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High-dose ifosfamide with mesna uroprotection in Ewing's sarcoma*,**

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Summary. The German Society of Pediatric Oncology (GPO) has studied the efficacy of high-dose ifosfamide with mesna uroprotection in patients with Ewing's sarcoma. A phase II trial of ifosfamide (IFO) (2 g/m^2 per day, days 1–5) in eight patients with recurrent evaluable disease resulted in three partial and two complete responses lasting from 3 to 12 months (median, 6 months). In a second phase II trial in 15 patients, the combination of IFO and cisplatin (20 mg/m^2 per day, days 1–5) resulted in 7 partial and 2 complete responses lasting from 3 to 32 months (median, 6 months). Consequently, in 1985 IFO was incorporated into first-line chemotherapy for newly diagnosed patients (replacing cyclophosphamide) and given in combination with vincristine, actinomycin D, and Adriamycin (VAIA) in patients considered to be at high risk for relapse. IFO was given at a dose of 3 g/m per day on days 1 and 2 as a 48-h continuous infusion, in combination with actinomycin D (0.5 mg/m^2 per day on days 1–3) or Adriamycin (30 mg/m^2 per day on days 1 and 2). The study was piloted from March to December 1985 and has been open since January 1986; 37 patients were entered during the pilot phase and 65 have been entered in the ongoing main trial since January 1986. At present, Kaplan-Meier disease-free survival projects that disease-free survival in patients with large primary tumors has improved compared with that reported for the previous CESS 81 trial. The toxicity of the VAIA regimen was comparable with that of the conventional vincristine, actinomycin D, cyclophosphamide, and Adriamycin (VACA) regimen used in the previous CESS 81 trial.

Introduction

With the use of aggressive combination chemotherapy, disease-free survival in patients with primary Ewing's sarcoma of bone has improved remarkably, and >50% of all patients can now be cured [6, 11, 13, 16]. Conventional four-drug regimens consisting of vincristine, actinomycin D, cyclophosphamide, and Adriamycin are widely used. Recently, better results have been reported with more aggressive combination chemotherapy [6, 13], which requires intensive supportive care during bone marrow depression. In comparison with cyclophosphamide, ifosfamide (IFO) has been shown to be less myelotoxic [2, 3, 20]. It is active against a variety of tumors, including bone and soft-tissue sarcomas, and in tissue cultures, animal studies, and clinical trials, IFO has also proved to be more effective than its analogue [1, 12, 14]. A lack of cross-resistance with cyclophosphamide has been postulated in preclinical and clinical studies [2, 3, 18].

The previously dose-limiting side effect, hemorrhagic cystitis, can be overcome with mesna, which detoxifies aggressive IFO metabolites in the lower urinary tract [4, 10]. IFO was evaluated in phase II studies as a single agent and in combination with cisplatin and then incorporated into first-line chemotherapy for newly diagnosed patients, given in combination with vincristine, actinomycin D, and Adriamycin.

Phase II studies

Patients and methods

Children and adolescents with recurrent or refractory Ewing's sarcoma were treated with IFO alone and IFO in combination with cisplatin. A total of 23 patients with histologically proven Ewing's sarcoma, diagnosed in 14 different institutions participating in the Cooperative Ewing's Sarcoma Trial of the German Society of Pediatric Oncology, were entered consecutively in either group 1 (treatment with IFO alone) or group 2 (treatment with IFO and cisplatin; IFO + DDP) after recurrence or progression of the disease during first-line chemotherapy was diagnosed. All patients were pretreated with combination chemotherapy consisting of at least four drugs (vincristine, actinomycin D, cyclophosphamide, and Adriamycin) according to the CESS 81 trial of the German Society of Pediatric Oncology. In addition, they had previously received local therapy (either surgery and/or radiation therapy) to the primary tumor.

Eight patients received schedule I (IFO); their median age was 15 years (range, 5–21 years). 15 patients received schedule II (IFO + DDP); their median age was 14 years (range, 3–40 years). The sex ratio (femal:male) was

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4:4 and 8:7, respectively. In 5/8 patients in group 1 and 8/15 in group 2, the site of failure was the area of the primary tumor, and the remaining patients presented with systemic disease. In group 1, 7/8 patients had presented with recurrent disease while off therapy, and only 1 patient presented with progressive disease during first-line chemotherapy. In group 2, 9/15 patients presented with recurrent disease while off therapy, and the remaining 6 patients had progressive disease during first-line chemotherapy. The median duration of the first remission was 15 months (range, 5–21 months) in the group treated with IFO alone and 11 months (range, 4–9 months) in the group treated with IFO and cisplatin.

