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A phase II study of irinotecan in children with relapsed or refractory neuroblastoma: A European cooperation of the Société Française d'Oncologie Pédiatrique (SFOP) and the United Kingdom Children Cancer Study Group (UKCCSG)

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ABSTRACT

Purpose: To evaluate the efficacy and safety of irinotecan in paediatric recurrent or refractory neuroblastoma.

Patients and Methods: Thirty seven patients aged between 6 months and ⩽20 years, with relapsed or refractory neuroblastoma, received irinotecan at 600 mg/m^2 administered as a 60-min infusion, every 3 weeks. Tumour response was evaluated by conventional radiological and mIBG scans every two cycles.

Results: No objective response was observed during the study. Stable disease was observed in 13% of evaluable patients. Median times to progression and survival were 1.4 months (range, 1.2–1.5 months) and 8.8 months (range, 6.7–11.3 months), respectively. One forty two cycles were administered, with a median of two cycles per patient (range, 1–17 cycles). The most common grade 3–4 toxicities were neutropenia (65% of patients), anaemia (43%), thrombocytopenia (38%), vomiting (14%), abdominal pain or cramping (8%), and nausea (5%).

Conclusion: Irinotecan administered intravenously as a single agent every 3 weeks induced no objective response in relapsed or refractory neuroblastoma.

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1. Introduction

Neuroblastoma is a neural crest derived paediatric malignancy that occurs predominantly in early childhood. More than half of the patients with neuroblastoma have metastatic disease at diagnosis. Its prognosis and treatment depends on many factors including age at diagnosis, clinical stage, the site of primary tumour, histology, and tumour biological characteristics (such as MYCN gene amplification). In general, children aged <1 year at time of diagnosis and/or with localised disease have an overall better prognosis, mainly depending on the degree of tumour resection, and they require little or no adjuvant therapy. On the contrary, older children often show bone marrow involvement at diagnosis and the majority die from disease progression despite intensive multimodal therapy.[1,2] These children are defined as high-risk patients and more than 50% of them relapse. Thus, new active drugs are urgently needed.

Topoisomerase I targeted camptothecin analogues represent promising new anticancer agents for the treatment of childhood cancer. Irinotecan was shown to be highly active against a variety of experimental paediatric tumour models such as neuroblastoma, rhabdomyosarcoma and central nervous system (CNS) tumours.[3–6] Several paediatric phase I trials have been completed following different schedules, from a single infusion every 3 weeks to a protracted administration (daily dosing for 5 days per week for 2 weeks in a row, every 21 days).[7–11]

The present phase II study retains the experience of the French phase I study which evaluated irinotecan as a single infusion every 3 weeks in children with refractory or recurrent solid tumours.[10] In the phase I study the recommended dose was assessed at 600 mg/m^2. Neutropenia and delayed diarrhoea were observed as dose limiting toxicities (DLTs) in heavily pre-treated and in less heavily pre-treated patients, respectively.

This prospective, open, multicentre phase II study was designed to evaluate the efficacy of irinotecan at 600 mg/m^2 in three childhood solid tumours: neuroblastoma, rhabdomyosarcoma, and medulloblastoma. We present herewith data concerning its clinical efficacy and safety in the neuroblastoma cohort.

2. Patients and methods

2.1. Patients

Patients aged between 6 months and $\leqslant$20 years at time of inclusion into the study with histologically confirmed neuroblastoma, which was relapsed or refractory to standard treatments, were eligible to participate in the study. Other inclusion criteria included: measurable or evaluable primary and/or metastatic disease by mIBG (meta-iodobenzylguanidine) scan; World Health Organisation (WHO) performance status $\leqslant$2; life expectancy $\geqslant$8 weeks; neutrophils $\geqslant 1.0\times10^9$/L; platelets $\geqslant 100\times10^9$/L (or $\geqslant 75\times10^9$/L in case of bone marrow disease or high dose chemotherapy with stem transplant); bilirubin $\leqslant$1.5 upper normal limit (UNL) in the presence of haepatic metastases or otherwise $\leqslant$1.25 UNL; transaminases $\leqslant$ 2.5 $\times$ UNL; normal renal function defined as less than or equal to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade 1; prior treatments consisted of no more than one salvage therapy for relapse; no prior chemotherapy or radiotherapy within 4 and 6 weeks of study entry, respectively (within 6 weeks for nitrosoureas).

