

Hepatoblastoma throughout SIOPEL trials - clinical lessons learnt

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1. ABSTRACT

International Childhood Liver Tumors Strategy Group (SIOPEL) introduced the concept of preoperative chemotherapy in hepatoblastoma, most common malignant liver tumor in children. This required introduction of the preoperative tumor staging system called PRETEXT. SIOPEL 1 study proved the value of preoperative chemotherapy consisting of cisplatin and doxorubicin (PLADO) in hepatoblastoma leading to 5-year overall survival of 75% and event-free-survival of 66%. Both presence of metastases and PRETEXT were significant prognostic factors which led to development of two risk categories: standard (SR) and high risk (HR) hepatoblastomas. In SIOPEL 2 study two different strategies were developed for SR and HR tumors with corresponding 3-year overall and progression-free survival of 91% and 89%, and 53% and 48% respectively. In the next SIOPEL 3 SR arm study monotherapy regimen based on CDDP alone was non-inferior to PLADO for SR hepatoblastoma and less toxic. Cisplatin-based chemotherapy in combination with delayed definitive surgery / liver transplantation improved the survival of children with hepatoblastoma. However certain patients, especially those with metastatic disease and low alphafetoprotein still have inferior prognosis.

2. INTRODUCTION

Hepatoblastoma is the most common malignant liver tumor in children. It can be associated with some genetic syndromes like Beckwith-Wiedemann, Familial Adenomatous Polyposis or isolated hemihyperplasia (1,2,3). Other predisposing factors can be very low birth weight or parental smoking (4,5,6). Recently a slight rate increase for hepatoblastoma by 4,3% has been noted which might correlate with increased frequency of low and very low weight births (7).

Treatment of hepatoblastoma in children represents a true success story in pediatric oncology over the last 25 years. From initial survival of 20-30% due to the use of adjuvant and neoadjuvant chemotherapy the patients' outcome has been pushed to the range of 70-80% (8,9). This progress was possible not only due to the introduction of new drugs (i.e. cisplatin and doxorubicin) and new approaches (i.e. liver transplantation) but first of all due to cooperative effort of major multicenter international study groups, e.g. SIOPEL, North-American COG and German GPOH.

SIOPEL stands for International Childhood Liver Tumors Strategy Group. It was founded in 1988 under the umbrella of the International Society of Paediatric

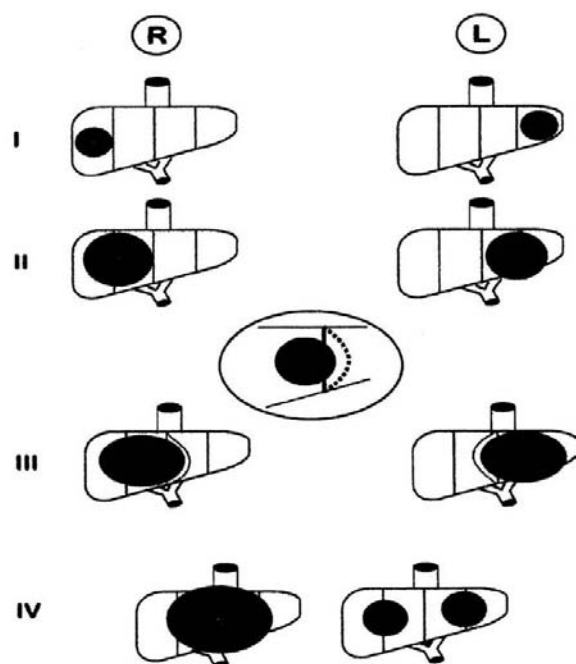


Figure 1. Schematic representation of the PRETEXT system.

Oncology (SIOPEL). Its main aim is to promote basic and clinical research on childhood malignant neoplasms of the liver, mainly hepatoblastoma and hepatocellular carcinoma. SIOPEL group has had so far completed and fully published three generations of prospective clinical trials and a Phase II study, called:

- SIOPEL 1 – 1990/1994
- SIOPEL 2 – 1994/1998
- Phase II study on High dose Cyclophosphamide – 1996/2001
- A prospective randomised clinical trial on standard risk hepatoblastoma – SIOPEL3 SR-HB – 1998-2005

Three other hepatoblastoma studies have been completed but their results have not been published, yet:

- A prospective single arm trial on high risk hepatoblastoma – SIOPEL 3 HR-HB – 1998/2004
- A Phase II study on Irinotecan – 2003/2008.
- A study on high risk hepatoblastoma; SIOPEL 4 – 2005/2009

Throughout the history of consecutive SIOPEL clinical trials several lessons have been learnt which will be briefly reported.

