A Southwest Oncology Group and Cancer and Leukemia Group B Phase II Study of Doxorubicin, Dacarbazine, Ifosfamide, and Mesna In Adults with Advanced Osteosarcoma, Ewing's Sarcoma, and Rhabdomyosarcoma

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BACKGROUND. Ewing's sarcomas, osteosarcomas, and rhabdomyosarcomas are significantly more responsive to chemotherapy than other sarcomas. Adjuvant chemotherapy is used routinely based on data from randomized trials. Although a percentage of children with locally advanced or metastatic tumors remain curable, few data exist regarding the tumor's natural history or response and survival in adults.

METHODS. This Phase II study evaluated doxorubicin, dacarbazine, ifosfamide, and mesna (MAID) in adults with inoperable or metastatic Ewing's sarcoma, rhabdomyosarcoma, or osteosarcoma.

RESULTS. Between 1987–1991, 81 patients were entered; 69 patients were eligible. One patient died of neutropenic infection. Ten patients (14%) responded completely and 34 patients (49%) had a complete or partial response. Response rates were significantly higher for patients with Ewing's sarcoma and rhabdomyosarcoma than for those with osteosarcoma (77%, 64%, and 26%, respectively; $P < 0.005$). Although there were no significant differences in progression free survival by histology, survival for patients with Ewing's sarcoma was significantly longer than for patients with osteosarcoma ($P = 0.004$.) At the time of last follow-up, 7 patients (10%) were alive without progression: 3 with Ewing's sarcoma, 1 with osteosarcoma, and 3 with rhabdomyosarcoma.

CONCLUSIONS. MAID chemotherapy is an active regimen in adults with advanced or metastatic Ewing's sarcoma and rhabdomyosarcoma. Although there was no direct comparison with a doxorubicin and cisplatin-based regimen, the response rate and survival in patients with osteosarcoma suggest that doxorubicin and cisplatin-based chemotherapy would remain the accepted initial chemotherapy regimen. For patients with rhabdomyosarcoma and Ewing's sarcoma, 10–20% of patients remained disease free at 5 years. ***Cancer* 1998;82:1288–95.** *© 1998 American Cancer Society.*

KEYWORDS: adult, rhabdomyosarcoma, Ewing's sarcoma, osteosarcoma.

Bone and soft tissue sarcomas currently comprise 1% of adult malignancies and 15% of pediatric malignancies.[1] Ewing's sarcoma, osteosarcoma, and rhabdomyosarcoma (RMS) differ from other sarcomas in their considerably higher response rates to chemotherapy.

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Adjuvant chemotherapy now is used routinely in the treatment of these malignancies based on data from randomized trials.[2–6] A percentage of children with these tumors remain curable, even when disease is locally advanced or metastatic.

Few data exist regarding the natural history, response, or survival of adults with Ewing's sarcoma, osteosarcoma, and RMS.[7–9] Most of these studies suggest that adults with these malignancies have poorer survival than children, stage for stage. Inoperable or metastatic disease in adults is believed to be generally fatal although some selected patients can be salvaged by resection of pulmonary metastases.

This study was designed to accrue adults with inoperable or metastatic Ewing's sarcoma, RMS, and osteosarcoma to a Phase II trial of doxorubicin, dacarbazine, and ifosfamide. The combination of doxorubicin and dacarbazine was based on three randomized trials in adults with soft tissue sarcomas that all had higher response rates with the addition of dacarbazine to a doxorubicin-based regimen, which was significant in two of the three studies,[10–13] and the activity of ifosfamide in tumors that had progressed after treatment with doxorubicin-based chemotherapy. The patients in this Phase II study were accrued concurrently with accrual of patients with other histologic variants of sarcoma onto a randomized Phase III trial of doxorubicin and dacarbazine with or without ifosfamide.[14] The only data available for adults are from small single institution studies of variably treated patients. A Southwestern Oncology Group (SWOG) and Cancer and Leukemia Group B (CALGB) intergroup study was required to allow the accumulation of the numbers reported in this article. Even with an intergroup study, the numbers of adults with these histologies were believed to be insufficient to answer a randomized question.

