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Original Paper

Ifosfamide and Etoposide in Childhood Osteosarcoma. A Phase II Study of the French Society of Paediatric Oncology

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The aim of this phase II study was to determine the efficacy of high-dose ifosfamide with moderate dose etoposide in childhood osteosarcoma. From January 1992 to January 1995, 27 children (15 male, 12 female) with relapsed or refractory evaluable osteosarcoma were included in a phase II study of two courses of ifosfamide 3g/m^2/day and etoposide 75 mg/m^2/day for 4 days. Median age was 14 years (7–19 years). All but one had received high-dose methotrexate and doxorubicin as first-line treatment. 22 patients had previously received ifosfamide. This regimen was given as first-line in 1 patient, second-line in 23 and third-line in 3. Evaluable disease was lung metastases in 21 patients, local relapse in 5 and adenopathy in 1. There were six complete responses, seven partial responses, three minor responses, six stable disease and five progressive disease (including one mixed response). Response rate was 48% (95% confidence interval, 29–67%). Duration of response was not available (10 responding patients had other treatments). Response rate was equivalent in the subgroup of 22 patients who had previously received ifosfamide (4 CR, 6 PR). Among 3 patients who received the phase II regimen as third-line chemotherapy, there was 1 PR. All but 4 patients had a well tolerated grade 4 neutropenia. Transient mild confusion or seizures were each observed once. 5 patients are alive 15–31 months after the beginning of chemotherapy. This combination of drugs at this dosage has tolerable toxicity, is efficient and deserves evaluation in phase III studies. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: osteosarcoma, children, ifosfamide, etoposide, chemotherapy

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INTRODUCTION

THE PROGNOSIS of osteosarcoma has dramatically improved over the last two decades with the development of neoadjuvant chemotherapy. Nevertheless, survival rates remain low in patients with metastatic, chemoresistant or relapsed disease. The search for effective new agents or combinations of drugs is necessary to improve the prognosis of these subgroups of patients. Ifosfamide's usefulness has been demonstrated in a variety of childhood malignancies including osteosarcoma, either alone [1–3] or in combination with etoposide [4, 5]. Etoposide's efficiency, though less marked, has also been documented in childhood cancers [6–8]. In phase II studies with ifosfamide used as a single drug, the response rate of osteosarcoma ranges from 16 to 62% [3–5, 9–13], depending mainly on the dose. Furthermore, the superiority of the combination of both drugs has been suggested by Miser and associates in a phase II study which used ifosfamide 1800 mg/m^2/d × 5 and etoposide 100 mg/m^2/d × 5. This showed three responses in 8 patients with recurrent osteosarcoma [14]. In addition, phase III studies suggest that the outcome of patients with osteosarcoma is

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related to dose-intensity [15–17]. Thus, in 1992, the French Society of Paediatric Oncology initiated a phase II study of high-dose ifosfamide in association with moderate doses of etoposide.

PATIENTS AND METHODS

Criteria for eligibility were: histological diagnosis of osteosarcoma; evaluable disease; minimum delay after the last treatment (chemotherapy: 1 month, radiotherapy: 2 months); white cell, neutrophil and platelet counts, respectively, >3000, 2000 and 100 000/mm^3; glomerular filtration rate above 50 ml/min/1.73 m^2; hepatic enzymes and serum electrolytes not exceeding a WHO [18] grade 1 change (except for alkaline phosphatases).

Each chemotherapy course consisted of ifosfamide 3 g/m^2/day i.v. over 3 h in 250–500 ml DW5, mesna 3.6 g/m^2/day by continuous infusion and etoposide 75 mg/m^2/day i.v. over 1 h in 250–500 ml DW5, each given daily for 4 days. A minimum hydration of 2000 ml/m^2/day was required. The interval between the two courses was 3–4 weeks; the second course started when the absolute neutrophil and platelet counts were, respectively, greater than 1500 and 100 000/mm^3. Toxicities were defined according to WHO criteria [18]. Blood counts, hepatic enzymes, serum electrolytes, urea and creatinine were recorded before each treatment. Blood count was planned to be verified once a week between each course.

Response was evaluated by computed tomography of the chest for metastatic disease and by computed tomography and/or magnetic resonance imaging for bone and/or soft tissue lesions. Lesions which were resected were evaluated for their histological response to the chemotherapy.

The evaluation was performed before the beginning of the study and during the fourth week following the second course, except for patients with clinical symptoms of progressive disease after one course.

The definitions of response were as follows: a complete response (CR) was the complete disappearance of all the measurable disease by appropriate imaging or the absence of residual tumour cells on histological examination. A partial response (PR) was the reduction in size of all the tumours by at least 50% as determined by the sum of the products of the two maximum perpendicular diameters of each lesion or the presence of less than 10% tumour cells on histological examination. There was no time duration requirement. Minor response (MR) was the reduction in size of all the tumours between 25 and 50% and/or evident clinical effect (e.g. disappearance of pain or inflammation) and/or evident improvement of bone scan imaging. MR was not taken into account to determine the response rate. Stable disease (SD) was a reduction or an increase in tumour size of less than 25%. Progressive disease (PD) was defined as an increase in size of any tumour by more than 25% or appearance of new lesions. 'Mixed responses', with some lesions responding and other lesions progressing, were scored as PD.

With a minimum expected response rate of 35%, the minimum required number of patients was 25, according to Gehan's method [19]. Informed consent was obtained from each patient or the parents or guardians prior to study entry.

RESULTS

Patients' characteristics are summarised in Table 1. 27 patients were included. Median age was 14 years (range 7–19 years). There were 15 males. All but one had received high-dose methotrexate and doxorubicin during their first treatment. 22 children had previously received ifosfamide containing chemotherapy as first- or second-line treatment, at a dose level of 6 g/m^2 per course (median cumulative dose: 24 g/m^2, range: 12–48). 22 patients had received cisplatin in their first-line treatment. Sites of evaluable disease comprised lung metastases (21 cases, 13 bilateral), local relapse (5 cases) and adenopathy (1 case).

Tumour response

A response was observed in 13 patients (Table 2), leading to an overall response rate (RR) of 48% (95% confidence interval, 29–68%). One patient (number 14) with multifocal tumour who received the phase II combination as front-line therapy showed an objective response (pain relief, improvement of bone scan imaging and normalisation of alkaline phosphatase blood level). CR or PR was acheived in 11 out of 23 patients treated by IFO/VP-16 as second-line therapy. In 3 patients who received the phase II regimen as third-line chemotherapy, there were 1 PR, 1 SD and 1 PD. Duration of response to the phase II regimen alone was not evaluable since 10 of the patients who achieved CR or PR underwent surgery and/or received further radio- or chemotherapy. 3 responding patients did not receive any other treatment: 2 progressed at 3 and 8 months, the third child remaining free of disease at 15 months.

Among 13 responding patients, 5 are alive 15–31 months after the beginning of the chemotherapy (median: 24 months; mean: 24 months). Median time to death was 12 months for the remaining 8 children (mean: 19; range: 8–52). Figure 1 shows the Kaplan–Meier curve of the estimated survival rates for the 27 patients, and for the responding and non-responding groups of patients.

Toxicity

Fifty courses were evaluated for toxicity in 25 patients: 38 episodes of WHO grade 4 neutropenia occurred (median duration: 7 days; range: 4–18). Fever of unknown origin was noted in 7 cases, but there were no life-threatening infection. One patient required three platelet transfusions. No patient received haematopoietic growth factor. Neurological toxicity was seen in 2 patients. One had mild transient confusion, and one had seizures controlled by anticonvulsants. In both patients, the neurological problems did not recur with subsequent ifosfamide, etoposide and mesna. Gastro-intestinal toxicity was generaly mild. No significant liver or renal toxicity occured. There were no toxic deaths.

DISCUSSION

The majority of phase II studies of ifosfamide alone in osteosarcoma have been conducted at dose levels of 8–9 g/m^2 per course and led to response rates ranging from 30 to 43% in series never exceeding 20 patients [3, 4, 9–11]. At a dose level of 14 g/m^2 per course, Chawla and colleagues reported 10 responses in 16 patients [12]. The 48% response rate obtained in our series of 27 children compares favourably with these previous data. The results obtained by this two-drug combination in half of the patients previously

Table 1. Patients' characteristics and follow-up

Patient no.	Age (years)/sex	First-line CT (Response)	Second-line treatment (Response)	Previous ifo cumulated dose (g/m^2)	Site of evaluable disease	Response	Further treatment(s)	Follow-up* (months)
1	8.5/F	OS 89 (GR)	None	24	Local relapse	CR (100% necrosis)	Idem × 4 Surgery	Prog 7 m D 11 m
2	16/F	T 10 (BR)	Surgery	0	Lungs	CR (100% necrosis)	Idem × 1 Surgery (× 4) HDCT	Prog 24 m D 42 m
3	15/M	OS 89 (NE)	None	24	Lungs	CR (100% necrosis)	Surgery Idem × 2 HDCT	AWD 31 m
4	19/M	OS 89 (NE)	None	36	Lungs	CR	Idem × 6	Prog 8 m D 17 m
5	19/F	OS 87 (GR)	None	0	Lungs	CR	Idem × 1	Prog 3 m D 12 m
6	14/F	OS 89 (NE)	None	24	Lungs	CR	idem × 4	ANED 15 m
7	14/F	OS 87 (NE)	MTX-DOX-Ifo-DTIC (PD)	18	Lungs	PR	Idem × 2 HDCT Surgery	D 52m
8	7/M	OS 89 (NE)	IL-6 (PD)	24	Lungs	PR	RT	Prog 3 m D 8 m
9	17/F	OS 89 (NE)	None	12	Lungs	PR	Idem × 2 Surgery	Prog 10 m D 13 m
10	13.5/M	OS 89 (GR)	None	24	Local relapse	PR (> 90% necrosis)	Surgery	ANED 24 m
11	13.5/M	OS 89 (GR)	None	18	Lungs	PR (CR after 9 courses)	Idem × 7 HDCT	ANED 24 m
12	14/F	MTX-DOX (BR)	None	0	Lungs	PR	Cisplatinum HDCT Surgery	Prog 6 m D 8 m
13	12/F	OS 89 (GR)	None	24	Lungs	PR	Idem × 2 Surgery-IFN HDCT	Prog 4 m AWD 24 m
14	10/M	None	None	0	Lungs and bones	MR	Idem × 2	Prog 6 m D 12 m
15	13/F	OS 87 (BR)	None	36	Lung	MR	Idem × 2 Surgery	Prog 9 m D 16 m

16	13/M	OS 87 (BR)	Surgery	24	Lung	MR	Idem × 1 Surgery HDCT	Prog 4 m D 14m
17	15/F	OS 87 (GR)	None	0	Bulky pelvic mass (adenopathy)	SD (MR after three courses)	Idem × 2	Prog 5 m D 10 m
18	18/F	OS 87 (BR)	None	36	Local relapse	SD	Surgery	Prog 10m AWD 62 m
19	10/M	OS 87 (BR)	None	12	Local relapse	SD	Idem × 1 RT	D 17 m
20	18/M	OS 89 (GR)	Surgery MTX (NE)	24	Lungs	SD	Surgery	DC 6 m
21	12/F	OS 87 (BR)	None	36	Lung (80% necrosis)	SD	Surgery Idem × 4	Prog 14 m D 17 m
22	14/M	OS 89 (BR)	None	24	Lungs and Bone	SD	none	D 10 m
23	19/M	OS 87 (BR)	None	36	Lungs and Bone	PD	none	LFU
24	13/M	OS 87 (BR)	MTX-Carbo-VP (NE)	36	Lung	PD	Surgery HDCT RT	D 15 m
25	9.5/M	OS 87 (BR)	None	48	Lungs	PD	Surgery IFN	D 19 m
26	17/M	OS 89 (NE)	None	24	Local relapse	PD	RT	D 8 m
27	12/M	OS 87 (BR)	Surgery	36	Lungs	PD (mixed response)	Surgery Idem ×2	Prog 6 m D 12 m

