Irinotecan single-drug treatment for children with refractory or recurrent hepatoblastoma

A Phase II trial of the Childhood Liver Tumours Strategy Group of SIOP (SIOPEL)

Study Co-ordinators:

Dr József Zsíros
Dr Laurence Brugières
Dr Peppy Brock (UK)

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1.0 KEY CONTACT NAMES AND ADDRESSES

**Study Co-ordinators**

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Institution</th>
<th>Address</th>
<th>Phone Numbers</th>
<th>Fax Numbers</th>
<th>Email Addresses</th>
</tr>
</thead>
<tbody>
<tr>
<td>József Zsíros</td>
<td>Consultant Paediatric Oncologist</td>
<td>Emma Children's Hospital</td>
<td>Meibergdreef 9 1105 AZ Amsterdam, The Netherlands</td>
<td>+31-20-566-9111</td>
<td>+31-20-691-7735</td>
<td><a href="mailto:j.zsiros@amc.uva.nl">j.zsiros@amc.uva.nl</a></td>
</tr>
<tr>
<td>Laurence Brugières</td>
<td>Service d'Oncologie Pediatrique</td>
<td>Institut Gustave Roussy</td>
<td>11 Rue Camille Desmoullins 94805 Villejuif, France</td>
<td>+33-1-42-11-4211/4178</td>
<td>+33-1-42-11-5283/5275</td>
<td><a href="mailto:brugiere@igr.fr">brugiere@igr.fr</a></td>
</tr>
<tr>
<td>P Brock</td>
<td>Consultant Paediatric Oncologist</td>
<td>Great Ormond Street Hosp. Great Ormond Street</td>
<td>London WC1N 3JN, United Kingdom</td>
<td>+44-207-405-9200</td>
<td>+44-207-813-8588</td>
<td><a href="mailto:brockp@gosh.nhs.uk">brockp@gosh.nhs.uk</a></td>
</tr>
</tbody>
</table>

**SIOPEL Trial co-ordination/data management, statistics**

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Institution</th>
<th>Address</th>
<th>Phone Numbers</th>
<th>Fax Numbers</th>
<th>Email Addresses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ms Margaret Childs</td>
<td>trial co-ordinator</td>
<td>UKCCSG</td>
<td>9 Princess Road West, Leicester, LE1 6TH, United Kingdom</td>
<td>+44-116-2494465 (Direct line)</td>
<td>+44-116-2494460 (Switchboard)</td>
<td><a href="mailto:msc8@le.ac.uk">msc8@le.ac.uk</a></td>
</tr>
<tr>
<td>Rudolf Maibach</td>
<td>statistician</td>
<td>Coordinating Centre</td>
<td>Effingerstrasse 40, CH-3008 Bern, Switzerland</td>
<td>+41-31-389-9191</td>
<td>+41-31-389-9200</td>
<td><a href="mailto:rmaibach@sakk.ch">rmaibach@sakk.ch</a></td>
</tr>
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</table>
2.0 BACKGROUND AND RATIONALE

2.1 Introduction
Hepatoblastoma (HB) is a rare and aggressive tumour of childhood. Although, in the last decade, overall (OS) and event free survival (EFS) of children with HB has been markedly improved due to cisplatin-based chemotherapy and wider availability of advanced surgical techniques, treatment results are still unsatisfactory in children with advanced disease. Treatment according to the SIOPEL 1 protocol, the first international multicentre trial of the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL) on hepatoblastoma, resulted in a 5 year EFS of 66% for the 154 children accrued in the study (Pritchard J, 2000). The extent of intrahepatic disease pre-treatment (PRETEXT) and presence of pulmonary metastases proved to be independent prognostic factors (Brown J, 2000). Patients with metastases at diagnosis had a very poor 5 year EFS of only 28% (Perilongo G, 2000). In the SIOPEL 2 trial - using a more intensive cisplatin-based chemotherapy regimen for high risk patients - 3 year OS and EFS were 52% and 47%, respectively, for high risk patients, suggesting that some improvement might have been achieved in the treatment of children with locally advanced disease (PRETEXT IV) and/or with metastases at diagnosis (preliminary results).

For the cure of HB, complete resection of the tumour is required. However, since more than half the patients present with unresectable disease at diagnosis, pre-operative chemotherapy that can render the tumour resectable has a major role in the treatment. Although most patients experience (initial) partial response to first line chemotherapy, insufficient shrinkage or tumour progression during therapy leads to failure of the treatment in a significant proportion of children. In the SIOPEL 2 trial, overall response rate to pre-operative chemotherapy was 90% for standard risk patients (PRETEXT I-II-III disease) and 76% in high-risk patients with locally advanced disease (PRETEXT IV) and/or with metastases at diagnosis. Complete resection rate - including orthotopic liver transplantation - was, however, 97% for standard risk but only 66% for high-risk patients.

For those patients who do not achieve a tumour-free status with first line therapy or who relapse with unresectable disease, there is currently no standard treatment available. Although second line or salvage chemotherapy with different drug combinations, e.g. Carboplatin+Etoposide, occasionally results in an objective response, most efforts towards cure are disappointing mainly due to resistance of the tumour to known anti-cancer agents. Since the vast majority of failure patients have unresectable disease with a very poor prognosis, the need for an effective salvage drug or regimen is urgent.

Due to lack of consensus on, and recommendations for, second line and salvage treatment for children with refractory or recurrent HB, most patients receive individual therapy regimens with different drugs and dose schedules based on the decision of their local physician. In addition, these very few patients are treated in many centres and data concerning clinical features and response to the different therapies are not collected and registered systematically. This prevents us from gaining sufficient knowledge and experience with the management of this difficult problem.

The SIOPEL group has therefore decided to give recommendations for the evaluation and management of children with refractory and recurrent hepatoblastoma. Main objectives of the recommendations are:
- to develop a uniform way of management of recurrent/refractory HB in order to be able to collect data on clinical features and response to treatment, preferably in all available patients
- to provide a framework for efficient scientific evaluation of potentially effective therapeutic interventions.

The second objective is addressed by the initiation of sequential prospective clinical trials to identify novel effective drugs that - in the first instance - can be used as salvage or second line therapy and - at a later stage, when clinical efficacy is proven - as a part of the first line treatment. It is expected that a novel drug could significantly contribute to a higher efficacy and/or less toxicity of HB treatment.

The aim of this first prospective Phase II clinical trial is to test the feasibility and efficacy of Irinotecan as a salvage therapy for children with refractory or recurrent hepatoblastoma.

2.2. Irinotecan:
Irinotecan is an important and attractive new chemotherapeutic agent that demonstrates activity against a broad spectrum of malignancies, including carcinomas (colon, stomach, lung, ovary, cervix), lymphomas and different childhood tumours.

Irinotecan (CPT-11) is a semisynthetic analogue of the plant alkaloid camptothecin, the prototypical DNA topoisomerase I interactive agent. Other camptothecin analogues are topotecan, and 9-aminocamptothecin. These agents interact with the topoisomerase I-DNA complex and prevent resealing topoisomerase I-mediated DNA single-strand breaks. This eventually leads to double-strand DNA breaks and apoptosis or cell death.

Irinotecan is bioactivated by a carboxylesterase-converting enzyme to form the biologically active metabolite, the topoisomerase I inhibitor SN-38. Bioactivation of intravenously administered Irinotecan by carboxylesterases occurs predominantly in the liver. High concentrations of drug commonly coadministered with Irinotecan do not inhibit carboxylesterase activity. The half-lives of Irinotecan and SN-38 are relatively long, and both are commonly found in the lactone form. SN-38 is eliminated mainly through conjugation by hepatic uridine glucuronosyltransferase, the same isoenzyme that is responsible for glucuronidation of bilirubin (Abang AM 1998; Kuhn JG 1998).

2.3. Efficacy profile of Irinotecan in children:
Preliminary results with camptothecin derivatives show very encouraging results in childhood malignancies. Irinotecan, in particular, is highly active in a broad spectrum of paediatric solid tumour xenograft models, including rhabdomyosarcoma, neuroblastoma, peripheral primitive neuroectodermal tumour, medulloblastoma, ependymoma, malignant glioma and juvenile colon cancer (Hare CB 1997; Thompson J 1997a; Thompson J1997b; Vassal G 1997a; Vassal G 1997b; Vassal 1996).

In a pediatric Phase I trial, one very heavily pretreated patient with refractory hepatoblastoma responded with a fall in alpha-fetoprotein from 1.2 x 10^6 ng/ml to 1.2 x 10^5 ng/ml after three courses of Irinotecan (Furman WL 1998 + personal communication). Four other heavily pre-treated patients treated with a similar dose and schedule in the US, have also had clinically significant responses (Malogolowkin M. personal communication). These encouraging responses make Irinotecan a very attractive drug to evaluate further in hepatoblastoma patients.
The efficacy of Irinotecan appears to be strongly schedule dependent. Data suggest that smaller doses of a topoisomerase I inhibitor administered repeatedly may result in greater anti-tumor activity than large doses administered intermittently. A prolonged schedule of administration - given continuously at low doses or frequent intermittent dosing schedules - appears to be the most effective (Furman WL 1999; O’Leary J 1998; Pazdur R 1998). However, the optimal schedule of administration in children remains an issue that needs to be addressed.

