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# Phase II study of ifosfamide as a single drug for relapsed paediatric patients

**E. Schwartzman, M. Scopinaro, and N. Angueyra**

Paediatric Oncology Service, Buenos Aires Children's Hospital, Buenos Aires, Argentina

**Summary.** A total of 22 patients with different solid tumours refractory to previous chemotherapy were treated between May 1985 and December 1986 (osteosarcoma, 7; Wilms' tumour, 6; rhabdomyosarcoma, 2; Ewing's sarcoma, 2; non-Hodgkin's lymphoma, 2; retinoblastoma, 1; cavum lymphoepithelioma, 1; dyktioma, 1). Patients were aged between 3 and 20 years (mean, 10.6 years). There was a 3.4:1 male-to-female ratio. The treatment consisted of ifosfamide given i.v. as a single agent at a dose of 3,000 mg/m$^2$ over 1 h on days 1 and 2. Mesna was given as a uroprotector at 600 mg/m$^2$ every 4 h, up to a total of 13 doses. The courses were repeated every 3 weeks. Every patient except those with osteosarcoma had previously received cyclophosphamide. There were 3 (13.6%) complete responses (CRs) in 2 osteosarcomas and 1 abdominal non-Hodgkin's lymphoma, lasting 12, 8 and 2 months, respectively; 4 (18.2%) partial reponses (PRs) in 2 Wilms' tumours, 1 Ewing's sarcoma and 1 abdominal non-Hodgkin's lymphoma; 4 absences of remission (ARs); and 11 (50%) cases of progressive disease (PD). In all, 81 courses were given, and the toxicities found were leukopenia (<2,000 leukocytes) in 15 courses, thrombocytopenia in 3, microhaematuria in 7, neurotoxicity in 8, fever in 8 and hypertension in 2. The overall response rate (31.8%) was encouraging and the toxicity, acceptable and reversible. These results demonstrate that ifosfamide should be considered for introduction into phase III protocols for the treatment of solid malignancies in children.

## Introduction

In the last few decades a dramatic improvement in survival has been achieved with multi-modal treatments of the principal paediatric tumours. One of the most effective agents used in treating these diseases is cyclophosphamide, an alkylating drug. However, a group of patients remain who do not respond to classic treatment protocols. As ifosfamide, another oxazaphosphorine, is a non-cross-resistant structural isomer of cyclophosphamide with a lower myelotoxic potential [2], the possibility of using the former in tumours where alkylating agents are first-line drugs is a tempting approach. Ifosfamide has shown antineoplastic activity against solid tumours and haematological malignancies [1, 5]; its effectiveness in paediatric tumours has also been demonstrated [3, 4, 6]. Toxicity to the urogenital epithelium, principally causing haemorrhagic cystitis, is the most important side effect that has been observed. However, with the development of mesna (sodium 2-mercaptoethane sulfonate), it has become possible to reduce substantially the urologic toxicity of ifosfamide without any interference with its antineoplastic activity. Taking all of this into consideration, we developed an ifosfamide-mesna protocol similar to that described by de Kraker and Voûte [4], but without vincristine; the results are evaluated in this report.

*Offprint requests to:* E. Schwartzman

## Patients and methods

We treated 22 patients with ifosfamide-mesna between May 1985 and December 1986. All patients except those with a diagnosis of osteosarcoma had previously received chemotherapy including cyclophosphamide. The histological diagnoses of our patients, aged between 3 and 20 years (mean, 10.6 years), are shown in Table 1. The male-to-female ratio was 3.4:1. The treatment consisted of ifosfamide given i.v. as a single agent at a dose of 3,000 mg/m$^2$ over 1 h on days 1 and 2, with a 48-h infusion of dextrose saline at 3,000 ml/m$^2$ per day. Mesna was given as a uroprotector at 600 mg/m$^2$ every 4 h, beginning at the start of hydration, for a total of 13 doses. The courses were repeated every 3 weeks (Fig. 1) for a total of six, unless progressive disease or major organ dysfunction related to chemotherapy was detected.