The study was conducted in accordance with the Good Clinical Practices and was approved by the local Ethics Committees. Parents or legal representatives provided a written informed consent and the patient's assent was obtained, when needed.

2.2. Treatment schedule

Irinotecan (Campto®) was supplied by Aventis Laboratory (Paris, France) as a sterile solution of 20 mg/ml, in 5 ml vials. Irinotecan was administered intravenously over 60 min as a single injection every 3 weeks at a dose of 600 mg/m^2 per patient, or 20 mg/kg (equivalent to a 1/3 dose reduction) per patient with a body weight less than 10 kg. In case of grade 4 neutropenia lasting more than 7 days, or concomitant grade 3–4 infection or delayed diarrhoea, the dose of the following cycle was reduced to 500 mg/m^2 or to 17 mg/kg. In case of persistent toxicity, the dose was further reduced to 420 mg/m^2 or 14 mg/kg. In case of a second recurrence, treatment was to be stopped, unless a clinical benefit related to irinotecan justified its prosecution. If the blood cell counts at day 21 were less than 1.0×10^9/L for neutrophils or less than 75×10^9/L for platelets, the next irinotecan cycle was delayed by 1 week and the dose was reduced by 20%. If there was no recovery at day 28, the treatment was delayed by another week. If there was no recovery after a 2-week delay (day 35), the treatment was terminated and the patient was withdrawn from the study, unless a clear drug-related benefit for the patient was shown. Irinotecan treatment was continued until progression, unacceptable toxicities or patient's refusal. At the clinician's discretion, irinotecan therapy could be continued for up to 16 courses.

Concomitant treatments included atropine (20 μg/kg, subcutaneously) for cholinergic symptoms (preventive treatment for patients having suffered severe acute cholinergic symptoms during a previous cycle) and loperamide was added if the patient subsequently developed diarrhoea. Preventive antiemetic treatment according to each centre's preferred practice for highly emetogenic antineoplasic drugs was allowed.

2.3. Treatment assessment

During treatment, anti-tumour efficacy was assessed according to WHO criteria every two cycles and/or at the end of treatment, then, during follow-up, every 2 months. The initial target lesions were measured by baseline method. Response was defined according to the INSS (International Neuroblastoma Staging System) criteria including mIBG evaluation.[12] An External Response Review Committee (ERRC), consisting of independent experts in the evaluation of paediatric tumours, reviewed all data.

Complete response (CR) required disappearance of all active disease for at least $\geqslant$4 weeks. Partial response required $\geqslant$50% reduction of the tumour size observed for at least $\geqslant$4 weeks. Thus, any tumour response needed to be confirmed

4 weeks apart. Progressive disease comprised all stages not already defined, including the appearance of any new lesion. Stable disease (SD) was defined as <50% reduction of the tumour size and minor response (MR) as a regression of the tumour size between 25% and 50%. The duration of response was calculated a) for patients in PR as the interval between the date of the first infusion and the date of documented progression and b) for patients in CR as the interval between the date of the first documentation of a CR and the date of the first documented progression. Time to progression was calculated from the date of the first infusion to the first date of documented progression. The overall survival (OS) was defined as the time from the first infusion until death.

Toxicity, graded according to the NCI-CTC, was assessed by clinical and biological examinations before each cycle (weekly within a cycle for haematological toxicity), and then at the end of treatment.

2.4. Statistical analysis

The study was designed as a two-stage modified Fleming phase II, to detect a true response rate of 20%.[13] A total of 20 patients were to be entered in the first stage. If at least one response was observed in the first 20 patients, fifteen additional patients evaluable for response were to be accrued (a total of 35 patients).