3. MAIN FEATURES OF THE SIOPEL EXPERIENCE

3.1. PRETEXT

From the beginning cardinal feature of all SIOPEL hepatoblastoma trials have been the use of preoperative neoadjuvant chemotherapy. Such approach

required introduction of the preoperative tumor staging system which was called PRETEXT (PRE-treatment Tumor EXTension). Since it has been described in several previous publications it will not be presented in details (10,11,12). In short, however, it describes the number of liver sections involved, as well as presence of extrahepatic disease or vascular involvement coded by additional letters (V, P, E, M) (Figure 1). This was an important step in order to judge tumor resectability at diagnosis and after preoperative chemotherapy. PRETEXT has been shown recently to be of moderate accuracy with a tendency to overstage patients, showed good reproducibility and superior predictive value for survival and possibility to monitor treatment response (11). Thus it was recommended to be implied in all hepatoblastoma trials and indeed nowadays PRETEXT system had been accepted by all other major liver tumors study groups (13).

3.2. SIOPEL 1

SIOPEL 1 study was based on uniform application of preoperative chemotherapy based on four courses of cisplatin (80 mg/m² d.1 in 24 hrs i.v. infusion) and doxorubicin (30 mg/m²/day d.1 and 2 in 24 hrs i.v. infusion) given tri-weekly, called PLADO. Postoperatively two additional chemotherapy courses were given. Details of treatment are given elsewhere (14). In 154 patients analyzed the value of preoperative chemotherapy concept was proven leading to overall response rate of 82% (95% CI: 76-88%), as well as an impressive 5-year overall survival (OS) of 75% (95% CI: 68-82%) and event-free-survival (EFS) of 66% (95% CI: 59-74%) (Figure 2 and 3). It has been a remarkable improvement in comparison with historical series, in which only 30%-50% of hepatoblastoma patients were amenable to primary surgical resection (10,14). Thirty two out of 115 patients were downstaged after initial treatment with PLADO (10). Moreover, 9 patients with initially PRETEXT 4 unresectable tumors involving the whole liver were downstaged and rendered operable (10). The toxicity of PLADO regimen was acceptable and manageable. However certain subsets of patients were not doing as good as others. This concerned mainly patients with initial metastases (31/154 – 20%) and those with PRETEXT 4 tumors (Figure 4 and 5). Although pulmonary metastases in 26 children (84%) responded to PLADO and in 17 patients (55%) complete clearance of metastases was achieved, 5-year overall survival and EFS for metastatic patients were inferior being 57% (95% CI: 39-75%) and 28% (95% CI: 12-44%) respectively. Similarly 5-year OS of the PRETEXT 4 group was lower – 57% (95% CI: 41-73%) (14,15,16). Both variables were considered significant in prognostic multivariate analysis (15). PRETEXT category had a very good value in discrimination patients' survival (Figure 4 and 5). Above findings led in turn to development of two clear risk categories: standard risk (initially called low risk) and high risk hepatoblastomas. Standard risk (SR) tumors included those limited to the liver (PRETEXT 1-3), while high risk (HR) ones included PRETEXT 4 tumors involving the whole liver and/or metastatic ones and/or those with extrahepatic or vascular extension into all 3 hepatic veins, main portal vein or its both trunks, or inferior vena cava.

Hepatoblastoma throughout SIOPEL trials

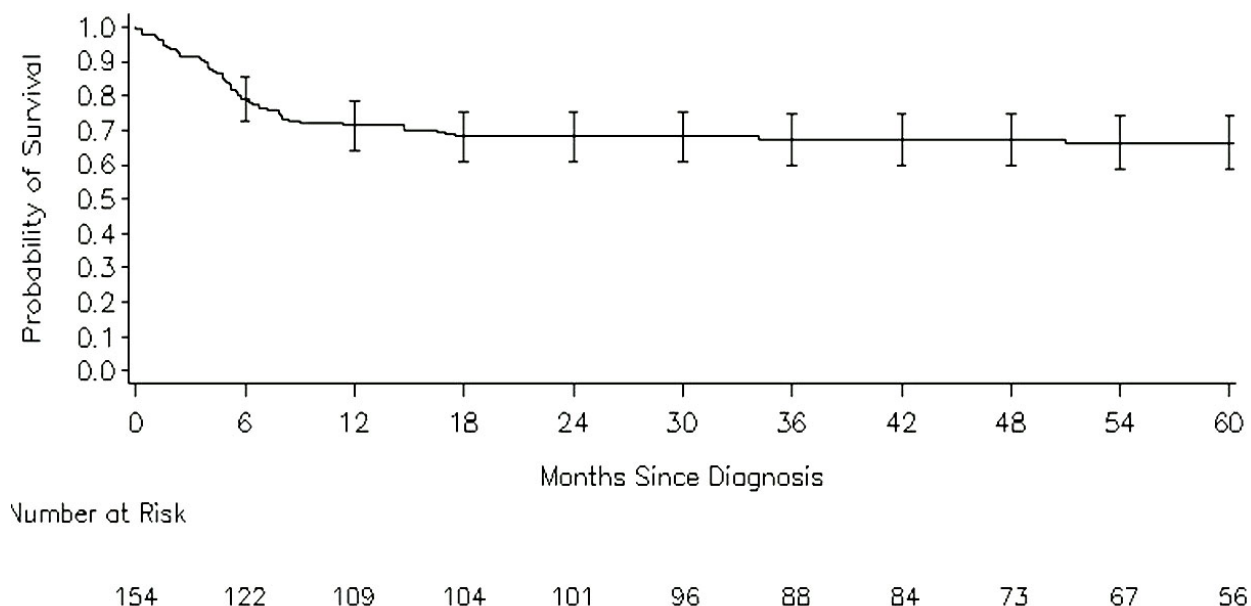


Figure 2. Event-free-survival in SIOPEL 1 study.

