table 9: Follow up investigations after stopping therapy

<table>
<thead>
<tr>
<th>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 6 months</td>
<td>yearly</td>
</tr>
<tr>
<td>Alpha-fetoprotein</td>
<td>every 2-3 months</td>
<td>every 6 months</td>
<td>yearly</td>
</tr>
<tr>
<td>Chest-X ray *</td>
<td>every 2-3 months</td>
<td>every 6 months</td>
<td>yearly</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>every 2-3 months</td>
<td>every 6 months</td>
<td>yearly</td>
</tr>
<tr>
<td>Serum magnesium</td>
<td>yearly</td>
<td>yearly</td>
<td>yearly</td>
</tr>
<tr>
<td>Cr(^{51}) EDTA -GFR</td>
<td>1 year off treatment to be repeated yearly if &lt;80 ml/min/1.73m(^2)</td>
<td>yearly if &lt;80 ml/min/1.73m(^2)</td>
<td>yearly if &lt;80 ml/min/1.73m(^2)</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+</td>
</tr>
<tr>
<td>Echocardiogram - measurement of shortening fraction</td>
<td>1 year off treatment and yearly</td>
<td>yearly</td>
<td>yearly</td>
</tr>
</tbody>
</table>

* In patients who had lung metastases at diagnosis, lung CT scan is recommended every 6 months for the first 2 years.
HR.6.0 STATISTICAL CONSIDERATIONS

HR6.1 STATISTICAL CONSIDERATIONS

The principal comparison will be to establish improvement or equivalence in response to pre-operative chemotherapy and subsequent resection rates between the single treatment arm and the historical control patients entered onto SIOPEL1.

Due to the small number of high risk HB patients who are expected to be recruited into SIOPEL 3, a prospective randomised controlled trial is impractical, and thus only a prospective single arm study, in which current patients are compared to historical controls, has been considered. Thus, 90 patients entered onto SIOPEL3 and evaluated would provide 80% power that an 11% improvement on this treatment is detected. This assumes the observed response rate of 85% on SIOPEL1 (Julia Brown, Personal Communication) for similar patients, and that a 90% Confidence Interval (CI) is used to assess the difference in response rates (32).

The 90% CI for a response rate of 85% would have a width of approximately ± 6%, for a resection rate of 70% it would be ± 8%.

The accrual of these patients onto SIOPEL2 pilot was approximately 20 per year, so this number of patients could be recruited in 5 years.

Survival (OS) and event free survival will be secondary end-points of the study. After a minimum of 3 years follow up the width of the 90% CI for an OS of 70% would have expected width of ± 8%.

HR 6.2 INTERIM ANALYSIS AND DATA MONITORING COMMITTEE

An early interim analysis will be performed on HR patients after a year of entry. An Independent Data Monitoring Committee (IDMC) will be formed to review the data in particular with regard to toxicity, response and resection rates and advise on further recruitment.

Statistical tests will be interpreted conservatively and if recruitment continues the timing of further reviews will be decided with the IDMC.
HEPATOCELLULAR CARCINOMA
Therapeutic Guidelines
HCC 1.0 THERAPEUTIC GUIDELINES FOR CHILDHOOD HEPATOCELULAR CARCINOMA

Only general therapeutic guidelines have been elaborated for childhood HCC. The data from the SIOPEL 1 study indicate that the prognosis of the patients affected by HCC is considerably worse than for those with HB. However, the 3 year overall survival of the 40 children affected by HCC entered in the study is 28%, an improvement in median survival compared with historical data. Of the 12 patients in SIOPEL 1, who had complete tumour resection, 7 are alive NED with follow-up ranging from 10 to 46 months. Thus, it seems that those children with HCC who can have the tumour completely resected may have a reasonable chance of cure - an observation also made in other trials. The main reason for the relatively poor prognosis is that a large percentage of these tumours are multifocal and unresectable.

In the fibrolamellar variant of HCC the possibility of resection appears to be greater than in the other types.

Because of this, the **following therapeutic suggestions** have been elaborated:

- Tumour biopsy should be performed.

- If the tumour seems to be 'resectable', **primary surgery** should be performed. Subsequently, patients should receive chemotherapy according to the 'high risk hepatoblastoma protocol up to and including day 85 (ie 4 courses of CDDP and 3 of CARBO/DOXO).

- If the tumour is not resectable and/or if metastases are present, children should be treated according to the intensive regimen designed for "High risk HB". Tumour response should be monitored carefully and in case of stable or progressive disease alternative therapy should be considered early.

