

ORIGINAL ARTICLE

Addition of Ifosfamide and Etoposide to Standard Chemotherapy for Ewing's Sarcoma and Primitive Neuroectodermal Tumor of Bone

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ABSTRACT

BACKGROUND

Ewing's sarcoma and primitive neuroectodermal tumor of bone are closely related, highly malignant tumors of children, adolescents, and young adults. A new drug combination, ifosfamide and etoposide, was highly effective in patients with Ewing's sarcoma or primitive neuroectodermal tumor of bone who had a relapse after standard therapy. We designed a study to test whether the addition of these drugs to a standard regimen would improve the survival of patients with newly diagnosed disease.

METHODS

Patients 30 years old or younger with Ewing's sarcoma, primitive neuroectodermal tumor of bone, or primitive sarcoma of bone were eligible. The patients were randomly assigned to receive 49 weeks of standard chemotherapy with doxorubicin, vincristine, cyclophosphamide, and dactinomycin or experimental therapy with these four drugs alternating with courses of ifosfamide and etoposide.

RESULTS

A total of 518 patients met the eligibility requirements. Of 120 patients with metastatic disease, 62 were randomly assigned to the standard-therapy group and 58 to the experimental-therapy group. There was no significant difference in five-year event-free survival between the treatment groups ($P=0.81$). Among the 398 patients with nonmetastatic disease, the mean (\pm SE) five-year event-free survival among the 198 patients in the experimental-therapy group was 69 ± 3 percent, as compared with 54 ± 4 percent among the 200 patients in the standard-therapy group ($P=0.005$). Overall survival was also significantly better among patients in the experimental-therapy group (72 ± 3.4 percent vs. 61 ± 3.6 percent in the standard-therapy group, $P=0.01$).

CONCLUSIONS

The addition of ifosfamide and etoposide to a standard regimen does not affect the outcome for patients with metastatic disease, but it significantly improves the outcome for patients with nonmetastatic Ewing's sarcoma, primitive neuroectodermal tumor of bone, or primitive sarcoma of bone.

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EWING'S SARCOMA IS A HIGHLY MALIGNANT tumor of bone that occurs in children, adolescents, and young adults. When treated with local control measures only (surgery or radiation therapy), the disease has an extremely high fatality rate.¹ The use of adjuvant chemotherapy, which began in the early 1970s, resulted in a marked improvement in the outcome. Since the first Intergroup Ewing's Sarcoma Study demonstrated improved outcomes with the inclusion of doxorubicin, nearly every chemotherapy protocol for Ewing's sarcoma has been based on four drugs: doxorubicin, cyclophosphamide, vincristine, and dactinomycin.²⁻⁴

In the early 1980s, treatment with ifosfamide, with or without etoposide, produced remarkable responses in patients who had had a relapse after standard therapies for Ewing's sarcoma.⁵⁻⁹ Of 72 patients treated with ifosfamide plus etoposide, 30 had complete or partial responses (combined data from two separate trials).^{8,9} This promising result led the Children's Cancer Group and the Pediatric Oncology Group to initiate a randomized, controlled trial, in which we investigated whether the combination of ifosfamide and etoposide, when alternated with standard drugs, would improve the outcome in Ewing's sarcoma.

METHODS

PATIENTS

National Cancer Institute protocol INT-0091 (CCG-7881 and POG-8850) was opened to all member institutions of the Children's Cancer Group and the Pediatric Oncology Group in December 1988 and closed in November 1992. Eligible patients were 30 years old or younger at diagnosis and had primary bone tumors diagnosed as Ewing's sarcoma, peripheral neuroectodermal tumors of bone, or primitive sarcomas of bone. Patients with primitive neuroectodermal tumors were included because we recognized that these tumors are a subgroup of Ewing's sarcoma, rather than a separate entity.¹⁰ Both tumors typically contain the characteristic translocation t(11;22) seen in Ewing's sarcoma or another of the closely related translocations,¹¹⁻¹³ and these tumors are now considered to be members of the same family of neoplasms. Patients who had had anticancer therapy other than surgery for diagnosis were not eligible. For patients to remain eligible, protocol chemotherapy had to start within one month after the diagnostic biopsy. Patients or their

guardians gave written informed consent according to institutional and National Cancer Institute guidelines, and the protocol was approved by the institutional review boards at all participating centers.