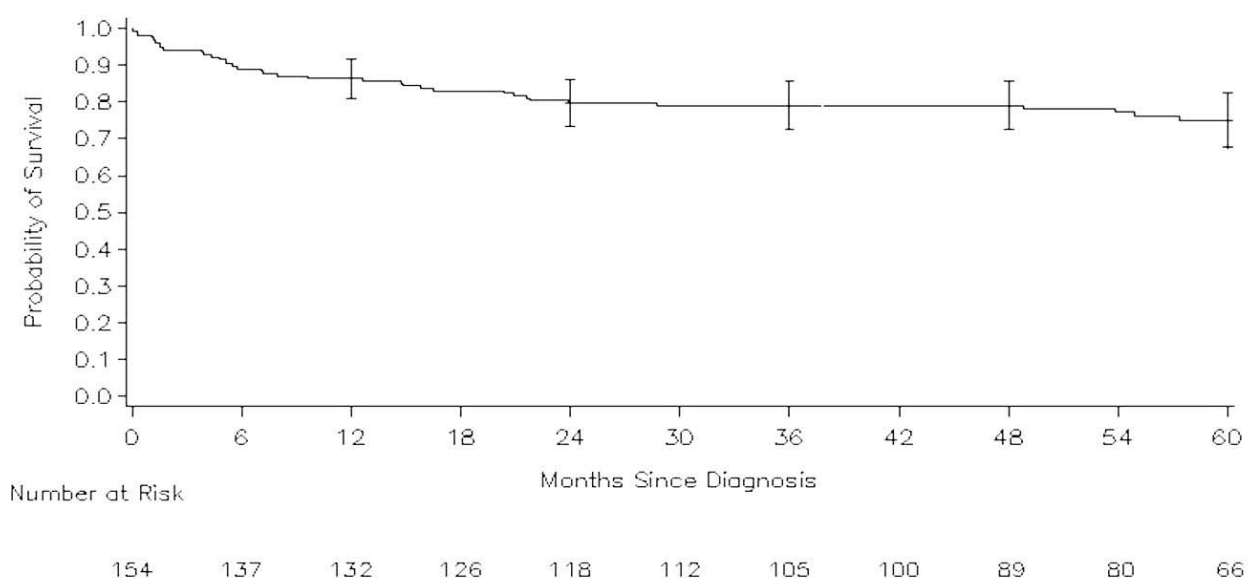


Figure 3. Overall survival in SIOPEL 1 study.

3.3. SIOPEL 2

Division into standard and high risk tumors has been validated by results of the SIOPEL 2 study, which also introduced for the first time an important concept of monotherapy based on cisplatin only. In this study two different strategies were developed for SR and HR hepatoblastoma (Figure 6 and 7). SR treatment consisted of 6 cisplatin courses given biweekly at the dose of 80 mg/m² in 24-hrs i.v. infusion, while chemotherapy for HR tumors was intensified by addition of carboplatin and decrease of chemotherapy interval from 3 to 2 weeks (17). Hundred and thirty five patients were registered and evaluable: 77 – SR and 58 – HR. Response rates were as follows: for SR

arm – 90% (95% CI: 80-96%) and for HR arm – 78% (95% CI: 65-87%), while corresponding resection rates were 97% (95% CI: 87-99%) and 67% (95% CI: 54-79%) respectively (17). Three-year OS and progression-free survival (PFS) was 91% (+ 7%) and 89% (+ 7%). For HR patients OS and PFS were 53% (+ 13%) and 48% (+ 13%). Myelotoxicity of the new HR regimen was relatively high but in less than 10% of patients dose reduction was required. Delay in chemotherapy cycles occurred in 19% of children. There were no toxic deaths reported. Presence of metastases but also low (<100 ng/ml) alpha-fetoprotein (AFP) at diagnosis were poor prognostic factors.