Phase II trials with Irinotecan are also ongoing in children with CNS or solid tumours (Fabbro M 2000). It is expected, however, that these studies will provide insufficient information about the activity of the drug in HB due to the very low accrual rate of HB patients in these trials.

In the present trial Irinotecan will be administered - based on the results of pre-clinical studies - on a prolonged schedule: daily for 5 consecutive days, followed by 2 days off, for 2 weeks out of 3 \((d5)2\times\).

### 2.4. Toxicity of Irinotecan in paediatric Phase I trials

The same protracted schedule of Irinotecan as will be given in this study was found to be well tolerated in the Phase I trial of Furman et al 1999 who treated children aged 2.9-21.3 years (median 14.2 years) with different solid tumours. The dose-limiting toxicity (DLT) was, despite the early use of loperamide, diarrhoea and/or abdominal cramp that occurred in six of 12 patients treated at a dose level of 24 mg/m²/d. This resulted in the maximum-tolerated dose (MTD) for this schedule being established as 20 mg/m²/d. At a dose of 24 mg/m² nine additional patients had NCI grade 1-2 diarrhoea and/or abdominal cramp. On the 20 mg/m²/d dose level, five and three of nine patients experienced diarrhoea of grade 1-2 and 3-4, respectively. Irinotecan-induced diarrhoea typically began during the second week of treatment, usually more than 8 hours after an infusion, and was often accompanied by mild to moderate cramping. It resolved a median of 7 days after onset (range 1 to 16 days). Grade 1-2 diarrhoea was easily managed, without hospitalisation, with early initiation of loperamide. Nausea and vomiting was also modest and was easily controlled by ondansetron +/- dexamethasone. Neutropenia was minimal and not dose limiting. Toxicity observed in this trial is summarised in table below (adapted from Furman W et al, JCO 17:1815,1999):

<table>
<thead>
<tr>
<th>Irinotecan dose level (mg/m²/d)</th>
<th>20; N= 9</th>
<th>24; N= 12</th>
<th>29; N= 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOXICITY</strong></td>
<td>Gr. 1-2</td>
<td>Gr. 3-4</td>
<td>Gr. 1-2</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5</td>
<td>3*</td>
<td>7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>4*</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
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* duration: 1,2,3,6 days; ** duration: 1,1,11 days; ***duration: 4,5 days
\* = one patient's diarrhoea was caused by Clostridium diff.

In the study of Blaney et al 2001 Irinotecan was administered as a 60 min i.v. infusion, daily for 5 days, every 21 days, to 30 children of 1 to 20 years of age (median: 9 y). Irinotecan was well tolerated on dose-levels 30, 39 and 50 mg/m²/d. Although neutropenia was dose-limiting in two heavily pre-treated patients, myelosuppression was not a significant toxicity for the majority of patients. Only 20% of patients experienced grade 4 neutropenia and <15% had grade 4 thrombocytopenia. Late diarrhoea, primarily grade 1-2, occurred in approximately 7%.
two-thirds of patients. Three patients experienced diaphoresis and flushing which in some was also accompanied by (early) diarrhoea. This symptom complex resolved spontaneously or after the administration of a single dose of atropine.

In a Phase I trial of Vassal G et al 2000 Irinotecan was administered to children between 0.9 and 18.5 years of age as a 60-120 min i.v. infusion every 3 weeks with a dose ranging from 200 mg/m$^2$/d to 720 mg/m$^2$/d. The recommended dose was established as 600 mg/m$^2$/d. In non-heavily pre-treated patients (n=48) 1 cardiac failure, 1 grade 3 neutropenia with grade 3 infection, 1 grade 3 cholinergic syndrome and 2 grade 4 late diarrhoea were observed as dose-limiting toxicity. In heavily pre-treated patients (n=33) DLT was observed in two patients (grade 4 neutropenia lasting >7 days).

Results of other paediatric trials using different dose regimens of Irinotecan showed no substantial difference in toxicity (Langevin AM 1998; Furman WL 1998; Vassal G 1998; Vassal G 1999).

3.0 OBJECTIVES OF THE STUDY

3.1. Primary objective
To assess the biologic activity of Irinotecan single drug treatment - when given on a prolonged schedule - in children with refractory or recurrent hepatoblastoma measured by tumour response rate (RR) and rate of early progression (RP).

3.2. Secondary objectives
• To assess duration of response within the time frame of the study in children showing stable disease, or an objective response (PR or CR), to Irinotecan treatment

• To estimate overall survival of children with refractory or recurrent hepatoblastoma treated with Irinotecan on a prolonged schedule

• To assess time to progression of children with refractory or recurrent hepatoblastoma treated with Irinotecan on a prolonged schedule

• To assess rate of resectability in children with refractory or recurrent non-resectable hepatoblastoma when treated with Irinotecan on a prolonged schedule

• To assess toxicity of Irinotecan in children when given on a prolonged schedule.
4.0 STUDY DESIGN

The study will be performed as a prospective multi-centre phase II trial in patients under 21 years.

All patients included in the trial will be treated with a total of 4 courses of Irinotecan given 3 weekly as single agent chemotherapy unless tumour progression occurs or resectability of the tumour is achieved (see flowchart next page).

After each course of Irinotecan, tumour response and toxicity evaluation must take place to exclude tumour progression and/or unacceptable toxicity. Based on the evaluation results, the local physician has to decide whether the patient can proceed on the trial or should be off trial treatment (see flowchart). In case of severe toxicity (grade 3 and 4) dose modification should be considered according to the guidelines given in section 10. For response evaluation and toxicity criteria see sections 8 and 10 and Appendix E

- Patients with stable disease or partial response will continue with the next Irinotecan course until in total 4 courses have been given or resectability of the tumour is achieved.
- When complete response is achieved during the study (without surgical resection of the tumour), the patient should be further treated according to SIOPEL guidelines (see Appendix A).
- During trial treatment, surgical evaluation must take place after the 2nd, 3rd and 4th chemotherapy courses. If the tumour is resectable at any of these time points, resection of the (multiple) tumour localisation(s) should be performed. An aggressive approach (e.g. multiple operations for the local and metastatic tumours) is justified if the tumour can be completely resected and there was a favourable response to preoperative chemotherapy.

If the tumour already seems resectable after the 1st course of Irinotecan we recommend giving a second course to measure the greatest possible effect of the drug on the tumour and performing tumour resection after the second chemotherapy course and the subsequent evaluation.

- When (complete or incomplete) tumour resection is achieved during or at the end of the trial treatment (4 courses of Irinotecan) the patient should be evaluated and treated according to the recommendations of the SIOPEL group (Appendix A).

- For treatment recommendations for patients with tumour progression please consult one of the Study Co-ordinators.
Baseline evaluation

Irinotecan 1st course

PD

Off study
Consider other Phase I/II studies

Irinotecan 2nd course

PD

Surgery

Irinotecan 3rd course

PD

Surgery

Irinotecan 4th course

PD

Surgery

End of study
5.0 PATIENT SELECTION CRITERIA

This study is open for children and young people with a **refractory or recurrent hepatoblastoma** - with or without metastases - after first or second line treatment. Within the restrictions defined in the eligibility and exclusion criteria, all patients may enter the trial regardless of the type and duration of prior chemotherapy.

5.1. Eligibility Criteria:

- **Disease characteristics**
  - Diagnosis: refractory or recurrent hepatoblastoma (regardless of histological subtype). For definition see section 7.1.
  - Measurable disease (Measurable disease is defined by the presence of at least one measurable lesion [as defined in section 8.1] with or without elevated serum alpha-fetoprotein (AFP)

- **Patients characteristics**
  - Age: under 21 yr
  - Good performance status (Lansky score 50-100 in children 10 years and under or Karnofsky score 50-100 in patients over 10 years of age). For performance criteria see Appendix B.
  - Adequate renal function (serum creatinine $\leq$ three times normal)
  - Adequate liver function (serum bilirubin and ALT/AST $\leq$ two times normal)
  - Normal metabolic parameters (serum electrolytes, glucose, calcium, and phosphate)
  - Adequate haematological status (haemoglobin level above 8g/dl, absolute neutrophil count greater than $1.0 \times 10^9/l$ and platelet count greater than $100 \times 10^9/l$)
  - Recovery from the toxicity of prior therapy
  - No history of severe entero-colitis
  - Life expectancy greater than 8 weeks

1. **Other**
   - Written and signed informed consent must be obtained according to institutional guidelines (see Appendix E)
   - Protocol and informed consent must be approved by the local Institutional Review Board/Ethics Committee prior to any patient registration

5.2. Criteria for exclusion

- Patients with hepatocellular carcinoma
- Chemotherapy within 3 weeks before start of the study
- Prior treatment with Irinotecan.
- Any concurrent anticancer therapy (other than indicated in the protocol)
- Severe uncontrolled infection or entero-colitis
- Pregnancy or breastfeeding
**6.0 REGISTRATION AND DRUG SUPPLY**

To register a patient, the registration form may be available from the password protected area of the SIOPEL web site – [www.siopel.org](http://www.siopel.org)
or contact **Margaret Childs** – Trial Co-ordinator (see page 3). The completed registration form should be faxed to Margaret Childs at the UKCCSG Data Centre: fax number **+44-(0)116-2549504**. The Data Centre is open during normal office hours, 9.00 am – 5.00 pm, Monday to Friday.

