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Phase II study of high-dose cyclophosphamide in relapsing and/or resistant hepatoblastoma in children: a study from the SIOPEL group

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Abstract

The study sought to evaluate the response to cyclophosphamide (CPM) in hepatoblastoma (HB). Patients with a refractory or relapsing HB after first-line therapy as per SIOPEL 2 and 3 protocols were eligible. All patients were to receive two courses of CPM 2 g/m^2 on days 1 and 2 at 3-week intervals. Eighteen patients were included; 17 were evaluable for response. Prior treatment was *cis*platinum alone (1 patient) or *cis*platinum–carboplatin–doxorubicin (17 patients). The disease status at the beginning of CPM was: progressive during first-line treatment (10 patients), persistent unresectable disease at the end of the protocol (2 patients), relapse (6 patients). Tumour response was partial response (1 patient), stable disease (1 patient), progressive disease (15 patients) and not evaluable in one. All patients died, 17 of progressive disease and one of surgery complications. The low response rate (1/17) led the SIOPEL group to conclude that single-agent CPM is not effective for the treatment of relapsing or refractory HB.

Keywords: Hepatoblastoma; Cyclophosphamide; Phase II study

1. Introduction

Hepatoblastoma (HB) is the most common primary liver tumour in children, accounting for approximately 1–3% of childhood cancers [1]. Complete surgical resection is the most effective treatment, but less than 50% of tumours are resectable when diagnosed [2]. The 5-year overall survival (OS) rate with surgery alone is between 10% and 30% [1–3]. Chemotherapy is administered as adjuvant therapy for completely resected tumours and it is also used both preoperatively and as an adjuvant, for tumours that are initially considered unresectable or when primary resection is hazardous.

The chemotherapy regimens currently used to treat HB are *cis*platin based. During the last two decades, therapy has been refined, *cis*platin has been introduced into the therapeutic armamentarium of childhood HB,and new surgical techniques have significantly improved the prognosis of these patients. Response to chemotherapy and the resectability rate in the largest series of unresectable HB treated with *cis*platinum-based protocols are around 67% and 80%, respectively [4–10], with corresponding 5-year OS rates well above 60%.

Although recent data from multicentre trials bear witness to the marked improvement in therapeutic

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results, the prognosis of advanced or recurrent HB is still not satisfactory [11–13]. Management of metastatic, diffuse and multifocal disease and of recurrent tumours continues to be problematic. Even though salvage treatment with combination carboplatin–etoposide has been described by a German group [13], there is no consensus about treatment for children suffering from refractory or recurrent HB. Each physician has to decide which option to choose. Investigating new agents for HB is therefore becoming an urgent requirement.

The chemotherapeutic armamentarium for childhood HB is quite limited. If we look carefully, we discover that only a few agents have been tested using the classic phase II approach and they are *cis*platin, doxorubicin and carboplatin [14–18]. All the other drugs currently used in combination with *cis*platin by the various HB study groups – mainly vincristine, 5-fluorouracil, cyclophosphamide (CPM), ifosfamide, and VP-16 – have never been tested alone on HB to prove whether they are really efficient individually. The rarity of HB explains the limited amount of published data on phase II studies on this tumour.

As the effectiveness of CPM had never been correctly assessed, the SIOPEL Group (Childhood Liver Tumors Strategy Group of the International Society of Pediatric Oncology) launched a phase II trial of high-dose CPM in the early 1990s for HB patients who failed the SIOPEL 2 and 3 protocols. The purpose of this report is to present the results of this international, multicentre, phase II study.

2. Materials and methods

2.1. Study treatment

This was a phase II study based on high-dose CPM that began accruing patients when the SIOPEL 2 study was launched in June 1994. Patient enrollment continued until February 2001, thus overlapping the opening of the third generation of SIOPEL clinical trials, the SIOPEL 3 studies. This was done so that a sufficient number of patients would be recruited to be able to reach a definitive conclusion concerning the effect of this drug on these tumours.