Since there is evidence for the higher efficacy of long-term infusions [8, 9], IFO was given as a continuous infusion over 5 days at a dose of 2 g/m^2 per day. Following an i.v. push dose of mesna at 30% of the daily IFO dose, mesna was continued at the same daily dose as IFO for a total of 7 days, to account for the prolonged half-life of the latter. In group 2, cisplatin was added at a dose of 20 mg/m^2 per day, given as an infusion over 5 h. These schedules were repeated every 3–4 weeks, according to bone marrow recovery. The median number of courses was three in both groups (range, two to eight courses). The tumor response was evaluated after three courses on the basis of plain X-rays and/or computerized axial tomography. A complete remission (CR) was defined as the lack of measurable evidence of disease, and a partial remission (PR), as a regression of $>50\%$ in the tumor mass. Patients with stable disease (SD), or patients with a tumor response of $<50\%$, and patients with progressive disease (PD) were classified as nonresponders. After being evaluated for response to chemotherapy, responders received additional local therapy, if feasible, to maintain the remission.

Results

In group 1 (IFO), two patients had CRs, three underwent PRs, and five did not respond. The duration of response ranged from 3 to 12 months (median, 5 months). In group 2 (IFO + DDP), two patients showed CRs, seven underwent PRs, and six had PD. The duration of response ranged between 3 and 12 months (median, 5 months). The overall response rate was 63% in group 1 and 60% in group 2.

Severe nausea and vomiting were reported in both groups; however, both the incidence and severity were higher in patients treated with IFO and cisplatin. Other side effects included severe bone marrow depression with risk of bleeding and infectious complications. There was

