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Risk-adapted treatment for childhood hepatoblastoma: final report of the second study of the International Society of Paediatric Oncology—SIOPEL 2☆

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Abstract

SIOPEL 2 was a pilot study designed to test the efficacy and toxicity of two chemotherapy (CT) regimens, one for patients with hepatoblastoma (HB) confined to the liver and involving no more than three hepatic sectors ('standard-risk (SR) HB'), and one for those with HB extending into all four sectors and/or with lung metastases or intra-abdominal extra hepatic spread 'high-risk (HR) HB'. SR-HB patients were treated with four courses of cisplatin (CDDP), at a dose of 80 mg/m^2 every 14 days, delayed surgery, and then two more similar CDDP courses. HR-HB patients were given CDDP alternating every 14 days with carboplatin (CARBO), 500 mg/m^2, and doxorubicin (DOXO), 60 mg/m^2. Two courses of CARBO/DOXO and one of CDDP were given postoperatively. Between October 1995 and May 1998, 77 SR-HB (10 of whom were actually treated with the HR protocol) and 58 HR-HB patients were registered and all 135 could be evaluated. Response rates for the entire SR-HB and HR-HB groups were 90% (95% CI 80–96%) and 78% (95% CI 65–87%), and resection rates were 97% (95% CI 87–99%) and 67% (95% CI 54–79%) including several children undergoing liver transplantation. For SR-HB patients, 3-year overall and progression-free survivals were 91% (±7%) and 89% (±7%) and for the HR-HB group 53% (±13%) and 48% (±13%), respectively. The short-term toxicity of these regimens was acceptable, with no toxic deaths. A treatment strategy based on CDDP monotherapy and surgery thus appears effective in SR-HB but, despite CT intensification, only half of the HR-HB patients are long-term survivors. For SR-HB patients, the efficacy of CDDP monotherapy and the CDDP/DOXO ('PLADO') combination are now being compared in a prospective randomised trial (SIOPEL 3).

Keywords: Hepatoblastoma; Cisplatin; Children; Chemotherapy; Prognostic factor

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1. Introduction

SIOPEL 1, the first prospective international clinical trial on childhood hepatoblastoma (HB), run by the Childhood Liver Tumor Strategy Group of the International Society of Pediatric Oncology (SIOPEL), aimed *inter alia* to investigate the prognostic significance of several pretreatment characteristics, both of patients and of their tumours [1–3]. In SIOPEL 1, there was no stratification by clinical and histological characteristics and all patients received similar therapy. The treatment strategy in SIOPEL 1 used preoperative chemotherapy, with a combination of cisplatin (CDDP) and doxorubicin (DOXO) (the 'PLADO' regimen), then delayed resection of the primary tumour. Before treatment, both the extent of intrahepatic disease, as defined by the pretreatment extension of disease (PRETEXT) system (see below), and the presence of lung metastases were identified as prognostic factors for 5-year event-free survival (EFS), but in multivariate analysis the PRETEXT category was the only statistically significant prognostic factor for 5-year overall survival (OS) [1]. Based on these findings, the SIOPEL group decided, for the subsequent SIOPEL 2 trial, to stratify treatment according to the intrahepatic extent of the disease (as expressed by the PRETEXT system) and the presence of lung metastases. More precisely, we decided to investigate whether intensification of therapy would improve the prognosis of those children affected by HB involving all four hepatic sectors (PRETEXT IV) and/or those with metastases and if it would be possible to reduce therapy, without jeopardising the overall outcome, in those patients whose tumour was completely confined to the liver and involved, at most, three hepatic sectors. The first group of HB were designated 'high-risk' (HR) tumours and the second 'standard-risk' (SR) tumours. Within the HR group, patients with intra-abdominal extension of the tumour beyond the liver were also included, even though there was no definite evidence that these factors worsened prognosis.

Concerns about the short- and long-term cardiotoxicity of DOXO, as well as the belief that CDDP is probably the most effective drug for HB [4,5], motivated us to investigate whether SR-HB patients could be cured with a treatment strategy based on surgery and CDDP alone (CDDP 'monotherapy'). For HR-HB patients, it was decided to intensify the treatment by adding carboplatin (CARBO) to the PLADO regimen using the three drugs in a rapidly alternating sequence. Data indicating that CARBO had some activity in HB were available at the time the study was launched [6,7].

The relatively high proportion (70%) of patients with SR-HB in SIOPEL 1 meant that it was possible to conduct a prospective randomised trial of the efficacy of treatment with surgery and CDDP versus that of surgery and PLADO. However, before launching this trial, a pilot study was deemed essential (i) to substantiate existing data on the efficacy of CDDP monotherapy, (ii) to alleviate concerns about treating this malignancy with just one agent, and (iii) to investigate the toxicity of the proposed rapid (every 15 days) schedule for administering CDDP. By contrast, the cohort of HR-HB patients is smaller (30%) and randomised controlled trials more difficult to mount, and a cohort study was designed instead. In summary, SIOPEL 2 was a pilot study whose principal aims were to investigate the efficacy and toxicity of two new therapeutic strategies: (i) a regimen based on CDDP monotherapy and surgery directed at a selected cohort of HB with favourable presenting features, and (ii) an intensified multi-agent regimen directed at a group of HB with unfavourable clinical characteristics. The trial should also provide data to help determine whether the notion of clustering patients into two 'risk groups' was valid and helpful.