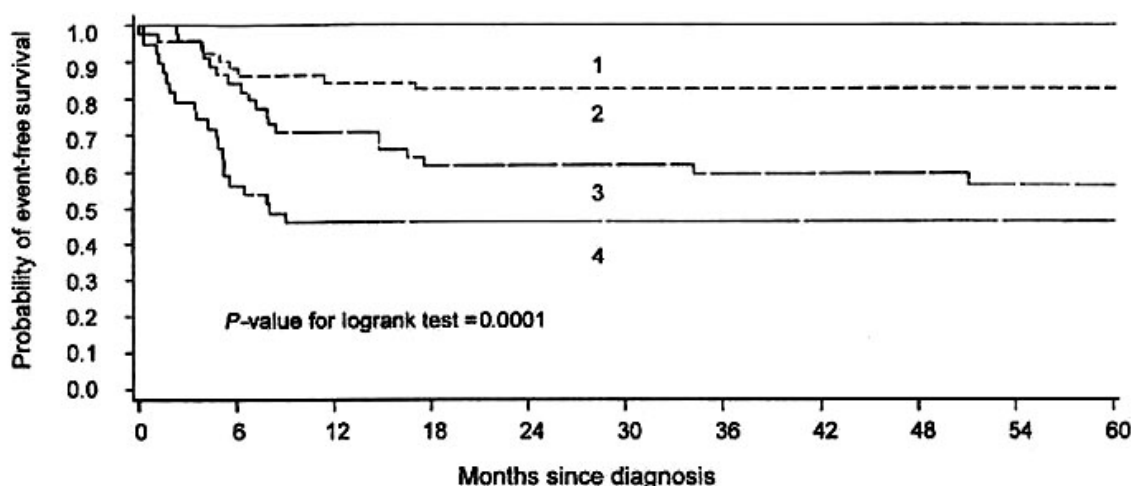


Figure 4. Event-free-survival and PRETEXT category in SIOPEL 1 study.

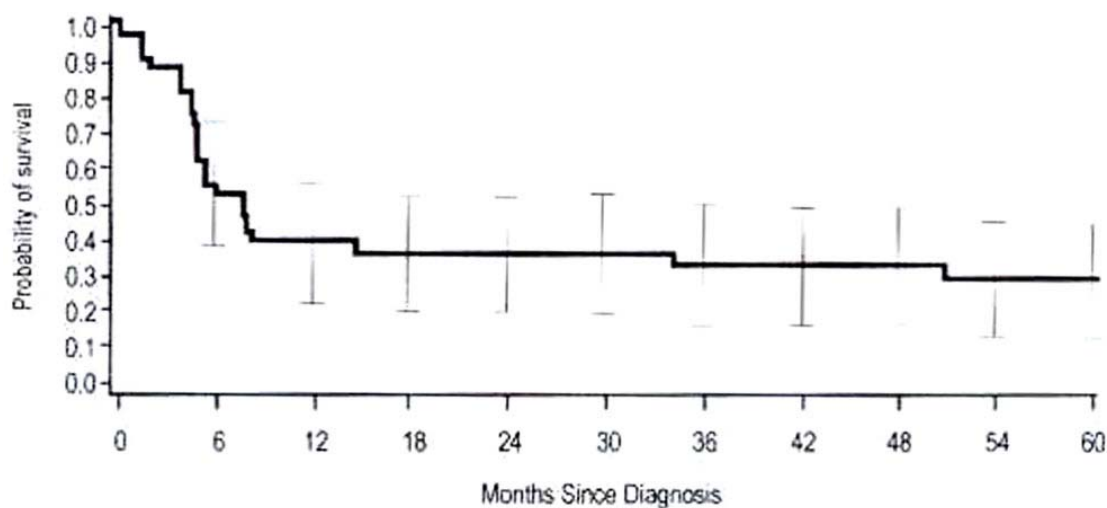


Figure 5. Event-free-survival and presence of metastases in SIOPEL 1 study.

In summary cisplatin monotherapy seemed to be a promising strategy in SR hepatoblastoma which deserved further attention by the comparison with PLADO by the means of the prospective randomized trial. No significant improvement has been achieved, however, in the HR group. New group of low AFP patients with very poor prognosis emerged which has been in line with earlier German reports (18). Clearly low AFP and metastatic patients required new treatment approach in order to improve outcome. An issue of PRETEXT 4 patients have been solved by the more frequent use of liver transplantation (LTX) which will be discussed further in the paper's course.

3.4. SIOPEL 3

Lessons collected throughout SIOPEL 1 and 2 trials influenced design of the next prospective randomized study – SIOPEL 3 (19). Patients remained stratified into 2 categories: SR and HR, however HR definition was modified by an inclusion of low AFP tumors and with time

also those which ruptured at diagnosis. All patients initially received one course of CDDP (80 mg/m²/24hrs) and those assigned as SR HB were then randomised between CDDP alone (q.14d) or PLADO (CDDP d.1, DOXO 60 mg/m²/48hrs d.2&3 q.21d), given in 3 preoperative and 2 postoperative cycles (Figure 8). Altogether 506 hepatoblastoma were registered between June 1998 and December 2006. A total of 310 patients were included in SR arm, derived from 24 countries and 92 institutions: 43 patients were registered but not randomized, thus 267 patients were randomized. Twelve patients were then excluded from further analysis, 5 because of an early revision of diagnosis before the start of therapy and lack of proper documentation in 7. Thus, 255 patients were eligible for further analysis. In the intention-to-treat analysis the complete resection rate (CRR), which was considered a surrogate for survival, of CDDP vs. PLADO arm were 95% (95%CI 90-98%) Vs 93% (95%CI 87-97%) and in the per-protocol analysis 99% (95%CI 95%-100) and 95% (95%CI 89-98%) respectively. The non-inferiority of CDDP was

