Ifosfamide and Etoposide plus Vincristine, Doxorubicin, and Cyclophosphamide for Newly Diagnosed Ewing's Sarcoma Family of Tumors

Leonard H. Wexler, M.D.[1]
Thomas F. DeLaney, M.D.[2]
Maria Tsokos, M.D.[3]
Nilo Avila, M.D.[4]
Seth M. Steinberg, Ph.D.[5]
Linda Weaver-McClure, M.S.[1]
Joan Jacobson, M.D.[2]
Paul Jarosinski, Ph.D.[6]
Yasmine M. Hijazi, M.D.[3]
Frank M. Balis, M.D.[1]
Marc E. Horowitz, M.D.[1]

[1] Pediatric Branch, National Cancer Institute, Bethesda, Maryland.

[2] Radiation Oncology Branch, National Cancer Institute, Bethesda, Maryland.

[3] Laboratory of Pathology, National Cancer Institute, Bethesda, Maryland.

[4] Department of Radiology, Clinical Center, National Institutes of Health, Bethesda, Maryland.

[5] Biostatistics and Data Management Section, National Cancer Institute, Bethesda, Maryland.

[6] Department of Pharmacy, Clinical Center, National Institutes of Health, Bethesda, Maryland.

Preliminary results of this study were presented in abstract form at the 24th Annual Meeting of the American Society of Clinical Oncology, New Orleans, Louisiana, May 22–24, 1988.

The authors are indebted to Marianne Owens for her secretarial support and assistance in the preparation of this article, to Emeline Thompson for her assistance in the collection of the data, and to the nurses, nurse practitioners, and Clinical Associates of the Pediatric Branch, without whose commitment and devotion to the care of children with cancer this study would not have been possible.

Leonard H. Wexler's current address: Department of Pediatrics, Columbia University, College of Physicians and Surgeons of Columbia University, 1810 Fort Washington Ave., New York, NY 10032.

Thomas F. Delaney's current address: Department of Radiation Oncology, Boston University, Medical Center Hospital, Boston, Massachusetts.

Joan Jacobson's current address: West Tennessee Cancer Center, Jackson, Ten-nessee.

Marc E. Horowitz' current address: Texas Children's Cancer Center, Texas Children's Hospital and Baylor College of Medicine, Houston, Texas.

Address for reprints: Leonard H. Wexler, M.D., Pediatric Branch/National Cancer Institute, 9000 Rockville Pike, Building 10/Room 13N240, 10 Center Drive MSC 1928, Bethesda, MD 20892-1928.

Received October 20, 1995; revisions received March 15, 1996, and April 23, 1996; accepted May 6, 1996.

BACKGROUND. This study was conducted to determine the feasibility of, and improve outcome by, incorporating ifosfamide and etoposide (IE) into the therapy of newly diagnosed patients with Ewing's sarcoma family of tumors of bone and soft tissue.

METHODS. Fifty-four newly diagnosed patients received 7 cycles of vincristine, doxorubicin, and cyclophosphamide (VAdriaC) and 11 cycles of IE. Radiation therapy after the fifth chemotherapy cycle was the primary approach to local control.

RESULTS. Actuarial 5-year event-free survival (EFS) and overall survival rates were 42% and 45%, respectively, with a median duration of potential follow-up of 6.8 years. EFS was significantly better for patients with localized tumors than for those with metastatic lesions (64% v. 13%, $P < 0.0001$). Actuarial local progression-free survival at 5 years was 74%, and did not correlate with primary tumor size or site, histologic subtype, or the presence of metastases. Febrile neutropenia developed after 49% of cycles, and clinical or sub-clinical cardiac dysfunction was common (7% and 40% respectively). There were four toxic deaths and one case of secondary myelodysplastic syndrome.

CONCLUSIONS. Despite substantial toxicity, the integration of IE into the front-line, VAdriaC-based therapy of patients with Ewing's sarcoma family of tumors is feasible and appeared to significantly improve the outcome for patients with high risk localized tumors, but had no impact on the poor prognosis of patients with metastatic tumors. Local control can be achieved in the vast majority of patients using radiotherapy exclusively, even among patients with bulky, central axis tumors. Longer follow-up is needed to evaluate the late effects of this intensive therapy. *Cancer* **1996; 78:901–11.** © *1996 American Cancer Society.*

KEYWORDS: Ewing's sarcoma family of tumors (Ewing's sarcoma, peripheral primitive neuroectodermal tumor, peripheral neuroepithelioma), ifosfamide, etoposide, doxorubicin, cyclophosphamide, vincristine, radiation therapy, local control, prognostic factors.

Over the past two decades, the prognosis for patients with Ewing's sarcoma has steadily improved. Whereas fewer than 20% of patients were cured in the early 1970s, the majority of patients with localized tumors can now be expected to be cured with local therapy (surgery and/or radiation therapy) and the use of multiagent chemotherapy regimens for control of systemic micrometastases.[1-11] Advances in supportive care have resulted in the ability to safely administer increasingly intensive and toxic therapies, whereas advances in radiographic imaging, radiation treatment planning, and surgical techniques have resulted in the achievement of long term control of the primary tumor in most patients.[12-14] However, patients with metastatic tumors and those with localized, but bulky (≥8 cm) or central axis tumors continue to fare poorly.[15-19]

During the 1980s, the Pediatric Branch of the National Cancer Institute (NCI) conducted a series of three sequential studies designed to evaluate the objective response rate to brief duration (generally four to five cycles), dose-intensive induction therapy with vincristine, doxorubicin, and cyclophosphamide (VAdriaC), and, in patients achieving a complete response, to explore the role of consolidation with 800 centigray (cGy) total body irradiation (TBI) with autologous bone marrow rescue.[20,21] Radiation therapy was used as the primary local control modality. Although nearly 90% of patients achieved an objective response to induction therapy, most patients eventually developed recurrent disease at distant locations.[19] In 1987, after the demonstration of ifosfamide's single agent activity, Magrath et al. and Miser et al. reported their preliminary results for the combination regimen of ifosfamide and etoposide (IE) among patients with recurrent pediatric sarcomas.[22,23] Sixteen of 17 patients with relapsed Ewing's sarcoma and 4 of 8 patients with recurrent peripheral neuroepithelioma responded to this salvage regimen. Because virtually all of the patients treated on that study had previously received VAdriaC chemotherapy, the demonstration of such a strikingly high response rate suggested that IE might be a non-cross-resistant regimen that could improve outcome if incorporated into the treatment of newly diagnosed patients. In 1986, based upon these early encouraging results, the Pediatric Branch opened a single institution, pilot protocol to determine the feasibility and efficacy of adding IE to the core regimen of VAdriaC in patients with newly diagnosed Ewing's sarcoma family of tumors.