A complete remission (CR) was defined as the disappearance of all clinical and measurable evidence of tumoural disease. A partial remission (PR) was defined as a 50% reduction in all measurable tumour areas. The ab-

**Table 1.** Histological diagnoses

| Disease | Patients |
|---|---|
| Osteosarcoma | 7 |
| Wilms' tumour | 6 |
| Rhabdomyosarcoma | 2 |
| Ewing's sarcoma | 2 |
| Non-Hodgkin's lymphoma | 2 |
| Retinoblastoma | 1 |
| Dyktioma | 1 |
| Cavum lymphoepithelioma | 1 |
| Total | 22 |

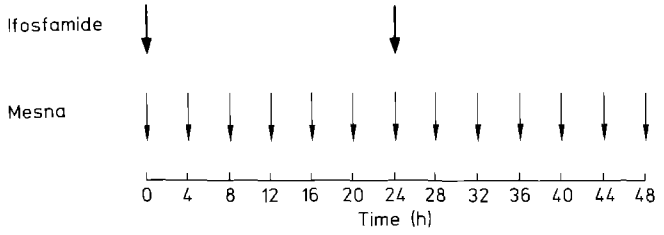


**Fig. 1.** Therapeutic regimen: ifosfamide was given over 1 h at a dose of 3000 mg/m$^2$ at 0 and 24 h (*large arrows*); mesna was given at 600 mg/m$^2$ every 4 h (*small arrows*)

sence of remission (AR) was considered to be a reduction of $<50\%$ in all measurable tumours. Progressive disease was defined as a 25% increase in any measurable tumour mass or the appearance of new lesions. Toxicity was determined according to WHO criteria. The duration of response and survival were calculated from the beginning of treatment.

## Results

There were 3 CRs (13.6%) in 2 osteosarcomas and 1 abdominal non-Hodgkin's lymphoma, lasting 12, 8 and 2 months, respectively; 4 PRs (18.2%) in 2 Wilms' tumours, 1 Ewing's sarcoma and 1 abdominal non-Hodgkin's lymphoma, lasting 7, 6, 3 and 1 month(s), respectively; 4 ARs in 2 osteosarcomas, 1 dyktioma and 1 cavum lymphoepithelioma, lasting 9, 3, 5 and 8 months, respectively; and 11 patients (50%) (Table 2) with PD. All responses were observed before the third course of treatment.

### *Toxicity*

In all, 81 courses were given, and the toxicity found involved leukopenia ($<2{,}000$ leukocytes) in 15 courses and grade 3 thrombocytopenia in only 3 courses. Intractable vomiting was seen in 7 courses. In only 7 courses was microhaematuria detected (Table 3). With respect to neurotoxicity, we recorded headache in 3 courses, mental confusion in 3, blindness in 1 and facial palsy in 1. Moreover, we detected hypertension in 2 courses and hyperthermia in 8 (6 courses in the same patient). All of these side effects were reversible, and no therapy-related deaths were observed in this study.

**Table 2.** Therapy results[a])

| Histology | Patients (*n*) | CR | PR | AR | PD |
|---|---|---|---|---|---|
| Osteosarcoma | 7 | 2 | 0 | 2 | 3 |
| Wilms' tumour | 6 | 0 | 2 | 0 | 4 |
| Rhabdomyosarcoma | 2 | 0 | 0 | 0 | 2 |
| Ewing's sarcoma | 2 | 0 | 1 | 0 | 1 |
| Non-Hodgkin's lymphoma | 2 | 1 | 1 | 0 | 0 |
| Retinoblastoma | 1 | 0 | 0 | 0 | 1 |
| Dyktioma | 1 | 0 | 0 | 1 | 0 |
| Cavum lymphoepithelioma | 1 | 0 | 0 | 1 | 0 |
| Totals | 22 | 3 | 4 | 4 | 11 |

[a] Response rate, 31.8% (7/22 patients)

**Table 3.** Toxicity of 81 courses of ifosfamide-mesna

| | WHO grade: | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Leukopenia | 50 | 5 | 11 | 12 | 3 |
| Thrombocytopenia | 74 | 4 | 3 | 0 | 0 |
| Nausea/vomiting | 10 | 20 | 17 | 27 | 7 |
| Haematuria | 74 | 7 | 0 | 0 | 0 |
| Fever | 73 | 0 | 2 | 6 | 0 |

## Conclusions

The overall response rate for this single-agent study was 31.8%. All responses were obtained before the third course. Our results were similar to those of Pinkerton et al. [6], who treated 20 children suffering from recurrent solid tumours with infusions of 5 g/m$^2$ ifosfamide over 24 h, resulting in CRs in 3 cases, PRs in 3, stable disease in 4 and PD in 11 patients. Toxicity was acceptable and reversible. These results demonstrate that ifosfamide should be considered for introduction into phase III protocols for the treatment of children with solid malignancies.

## References

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