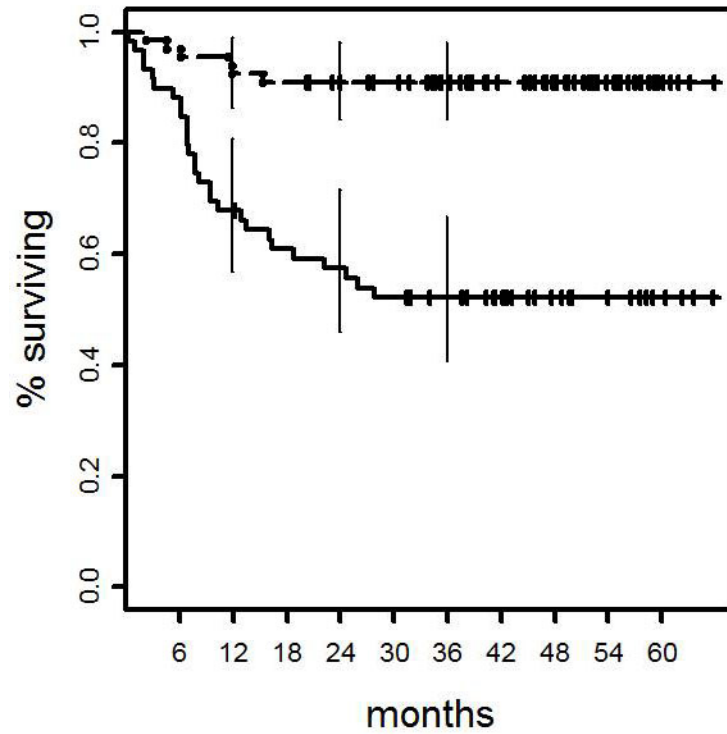


Figure 6. Kaplan-Meier overall survival curve for the SIOPEL 2 study (Upper curve – SR HB, Lower curve – HR HB).

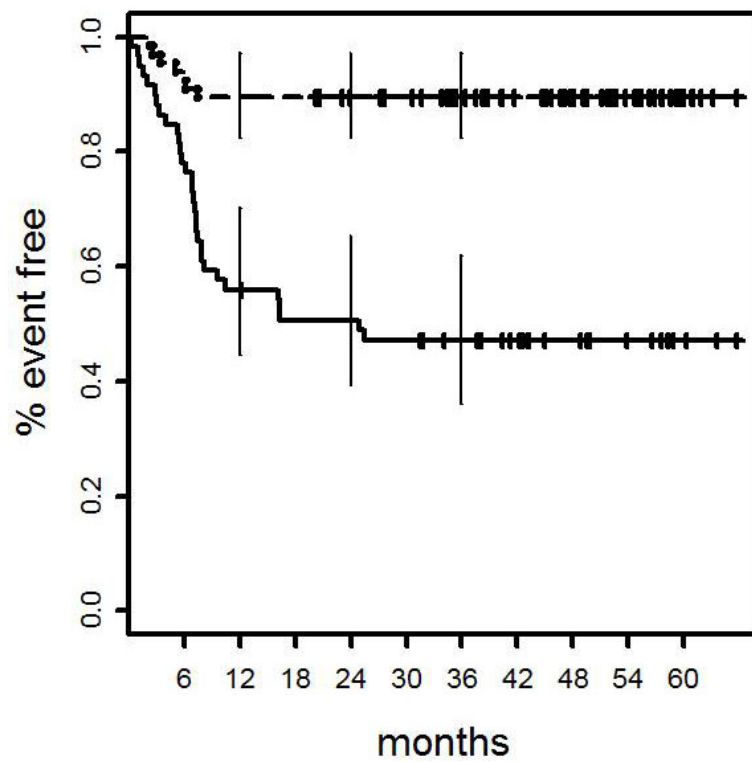


Figure 7. Kaplan-Meier event-free survival curve for the SIOPEL 2 study (Upper curve – SR HB, Lower curve – HR HB).