2. Patients and methods

SIOPEL 2 was an international, prospective, clinical trial with stratification by specific pretreatment characteristics, into groups of patients considered to be at 'standard' (SR) or 'high' (HR) risk of treatment failure, respectively. It was open to patient registration between October 1995 and May 1998. Children under the age of 16 years with untreated HB were eligible; participating institutions were encouraged to enter all patients referred to them. Central review of the diagnostic histopathology slides and, if biopsy had not been carried out at the time of diagnosis (see below), of the pathological material derived from delayed surgery was required.

2.1. Diagnostic biopsy

Biopsy of the primary tumour was mandatory in children (i) under 6 months of age, because of the wide differential diagnosis of hepatic masses and the possible confounding effect of an 'elevated' serum α-fetoprotein (α-FP) at this age; and (ii) over 3 years, because of the risk of misdiagnosing hepatocellular carcinoma. In children between 6 months and 3 years of age with clinical findings strongly favouring the diagnosis of HB (radiological evidence of an intrahepatic mass, elevated α-FP, thrombocytosis), biopsy was only 'strongly recommended', as pathological material would eventually be available after tumour resection. Obtaining informed consent from parents and/or patients was the responsibility of individual centres in accordance with their own national and institutional guidelines, and included approval by local research ethics committees.

The staging procedures and PRETEXT system adopted for SIOPEL 1 were also used for this trial (Fig. 1) [1,2].

2.2. Definition of risk groups

Children whose tumour involved one, two or three sectors (PRETEXT I, II and III), entirely confined to the liver and with no metastases in the lung, were considered to be SR patients. All those with (a) a tumour involving all four hepatic sectors (PRETEXT IV) or (b) evidence of extrahepatic disease [metastases (M) or extrahepatic abdominal disease (E), or portal/hepatic venous involvement (P/V)] were considered to be in the HR group.

2.3. Detailed treatment strategy—standard-risk patients (Fig. 2a)

After diagnosis, SR-HB patients were to be treated with four courses of CDDP monotherapy, administered every 14 days, at a dose of 80 mg/m^2 in a continuous 24-h infusion. During this phase, the serum α-FP was monitored before each course of CDDP, but a formal evaluation of the response was requested after two and after four courses. After four courses of CDDP, tumour resectability was assessed and, if feasible, definitive resection was then performed. Thereafter, two more CDDP courses were given. If there was evidence of stable (SD) or progressive (PD) disease (see below) at either time point, the patient was to be treated with CARBO/DOXO according to the HR-HB regimen (see below) or by definitive surgery, if feasible. If, after the first four doses of CDDP, the tumour was responding to chemotherapy, but still considered unresectable, two more courses were to be given before surgery, but none afterwards. Thus, a maximum of six courses of CDDP were to be administered to each patient. Ratiotherapy was not part of the treatment protocol.

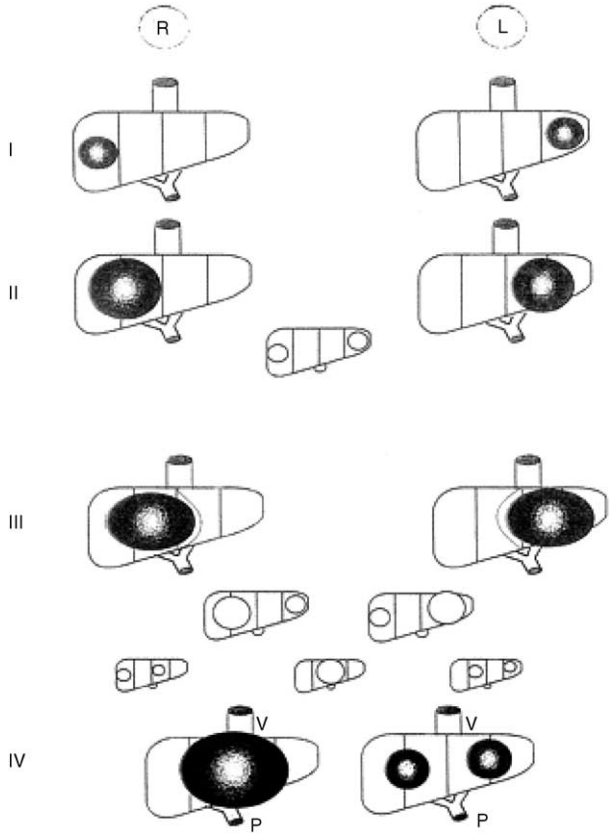

Fig. 1. PRETEXT system. V, extension into the vena cava and/or all three hepatic veins; P, extension into the main portal vein and/or both left and right portal branches; R, right; L, left.

2.4. High-risk patients (Fig. 2b)

After diagnosis, HR-HB patients were to be treated with 14-day alternating courses of a combination of CARBO, 500 mg/m^2 in a 1-h infusion, followed by DOXO, 60 mg/m^2 as a 48-h continuous intravenous infusion, and CDDP alone, as in the SR regimen. The preoperative phase included four courses of CARBO/DOXO and three of CDDP, over 85 days. Formal evaluation of tumour response was requested at days 43 and 85. If there was evidence of SD or PD at either time point, the patient was assigned to alternative chemotherapy or, if feasible, to definitive surgery. After day 85, resectability was assessed and, if possible, resection was performed. Subsequently, two more courses of CARBO/DOXO and one of CDDP were given. If, after day 85, the tumour was responding to chemotherapy, but was still considered unresectable, two more courses of CARBO/DOXO and one of CDDP were to be given. Thus, no more than six courses of CARBO/DOXO and four of CDDP were to be administered to each patient. If the tumour was still unresectable, even by liver transplantation, alternative treatment was given, as decided by the treating centre.