2.2. Previous treatment

In the SIOPEL 2 and 3 protocols, treatment was stratified into two risk groups according to tumour extension at diagnosis, as described by the PRETEXT system (pretreatment tumour extension) [1]. Patients were defined as standard-risk (SR) cases if the tumour involved, at most, three hepatic sections without extrahepatic disease, i.e., group I to III in the PRETEXT classification. If the tumour involved four hepatic sections and/or was associated with extrahepatic disease, patients were considered as high-risk (HR) cases.

The chemotherapy regimens in the SIOPEL 2 protocol (1994–1998) were:

- four preoperative courses of *cis*platin (80 mg/m^2) every 15 days, and two after surgery for SR patients;
- four to six courses of carboplatin (500 mg/m^2) and doxorubicin (60 mg/m^2) alternating with *cis*platin (80 mg/m^2) and delayed surgery for HR patients.

In the SIOPEL 3 protocol, opened for recruitment on 1 June 1998, all patients received one course of *cis*platin. SR patients were then randomised to receive:

- treatment A: *cis*platin (80 mg/m^2), and doxorubicin (60 mg/m^2) (PLADO) every 21 days, three courses before and two after surgery; or
- treatment B: *cis*platin (80 mg/m^2) every 15 days, three preoperative and two postoperative courses.

HR patients received carboplatin (500 mg/m^2) and doxorubicin (60 mg/m^2) alternating with *cis*platin (80 mg/m^2), three preoperative and two postoperative courses.

3. Patient eligibility

Eligible patients were all children with:

(a) an unresectable HB after completion of the first-line chemotherapy protocol and ineligible for liver transplantation;
(b) progressive disease, defined as an increase in tumour volume and/or with continuous elevation of serum α-fetoprotein (AFP);
(c) recurrent disease diagnosed on the basis of imaging studies and/or with continuous elevation of AFP.

Life expectancy had to be greater than 3 weeks before entry into the study.

Approval of the protocol was obtained in accordance with the ethical and legal requirements in each country and the informed consent of the parents was requested before entry into the study.

4. Dose and schedule

CPM was to be administered at 2 g/m^2 in a 2-h continuous infusion on days 1 and 2 (total dose 4 g/m^2 every 21 days along with MESNA (2400 mg/m^2, continuous infusion). Before, during and 12 h after the CPM infusion, children had to be hydrated with glucose saline (3 l/m^2 per day). Drug doses were calculated per kg for children weighing less than 10 kg and they were given 66.5 mg/kg on days 1 and 2. An accurate hydroelectrolyte balance was recommended during therapy.

Before evaluation of tumour response, patients were to be given at least two courses of CPM unless unequivocal tumour progression occurred after the first course.

5. Response criteria

The serum AFP and imaging techniques (ultrasonography, computed tomography, radiography) were used to determine response. Response was evaluated in the study using the following criteria.

Complete response (CR): complete disappearance of tumour and a negative serum AFP.

Partial response (PR): any tumour volume shrinkage associated with a decreasing serum AFP >1 log below the baseline measurement.

Stable disease (SD): no change in tumour volume and/or <1 log drop in serum AFP concentration.

Progressive disease (PD): an unequivocal increase in tumour size in one or more dimensions or an unequivocal increase in the serum AFP concentration even without any clinical (physical and/or radiological) evidence of tumour regrowth.

After two courses of chemotherapy, tumour response and resectability were evaluated. If after two courses of high-dose CPM, a response was confirmed but surgical resection was not feasible, patients received additional cycles of CPM until the tumour became resectable or progressed.

6. Toxicity

Toxicity was graded according to NCI common toxicity criteria.

7. Patient characteristics

From June 1994 to February 2001, 18 patients diagnosed as having HB were included in the phase II study, according to protocol recommendations. All patients had previously been treated according to the SIOPEL 2 (13 patients) or 3 protocols (5 patients).

Seventeen of the 18 patients were evaluable, 15 males and two females, aged from 3 to 59 months at the time of the diagnosis (median 16 months).

One patient was excluded from further analysis because he was switched to another protocol when he achieved disease stabilisation after the first course of CPM.

At the time of the diagnosis, the patients were classified according to the PRETEXT classification, as follows: pretext II (4 patients), pretext III (7 patients) and pretext IV (6 patients).