SIOPEL 3 – STUDY DESIGN

Standard Risk Hepatoblastoma

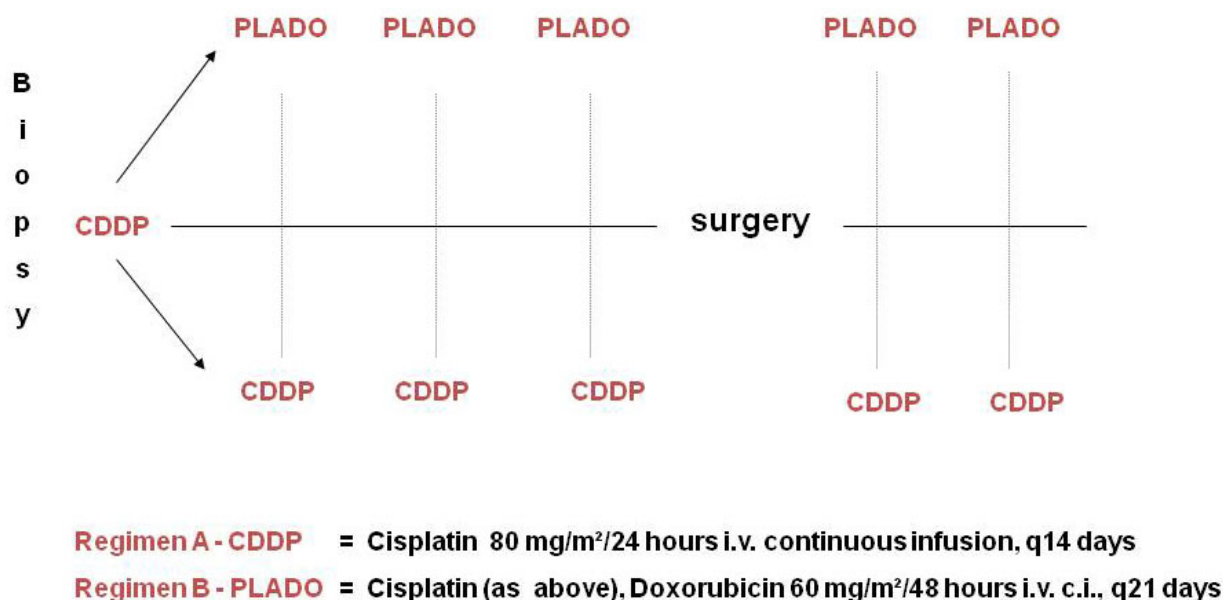


Figure 8. SIOPEL 3 Study Design.

confirmed at the 5% significance level (Table 1). The 3-year event-free-survival (EFS) and overall-survival (OS) of the patients treated according to CDDP arm and PLADO arm were 83% (95%CI 77-90%) and 95% (95%CI 91-99%) and 85% (95%CI 79-92%) and 93% (95%CI 88-98%) respectively (median follow-up 45 months) (Figure 9 and 10). Hence it was concluded that CDDP-based monotherapy regimen was non-inferior to PLADO regimen in terms of CRR for SR-HB, bringing also to comparable 3-year EFS and OS.

In summary the SIOPEL 3 SR arm study has documented that a simple monotherapy regimen based on CDDP alone is non inferior to the combination CDDP/DOXO (PLADO) for standard risk hepatoblastoma and, as predicted, clearly less toxic. Treatment of childhood high risk hepatoblastoma in SIOPEL 3 trial was based on intensified chemotherapy and indeed the results were slightly superior to SIOPEL 2 (20), probably due to cisplatin intensification (4 preoperative courses instead of 3) and progress in liver surgery (liver transplantation), but this will be soon reported in details elsewhere.

Next generation of SIOPEL trials for high risk tumors, SIOPEL 4, was based on further timely intensification of cisplatin which was given in a weekly fashion preoperatively. The study has been just completed

and its data are in the process of collection, while results await final analysis. Current standard risk study, SIOPEL 6, focuses on the issue of cisplatin-induced hearing loss prevention by randomized use of sodium thiosulfate in the course of cisplatin monotherapy.

3.5. Lessons in surgery and liver transplantation

Throughout consecutive trials diagnostic biopsy in hepatoblastoma was proven to be safe and reliable (10, 21). There were no episodes of tumor seeding. Biopsy-related complications were infrequent (7% in SIOPEL 1) and minor only, which mostly did not require any treatment (10). Initially open biopsy was advocated but now closed needle biopsy under ultrasonographic or laparoscopic guidance is preferred (21).

Many surgeons reported that tumor resection after preoperative chemotherapy was easier due to its more solid character and better demarcation from the surrounding healthy liver tissue, as well as less bleeding, although the latter was not proven (10).

Another important issue is microscopic tumor residuum after resection. In SIOPEL 1 trial only 2 of 16 patients (13%), who died, had microscopic residuum after surgery (10). In SIOPEL 2 microscopic residual disease was identified in 13 SR patients and all 13 are long term