PATIENTS AND METHODS

Study Population

Fifty-four patients aged 7 to 24 years with previously untreated Ewing's sarcoma, peripheral primitive neuroectodermal tumor (PNET, also known as peripheral neuroepithelioma), primitive sarcoma of bone (PSOB), and ectomesenchymoma (collectively referred to as Ewing's sarcoma family of tumors[24]) were enrolled on NCI-Pediatric Branch protocol 86C169 between October 1986 and August 1992. All pathologic specimens were reviewed centrally by one of the authors (M.T.). The histologic criteria used to subclassify Ewing's sarcoma and PNET were similar to those proposed by Schmidt et al.[25] with minor modifications. Specifically, tumors with: 1) Homer Wright rosettes 2) cell processes with dense core granules, or 3) two neural markers (*NSE*, S-100, NFTP, or HNK-1) were classified as PNET. Tumors comprised of sheets or nests of cohesive small round cells with scant cytoplasm and 1) primitive ultrastructure with ample cytoplasmic glycogen and no other specific cellular or extracellular features or 2) lacking or expressing only one neural marker were classified as typical or atypical Ewing's sarcoma. Three tumors were classified as ectomesenchymoma on the conceptual basis of coexistent neuroectodermal and mesenchymal elements. Five cases were classified as PSOB and exhibited areas with dense collagenous and/or myxoid stroma, in addition to the compact round cell areas.

Staging and Treatment

Diagnostic studies required prior to entry onto the protocol included computerized axial tomography (CT) and/or magnetic resonance imaging (MRI) of the primary site; posteroanterior and lateral plain radiographs and CT scan of the chest, and CT scans of the abdomen and pelvis to rule out metastatic pulmonary or visceral disease; bilateral iliac crest bone marrow aspirates and biopsies; and ^{99}technetium-diphosphonate bone scan with plain films and/or CT scans of any abnormal areas. Other than bone marrow aspirates and biopsies, sites of suspected metastatic lesions were not routinely biopsied for histologic confirmation. Multigated radionuclide angiography scans were performed to determine resting left ventricular ejection fraction (LVEF) prior to the first dose of chemotherapy and serially thereafter. Patients were fully restaged prior to Cycles 3, 5, 9, 13, and 17 while receiving therapy, at 3-month intervals for the first 6 months after completing treatment, every 6 months for the next 18 months, and annually thereafter. Two consecutive negative bone marrow examinations were required for patients with an initially positive bone marrow aspirate or biopsy. All CT and MRI studies were centrally reviewed by one of the authors (N.A.) using standard response criteria.[26] Residual radiographic abnormalities at the completion of treatment were fol-

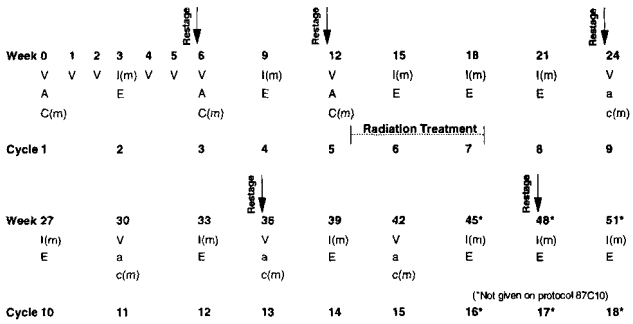

FIGURE 1. Patients received 18 cycles of chemotherapy at approximately 3-week intervals. Dosages, routes, and schedules of administration are as described. Radiation therapy was the primary modality used for achieving local control and was scheduled to commence after the administration of the 5th cycle of chemotherapy, approximately 12 weeks after the initiation of systemic chemotherapy. (v: vincristine intravenous (i.v.) push [2 mg/m^2, maximum 2 mg]; A: doxorubicin i.v. bolus 45 mg/m^2/day × 2 [86C169i] or 35 mg/m^2/day × 2 [86C169ii] or 75 mg/m^2 i.v. over 4 hours [87C10]; a: doxorubicin i.v. bolus 35 mg/m^2/day × 2 [86C169i] or 50 mg/m^2 × 1 [86C169ii] or 75 mg/m^2 i.v. over 4 hours [87C10]; C: cyclophosphamide 900 mg/m^2/day × 2 [86C169i and 86C169ii] or 1200 mg/m^2 ×1 [87C10] i.v. over 1 hour; c: cyclophosphamide 900 mg/m^2/day ×2 [86C169i] or 1200 mg/m^2 [86C169ii and 87C10] i.v. over 1 hour; (m): mesna [360 mg/m^2/dose at hours 0–1, 1–4, 4, 7, 10, 13, 16, and 19], I: ifosfamide 100 mg/m^2/day ×5 [86C169i; and 86C169ii] or ×3 [87C10] i.v. over 1 hour; E: etoposide 100 mg/m^2/day ×5 [86C169; and 86C169ii] or ×3 [87C10] i.v. over 1 hour).

lowed with serial physical examinations and radiographic studies.

Dosages, routes, and schedules of chemotherapy administration are illustrated in Figure 1. Due to an unexpectedly high incidence of profound and protracted myelosuppression and cardiomyopathy, the study was amended in February 1989 to decrease the dosages of doxorubicin and cyclophosphamide. The original version of the protocol is indicated as 86C169i, whereas the amended version of the protocol is indicated as 86C169ii. Two companion randomized studies were also initiated in February 1989 to evaluate the ability of granulocyte-macrophage–colony stimulating factor to ameliorate hematologic toxicity and the ability of dexrazoxane (ICRF-187) to reduce the incidence of doxorubicin-associated cardiotoxicity.[27,28] In addition, we have included three patients treated on a short-lived, contemporaneous protocol (87C10) that was designed primarily to evaluate the cardiotoxicity of a 4-hour infusion of doxorubicin in "moderate risk" patients with localized, nonpelvic, nonproximal extremity tumors.

Chemotherapy was delayed for up to 1 week without modification if the absolute neutrophil count (ANC) was less than 500/mL^3 or the platelet count was less than 50,000/mL^3 on Day 21 prior to Cycles 2–5, or if the ANC was less than 1000/mL^3 or the platelet count was less than 75,000/mL^3 on Day 21 prior to Cycles 6–18. Delays of more than 7 days due to protracted myelosuppression resulted in 25% cyclophosphamide (in VAdriaC cycles) or ifosfamide and etoposide (in IE cycles) dose reductions. Doxorubicin was discontinued if the resting LVEF fell to less than 45% or by more than 20 percentage points from baseline, or in any patient with symptomatic acute congestive heart failure. Vincristine was reduced by 50% for patients with evidence of Grade 2 peripheral neuropathy and was held for patients with evidence of ileus or Grades 3–4 neurotoxicity. Toxicities were scored in accordance with standard NCI grading criteria.[26] Other supportive care interventions were employed as previously described.[28]

Definitive local therapy was scheduled to commence immediately after Cycle 5. Radiation therapy was the primary modality for achieving local control in this study; however, patients with small primary tumors in sites that were easily resectable or in expendable bones could undergo surgical resection. Chemotherapy dose modifications were not routinely made during radiation therapy. Radiation therapy was delivered to the primary site using conventional daily fractionation at 1.8–2 Gray (Gy)/day to planned total doses of 50–60 Gy.