On receipt of the Registration Form in the UKCCSG Data Centre, arrangements will be made for distribution of Irinotecan. The process will be initiated with the pharmacy at Great Ormond Street Hospital:

**Pharmacy**
Great Ormond Street Hospital  
Great Ormond Street  
London. WC1N 3JN  
Fax: +44 (0)207-829-8800  
Tel: +44 (0)207.829-8854

Centres must allow sufficient time for shipment of drug. Drug requests received by Great Ormond Street Hospital Pharmacy, before 1500 hours Monday – Friday, will be dispatched the same day. After 1500 hours, drug will be shipped the next day, or if Friday on the following Monday.

The full supply of drug, 40 vials per patient, will be issued. Any unused drug, if patients leave the study, will be automatically recalled back to the Pharmacy by the UKCCSG Data Centre. It is vital, therefore, that the Data Centre is notified promptly of any withdrawals/deaths.

**7.0 REQUIRED DIAGNOSTIC AND CLINICAL INVESTIGATIONS**

**7.1. Diagnostic procedure**

**7.1.1. Definition of refractory disease**
Persistent or growing tumour lesion(s) with or without elevated alphafetoprotein (AFP) level showing insufficient or no response to previous chemotherapy

**7.1.2. Definition of recurrent disease**

- recurrent tumour lesion(s) (local or metastatic) detected by imaging techniques and serial elevation of serum AFP (at least 3 consecutive rising values, taken at weekly intervals) (NB: in patients with elevated serum AFP biopsy of the tumour is recommended but not compulsory)  
  or
- recurrent tumour lesion(s) (local or metastatic) with normal AFP, histologically confirmed by biopsy (NB: biopsy of recurrent tumour is compulsory in patients with normal serum AFP); Central review of pathology will be requested.

When there is only an increased AFP, without detectable tumour lesions, we advise waiting and following the serum AFP level and, if it continues to increase, performing repeated
imaging studies (ultrasound, CT, MRI, PET–scan, bone scan etc.) to detect recurrent tumour mass. Past experience indicates that an elevated AFP can precede by many weeks the actual documentation of tumour recurrence. One should, however, wait until the site of recurrence is clear so that local treatment can be performed (if necessary, after chemotherapy).

7.2. Baseline evaluation
The aim of clinical evaluation at entry is to know the exact extent of the disease and the general condition of the patient. For a schedule of investigations see Appendix C.
- Medical history with special attention to gastro-intestinal symptoms, infections and performance status.
- Physical examination with special attention to respiratory distress, hepato-splenomegaly, ascites.
- Laboratory investigations: Complete blood count, blood chemistry including serum creatinine, sodium, potassium, bilirubin, liver enzymes (ALT, AST), albumin, and serum AFP.
- Imaging studies: The extent of disease (including PRETEXT stage) is assessed from pre-treatment imaging with contrast enhanced abdominal CT and/or MR and chest x-ray (PA and lateral) and/or CT of the thorax. NB: If the chest radiography shows no metastases, CT of the thorax is compulsory. The imaging radiologist must also determine the number of tumour lesions and the longest diameters of the target lesions (see 8.1 and 8.2). It is acknowledged that there may be difficulties in correctly assigning tumour extent according to the Couinaud’s nomenclature and the SIOPEL PRETEXT system because of altered anatomy of the liver due to previous resection.
- Specific investigations / imaging studies to measure tumour lesions other than specified above

Note: All baseline evaluations should be performed as closely as possible to the beginning of treatment and definitively within two weeks prior to the start of the first course.

7.3. Clinical and radiological investigations during treatment
The aim of these investigations is to evaluate response (extent of the disease), surgical resectability, treatment related toxicity and general condition of the patient. This evaluation must take place after each chemotherapy course. Investigations required for the assessment of response and resectability (imaging studies and AFP) should be performed in the 3rd week of a course just before the subsequent course of Irinotecan. For a schedule of investigations see Appendix C.

- Medical history with special attention to gastro-intestinal symptoms and infections
- Physical examination with special attention to signs of entero-colitis and/or infection
- Laboratory investigations: Complete blood count, blood chemistry including serum creatinine, sodium, potassium, bilirubin, liver enzymes (ALT, AST), albumin
- Serum AFP if elevated at entry
- Imaging studies: x-ray, CT or MR - with measurement of target lesion(s) - whichever is appropriate to evaluate response and surgical resectability (see section 8.)

Note: The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up.
7.4. Rapid central review of radiological findings
In order to assist the local radiologists and oncologists in interpreting the radiological findings and measurement criteria outlined in section 8, both during baseline and response evaluation, Dr Derek Roebuck, has agreed to coordinate a service for a rapid central review of the radiological findings (RRR). This means that upon request films will be reviewed and the opinion of an expert will be forwarded urgently (by fax or email) to the referring centre. (A copy of the results will be sent to the UKCCSG Data Centre). A special form (Radiology Rapid Review Request) has been devised for this review.

To submit a case for RRR, as many images as possible should be submitted. The completed form and all the pertinent radiological studies should be sent, either 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
United Kingdom

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

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

Central review of the diagnostic images is not mandatory to enter patients into the trial but is strongly encouraged.

7.5. Central review of radiological findings
The quality and value of this trial is largely dependent on the accuracy of evaluating response to therapy. In order to ensure a quality as high as possible a central review of all relevant radiological investigations (films) will be performed. Images must be submitted, upon request of the Trial Co-ordinator, using the same system as for rapid radiological review (see above).
8.0 RESPONSE EVALUATION CRITERIA

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Therasse P 2000).

8.1. Measurability of tumour lesions
At baseline, tumour lesions will be categorised as follows:

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

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

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

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

8.2. Baseline documentation of “target” and “non-target” lesions

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

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

**Tumour marker**
In this study, the level of serum **alpha fetoprotein** (AFP), a specific tumour marker in hepatoblastoma, will also be used to determine response.
8.3. Tumour response evaluation

Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum LD

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Note: Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria

Evaluation of non-target lesions and tumor marker level

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

Incomplete Response / Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions and/or >1 log.increase in tumor marker level

Evaluation of overall response

<table>
<thead>
<tr>
<th>Target lesions</th>
<th>Non-Target lesions</th>
<th>New Lesions</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR PR</td>
<td>Incomplete response/SD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR PD</td>
<td>Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD PD</td>
<td>Non-PD</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>PD Any PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>
In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

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

8.4. Confirmation
To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments. During the trial, this will be achieved by the regular evaluation after each course of Irinotecan. When the study is completed with PR/CR or the patient is off study due to achievement of CR, an additional assessment of response status should be performed at a minimum of 3 weeks after the last evaluation.

In the case of SD, follow-up measurements must have met the SD criteria at least twice after study entry at a minimum interval of 6 weeks

8.5. Duration of response
Duration of overall response
The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease
Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Early progression – Any progression occurring within the first 42 days after the start of treatment will be considered an early progression and used accordingly in the response evaluation (see section 12.1)
9.0 TREATMENT PLAN

9.1. Dose and schedule of Irinotecan
Irinotecan will be administered as a 60 minute intravenous infusion at a dose of 20 mg/m² daily for 5 consecutive days and for two consecutive weeks repeated every 21 days [(20 mg/m² /day) x5] x2 (day 1-5 and 8-12).

<table>
<thead>
<tr>
<th>Irinotecan</th>
<th>↓↓↓↓↓↓↓↓↑ ↑</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/m²/day</td>
<td>i.v. in 60 min</td>
</tr>
<tr>
<td>days: 1, 2, 3, 4, 5, 8, 9, 10, 11, 12</td>
<td></td>
</tr>
</tbody>
</table>

9.2. Criteria for commencing treatment courses
A new course of therapy should not begin until the absolute neutrophil count (ANC) has recovered to $\geq 1.0 \times 10^9$/l, the platelet count has recovered to $\geq 75 \times 10^9$/l, and treatment-related diarrhoea or other non-haematological toxicity is fully resolved. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing the trial. For dose modifications after treatment delay see 10.3.