The primary end-point of the study was the objective response rate (ORR) (complete plus partial responses) as assessed by the ERRC, and its exact 95% confidence interval (CI). Tumour responses were to be confirmed by two evaluations taken at least 4 weeks apart to be considered. The secondary efficacy criteria were the duration of response, the time to progression (TTP), and survival. The worst toxicity grade for each patient in all cycles of chemotherapy was used. The efficacy analyses were performed on the Full Analysis Population (FAP) defined as all treated patients. The safety analysis was performed in all patients who received at least one dose of study drug.

3. Results

3.1. Patient characteristics

A total of 37 patients were recruited by France and UK into the study. Five patients were found to be ineligible at study entry due to missing bone marrow evaluation (two cases), prior administration of more than one salvage therapy (1) and inadequate biological function (2), thus leading to a total of 32 patients eligible for this analysis. Patient characteristics at baseline are depicted in Table 1.

The majority of patients were male (70%) with a median age of 4 years (range, 1–14 years) and had stage 4 disease (86.5% versus 13.5% of stage 3). Thirty-two patients had an abdominal tumour (adrenal in 26 cases) and five patients had a thoracic tumour (mediastinal in three). All patients presented with metastatic disease at study entry with more than half of the patients with four or more organs involved. The median time from diagnosis to the first irinotecan infusion was 16.8 months (range, 5–55.8 months). The majority of patients (68%) were at first relapse and 4% had a refractory tumour. All patients had received prior chemotherapy (mainly anthracyclines, platinum and vinca-alkaloids compounds) and the majority of them had also undergone surgery of the primary tumour (78%). Half of the patients received prior high-dose chemotherapy with autologous stem cell transplantation (Table 1).

Table 1 – Patient characteristics at baseline (N=37)

Characteristic		No.of pts	%
Sex			
	Male	26	70
	Female	11	30
Age			
	Median [min-max] (years)	4.0 [1–14]	
	[0–23] months	4	11
	[2–11] years	31	84
	[12–16] years	2	5
WHO Performance Status			
	0	25	68
	1	9	24
	2	2	5
	3	1	3
Clinical stage at diagnosis			
	IV	5	13
	III	32	86
Time from diagnosis to 1st study treatment			
	Median [min-max] (months)	16.8 [5.0–55.8]	
Extent of disease			
	Metastatic	37	100
Relapse/refractory			
	First relapse	25	68
	Second relapse	3	8
	Refractory	9	4
Time from relapse/progression to 1st study treatment			
	Median [min-max] (weeks)	2.0 [0.4–35.1]	
Number of organs involved			
	1	0	0
	2	6	16
	3	9	24
	4 or more	22	59
	Median [min-max]	5 [2–8]	
Prior therapy			
	Chemotherapy	37	100
	Radiation therapy	10	27
	Surgery	29	78
	CT high dose / Transplantation	19	51
Time from last CT to 1st treatment			
	Median [min-max] months	8.4 [0.7–49.3]	
Number of prior lines			
	Median [min-max]	1.0 [1–3]	

Abbreviations: CT, chemotherapy; min, minimum; max, maximum; WHO, World Health Organisation.

3.2. Treatment

A total of 142 cycles were administered to 37 patients, with a median number of two cycles per patient (range, 1–17 cycles). The median dose intensity (197 mg/m^2/week) corresponded to 99% of the scheduled dose. Sixty-one percent of patients

did not need any dose reduction or treatment delay during the study. The dose was reduced in 8% of patients and 2% of cycles, due to haematological and non-haematological toxicities. Treatment had to be delayed in 33% of patients and 13.5% of cycles, mainly due to reasons other than toxicity. The reasons for treatment discontinuation were progressive disease (27 patients), disease related death (four), no further expected benefit (two), occurrence of an adverse event (one), requirement for chemotherapy plus surgery (one), consent withdrawn (one) and others (one).

3.3. *Efficacy*

Two patients were not assessable for response evaluation due to early discontinuation of treatment and inappropriate response assessment according to ERCC. No objective response was observed during the study. Thus, this resulted in 30 patients being assessable for response. Two out of twenty patients accrued in the first stage experienced a partial response as reported by investigators. Those partial responses were confirmed 4 weeks apart and patients were accrued in the second stage according to study design. At the end of the study, an external review committee was set up and the two partial responses were re-assessed as stable diseases. Overall, stable disease was noted in 13.3% of patients. The median time to progression was 1.4 months (95%; CI; range, 1.2–1.4 months) and the median survival time was 8.8 months (95% CI; range, 6.7–11.2 months) (Table 2).