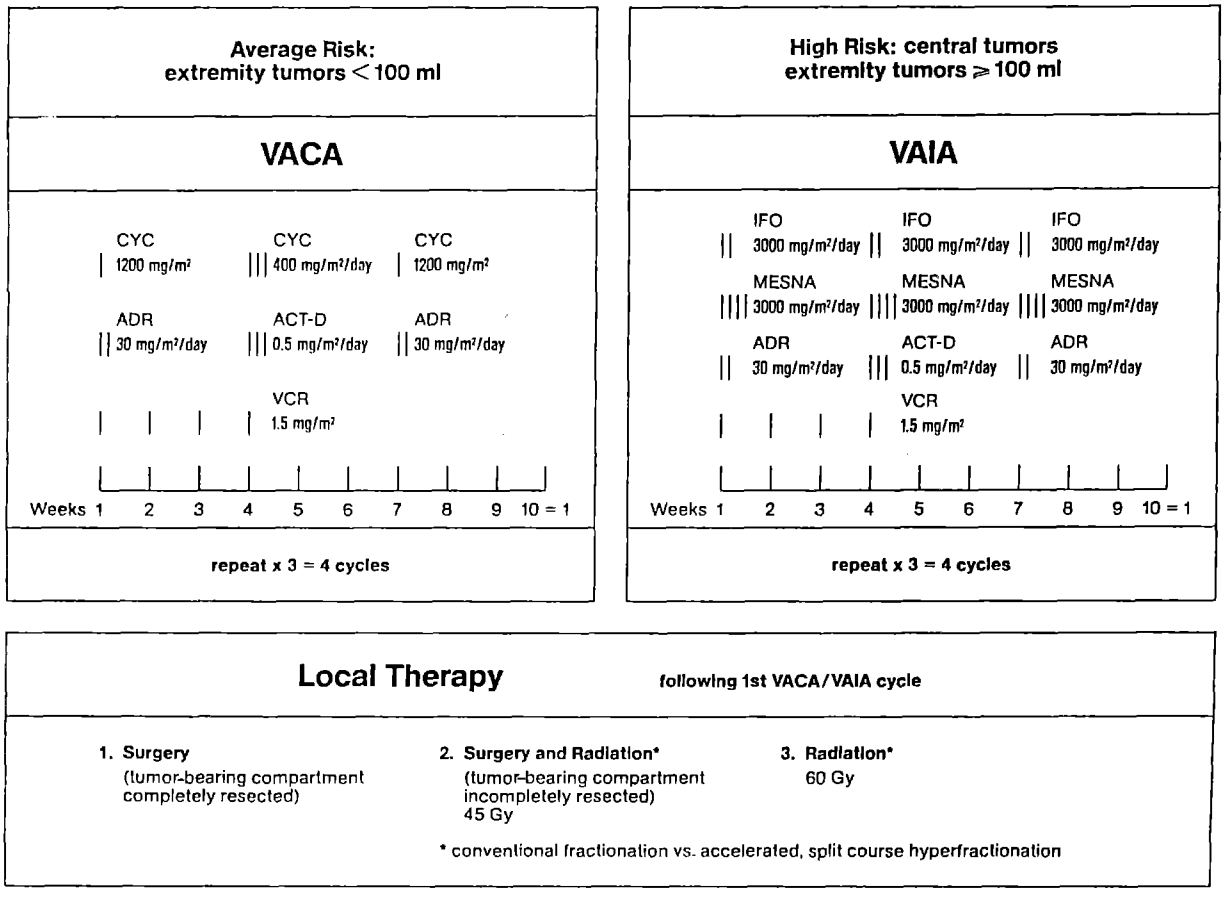

Fig. 1. Combination chemotherapy regimen for patients with primary Ewing's sarcoma of bone. Patients with small extremity tumors (tumor volume, <100 ml) received vincristine (*VCR*), actinomycin D (*ACT-D*), cyclophosphamide (*CYC*), and Adriamycin (*ADR*) (*VACA*) at doses outlined in the diagram (maximal single dose: VCR, 2.0 mg; ACT-D, 0.8 mg). In patients considered at high risk for relapse (central tumors and large extremity tumors with a volume of >100 ml, ifosfamide (*IFO*) was substituted for cyclophosphamide. Local therapy was postponed until the first cycle (9 weeks) of chemotherapy had been completed

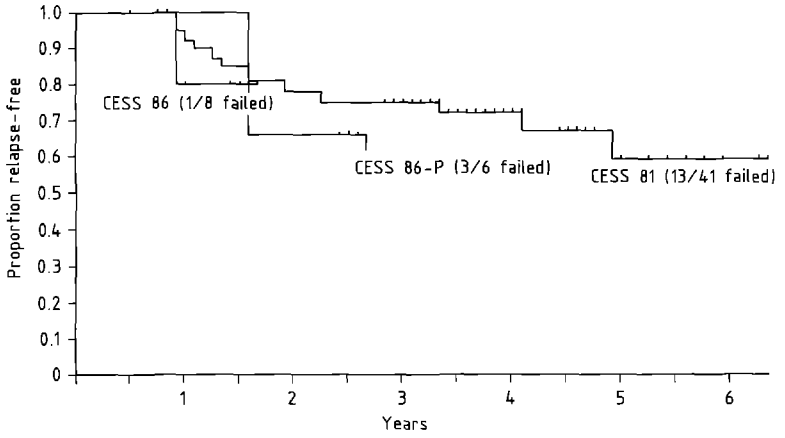

Fig. 2. Kaplan-Meier life-table analysis of disease-free survival (DFS) in patients at average risk for relapse, treated according to the CESS 81 trial (DFS, 60%±10% at 72 months), the CESS 86 pilot trial (DFS, 65%±19% at 30 months), and the CESS 86 trial (DFS, 80%±18% at 18 months) ($P > 0.05$)

one severe infection with a lethal outcome; the patient died of fungal septicemia during pancytopenia following IFO and cisplatin. Two cases of hemorrhagic cystitis were reported; both occurred in patients who had received IFO and cisplatin, during periods of thrombocytopenia. One patient had a transient reduction in creatinine clearance, and one showed transient symptoms of tubular damage. The latter patient eventually died of septicemia; on post-mortem examination, tubular necrosis was detected. Transient disorientation and dizziness were seen in one patient in each treatment group. CNS toxicity associated with IFO has previously been documented [15]. Severe ototoxicity with hearing loss was reported in one patient in the cisplatin group.

CESS 86 trial

Patients and methods

The response obtained with IFO in patients recurrent disease encouraged the drug's incorporation in first-line chemotherapy. A previous Ewing's sarcoma study of the German Society of Pediatric Oncology, CESS 81, conducted between January 1981 and February 1985, had shown tumor volume to be the major determinant of prognosis in patients with primary Ewing's sarcoma of bone [5, 7]. In patients with small tumors (< 100 ml tumor volume), the disease-free survival at 3 years was 80%, compared with only 32% in patients with large primary tumors [7].

For the follow-up study, CESS 86, it was decided to maintain the conventional cyclophosphamide-containing, four-drug regimen for patients at average risk of relapse, i.e., patients with small extremity tumors. In high-risk patients, large extremity tumors, and all central tumors, conventionally dosed cyclophosphamide was replaced by high-dose IFO. The exposure to high-dose IFO was limited to patients at high risk for relapse, since it is presently not known whether an increase in cumulative doses of alkylating agents will raise the risk of late side effects, particularly gonadal damage and second malignancies.