9.3. Guidelines for Administration
The appropriate amount of Irinotecan should be mixed with 5% Dextrose Injection. The package insert recommends that the final Irinotecan concentration remain between 0.12 and 1.1 mg/ml. If this results in too much fluid volume for a 60-minute infusion (particularly with higher doses), a higher concentration of Irinotecan may be used, but the concentration of Irinotecan should not exceed 2.8 mg/ml. The total volume is infused through a free-flowing intravenous catheter at a constant rate over 60 minutes. Once diluted, the admixture should be administered within 6 hours if stored at room temperature, or 24 hours if stored refrigerated. Nothing else may be added to the bag.

Generally, Irinotecan can be administered in an outpatient setting. However, patients should be observed for two hours after each infusion for evidence of cholinergic symptoms. Administration of Irinotecan to children under the age of 2 years should be restricted to paediatric oncology centres and should not been done in an out-patient setting.

Pre-medication and detailed supportive care measures are given in section 10.

9.4. Formulation & Stability
Irinotecan is available in 2 ml and 5 ml vials containing 40 mg and 100 mg, respectively. Irinotecan is stable to heat in both the solid and solution states but is slightly unstable to light. The stock solution is stable for at least 3 years at room temperature when protected from light. Admixtures with 5% Dextrose Injection are chemically and physically stable for at least 24 hours at ambient temperature and lighting when stored in clear glass bottles.
9.5. Supplier
Global Aventis are kindly providing sufficient Irinotecan to treat 30 patients. The drug will be sent to the treating centre from the pharmacy at The Hospital for Sick Children, Great Ormond Street, London, on receipt of the Registration Form in the Trial Office. (See Section 6.0).

9.6. Precautions
- **Contraindications**
  Irinotecan is contraindicated in patients with known hypersensitivity to the drug.

- **Drug interactions**
  It would be expected that laxative use during therapy with Irinotecan would worsen the incidence or severity of diarrhoea, but this has not been studied. In view of the potential risk of dehydration secondary to vomiting or diarrhoea, or both, induced by Irinotecan, the physician may wish to withhold diuretics during treatment with Irinotecan and, certainly, during periods of active vomiting or diarrhoea.

- **Infusion site**
  Irinotecan is administered by intravenous infusion. Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile water and applications of ice are recommended.

- **Patients at particular risk**
  Physicians should exercise particular caution in monitoring the effects of Irinotecan in patients who have previously received pelvic/abdominal irradiation. These patients are at increased risk of severe myelosuppression following the administration of Irinotecan. The concurrent administration of Irinotecan with irradiation has not been adequately studied and is not recommended.

  The use of Irinotecan in patients with significant hepatic dysfunction has not been established and therefore not recommended.

- **Pregnancy**
  Irinotecan may cause foetal harm when administered to a pregnant woman.
10.0  TOXICITY, SUPPORTIVE CARE, DOSE MODIFICATIONS

10.1. Toxicity profile of Irinotecan:

- **Cholinergic syndrome and early diarrhoea**
  Irinotecan can induce cholinergic syndrome resulting from the inhibition of acetylcholinesterase activity and is frequently seen during or shortly after infusion of Irinotecan. Patients may experience one or more of the following symptoms: diarrhoea, rhinitis, increased salivation, contraction of pupils (myosis), lacrimation, diaphoresis, flushing and intestinal hyperperistalsis that can cause abdominal cramping. Symptoms are usually transient and only infrequently severe. Early diarrhoea and other cholinergic symptoms may be prevented and/or easily controlled with atropine (see Management of side effects – Section 10.2).

- **Late-onset diarrhoea**
  In the Phase I studies the main dose-limiting toxicity of Irinotecan when given on a prolonged schedule was late diarrhoea. It occurred in the majority of patients and was NCI grade 3 or 4 in up to 40%. It appears to be related to the effects on the bowel of SN-38, the active metabolite of Irinotecan, which undergoes biliary excretion and inactivation. Late diarrhoea generally occurs more than 24 hours after administration of Irinotecan and may be severe, prolonged, may lead to dehydration and electrolyte imbalance and can be life threatening. Early recognition and treatment of late diarrhoea with loperamide - and fluid and electrolyte replacement, if necessary - effectively control the diarrhoeal episodes and reduce patient morbidity (Bleiberg H 1996; Hecht JR 1998; Saliba F 1998; Van Huyen JP 1998, Siu LL 1998).

- **Neutropenia**
  Irinotecan can induce myelosuppression, particularly neutropenia. Haematological toxicity was dose limiting in several adult Phase I trials using weekly or three-weekly schedules of Irinotecan. Deaths due to sepsis following severe neutropenia have also been reported in adult patients treated with Irinotecan. Among patients on the weekly schedule, Grade 3 or 4 neutropenia has been found to be significantly higher in patients with previous pelvic/abdominal irradiation and in patients with modestly elevated baseline serum total bilirubin levels (>17 µmol/l). Neutropenia is much less frequent on the prolonged schedule.

- **Nausea and vomiting**
  Irinotecan is emetogenic. When observed, nausea and vomiting usually occur during or shortly after administration of Irinotecan. However, delayed-onset nausea and vomiting may also occur.

The toxic effects of Irinotecan seem to be schedule-dependent with diarrhoea being the predominant toxicity on prolonged (continuous or intermittent) dosing schedules and neutropenia predominating on a single dose schedule (Eckhardt SG 1998). It appears that with a prolonged low dose schedule normal haemopoietic cells with low topoisomerase I levels may be spared (O’Leary J 1998).

10.2. Management of side effects

- **Cholinergic symptoms and early diarrhoea:**
  Administration of intravenous or subcutaneous atropine should be considered (unless clinically contraindicated) in patients experiencing diaphoresis, abdominal cramping or
early diarrhoea. This should result in prompt resolution of the symptoms. Prophylactic administration of atropine prior to subsequent doses of Irinotecan is at the discretion of the local physician.

*Early diarrhoea:* Patients who have the onset of diarrhoea during the Irinotecan infusion or within two hours following the completion of the Irinotecan infusion should receive a dose of *atropine* 0.01 mg/kg (maximum 0.4 mg) i.v./s.c. Early onset diarrhoea is usually presaged by diaphoresis, abdominal cramping and other cholinergic manifestations.

*Since Irinotecan is being administered on a daily x 5 schedule, it may be difficult to distinguish early versus late diarrhoea. If a patient with presumed early diarrhoea does not improve with administration of atropine, they should be instructed to begin the treatment for late diarrhoea that is outlined below.*

- **Late-onset diarrhoea**
  Late onset diarrhoea is defined in this trial as diarrhoea with an onset more than two hours after completion of the Irinotecan infusion.

If late diarrhoea occurs, the patient should be treated promptly with *loperamide*. Parents/patients must be instructed to have loperamide available at home and begin treatment immediately at the first episode of poorly formed or loose stools, or at the earliest onset of bowel movements more frequent than normally expected for the patient. Each patient/parent must receive with each course of Irinotecan a copy of instructions for loperamide administration (Appendix D). Diarrhoeal episodes and administration of loperamide, with the dose given, must be recorded on the instruction sheet. Parents/patients should also be instructed to notify their physician if any diarrhoea occurs.

**Loperamide dosing recommendation for late diarrhoea:**

*Under 10 kg:*
- 1 mg after the first loose bowel movement followed by
- 0.5 mg every 3 hours
- maximum 0.5 mg/kg/day

*11-20 kg:*
- 1 mg after the first loose bowel movement followed by
- 1 mg every 3 hours
- maximum 0.5 mg/kg/day

*21-30 kg:*
- 2 mg after the first loose bowel movement followed by
- 1 mg every 3 hours
- maximum 0.5 mg/kg/day

*31-40 kg:*
- 2 mg after the first loose bowel movement followed by
- 1 mg every 2 hours
- maximum 0.5 mg/kg/day
**Above 40 kg:**
- 4 mg after the first loose bowel movement followed by
- 2 mg every 2 hours

NB.: Because of a generally decreased metabolising (conjugation) capacity of young children loperamide is contraindicated for children under two years of age in many countries. Despite this formal contraindication we recommend the usage of loperamide for all ages since no effective alternative drug exists for the treatment of this specific side effect.

Loperamide should be continued until a normal pattern of bowel movements returns and patients should stop taking loperamide only after a 12-hour diarrhoea-free period.

Patients with severe diarrhoea should be carefully monitored. If the diarrhoea is not controlled after 3 consecutive days of regular loperamide, or if the patient is dehydrated, loperamide must be stopped and the patient hospitalised for intravenous fluids (and electrolytes, if necessary). If blood or mucus is found in the stools at any time during diarrhoea, loperamide must be stopped and the patient hospitalised.

