Cancer Chemother Pharmacol (1989) 24 (Suppl): S45–S47

Cancer Chemotherapy and Pharmacology

Initial chemotherapy including ifosfamide in the management of Ewing's sarcoma: preliminary results A protocol of the French Pediatric Oncology Society (SFOP)

F. Deméocq, O. Oberlin, E. Benz-Lemoine, A. Boilletot, J. C. Gentet, J. M. Zucker, C. Behar, P. Poutard, D. Olive, M. Brunat-Mentigny, M. C. Demaille, C. Patte, G. Contesso, and J. Lemerle

French Society of Pediatric Oncology

Summary. Phase II studies using ifosfamide both alone and combined with vindesine and cisplatin have shown the effectiveness of this drug in patients with Ewing's sarcoma (ES) who had relapsed during VAC (vincristine, actinomycin, cyclosphosphamide)/VAd (vincristine, Adriamycin) therapy. In November 1984, these results led the SFOP to adopt a protocol consisting of (1) initial chemotherapy with three cycles of IVA (ifosfamide, 3 g/m^2 on days 1 and 2; actinomycin D, 750 μg/m^2 on days 1–3; vincristine, 1.5 mg/m^2 on day 1) alternating every 3 weeks with IVAd (vincristine on day 22; ifosfamide on days 21–23; Adriamycin, 60 mg/m^2 on day 22); (2) radical surgery if possible; (3) local radiotherapy (RT); and (4) maintenance chemotherapy with alternating IVA and VAd (vincristine, Adriamycin) for up to 9 months. In May 1987, 87 patients with previously untreated ES entered the study; 61 had localized ES. To date, 54 patients with localized disease and 22 with metastatic disease have finished initial chemotherapy; 40 patients with localized disease have been evaluated. In all, 28 patients (70%) were in complete remission (17 patients) or had a tumor regression of > 50% (11 patients) and were considered to be good responders; 12 patients were considered to be poor responders. After local radiotherapy in all but 7 patients and surgical resection in 29, 52 of 54 were considered to be in clinical remission. A total of 13 patients with metastatic disease were good responders at the completion of the initial chemotherapy. These results confirm the efficacy of primary chemotherapy using ifosfamide for the treatment of ES.

Introduction

Since 1970 the concomitant use of adjuvant chemotherapy and radiotherapy has greatly increased the long-term survival of patients with Ewing's sarcoma (ES) [9]. In 1978 the French Society of Pediatric Oncology (SFOP) [1], in conjunction with other groups [4], started a cooperative study based on a primary combined chemotherapy beginning as soon as possible after biopsy. This combination consisted of alternating VAC (vincristine, actinomycin D, cyclosphosphamide) and VAd (vincristine and Adriamycin) regimes. The purpose of the early use of effective drugs was to prevent metastases and improve the conditions of subsequent local therapy (radiotherapy in all cases and surgical resection in selected cases) [2]. A total of 95 patients with localized ES were included in the study. In May 1984, 41 of the 67 evaluable patients (61%) were at the end of initial chemotherapy and in complete remission (14 patients) or had a tumor regression of > 50% (27 patients) [7].

To determine the efficacy of initial chemotherapy with ifosfamide combined with the other drugs previously used, the SFOP adopted a new protocol consisting of initial chemotherapy with IVA (ifosfamide, actinomycin D, vincristine) alternating with IVAd (ifosfamide, vincristine, Adriamycin), followed by maintenance chemotherapy with the same drugs after radical surgical therapy (if possible) and radiotherapy [3]. We report the results of the 87 patients included in this protocol.

Patients and methods

By May 1987, 87 patients from 21 centers in France and Switzerland had entered the cooperative study of the SFOP; 61 of them had localized ES. Their ages ranged between 3 and 18 years (median, 11.5 years). Diagnosis was made by surgical biopsy; all histological samples were reexamined by the same team of pathologists. The distribution of primary sites is shown in Table 1. Pretreatment investigations consisted of complete clinical and radiological examinations, bone scans for all patients, and computerized axial tomography (CAT).

During initial chemotherapy (Tables 2, 3), patients received three cycles of IVA (ifosfamide, 3 g/m^2 i.v. on days 1 and 2; vincristine, 1.5 mg/m^2 i.v. on day 1; actinomycin D, 750 μg/m^2 i.v. on days 1–3) alternating every 3 weeks with IVAd (ifosfamide and vincristine, same doses as above; Adriamycin, 60 mg/m^2 on day 1). Adriamycin was

Table 1. Distribution of primary sites in patients with localized and metastatic Ewing's sarcoma[a]

Pelvis	26 (13)	Femur	12 (1)
Ribs	12 (3)	Tibia	8 (1)
Scapula	4	Fibula	6
Spine	3 (2)	Calcaneum	3 (1)
Maxilla	2	Toe	1
Skull	1	Humerus	5 (3)
Sacrum	4 (2)		
Totals	52 (20)		35 (6)