Three randomized trials have been published to date evaluating the efficacy of the addition of ifosfamide to a doxorubicin-based regimen. The response rates for the ifosfamide-containing arm were significantly higher in the SWOG and Eastern Cooperative Oncology Group studies but not different in the European Organization for Research and Treatment of Cancer study. Survival was not improved significantly in any of the three studies.[14–16]

METHODS

Patient Population

Eligible patients had measurable, histologically documented metastatic or unresectable osteosarcoma, Ewing's sarcoma, or RMS, a CALGB performance status of 0 to 2, a leukocyte count $> 3000/\mu L$, platelet count $> 100{,}000/\mu L$, and creatinine, bilirubin, and aspartate aminotransferase < 1.5-fold normal. Patients who had received any prior chemotherapy for sarcoma or previous administration of doxorubicin for another primary tumor were excluded. Patients with a previous nonsarcomatous primary tumor were included if the measurable lesions were biopsy proven eligible variants of sarcoma. These patients intentionally were included to allow evaluation of response in sarcomas arising in previous radiation ports. At least a 1-week delay after surgery and bone marrow recovery after radiotherapy were required prior to entry. Other sarcomas were accessioned onto a study randomizing patients between doxorubicin and dacarbazine with or without ifosfamide and mesna.[14]

Informed consent was obtained for all patients according to OPRR guidelines and SWOG and CALGB audit procedures.

Statistical Methods

The accrual goal was 25 patients evaluable for response in each histologic group.

Partial or complete remission required a 50–99% or 100%, respectively, reduction of the product of perpendicular greatest dimensions of all measurable lesions for at least 4 weeks. Stable disease was defined as a $<50\%$ reduction or $<25\%$ increase of the same parameters for >8 weeks, and disease progression required a $>25\%$ increase or the appearance of any new lesions. Time to progression was calculated from the day of registration to the documentation of progression.

Chi-square and logistic regression tests[17] were used to compare response and toxicity rates within various patient subgroups, and log rank tests[18] and Cox regression analysis[19] were used to analyze time to progression and survival. Survival and time to progression curves were calculated using the product-limit method.[20]

Treatment

All patients entered received a continuous intravenous infusion of doxorubicin at 15 mg/m^2/day (total 60 mg/m^2) and dacarbazine, 250 mg/m^2/day (total 1000 mg/m^2) through a central venous access device over 4 days. Ifosfamide, 2500 mg/m^2/day (total 7500 mg/m^2), and mesna, 2500 mg/m^2/day (total 10,000 mg/m^2), continuously were infused intravenously over 3 and 4 days, respectively.

The study was amended to decrease the dose of ifosfamide and mesna from 2500 mg/m^2/day to 2000 mg/m^2/day (total 6000 mg/m^2 of ifosfamide and 7500 mg/m^2 of mesna per course) after the first 15 patients were accrued because of unacceptable myelosuppression. Courses were repeated at 21 days, or when the leukocyte count reached $3000/\mu L$, and the platelet count reached 100,000/uL. Ifosfamide was withheld

TABLE 1
Registration, Eligibility, and Evaluability

No. registered	81
Wrong histology	3
Started treatment before registration	1
Data insufficient to verify eligibility	7
Tumor measurements >14 days old	1
Total ineligible (6 Ewing's, 1 RMS, 2 osteosarcoma, 3 other)	12
Eligible	69
Evaluable for toxicity	69
Evaluable for response	69
Number off treatment other than for disease progression	
Due to toxicity	3
Due to death	1
Other	12
Major deviations	0

Ewing's: Ewing's Sarcoma; RMS: rhabdomyosarcoma.

for any significant neurologic abnormality, elevated creatinine $>$ 2.0 mg/dL, or a daily urinary red blood cell count $>$ 50/high-power fields until the toxicity resolved. Resection or radiation of any residual disease was encouraged if feasible after at least four cycles of chemotherapy. Chemotherapy treatment was to be continued for patients with response or stable disease until disease progression or until a 450/m^2 cumulative dose of doxorubicin.