When hospitalisation is necessary administration of Irinotecan must be interrupted. Subsequent courses should be delayed until the patient recovers and subsequent doses should be reduced (see 10.3 for dose modifications).

Patients with concomitant grade 3 or 4 diarrhoea and grade 3 or 4 neutropenia should be hospitalised and treated aggressively (i.v. hydration, loperamide, antibiotics).

- **Neutropenia**
  Careful monitoring of the white blood cell count with differential, haemoglobin, and platelet count is recommended during and after each course of Irinotecan. Administration of Irinotecan should be interrupted if neutropenic fever occurs. Patients with neutropenic fever should be hospitalised and treated with i.v. antibiotics according to local guidelines. Subsequent courses should be delayed until the patient recovers and subsequent doses should be reduced (see 10.3 for dose modifications). Routine administration of a colony-stimulating factor (G-CSF) is not necessary, but physicians may wish to consider G-CSF use in individual patients experiencing significant neutropenia or neutropenic fever.

- **Nausea and vomiting**
  Pre-medication and treatment with antiemetic agents - preferably the combination of a 5-HT3 blocker and dexamethasone - is recommended. If the patient experiences protracted nausea and vomiting, they should receive antiemetic agents for at least 48 to 72 hours following administration of Irinotecan. NOTE: The administration of prochlorperazine on the same day as Irinotecan has been associated with a higher incidence of akathisia and is therefore not recommended.

10.3. **Dose and schedule modifications**

A new course of therapy should not begin until the absolute neutrophil count (ANC) has recovered to $\geq 1.0 \times 10^9/l$, the platelet count has recovered to $\geq 75 \times 10^9/l$, and treatment-related diarrhoea or other non-haematological toxicity is fully resolved. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing the trial treatment. In patients
who experience reversible grade 3-4 toxicity, a 20% dose reduction is permitted for the subsequent courses.

11.0 ASSESSMENT OF SAFETY AND SERIOUS ADVERSE EVENTS

Monitoring for safety and toxicity will be performed throughout the study, and an evaluation of toxicity using standard criteria will be recorded. Toxicity will be graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). For selected items see Appendix E. The full text version can be downloaded from http://ctep.cancer.gov/reporting/ctc.html.

11.1 Serious Adverse Events

All serious adverse events (SAE) occurring during therapy must be reported immediately within 24 hours – by fax to the trial office using the Serious Adverse Event Form.

A serious adverse event (SAE) is defined as:

- any unexpected or untoward medical occurrence that:
  - results in death
  - is life-threatening
  - results in persistent or significant disability/incapacity
  - requires or prolongs hospitalisation

- any unexpected grade 4 toxicity (other than diarrhoea, neutropenia or vomiting)

The Study Co-ordinators will be responsible for the further reporting of Serious Adverse Events.

12.0 STATISTICAL CONSIDERATIONS

This is a prospective Phase II trial to determine the biological activity of Irinotecan in children with refractory or recurrent hepatoblastoma. Phase II trials do however not allow a definite answer on the clinical value of the compound under study. Rather, they lead to the recommendation whether or not to explore it in further trials.

For the present trial we use the multinomial design proposed by Zee et al (Zee B 1999; Dent S 2001). This two-stage design is based on the simultaneous assessment of both response and early progression in the patients. Accrual is stopped after stage 1 if the required number of responses is not attained or the rate of early progression is elevated. Otherwise recruitment continues up to the total planned sample size.

12.1 Two-stage design and sample size:
The sample size considerations are based on the following decision parameters: The rate of response (RR, defined by CR plus PR) should be at least 20% in order for Irinotecan to be considered a promising compound. If the true underlying RR is ≤5% and the true rate of early
progression is $\geq 60\%$ then the probability of accepting the drug as promising should not exceed 5% (type 1 error probability $\alpha=5\%$). If however the true RR is $\geq 20\%$ or the true rate of early progression is $\leq 40\%$ then the probability of rejecting the drug should not exceed 20% (type 2 error probability $\beta=20\%$, power=80%).

The maximal sample size is chosen to be 30 patients. After 15 patients are evaluable for response and early progression, the stage 1 analysis is carried out. The trial is stopped and the drug rejected as not promising in the following situations:

- 0/15 response
- 1/15 response and $\geq 7/15$ early progressions
- $\geq 9/15$ early progressions

Otherwise the trial continues up to the final sample size of 30 patients.

The final analysis of all 30 patients will state that the drug is promising for further study in case of:

- $\geq 2/30$ responses and $\leq 13/30$ early progressions
- $\geq 3/30$ responses and $\leq 14/30$ early progressions
- $\geq 4/30$ responses and $\leq 16/30$ early progressions

Otherwise the drug will be rejected as not promising for further research in the treatment of patients with recurrent and refractory hepatoblastoma.

12.2. Duration of the trial:

Based on the accrual rates of the SIOPEL 2 trial (45 pts / year) and the SIOPEL3 trial (79 pts in the year 2000) and the estimated cumulative failure rate in the SIOPEL 1 and 2 studies (ca. 25%), approximately 15-20 pts/year are expected to have a refractory or recurrent disease. Supposing that some of the patients have a resectable disease or can/will not be enrolled in the study, accrual of 12 patients per year can be predicted. With that accrual it will take 1.3 years to complete stage I, and about 2.6 years to complete the total trial (stage I and II). The Children’s Oncology Group (COG) is running a parallel study and it is hoped that results from the two studies can be pooled. Such international co-operation will reduce the accrual period.

12.3. Endpoints:
- For the assessment of response rate the best overall response will be evaluated. A responder is defined as: any patient with CR or PR in the period from the start of Irinotecan treatment until disease progression / recurrence. All other cases will be defined as non responders.
- Early progression
- For the assessment of overall survival and time to progression, end point will be death and disease progression, respectively. Overall survival time and time to progression will be calculated from the start of treatment.
- For the assessment of duration of overall response disease progression or recurrence will be used as endpoints. The duration of overall response will be measured from the time measurement criteria are met for CR or PR (whichever is first recorded). The duration of overall CR is measured from the time measurement criteria are first met for CR.
- For the assessment of resection rate surgical resection (complete or incomplete) will be taken as the end point.
12.4. Data Analysis
Rates of response, early progression and resectability will be reported together with a 95% confidence interval. Time to progression and overall survival will be estimated by the Kaplan-Meier method. Toxicity will be described in detail.

12.5. Interim analysis and stopping rules:
Stopping rules, based on the primary endpoints response and early progression, are detailed in section 12.1. The trial will also be closed prematurely if 2 toxic deaths occur in the first 15 patients.

12.6. Reporting of results and exclusions

12.6.1. Evaluation of toxicity.
All patients will be evaluable for toxicity from the time of their first treatment with Irinotecan.

12.6.2. Evaluation of Response
All patients included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria will be included in the main analysis of the response rate and progression rate. Patients in response categories 4-9 will be considered as failing to respond to treatment (disease progression). (Note: An incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.)

All conclusions will be based on all eligible patients.

The 95% confidence intervals will be provided.

All registered patients will be followed until death, or for a maximum of 10 years.
Patients who do not meet the eligibility criteria will be followed for survival and for response to the given treatment.

13.0 STUDY CONDUCT
This is an international study, which will be conducted in accordance with the requirements of Good Clinical Practice (ICH GCP). The study will have to be approved by the institutional or national review board of all participating centres.
14.0 REFERENCES

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APPENDIX A  RECOMMENDATION FOR THE TREATMENT OF CHILDREN OFF STUDY

Irinotecan Phase II study

- Progressive disease
  - Consider other Phase II studies

- Complete response (without surgery)
  - Give 2 more courses of Irinotecan
    - Contact study co-ordinator

- Surgical resection (after response to Irinotecan)
  - Complete resection
    - Consider more courses of Irinotecan
      - Contact study co-ordinator
  - Incomplete resection
    - Consider other Phase II studies

- Unresectable
  - Partial response to Irinotecan
  - Stable disease
APPENDIX B PERFORMANCE CRITERIA

I. Patients less than or equal to 10 years of age:

**MODIFIED LANSKY SCORE** (Score as 0 – 100)

A. Normal Range
   100 = Fully active
   90 = Minor restrictions in physically strenuous play
   80 = Restricted in strenuous play, tires more easily, otherwise active

B. Mild to Moderate restriction
   70 = Both greater restrictions of and less time spent in active play
   60 = Ambulatory up to 50% of time, limited active play with assistance/supervision
   50 = Considerable assistance required for any active play; full ability to engage in quiet play

C. Moderate to severe restriction
   40 = Able to initiate quiet activities
   30 = Needs considerable assistance for quiet activity
   20 = Limited to very passive activity initiated by others (e.g. TV)
   10 = Completely disabled, not even passive play
   0 = Unresponsive, coma