[a] Numbers in parentheses indicate metastatic disease

Offprints requests to: F. Deméocq, Department of Pediatrics B, Hotel Dieu, B. P. 69, F-63003 Clermont Ferrand Cedex, France

Table 2. Chemotherapeutic regimens

IVA	Ifosfamide	3.0 g/m²	Days 1, 2
	Actinoycin D	750.0 μg/m²	Days 1–3
	Vincristine	1.5 mg/m²	Day 1
IVAd	Ifosfamide	3.0 g/m²	Days 1, 2
	Adriamycin	60.0 mg/m²	Day 1
	Vincristine	1.5 mg/m²	Day 1

Table 3. Treatment schedule

Primary chemotherapy →	Surgery →	Maintenance chemotherapy
IVA alternating with IVAd every 3 weeks × 3	+ Radiotherapy	IVA alternating with VAd every 3 weeks for up to 9 months

given over 15 min and ifosfamide, over 3 h with mesna uroprotection.

Radical surgical therapy was then considered for each case. Radiotherapy was given afterward at 40 Gy in patients who underwent complete surgical resection of their tumors or at 45–60 Gy (according to the site of the tumor) in those who had incomplete or no surgery. Maintenance chemotherapy with alternating IVA (with ifosfamide) and VAd (without ifosfamide) was continued for a total treatment of 1 year.

On their completion of the initial chemotherapy sequence, all patients were reevaluated by clinical examination, radiography, and/or CAT scan and then classified as good or poor responders. Survival data were analyzed in July 1987; actuarial curves were plotted according to the Kaplan-Meier method.

Results

Localized Ewing's sarcoma

Response to primary chemotherapy. Of the 54 patients, 14 could not be evaluated for their response to chemotherapy due to the following reasons: 6 had surgical tumor resection at diagnosis, 6 had no measurable soft-tissue mass, 1 was excluded from the protocol after two cycles because of seizures and received cyclophosphamide instead of ifosfamide for the subsequent cycles, and for 1 there was no data available on the clinical response.

Of the 40 patients who could be evaluated (Table 4), 28 (70%) were considered to be good responders: 17 attained complete remission, with complete disappearance of soft-tissue mass and improvement of the bone lesion, and 11 exhibited a large reduction in their soft-tissue mass, although a minimal residual mass persisted (< 50% of the initial volume). In all, 12 patients were considered to be poor responders; their tumors grew or remained stable in 3 children and showed a moderate reduction (< 50%) in 2. In 7 patients, the tumor began to shrink after the first or second cycle and, although functional symptoms rapidly improved, pain, inflammation, or paralysis reappeared a few days before the subsequent cycle without palpable recurrence of the soft-tissue mass. When such a transitory efficacy was noted after the first cycle, it was often observed after the following one, even when different drugs were given.

Table 4. Response to primary chemotherapy in 40 evaluable patients with localized Ewing's sarcoma

Good responders (n = 28)
17 Complete remission
11 Minimal residual mass (regression > 50%)
Poor responders (n = 12)
3 Stable or progressive disease
2 Moderate regression of tumor (< 50%)
7 Transient efficiency of chemotherapy

Follow-up after primary chemotherapy. Of the 54 patients who completed their initial chemotherapy, 29 could undergo surgical resection of their tumor. In all, 26 underwent conservative surgery, with reconstruction in 11 cases (4 femurs, 2 tibias, 2 iliums, 2 humerus, and 1 maxilla, and 3 patients had amputations (2 due to a poor response to chemotherapy and 1 due to a very large tumor of the calcaneum).

The histological response to chemotherapy was evaluated in 24 patients according to the grading designed by Rosen and Huvos [9] for osteosarcomas: 9 had no viable tumors, 6 had < 10% viable tumors, 3 had 10%–50% viable tumors, and 6 had > 50% viable tumors. Among the patients who underwent conservative surgery, ten who had undergone complete resection of tumors received 40-Gy radiotherapy; to avoid jeopardizing the functional results of a complete resection of a mass containing < 5% viable tumor, seven did not receive radiotherapy. None of these 17 patients relapsed later. Five patients received classic high-dose radiation therapy due to uncertainty as to the microscopic resection of their tumors; two of these underwent locoregional relapses. One poor responder to chemotherapy developed metastasis before the radiotherapy started, and three are currently being irradiated.

The relapse-free survival at 24 months was 73% ± 8% (Fig. 1). To date, nine patients have relapsed; of the seven whose primary chemotherapy was transiently effective, five developed metastases within 8 months of diagnosis (median, 5.4 months) in spite of local control by radiation therapy. Two patients developed local recurrence after incomplete surgery, with > 50% viable tumor and in spite of high-dose radiotherapy. Among the good responders, two developed metastases at 13 and 16 months after the initial diagnosis.

Metastatic Ewing's sarcoma

Among the 22 patients with metastatic disease at diagnosis, 13 were considered to be good responders (6 attained complete remissions and 7 had a tumor regression of > 50%); 9 were poor responders.