RESULTS

Patient Entry

Between May 1987 and July 1991, 81 patients were entered to this Phase II trial. A total of 12 patients were ineligible (Table 1). (The SWOG statistical office allows no exceptions from exact eligibility and data submission requirements.) Thus, 69 patients were fully eligible. There were no major treatment deviations and all eligible patients were evaluable for tumor response. Accrual goals were achieved for osteosarcoma and RMS, but not for the less common Ewing's sarcoma.

Patient characteristics are shown in Table 2. The median age was 31 years (range, 18–76 years), with 13% of patients age $>$ 60 years. Twenty-four patients (35%) had inoperable locally advanced disease that could not be resected for cure as accessed by the surgeon; the remainder had metastases with or without recurrent or residual primary disease. Approximately 7% of patients had radiation-induced sarcomas.

Toxicity

Toxicities are shown in Table 3. One treatment-related death in a patient with RMS was due to infection. There were no reported cardiomyopathies. The protocol was amended in August 1988 (after the first 15 patients were accrued [1 with Ewing's sarcoma, 9 with osteosarcoma, and 5 with RMS]) to reduce the starting dose of ifosfamide from 7.5 g/m^2 to 6 g/m^2 per course because of life-threatening myelosuppression.

Response

Patient response, progression free survival, and survival by histology are shown in Table 4. Of the 69 eligible patients, 10 (14%) responded completely and 34 (49%) had a complete or partial response. Response rates were significantly higher for patients with Ewing's sarcoma and RMS than for those with osteosarcoma (77% and 64%, respectively vs. 26%; $P < 0.005$). Although there were no significant differences in progression free survival by histology, survival for patients with Ewing's sarcoma was significantly longer than for those with osteosarcoma ($P = 0.004$) (Figs. 1a, 1b).

Survival

At last follow-up, of the 69 eligible patients, 62 (90%) had died. The median survival was 14 months. Age ($P = 0.27$ for cutoff at 30; $P = 0.33$ for continuous variable), extent of disease ($P = 0.07$), Histologic grade 1 and 2 versus grade 3 ($P = 0.19$), or gender ($P = 0.33$) did not significantly affect survival.

Although there were no significant differences in progression free survival by histology, survival for patients with Ewing's sarcoma was significantly longer than for patients with osteosarcoma ($P = 0.01$.)

Long Term Survivors

At last follow-up, 7 patients (10%) were alive without progression: 3 with Ewing's sarcoma, 1 with osteosarcoma, and 3 with RMS (Table 5). All the long term disease free survivors received multimodality therapy with surgery, radiotherapy, or both to sites of residual or prior disease.

DISCUSSION

This study demonstrates response rates of 77% and 64% for the combination of mesna, doxorubicin, ifosfamide and dacarbazine (MAID) in patients with advanced Ewing's sarcoma and RMS, in contrast to a response rate of 26% for patients with osteosarcoma.

Because of the lower than expected response rate for osteosarcomas, we specifically reviewed the grading data. Low grade osteosarcomas may have been more likely to be included in this study, whereas patients with high grade osteosarcomas preferentially received doxorubicin and cisplatin-based standard therapy, potentially resulting in a lower response rate. However, the response rate was lower for osteosarcoma even when only patients with high grade lesions were considered. Although response in patients with

TABLE 2
Patient Characteristics

	Ewing's sarcoma		Osteosarcoma		Rhabdosarcoma		Total	
	No.	%	No.	%	No.	%	No.	%
No. of eligible patients	13		31		25		69	100
Age (yrs)								
Median	27		35		30			31
>50	0	0	5	16	3	12		
>60	0	0	7	23	2	8		
Gender								
Men	9	69	17	55	17	68	43	62
Women	4	31	14	45	8	32	26	38
Race								
White	13	100	25	80	23	92	61	88
Black	0	0	3	10	2	8	5	7
Other	0	0	3	10	0	0	3	4
Stage								
Metastatic	5	38	24	77	16	64	45	65
Inoperable primary	8	62	7	22	9	36	24	35
Grade								
I or II	1	8	12	39	3	12	16	23
III	12	92	19	61	22	88	53	77
Radiotherapy-associated sarcoma	2	11	3	10	0	0	5	7