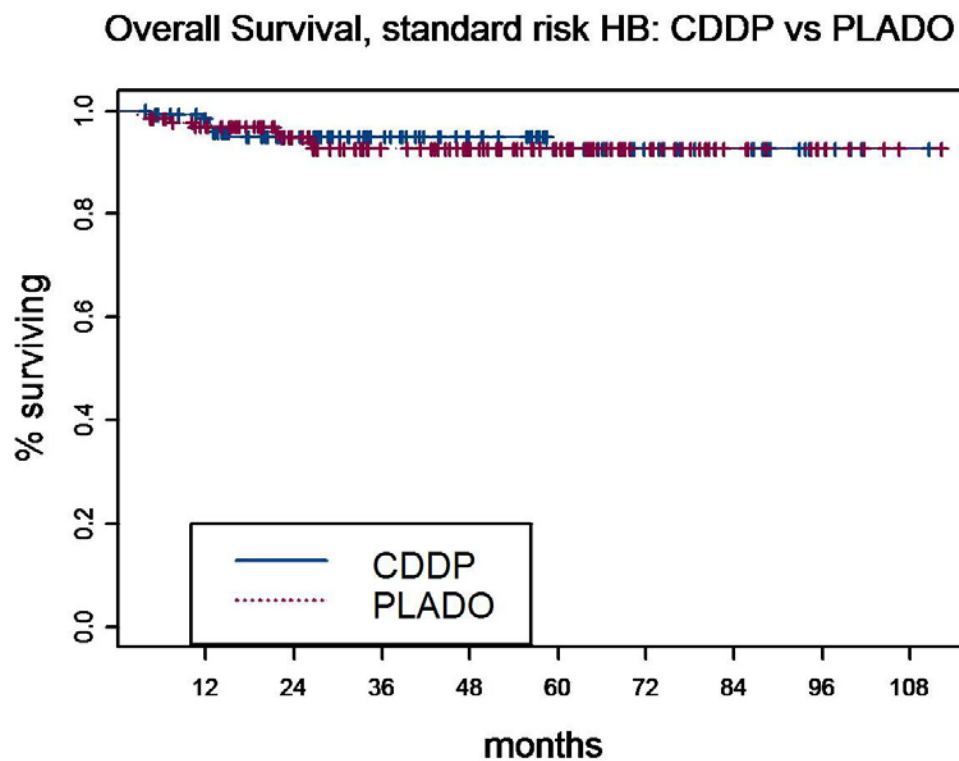


Figure 9. 3-year SIOPEL 3 SR arm overall survival by randomization arm.

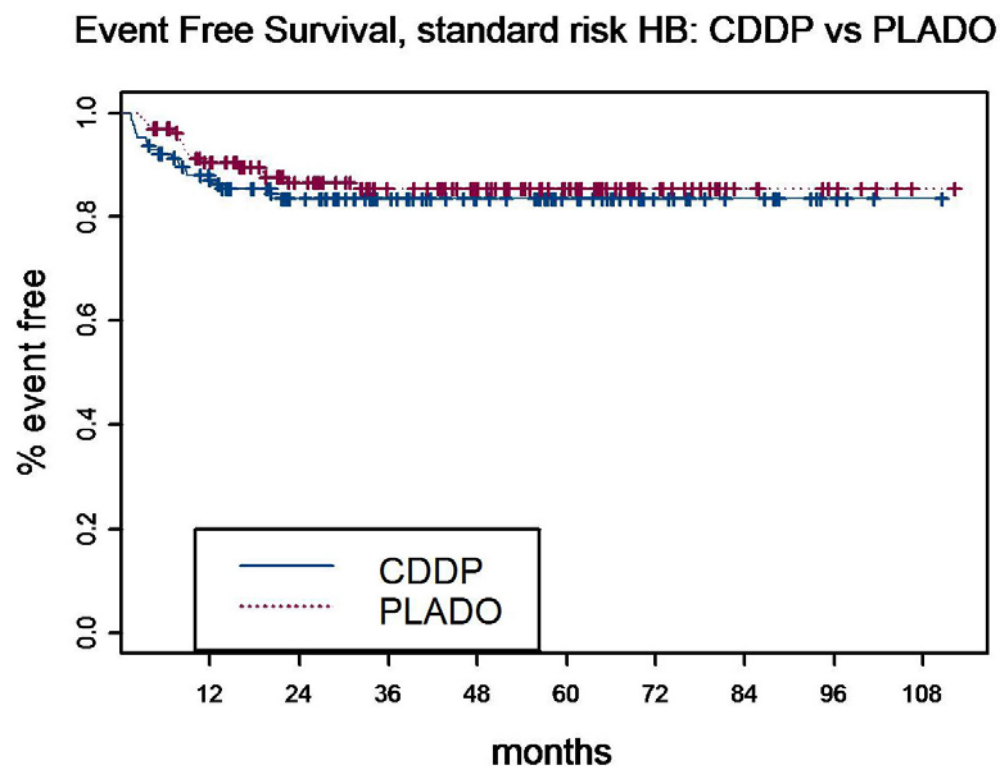


Figure 10. 3-year SIOPEL 3 SR arm event-free survival by randomization arm.

Table 1. SIOPEL 3 Standard Risk arm results.