These studies were approved by the Institutional Review Board of the NCI, and written informed consent was obtained from all patients or their legal guardian. When deemed appropriate by the family and physician, witnessed verbal and/or written assent was also obtained from patients younger age than 18 years.

Statistical Analysis

Durations of survival, event free survival (EFS) and time to local failure were calculated from the on-study date until the date of death, relapse/progression/toxic death, local relapse, or last follow-up as appropriate for each analysis. The probability of survival, EFS, and local failure as a function of time were calculated by the Kaplan–Meier method, with the statistical significance of the difference between pairs of Kaplan–Meier curves calculated by the Mantel-Haenszel technique. The association between potential prognostic factors and whether or not there was eventual local failure was statistically assessed by the (Wilcoxon rank sum test for continuous factors (age, radiation dose, and tumor size), and by Fisher's exact test for discrete variables. All P values are two-sided.

RESULTS

Patient Characteristics

Table 1 lists the baseline clinical features of the 54 patients treated on this study. Nine of the 23 patients

TABLE 1
Characteristics of 54 Patients with Ewing's Sarcoma Family of Tumors

Feature	All patients (N = 54) No. (%)	86C169i (N = 31) No. (%)	86C169ii (N = 20) No. (%)	87C10[a] (N = 3) No. (%)
Histology				
Ewing's sarcoma	22 (41)	14 (45)	7 (35)	1 (33)
Peripheral primitive neuroectodermal tumor[b]	24 (44)	12 (39)	10 (50)	2 (67)
Primitive sarcoma of bone	5 (09)	5 (16)	0	
Ectomesenchymoma	3 (06)	0	3 (15)	
Extent of disease				
Localized	31 (57)	16 (52)	13 (65)	2 (67)
Metastatic	23 (43)	15 (48)	7 (35)	1 (33)
Lung	14 (26)	10 (32)	3 (15)	1 (33)
Bone	8 (15)	5 (16)	3 (15)	0
Bone marrow	5 (09)	3 (10)	2 (10)	0
Other[c]	10 (19)	6 (19)	4 (20)	0
Primary tumor site				
Proximal extremity	10 (19)	3 (10)	7 (35)	0
Distal extremity	4 (07)	3 (10)	1 (5)	0
Trunk	40 (74)	25 (81)	12 (60)	3 (100)
Pelvis	17 (31)	13 (42)	4 (20)	0
Chest wall	12 (22)	7 (23)	3 (15)	2 (67)
Spine	5 (9)	3 (10)	1 (5)	1 (33)
Other trunk[d]	6 (11)	2 (6)	4 (20)	0
Primary tumor type				
Bone	29 (54)	18 (58)	11 (55)	1 (33)
Soft tissue	25 (46)	13 (42)	9 (45)	2 (67)
Primary tumor size, median (range), cm[e]	12 (2–25)	12 (2–25)	13 (5–24)	12 (5–24)
1–7	9 (17)	5 (16)	3 (15)	1 (33)
8–14	21 (39)	12 (39)	8 (40)	1 (33)
15–21	17 (31)	11 (35)	6 (30)	0
22+	4 (7)	1 (3)	2 (10)	1 (33)
Not evaluable	3 (6)	2 (6)	1 (5)	0
Age at diagnosis, median (range) (yrs)	19 (7–24)	18 (8–24)	19 (7–24)	21 (14–24)
1–10	9 (17)	5 (16)	4 (20)	0
11–15	9 (17)	4 (13)	3 (15)	1 (33)
16–20	18 (33)	11 (35)	7 (35)	0
21–24	19 (35)	11 (35)	6 (30)	2 (67)
Sex				
Male	34 (63)	22 (71)	10 (50)	2 (67)
Female	20 (37)	9 (29)	10 (50)	1 (33)
Race				
White	48 (88)	28 (90)	17 (85)	3 (100)
African American	2 (4)	1 (3)	1 (5)	0
Hispanic	2 (4)	1 (3)	1 (5)	0
Asian	2 (4)	1 (3)	1 (5)	0

[a] One patient on 87C10, believed to have a localized vertebral tumor with soft tissue extension, was retrospectively determined to have had pulmonary metastases at the time of diagnosis.

[b] Also known as peripheral neuroepithelioma (PNET).

[c] Other sites of metastatic disease include pleural effusion (n = 5), lymph node (n = 2), and one case each of the liver, spinal cord, and abdomen. Nine patients had two or more sites of metastatic disease (seven on 86C169i and two on 86C169ii).

[d] Other truncal primary sites include one case each of retroperitoneum, mediastinum, clavicle, scapula, back, and unknown.

[e] Maximal tumor diameter was measured in either the anteroposterior or transverse dimension on radiographic imaging (computed tomography or magnetic resonance imaging), or, for patients undergoing complete surgical resection without adequate preoperative imaging studies, the maximal tumor diameter as determined at the time of initial operative resection. No difference was observed in the size of the primary tumor in patients with localized lesions (median, 12 cm, range, 3 cm–25 cm) compared with those with metastatic lesions (median, 13 cm, range 2 cm–22 cm).

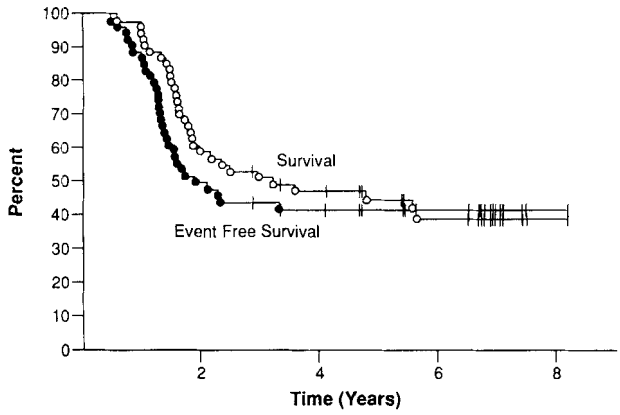

FIGURE 2. The median duration of potential follow-up was 6.8 years for all 54 patients (7.3 years for the 31 patients treated on 86C169i, 8.2 years for the 3 patients treated on 87C10, and 4.8 years for the 20 patients treated on 86C169ii). Five-year actuarial event free survival (●) and overall survival (○) were 42% and 45%, respectively. Four patients died of treatment-related toxicities. Twenty-seven patients relapsed or progressed and all subsequently died of uncontrolled malignant disease.