If other therapeutic strategies are used (eg chemoembolisation, etc) in registered patients, the technique as well as the outcome should be notified to the Trial Centre.
ADDENDUM I

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ADDENDUM II

SIOP LIVER TUMOUR STUDY GROUP MEMBERSHIP

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Dr. Liz Shafford

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Dr. Rudolf Maibach (SIAK Statistician)
Mrs. Margaret Childs (UKCCSG Trial Coordination/data management)

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Dr. Laurence Brugieres (Coordinator)
Dr. Marcelo Scopinaro

Pathology panel:
Dr. Jean Keeling
Dr. Massimo Rugge
Prof. Arthur Zimmerman (Coordinator)

Radiology:
Dr Derek Roebuck

Radiotherapy:
Dr. Jean-Louis Habrand

Surgery panel:
Dr. Paulo Chapchap
Dr. Piotr Czauderna
Dr. M. Guglielmi
Mr. Gordon MacKinlay
Tissue Bank:
Dr. Giuseppe Basso

Advisors:
Transplantation - Prof. J.B. Otte
Toxicity/Late Effects - Prof. Peppy Brock
Scientific - Dr. Jon Pritchard

Continental Representatives:
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Dr. Paulo Chapchap (S. America)
Dr. Marcelo Scopinaro (S. America)
Dr. Peter Hesseling (S. Africa)

SIOP Scientific Committee Representative:
Dr. Jan de Kraker
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<td><strong>Secretary Swiss Pediatric Oncology Group SPOG)</strong></td>
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<td>Jack Plaschkes</td>
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ADDENDUM III

CHILDHOOD LIVER TUMOUR TISSUE STORAGE PROGRAMME

*Note that the arrangements for tumour tissue storage are likely to be revised during the course of SIOPEL 3 - participating centres will all be notified of any changes made.*

Since 1988 a Childhood Liver Tumour Tissue Storage programme has been active in Italy. As of September 1990 this programme has been open also to other European paediatric oncology centres. The aim of this project is to make available biological material derived from cancer patients with the aim of running basic science research projects and hopefully in the not too distant future, of testing prospectively therapeutic hypotheses based on biologic tumour’s and/or patient’s characteristics.

This project is centred at the Tissue Bank located in:
  Dott. Giuseppe Basso's laboratory
  Laboratory of Ematology-Oncology
  Division of Paediatric Hematology Oncology
  Department of Paediatrics - University of Padova
  via Giustiniani 3 - 35128 Padova, Italy
  Tel + 49.821.3505/06/07 - FAX +49.821.3510

**Kit for shipping the biological material**

A kit for shipping biological material can be sent to all the participating institutions. The kit contains:
- a glass bottle containing 50 cc of sterile tissue culture medium;
- a 50 cc plastic tube
- a 10 cc plastic tube
- three 10 cc glass tubes
- a 1 cc vial with Gentamycin
- a sterile plastic fork
- a 1 cc sterile plastic syringe
- two blue ice packages

*If you do not have a kit, please notify the Tissue Bank which will make sure you will receive one as soon as possible.*
How to keep the Kit - The kit can be maintained for 12 months at +4°C centigrade. The blue ice packages should be kept frozen (-20°C) until the very last moment before shipping the kit back to the tissue bank. In this way the biological material will be kept close to +4°C during the time of delivering.

Who are the patients whose biological material should be centralised? - All children affected by a malignant or benign primary hepatic tumour.

What to send to the tissue bank?
Ideally for each eligible patient for the tissue storage programme the following is requested:
- 1 cc3 of tumour tissue
- 1 cc3 of healthy liver tissue
- 10 cc of heparinised patient's peripheral blood or a piece of skin biopsy
- 10 cc of patient's parents' peripheral blood

How to use the Kit and where to put the biological material in the Kit
The kit should be used in the operating room. When using the kit respect the following steps.
INITIALLY
- open the glass bottle with the sterile tissue culture medium aseptically;
- add to the sterile tissue culture medium the 1 cc of Gentamycin using the plastic 1 cc syringe aseptically;
- transfer 10 - 20 cc of sterile tissue culture medium (containing Gentamycin) in the 50 cc plastic tube aseptically;
- add 5 cc of formalin in the 10 cc plastic tube aseptically;
- put the 1 cc3 of tumour tissue in the glass bottle aseptically - make sure that the tumour tissue is completely covered by it; mark this bottle with an adhesive label giving the name of the patient, the date of sampling and the contents.
- put the 1 cc3 of healthy liver tissue or the skin biopsy, if you are not going to send the normal healthy liver tissue, in the 50 cc plastic tube containing the tissue culture medium aseptically - make sure that the material is completely covered by it; mark this tube with an adhesive label giving the name of the patient, the date of sampling and the contents.
- put a piece of tumour tissue in the 10 cc plastic tube containing formalin aseptically - make sure that the tumour tissue is completely covered by formalin.