Patient characteristics at the time of the diagnosis and tumour status before the initiation of high-dose CPM are detailed in Table 1.

Ten patients never achieved CR after the first-line protocol and were treated with high-dose CPM for primary progressive disease (9 patients) or persistent unresectable tumour after the end of the protocol (2 patients). Six patients were treated for a documented local [1], metastatic [2], or combined relapse (local and metastasis) [2] or for an isolated rise in AFP [1].

Evaluable lesions were a hepatic tumour (14 patients), lung metastasis (9 patients). Thirteen patients had an elevated AFP. In one patient, only AFP was evaluable.

Table 1
Patient characteristics at the time of the diagnosis and before inclusion in the phase II study

Patient no.	Status at diagnosis			First-line treatment		Status before HD cyclophosphamide	
	Age (months)/sex	Metastases	Pretext	Protocol	Surgery	Status at inclusion	Evaluable lesions
1	3/M	No	II	SIOPEL 3 HR	Complete	PD	Liver/AFP
2	19/M	No	III	SIOPEL 3 HR	Inoperable	SD/UR	Liver/AFP
3	17/M	Lung	IV	SIOPEL 3 HR	Inoperable	PD	Liver/lung/AFP
4	9/F	None	III	SIOPEL 3 SR	Complete	LR	Liver/AFP
5	7/M	None	III	SIOPEL 3 SR	Inoperable	PD	Liver/lung
6	23/M	None	III	SIOPEL 2 HR	Inoperable	PD	Liver/AFP
7	50/M	None	II	SIOPEL 2 HR	Inoperable	PD	Liver/AFP
8	18/M	None	IV	SIOPEL 2 HR	Complete (OLT)	MR	lung/AFP
9	8/M	None	IV	SIOPEL 2 HR	Inoperable	PD	Liver/lung/AFP
10	13/M	None	III	SIOPEL 2 SR	Complete	LR/MR	Liver/lung/AFP
11	16/M	None	III	SIOPEL 2 HR	Complete	MR	Lung
12	13/M	None	IV	SIOPEL 2 HR	Incomplete	PD	Liver/AFP
13	36/M	None	II	SIOPEL 2 HR	Complete	Rise of AFP	AFP
14	24/M	Lung	IV	SIOPEL 2 HR	Inoperable	PR/UR	Liver/lung
15	59/M	Lung	II	SIOPEL 2 HR	Inoperable	PD	Liver/lung/AFP
16	7/M	None	IV	SIOPEL 2 HR	Complete	LR/MR	Liver/lung
17	16/F	Lung	II	SIOPEL 2 HR	Inoperable	PD	Liver/lung/AFP

AFP, α-Fetoprotein; HD, high-dose; HR, high-risk; SR, standard-risk; PD, progressive disease; SD, stable disease; UR, unresectable tumour; LR, local relapse; MR. metastatic relapse; OLT, orthotopic liver transplant.

The median interval between the beginning of prior therapy and inclusion in this trial was 5 months (range 2–16 months).

8. Results

The 17 evaluable patients received a total of 34 courses of high-dose CPM: one course (5 patients), two courses (9 patients), three courses (1 patient), and four courses (2 patients).

Table 2
Status after high-dose cyclophosphamide

Patient	Tumour	AFP	Overall response
1	PD	Stable	PD
2	SD	Stable	SD
3	SD	Rising	PD
4	SD	Rising	PD
5	PD	NE	PD
6	PD	Rising	PD
7	PD	Rising	PD
8	PD	Stable	PD
9	PD	Rising	PD
10	PR	Decreasing	PR (after 2nd courses) CR (after 3rd courses)
11	PD	NE	PD
12	PD	Rising	PD
13	PD	Rising	PD
14	PD	Rising	PD
15	SD	Rising	PD
16	PD	NE	PD
17	PD	Rising	PD

AFP, α-Fetoprotein; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete remission; NE, not evaluable.

8.1. Response

Data concerning responses are presented in Table 2.

Of the 17 evaluable patients, only one responded (patient no. 10), achieving a PR after two courses, and a CR after three courses, of CPM (Fig. 1). Another patient (patient no. 2) had SD and all the others (15 patients) experienced disease progression. Two patients (nos. 7 and 14) were not evaluated after two courses, but after four courses and both were considered as PD.