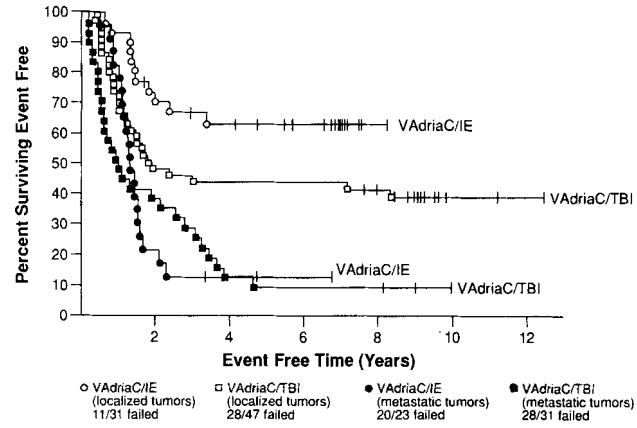

FIGURE 3. Five-year actuarial event free survival was significantly better for patients with localized tumors (○) treated on the current study (VAdriaC/IE [86C169]) than for patients with metastatic tumors (●) (64% [95% confidence interval (CI), 46–79%] vs. 13% [95% CI, 5–32%], overall $P < 0.0001$). Compared with the most recent group of historic control patients with localized tumors (□) treated at the National Cancer Institute/Pediatric Branch (VAdriaC/TBI),[19] 5-year actuarial event free survival was significantly improved by the addition of ifosfamide and etoposide. (64% vs. 45% [95% CI, 31–59%], overall $P < 0.05$). No improvement in 5-year event free survival was observed for patients with metastatic tumors treated on the current study compared with historical controls (■)[19] (13% vs. 10% [95% CI, 3–25%], overall $P = 0.86$). (VAdriaC/IE: vincristine, doxorubicin, and cyclophosphamide with incorporation of ifosfamide and etoposide, VAdriaC/TBI: vincristine, doxorubicin, and cyclophosphamide with total body irradiation).

who presented with metastatic disease had involvement of 2 or more sites. There was no significant difference in primary tumor size in patients with localized (median, 12 cm; range, 3–25 cm) versus metastatic (median, 13 cm; range, 2–22 cm) tumors.

Response to Induction Chemotherapy

Thirty-five patients were evaluable for response after the first 2 cycles of chemotherapy (Week 6), whereas 43 patients were evaluable after 4 cycles of therapy (Week 12). (The difference in the number of evaluable patients at each time point was due to some patients having incomplete imaging studies at the earlier time point.) Thirty-one of 35 evaluable patients achieved an objective response at Week 6 (3 complete responses [CR] and 28 partial responses [PR]; overall response rate = 89% [95% confidence interval (CI), 73–97%]), whereas 38 of 43 evaluable patients achieved an objective response at Week 12 (7 CR, 31 PR; overall response rate = 88% [95% CI, 75–96%]). One patient developed progressive metastatic disease prior to the initiation of the planned local control intervention at Week 12. There were no significant differences in the Week 12 objective response rates by histologic subtype (15 of 19 [79%] in patients with Ewing's sarcoma [95% CI, 54–94%] versus 18 of 18 [100%] in patients with PNET [95% CI, 81–100%]; $P = 0.10$), or the presence or absence of metastatic disease at diagnosis (21 of 24 [88%] for patients with localized tumors [95% CI, 68–97%] versus 17 of 19 [89%] for patients with metastatic disease [95% CI, 67–99%]; $P = 1.00$).

Event Free and Overall Survival

With a median duration of potential follow-up of 6.8 years (7.3 years for 86C169i, 8.2 years for 87C10, and 4.8 years for 86C169ii), and a minimum follow-up of 3 years, the actuarial 5-year EFS for all 54 patients is 42% (95% CI, 30–55%) (Fig. 2). Four patients (7%) died of therapy-related complications whereas 27 patients developed progressive or recurrent tumors (all of whom subsequently died of uncontrolled malignant disease). The median duration of EFS was 1.9 years, and exceeded 2 years in only 4 of the 27 patients who relapsed (2.1, 2.3, 2.3, and 3.3 years, respectively). Actuarial 5-year overall survival is 45% (95% CI, 32–58%), with a median duration of survival of 3.1 years (Fig. 2). Five-year actuarial EFS and the duration of EFS were significantly greater for patients presenting with localized tumors than for those with metastatic tumors (64% [95% CI, 46–79%] and median not reached versus 13% [95% CI, 5–32%] and 1.3 years median, respectively; overall $P < 0.0001$) (Fig. 3). Three patients with metastatic disease at diagnosis are long term survivors. All had chest wall tumors with a malignant pleural effusion as the only site of metastatic disease.

TABLE 2
Impact of Clinical Features on Outcome[a]

Feature	Actuarial 5-year event free survival (%)	P value
Extent of disease at diagnosis		
Localized	64	
Metastatic	13	$P < 0.0001$
Treatment series[b]		
V AdriaC/TBI-localized tumors	45	
V AdriaC/IE-localized tumors	64	$P = 0.05$
V AdriaC/TBI-metastatic tumors	10	
V AdriaC/IE-metastatic tumors	13	$P = 0.86$
86C169i-localized tumors	75	
86C169ii-localized tumors	52	$P = 0.19$
Age at diagnosis		
≤ 10 yrs	100	
≥ 11 yrs	53	$P = 0.05$
Histological subdiagnosis		
Ewing's sarcoma	76	
PNET	50	$P = 0.17$[c]
Tumor size		
≤ 7 cm	83	
≥ 8 cm	57	$P = 0.24$
Tumor location		
Pelvis	65	
Nonpelvis	64	$P = 0.89$
Tumor type		
Bone	70	
Soft tissue	55	$P = 0.51$
Doxorubicin dose intensity		
≤ 16.75 mg/m^2/week	59	
≥ 16.76 mg/m^2/week	83	$P = 0.24$
LDH[d]		
≤ 350 U/L	65	
≥ 351 U/L	60	$P = 0.70$

VAdriaC/TBI: vincristine, doxorubicin, and cyclophosphamide and total body irradiation; VAdriaC/IE: vincristine, doxorubicin, and cyclophosphamide with incorporated ifosfamide and etoposide; PNET: peripheral primitive neuroectodermal tumor (also known as peripheral neuroepithelioma); LDH: lactate dehydrogenase.

[a] Comparison of event free survival according to presenting clinical feature is for patients with localized tumors only, unless otherwise indicated.

[b] Treatment series indicated as VAdriaC/TBI refers to historic control patients treated at the National Cancer Institute/Pediatric Branch from 1981 to early 1986.[19] VAdriaC/IE refers to patients treated on the current study.

[c] P value for patients with Ewing's sarcoma versus PNET. Only 1 of 5 patients with primitive sarcoma of bone and 1 of 3 patients with ectomesenchymoma had localized tumors at diagnosis (both are long term survivors); hence, these subtypes were excluded from the analysis.

[d] Upper limit of institutional normal is 226 Units per liter.