TABLE 3
Toxicity for Doxorubicin, Dacarbazine, and Ifosfamide with Mesna

Grade	Unknown	0	1	2	3	4	5
Leukopenia	0	3	1	4	17	44	0
Granulocytopenia	0	13	0	1	6	49	0
Anemia	0	25	9	20	14	1	0
Thrombocytopenia	0	41	4	6	8	10	0
Infections	0	68	0	0	0	0	1
Hematuria/bladder	0	63	5	1	0	0	0
Somnolence/coma	3	59	5	1	1	0	0
Nausea/emesis/anorexia	0	13	16	34	6	0	0
Mucositis/ulcers/stomatitis	0	46	12	6	5	0	0
Diarrhea	0	59	6	4	0	0	0
GI other	0	60	4	2	3	0	0
Cardiac	0	69	0	0	0	0	0
Maximum grade any toxicity	0	1	0	3	11	53	1

GI: gastrointestinal.

osteosarcoma is difficult to evaluate because malignant osteoid does not tend to decrease in size despite pathologic documentation of tumor necrosis, the short progression free survival and survival for patients with osteosarcoma suggests that this chemotherapy regimen is less effective in patients with osteosarcoma than in those with Ewing's sarcoma or RMS.

Toxicity was acceptable for this population of relatively young patients (median age 31 years, which is significantly younger than the median age of 52 years for sarcoma patients with other histologies accrued to the Phase III portion of the study; $P < 0.001$). Progression free survival appeared superior to that for patients with other histologies, although survival was not different (Figs. 2a and 2b).

Osteosarcoma

The most common sarcoma of bone (and the second most common primary malignancy of bone after myeloma), osteosarcoma is defined as a primary ma-

TABLE 4
Response, Progression Free Survival, and Survival by Histology (Actual Numbers for Small Subsets are not Provided)

	Ewing's		Osteo		RMS		Total	
	No.	%	No.	%	No.	%	No.	%
No. of eligible patients	13		31		25		69	100
Complete response	2	15	1	3	7	28	10	14
Partial response	8	62	7	23	9	36	24	35
Stable/no response	1	8	9	29	3	12	13	20
Diasease progression	1	8	9	29	3	12	13	20
No eval., assumed no resp.	1	8	5	16	3	12	9	13
Response rate	10	77	8	26	16	64	34	49
95% confidence limits		46–95		12–45		43–82		
Response rate								
Grade 3	10/12	83	6/19	32	15/22	68	31/53	58
Grade 1, 2							3/16	19
Response rate								
Metastatic	5	100	24	100	16	100	22/45	49
Complete response	1	20	1	4	4	25	6/45	13
Partial response	4	80	6	25	6	38	16/45	36
Inoperable primary tumor	8	100	7	100	9	100	12/24	50
Complete response	1	12	0	0	3	33	4/24	17
Partial response	4	50	1	14	3	33	8/24	33
Radiation-associated							3/5	60
Not associated							31/64	48
Age (yrs)								
< 30							13/27	48
30–45							14/22	64
> 45							7/20	35
Pre- and postamendment								
7.5 gm/m^2 ifosfamide	1		9		5		7/25	47
6.0 gm/m^2 ifosfamide	12		22		20		27/54	50
Median months								
To progression	14		6		10			9
Survival	28		10		15			15

Ewing's: Ewing's sarcoma; Osteo: osteosarcoma; RMS: rhabdomyosarcoma; Eval: evaluation; Resp: response.