STUDY DESIGN

The patients were assigned randomly at study entry to receive standard chemotherapy with doxorubicin, vincristine, cyclophosphamide, and dactinomycin or experimental therapy consisting of these four drugs in alternation with courses of ifosfamide and etoposide. The patients were stratified into groups according to the presence or absence of metastases. This study was designed initially to include patients with or without metastatic disease at presentation. Enrollment was higher than expected, and at the first interim analysis the study committee decided to restructure the protocol to allow assessment of the effect of the addition of ifosfamide and etoposide in patients who presented with nonmetastatic disease. Although this report will focus on the results in patients who presented without evidence of metastatic disease at diagnosis, the results in patients presenting with metastases are also summarized.

In both the standard and the experimental treatment regimens, the planned courses of standard therapy consisted of 2 mg of vincristine per square meter of body-surface area (maximal dose, 2 mg), doxorubicin given as a bolus infusion at a dose of 75 mg per square meter, and 1200 mg of cyclophosphamide per square meter, followed by mesna, given to prevent hemorrhagic cystitis caused by cyclophosphamide. Dactinomycin at 1.25 mg per square meter per dose was substituted for doxorubicin when a total doxorubicin dose of 375 mg per square meter was reached. For the ifosfamide and etoposide courses in the experimental-therapy group, we planned to administer 1800 mg of ifosfamide per square meter per day for five days, given with mesna, and 100 mg of etoposide per square meter per day over the same five days.

The courses of chemotherapy were administered every three weeks for a total of 17 courses. The duration of chemotherapy was planned to be 49 weeks. Hematopoietic cytokines were not available at the start of the protocol, but filgrastim and sargramostim were approved during the course of the study and were used at the discretion of the treating physicians. The use of cytokines was not included in central data reporting.

Local control, planned to occur at week 12, con-

sisted of radiation therapy, surgery, or both. The treating physicians decided which method of local control to use in each case; the protocol allowed surgery for tumors that were deemed resectable. For patients who received radiotherapy alone, the initial tumor volume (extent of soft-tissue and osseous tumor) with a 3-cm margin was treated with 4500 cGy. The treatment volume was then reduced to the postchemotherapy, preradiotherapy tumor extent, and an additional 1080 cGy was given, for a total dose of 5580 cGy. A smaller margin was allowed when it was necessary to avoid radiation to the epiphysis. Patients who had residual tumor after surgery also received radiation according to these dose-volume guidelines for gross residual disease; for microscopic residual disease, irradiation was limited to 4500 cGy administered to the original volume with a 1-cm margin. No supplemental radiotherapy was administered to patients in whom the primary tumor was completely resected with clear margins.

STATISTICAL ANALYSIS

The study was initially designed to enroll between 380 and 400 patients. The primary end point for the estimation of relative efficacy was event-free survival. The risk of adverse events was compared between regimens by a log-rank test,¹⁴ which made it possible to detect a halving of the failure rate within two years of follow-up after the last patient was entered, with a probability of 0.80 in a two-sided test with a significance level of 0.05. Enrollment during the trial was approximately 50 percent greater than expected. The study was amended to allow the enrollment of approximately 400 patients who had non-metastatic disease at entry. This change provided the study with similar power to detect a halving of the failure rate within three years of follow-up in the subgroup of patients without metastases in a two-sided test at a level of significance of 0.05. The enrollment goals were amended without access to results regarding the relative efficacy of the two regimens. The revised power calculations were based on planning parameters derived before the study was begun. Data obtained through August 2000 were used in this analysis.

Event-free survival was defined as the time from entry into the study until the occurrence of an adverse event or until the last contact with the patient, whichever came first. Adverse events included disease progression, the diagnosis of a second malignant neoplasm, or death before the occurrence of disease progression or a second malignant neo-

plasm. Disease progression was further subclassified according to the site of recurrence as local progression (at the primary site only), systemic progression (at a site other than the primary site), local plus systemic progression (at the primary site and another site), and progression at an unknown site (insufficient data submitted to determine the site of recurrence). The cumulative incidence of each type of event for patients without metastases was calculated for each regimen and compared by the method proposed by Gray.¹⁵

Event-free survival was estimated by the method of Kaplan and Meier.¹⁴ The log-rank statistic was used to compare the risk of an adverse event between groups as defined by treatment or prognostic factors.¹⁴ The patients' randomized treatment assignments were used in all comparisons involving regimens. The prognostic significance of various characteristics of the patients that were measured at study entry and the associated relative risk were assessed in a proportional-hazards regression model in which the characteristic of interest was the only component.¹⁴ Confidence intervals for relative risks were derived from the proportional-hazards regression model. Interim monitoring was conducted after the second, third, and fourth years of the study. A P value of less than 0.001 was used as the monitoring boundary for all interim analyses.