Compared with patients treated on our previous series of TBI consolidation protocols, 5-year actuarial EFS and duration of EFS were significantly improved in the current study only for patients with localized tumors (5-year EFS 45% vs. 64%; median EFS duration 1.8 years vs. not reached; overall $P = 0.05$) (Fig. 3). Table 2 summarizes the relationship between a variety of clinical features and outcome. For patients with localized tumors, only an age of 10 years or younger was found to be favorably associated with outcome ($P = 0.05$).

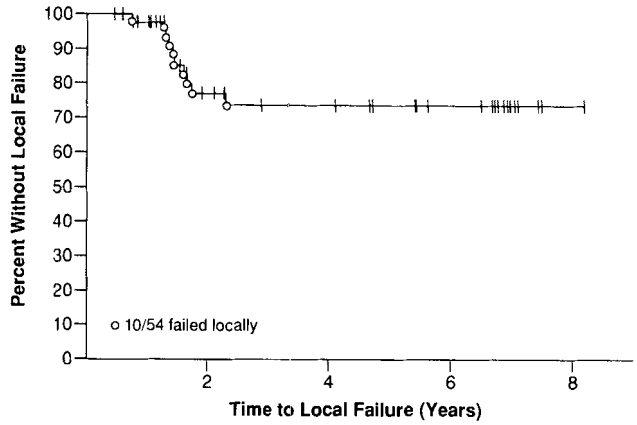

FIGURE 4. Five-year actuarial local event free survival was 74% (95% confidence interval 58–85%). There was no difference in the probability of remaining locally event free based upon the site or size of the primary tumor, the presence or absence of metastatic disease, the histologic subtype of the tumor, or the dose of radiation therapy received.

Local Control

The 5-year actuarial local progression free survival rate is 74% (95% CI, 58–85%), with a minimum follow-up time from commencement of local therapy of 2 years (Fig. 4). No patient progressed in the primary site prior to the initiation of definitive local therapy. In all but one instance, the time to local recurrence/progression was less than 1.5 years from the beginning of local irradiation (the single exception occurred at 2 years). The median radiation dose for the 46 patients receiving local irradiation was 5538 cGy (range, 2670–6300 cGy). An incomplete treatment course was received by 1 patient (a long term survivor) with a 13-cm chest wall tumor and a malignant pleural effusion who electively discontinued treatment after 6 cycles of chemotherapy and 2670 cGy of radiation.

Eight patients received no radiation therapy: five of six patients with chest wall or other thoracic primary tumors underwent complete surgical resections either prior to chemotherapy or on reexploration after Cycle 5 (n = 3). Of the three remaining patients who were not irradiated, one patient with a chest wall tumor had extensive pleural disease and a malignant pleural effusion for which it was not felt that an acceptable treatment field could be planned, one patient had widespread bony metastases that had not fully responded to chemotherapy, and one patient had a widely metastatic soft tissue tumor for which no primary site could be established.

Three patients had radiation therapy initiated

prior to Cycle 5: two patients received it emergently at the time of entry onto the study for rapidly evolving spinal cord compression, whereas the third patient's personal physician opted to begin radiation therapy after the third cycle of chemotherapy because of concern that the patient might develop a spinal cord compression if radiation was deferred. One patient with a 16-cm sacral tumor and lumbosacral plexopathy had radiation delayed for 11 months until the elective discontinuation of treatment after 13 cycles of chemotherapy. A pathologic fracture of the primary tumor occurred in two patients with proximal extremity lesions. Of particular note, long term local control was achieved in both patients, without surgical intervention, with radiation doses of 5400 and 5580 cGy, respectively.

Local recurrence was documented in 10 patients (19%), 4 with an isolated local relapse and 6 with a simultaneous recurrence in both the primary and metastatic sites. The radiation dose was not significantly different among the ten patients in whom a local recurrence developed compared with those in whom local disease control was achieved. Only one patient who recurred locally did not receive radiation treatment; this patient had a chest wall primary tumor with a rind of pleural tumor and a malignant pleural effusion. Neither the site nor size (maximum tumor diameter) of the primary tumor, the histologic subtype, or the presence or absence of metastases were found to correlate with the likelihood of long term local disease control.

Toxicities

Eight-hundred and sixty-two cycles of chemotherapy were administered to the 54 patients: 495 cycles to the 31 patients on 86C169i, 45 cycles to the 3 patients on 87C10, and 322 cycles to the 20 patients on 86C169ii. Table 3 summarizes the worst grade of toxicities observed with this regimen. Dose modifications were more common on 86C169i than on 86C169ii/87C10 (22 of 31 vs. 8 of 23; $P = 0.008$ by the chi-square test) and were made in 97 cycles (11%), primarily for hematologic (67%) or cardiac (19%) toxicities, or both (9%).

There were 4 toxic deaths: 2 patients died of anthracycline-associated cardiomyopathy (after cumulative doxorubicin dosages of 525 mg/m^2 [with chest wall irradiation] and 450 mg/m^2), 1 patient died of neutropenic sepsis, and 1 patient (who had received abdominal irradiation) died of postoperative complications after surgery for a gastrointestinal hemorrhage while thrombocytopenic. One additional patient developed secondary myelodysplasia (refractory anemia with excess blasts) 27 months after completing 13 cycles of chemotherapy (cumulative etoposide dose of 3500 mg/m^2 and 54 Gy whole pelvic irradiation). More detailed descriptions of hematologic and cardiac toxicities after revision of the protocol in 1989, and of ifosfamide-related nephrotoxicity, have been reported elsewhere.[27–29]

Hematologic Toxicity and Infectious Complications

Grades 3 or 4 neutropenia and thrombocytopenia were observed after 4% and 95%, and 26% and 21%, respectively, of all evaluable cycles. Fever developed during 404 of 818 evaluable cycles (49%) (246 of 463 86C169i cycles [53%] vs. 158 of 355 86C169ii/87C10 cycles [45%]; $P = 0.01$) and a documented infection was observed in 155 of the febrile episodes (38%), including 53 episodes of bacteremia (13% of all febrile episodes, and 38% of febrile episodes in which an infection was confirmed). There were no significant differences in the incidence of documented infections (21% vs. 25%; $P = 0.26$) or bacteremias (5% vs. 8%; $P = 0.09$) among patients treated on 86C169i versus 86C169ii/87C10.

Cardiac Toxicity

Four patients (7%) developed symptomatic congestive heart failure. Two died, 1 underwent a cardiac transplant (cumulative doxorubicin dose of 480 mg/m^2), and 1 recovered spontaneously with minimal medical support after receiving 210 mg/m^2. Twenty of the remaining 50 patients (40%; 95% CI, 25–55%) developed asymptomatic cardiotoxicity after a median cumulative doxorubicin dose of 340 mg/m^2; it was observed in 11 of 33 patients treated on 86C169i and 87C10, and 9 of 17 patients treated on 86C169ii (7 of 9 patients receiving doxorubicin alone vs. 2 of 9 patients receiving doxorubicin plus ICRF-187).