3.4. *Toxicity*

Myelosuppression and gastrointestinal disorders were the main toxicities. Grade 3–4 neutropenia occurred in 65% of patients and in 36.5% of cycles with a median time to nadir of 8 days (range, 7–21 days) and a median time for recovery gaining at least a grade 2 occurring within 5 days (range, 1–10 days). Three patients experienced grade 4 neutropenia lasting more than 7 days. One patient received G-CSF. Only one patient experienced febrile neutropenia. Grade 3–4 anaemia occurred in 43% of patients and 13% of cycles. Thrombocytopenia occurred in 59.5% of patients including 38% of patients with grade 3 or 4 toxicity. Abnormalities of haepatic or renal enzymes were generally mild to moderate and reversible (Table 3).

Vomiting, nausea, abdominal pain or cramping, cholinergic syndrome and diarrhoea were the most common non-haematological drug-related toxicities observed (Table 4), but they were mild and manageable in the majority of patients. All patients but four received at least one administration of atropine. Fourteen patients received anti-diarrhoeal treatment. Grade 3–4 toxicity consisted mainly of vomiting (13.5% patients and 7% of cycles), abdominal pain or cramping (8% of patients and 2% of cycles) and nausea (5% patients and 2% of cycles). No treatment-related death occurred during the study.

4. Discussion

During the 1990s, studies on topoisomerase I inhibitors were started and developed in paediatrics. Topotecan, a camptothecin analogue, was the first to undergo evaluation in children and is currently in phase III trials for rhabdomyosarcoma and neuroblastoma. Irinotecan has been evaluated in phase II clinical studies using different schedules. In the US, irinotecan administered as a protracted or a weekly schedule was

Table 2 – Efficacy results of irinotecan in the Per Protocol Population (N=30)

	No. pts	%
Best tumour response		
Complete response	0	0
Partial response	0	0
Stable disease	4	13
Progressive disease	26	87
Overall best response rate [95% CI] (%)	0.0 [0.0–11.6]	
Median time to progression [95% CI] (months)	1.38 [1.22–1.45]	
Median survival time [95% CI] (months)	8.8 [6.70–11.24]	

Table 4 – Grade 3–4 NCI-CTC non-haematological irinotecan related toxicity (N=37)

Event	No. pts	%
Vomiting	5	13
Abdominal pain or cramping	3	8
Nausea	2	5
Cholinergic syndrome	1	3
Diarrhoea	1	3
Infection without neutropenia	1	3
Bilirubin	1	3
Urticaria	1	3
Bone pain	1	3
Total number of patients with at least one grade 3–4 related AE	11	30

Table 3 – Grade 3–4 NCI-CTC haematological irinotecan related toxicity (N=37)

	Grade 3				Grade 4			
	No. pts	%	No. cycles	%	No. pts	%	No. cycles	%
Leucopoenia	13	35	18	13	3	8	3	2
Neutropenia	14	38	33	24	10	27	17	12.5
Thrombocytopenia	6	16	8	6	8	22	9	7
Anaemia	12	32	14	10	4	11	4	3

shown to be active in newly diagnosed metastatic rhabdomyosarcoma[14] and in high-risk malignant brain tumours.[15] In Europe, irinotecan administered as a 3-week schedule showed an interesting, albeit modest, antitumour activity in recurrent rhabdomyosarcoma (ORR= 11.4%) and recurrent medulloblastoma (ORR= 17.6%).[16,17]