For both groups of patients, no additional therapy was recommended if there were only microscopic residual disease after surgery, so long as serum α-FP levels had fallen to within normal limits.

2.5. Dose modification, drug administration and tumour response

SIOPEL 1 guidelines for the administration of CDDP and DOXO were also followed in SIOPEL 2 [2]. If there were renal dysfunction, the actual dose of CARBO to be administered was calculated according to a modified Calvert's formula as proposed by Newell and colleagues in Ref. [8].

SIOPEL-1 criteria for judging tumour response were also used in this trial [1,2].

2.6. Statistical methods

The results of SIOPEL-2 are expressed in terms of response to chemotherapy, resection rate, overall survi-

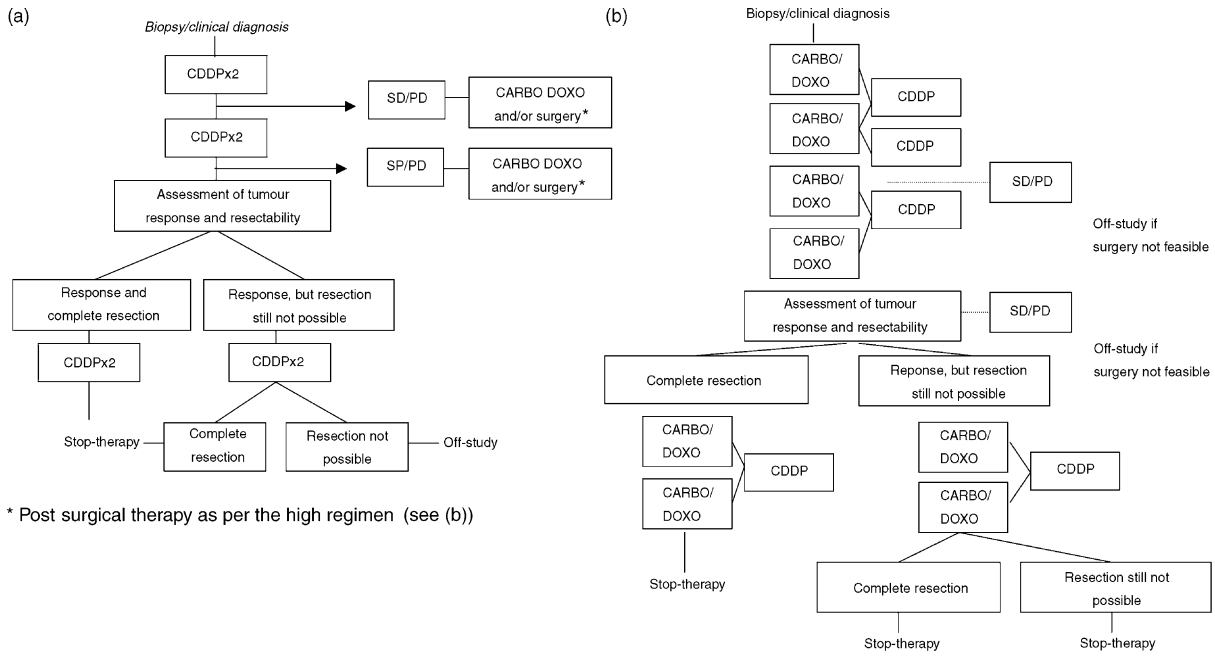

Fig. 2. (a) SIOPEL 2 treatment strategies by risk category—standard-risk hepatoblastoma. CDDP, Cisplatin 80 mg/m^2 in 24 h continuous infusion; CARBO, carboplatin 500 mg/m^2 1 h infusion; DOXO, doxorubicin 60 mg/m^2 48 h continuous infusion. (b) SIOPEL 2 treatment strategies by risk category—high-risk hepatoblastoma. CDDP, cisplatin 80 mg/m^2 in 24 h continuous infusion; CARBO, carboplatin 500 mg/m^2 1 h infusion; DOXO, doxorubincin 60 mg/m^2 48 h continuous infusion; PD, progressive disease; SD, stable disease.

val (OS), progression-free survival (PFS), and event-free survival (EFS). Analysis was by 'intention to treat'—that is, all patients in whom treatment was intended or received were counted in evaluating the tumour response, regardless of the total number of courses of chemotherapy. The complete resection rate is also based on all patients, irrespective of whether surgery was attempted or not, and upon the evaluation of the resected tumour by the 'local' pathologist. OS was defined as the time interval between the date of diagnosis and the date of death (from any cause) or the date of the last follow-up. EFS was defined as the time interval from the date of diagnosis to (i) the date of progression, (ii) the date of any change of chemotherapy, (iii) the date of relapse, (iv) the date of death, or (v) the date of the last follow-up, whichever occurred first. PFS was calculated in the same way as EFS except that switching of chemotherapy was not counted as an 'event'. The Kaplan–Meier method was used to derive the survival curves and the log-rank test to compare the curves [9,10]. 95% Confidence Intervals (CI) were calculated using Greenwood's formula [11] for survival estimates and by using the exact binomial distribution for rates. Multivariate analysis of OS was done by Cox regression. All statistical procedures were carried out using the SAS statistical package version 8.2.