8.2. Outcome

The patient who achieved a CR had previously been treated according to the SIOPEL 2 SR protocol (*cis*platinum alone) and was subsequently included in the phase II study for a local and a metastatic relapse that occurred while on therapy. After third course of high-dose CPM, this patient was treated with carboplatin and doxorubicin but he relapsed again, 8 months after high-dose CPM, and died of brain metastasis.

The patient with disease stabilisation (patient 2) was treated with three consecutive cycles of chemoembolisation and hepatic surgery thereafter but he died during surgery due to a cardiac arrest, the reason for which remains unknown.

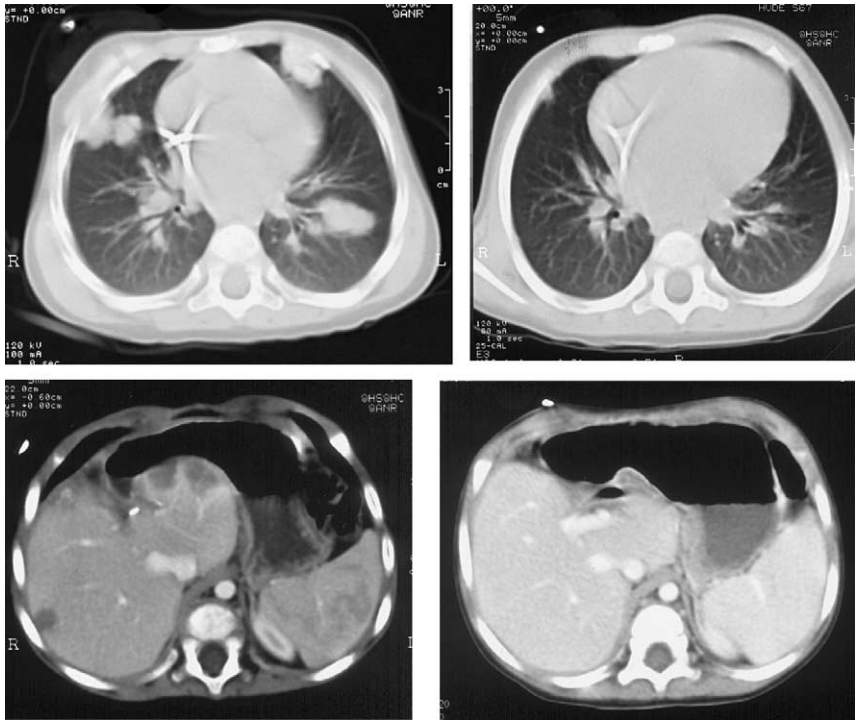

Fig. 1. CT scans before and after two courses of high-dose cyclophosphamide in the child who achieved a response.

The patients who had progressive disease after high-dose CPM were treated with additional chemotherapeutic regimens and/or radiotherapy, 6 patients received no further therapy and three underwent surgical treatment (orthotopic transplantation).

All 15 non-responders died of progressive disease. The median time to death after high-dose CPM was 7 months (range 2–24 months).

8.3. Toxicity

Data on acute toxicity were evaluable in 33/34 courses (97%). Platelet and packed red blood cell transfusions were required in 11 of the 33 courses (33%) and 19 of the 33 (57%) courses, respectively. Fever and neutropenia occurred in 29/33 courses (87%) and 10 (30%) had documented infection. Other toxicities were: grade 2/3 mucositis (3 patients), hepatic (with grade 3 hyperbilirubinaemia (1 patient) and veno-occlusive disease (1 patient), grade 2 diarrhoea (1 patient), and nephrotoxicity (alteration of glomerular filtration rate) (1 patient). Only three courses were delayed due to infection and febrile neutropenia and only 2 patients required a dose reduction in at least one course (veno-occlusive disease and nephrotoxicity). No patient experienced haemorrhagic cystitis.

9. Discussion

Introducing chemotherapy, before or after surgical resection of HB [1,2] has significantly improved the prognosis of malignant epithelial hepatic tumours in children. Combined chemotherapy and surgery result in disease-free survival and OS rates of 55–75% and 60–72%, respectively, in the main international series [4–10].