The 10 cc of patient's and patient's parent's peripheral blood must be put in the three 10 cc glass tubes. Mark each tube with an adhesive label giving the name of the
patient or the name of the patient's parents (specify clearly if he/she is the mother or the father), the date of sampling and the contents.

**When and how and where to send the kit back**

As soon as the material has been sampled, assemble the kit ensuring that each component is stable. Add the frozen blue ice packages which have been kept at -20 °C and then using an express overnight mailing service send it back to Dr. Giuseppe Basso’s laboratory (see address above). Please, remember to notify by FAX dott. Giuseppe Basso that a kit is arriving. Finally, please cover the expenses of sending back the kit to the tissue bank.
**ADDENDUM IV - ROAD MAPS**

**SIOPEL 3 STUDY FOR 'STANDARD RISK' HEPATOBLASTOMA**  
Regimen A

*Cisplatin (CDDP)* 80 mg/m² in continuous i.v. infusion for 24 hours (2.6 mg/kg if body weight less than 10 kg).  
*Doxorubicin (DOXO)* 60 mg/m² in 48 hours continuous infusion (2.0 mg/kg if body weight less than 10 kg).

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**TUMOUR RESPONSE EVALUATION**  
GFR + Audiogram + Echocardiogram  
**DELAYED SURGERY**

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**END OF TREATMENT**  
GFR + Audiogram + Echocardiogram  
1 full blood cell count; 2 electrolytes (including Ca++/Mg++); 3 α-fetoprotein
Cisplatin (CDDP) 80 mg/m² in continuous i.v. infusion for 24 hours (2.6 mg/kg if body weight less than 10 kg)

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TUMOUR RESPONSE EVALUATION

GFR + Audiogram

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DELAYED SURGERY

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END OF TREATMENT

GFR + Audiogram

1 full blood cell count; 2 electrolytes (including Ca++/Mg++); 3 α-fetoprotein
ADDENDUM IV - ROAD MAPS

SIOPEL 3 STUDY FOR 'HIGH RISK' HEPATOBLASTOMA

Carboplatin (CARBO) 500 mg/m² 1 hour infusion (16.67 mg/kg if body weight less than 10 kg).
Doxorubicin (DOXO) 60 mg/m² in 48 hours continuous infusion (2.0 mg/kg if body weight less than 10 kg).
Cisplatin (CDDP) 80 mg/m² in continuous i.v. infusion for 24 hours (2.6 mg/kg if body weight less than 10 kg).

*See protocol for dose modification by age and weight.

<table>
<thead>
<tr>
<th>Day</th>
<th>Actual date</th>
<th>CARBO</th>
<th>DOXO</th>
<th>CDDP</th>
<th>G-CSF</th>
<th>Investigations before instituting therapy</th>
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<td></td>
<td></td>
<td></td>
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TUMOUR RESPONSE EVALUATION, GFR, AUDIOGRAM AND ECHOCARDIOGRAM
DELAYED SURGERY

<table>
<thead>
<tr>
<th>Day</th>
<th>Actual date</th>
<th>CARBO</th>
<th>DOXO</th>
<th>CDDP</th>
<th>G-CSF</th>
<th>Investigations before instituting therapy</th>
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<td></td>
<td></td>
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<td>X</td>
<td></td>
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</tbody>
</table>

END OF TREATMENT - GFR + AUDIOGRAM + ECHOCARDIOGRAM

* If the first course of CARBO has been complicated by severe and protracted neutropenia (regardless of the occurrence of fever) which delayed the institution of the subsequent course of CARBO. G-CSF is administered subcutaneously at the dosage of 5 μg/kg, 24 hours after the administration of CDDP; it must be administered until the absolute neutrophil count is >500mm³ for at least two consecutive days.
ADDENDUM V

RADIOTHERAPY GUIDELINES

When considering any patient for radiotherapy, please consult the Radiotherapy Coordinator - See Addendum II.