lignancy of bone that produces osteoid.[21] Approximately 900 new cases occur per year in the U.S., with a ratio of men to women of approximately 1.5:1. The age distribution is bimodal, with a peak in adolescence and a second in the sixth decade.[22] Osteosarcoma in older patients tends to develop in previously irradiated sites or in existing benign bone lesions such as Paget's disease (0.2% risk of osteosarcoma), solitary osteochondromas, or multiple enchondromatosis (Ollier's disease). Although axial lesions occur in <10% of pediatric patients, they occur in 30–50% of adults, contributing to a poorer prognosis. The adjuvant regimen of choice appears to be doxorubicin and cisplatin with or without high dose methotrexate. Ifosfamide appears to have significant activity in patients who recur despite adjuvant chemotherapy. There are few data on adults presenting with advanced measurable disease. Nevertheless, based on the response and survival data in this study, a doxorubicin and cisplatin-based regimen would remain the standard of care.

Ewing's Sarcoma

Ewing's sarcoma comprises 10–14% of primary malignant bone tumors in whites but is rare in African-Americans.[22] The incidence of Ewing's sarcoma peaks between the ages 10 and 25 years with a 2:1 male-to-female ratio. Patients present with fever, weight loss, malaise, poorly localized bone pain, and a rapidly enlarging mass. The most common sites include the femur (27%), pelvis (18%), and tibia and fibula (17%). The diagnosis of Ewing's sarcoma involving the pelvic bones frequently is delayed because of poorly localized pain and a clinically inapparent mass.[23]

Clinically detectable metastases are present in approximately 33% of patients at diagnosis, most frequently in the lung, bone, marrow, and vertebrae (commonly leading to cord compression). However,

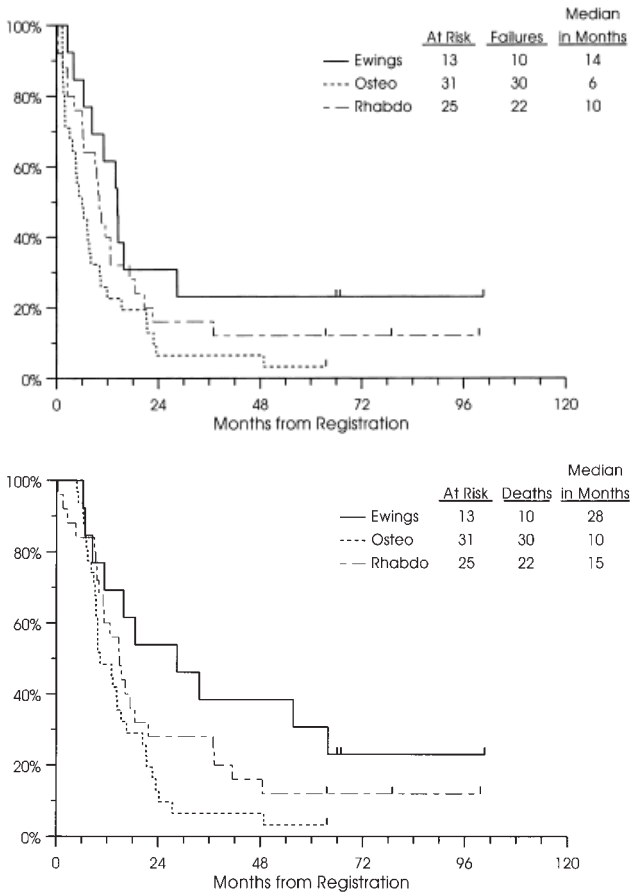

FIGURE 1. (top) Progression free survival by histology. (bottom) Survival by histology. Ewings: Ewing's sarcoma; Osteo: osteosarcoma; Rhabdo: rhabdomyosarcoma.