II. Patients greater than 10 years of age:

**KARNOFSKY SCALE**

100 = Normal; no complaints
90 = Able to carry on normal activities; minor signs or symptoms of disease
80 = Normal activity with effort
70 = Cares for self. Unable to carry on normal activity or do active work.
60 = Requires occasional assistance but able to care for most of his/her needs.
50 = Requires considerable assistance and frequent medical care
40 = Disabled; requires special care and assistance.
30 = Severely disabled; hospitalization indicated though death not imminent.
20 = Very sick. Hospitalization necessary. Active support treatment necessary.
10 = Moribund
0 = Dead
### APPENDIX C SCHEDULE OF INVESTIGATIONS BEFORE AND DURING TRIAL TREATMENT

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>Course 1</th>
<th>Course 2</th>
<th>Course 3</th>
<th>Course 4</th>
<th>Confirmation of response* (3 wks after last evaluation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan administration (IR)</td>
<td></td>
<td>IR</td>
<td>IR</td>
<td>–</td>
<td>IR</td>
<td>IR IR -- IR IR -- IR IR -- IR IR --</td>
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<tr>
<td>Week</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5 6 7 8 9 10 11 12 15</td>
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<tr>
<td>Medical history</td>
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<td>×</td>
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<tr>
<td>Record of diarrhoea</td>
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<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>× × × × × × × × × × × × X X X X</td>
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<tr>
<td>Physical examination</td>
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<td>×</td>
<td>×</td>
<td>×</td>
<td>× × × × × × × × × × × × X X X X</td>
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<tr>
<td>Full blood count</td>
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<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>× × × × × × × × × × × × X X X X</td>
</tr>
<tr>
<td>Electrolytes, renal- and liver function</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>× × × × × × × × × × × × X X X X</td>
</tr>
<tr>
<td>Serum AFP</td>
<td>×</td>
<td>×</td>
<td></td>
<td>×</td>
<td></td>
<td>× × × × × × × × × × × × X X X X</td>
</tr>
<tr>
<td>Measurement of target-lesions**</td>
<td>×</td>
<td>×</td>
<td></td>
<td>×</td>
<td></td>
<td>× × × × × × × × × × × × X X X X</td>
</tr>
<tr>
<td>Assessment of non-target lesions**</td>
<td>×</td>
<td>×</td>
<td></td>
<td>×</td>
<td></td>
<td>× × × × × × × × × × × × X X X X</td>
</tr>
<tr>
<td>Assessment of PRETEXT stage</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>× × × × × × × × × × × × X X X X</td>
</tr>
</tbody>
</table>

* When the patient completes the study with PR or CR, additional assessment of response have to be performed min. 3 weeks after the last evaluation (see 8.4.)

** For the measurement and assessment of target and non-target lesions appropriate imaging studies should be performed (for details see section 7.0)
APPENDIX D
(To be printed on headed paper)

The International Society for Paediatric Oncology (SIOP) Liver Tumour Study Group Phase II Study of Irinotecan for relapsed or resistant Hepatoblastoma (LT 2003 01)

PARENT INSTRUCTIONS FOR TREATING DIARRHOEA

Be aware of your child's bowel movements. At the first sign that they are becoming softer than usual or if your child has any increase in the number of bowel movements over what is normal for him/her, begin giving him/her loperamide (Imodium).

If he/she does not start taking the loperamide right away, the diarrhoea may become severe and last several days or require hospitalisation.

Please follow these directions carefully:

♦ Give _______ mg loperamide at the first sign of diarrhoea.
(to be filled in by the doctor according the following table)

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 20 kg</td>
<td>1 mg</td>
</tr>
<tr>
<td>21-40 kg</td>
<td>2 mg</td>
</tr>
<tr>
<td>Above 40 kg</td>
<td>4 mg</td>
</tr>
</tbody>
</table>

♦ Continue giving _______ mg loperamide every _________ hours until the pattern of bowel movements returns to normal. Repeat the same doses and frequency if the diarrhoea returns. Do not give more than _________ mg loperamide in 24 hours.
(to be filled in by the doctor according the following table)

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 10 kg</td>
<td>0,5 mg every 3 hours max 0,5 mg/kg/day</td>
</tr>
<tr>
<td>11-20 kg</td>
<td>1 mg every 3 hours max 0,5 mg/kg/day</td>
</tr>
<tr>
<td>21-30 kg</td>
<td>1 mg every 3 hours max 0,5 mg/kg/day</td>
</tr>
<tr>
<td>31-40 kg</td>
<td>1 mg every 2 hours max 0,5 mg/kg/day</td>
</tr>
<tr>
<td>Above 40 kg</td>
<td>2 mg every 2 hours</td>
</tr>
</tbody>
</table>

♦ Please call your doctor/oncologist to notify him/her that your child has diarrhoea and that he/she has started taking loperamide.

♦ Please call your doctor/oncologist if you have any questions about your child taking loperamide, if your child’s diarrhoea is not under control after two days, or if he/she is feeling extremely weak, light headed or dizzy.

♦ Make an extra effort to give your child lots of fluid (several glasses of oral rehydration solution, fruit juices, or soup, etc.).

♦ Side effects of loperamide may include tiredness, drowsiness, or dizziness. If your child experiences these side effects, or if your child is urinating less frequently than usual, please contact your child’s doctor.

♦ Do not give your child any laxatives without consulting with his/her doctor.

♦ Please record all diarrhoeal episodes and administration of loperamide with the dosage in the table on the next page and bring it to the next consultation.
APPENDIX D
(To be printed on headed paper)

The International Society for Paediatric Oncology (SIOP) Liver Tumour Study Group Phase II Study of Irinotecan for relapsed or resistant Hepatoblastoma (LT 2003 01)

PATIENT INSTRUCTIONS FOR TREATING DIARRHOEA

Be aware of your bowel movements. At the first sign they are becoming softer than usual or if you have any increase in the number of bowel movements over what is normal for you, begin taking loperamide (Imodium).

If you do not start taking the loperamide right away, the diarrhoea may become severe and last several days or require hospitalisation.

Please follow these directions carefully:

♦ Take ________ mg loperamide at the first sign of diarrhoea.
   (to be filled in by the doctor according the following table)
   Under 20 kg: 1 mg
   21-40 kg: 2 mg
   Above 40 kg: 4 mg

♦ Continue taking ________ mg loperamide every _________ hours until the pattern of bowel movements returns to normal. Repeat the same doses and frequency if the diarrhoea returns. Do not take more than ________ mg loperamide in 24 hours.
   (to be filled in by the doctor according the following table)
   Under 10 kg: 0,5 mg every 3 hours  max 0,5 mg/kg/day
   11-20 kg  1 mg every 3 hours  max 0,5 mg/kg/day
   21-30 kg: 1 mg every 3 hours  max 0,5 mg/kg/day
   31-40  1 mg every 2 hours  max 0,5 mg/kg/day
   Above 40 kg: 2 mg every 2 hours

♦ Please call your doctor/oncologist to notify him/her that you have diarrhoea and that you have started taking loperamide.

♦ Please call your doctor/oncologist if you have any questions about taking loperamide, if your diarrhoea is not under control after two days, or if you are feeling extremely weak, light headed or dizzy.

♦ Make an extra effort to drink lots of fluid (several glasses of oral rehydration solution, fruit juices, or soup, etc.).

♦ Side effects of loperamide may include tiredness, drowsiness, or dizziness. If you experience these side effects, or if you are urinating less frequently than usual, please contact your doctor.

♦ Do not take any laxatives without consulting with your doctor.

♦ Please record all diarrhoeal episodes and administration of loperamide with the dosage in the table on the next page and bring it to the next consultation.
<table>
<thead>
<tr>
<th>Diarrhoeal episode</th>
<th>Administration of loperamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>date</td>
<td>day</td>
</tr>
<tr>
<td>time</td>
<td>time</td>
</tr>
<tr>
<td></td>
<td>dosage</td>
</tr>
</tbody>
</table>
## COMMON TOXICITY CRITERIA (NCI CTC) Version 2.0

NB: This is a short version only containing the most common side effects. The full text version can be downloaded from: [http://ctep.cancer.gov/reporting/ctc.html](http://ctep.cancer.gov/reporting/ctc.html)

### Grade 0

**ALLERGY/IMMUNOLOGY**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient rash, drug fever &lt; 38°C (≤100.4°F)</td>
<td>Symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema</td>
</tr>
<tr>
<td>Urticaria, drug fever ≥ 38°C (&gt;100.4°F), and/or asymptomatic bronchospasm</td>
<td>Anaphylaxis</td>
</tr>
</tbody>
</table>

Note: Urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.