Rationale

Before the introduction of efficient polychemotherapy, radiotherapy was frequently used to induce tumour shrinkage and facilitate dissection. It was used by the POG-CCSG group post-operatively in 16 patients with microscopic residual disease. The three year progression-free survival of these children was close to that of completely resected patients (60 vs 67%). At the Institut Gustave Roussy between 1980 and 1987, 8 patients received radiation for minimal macroscopic residual (also known as 'miniscopic') disease. 7 out of 8 are still alive and doing well. By contrast, very few patients with gross residual disease or unresectable tumours treated with radiation have had effective local control. (17)

Indications

Post-operatively, radiotherapy may be indicated in patients with definite or suspected minimal macroscopic residual abdominal disease if the centre elects to do so. Lung irradiation can be considered for selected cases of patients with lung metastases which do not disappear with chemotherapy, and are not amenable to surgical resection. (Contact Radiotherapy Coordinator - See Addendum II). Radiotherapy can also be considered for palliation of progressive or unresectable disease.

Technique and radiation dosages

Residual primary tumour
The patients will be treated with high energy x-rays or a Cobalt unit. They will be treated in 5 weekly sessions of 1.4 to 1.8 Gy.

The target volume will cover only the area of suspected/known residual disease, after surgery. The surgical report, clips and modern imaging will help to shape the fields correctly. Multiple field arrangements are recommended, complying with the usual principles and organ tolerance in children, which include the irradiation of the full width of vertebrae. Maximum dose to both kidneys will be 12 Gy, and to the spinal cord 45 Gy.

Total tumour dose will be kept to a maximum of 45 Gy above 2 years of age and 35 Gy for ages 2 years and below. Where the target volume exceeds a third of the liver, dose will be cut down by 10 to 20%. Dose to the entire liver should never exceed 30 Gy.
ADDENDUM VI

THERAPEUTIC SUGGESTIONS FOR RELAPSING AND/OR RESISTANT HEPATOBLASTOMA AND HEPATOCELLULAR CARCINOMA

For relapsing and/or resistant HB and HCC a phase II study with high dose Cyclophosphamide is proposed.

During the SIOPEL 2 study a phase II study of high dose Cyclophosphamide has been operating for relapsing and/or resistant HB and HCC. This study will continue through SIOPEL 3 in order to recruit a sufficient number of patients to be able to reach a definitive conclusion about the effect of this drug on these tumours. It is expected that, if the number of patients* required to close this study, is reached before the closure of the main trial, another phase II study will then be incorporated within the main trial as a salvage regimen. (See Statistical Considerations).

Upon entering a patient into the Phase II study, please notify the Trial Office and/or contact the Chemotherapy Coordinator. It is extremely important to keep track of these patients and of the effects of the salvage regimen they are treated with, in order to expand the therapeutic armamentarium available for childhood HB and HCC.

Finally, please, also note that Dr. Laurence Brugières at the Institut Gustave Roussy in France is piloting a regimen utilising high dose chemotherapy and peripheral stem cell rescue for relapsing and resistant HB and HCC. For further information, please contact her directly (see Addendum II).

PHASE II STUDY OF HIGH DOSE CYCLOPHOSPHAMIDE

Patient eligibility

a) Patients with an unresectable HB/HCC after first line chemotherapy as indicated in the protocol and ineligible for liver transplantation.
b) Patients without macroscopic evidence of tumour recurrence but with a steadily rising \(\alpha\)-FP elevation (three consecutive rising values at weekly intervals).

c) Patients with high risk hepatoblastoma and stable disease at day 43 (not eligible for orthotopic liver transplant).

d) Patients must have a life expectancy greater than 3 weeks before entering the study.

_Treatment plan_

The chemotherapy recommended for relapsing and/or resistant hepatoblastoma and hepatocellular carcinoma consists of high dose cyclophosphamide (CPM)/MESNA. Initially, patients will receive two courses of high dose CPM administered every 3 weeks. After two courses tumour response and resectability will be evaluated. If after two courses of high dose CPM a response is confirmed but surgical resection is not feasible patients should receive additional cycles of CPM, until the tumour becomes resectable (for selected cases, concurrent RT can be considered) or progresses.

_Chemotherapy guidelines_

_Dose and schedule_

**Cyclophosphamide** 2 g/m\(^2\) in a 2 hour infusion on day 1 and day 2 (total dose 4 g/m\(^2\)) to be administered every 21 days.

_Administration_

1. Start hydration at a rate of 3000 ml/m\(^2\)/day at least 2 hours prior to the administration of CPM with 5% glucose and NaCl 25 mmol (25mEq)/l, KCl 20 mmol (20mEq)/l and Calcium Gluconate 3 mmol (6mEq)/l.