RESULTS

PATIENT CHARACTERISTICS

Five hundred thirty patients were enrolled, of whom 525 had Ewing's sarcoma or primitive neuroectodermal tumor of bone and only 5 had primitive sarcoma of bone. Nine patients were found to be ineligible because the diagnosis of Ewing's sarcoma, primitive neuroectodermal tumor of bone, or primitive sarcoma of bone was not confirmed by central pathological review. Three patients were found to be ineligible because more than one month had elapsed between diagnosis and study entry. Among the remaining 518 patients, 120 (23 percent) had metastases at diagnosis; 62 were assigned randomly to the standard-therapy group and 58 to the experimental-therapy group that received ifosfamide and etoposide. Our analysis is based primarily on the 398 patients with nonmetastatic Ewing's sarcoma, primitive neuroectodermal tumor of bone, or primitive sarcoma of bone. Of these, 200 were randomly assigned to the standard-therapy group, and 198 were assigned to the experimental-therapy group that received ifosfamide and etoposide.

The characteristics of the patients without metastases are shown in Table 1. Fifty-seven percent of the patients were male; 30 percent were younger than 10 years at presentation, 57 percent were between the ages of 10 and 17 years, and 13 percent were older than 17 years. The racial and ethnic distribution reflected the extreme rarity of Ewing's sarcoma and primitive neuroectodermal tumor of bone among Asians and blacks. The distribution of primary sites of the tumor did not differ materially between groups (Table 1).

METHOD OF LOCAL CONTROL

The method of local control was determined among patients without metastases. The data from 27 patients were insufficient for review. Of the remaining 371 patients, 145 (39 percent) were treated with radiation only, 140 (38 percent) were treated with surgery only, 84 (23 percent) were treated with both radiation and surgery, and 2 (1 percent) received neither treatment. These two had primary tumors of the head and neck and refused radiation or surgery. One subsequently had a local recurrence, and the other had simultaneous local and systemic relapse. The choice of local control therapy did not differ between the randomized treatment groups (Table 2).

OUTCOME

Patients with Metastases

Among patients who had metastatic disease at diagnosis, the mean (\pm SE) five-year rate of event-free survival among patients in the experimental-therapy group was 22 ± 5 percent, as compared with 22 ± 6 percent among patients in the standard-therapy group (Fig. 1). The relative risk of an event associated with the standard regimen was 1.1 (95 percent confidence interval, 0.70 to 1.6; $P=0.81$). The overall five-year survival rate was also not significantly different when patients in the experimental-therapy group were compared with patients in the standard-therapy group (34 percent vs. 35 percent; relative risk of death with the standard regimen, 0.84; 95 percent confidence interval, 0.54 to 1.3; $P=0.43$). All subsequent results in this report will be restricted to patients with nonmetastatic disease at diagnosis.

Patients without Metastases

The five-year event-free survival rate among patients in the experimental-therapy group was 69 ± 3 percent, as compared with 54 ± 4 percent among patients in the standard-therapy group (Fig. 1). The

Table 1. Characteristics of 398 Patients without Metastases at Study Entry.

Characteristic	Standard Therapy	Experimental Therapy	Total
	number (percent)		
Sex			
Male	106 (53)	120 (61)	226 (57)
Female	94 (47)	78 (39)	172 (43)
Race or ethnic group			
White	171 (86)	175 (88)	346 (87)
Black	4 (2)	3 (2)	7 (2)
Hispanic	20 (10)	17 (9)	37 (9)
Other	2 (1)	1 (1)	3 (1)
Not reported	3 (2)	2 (1)	5 (1)
Age			
≤ 9 yr	63 (32)	58 (29)	121 (30)
10–17 yr	116 (58)	111 (56)	227 (57)
≥ 18 yr	21 (10)	29 (15)	50 (13)
Site of primary tumor			
Head	14 (7)	9 (5)	23 (6)
Vertebrae	14 (7)	11 (6)	25 (6)
Total pelvis	50 (25)	43 (22)	93 (23)
Sacrum	11 (6)	5 (3)	16 (4)
Ilium	26 (13)	28 (14)	54 (14)
Ischium	6 (3)	5 (3)	11 (3)
Pubis	7 (4)	5 (3)	12 (3)
Rib	27 (14)	26 (13)	53 (13)
Clavicle	2 (1)	1 (1)	3 (1)
Scapula	6 (3)	7 (4)	13 (3)
Humerus	13 (6)	16 (8)	29 (7)
Lower arm or hand	4 (2)	9 (5)	13 (3)
Femur	38 (19)	35 (18)	73 (18)
Tibia	19 (10)	19 (10)	38 (10)
Fibula	10 (5)	14 (7)	24 (6)
Foot or ankle	3 (2)	8 (4)	11 (3)