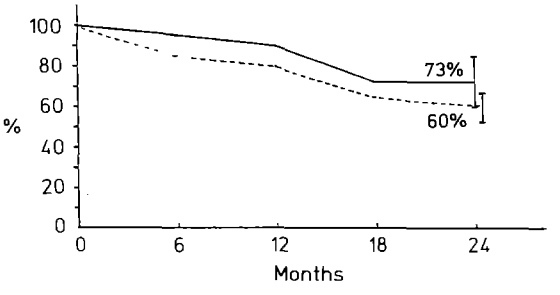

Fig. 1. Relapse-free survival in localized Ewing's sarcomas

Toxicity

The regimen was generally well tolerated, with moderate myelosuppression and no nephrotoxicity. Two patients had seizures. Three severe cardiac failures occurred just after the end of the treatment after cumulative doses of 420–480 mg/m^2 Adriamycin.

Discussion

In an attempt to develop a new therapeutic regimen for ES, we evaluated the efficacy of ifosfamide instead of cyclophosphamide given in combination with Adriamycin, vincristine, and actinomycin D as initial chemotherapy.

Phase II studies using ifosfamide alone and the combination of ifosfamide, vindesine, and cisplatin have shown the efficacy of this drug in patients with ES who had relapsed during VAC/VAd therapy. Of 12 patients, 5 underwent complete remissions and 8 had partial remissions [3]. Recent studies using ifosfamide as a single agent or in combination with other drugs have demonstrated the activity of ifosfamide in recurrent ES [6, 8].

Our results indicate that in previously untreated ES with localized disease, 70% of patients were good responders at the end of initial chemotherapy, whereas in the previous protocol 61% were good responders (not statistically significant) [7]. The follow-up was too short for conclusions to be drawn as to the outcome of the patients. Nevertheless, the 73% relapse-free survival observed at 24 months in the present study seems to be better than the 60% survival observed in the previous study [7].

Initial chemotherapy with IVA/VAd was interesting because it led to a reduction in the tumor volume to be irradiated and enabled more patients to undergo surgery. In metastatic disease, the nonaggressive chemotherapy delivered in the study by Hayes et al. [4, 5] provides better disease control than in our protocol. The unexpected cardiac toxicity observed in three patients remains unexplained. One hypothesis is that ifosfamide enhances the cardiac toxicity of Adriamycin, and this toxicity is likely to be related to the modalities of the administration of Adriamycin over 15 min and of ifosfamide over 3 h.

References

1. Deméocq F, Carton P, Patte C, Oberlin O, Sarrazin D, Lemerle J (1984) Traitement du sarcoma d'Ewing par chimiothérapie initiale intensive. Presse Med 13: 717
2. Deméocq F, Oberlin O, Brunat-Mentigny M, Carton P, Lacombe MJ, Olive D, Patte C, Sarrazin D, Tron P, Lemerle J (1984) Primary chemotherapy and tumor resection in Ewing's sarcoma of the ribs. Report of the French Society of Paediatric Oncology. Eur Paediatr Hematol Oncol 1: 245
3. Deméocq F, Oberlin O, Benz-Lemoine E, Boilletot A, Bui B, Brunat-Mentigny M, Carton D, Demaille MC, Noir A, Patte C, Tron P, Lemerle J (1985) Initial chemotherapy including ifosfamide in the management of Ewing's sarcoma. In: Proceedings of the XVIIth Meeting of the International of Pediatric Oncology (SIOP), Venice, p 274
4. Hayes FA, Thompson EI, Hustu HO, Kumar M, Coburn T, Webber B (1983) The response of Ewing's sarcoma to sequential cyclophosphamide and Adryamicin induction therapy. J Clin Oncol 1: 45
5. Hayes FA, Thompson EI, Parvey L, Rao B, Kun L, Parham D, Hutsu HO (1987) Metastatic Ewing's sarcoma: remission induction and survival. J Clin Oncol 5: 1199
6. Magrath I, Sandlund J, Raynor A, Rosenberg S, Arasi V, Miser J (1986) A phase II study of ifosfamide in the treatment of recurrent sarcomas in young people. Cancer Chemother Pharmacol 18 [Suppl 2]: 525
7. Oberlin O, Patte C, Deméocq F, Brunat-Mentigny M, Demaille MC, Tron P, Bui B, Lemerle J (1985) The response to initial chemotherapy as a prognostic factor in localized Ewing's sarcoma. Eur J Cancer Clin Oncol 21: 463
8. Pinkerton CR, Rogers H, James C, Bowman A, Barbor PR, Eden OB, Pritchard J (1985) A phase II study of ifosfamide in children with recurrent solid tumors. Cancer Chemother Pharmacol 15: 258
9. Rosen G, Juergens H, Nirenberg A, Huvos AG, Marcove RC (1981) Combination chemotherapy (T6) in the multidisciplinary treatment of Ewing's sarcoma. Natl Cancer Inst Monogr 56: 289