   Pre-hydration should be given until the urine specific gravity is < 1010.
2. Give Mesna 400 mg/m\(^2\) i.v. bolus just before starting the CPM infusion.

3. Give CPM 2g/m\(^2\) as a 2 hour infusion in glucose 2.5% sodium chloride 0.45% at a rate of 125 ml/m\(^2\)/hour.

4. Continue with above hydration (para. 1) at the rate of 125 ml/m\(^2\)/hour with Mesna 2g/m\(^2\)/day until 24 hours after the second dose of CPM.

It is important that the urine output is maintained at a minimum of 3 ml/kg/hour and urine specific gravity < 1010.

Frusemide (0.5 mg/kg) i.v. should be administered 1 hour after the CPM infusion.

CPM is a strongly emetogenic drug; thus it is recommended to precede its infusion with an anti-emetic cocktail. The 5-HT3 receptor antagonists are the drugs of first choice.

**Note - Weight** must be monitored twice a day and electrolytes once a day. **Echocardiogram** must be performed before each course of CPM because of the potential cardiotoxicity of the drug (particularly if the patient has been previously treated with anthracycline).

**Therapy modification**

**By age** - Children less than 10 Kg of body weight will have drug doses calculated per Kg, assuming that: 1 m\(^2\) = 30 Kg. In infants with body weight less than 5 Kg a further 1/3 dose reduction is recommended.

According to this equation the dose of the drugs, expressed per Kg are:

- CPM 66.5 mg/Kg day 1 and 2
- Mesna 13mg/kg bolus then 66 mg/kg in continuous infusion.

**The infusion solution should be adapted to the child's weight.**
**For toxicity**

Contact the chemotherapy coordinator for any life threatening, lethal, unexpected or unusual toxicity. (See also Section 10.0 - Serious Adverse Events).

Try to avoid indiscriminate dose-reduction or delay of chemotherapy. Give each patient the maximum recommended and tolerable dose of the drugs at the appropriate time.

**Bone marrow toxicity** - An ANC greater than 1000/mm$^3$ and a platelet count greater than 100,000/mm$^3$ are necessary before starting chemotherapy. It is better to delay the institution of chemotherapy until these criteria are met, rather than decreasing the dose. If a delay of one or more additional weeks is required, decrease dosage by 25% for the next course only. If a course of chemotherapy results in severe neutropenia (ANC < 500/mm$^3$) 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 those events resume the full dosage of the drugs. Consider the use of **Granulocyte colony stimulating factor (G-CSF)** if the first course of CPM has been complicated by severe and protracted neutropenia with fever. G-CSF is administered subcutaneously at a dosage of 5 µg/kg: from day 4 after the administration of CPM until the absolute neutrophil count is >500/mm$^3$ for at least two consecutive days. G-CSF should be stopped for 48 hours before the next dose of cyclophosphamide.

**Bladder injury** - If microscopic (> 10 RBC/hpf on at least 2 urine analyses) or gross hematuria occurs (hemorrhagic cystitis), double the dose of MESNA. If microscopic or gross hematuria persists or recurs, delete subsequent CPM doses.
Statistical Considerations

With the anticipated accrual onto SIOPEL 3 over 5 years, and if the failure rate of SIOPEL 1 holds, up to 120 treatment failures of HB and HCC patients may eventually occur. This would lead to an average of up to 15 patients a year eligible for a phase II study over the entire study period (including 3 years of follow up). A Gehan two stage method will be used to analyse the study. (16)

The least level of activity considered to be of clinical interest would be a response rate of 30%. In order to reject the treatment with a minimum number of patients, but to reject it wrongly only with $\beta = 5\%$, in the first stage 9 patients successively entered will be evaluated and if any response is confirmed further patients will be entered. The following number of additional patients will be evaluated, depending on the number of initial responses, in order to estimate the effectiveness with standard error 10%.

<table>
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<th>Number of responses:</th>
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<th>4 or more</th>
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</thead>
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<tr>
<td>Number of additional patients:</td>
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<td>15</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

A total of 25 patients may be entered in 2 years.
ADDENDUM VII

PARENT/PATIENT INFORMATION SHEET/INFORMED CONSENT

Because of the number of different countries/institutions participating, and the different languages involved, it is left to each single institution to write its own parent/patient information sheet and informed consent form, as required. The following parent/information sheet prepared for use within the U.K. may be adapted by other participants. Alternatively a list of key points is given, which should be included in any parent/information sheet.