3. Results

3.1. The study population

A total of 150 children were enrolled into the trial by 72 centres from 19 countries worldwide. Upon central histopathological review of all cases, 6 children were excluded from further analysis because of an incorrect diagnosis (1 rhabdoid tumour, 1 embryonal sarcoma, 1 rhabdomyosarcoma, 1 non-Hodgkin's lymphoma, and 2 cases of nodular focal hyperplasia). Additionally, 5 patients were excluded because a precise risk assessment was not available, 3 because they had been treated with 'up-front' surgery and 1 because there was insufficient documentation. Thus, the study population consisted of 135 children, 77 of whom were considered to have SR-HB and 58 to have HR-HB. 67 SR-HB children started treatment according to the SR regimen and the other 10 with the HR treatment. The original imaging of 7 of these 10 patients was reviewed centrally. We found that the reasons for the wrong risk assignment were: erroneous interpretation of the criteria for vascular tumour involvement in 4 cases; overestimation of tumour extent in a large PRETEXT III HB in 2, and tumour rupture at presentation in one case (a PRETEXT II HB). For 3 patients, the reasons for upgrading the 'risk group' were

Table 1
Clinical and individual characteristics of the SIOPEL 2 population by risk group and treatment

	SR-HB	HR-HB	SR-HB treated as HR
No. of patients	67	58	10
Gender			
Female	32	19	3
Male	35	39	7
Age (months)			
Median (range)	16 (0–82)	18 (4–169)	28 (5–49)
α-fetoprotein (μg/l)			
=100	1	5	
>100 and =1 000 000	61	46	9
>1 000 000	4	7	1
Missing data	1		
PRETEXT			
I	6	6	3
II	36	19	8
III	25	33	
IV			
Extrahepatic disease			
P		2	
V		1	
E		3	
V+P		5	
V+P+E		3	
Presence of metastases			
No	67	33	10
Yes		25	

SR-HB, standard-risk hepatoblastoma; HR-HB, high-risk hepatoblastoma; V, extension into the vena cava and/or all three hepatic veins; P, extension into the main and/or both left and right branches of the portal vein; E, extrahepatic disease other than P and V.

not given. All 58 HR-HB by contrast, were treated according to the HR regimen.

3.2. Clinical characteristics

The clinical characteristics of the study population by risk group and treatment received are listed in Table 1. One hundred children (74%) had a biopsy confirming HB before any treatment. In the other 35, the diagnosis was based on clinical findings and raised serum α-FP levels, all 35 of these children later had the diagnosis of HB confirmed histologically at delayed surgery.

3.2.1. Treatment outcome (Table 2)

3.2.1.1. Standard-risk hepatoblastoma. 60 of the 67 patients treated on the SR-HB regimen with CDDP monotherapy had a partial response (PR), an overall response rate of 90% (95% CI 80–96%). 2 other children had PD and in 5, disease was stable (SD); 6 of these 7 were then switched to CARBO/DOXO and 4 achieved a PR, 1 continued with SD and 1, with a centrally located PRETEXT III α-FP-negative HB that was never considered respectable, continued to show PD and ultimately died of it. The remaining child with SD had his tumour completely removed, but 2 months after surgery presented with a combined local and lung recurrence and ultimately succumbed at 15 months from diagnosis. Overall, therefore, 64 of the 67 children treated according to the SR strategy had a response to preoperative chemotherapy (96% CI 87–99%).

The rate of primary tumour resection was also impressively high. Five children, despite having achieved a PR to CDDP alone, then had either one or two courses of CARBO/DOXO, via the treating physician's clinical decision, in an attempt to reduce the tumour volume further and make a complete resection more likely. Thus, preoperatively, 56 (84%) of the total had only CDDP and 11 also had some doses of CARBO/DOXO. All but 1 of the 56 children treated with CDDP alone, and 10 of the 11 also treated with CARBO/DOXO, including 1 who had an orthotopic liver transplant (OLT), had a complete tumour resection at delayed surgery, an overall complete resection rate of 97% (95% CI 87–99%).

After complete resection, 2 children were treated with two courses of CARBO/DOXO, because microscopic residual disease in 1 (the treating physician's decision) and a reduced glomerular filtration rate (GFR) in the other. Thus, overall, 13 children received some CARBO/DOXO during their treatment. The 3-year EFS of the 67 SR-HB treated as SR (categorising any switch to the HR regimen at any time point during treatment as an 'event') was 73% (±11%) and the OS was 91% (±7%) (Fig. 3). Median follow-up time for survivors was 48 months. No relapses have been observed among SR-HB patients rendered disease-free (normal serum α-FP and no evidence of disease) by CDDP and surgery. Of the 7 children who did not respond to CDDP, 4 died of disease and one from surgical complications; among those who responded to CDDP, one died of the disease while waiting for a transplant to become available and the other from surgical complications. 12 patients received only CDDP preoperatively and no postoperative chemotherapy; 6 of these children received four doses of CDDP, 2 had five doses, and 4 had six doses. One child had no tumour resection; of the 11 who went on to delayed surgery, 1 died of surgical complications and 1 from the disease but 10 (81%) are alive with no evidence of disease.

Microscopic residual disease after delayed surgery was documented in 13 children; 8 were then treated, as the protocol directed, with CDDP; 4 also received two courses of CARBO/DOXO (two of these patients also received CARBO/DOXO before surgery), but 1 was simply observed. All 13 patients are alive with no evidence of disease.