	CDDP alone n. 126	PLADO n. 129
Positive response rate	90% - (114/126)	95% (122/129)
95% confidence interval	84-95	89-88
Intention to-treat analysis		
Complete resection rate	95% (120/126)	93% (120/129)
95% confidence interval	90-98%	87-93%
3-years event-free survival	83% (95% CI 77-90%)	85% (95% CI 79-92%)
3-years overall survival	95% (95% CI 91-99%)	93% (95% CI 88-98%)

survivors, even though 8 of them did not receive any additional treatment than prescribed by the protocol (17). In the SIOPEL 3 SR arm only 2 out of the 28 patients with microscopical residual suffered an event and actually one of those was of higher risk of tumor relapse because of the initial intra-peritoneal tumour spillage. Thus it seems that microscopic residuum does not confer worse prognosis per se. Nevertheless radical tumor excision is recommended in every case.

One of the techniques, which contributed to the progress in SIOPEL trials was introduction of liver transplantation (LTX) into the field of hepatoblastoma. In SIOPEL 1 study 12 patients (8% of all) underwent LTX: 7 as the first-line surgical option and 5 as rescue procedure after previous attempt of tumor resection. Overall patients survival after LTX was 75% at 5 years and 66% at 10 years (21). Even patients with pulmonary metastases and macroscopic vascular involvement could be cured with LTX, providing lung mets cleared with chemotherapy: 4 of 5 transplanted children with lung metastases became long time survivors. However it needs to be mentioned that worldwide hepatoblastoma liver transplantation experience collected by JB Otte revealed that rescue transplantations were associated with much lower survival than primary ones: 28% vs. 72% (22). Out of 5 SIOPEL 1 patients transplanted in rescue setting only 2 survived, although 2 deaths were contributed to transplant complications and not tumor recurrence (23). Taking above observations into account it was proposed that hazardous liver resections carrying a high chance for macroscopic tumor residuum and hence future relapse and possible requirement of rescue liver transplantation should be avoided whenever possible. Current SIOPEL recommendations for consideration of liver transplantation in hepatoblastoma include (21, 23):

1. multifocal PRETEXT4 tumors (this is believed to be valid, even if one of the sectors clears with preoperative chemotherapy, although this recommendation is based on rather anecdotal reports) (23),
2. large solitary PRETEXT4 tumors, although they are infrequent, unless clear tumor downstaging to PRETEXT 3 is documented indication rather prior compression/displacement than true invasion (23),
3. some PRETEXT 3 centrally located unifocal tumors (with direct involvement of major hepatic vascular structures)
4. tumor extension/invasion into all 3 hepatic veins, inferior vena cava, main portal vein or its both branches.

No doubt, through consecutive SIOPEL trials it has been learnt that liver transplantation has become an important

part of modern armamentarium in hepatoblastoma treatment. The only absolute contraindication to LTX is resistance to chemotherapy and persistence of extrahepatic deposits / metastases which cannot be cleared with chemotherapy and/or surgery.

Surgery has also an important role in the resection of pulmonary hepatoblastoma metastases, either persisting or relapsed ones. In SIOPEL 1 all 4 of 22 children, who had pulmonary metastases at diagnosis and underwent delayed metastasectomy survived (10).

3.6. Phase II trials

Two phase II trials were performed by the SIOPEL group: the first one based on cyclophosphamide and the second one based on irinotecan. Cyclophosphamide use was unsuccessful. In the study, which recruited 18 relapsed or refractory hepatoblastoma patients (17 evaluable) only 1 one partial response and 1 disease stabilization were noted (24). Low response rate observed led to the conclusion that single-agent cyclophosphamide is not effective in relapsing or refractory hepatoblastoma. Irinotecan approach was more successful with trial closed prematurely due to proven efficacy, however soon these results will be reported elsewhere.

4. DISCUSSION AND FUTURE PERSPECTIVES

Throughout consecutive SIOPEL studies it has been learnt that introduction of cisplatin-based chemotherapy in combination with delayed definitive surgery has dramatically improved the survival of most children with hepatoblastoma. However certain patients subsets with, so called, high risk tumors (those with whole liver involvement, extrahepatic/metastatic disease) remained to have inferior prognosis. Thus a new treatment strategy was developed, which was based on pre-operative chemotherapy with intensified cisplatin use and more frequent application of liver transplantation (SIOPEL 3). However even with this approach certain subsets of patients were doing worse, i.e. metastatic ones and particularly those with low AFP level at diagnosis (25). Taking into account modern tendency towards more personalized medical oncology, aimed at improving treatment for poor risk tumours and avoidance of overtreatment with long term sequelae in those with good prognosis, it seems that a new international stratification of hepatoblastoma is required. This view is supported further by the findings of American colleagues showing that certain hepatoblastoma subsets (pure fetal histology tumors) can be cured just with complete surgical resection without any chemotherapy at all (26). Quite possibly, newly established stratification will include following subgroups: low, standard, high and very high risk hepatoblastoma.

Unluckily large patients numbers required for phase III trials make it difficult to test new agents and approaches, unless truly global cooperation and new innovative trial designs based on common patients stratification are introduced. Hepatoblastoma is a very good example of a very rare malignancy, that in order to achieve further progress requires international collaborative research and organization of international trials with global participation of study groups including across Europe, as well as overseas.

5. ACKNOWLEDGEMENTS

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