DISCUSSION

At the beginning of the 1980s, curative therapy still did not exist for most patients with high risk localized and metastatic Ewing's sarcoma family of tumors.[4–11,19] Preliminary reports in the early and mid-1980s suggested that ifosfamide, either alone or in combination with etoposide, was highly active in patients with recurrent sarcomas,[22,23] and might improve the efficacy of systemic treatment if incorporated into the front-line management of these patients.[30] To better assess the feasibility of this approach, we initiated a pilot protocol in 1986 in which 11 cycles of IE were intercalated into the core regimen of 7 VAdriaC cycles, with radiation therapy used as the primary modality for achieving local control. The results of this study indicate that the integration of IE into the front-line therapy of newly diagnosed patients with Ewing's sarcoma family of tumors was feasible, despite a relatively high

TABLE 3
Worst Grade of Toxicity

Toxicity	Grade 0	1	2	3	4	NE
Neutropenia[a]	0	0	0	0	54[a]	0
Thrombocytopenia	0	2	4	4	41[a]	4
Anemia	0	0	0	31	19	4
Infection[a]	5	11	7	24	6[a]	0
Mucositis	7	13	19	10	5	0
Esophagitis	40	1	7	5	1	0
Nausea/vomiting	37	1	9	7	0	0
Diarrhea	41	3	5	5	0	0
Constipation	44	4	6	0	0	0
SGOT/SGPT	33	7	10	3	1	0
Bilirubin[b]	50	—	0	3	1	0
Weight loss	25	7	18	4	0	0
Peripheral sensorimotor neuropathy[c]	16	22	10	6	—	—
Neurologic—mood	48	2	3	1	0	0
Dermatologic[d]	43	2	2	2	4	0

NE: not evaluable; SGOT: aspartate aminotransferase (serum glutamic-oxaloacetic transaminase). SGPT: alanine aminotransferase (serum glutamic-pyruvic transaminase).

[a] One case each of Grade 4 thrombocytopenia/hemorrhage and neutropenia/infection were fatal.

[b] No Grade 1 for hyperbilirubinemia.

[c] No Grade 4 for peripheral sensorimotor neuropathy.

[d] Refers to either skin rashes or skin breakdown subsequent to radiation therapy.

Other toxicities included two cases of each symptomatic radiation colitis and pneumonitis, and two cases of pathologic fracture of the primary tumor.

incidence of severe or life-threatening complications, and appeared to improve the outcome for patients with high risk localized tumors. However, although nearly all patients with metastatic tumors responded well to initial therapy, their outcome was not significantly improved.

Although encouraging, the results of this series must be tempered by the fact that the 11 IE cycles clearly added to the complexity and increased the acute toxicities of the core VAdriaC regimen. The toxic death rate of 7% in this study compares favorably with our previous generation of TBI consolidation studies,[19] suggesting that the overwhelming majority of patients can be successfully managed through these complications. It is worth noting, however, that there was a significantly greater toxic death rate on the VAdCA + IE arm of IESS-3 than on the VAdCA arm.[31] In addition, an unexpected and unusually high proportion of our patients developed asymptomatic cardiotoxicity and most were unable to receive the full dose of doxorubicin without the use of a cardioprotective agent.[27] Thus, we cannot exclude the possibility, as has been suggested by others,[32] that IE increases the risk of anthracycline cardiotoxicity. Finally, other unique IE-related toxicities, such as etoposide-related secondary acute myelogenous leukemia,[33] or late ifosfamide-related nephrotoxicity,[34] may become more prevalent over time. Clearly, longer follow-up is needed to determine whether the apparent improvement in EFS at 5 years will be compromised by an increased number of life-threatening or fatal late, IE-associated, toxic events.

Also left unanswered by this study is the benefit of administering 9 to 12 months of relatively toxic "adjuvant" chemotherapy after the completion of definitive local therapy. The median duration of therapy was 61 weeks for the 32 patients successfully completing treatment; only 9 patients completed therapy within 1 month of schedule. The degree to which therapy can be shortened without adversely affecting outcome is likely only to be discovered by future randomized studies.

The improved outcome for the 31 patients with localized tumors in this series is especially noteworthy because most had 1 or more high risk features (median age of 18 years, median tumor size of 12 cm, and 71% central axis primary tumors with a predominance of pelvic lesions).[1-12,17,35] Given the nature of our patient population, we are unable to comment upon the impact of IE on the prognosis of patients with "favorable" localized tumors; however, others have questioned whether IE is of significant benefit to this group of patients.[32,36] Unfortunately, the inferior outcome of

patients treated on the standard arm of IESS-3 (compared with previously published results using the same regimen), is likely to cloud a definitive assessment of this issue.[9,11,31]

We found no evidence that primary tumor size or histologic subtype impacts EFS, contrary to what has been reported by others.[17,18,25,37] Similarly, we saw no difference in outcome in osseous versus extraosseous tumors. That these tumors behave clinically similar is not surprising given recent cytogenetic and molecular genetic observations demonstrating shared tumor specific abnormalities.[38–42]

Our primary radiotherapy approach achieved a local control rate that compares favorably with the best results reported to date in series incorporating postoperative radiation after "debulking" surgical resection.[43] These results are especially noteworthy because the majority of our patients had bulky truncal tumors.[44] Although efforts to reduce the acute and late risks of radiation-related normal tissue damage are appropriate, without any convincing evidence that surgical resection improves EFS,[43,45,46] the high rate of local control that can be achieved with radiotherapy for patients without good surgical options must not be compromised.

Finally, the disappointing results observed in this study in patients with metastases confirms that distant tumor spread remains the single most important prognostic variable.[18,19] Only 3 of 23 patients with metastatic lesions are long term event free survivors, and each had a chest wall primary tumor with a malignant pleural effusion as the only site of metastatic disease. It is worth emphasizing that patients with metastases did not differ significantly from patients with localized tumors with regard to the size or site of their primary tumors or their initial chemo- or radioresponsiveness. The magnitude of the difference suggests that as-yet poorly defined intrinsic host and tumor biologic factors, and not simply delays in diagnosis or total body tumor burden, play a significant role in the poorer prognosis of patients with metastatic tumors.[47] The recent report by Burdach et al. suggests that the use of high dose melphalan plus TBI may offer promise to patients with metastatic tumors.[48] Further dose escalation of the known active agents, and the identification of active new agents with novel mechanisms of action, are strategies that are currently undergoing clinical evaluation. However, it is likely that significant improvement in the outcome of patients with metastatic tumors will depend upon the development of treatment strategies that exploit the basic and unique pathogenetic mechanisms of these tumors.[49–52]