### Grade 1

**BLOOD/BONE MARROW**

<table>
<thead>
<tr>
<th>Hemoglobin (Hgb) WNL</th>
<th>≤ LLN - 10.0 g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ LLN - 100 g/L</td>
<td>≤ LLN - 6.2 mmol/L</td>
</tr>
<tr>
<td>(&gt;2000 - 3000 mm³)</td>
<td>Only laboratory evidence of hemolysis (e.g., direct antiglobulin test (DAT, Coombs), eschistocytes)</td>
</tr>
<tr>
<td>&gt;2000 - 3000 mm³</td>
<td>Evidence of red cell destruction and ≥ 2 gm decrease in hemoglobin, no transfusion</td>
</tr>
<tr>
<td>≤ LLN - 8.0 g/dL</td>
<td>≤ LLN - 10000/mm³</td>
</tr>
<tr>
<td>&gt;10000 - &lt;20000/mm³</td>
<td>≤ LLN - 1.0 x 10⁹/L</td>
</tr>
<tr>
<td>≥25 - &lt;50 % LLN</td>
<td>≥0.5 - &lt;1.0 x 10⁹/L</td>
</tr>
<tr>
<td>≥75 - &lt;100 % LLN</td>
<td>≥10000 - &lt;50000/mm³</td>
</tr>
<tr>
<td>≥1500 - &lt;2000/mm³</td>
<td>≥50 - &lt;75 % LLN</td>
</tr>
<tr>
<td>≥1000 - &lt;1500/mm³</td>
<td>&gt;25 - &lt;50 % LLN</td>
</tr>
<tr>
<td>≥500 - &lt;1000/mm³</td>
<td>≥0.5 - &lt;1.0 x 10⁹/L</td>
</tr>
<tr>
<td>≥250 - &lt;500/mm³</td>
<td>≥1000 - &lt;2000/mm³</td>
</tr>
<tr>
<td>≥100 - &lt;200/mm³</td>
<td>≤ LLN - 1000/mm³</td>
</tr>
<tr>
<td>≥50 - &lt;100/mm³</td>
<td>≥10 - &lt;20 mm³</td>
</tr>
<tr>
<td>≥25 - &lt;50/mm³</td>
<td>≥2 - &lt;5 mm³</td>
</tr>
<tr>
<td>≥10 - &lt;25/mm³</td>
<td>≥1 - &lt;2 mm³</td>
</tr>
<tr>
<td>≥5 - &lt;10/mm³</td>
<td>≥0.5 - &lt;1 mm³</td>
</tr>
<tr>
<td>≥2 - &lt;5/mm³</td>
<td>≥0.1 - &lt;0.5 mm³</td>
</tr>
<tr>
<td>≥1 - &lt;2/mm³</td>
<td>≤0.1 mm³</td>
</tr>
</tbody>
</table>

**Leukocytes (total WBC) WNL**

| ≤ LLN - 3.0 x 10⁹/L |
| ≥2.0 - <3.0 x 10⁹/L |
| ≤ LLN - 80 - <100 g/L |
| ≥4.9 - <6.2 mmol/L |
| ≤ LLN - 1.0 - <1.5 x 10⁹/L |
| >2000 - <3000/mm³ |
| ≤ LLN - 9.0 - <10.0 g/dl |
| ≥4.0 - <4.9 mmol/L |
| ≤ LLN - 100 - <150/mm³ |
| ≥50 - <75 % LLN |
| ≥75 - <100 % LLN |
| >25 - <50 % LLN |
| ≥0.5 - <1.0 x 10⁹/L |
| ≥10000 - <50000/mm³ |
| ≥1500 - <2000/mm³ |
| ≥500 - <1000/mm³ |
| ≥250 - <500/mm³ |
| ≥100 - <200/mm³ |
| ≥50 - <100/mm³ |
| ≥25 - <50/mm³ |
| ≥10 - <25/mm³ |
| ≥5 - <10/mm³ |
| ≥2 - <5/mm³ |
| ≥1 - <2/mm³ |
| ≥0.5 - <1 mm³ |

**Hemoglobin** (Hgb) WNL: ≤ LLN - 10.0 g/dL

**Platelets** WNL: ≤ LLN - 75000/mm³

**Neutrophils/granulocytes (ANC/AGC)** WNL: ≥1500 - <2000/mm³

**Lympohopenia** WNL: ≤ LLN - 1000/mm³

**Transfusion: Platelets** None

- Yes

**Transfusion: PHBCs** None

- Yes

<table>
<thead>
<tr>
<th>Grade</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Increased fatigue over baseline, but not altering normal activities</td>
</tr>
<tr>
<td>2</td>
<td>Moderate (e.g., decrease in performance status by ≥ 1 ECOG level ≥ 20% Karnofsky or Lansky) or causing difficulty performing some activities</td>
</tr>
<tr>
<td>3</td>
<td>Severe (e.g., decrease in performance status by ≥ 2 ECOG levels or ≥ 40% Karnofsky or Lansky) or loss of ability to perform some activities</td>
</tr>
</tbody>
</table>

Note: See Appendix III for performance status scales.

**CONSTITUTIONAL SYMPTOMS**

<table>
<thead>
<tr>
<th>Fatigue (lethargy, malaise, asthenia)</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased fatigue over baseline, but not altering normal activities</td>
<td>Severe (e.g., decrease in performance status by ≥ 2 ECOG levels or ≥ 40% Karnofsky or Lansky) or loss of ability to perform some activities</td>
</tr>
</tbody>
</table>

Note: See Appendix III for performance status scales.

**Fever** (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 10⁹/L)

| 38.0 - 39.9°C (100.4 - 102.2°F) |
| 39.1 - 40.0°C (102.3 - 104.0°F) |
| > 40.0°C (>104.0°F) |

For < 24 hrs |

For > 24 hrs |

**Hot flashes** are graded in the ENDOCRINE category.

**Rigors, chills** None

| Mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication |
| Severe and/or prolonged, requiring narcotic medication |
| Not responsive to narcotic medication |

**Sweating (diaphoresis)** Normal

| Mild and occasional |
| Frequent or drenching |

**Common Toxicity Criteria** (CTC) Version 2.0 is a grading system for the assessment of side effects of cancer treatments. It is a classification system for adverse events reported during clinical trials of cancer drugs. The CTC is used to standardize the reporting of adverse events, allowing for better comparison of results across different studies. It is based on a four-level scale: Grade 0 (none), Grade 1 (mild), Grade 2 (moderate), and Grade 3 (severe). The grading system is used to determine whether an adverse event is related to the treatment being studied and to assess the severity of the event.

**Endocare** is a category of adverse events related to endocrine therapy. It includes symptoms such as sweating, rigors, chills, and hot flashes. These symptoms are typically managed with supportive care, such as hydration, cool clothing, and rest.

**Constitutional symptoms** are common side effects of cancer treatments that affect the body as a whole, such as fatigue, nausea, and vomiting. They can be managed with rest, hydration, and other supportive care measures.

**Grade 0** indicates that the symptom is absent or does not cause any functional impairment.

**Grade 1** indicates a mild symptom that does not interfere with normal activities.

**Grade 2** indicates a moderate symptom that may cause symptoms of fatigue, weakness, or decreased performance.

**Grade 3** indicates a severe symptom that results in significant functional impairment or requires medical intervention.

**Appendix E** contains additional information and resources related to the common toxicity criteria, such as the full text version and performance status scales.
## Grade 0 1 2 3 4
### Toxicity

<table>
<thead>
<tr>
<th>Weight gain</th>
<th>&lt; 5%</th>
<th>5 - &lt;10%</th>
<th>10 - &lt;20%</th>
<th>≥ 20%</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Also consider Ascites, Edema, Pleural effusion.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight gain - veno-occlusive disease (VOD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Note: The following criteria is to be used ONLY for weight gain associated with Veno-Occlusive Disease.</td>
</tr>
<tr>
<td>&lt;2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight loss</th>
<th>&lt; 5%</th>
<th>5 - &lt;10%</th>
<th>≥20%</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Also consider Vomiting, Dehydration, Diarrhea.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Constitutional Symptoms

<table>
<thead>
<tr>
<th>(Specify, ______)</th>
</tr>
</thead>
<tbody>
<tr>
<td>none mild moderate severe life-threatening or disabling</td>
</tr>
</tbody>
</table>

### Dermatology/Skin

<table>
<thead>
<tr>
<th>Alopecia</th>
<th>normal</th>
<th>mild hair loss</th>
<th>pronounced hair loss</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry skin</td>
<td>normal</td>
<td>controlled with emollients</td>
<td>not controlled with emollients</td>
<td>-</td>
</tr>
<tr>
<td>Flushing</td>
<td>absent</td>
<td>present</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Injection site reaction

| none | pain or itching or erythema | pain or swelling, with inflammation or phlebitis | ulceration or necrosis that is severe or prolonged, or requiring surgery | - |

### Pruritus

| none | mild or localized, relieved spontaneously or by local measures | intense or widespread, relieved spontaneously or by systemic measures | intense or widespread and poorly controlled despite treatment | - |

