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The role of ifosfamide in paediatric soft tissue sarcomas

J. de Kraker and P. A. Voûte

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

Summary. Early clinical trials in adults showed favourable results of ifosfamide (IF) in several tumours. In a previous study we used IF and vincristine (VCR) and observed 6 complete responses (CR) among 25 previously heavily treated children. Especially patients with rhabdomyosarcoma (RMS) responded well, with 4 partial responses (PR) and 2 CR among 6 patients. This and the fact that the combination of VCR, actinomycin D (ACD) and cyclophosphamide (CYT) still give good results in RMS patients led us to replace CYT with IF in this combination.

This IVA protocol consists of IF 3000 mg/m^2 i.v. in 1 h on days 1 and 2, VCR 1.5 mg/m^2 by i.v. push on day 1, and ACD 900 μg/m^2 by i.v. push on days 1 and 2. The course is repeated at 28-day intervals. VCR 1.5 mg/m^2 is given on day 14.

We used this protocol als induction therapy in 18 newly diagnosed RMS patients. The primary sites were: abdomen (4 patients), bladder and prostate (3), head and neck (9: orbita 5), extremity (1), chest wall (1). At diagnosis, 9 patients had stage I, 4 stage II and 5 stage IV disease. Except for one mixed mesodermal type, all were of the embryonal type. The patients age at diagnosis varied from 2 to 16 years. After three courses, in some patients surgery was performed if radical tumour extirpation seemed possible. The first evaluation took place after three courses. At this point one patient had no response, one had a reduction in tumour mass of < 50% (partial response PR), 9 patients had > 50% tumour-reduction (good partial response [GPR]), and 7 were in complete remission (CR). In 2 of these 7 (CR) no tumour was found on histopathological examination of the specimen. In patients with GPR or CR therapy was continued for 6 months and then stopped. Thirteen patients have been disease-free for 1–20 months from the date of CR. Four patients relapsed 4, 6, 11 and 11 months after CR. There was one therapy-related death. Except for this patient no major toxicity was encountered. These results indicate that by replacing CYT with IF, remission induction can be improved with a major contribution to survival and to enhanced quality of life in these patients.

Introduction

Favourable results in adult patients and lack of data in the paediatric age group led us to perform a phase II study of ifosfamide (IF) in combination with vincristine (VCR). In 25 patients, all with resistant forms of cancer, 8 partial responses (PR) and 6 complete responses (CR) were obtained. Of rhabdomyosarcoma (RMS) patients 4 had a PR and 2 a CR [1].

The results (in terms of efficacy and toxicity) observed with the combination of IF, VCR, and actinomycin D (ACD) are presented here.

Offprint requests to: J. de Kraker

Patients and methods

In all, 30 children were included in this study, 18 of whom had histologically confirmed RMS for which they had received no previous treatment. Except for one mixed mesodermal type, all the tumours were embryonal in type. Primary sites were orbita in 5 patients abdomen in 4, bladder or prostate in 3, extremities in 1, head and neck in 4 and trunk in 1. Five patients had a RMS but had already been treated with multimodality treatment including CYT. Four of them had recurrence; one did not achieve PR or CR and was then treated with IVA. Seven patients had soft tissue sarcomas (STS) other than RMS, but were treated with IVA as first mode of therapy. There were two synoviosarcomas, two clear cell sarcomas, one Ewing's sarcoma und two malignant mesenchymal tumours in this group.

When the diagnosis was confirmed by the pathologist, these patients entered the study. They received IF, VCR and ACD according to the dose and time schedule shown in Fig. 1. The antitumour activity was evaluated after 3 treatment cycles, and in some patients surgery was then performed to remove the residual tumour. Complete remission (CR) was defined as disappearance of all clinical evidence of the disease, including relief of tumour-related symptoms. Partial remission (PR) was defined as reduction of > 50% in all measurable tumours, with no increase in the size of any lesions and no appearance of any new lesions. Stable disease (SD) was defined as a reduction of < 50% in measurable tumour size or no reduction. Progressive disease (PD) was used to describe increase in tumour size or appearance of new lesions. Duration of response and survival were measured from the onset of treatment.

For all patients, peripheral granulocyte and platelet counts and urinanalysis were performed before every course of treatment. During the in-patient period urinanalysis was performed daily. A vomiting pattern was calculated in accordance with WHO criteria.

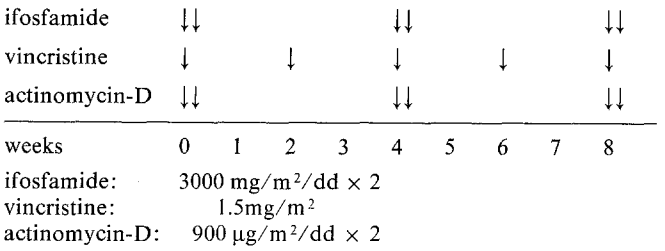

Fig. 1. IVA schedule

Results

Of 18 newly diagnosed RMS patients, 14 had achieved CR at the time of the first evaluation, while 4 had not yet reached this point. Of 14 CR patients 5 had a recurrence, 2 at the original site, 2 in distant lymph nodes, and 1 in a bone not previously affected. So far, 2 patients have died, and in 1 of these death was therapy-related. Follow-up is now 2–26 months.

Five patients with recurrent or therapy-resistant RMS were given IVA. Three went into CR but the other two had no response. The duration of remission so far is 9, 10 and 6 months.

All the seven non-RMS patients mentioned earlier were in CR at the time of first evaluation and have remained in CR for 3–20 months (mean 12) so far.

Toxicity

Vomiting is by far the most acute toxity. Encephalopathy sometimes occurs, but mostly after a high total dose or a long duration of treatment with IF. Bladder toxicity can be countered by hyperhydration and the use of mesna. Bone marrow depression is mild, with a nadir at approximately 10 days. When using the drug for longer times, renal toxicity, especially of tubular origin, is found in some cases. Glucosuria and aminoaciduria with metabolic acidosis can be found in these circumstances.

Conclusion

The IVA protocol is effective in all kinds of STS. Even in the case of such tumours that have been treated previously with combinations containing Endoxan, IF is a valuable addition to the therapeutic arsenal in paediatric practice, but more information is necessary to establish its true value.

Reference

1. Kraker J de Voûte PA (1984) Ifosfamide and vincristine in paediatric tumours. A phase II study. Eur Paediatr Haematol Oncol 1: 47–50