Complete tumour resection remains the best hope for long-term survival. Nevertheless, efficient chemotherapy may permit cure in initially unresectable or metastatic disease. In addition, tumours that remain unresectable after chemotherapy or relapse locally may be treated by liver transplantation [19]. However, the prognosis of unresectable, relapsing and/or refractory HB remains very poor [11–13].

Only a few phase II clinical trials have evaluated the efficacy of single agents in children with HB. The rarity of these tumours explains the limited number of published data on chemotherapy in HB.

Different HB study groups [4–9] recommend combined therapy, with surgery and multi-agent chemotherapy. The efficacy of single agents or combinations of drugs such as vincristine, doxorubicin, CPM, actinomycin D, 5-fluorouracil, ifosfamide, VP 16, carboplatin and *cis*platin has been reported, but only *cis*platin [14–16], doxorubicin [18], and carboplatin [17] have demonstrated efficacy in HB as single agents. The efficacy of *cis*platin in HB was well established in the SIOPEL 2 protocol in SR patients [9,20]. The effectiveness of doxorubicin remains questionable, as the series published was small: only five children with primary hepatic malignancies were treated with continuous infusions of doxorubicin alone. A positive response to therapy was evidenced in 4/5 children and disease stabilisation was achieved in the fifth child [18]. In contrast, the recent study on carboplatin reports results on a larger group of patients: 18 (55%) of 33 patients with unresectable and metastatic HB, diagnosed as stage III in 12 and stage IV in six, responded after one course of carboplatin [17].

Few studies have been performed on refractory or relapsed HB. The German Cooperative Pediatric Liver Tumor Study Group reported on the efficacy of carboplatin and etoposide, demonstrating response in six of 14 children with advanced and recurrent HB [13].

Preclinical studies of xenotransplanted HB, derived from HB cell suspensions from three children, were conducted to test the effectiveness of *cis*platin, ifosfamide, doxorubicin, carboplatin and VP 16. There was a marked reduction in tumour volume with *cis*platinum and doxorubicin in the tumours derived from 2/3 children whereas only *cis*platinum induced a significant reduction of tumour volume of the tumours derived from the third HB [21]. Another study suggested that pacitaxel could be an effective antineoplastic agent in xenotransplanted HB. HB cell suspensions from three children were transplanted into nude mice, and pacitaxel induced a response in all three animals [22].

The present study is the first multi-institutional phase II trial evaluating the antitumour activity of high-dose CPM as single-agent therapy in 17 patients with relapsing and/or refractory HB. The choice of CPM was based on the current use of ifosfamide in the German Cooperative Pediatric Liver Tumor Study Group [7].CPM was chosen rather than ifosfamide because renal toxicity is lower, making its use easier after first-line treatment including high-doses of *cis*platin.

Only one patient (no. 10) responded to CPM, achieving a CR after three courses. This patient had received four courses of *cis*platin as first-line treatment according to the SIOPEL 2 protocol for SR patients.

Since this patient had received less intensive first-line treatment compared to the other patients, it can be hypothesised that CPM might be effective for first-line treatment of HB. Moreover, as HB is a tumour that often develops multiple drug resistance during initial chemotherapy, conclusions drawn from treatment of refractory/recurring tumours are somewhat limited in relation to the possible effect of the drug if given as primary treatment. However, given the low response rate in the whole series and the severe side-effects of CPM, both acute (haemorrhagic cystitis, haematological, and hepatic toxicity) and long-term sequelae such as

impairment of fertility, its applicability in newly diagnosed HB patients remains limited.

Due to the frequently observed cross-resistance between CPM and ifosfamide, the low response rate observed in our study renders questionable the usefulness of ifosfamide currently administered in first-line treatment in the IPA protocol conducted by the German Group. A randomised study comparing IPA to *cis*platin–adriamycin might be warranted.

The challenge we are faced with in the immediate future is to conduct rigorously planned phase II studies to test the efficacy and tolerability of novel agents as salvage therapy for children with refractory or recurrent HB.

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