### Rash/desquamation

| none | macular or papular eruption or erythema without symptoms | macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area | symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area | generalized exfoliative dermatitis or ulcerative dermatitis |

### Also consider Allergic reaction/hypersensitivity.

Note: Erythema multiforme (Stevens-Johnson syndrome) is graded separately as Erythema multiforme.

| Urticaria (hives, welts, wheals) | none requiring no medication | requiring PO or topical treatment or IV medication or steroids for <24 hours | requiring IV medication or steroids for ≥24 hours | - |

### ENDOCRINE

<table>
<thead>
<tr>
<th>Hot flashes/flushes</th>
<th>none</th>
<th>mild or no more than 1 per day</th>
<th>moderate or greater than 1 per day</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIADH (syndrome of inappropriate antidiuretic hormone)</td>
<td>absent</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### GASTROINTESTINAL

<table>
<thead>
<tr>
<th>Anorexia</th>
<th>none</th>
<th>loss of appetite</th>
<th>oral intake significantly decreased</th>
<th>requiring IV fluids</th>
<th>requiring feeding tube or parenteral nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites (non-malignant)</td>
<td>none</td>
<td>asymptomatic</td>
<td>symptomatic, requiring diuretics</td>
<td>symptomatic, requiring therapeutic paracentesis</td>
<td>life-threatening physiologic consequences</td>
</tr>
<tr>
<td>Collitis</td>
<td>none</td>
<td>-</td>
<td>abdominal pain with mucus and/or blood in stool</td>
<td>abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation of 4 thrombocytopenia, Melena/GI bleeding, Rectal perforation or requiring surgery or toxic megacolon</td>
<td></td>
</tr>
</tbody>
</table>

### Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or bleeding/hematochezia, Hypotension.

<table>
<thead>
<tr>
<th>Constipation</th>
<th>none</th>
<th>requiring stool softener or dietary modification</th>
<th>requiring laxatives</th>
<th>requiring manual evacuation or enema</th>
<th>obstruction or toxic megacolon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
<td>none</td>
<td>requiring IV fluid replacement (brief)</td>
<td>requiring IV fluid replacement (sustained)</td>
<td>fluid physiologic consequences requiring intensive care; hemodynamic collapse</td>
<td></td>
</tr>
</tbody>
</table>

### Also consider Hypotension, Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis).

| Diarrhea | none | increase of < 4 stools/day over pre-treatment | increase of 4-6 stools/day, or nocturnal stools | increase of ≥7 stools/day or need for parenteral support for dehydration | physiologic consequences requiring intensive care; or hemodynamic collapse |

### Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or thrombocytopenia, Pain, Dehydration, Hypotension.
<table>
<thead>
<tr>
<th>Grade</th>
<th>Toxicity</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastritis</td>
<td>none</td>
<td>-</td>
<td>requiring medical management or non-surgical treatment</td>
<td>uncontrolled by outpatient medical management; requiring hospitalization or surgery</td>
<td>-</td>
<td>Life-threatening bleeding, requiring emergency surgery</td>
</tr>
<tr>
<td>Mouth dryness</td>
<td>normal</td>
<td>mild</td>
<td>moderate</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Mucositis**

Note: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginitis.

Radiation-related mucositis is graded as Mucositis due to radiation.

**Nausea**

none | able to eat | oral intake significantly decreased | no significant intake, requiring IV fluids | severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation |

**Stomatitis/pharyngitis** (oral/pharyngeal mucositis)

none | painless ulcers, erythema, or mild soreness in the absence of lesions | painful erythema, edema, or ulcers, but can eat or swallow | painful erythema, edema, or ulcers requiring IV hydration | severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation |

**Note:** Radiation-related mucositis is graded as Mucositis due to radiation.
<table>
<thead>
<tr>
<th>Grade</th>
<th>Toxicity</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection neutropenia</td>
<td>without</td>
<td>none</td>
<td>mild, no active treatment</td>
<td>moderate, localized infection, requiring local or oral treatment</td>
<td>severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization</td>
<td>life-threatening sepsis (e.g., septic shock)</td>
</tr>
<tr>
<td>Infection/Fever</td>
<td>Neutropenia-Other</td>
<td>(Specify, _ ___________)</td>
<td>none</td>
<td>mild</td>
<td>moderate</td>
<td>severe</td>
</tr>
</tbody>
</table>

**METABOLIC/LABORATORY**

| Acidosis (metabolic or respiratory) | normal | pH < normal, but ≥ 7.3 | - | pH < 7.3 | pH < 7.3 with life-threatening physiologic consequences |
| Alkalosis (metabolic or respiratory) | normal | pH > normal, but ≤ 7.5 | - | pH > 7.5 | pH > 7.5 with life-threatening physiologic consequences |
| Hyperkalemia | WNL | < ULN - 5.5 mmol/L | ≥ 5.5 - 6.0 mmol/L | ≥ 6.0 - 7.0 mmol/L | > 7.0 mmol/L |
| Hypomagnesemia | WNL | < ULN - 2.0 mg/dl | ≥ 2.0 - < 2.5 mg/dl | ≥ 2.5 - < 3.0 mg/dl | ≥ 3.0 mg/dl |
| Hypokalemia | WNL | < ULN - 1.7 mmol/L | ≥ 1.7 - < 2.0 mmol/L | ≥ 2.0 - < 2.5 mmol/L | ≥ 2.5 mmol/L |
| Hypophosphatemia | WNL | < ULN - 0.8 mmol/L | ≥ 0.8 - < 1.0 mmol/L | ≥ 1.0 - < 1.2 mmol/L | ≥ 1.2 mmol/L |

**OCULAR/VISUAL**

| Dry eye | normal | mild, not requiring treatment | moderate or requiring artificial tears | severe, interfering with activities of daily living |
| Tearing (watery eyes) | none | mild, not interfering with function | moderate: interfering with function, but not interfering with activities of daily living | severe, interfering with activities of daily living |
| Vision- blurred vision | normal | - | symptomatic and interfering with function, but not interfering with activities of daily living | severe, symptomatic and interfering with activities of daily living |
| Ocular/Visual-Other (Specify, _ ___________) | normal | mild | moderate | severe | unilateral or bilateral loss of vision (blindness) |

**PAIN**

| Abdominal pain or cramping | none | mild, not interfering with function | moderate: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living |
| Headache | none | mild, not interfering with function | moderate: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living |
| Hepatic pain | none | mild, not interfering with function | moderate: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living |
| Rectal or perirectal pain (proctalgia) | none | mild, not interfering with function | moderate: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living |

**RENAI GENITOURINARY**

| Bladder spasms | absent | mild symptoms, not requiring intervention | symptoms requiring antispasmodics | severe symptoms requiring narcotic |
| Creatinine | WNL | > ULN - 1.5 x ULN | > 1.5 - 3.0 x ULN | > 3.0 - 6.0 x ULN | > 6.0 x ULN |

*Note: Adjust to age-appropriate levels for pediatric patients.*
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, as required. A list of key points is given which should be included in any parent/patient information sheet.

- Nature of disease and prognosis
- Purpose of the study
- Nature of the treatment and possible side effects
- Emphasise that the well-being of the child is the primary concern, rather than rigid adherence to protocol guidelines
- Involvement in the study is purely voluntary. Non-inclusion of the child in the study will in no way interfere with his/her care
- Inform parent that data on his/her child will be anonymised and transferred and stored at the UKCCSG Data Centre. There may be central review of pathology and imaging. Data may also be shared with the Children’s Oncology Group (COG) in America
(Form to be on headed paper)

Centre Number:    :  
Study Number:  
Patient Identification Number for this trial:

Parent/Child CONSENT FORM

Title of Project:  
The International Society of Paediatric Oncology Liver Tumour Study Group  
Phase II Study of Irinotecan for Relapsed/Resistant Hepatoblastoma

Name of Researcher:

Please initial box

1. I confirm that I have read and understand the information sheet dated ....................... for the above study and have had the opportunity to ask questions.  

2. I understand that my child’s participation is voluntary and that I am free to withdraw him/her at any time, without giving any reason, without his/her medical care or legal rights being affected.  

3. I understand that sections of any of my child’s medical notes may be looked at by responsible individuals from SIOPEL or from regulatory authorities where it is relevant to my child taking part in research. I give permission for these individuals to have access to my child’s records.  

4. I understand that data on my child may be shared with Children’s Oncology Group, which may not have data protection laws that are similar to those in the UK.  

5. I agree to my child taking part in the above study.  

_________________________ ________________  ____________________  
Name of Patient    Date  Signature of Parent

_________________________  ________________  ____________________  
Name of Person taking consent   Date  Signature  
(if different from researcher)

_________________________ ________________  ____________________  
Researcher                Date   Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes