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A phase II study of ifosfamide in the treatment of relapses in Wilms' tumor

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Summary. The purpose of this study was to evaluate the antitumor activity and tolerability of ifosfamide (IFO) at a dose of 3 g/m^2, given on 2 consecutive days every 2 weeks, in advanced Wilms' tumor patients in whom conventional therapy had failed. Mesna and hyperhydration were concomitantly given to minimize bladder toxicity. A total of 21 patients with advanced Wilms' tumor were entered in the study. The response observed after two courses was complete in 6 patients and partial in 5; 10 did not respond; the median duration of response was 2 months (range, 1–7 months). Leucopenia caused a delay in therapy for 1 or 2 weeks in only three cases. Neither fever nor infection were observed. Of 7 patients who developed hematuria, 3 were among the 17 who concurrently received mesna. The urotoxicity did not interfere with subsequent therapy in these three cases.

Introduction

Ifosfamide (IFO) is an alkylating agent chemically similar to cyclophosphamide [1]. Good results have been obtained with this drug in paediatric embryonal tumors [5, 7]. It has been shown that, compared with cyclophosphamide, IFO induces lower and shorter hematological toxicity, enabling the administration of high-dose and frequent courses. It is possible to minimize urinary tract toxicity by the co-administration of mesna [3]; thus, we tested IFO in Wilms' tumor in spite of the fact that cyclophosphamide is regarded to be a moderately active agent [8].

Less than 15% of the cases of Wilms' tumor represent refractory disease that is not curable by a conventional multimodal therapy using surgery, radiotherapy, and polychemotherapy [6] including vincristine, actinomycin D and/or doxorubicin, which are the only three drugs recognized be effective against this disease [2]. Recurrent disease is often seen in patients whose good general condition enables the use of vigourous chemotherapy. The response to drugs is usually prompt, within 2 weeks, making a rapid assessment of drug efficacy feasible.

Patients and methods

Histologically proven Wilms' tumor and measurable disease assessed by radiological and/or ultrasonographic examinations was a condition for entering the study. IFO was given i.v. at a dose of 3 g/m^2 over a 3-h period on 2 consecutive days every 15 days. Mesna, given i.v. at a dose of 3,600 mg/m^2 per 24 h, and hyperhydration were given concomitantly for the prevention of bladder toxicity. As no dose-limiting hematological toxicity was expected [6], a WBC count was carried out every 15 days just before each course of IFO. It was recommended to delay therapy only if leucopenia (< 1,500 leucocytes/mm^3) was observed.

Response was evaluated at day 30 (or 15 days after the second course) according to WHO criteria [9], based on bidimensional measurement. After evaluation, consent was given to operate or to irradiate and/or to continue IFO in monotherapy or in combination with vincristine and actinomycin D as maintenance therapy where useful and when possible.

A total of 21 patients with histologically proven Wilms' tumor were referred by eight French centers. All but one with clear-cell sarcoma had favorable histology. Patients had previously been treated according to the protocols of the International Society of Pediatric Oncology (SIOP). The stage of disease according to SIOP staging [4] was I for two patients, II for six patients, including two with lymph node involvement, III for four patients, IV for eight and V for one. The mean age was remarkably high: 10.71 years (range, 1–42 years) due to the fact that many of the patients reported were treated for a second or third relapse and that two adults with Wilms' tumour were included in this study (Table 1). The sites of metastases or recurrences involved the lung (11 patients), pelvis or abdomen (3), liver (1), remaining kidney after partial nephrectomy in bilateral Wilms' tumour (1) and multiple sites (5, including nodes in 3 and bones for the only case with unfavorable histology). All patients had completed therapy for 1–20 months prior to the relapse reported here, and all but one had attained complete remissions (Table 2). In all, 18/21 patients received two or more courses of IFO; 3 received only one due to progressive disease and/or intolerance. Four patients did not receive mesna because it was not available.

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Table 1. Patient characteristics

Sex		Age (years)		Stage (S.I.O.P.)					Histology	
M	F	Mean	Range	I	II	III	IV	V	FH	UH
10	11	10.71	1–42	2	6[a]	4	8	1	20	1

[a] 2 patients with N+
FH, favorable histology; UH, unfavorable histology, clear-cell sarcoma

Table 2. Status of patients before IFO therapy

Prior therapy			Site of relapse				Relapses			
VCR-ACT	VCR-ACT ADR	VCR-ACT ADR + other	Lung	Abdomen pelvis	Liver	Multiple	1	2	3	4
2	16	3	11	4[a]	1	5[b]	5	11	4	1

[a] 1 Remaining kidney stage V
[b] 3 patients with nodes and 1 with bone metastases
VCR, vincristine; ACT, actinomycin D; ADR, Adriamycin (doxorubicin)

Table 3. Treatment results in 21 patients

Phase II results: Response[a]	Patients (*n*)	Courses[b]						Duration (months)				
		1	2	3	4	5	10	1	2	5	6	7
Progressive disease	6	2	3	1	–	–	–	–	–	–	–	–
Stable disease	4	–	3	1	–	–	–	–	–	–	–	–
Partial response	5	1	–	1	1	–	2	2	–	2	–	1
Complete response	6	–	1	2	1	1	1	2	2	1	1	–
Totals	21	3	7	5	2	1	3	4	2	3	1	1

[a] Response evaluated after 2 courses of IFO (day 30)
[b] Number of courses given using IFO alone

Table 4. Tolerability of IFO in 21 patients

Mesna	Patients (*n*)	Courses	Courses with	
			Hematuria	Leucopenia[a]
–	4	5	4 Gross	–
+	17	69	3 Microhematuria	4
Totals	21	74	7	4

[a] $< 1{,}000$ leucocytes/mm^3

Results

Responses evaluated at day 30 according to WHO criteria [9] included complete responses in six patients, partial responses (> 50%) in five, stable disease in four and progressive disease in six. In the 11 patients with partial or complete responses, the effectiveness of IFO therapy was observed immediately after the first course. Responses to IFO alone lasted for 1–7 months, with a median duration of 2 months (Table 3). Immediate tolerance was evaluated for 21 patients and 74 courses (Table 4).

Of the four patients who had received IFO without mesna, three developed massive hematuria despite forced diuresis, which caused therapy to be discontinued. Among the 17 patients who received a total of 68 courses of IFO with mesna according to the protocol, hematuria occurred during only 3 courses in three different patients and did not constitute a reason to cease therapy. The hematological toxicity observed was mild, below grade 2 according to WHO classification [9] and without prohibitive toxic manifestations, except in three patients with grade 4 leucopenia for whom three second courses and one third course were delayed for 1–2 weeks. Neither fever nor infection were observed, and no neurotoxicity was seen.

Conclusion

This phase II study has demonstrated the possibility of obtaining partial or complete responses in Wilms' tumors with IFO, even in patients who had previously been treated with all forms of conventional therapy. The responses observed lasted as long as several months, even with IFO monotherapy.

Further studies will be necessary to collect data on the toxicity of IFO as a single agent or in association with other drugs and radiotherapy, especially on tubular nephrotoxicity, neurotoxicity, cardiotoxicity and long-term side effects, such as carcinogenicity and sterility in males, known to be associated with alkylating agents.

The role and the toxicity of IFO in the treatment of Wilms' tumor in a multimodal design will be studied using the SIOP 9 [4] protocol, which is restricted to very high-risk patients with unfavorable histology and refractory metastatic disease.

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