*End point was July 1996. RT, radiotherapy; CT, chemotherapy; HDCT, high-dose CT followed by stem cell rescue; Ifo, Ifosfamide; DTIC, dacarbazine; DOX, doxorubicin, MTX, methotrexate; Carbo, carboplatin; VP, etoposide; IFN, alpha-interferon; IL6, interleukin-6; Idem, phase II treatment; AWD, alive with disease; ANED, alive with no evidence of disease; D, died; LFU, lost to follow-up; Prog, progression; GR, good histological response; BR, poor histological response; CR, complete remission; PR, partial remission; MR, minor response; SD, stable disease; PD, progressive disease; NE, not evaluable; T 10, Rosen's protocol including high-dose MTX, bleomycin, cyclophosphamide, dactinomycin and DOX as pre-operative CT with the substitution of MTX for cisplatin as post-operative CT for poor histological responders; OS 87, protocol including high-dose MTX and DOX as pre-operative CT and ifo, cisplatin and vindesine as post-operative CT for poor histological responders; OS 89, protocol including high-dose MTX, ifo, vindesine, cisplatin and DOX as pre- and post-operative CT.

Table 2. Responses to treatment

	All patients (n = 27)	Previous ifo (n = 22)	No previous ifo (n = 5)	Second-line CT (n = 23)	Third-line CT (n = 3)
CR	6*	4	2	4	–
PR	7‡	6	1	8	1
MR	3	2	2	3	–
SD	6	5	–	4	1
PD	5	4	–	4	1

Ifo, ifosfamide; CT, chemotherapy.
*Including 3 patients with complete pathological necrosis; ‡Including 1 patient with > 90% necrosis.

exposed to ifosfamide at lower doses suggests a dose effect for this drug and/or a synergistic effect with etoposide. These results are in contrast with data from a recent study of the Paediatric Oncology Group in which Harris and associates showed a 10% response rate in 30 patients with recurrent disease who received ifosfamide at a cumulated dose of 12 g/m^2 per course, the same dosage as our regimen [13]. Furthermore, none of these children had previously received this drug. Our results suggest the superiority of the association of etoposide with ifosfamide versus ifosfamide alone.

Recent studies have emphasised the role of ifosfamide in osteosarcoma, and demonstrated the possibility of avoiding the use of methotrexate [20–22]. The same question might be raised for doxorubicin since improving cure rate while limiting treatment-related long-term sequelae remains an important challenge in childhood osteosarcoma.

Our phase II combination of high-dose ifosfamide with moderate doses of VP-16 (300 mg/m^2 per course) produced an excellent response rate with tolerable toxicity. Furthermore, one can anticipate that haematological tolerance might be better in less heavily pretreated patients and/or with the use of haematopoietic growth factors. Thus, in our opinion, this regimen appears optimal with regard to the drugs' dosage and deserves further investigations.

The ongoing phase III trial of the French Society of Paediatric Oncology is assessing the role of this combination of drugs as first-line treatment for childhood osteosarcoma with regard to tumour response, relapse-free survival and toxicity. This randomised study is comparing the ifosfamide/etoposide regimen alternated with high-dose methotrexate to a reference arm including high-dose methotrexate and doxorubicin.

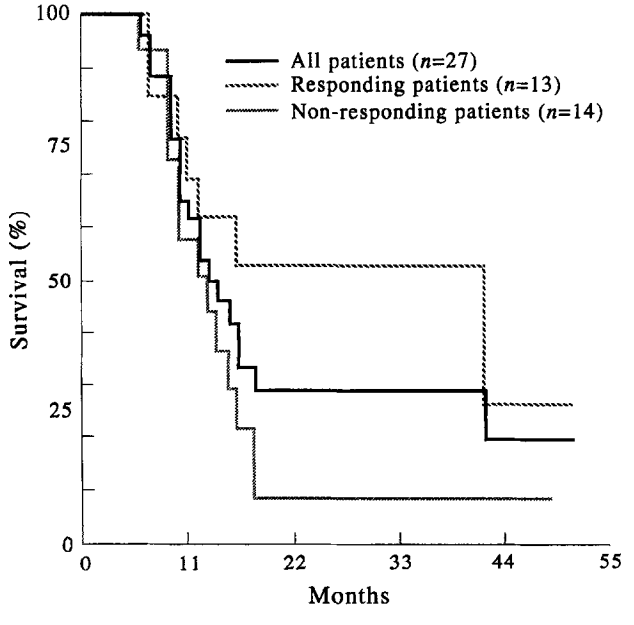

Figure 1. Kaplan–Meier curve of the estimated survival rates.

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