REFERENCES

1. Tefft M, Razek A, Perez C, Burgert EO, Gehan EA, Griffin P, et al. Local control and survival related to radiation dose and volume and to chemotherapy in non-metastatic Ewing's sarcoma of pelvic bones. *Int J Radiat Oncol Biol Phys* 1978;4:367–72.
2. Glaubiger DL, Makuch R, Schwarz J, Levine AS, Johnson RE. Determination of prognostic factors and their influence on therapeutic results in patients with Ewing's sarcoma. *Cancer* 1980;45:2213–9.
3. Pilepich MV, Vietti TJ, Nesbit ME, Tefft M, Kissane J, Burgert O, et al. Radiotherapy and combination chemotherapy in advanced Ewing's Sarcoma—Intergroup study. *Cancer* 1981;47:1930–6.
4. Wilkins RM, Pritchard DJ, Burgert EO Jr., Unni KK. Ewing's sarcoma of bone: experience with 140 patients. *Cancer* 1986; 58:2551–5.
5. Jürgens H, Exner U, Gadner H, Harms D, Michaelis J, Sauer R, et al. Multidisciplinary treatment of primary Ewing's sarcoma of bone: a 6-year experience of a European cooperative trial. *Cancer* 1988;61:23–32.
6. Bacci G, Toni A, Avella M, Manfrini M, Sudanese A, Ciaroni D, et al. Long-term results in 144 localized Ewing's sarcoma patients treated with combined therapy. *Cancer* 1989; 63:1477–86.
7. Hayes FA, Thompson EW, Meyer WH, Kun L, Parham D, Rao B, et al. Therapy for localized Ewing's sarcoma of bone. *J Clin Oncol* 1989;7:208–13.
8. Barbieri E, Emiliani E, Zini G, Mancini A, Toni A, Frezza G, et al. Combined therapy of localized Ewing's sarcoma of bone: analysis of results in 100 patients. *Int J Radiat Oncol Biol Phys* 1990;19:1165–70.
9. Burgert EO Jr., Nesbit ME, Garnsey LA, Gehan EA, Herrmann J, Vietti TJ, et al. Multimodal therapy for management of nonpelvic, localized Ewing's sarcoma of bone: Intergroup Study IESS-II. *J Clin Oncol* 1990;8:1514–24.
10. Nesbit ME Jr., Gehan EA, Burgert EO Jr., Vietti TJ, Cangir A, Tefft M, et al. Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: a long-term follow-up study of the First Intergroup Study. *J Clin Oncol* 1990;8:1664–74.
11. Evans RG, Nesbit ME, Gehan EA, Garnsey LA, Burgert O Jr., Vietti TJ, et al. Multimodal therapy for the management of localized Ewing's sarcoma of pelvic and sacral bones: a report from the Second Intergroup Study. *J Clin Oncol* 1991;9:1173–80.
12. Evans RG. The four S's of Ewing's sarcoma. *Int J Radiat Oncol Biol Phys* 1991;21:1671–3.
13. Dunst J, Sauer R, Burgers JMV, Hawliczek R, Kürten R, Winkelmann W, et al. Radiation therapy as local treatment in Ewing's sarcoma: results of the Cooperative Ewing's Sarcoma Studies CESS 81 and CESS 86. *Cancer* 1991;67:2818–25.
14. O'Connor MI, Pritchard DJ. Ewing's sarcoma: prognostic factors, disease control, and the reemerging role of surgical treatment. *Clin Orthop* 1991;262:78–87.
15. Hayes FA, Thompson EI, Parvey L, Rao B, Kun L, Parham D, et al. Metastatic Ewing's sarcoma: remission induction and survival. *J Clin Oncol* 1987;5:1199–204.
16. Arai Y, Kun LE, Brooks MT, Fairclough DL, Fontanesi J, Meyer WH, et al. Ewing's sarcoma: local tumor control and patterns of failure following limited-volume radiation therapy. *Int J Radiat Oncol Biol Phys* 1991;21:1501–8.