relative risk of an event associated with the standard regimen was 1.6 (95 percent confidence interval, 1.1 to 2.1; $P=0.005$). The overall five-year survival rate was also better among patients in the experimental-therapy group (72 ± 3.4 percent vs. 61 ± 3.6 percent; relative risk of death with the standard regimen, 1.6; 95 percent confidence interval, 1.1 to 2.2; $P=0.01$).

At the time of analysis, 161 patients had had adverse events: 92 in the standard-therapy group and 69 in the experimental-therapy group. The median

Table 2. Local Control Measures among Patients without Metastases, According to Study Group.*

Study Group	Surgery Only	Radiation Only	Surgery and Radiation	No Local Control
	number of patients			
Standard therapy	66	73	43	1
Experimental therapy	74	72	41	1

* Data on 27 patients were insufficient for review.

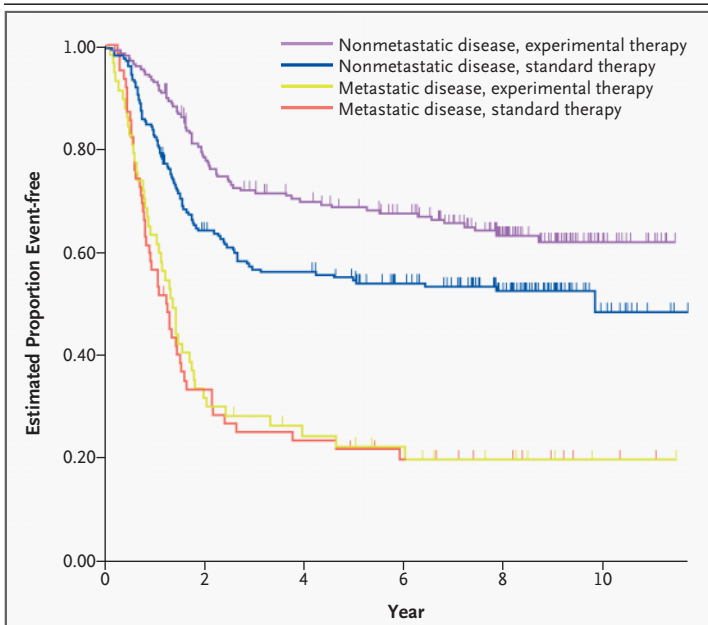


Figure 1. Event-free Survival According to Study Group and the Presence or Absence of Metastatic Disease.

follow-up times for those who had not had adverse events at the time of analysis were 98 and 97 months for patients enrolled in the standard- and experimental-therapy groups, respectively.

PATTERNS OF TREATMENT FAILURE

Twelve patients (five receiving standard therapy and seven receiving experimental therapy) died from toxic effects of the treatment. Second malignant neoplasms developed in seven patients (three receiving standard therapy and four receiving experimental therapy). The second cancers included two cases of acute myelogenous leukemia and one each of myelodysplastic syndrome, acute lymphoblastic leu-

kemia, malignant fibrous histiocytoma, osteosarcoma, and ovarian tumor. The malignant fibrous histiocytoma occurred in the radiation field of a patient with an initial primary tumor of the temporal bone. The osteosarcoma occurred in the radiation field of a patient with an initial tumor of the pelvis. There were 142 relapses, which accounted for 88 percent of treatment failures. The pattern of treatment failure according to treatment regimen is shown in Table 3. The beneficial effect of the experimental therapy was associated with a greater reduction in the rate of local recurrence than in the rate of systemic recurrence.

TOXIC EFFECTS

Seven of the 12 deaths due to toxic effects were from infections (1 in a patient receiving standard therapy and 6 in patients receiving experimental therapy). There were four deaths from cardiac toxic effects of doxorubicin, all among patients receiving standard therapy. One patient receiving experimental therapy died of uncontrollable hemorrhage. Infectious-disease toxicity was greater in the experimental-therapy group during the maintenance phase, as measured by the incidence of serious infections or episodes of fever and neutropenia (data not shown). Patients receiving experimental therapy spent more time in the hospital (an estimated median of 86 days) than those treated with standard therapy (estimated median, 49 days; $P < 0.001$). This difference can be explained in part by the fact that in the patients receiving experimental therapy, ifosfamide and etoposide were administered, for every other course of therapy, in the hospital over five days, whereas the courses of doxorubicin, vincristine, cyclophosphamide, and dactinomycin were administered in one day. Patients receiving experimental therapy had more red-cell transfusions, but there was no difference between the groups in the number of platelet transfusions.