The anti-tumour activity of irinotecan in neuroblastoma has been reported during five paediatric phase I trials using various schedules of administration. A total of six partial responses and 12 stable diseases have been observed in 56 patients with neuroblastoma (Table 5). In the present phase II study, irinotecan administered once every 3 weeks induced no objective response in 30 evaluable children with recurrent or refractory neuroblastoma. Any tumour response needed to be confirmed 4 weeks apart to be considered. In addition, mIBG scanning was used for assessment of tumour response. It has to be noted that two patients with adrenal gland as anatomic site were evaluated as PR by the investigators; therefore, enrolment continued after the first 20 patients. However, these patients were later assessed as stable disease by the ERRC. The absence of response could be in part explained by the poor prognosis of the population since all children were metastatic with a large tumour burden (median of five organs involved). Half of the patients had previously received high-dose chemotherapy with bone marrow transplantation. Moreover, the median time from diagnosis to first irinotecan administration was relatively short (17 months) suggesting aggressive tumours.

Those results are in agreement with those recently published by Bomgaars and colleagues in a prospective phase II trial of irinotecan (50 mg/m^2/day times 5 every 3 weeks) with one partial response in 18 patients with neuroblastoma.[18] Kushner and colleagues used the same dose and schedule as a palliative therapy in 44 patients with neuroblastoma.[19] In this retrospective study, only one patient experienced a very good partial remission while 20 patients had stable disease. Shitara and colleagues conducted a phase II study with 180 mg/m^2/day for 3 consecutive days, repeated once after 25 days off in 16 patients with paediatric malignancies.[20] Tumour response was evaluated on regression of tumour size and biomarkers, but no mIBG scan was performed. There was one partial remission and four patients with stable disease among seven patients with neuroblastoma. Iganaki and colleagues reported the case of a 1-year-old patient with a stage 3 neuroblastoma diagnosed through mass screening who experienced prolonged complete remission after irinotecan.[21] In a randomised phase II trial comparing single agent irinotecan (20 mg/m^2/day for 10 consecutive days, every 21 days) versus in combination with carboplatin (AUC 4 mg/mn/ml every 21 days) in 148 children with relapse or refractory malignant solid tumours, one complete remission with single agent irinotecan was observed out of 15 neuroblastoma patients in the randomised trial.[22] Overall, irinotecan seems to have little or no activity as a single agent in neuroblastoma, whatever the schedule of administration is. This is in contrast with the good response rates reported in relapsing rhabdomyosarcoma or in newly diagnosed patients with high-risk tumour.[14,16] More recently, irinotecan was combined with temozolomide, a methylating agent.[23] Only two complete remissions and one partial remission were observed in 36 assessable patients with refractory or relapsed neuroblastoma.

Topotecan has been extensively studied in neuroblastoma as a single agent and in combination with cyclophosphamide. Topotecan showed little activity when used in intermittent schedules in relapse or refractory neuroblastomas.[24–27] However, Santana and colleagues, using a pharmacokinetically-guided protracted administration of topotecan, reported one CR, 17 PR and 10 SD, i.e. 60% response rate, as evaluated by tumour size and biomarker reduction without mIBG scanning.[28] The activity was enhanced when topotecan was combined with cyclophosphamide.[29]

To understand the underlying mechanisms responsible for the lack of sensitivity to irinotecan in neuroblastoma, we developed an in vivo neuroblastoma xenograft model resistant to irinotecan.[30] In vivo resistance to irinotecan was significantly associated with down regulation of pleiotrophin, an ALK ligand[31] whose expression is correlated with a good prognosis in patients with neuroblastoma.[32] This suggests that neuroblastoma-specific molecular markers may play a role in the refractoriness to irinotecan.

The tolerance profile of irinotecan as a 3-week schedule was acceptable in these heavily pre-treated patients and was consistent with that obtained in the previous phase I trial.[10] At a higher dose than that used in adult patients (600 mg/m^2 versus 350 mg/m^2 every 3 weeks), irinotecan was well tolerated in children (even in adolescents) with manageable and reversible toxicities. Non-haematological adverse events related to irinotecan were similar to those observed in adults, i.e. mainly gastrointestinal disorders. Grade 3–4 non-haematological drug-related toxicities remained infrequent and were mainly vomiting, abdominal pain/cramping and nausea. Grade 3–4 diarrhoea or cholinergic syndrome was observed in only one patient, respectively. As already observed in the phase I study,[10] the rate of severe delayed diarrhoea was lower than that observed in adults (21% to 42% of grade 3–4 diarrhoea in patients with colorectal cancer).[33] Irinotecan-induced delayed diarrhoea was well managed with the anti-diarrhoeal guidelines. Cholinergic syndrome was well controlled by the atropine treatment. As expected, myelosuppression was among the main toxicities occurring during treatment, with a relatively high incidence of grade 3–4 neutropenia (65% of patients), which appeared higher than that observed in adult patients treated with single agent irinotecan (41–45% in phase II studies). However, few paediatric patients experienced complicated neutropenia.