Since its combination with cisplatin showed no superiority. IFO was given together with agents conventionally used in Ewing's sarcoma such as Adriamycin and actinomycin D. In combination with Adriamycin and actinomycin D, a dose of 6 g/m^2 IFO was given as a 48-h continuous infusion, with concurrent mesna uroprotection continued over 96 h (Fig. 1). Local therapy consisted of either

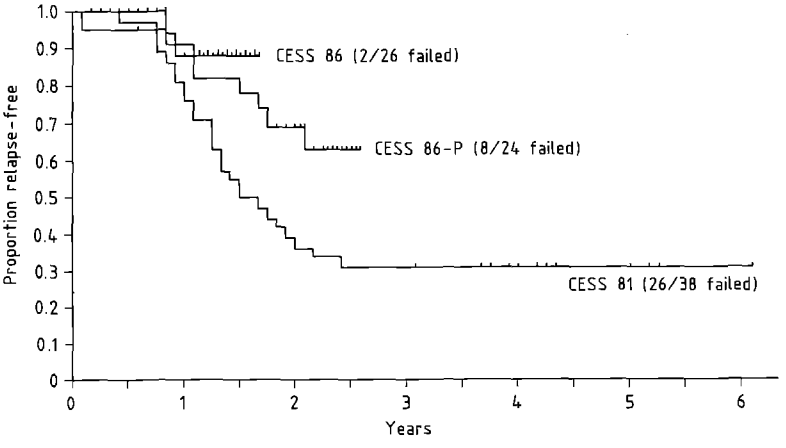

Fig. 3. Kaplan-Meier life-table analysis of disease-free survival (DFS) in patients with large tumors (> 100 ml tumor volume), treated according to the CESS 81 trial (DFS, 39%±8% at 72 months), the CESS 86 pilot trial (DFS, 63%±11% at 30 months), and the CESS 86 trial (DFS, 88%±8% at 18 months) ($P = 0.02$)

radical surgery, surgery followed by irradiation, or radiation therapy alone. All patients treated with radiation were randomized for conventional fractionation or an accelerated split-course hyperfractionation scheme. In all, four 9-week chemotherapy cycles were given to all patients. Local therapy followed the first rather than the second 9-week cycle to avoid the proliferation of chemotherapy-resistant tumor-cell lines.

The study was piloted from March to December 1985 and has been open since January 1986. All 37 patients entered during the pilot phase from March to December 1985 were not randomized for radiotherapy; some were switched from VACA to VAIA chemotherapy, and others received local therapy after the second rather than the first 9-week chemotherapy cycle. A total of 65 patients have been entered into the ongoing CESS 86 trial since January 1986; 42 were off therapy at the time of this evaluation.

Results

For average-risk tumors in which the çonventional regimen was maintained, there was no difference in disease-free survival was observed between these consecutive trials (Fig. 2). For large tumors, the relapse rate in patients receiving high-dose IFO was lower; however, stabilization of these differences with a longer follow-up is required before final conclusions can be drawn (Fig. 3).

The incidence of febrile episodes during periods of neutropenia, bacterial sepsis, bleeding, and red cell and platelet support was not different in patients receiving the conventional VACA schedule during the previous CESS 81 trial than in patients receiving the new VAIA schedule during the pilot and main phase of the present trial. No cases of severe cardiomyopathy or severe, irreversible hemorrhagic cystitis were reported.

Discussion

IFO alone and in combination with cisplatin has proved to be effective in patients with recurrent Ewing's sarcoma who have been pretreated with conventional-dose cyclophosphamide (1,200 mg/m^2) in combination with other agents. In the overall response rates, no superiority was noted for the combination therapy over the single-agent treatment. This observation is in accordance with reports of other authors who have compared IFO with IFO and cisplatin in patients with soft-tissue sarcomas [12, 17]. However, it may be argued that the number of patients with disease refractory to the first-line regimen was higher in the group of patients who received the combination of IFO and cisplatin, and these patients may have benefitted from the addition of cisplatin.

IFO was used as a long-term, continuous infusion, since Klein et al. [8, 9] have postulated a higher antitumor activity for a continuous schedule than for single-push or fractionated infusions. However, the optimal schedule still needs to be determined. The toxicity was tolerable in the group given 10 g/m^2 IFO per course as a single agent and appeared higher when cisplatin was added. However, the postmortem findings of tubular necrosis in one patient may indicate that subclinical renal dysfunction may be a relevant issue in patients receiving high-dose IFO.

Since combinations with actinomycin D and Adriamycin are more myelotoxic, a dose of 6 rather than 10 g/m^2 per course was chosen, particularly since a phase II trial has shown that the dose/response ratio beyond 5 g/m^2 (given as a 24-h continuous infusion) appeared to be less significant [19]. The preliminary experience with this schedule in the ongoing CESS 81 trial indicates that 6 g/m^2 IFO with mesna uroprotection in combination with either actinomycin D or Adriamycin is tolerated as well as 1,200 mg/m^2 cyclophosphamide in the same combination. The improved disease-free survival observed in the present trial in high-risk patients is encouraging, although definite conclusions can only be drawn when this difference has been maintained after a longer follow-up. Patients in whom this approach is curative must be carefully evaluated as to whether the exposure to such high cumulative doses of alkylating agents may increase the risk of late side effects, particularly the development of gonadal damage and second malignancies

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