9 of the 10 SR-HB patients treated according to the HR regimen had a PR to chemotherapy. Complete

Table 2
Relevant outcome data by risk and treatment group

	Standard-risk	High-risk	Standard-risk patients treated as high-risk
No. of patients	67	58	10
No. of responses			
Partial response	60	45	9
Stable disease	5	2	1
Progressive disease	2	7	
Missing data		4	
Response rate (95% CI)	90% (80–96%)[a]	78% (65–87%)	90% (65–100%)
No. and rate of	65[b]	39	10
No. and rate of macroscopic complete resections at the end of preoperative CT (95% CI)[c]	97% (87–99%)	67% (54–79%)	100%
3-year OS (95% CI)	91% (±7%)	53% (±13%)	86% (±26%)
3-year EFS (95% CI)	73% (±11%)	–	–
3-year PFS (95% CI)	89% (±7%)	48% (±13%)	89% (±21%)

CT, chemotherapy; CDDP, cisplatin; OS, overall survival; EFS, event-free survival; PFS, progression-free survival.
[a] Overall response rate to CDDP alone.
[b] No. and rate of macroscopic complete resections with CDDP alone: 55 (82%) (95% Confidence Interval (CI) 77–87%).
[c] Including patients undergoing orthotopic liver transplantation.

tumour removal, including microscopic clearance, was achieved in 8 by partial hepatectomy and by OLT in the remaining 2—in one of whom the transplant was performed because of acute liver failure following conventional surgery and in the other at the time of local regrowth in a non-responding patient. At 3 years, PFS in this group of children was 86% (±26%) and OS was 89% (±21%), with a median follow-up time of 40 months. The patient who did not respond to chemotherapy and had a transplant ultimately died of the HB at 28 months from diagnosis.

For the entire group of 77 SR-HB, the patient response (PR) and complete-resection (CR) rates were 90% (95%CI 80–96%; 69 patients) and 97% (95% CI 87–99%), respectively. The 3-year PFS and OS were 89% (±7%) and 91% (±7%), respectively (Figs 4 and 5).

3.2.1.2. High-risk hepatoblastoma. As a whole, 45 HR-HB children (78%; 95% CI 65–87%) had a PR to preoperative chemotherapy and in 32 a complete macroscopic resection was achieved by partial hepatectomy but, in 7 other children, complete tumour removal was achieved by total hepatectomy and OLT, an overall resection rate of 67% (95% CI 54–79%). In 15 patients, the tumour was never considered resectable, while in 4 cases delayed surgery was attempted, but macroscopic disease was left behind. One child died of surgical complications. Microscopic residual disease was documented in 6 children; all had postoperative CT as per protocol, but 1 also had an extra course of CDDP and CARBO/DOXO. At the last follow-up, 2 had died of the disease and 4 are alive with no evidence of disease. At 3 years, with a median follow-up time of 3 years and 10 months, PFS was 48% (±13%) and OS was 53% (±13%) (Table 2; Fig. 6).

Of the 7 HR patients who relapsed after achieving CR, 5 developed metastases (4 in the lung, and 1 also in the brain and skeleton) and 2 had local recurrences. Only one of these children survives disease-free; 5 have died and 1 is alive, but with persistent tumour. All 10 patients whose tumours either remained stable or progressed during therapy died of uncontrollable disease, despite alternative treatments.

3.2.2. Treatment results by PRETEXT category and by Serum α-FP at diagnosis

In order to assess the relevance of the risk-group assignment adopted for the trial, we also investigated the response and resection rates as well as the survival rates according to the four PRETEXT categories, the presence of metastases and intra-abdominal extrahepatic disease (V/P/E). The data are shown in Table 3.

We also analysed treatment outcome in relation to serum α-FP at diagnosis, clustering patients into three groups: $=100$ ng/ml (low α-FP), >100 and $<1\times10^6$ ng/ml (intermediate group), and $>1\times10^6$ ng/ml (very high α-FP). As reported in Table 1, there were 6 patients in the 'low' α-FP group, 12 in the 'very high' group and the rest in the 'intermediate' group. Of the 6 patients with a low α-FP, 5 died of their disease, including the single patient who was considered and treated as

SR-HB); 4 of the 12 children with a very high α-FP also died of their disease (all 4 belonged to the HR group). Of the 116 children with an 'intermediate' α-FP at diagnosis, 25, 19 HR-HB and 6 SR-HB, died of progressive tumour.

The association between OS and the PRETEXT categories, presence of metastases (M) and of intra-abdominal extrahepatic disease (V/P/E), and α-FP dichotomised as <100 versus $\geqslant 100$ ng/ml, was further evaluated in the 58 HR patients by multivariate analysis (Cox regression). An α-FP of <100 ng/ml at diagnosis was significantly associated with a reduced OS (hazard ratio 4.8, 95% CI 1.5–15.3, $P=0.0089$) as was the presence of metastases (hazard ratio 2.5, 95% CI 1.1–6.0, $P=0.037$). However, PRETEXT Group IV and the presence of extrahepatic disease (V, P or E) showed no association with OS. The OS in relation to PRETEXT Group IV without metastases, the presence of metastases (M) and of intra-abdominal extrahepatic disease (V/P/E) and of α-FP <100 ng/ml, considered separately, are shown in Fig. 7.