17. Göbel V, Jürgens H, Etspüler G, Kemperdick H, Jungblut RM, Stienen U, et al. Prognostic significance of tumor volume in localized Ewing's sarcoma of bone in children and adolescent. *J Cancer Res Clin Oncol* 1987;113:187–91.
18. Cangir A, Vietti TJ, Gehan EA, Burgert EO Jr., Thomas P, Tefft M, et al. Ewing's sarcoma metastatic at diagnosis: results and comparisons of two Intergroup Ewing's Sarcoma Studies. *Cancer* 1990;66:887–93.
19. Horowitz ME, Kinsella TJ, Wexler LH, Belasco J, Triche T, Tsokos M, et al. Total-body irradiation and autologous bone marrow transplant in the treatment of high-risk Ewing's sarcoma and rhabdomyosarcoma. *J Clin Oncol* 1993;11:1911–8.
20. Miser JS, Kinsella TJ, Triche TJ, Steis R, Tsokos M, Wesley R, et al. Treatment of peripheral neuroepithelioma in children and young adults. *J Clin Oncol* 1987;5:1752–8.
21. Miser JS, Kinsella TJ, Triche TJ, Tsokos M, Forquer R, Wesley R, et al. Preliminary results of treatment of Ewing's sarcoma of bone in children and young adults: six months of intensive combined modality treatment without maintenance. *J Clin Oncol* 1988;6:484–90.
22. Magrath I, Sandlund J, Raynor A, Rosenberg S, Arasi V, Miser J. A phase II study of ifosfamide in the treatment of recurrent sarcomas in young people. *Cancer Chemother Pharmacol* 1986;18(Suppl 2):S25–8.
23. Miser JW, Kinsella TJ, Triche TJ, Tsokos M, Jarosinski P, Forquer R, et al. Ifosfamide with mesna uroprotection and etoposide: an effective regimen in the treatment of recurrent sarcomas and other tumors of children and young adults. *J Clin Oncol* 1987;5:1191–8.
24. Horowitz ME, Delaney TF, Malawer MM, Tsokos MG. Ewing's sarcoma family of tumor: Ewing's sarcoma of bone and soft tissue and the peripheral primitive neuroectodermal tumors. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. Philadelphia: JB Lippincott Co., 1993:795–821.
25. Schmidt D, Herrmann D, Jürgens H, Harms D. Malignant peripheral neuroectodermal tumor and its necessary distinction from Ewing's sarcoma. A report from the Kiel Pediatric Tumor Registry. *Cancer* 1991;68:2251–9.
26. Green S, Weiss GR. Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. *Invest New Drugs* 1992;10:239–53.
27. Wexler LH, Andrich MP, Venzon D, Berg SL, Weaver-McClure L, Chen CC, et al. A randomized trial of the cardioprotective agent, ICRF-187, in pediatric sarcoma patients treated with doxorubicin. *J Clin Oncol* 1996;14:362–72.
28. Wexler LH, Weaver-McClure L, Steinberg SM, Jacobson J, Jarosinski P, Avila N, et al. A randomized trial of recombinant human granulocyte-macrophage colony-stimulating factor in pediatric patients receiving intensive myelosuppressive chemotherapy. *J Clin Oncol* 1996;14:901–10.
29. Ho PTC, Zimmerman K, Wexler LH, Blaney S, Jarosinski P, Weaver-McClure L, et al. A prospective evaluation of ifosfamide-related nephrotoxicity in children and young adults. *Cancer* 1995;76:2557–64.
30. Goldie JH, Coldman AJ, Gudauskas GA. Rationale for the use of alternating non-cross-resistant chemotherapy. *Cancer Treat Rep* 1982;66:439–49.
31. Grier H, Krailo M, Link M, Tarbell N, Fryer C, Pritchard D, et al. Improved outcome in non-metastatic Ewing's sarcoma (EWS) and PNET of bone with the addition of ifosfamide (I) and etoposide (E) to vincristine (V), Adriamycin (Ad), cyclophosphamide (C), and actinomycin (A): a Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) report, [abstract 1443]. *Proc Am Soc Clin Oncol* 1994;13:421.
32. Oberlin O, Habrand J-L, Zucker JM, Brunat-Mentigny M, Terrier-Lacombe M-J, Dubousset J, et al. No benefit of ifosfamide in Ewing's Sarcoma: a nonrandomized study of the French Society of Pediatric Oncology. *J Clin Oncol* 1992;10:1407–12.
33. Heyn R, Khan F, Ensign LG, Donaldson SD, Ruymann F, Smith MA, et al. Acute myeloid leukemia in patients treated for rhabdomyosarcoma with cyclophosphamide and low-dose etoposide on Intergroup Rhabdomyosarcoma Study III: an interim report. *Med Pediatr Oncol* 1994;23:99–106.
34. Skinner R, Sharkey IM, Pearson ADJ, Craft AW. Ifosfamide, mesna, and nephrotoxicity in children. *J Clin Oncol* 1993;11:173–90.
35. Kinsella TJ, Miser JS, Waller B, Venzon D, Glatstein E, Weaver-McClure L, et al. Long-term follow-up of Ewing's sarcoma of bone treated with combined modality therapy. *Int J Radiat Oncol Biol Phys* 1991;20:389–93.
36. Bacci G, Picci P, Ruggieri P, Ferrari S, Mercuri M, Fabbri N, et al. No advantages in the addition of ifosfamide and VP-16 to the standard four-drug regimen in the maintenance phase of neoadjuvant chemotherapy of Ewing's sarcoma of bone: results of two sequential studies. *J Chemother* 1993;5:247–57.
37. Kushner BH, Hajdu SI, Gulati SC, Erlandson RA, Exelby PR, Lieberman PH. Extracranial primitive neuroectodermal tumors: the Memorial Sloan-Kettering Cancer Center Experience. *Cancer* 1991;67:1825–9.
38. Whang-Peng J, Triche TJ, Knutsen T, Miser J, Kao-Shan S, Tsai S, et al. Cytogenetic characterization of selected small round cell tumors of childhood. *Cancer Genet Cytogenet* 1986;21:185–208.
39. Thiele CJ, McKeon C, Triche TJ, Ross RA, Reynolds CP, Israel MA. Differential protooncogene expression characterizes histopathologically indistinguishable tumors of the peripheral nervous system. *J Clin Invest* 1987;80:804–11.
40. Zucman J, Melot T, Desmaze C, Ghysdael J, Plougastel B, Peter M, et al. Combinatorial generation of variable fusion proteins in the Ewing family of tumours. *EMBO J* 1993;12:4481–7.
41. May WA, Gishizky ML, Lessnick SL, Lunsford LB, Lewis BC, Delattre O, et al. Ewing sarcoma 11;22 translocation produces a chimeric transcription factor that requires the DNA-binding domain encoded by FLI1 for transformation. *Proc Natl Acad Sci USA* 1993;90:5752–6.
42. Malpas JS, moderator. Meeting report: First children's solid tumor group workshop on Ewing's sarcoma. 30 June to 1 July 1989. *Br J Cancer* 1990;62:326–30.
43. Dunst J, Jürgens H, Sauer R, Pape H, Paulussen M, Winkelmann W, et al. Radiation therapy in Ewing's sarcoma: an update of the CESS 86 trial. *Int J Radiat Oncol Biol Phys* 1995;32:919–30.
44. Razek A, Perez CA, Tefft M, Nesbit M, Vietti T, Burgert EO Jr, et al. Intergroup Ewing's Sarcoma Study. Local control related to radiation dose, volume, and site of primary lesion in Ewing's sarcoma. *Cancer* 1980;46:516–21.
45. Sailer SL, Harmon DC, Mankin HJ, Truman JT, Suit HD. Ewing's sarcoma: surgical resection as a prognostic factor. *Int J Radiat Oncol Biol Phys* 1988;15:43–52.
46. Scully SP, Temple HT, O'Keefe RJ, Scarborough MT, Mankin HJ, Gebhardt MC. Role of surgical resection in pelvic Ewing's sarcoma. *J Clin Oncol* 1995;13:2336–41.

47. Hofbauer S, Hamilton G, Theyer G, Wollmann K, Gabor F. Insulin-like growth factor-I-dependent growth and in vitro chemosensitivity of Ewing's sarcoma and peripheral primitive neuroectodermal tumour cell lines. *Eur J Cancer* 1993; 29A:241–5.
48. Burdach S, Jürgens H, Peters C, Nürnberger W, Mauz-Körholz C, Körholz D, et al. Myeloablative radiochemotherapy and hematopoietic stem-cell rescue in poor-prognosis Ewing's sarcoma. *J Clin Oncol* 1993;11:1482–8.
49. Atzpodien J, Gulati SC, Shimazaki C, Bührer C, Öz S, Kwon JH, et al. Ewing's sarcoma: ex vivo sensitivity towards natural and lymphokine-activated killing. *Oncology* 1988;45: 437–43.
50. Wexler LH, Chen C, Dilsizian V, Weaver-McClure L, Jarosinksi P, Venzon D. Use of ADR-529 (Zinecard®, ZIN) in pediatric sarcoma patients (pts) receiving a highly doxorubicin (DOX)-dose-intensive (D.I.) regimen [abstract]. *J Cardiovasc Diagn Proc* 1996;13:116.
51. Jones CA, Shaw PJ, Stevens MM. Use of granulocyte colony stimulating factor to reduce the toxicity of super-VAC chemotherapy in advanced solid tumors in childhood. *Med Pediatr Oncol* 1995;25:84–9.
52. Wexler LH, Leitman SF, Carter CS, McClure L, Yu M, Fox MC. Peripheral blood progenitor cell (PBPC) transfusions permit repetitive cycles of myeloablative chemotherapy for pediatric sarcoma patients [abstract 1460]. *Proc Am Soc Clin Oncol* 1995;14:454.