The estimated median time to the completion of therapy for patients who did not have adverse events during treatment was 14 months for those receiving standard therapy and 15 months for those receiving experimental therapy. An additional 78 patients did not receive the total planned protocol therapy because of deviations from the treatment plan.

PROGNOSTIC FACTORS

The factors associated with decreased event-free survival were similar to those in previous studies of Ewing's sarcoma.¹⁶⁻¹⁸ Specifically, patients with

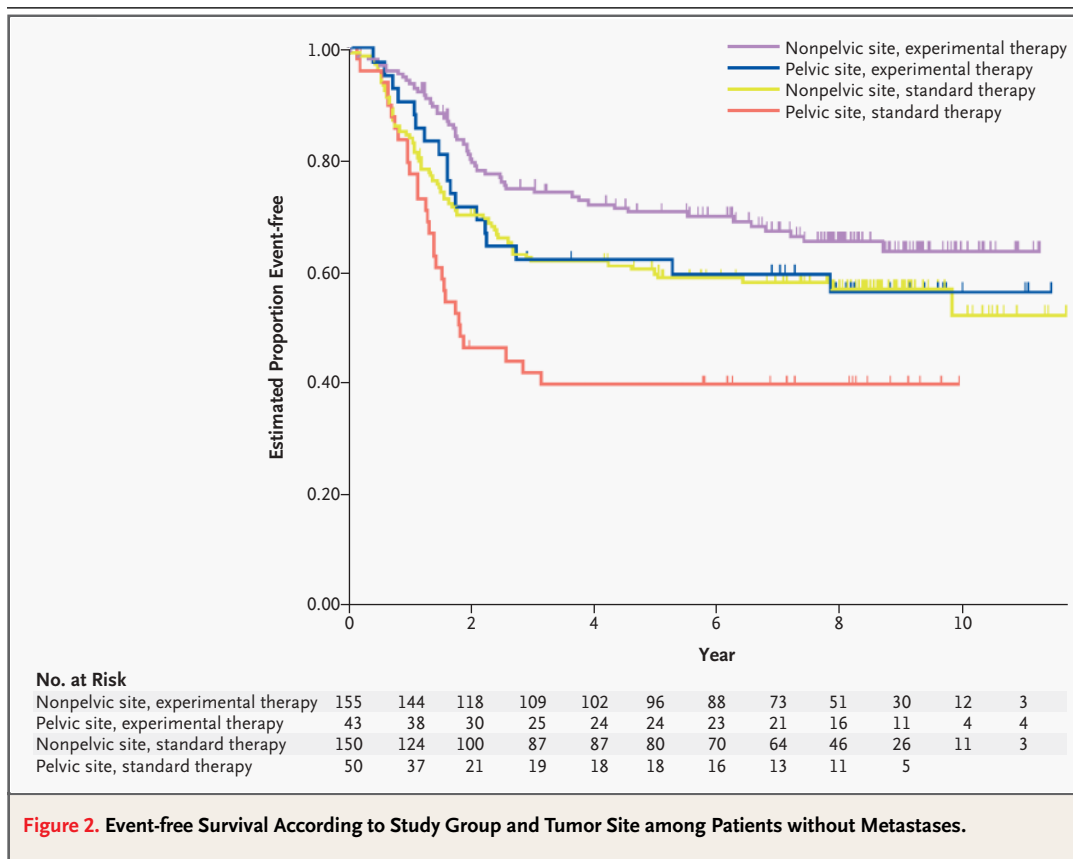
large tumors (with a maximal diameter of at least 8 cm) had a poorer outcome than those with smaller tumors (five-year event-free survival, 55 percent vs. 75 percent; relative risk of an event in those with large tumors, 2.1; 95 percent confidence interval, 1.4 to 3.1; $P < 0.001$). The site of the tumor was correlated with the outcome. The rate of event-free survival at five years was 68 percent among patients with tumors of the distal extremity, 61 percent among patients with tumors of the proximal extremity, and 50 percent among those with primary tumors of the pelvis ($P = 0.003$). Younger patients had a better outcome than older patients. The five-year event-free survival was 70 percent for patients under 10 years of age, 60 percent for those 10 to 17 years of age (relative risk of an event, as compared with those under 10 years, 1.4), and 44 percent for those 18 years old or older (relative risk as compared with those under 10 years, 2.5; $P = 0.001$). The sex of the patient was not significantly related to event-free survival: the five-year event-free survival was 59 percent for male patients and 65 percent for female patients (relative risk of an event in female patients, 0.85; $P = 0.32$).