The PFS and OS of all SR patients, regardless of treatment received, and of the HR patients are shown in Figs. 4 and 5, together with 95% CIs at yearly intervals. No formal statistical test for comparison was carried out because this was not the focus of the present publication, but the differences between the curves are readily seen.

3.3. Toxicity (Table 4)

A total of 279 courses of CDDP were administered to 67 SR-HB children, and 357 courses of CARBO/DOXO and single-agent CDDP to 58 HR-HB children. The haematological toxicity of CDDP monotherapy was moderate, almost always allowing delivery as scheduled, in terms of both timing and dosage. The myelotoxicity of the HR-HB regimen was relatively high, but less than 10% of the patients received reduced drug dosages and treatment courses were delayed in only 19%. Table 4 summarises the major toxic events. No deep fungal infections were documented and there were toxic deaths. Accurate data on GFR as measured by Cr^{51} ethylene diamine tetraacetic acid (EDTA) clearance were available in 38 SR and 45 HR patients: 4 (11%) and 12 (27%) patients the two groups, respectively, had a GFR <80 ml/min per 1.73 m^2 (ranges 43–61 and 54–77, respectively); however, in those two groups, 2 and 4 patients, respectively, were infants and these values for

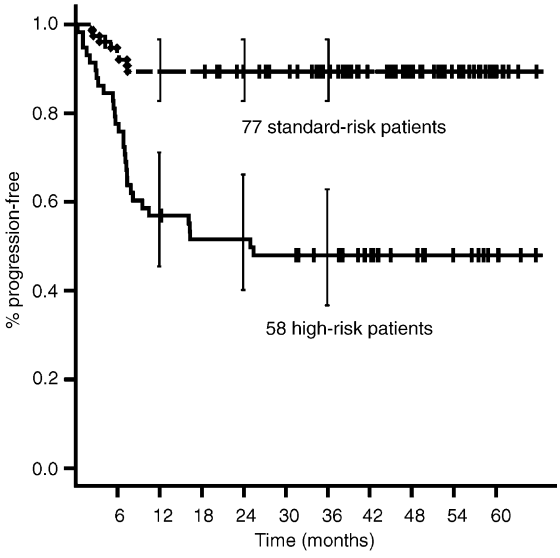

Fig. 4. Progression-free survival by risk category, with 95% Confidence Interval at 1, 2 and 3 years.

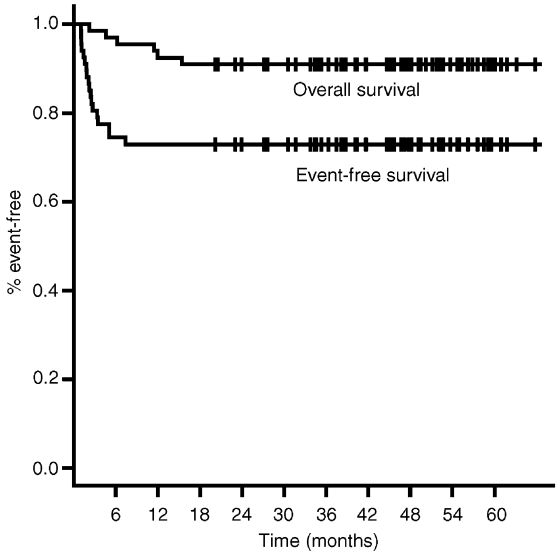

Fig. 3. Overall and event-free survival in 67 SR-HB treated as per the SR regimen.

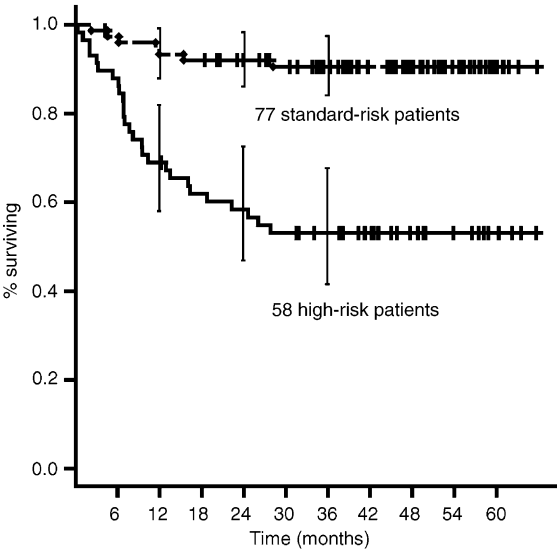

Fig. 5. Overall survival by risk category, with 95% Confidence Interval at 1, 2 and 3 years.

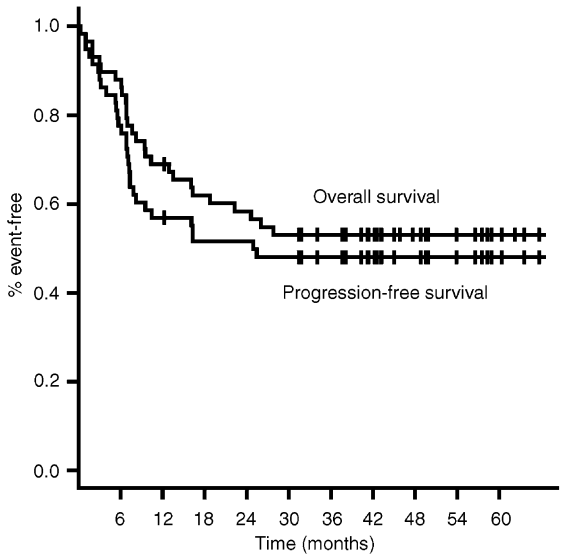

Fig. 6. Overall and progression-free survival of the 58 HR-HB.