List of key points for inclusion in Parents Information Letter:

1. Nature of disease and prognosis.

2. Outline of results of SIOPEL 1 - Overall survival for HB 79% at 3 years and for HCC - 28% at 3 years.

3. Identification of risk groups - patients with tumour involving all 4 liver sections, or with lung metastases or extra-hepatic abdominal disease at diagnosis, (the 'high risk' group) have a worse prognosis. Other patients are considered 'standard risk'.

4. Explanation of study design, including randomisation for 'standard risk' patients, and single arm for 'high risk'.

5. Rationale for single agent chemotherapy - to decrease toxicity in 'standard risk' group.

6. Rationale for triple chemotherapy - intensification of treatment for 'high risk' group with the aim of improving prognosis.

7. Outline of treatment and possible side effects.

8. Emphasise that the well-being of the child is of primary concern, rather than rigid adherence to protocol guidelines.

9. Involvement in the study is purely voluntary. Non-inclusion of the child in the study will in no way interfere with his/her care.

10. Inform patient that his/her data will be transferred to, and stored at, the UKCCSG Data Centre.
Hepatoblastoma

Your child has recently been diagnosed to have a hepatoblastoma. Hepatoblastoma is a rare malignant tumour (cancer) of the liver. Until the 1980s, few children with hepatoblastoma survived because 60% of the tumours could not be removed from the liver at surgery, and only complete removal of the tumour offers a real chance of cure. The use of chemotherapy (anti-cancer drugs) either before or after surgery has improved the cure rate dramatically.

In the last 10 years, the International Society of Paediatric Oncology (known, for short, as SIOP) has developed a major initiative to improve the cure rate of children with hepatoblastoma and the related tumour - hepatocellular carcinoma (HCC). SIOP has initiated and run a series of treatment ‘trials’ - known as the ‘SIOPEL (SIOP Epithelial Liver Tumour) studies’ to test different forms of chemotherapy. In the first SIOPEL study - SIOPEL 1 - which involved centres throughout the UK, Europe, South America and Australasia - all patients with hepatoblastoma were treated with up to six courses of the drugs Adriamycin and Cisplatin (PLADO) at three weekly intervals. In most cases the tumours responded to chemotherapy (PLADO), with a major reduction in their size and around 85% of tumours could be completely removed by the surgeon. The cure rate in SIOPEL 1 was 75-80% - a dramatic improvement compared with our previous experience.

Examination of the details of the patients in SIOPEL 1 showed that there were two distinct groups of children, a) those (now known as ‘standard risk’ children) in whom the tumour had not spread outside the liver and involved, in the liver itself, either one, two or three of the four ‘sections’ of the liver, and b) those in whom the tumour had obviously spread to the lungs and/or in whom all four of the liver ‘sections’ were involved by the cancer. In the second study - SIOPEL 2 - therefore, patients were grouped according to the extent of disease at diagnosis, ie ‘standard risk’ and ‘high risk’. ‘Standard risk’ children were treated pre-operatively with Cisplatin only (no Doxorubicin) whereas patients with ‘high risk’ hepatoblastoma were given more intensive chemotherapy using three drugs instead of two - Carboplatin was used in addition to Doxorubicin and Cisplatin. The preliminary results of ‘SIOPEL 2’, which was a pilot study involving only around 50 children (compared with 150 in SIOPEL 1) suggested, but did not prove, that Cisplatin, alone, was effective chemotherapy for ‘standard risk’ children.

In the SIOPEL 3 study, for which your child is eligible, patients with ‘standard risk’ hepatoblastoma are being ‘randomised’ to receive pre-operative chemotherapy with either PLADO or Cisplatin only. All the children will have their tumours resected, if the response to chemotherapy is good enough. The results of SIOPEL 1 show that PLADO is effective chemotherapy for hepatoblastoma but the inclusion of Doxorubicin means that there is a small risk of damage to the heart muscle, either during treatment (very unusual) or (rather more often) many years later, during adolescence or adult life. Cisplatin can cause reduction in kidney function and a degree of high tone hearing loss (both ears) but your child will be monitored throughout the treatment to try and minimise these side-effects. Using Cisplatin alone as ‘pre-operative chemotherapy’ avoids the potential risk of heart muscle damage.