Table 3. Five-Year Cumulative Incidence of the Various Types of Events among Patients without Metastases, According to Study Group.

Type of Event	Standard Therapy		Experimental Therapy		P Value*
	No.	Rate	No.	Rate	
Local progression	28	0.15	9	0.05	<0.001
Systemic progression	42	0.21	44	0.20	0.92
Local and systemic progression	10	0.05	4	0.02	0.10
Progression at an unknown site†	4	0.02	1	0.005	0.18
Death	5	0.02	7	0.03	0.56
Second malignant neoplasm	3	0.005	4	0.01	0.76

* P values were calculated by the method of Gray.¹⁵
 † The site of progression was not reported in five patients.

The intensity of the dose of chemotherapy administered did not appear to vary significantly according to age (data not shown). Although patients who were treated with surgery alone fared better than those who received radiation therapy alone or



both surgery and radiotherapy, patients with smaller tumors or tumors in accessible locations were more likely to be treated with surgery.

The salutary effect of the experimental therapy tended to decrease the adverse effect on outcome usually associated with large size and pelvic location of the primary tumor. The four event-free survival curves in Figure 2 compare the outcomes in patients with pelvic and nonpelvic primary tumors receiving standard and experimental treatments. The benefit of the addition of ifosfamide and etoposide was observed in younger patients, but not in patients older than 17 years (data not shown).

DISCUSSION

The addition of ifosfamide and etoposide to a regimen that contained doxorubicin, vincristine, dactinomycin, and cyclophosphamide improved outcomes in patients with nonmetastatic Ewing's sarcoma, primitive neuroectodermal tumor of bone, or sarcoma of bone. Subgroup analysis showed that the improvement appeared to be greatest among patients with large primary tumors or primary tumors of the pelvis (overlapping groups). Older age remained an adverse prognostic factor despite the addition of ifosfamide and etoposide. One must be careful to avoid overinterpretation of subgroup analyses, because the study was not designed for robust comparisons of subgroups.

In contrast to these results, the addition of ifosfamide and etoposide to standard therapy did not improve the outcome in patients who had metastatic disease at diagnosis. The outcome in these patients remained poor with either treatment.

After this study began, several groups reported outcomes in patients with sarcomas of the Ewing family who were treated with ifosfamide.¹⁹⁻²⁴ These nonrandomized trials compared newer regimens that included ifosfamide with treatment in histori-

cal controls. Some reported improved survival with ifosfamide,^{21,22} and others found no effect.^{16,20} It is impossible to determine whether the lack of improvement with ifosfamide in some of those trials was due to the comparison with historical controls or to differences between the study treatments and the experimental therapy used in our study.

Etoposide combined with ifosfamide may account for some of the improvement in outcome in the patients receiving experimental treatment in our study. The rationale for this combination is that etoposide might potentiate the cytotoxicity of alkylating agents (such as ifosfamide) by inhibition of topoisomerase II and consequent impairment of the DNA uncoiling that is necessary for the repair of alkylating-agent-induced DNA damage. Although the study by the French Society of Pediatric Oncology noted increased cardiac toxicity with the addition of ifosfamide,¹⁶ we were unable to identify an increase in cardiac toxicity in patients assigned to the experimental ifosfamide-containing regimen in our study. In fact, all of the patients who died of cardiac causes were in the standard-therapy group.

Controversy has arisen since our study began about whether ifosfamide overcomes cellular resistance to cyclophosphamide by acting as a separate drug or whether the results can be explained entirely by a dose effect.²⁴ Our study was not designed to answer this question, and we cannot exclude the possibility that higher doses of cyclophosphamide, perhaps administered with etoposide, might be equally effective. However, a prospective trial would need to show that the results of such an approach would equal the marked improvement in event-free survival that we found with the addition of ifosfamide and etoposide to standard therapy.

We are indebted to the clinical research assistants, nurses, and doctors who assisted with the research, and, most of all, to the patients and families who understood the importance of clinical trials and participated in this study.

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