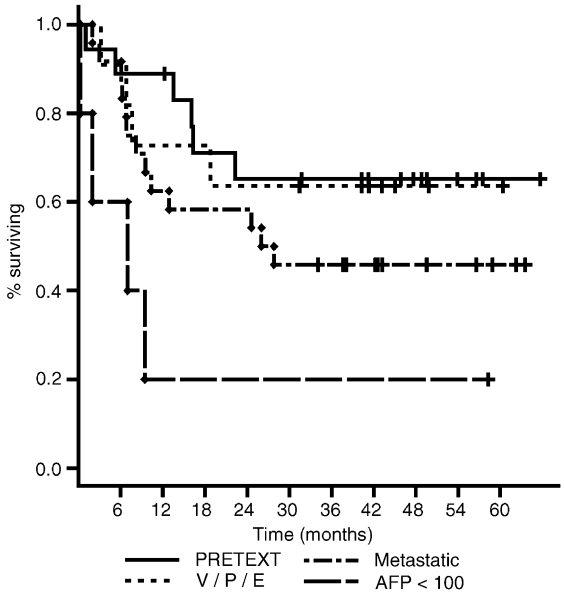

Fig. 7. Overall survival in 58 HR-HB, by PRETEXT IV category, intra-abdominal extrahepatic disease (V/P/E), presence of metastases and α-FP <100 ng/ml.

GFR can be considered normal in this age group. Only 2 patients aged >2 years in the SR arm ended SR treatment with a GFR <60 ml/min per 1.73 m^2. Accurate data on auditory function were available in 38 SR and 28 HR patients; only 1 in the HR regimen developed grade IV toxicity and only 4 (11%) and 2 (7%) in each group, respectively, had grade III hearing loss [11]. During therapy, 6 patients in the HR group had a shortening fraction of less than 28%, individually after one, four, five, five, five and six doses of DOXO, all administered as per protocol. At the last follow-up, the shortening fraction was 27% in 1, 33% in 1, 34% in 3 and 35% in 1 patient; none developed symptomatic cardiac dysfunction. 8 and 20 of the 43 SR and HR patients, respectively, whose end-of-treatment serum magnesium levels were available, had concentrations below the normal lower limits.

4. Discussion

The SIOPEL 2 study demonstrates that a treatment strategy based on surgery and only six courses of CDDP alone seems to guarantee a favourable outcome for children who present with 'SR' HB which we defined as a tumour confined to the liver and involving, at most, three hepatic segments. The 89% (±7%) 3-year PFS and, even more impressive, the 91% (±7%) 3-year OS are gratifying. There are several lines of evidence to suggest that HB is highly sensitive to CDDP [2,4,5,12–14]. SIOPEL 2 served as a pilot study and was felt to justify the SIOPEL Group's plans for a prospective randomised trial, SIOPEL 3. In this study, now in progress, the effectiveness of CDDP monotherapy is compared with the two-drug combination CDDP/DOXO, known as 'PLADO' and surgery, in SR-HB patients.

The results achieved in the HR group (48% (±13%) 3-year PFS and 53% (±13%) 3-year OS) are less satisfying. In SIOPEL 1, PRETEXT IV patients had a 5-year EFS and OS of 46% (95% CI 12–44%) and 57% (95% CI 41–73%), respectively; the corresponding figures for patients presenting with metastases were 28% (95% CI 12–44%) and 57% (95% CI 39–75%) [2]. Compared with SIOPEL 1, treatment intensity for HR patients in SIOPEL 2 was increased by alternating the administration of CDDP (every 14 days) with CARBO and DOXO. Longer follow-up is needed, but it is doubtful whether significant improvements in PFS and OS will be achieved.

A recent report [15] from the United States Pediatric Oncology Group (POG) on a cohort of 33 unresectable and metastatic HB records a 5-year EFS of 48%±9% and a 5-year OS of 57%±9%, similar to the results achieved SIODEL-2. To some extent, the results we have obtained for PRETEXT IV tumours can be compared with those achieved in trials based on an attempt at primary surgical resection in 'so-called' non-metastatic, unresectable tumours—stage III according to the North American postsurgical staging system. The most recently published POG series project an EFS of $>65\%$ at 3 and 5 years for this subset of patients [15]. In contrast, patients with metastases in all series published to date is around 30%, though OS varies from 27 to 57% at 5 years [15]. Interestingly, the best OS data have been reported in the SIOPEL trials, in which chemotherapy precedes surgery [2,3].

Both the SR- and the HR-HB group encompass a variety of tumour subtypes and further studies are needed to improve our risk-group assignment. In the

Table 3
Response, resection rates and 3-year overall survival (OS) by PRETEXT category and extrahepatic disease (all patients included)

	No. of patients	No of positive responses[a]	No of patients with a radical tumour resection (inc. OLT)[b]	No. of patients who died of surgical complications	No. of patients who died of disease	OS at 3 years (%)
Standard-risk	77					
PRETEXT						
I	6	6 (100%)	6 (100%)			100
II	30	37 (95%)	39 (100%)	1 (3%)	1 (3%)	95
III	32	26 (81%)	30 (94%)	1 (3%)	4 (13%)	84
High-risk	58					
PRETEXT IV only (no metastases)	21	17 (81%)	16 (76%)		8 (38%)	61
E/V/P+ (no metastases)	12	10 (83%)	8 (67%)	1 (8%)	4 (33%)	58
M+ patients	25	18 (72%)	15 (60%)	1 (4%)	13 (52%)	44

OLT, orthotopic liver transplantation; V, extension into the vena cava and/or all three hepatic veins; P, extension into the main portal vein and/or both left and right portal branches; E, extrahepatic excluding V or P (rare); M, presence of metastases.
[a] Complete and partial responses.
[b] Including patients with microscopic residual disease after surgery.