In conclusion, irinotecan as a single agent, at 600 mg/m^2 administered intravenously every 3 weeks, induced no objective response in children with relapsed or refractory neuroblastoma who have been heavily pre-treated, often with high-dose chemotherapy, and who have a high tumour burden. The good tolerance profile of irinotecan at 600 mg/m^2 in paediatric patients, especially when compared to that observed in adult patients, was confirmed in this phase II study.

Table 5 – Reported activity of irinotecan as a single agent in neuroblastoma

Author	year	ref.	type of study	Administration schedule	Dose range (mg/m^2 daily)	MTD (mg/m^2 daily)	Dose intensity (mg/m^2/week) at MTD	n patients	evaluable patients with NB	Complete or Partial Response	Stable Disease	Comments
Furman	1999	7	Phase I	daily x 5/week x 2 q 21 days	20-29	20	67	23	5	1	1	no mIBGscan
Blaney	2001	8	Phase I	daily x 5q 21 days	30-65	39[a] -50[b]	65[a] – 83[b]	30	7	1	1	no mIBGscan
Mugishima	2002	9	Phase I	daily x 3 q 21 days	60 - 200	160[a] -180[b]	160[a] -180[b]	28	26	3	4	evaluation on tumour size and tumour markers - no mIBG
Vassal	2003	10	Phase I	once every 21 days	240 - 750	600	200	81	16	1	5	mIBG scan evaluation
Bomgaars	2005	11	Phase I	weekly x 4	125-200	125[a] -160[b]	125[a] -160[b]	18	2	0	1	no mIBG scan
Petrilli	2004	22	randomized Phase II	daily x 5/week x 2 q 21 days ± carboplatin AUC4 mg.mn/ml		20	67	148	15	1		CR observed in the single agent arm
Kushner	2006	19	palliative treatment	daily x 5 q 21 days		50	83	44	44	1	20	mIBG scan evaluation
Shitara	2006	20	Phase II	daily x 3q 25		180	180	16	7	1	-	evaluation on tumour size and tumour markers - no mIBG
Iganaki	2007	21	case report	days daily x 3q 25 days		180	180	1	1	1		1 prolonged CR in a 1-yr **old** NB from mass screening
Bomgaars	2007	18	Phase II	daily x 5 q 21 days		50	83	161	18	1	-	mIBG scan evaluation?
present study			Phase II	once every 21 days		600	200	37	30	0	4	mIBG scan evaluation
Total								587	171	11	36	

a heavily pretreated patient group.
b less-heavily pretreated patient group.

Conflict of interest statement

The authors declare no conflicts of interest besides those who were employees of Sanofi-Aventis and Pfizer Inc.

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Appendix A

Birmingham Children's Hospital NHS Trust, Birmingham, United Kingdom (*Bruce Morland*); Children's Hospital, Nancy, France (*Chastagner Pascal*) Curie Institute, Paris, France (*Jean Michon*); Gustave Roussy Institute, Villejuif, France (*Gilles Vassal, Birgit Geoerger*); La Timone Hospital, Marseille, France (*Jean Claude Gentet*); Léon Berard Center, Lyon, France (Matthias Schell); Oscar Lambret Center, Lille, France (Fabienne Pichon); Purpan Hospital, Toulouse, France (Hervé Rubie); Royal Manchester Children's Hospital, United Kingdom (Bernadette Brennan); Sheffield Children's Hospital, United Kingdom (*Mary Gerrard*); University of Newcastle, Newcastle Upon Tyne, United Kingdom (*Andrew Pearson*).

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