We believe ‘single agent’ Cisplatin to be effective chemotherapy for ‘standard risk’ hepatoblastoma but to prove that it is as good as PLADO, we need to conduct what is known as a ‘randomised study’, comparing the two types of chemotherapy. What is a randomised trial? In this type of trial, a computer ‘decides’ which kind of chemotherapy treatment (Cisplatin only or PLADO) your child will receive. Can a
computer really ‘decide’ the best treatment? No, it cannot, but since we, the ‘experts’ do not know whether Cisplatin only or PLADO is the better treatment for children with ‘standard risk’ hepatoblastoma, we are asking the computer to make a random choice, to avoid bias in the selection of the patients. All children will be eligible for surgery to remove the primary tumour, once chemotherapy has been given for 4-6 courses. Your paediatric oncology doctor and/or paediatric specialist nurse, will go over the details of the randomised trial with you, to make sure you completely understand what you are being asked. If you would like your child to be entered into the randomised trial, you will be asked to sign the agreement. If you do not wish your child to be entered into the randomised trial, he/she would be treated with what is generally regarded to be the current ‘standard’ treatment programme for hepatoblastoma, ie PLADO and surgery. If your child has ‘high risk’ hepatoblastoma, he/she will be treated on the more intensive three drug protocol, as in SIOPEL 2. This treatment, we hope, will improve the cure rate for these patients. Because only one-quarter of all children fall into this category, it is not possible to run a ‘randomised’ study, but the results of SIOPEL 3 will be compared to those for similar patients treated with PLADO in SIOPEL 1.

**Hepatocellular Carcinoma**

Hepatocellular carcinoma (HCC) is relatively common in adults, but very rare indeed in children - only 10 patients per year were recruited into the SIOPEL 1 study from the whole of Europe. The prognosis for HCC patients is less good than for hepatoblastoma, with a probable cure rate between 25-30%. However, patients who have their tumour resected, do have a reasonable chance of cure, around 50%. HCC children, in SIOPEL 3, would be treated with the three drug regimen, identical to the ‘high risk’ hepatoblastoma children, in the hope of improving the overall cure rate.

Information on your child’s treatment and progress will be stored at the United Kingdom Children’s Cancer Study Group (UKCCSG) Data Centre in Leicester. The results of this study will be shared widely with other doctors treating this disease but patients will not be identified by name.

If, having read this information sheet, you have any queries please contact one of the doctors on the paediatric oncology team or one of the senior nurses. The trial, and its implications for children and their parents, has been discussed by an independent Research Ethics Committee (REC) who have concluded that it is, in every respect, a proper trial to run, and in which to request participation from parents and older children. If you have any queries about the trial, or complaints about the way it is being run by your local centre, please contact the Chairman of the REC in [Hospital, Address]. If you initially agree to enter the trial, you have the absolute right to withdraw from the trial at any time. Your child would then receive either ‘standard treatment’ (PLADO and surgery) or an alternative treatment recommended to you by your child’s doctor. We would like to stress that in the case that either a) you do not feel able to agree to enter your child in the trial, or b) having initially agreed, you want to withdraw your child from the trial, that is entirely your right and will in no way prejudice your or your child’s relationship with the treatment centre, or the team’s efforts to cure your child.
PARENT INFORMATION LETTER

SUGGESTED CONSENT FORM

I, .......................................................................................... parent/guardian of .................................................................................................... have read and understood the parents’ information letter, and have been given the opportunity to ask questions about the study. I understand and accept the replies given.

I hereby sign my free consent for my child being entered into the randomised trial/being treated on the high risk protocol (delete as appropriate).

I understand my rights at any time to seek further information from the doctor or other sources. I understand that I may also withdraw my child from the study at any time, and that doing this will not prejudice my, or my child’s relationship with the treatment centre, or the team’s efforts to cure my child.

Name of patient: ........................................................................................................

Name of parent/guardian: ............................................................................................

Signature: ................................................................................................................

Date: ......................................................................................................................

Name of physician: ......................................................................................................

Signature: ................................................................................................................