Table 4
Summary of toxicity data for the chemotherapy regimens used

	Standard-risk regimen	High-risk regimen
No of courses/no. of patients	279/67	357/58
Time from start of preoperative chemotherapy to surgery (days)		
Median (range)	81 (51–150) ($n=60$)	131 (56–345) ($n=42$)
No of courses administered with reduced doses		
CDDP	9 (3%)	12 (3%)
CARBO		23 (6%)
DOXO		22 (6%)
No of courses administered with delays	32 (11%)	68 (19%)
Total no. of patients		
Developing fever and neutropenia	29 (43%)	47 (81%)
Suffering from infections	27 (40%)	44 (76%)
Developing mucositis	1 (1%)	21 (36%)
Requiring RBC transfusion	10 (15%)	15 (26%)
Requiring platelet transfusion	3 (4%)	29 (50%)
Needing TPN	6 (9%)	18 (31%)

CARBO, carboplatin; CDDP, cisplatin; DOXO, doxorubicin; RBC, red blood cells; TPN, total parenteral nutrition.

multivariate analyses carried out to seek prognostic factors within the HR group, the presence of metastases was significantly predictive of a reduced OS, while PRETEXT IV, despite being associated with a lower OS, did not seem to be significantly predictive. Overall, the most powerful adverse prognostic factor for 3-year OS in the HR patients proved to be a low serum α-FP at diagnosis (<100 ng/ml). At the time that SIOPEL 2 was launched, the possible negative impact of a low serum α-FP at diagnosis on long-term survival had already been recognised, but at that time the data were not convincing enough to allow us to incorporate these patients into the HR group [16]. Now, in the SIOPEL 3-study these patients are now included in the HR group. The correlation between a low α-FP and 'undifferentiated' histology merits further investigation [17] and raises the question 'Are these tumours, which usually present in infancy, really hepatoblastomas?'

Other prognostic factors at diagnosis and in response to therapy have been emphasised elsewhere. They include (i) the growth pattern of the tumour within the liver (unifocal or multifocal), (ii) the invasion of large blood vessels (and/or microscopic tumour infiltration), [18], (iii) 'pure fetal' histology, but only for completely resected HB [17], (iv) the magnitude of the decrease in α-FP in response to therapy [19], and (v) a histologi-

cally-documented complete response to therapy [5]. It is expected that by combining 'static' (pretreatment) and 'dynamic' (in response to therapy), histological and clinical findings, the possibility of 'tailoring' treatment will improve considerably.

SIOPEL 1 and 2 are the first trials that have adopted an objective and reproducible method of evaluating tumour extent (the PRETEXT system) before any treatment is given, but the validity of PRETEXT in identifying risk categories of HB deserves further investigation. It is still not certain that PRETEXT is capable of predicting the 'complete' resectability of a tumour, an important prognostic factor. However, we can conclude from SIOPEL 2 that PRETEXT broadly identifies two groups of HB patients with different outcomes. The difference in the 3-year OS and PFS between these two groups is striking (Figs. 4 and 5). It has been known for many years that surgical 'unresectability' and the presence of distant metastases are both unfavourable prognostic features in HB [20].

When SIOPEL 2 began, there was concern about the potential toxicity, both of 2-weekly CDDP monotherapy and, of the HR-HB regimen. As anticipated, it turned out to be difficult to achieve good compliance with the protocol requirements for the frequent monitoring of toxicity, particularly oto- and nephrotoxicity, in very young children. Notwithstanding, the number of patients with severe oto- or nephrotoxicity was small though follow-up will be important as the GFR, particularly in young children, can improve with time [21]. Reassuringly, the rapid sequential CDDP of the SR regimen caused no more oto- or nephrotoxicity than the more intensive HR regimen. A relatively high rate of grade III and IV myelotoxicity was anticipated and observed in patients who received the HR-HB regimen, but there were no toxic deaths or other life-threatening complications.

Treatment-related toxicity in patients who have a good prognosis, as in the case of most HB patients, is always a matter of concern. The demonstration in SIOPEL 2 of an effective treatment strategy based on CDDP alone, directed towards almost 60% of all HB patients, represents a further important refinement for minimising treatment-related toxicity.

In summary, we believe that SIOPEL 2 contributes to research on childhood HB by demonstrating the potential for cure in a substantial cohort of HB patients presenting with favourable clinical findings—'so-called' SR-HB using a treatment strategy that uses only a relatively short course of CDDP monotherapy and surgery. However, definitive evidence of the effectiveness of this strategy will only be available when the SIOPEL 3 study the current prospective randomised trial comparing CDDP alone with the historical data is completed. The treatment of HR-HB patients still needs to be improved. Further refinement of the risk categories used in SIOPEL-2 is warranted. The PRETEXT system, though further validation is needed, seems to be sufficiently pragmatic and effective to justify its continuing use whilst even more effective methods are devised.

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