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Experience with ifosfamide in paediatric tumours

Jan de Kraker and Paul Antoine Voûte

Werkgroep Kindertumoren, Emma Kinderziekenhuis and Netherlands Cancer Institute, Spinozastraat 51, 1018 HJ Amsterdam, The Netherlands

Summary. Ifosfamide, alone or in combination, is used in a variety of childhood tumours. Soft-tissue sarcomas are especially sensitive, with a 78% actuarial survival. Hyperaminoaciduria and a brief transient decrease in the plasma level of certain amino acids are the earliest signs of tubular toxicity.

Introduction

After the introduction of ifosfamide (IF) in adult patients, paediatric oncologists initiated studies with this drug. After confirmation of the bladder-protecting capacity of mesna (sodium 2-mercapto-ethane sulphonate), a phase II study showed the effectiveness of IF in young patients [5]. The organ-related response showed a remarkable efficacy against tumours arising from striated muscle, even in patients with recurrent disease. In nonresponders on cyclophosphamide (CPM)-containing regimens, complete remissions lasting up to 10 months could be obtained with IF-containing protocols [5, 6]. Toxicity in regimens using 3,000 mg/m^2 for 2 consecutive days was widely studied. Even in previously heavily treated patients, a single-drug IF study showed tolerable toxicity [7]. However, the nephrotoxicity of IF, still an unsolved problem, sometimes requires the discontinuation of therapy.

Results

Effectivity in several paediatric tumours

The high response rate in rhabdomyosarcoma patients resulted in the replacement of CPM by IF in the vincristine (VCR)/actinomycin-D/CPM combination. Patients treated in our institution showed 79% survival at 3 years; the mean duration of survival from the time of diagnosis was 15.4±3.7 months [1]. A multicentre study has been undertaken by the International Society of Paediatric Oncology (SIOP). Results reported at the 19th annual SIOP meeting showed 83% CRs within 12 months; 50% of all patients are in first remission at 18 months follow-up. The 18-month crude survival is 78% [1].

Offprint requests to: J. de Kraker, Emma Kinderziekenhuis, Spinozastraat 51, 1018 HJ Amsterdam, The Netherlands

The European Neuroblastoma Study Group (ENSG) has conducted a single-agent study with IF in recurrent cases of neuroblastoma with widespread disease; a true response rate of 8% was noted [3]. A subsequent study, ENSG 3-A, has studied the response of newly diagnosed patients with stage IV neuroblastoma. A 22% CR or GPR was observed after two courses [4].

A study is now under way in which the OPEC regimen from the first ENSG study has been replaced by another combination of drugs: 400 mg/m^2 carboplatin was substituted for cisplatin and 3,000 mg/m^2 IF, for CPM for 2 days. This scheme also includes 1.5 mg/m^2 vincristine and 150 mg/m^2 VM-26 (VECI), with a 4-week interval between courses and a total of eight courses being scheduled. Thus far, six of seven patients have undergone surgery after four VECI courses. One patient developed progressive disease. In all surgical patients, >95% of the tumour burden could be resected. It is not possible at this stage to draw any conclusions from this study.

IF is used in the Ewing sarcoma protocol CESS 86; there are as yet no long-term results available. In osteosarcoma, IF seems to be effective in combination with cisplatin and Adriamycin (PIA). A pilot study conducted by the European Osteosarcoma Intergroup is expected to show the efficacy and toxicity of this combination.

Toxicity

Vomiting, alopoecia and haematological toxicity are well-known side effects. Bladder toxicity can be prevented in almost all patients by the use of mesna. Nephrotoxicity has also been noticed in children [2] but was very exceptional in our population. It sometimes interferes with the treatment of patients who respond well to IF-containing regimens.

What is the nature of the nephrotoxicity observed in these patients? Tubular toxicity was reported by St. Jude Children's Research Hospital, where the renal tubular enzyme *N*-acetyl-β-D-glucosaminidase was mainly studied [3].

We have looked at amino acids in the urine and serum of patients receiving single-drug IF and found that all patients develop a generalized hyperaminoaciduria. This phenomenon starts rather early in the treatment course. The most prominent amino acids involved are glutamine, threonine and serine; cysthathionine and B-aminoisobutyric acid are in most cases not excreted in elevated amounts. The reversibility seems to be determined by the

duration of treatment and the combination with other cytostatic agents. Within hours, cystine and methionine tend to fall to low levels in plasma, which does not correspond with increased urinary excretion. Recovery takes place within hours, despite massive hyperaminoaciduria. We have initiated a study to investigate the enzyme B_2-microglobulin; this will probably contribute to the understanding of the pathogenesis of this toxicity.

Conclusion

IF seems to be an effective drug in paediatric oncology. Shortly after its administration, some very clear disturbances occur in the blood and urinary level of certain amino acids. This finding might contribute to the understanding of the tubular toxicity, possibly even the neurotoxicity, of this drug and may even contribute to its antitumour effect. These findings justify further exploration of the pharmacology of IF.

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