Date: ......................................................................................................................
## ADDENDUM VIII

### AVERAGE NORMAL SERUM α-FETOPROTEIN OF INFANTS AT VARIOUS AGES

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<td>48,406 ± 34,718</td>
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<td>33,113 ± 32,503</td>
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<tr>
<td>2 wk, -1 month</td>
<td>43</td>
<td>9,452 ± 12,610</td>
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<td>2 months</td>
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<td>&gt; 8 months</td>
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*From: Wu, Book and Sudar Serum α-Fetoprotein (AFP) Levels in Normal Infants*  
*Paediatric Research 15 50-52 (1981)*
GLOMERULAR FILTRATION RATE

\[ \text{GFR (mls/min/1.73m)}^2 \]

\[ +2 \text{ SD} \]

\[ \text{Mean} \]

\[ -2 \text{ SD} \]

\( \text{Age (years)} \)

(From Winberg et al 1959)

(Siopel 3\final\May 98)
### ADDENDUM X

#### SCHEDULE FOR RETURN OF DATA FORMS

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<td>Form of Participation</td>
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<td>Registration Form (ALL liver tumour patients &lt; 16 years)</td>
<td>By fax - within 3 working days of diagnosis</td>
</tr>
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<td>2.1</td>
<td>Pathology Registration Form - A (Biopsy)</td>
<td>By fax - together with Registration Form, and local pathology report</td>
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<td>3.0</td>
<td>Rapid Radiology Review Request (Optional for “difficult cases”)</td>
<td>By international overnight delivery (together with radiological findings) to Dr. C. Staalman (see Section 6.6 in Protocol)</td>
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<td>Randomisation Form (Eligible standard risk patients only)</td>
<td>By fax - together with Registration Form or at latest before day 15 following start of first CDDP course</td>
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<td>Diagnostic Findings</td>
<td>Within 4 weeks of diagnosis</td>
</tr>
<tr>
<td>6.0</td>
<td>Radiology Form</td>
<td>Within 4 weeks of diagnosis</td>
</tr>
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<td>7.0</td>
<td>Pathology for Biopsy</td>
<td>[Form issued direct from UKCCSG Data Centre on receipt of Pathology Registration Form A (Form 2.1)]</td>
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<td>Pre-operative Chemotherapy “Standard Risk” Hepatoblastoma - Regimen A</td>
<td>Within 4 weeks of completion of pre-operative chemotherapy</td>
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<td>Pre-operative Chemotherapy “Standard Risk” Hepatoblastoma - Regimen B</td>
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<td>8.2</td>
<td>Pre-operative Chemotherapy “High Risk” Hepatoblastoma</td>
<td>Within 4 weeks of completion of pre-operative chemotherapy</td>
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<td>Delayed Surgery</td>
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<tr>
<td>9.1</td>
<td>Pathology Registration Form - B (Delayed Surgery)</td>
<td>Within 4 weeks of surgery (together with Surgery Form (9.0))</td>
</tr>
<tr>
<td>10.0</td>
<td>Pathology for Delayed Surgery</td>
<td>[Form issued direct from UKCCSG Data Centre on receipt of Pathology Registration Form B]</td>
</tr>
<tr>
<td>11.0</td>
<td>Post-operative Chemotherapy “Standard Risk” Hepatoblastoma - Regimen A</td>
<td>Within 4 weeks of completion of post-operative chemotherapy</td>
</tr>
<tr>
<td>11.1</td>
<td>Post-operative Chemotherapy “Standard Risk” Hepatoblastoma - Regimen B</td>
<td>Within 4 weeks of completion of post-operative chemotherapy</td>
</tr>
<tr>
<td>11.2</td>
<td>Post-operative Chemotherapy “High Risk” Hepatoblastoma</td>
<td>Within 4 weeks of completion of post-operative chemotherapy</td>
</tr>
<tr>
<td>12.0</td>
<td>Response Evaluation</td>
<td>Within 4 weeks of:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a) completion of pre-operative chemo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) change of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c) completion of high dose cyclophosphamide (Phase II study)</td>
</tr>
<tr>
<td>13.0</td>
<td>Serious Adverse Event</td>
<td><strong>By fax - within 24 hours of event</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>(see Protocol section 10.0)</em></td>
</tr>
<tr>
<td>14.0</td>
<td>Orthotopic Liver Transplantation</td>
<td>Within 4 weeks of transplant</td>
</tr>
<tr>
<td>15.0</td>
<td>Phase II Study (High Dose Cyclophosphamide chemotherapy)</td>
<td>Within 4 weeks of completion of chemotherapy</td>
</tr>
<tr>
<td>16.0</td>
<td>Follow Up</td>
<td>At the end of treatment and every 6 months until 3 years from diagnosis, then annually.</td>
</tr>
<tr>
<td>17.0</td>
<td>Progression/Relapse</td>
<td>Within 4 weeks of progression or relapse</td>
</tr>
<tr>
<td>18.0</td>
<td>Death</td>
<td>Within 4 weeks of death</td>
</tr>
</tbody>
</table>