Anti-Cancer Drugs, 2, pp. 339–341

Review paper

Ifosfamide in pediatric oncology

Jan de Kraker
Jan de Kraker is at the Emma Kinderziekenhuis/Children's Academic Medical Center, Department of Pediatric Oncology, Meibergdreef 9, NL-1105 AZ, Amsterdam, The Netherlands.
Tel.: (0)20-5663050, Fax: (0)20-6912231.

Since the number of patients seen in a pediatric oncology center is relatively small, it is difficult to perform single drug phase two studies, even on a national base. This also probably explains the lack of information on ifosfamide, despite the fact that it has now been used for more than 10 years in pediatrics. As long as chemotherapy plays such an important role in childhood cancer it remains of the utmost importance to determine the role of ifosfamide in the treatment of young cancer patients.

Key words: Ifosfamide, pediatric tumors.

Introduction

Ifosfamide (IF) is an oxazaphosphorine cytotoxic agent and an analog of cyclophosphamide (Endoxan). Early studies in adults showed that it has an advantage over its congener in being less myelotoxic, allowing higher doses to be given. Another toxic side effect, hemorrhagic cystitis, can be overcome by administering the drug together with sodium-2-mercaptoethane sulphonate (Mesna), enabling use of the drug in pediatric cancer patients.

IF is a prodrug the enzymatic activation of which produces cytotoxic metabolites. Peak plasma concentrations of ifosfamide are attained within 1 hour in adults. In children, IF alkylating activity in serum is biphasically cleared from the plasma. Relatively high levels of alkylating activity are found in the cerebrospinal fluid.[1] Capillary gas chromatographic determination of IF in microvolumes of urine and plasma is now possible, and thus will provide more accurate information on a short term.[2]

Administration of the ifosfamide dose in fractions over 3–5 days results in autoinduction of metabolism. During the metabolism of IF some toxic metabolites are formed, among which acroleine and chloroacetaldehyde are believed to be responsible for some of the toxic side effects.

Clinical experience

Our first experience with IF was in 1979. Twenty-four children with various recurrent or metastatic solid tumors, most of whom had failed to respond to previous cyclophosphamide therapy, received IF 3000 mg/m^2 for 2 consecutive days with vincristine 1.5 mg/m^2 on day 1. There were seven (29%) partial and six (25%) complete remissions (CR). Analysis of the organ-specific response in this early study showed that IF was highly effective in soft tissue sarcomas.[3]

In a pilot study, cyclophosphamide was replaced by IF in the well-known vincristine, actinomycin-D, cyclophosphamide (VAC) combination. After the first encouraging results VAC was replaced by ifosfamide, vincristine, actinomycin-D (IVA), and a multicenter trial using this combination was initiated by the International Society of Pediatric Oncology. In this study (SIOP–MMT 84) IF was given 3 g/m^2 on days 1 and 2 together with vincristine and actinomycin-D. Results reported in 1991[4] showed a 4-year survival rate in non-metastatic patients of 69%, which is better than the 52% of the previous study using VAC instead of IVA; 52% of the patients are in the first complete remission. A response rate of 31.8% was noted in 22 relapsed patients with various solid tumors.[5]

These encouraging results led to a more intensified regimen of 3 instead of 2 consecutive days IF with 3000 mg/m^2 every 3 weeks in the SIOP MMT-89 protocol.

Brain tumors and lymph node metastases are less sensitive to this treatment, probably because of a poorer blood supply. Higher doses of the drug can sometimes overcome the problem. Alkylating activity of 50% of the serum values have been reported for IF.[1] IF has also been used in different protocols for the treatment of bone tumors in children and young adults. In the German Cooperative Ewing's Sarcoma Study (CESS 86) IF was used in the treatment of high-risk patients. In a former study (CESS 81) there were clear differences between the high and normal risk groups; after introducing IF in the high risk group patients these differences disappeared, but the normal risk group showed the same outcome. In the near future it is to be expected that IF will play an important role for not only high risk but also normal risk patients.

In osteosarcoma, IF was used in combination with cisplatin and doxorubicin (PIA). The study included patients with primary metastases. Preliminary results indicate that this combination is effective enough to make it necessary for a randomized study comparing cisplatin/doxorubicin with PIA. In a phase II trial, 15 patients with osteosarcoma who already received prior alkylating agent therapy received IF as a single drug 1.6 $g/m^2 \times 5$ i.v. Five responses (CR1, PR3, MR1) were observed.[6]

In nephroblastoma patients IF was used in a single drug phase II study. A response rate of 52% was observed in patients with metastases.[7] It is now used in combination with vincristine, dactinomycin and epirubicin in patients with unfavorable histology.

In neuroblastoma patients, IF was tested as single drug therapy in patients with recurrent disease,[8] and a response rate of 8% was achieved. Another European Neuroblastoma Study Group (ENSG) paper mentioned a 22% CR or GPR rate in previously untreated disseminated neuroblastoma patients.[9] This is more than reported for cyclophosphamide (CPM). The response rates to IF used in combination with carboplatin, VP16 and vincristine are comparable to those obtained with other combinations using CPM and platinol.

Further data are needed to document whether IF is more effective if compared in the same combination corrected for dose.

Tolerability

The main dose-limiting toxicity of IF is myelosuppression. Leucopenia occurs more often than thrombopenia. The nadir for white blood cells after a 3 or 5 day regimen occurs on about day 10 and the incidence is clearly dose related. Complete recovery usually occurs within 3 weeks after a total dose of 6 g/m^2.

Nephrotoxicity in association with IF was first reported by van Dijk *et al.*[10] Prior to the use of mesna, the most common manifestation of this toxicity was hematuria or cystitis. Renal damage in adults was reported by Stuart-Harris despite the combination with a fractionated mesna schedule.[11] In pediatric patients tubular toxicity appeared to be of major importance,[12,13] especially in children less than 2 years of age who have received a cumulative dose of 6–9 g/m^2. Proteinuria, glucosuria and aminoaciduria, together with impaired phosphate reabsorption and low serum bicarbonate may develop into a full-blown Fanconi syndrome. As a consequence, rickets requiring supplementation therapy for many years is seen.

Hyperaminoaciduria (HAA) occurred in all of the 15 patients studied by Caron *et al.*[14] during treatment before any other sign of tubular toxicity was evident. HAA characterized by an α-amino-N/total N ratio of >10% and a massive generalized pattern predicts the development of a Fanconi syndrome with a sensitivity of 71.4% and a specificity of 87.6%. An even more accurate method to evaluate nephrotoxicity caused by IF is now being studied.[15] Using ^{99m}Tc-DMSA scintigraphy and calculating the absolute uptake in both kidneys it is now possible to show a decrease in uptake after IF therapy. In three children this appeared to be a sensitive and safe diagnostic method which gave more consistent results than biochemical methods.

Central nervous system toxicity was seen in 11 of 50 pediatric patients with malignant solid tumors who were treated with IF/mesna.[16] This complication is an exception in the pediatric age group in most studies. With prophylactic administration of antiepileptic drugs it was possible to continue treatment with IF in nearly all the patients.

Alopecia and vomiting are observed in up to 100% of patients treated with IF alone or in combination. If standard antiemetic drugs are administered before or simultaneously with if it is feasible to control these symptoms in the majority of patients.

Conclusion

IF/Mesna appears to be an important drug regimen in pediatric oncology, particularly for the treatment

of soft tissue sarcomas. There are few pharmacologic data relating to the use of this drug in the pediatric age group. New techniques that provide us with more accurate data concerning levels of the drug and its metabolites in the different body fluids will allow use of other treatment schedules which are probably more effective. Nephrotoxicity is of major concern: it is not clear how the tubulopathy caused by this drug should be dealt with. All of these questions preclude definitive statements about the efficacy of IF/Mesna in the treatment of malignancies in childhood.

References

1. Ninane J, Baurain R, De Kraker J, *et al.* Alkylating activity in serum, urine, and CSF following high-dose ifosfamide in children. *Cancer Chemother Pharmacol* 1989; **24 (Suppl.)**: 52–6.
2. Kaijser G, Beynen J, Bult A, *et al.* Capillary gas chromatographic determination of IF in microvolumes of urine and plasma. In press.
3. De Kraker J, Voûte PA. Ifosfamide, mesna and vincristine in paediatric oncology. *Cancer Treat Rev* 1983; **10 (Suppl. A)**: 165–6.
4. Flamant F, Rodary C, Rey A, *et al.* Assessing the benefit of primary chemotherapy in the treatment of rhabdomyosarcoma in children. Report from the International Society of Paediatric Oncology: RMS 84 study. *Proc ASCO*, 1991; **10**: 309.
5. Swartzman E, Scopinaro M, Augneyra N. Phase II study of ifosfamide as a single drug for relapsed paediatric patients. *Cancer Chemother Pharmacol* 1989; **24 (Suppl. 1)**.
6. Pratt CB, Horowitz ME, Meyer WH, *et al.* Phase II trial of ifosfamide in children with malignant solid tumours. *Cancer Treat Rep* 1987; **71**: 131–5.
7. Tournade MF, Lemerle J, Brunat-Mentigny M, *et al.* Ifosfamide is an active drug in Wilms' tumor: A phase II study conducted by the French Society of Pediatric Oncology. *J Clin Oncol* 1988; **6**: 793–6.
8. De Kraker J, Pritchard J, Hartmann O. Single agent ifosfamide in patients with recurrent neuroblastoma. *Paediatr Hematol Oncol* 1987; **4**: 101–4.
9. Kellie SJ, De Kraker J, Lilleyman JS, *et al.* Ifosfamide in previously untreated disseminated neuroblastoma. Results of study 3A of the European Neuroblastoma Study Group. *Eur J Cancer Clin Oncol* 1988; **24**: 903–8.
10. Van Dijk JJ, Falleson HC, Van der Merwe AM, Falkson G. Unexpected toxicity in patients treated with ifosfamide. *Cancer Res* 1972; **32**: 912–24.
11. Stuart-Harris R, Harper PG, Kaye SB, Wiltshaw E. High dose ifosfamide by infusion with mesna in advanced soft tissue sarcoma. *Cancer Treat Rev* 1983; **10 (Suppl. A)**: 163–4.
12. Goren MP, Wright RK, Horowitz ME, Pratt CB. Ifosfamide-induced subclinical tubular nephrotoxicity despite mesna. *Cancer Treat Rep* 1987; **71**: 127–9.
13. Patterson WP. Khojestek A. Ifosfamide-induced renal tubular defects. *Cancer* 1989; **63**: 649–51.
14. Caron H, Abeling N, de Kraker J, *et al.* Hyperaminoaciduria identifies patients at risk of developing ifosfamide induced renal tubular toxicity. *Med Pediatr Oncol* 1991.
15. Anninga JK, de Kraker J, Hoefnagel CA, Voûte PA. Ifosfamide induced nephrotoxicity, evaluated by ^{99m}Tc-DMSA renal scintigraphy. SIOP XXII Meeting-Abstracts. *Med Pediatr Oncol* 1990; **18**: 406.
16. Pratt CB, Green A, Horowitz M, *et al.* Central nervous system toxicity following the treatment of pediatric patients with ifosfamide/mesna. *J Clin Oncol* 1986; **4**: 1253–61.

(Received 28 June 1991; accepted 4 July 1991)