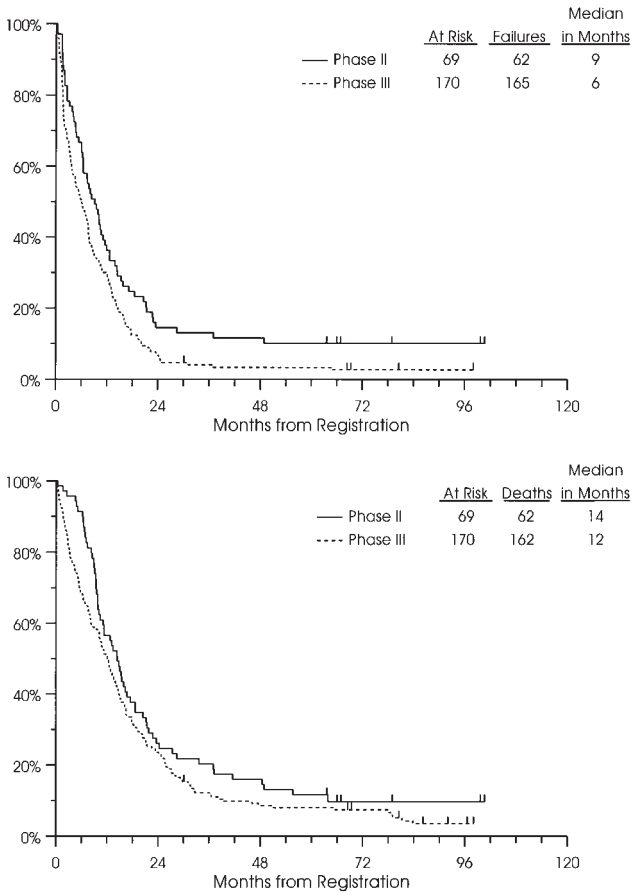

FIGURE 2. (top) Progression free survival for Ewing's sarcoma, rhabdomyosarcoma, and osteosarcoma (Phase II) versus other adult sarcomas (Phase III). (bottom) Survival for Ewing's sarcoma, rhabdomyosarcoma, and osteosarcoma versus other adult sarcomas.

because metastases develop in 90% of patients treated with surgery alone, Ewing's sarcoma clearly is generalized at presentation. Although current multimodality treatment results in cure in approximately 70% of children age < 10 years with localized disease and approximately 33% of children with metastases, survival rates correlate inversely with age (70% for patients age $<$ 10 years vs. 46% for those age > 16 years). Data for patients age > 25 years are few. In this study MAID chemotherapy in adults with inoperable or metastatic Ewing's sarcoma appears to be active with acceptable toxicity, and resulted in a few patients with long term disease free survival.

Rhabdomyosarcomas

Derived from striated muscle, RMS includes embryonal, alveolar, and pleomorphic variants. The peak incidence for embryonal RMS is approximately 4 years for orbital tumors and early adolescence for those of the genitourinary tract. Alveolar RMS, more common in adolescents and young adults, has a more serious prognosis. As evidenced by the development of disseminated disease in the absence of chemotherapy in 80% of patients, RMS is systemic at diagnosis. Although a percentage of children with locally advanced or metastatic disease can be cured, the prognosis in adults, even those with localized disease, is poor despite excellent responses to initial chemotherapy.[24] Of 18 adults with RMS treated at Stanford University with multimodality therapy, only 4 had not recurred 2–9 years after treatment. The median survival was 2 years.[9] In this study MAID chemotherapy appeared to be active, producing high response rates, and when combined with surgery, radiation, or both, resulted in long term, disease free survival in a few patients.

MAID chemotherapy has acceptable toxicity in this relatively young population with dose-limiting myelosuppression. Although myeloid growth factors were not used in this study, the incidence of neutro-

TABLE 5
Long Term Survivors

Age (yrs)	Gender	Disease	On study	Last follow-up	Response	Postprotocol treatment
Ewing's						
21	M	Primary	11/18/87	3/94	PR	Necrotic primary resected, postoperative RT
27	M	Primary	8/7/90	10/31/95	PR	RT to primary
38	M	Metastatic	3/22/90	5/96	PR	Etoposide/ifosfamide, RT to primary
Osteosarcoma						
31	F	Metastatic	7/6/90	4/96	ANR	Pulmonary mets resected × 5
Rhabdomyosarcoma						
18	F	Primary	9/29/87	3/29/94	CR	PCR at surgery; postoperative RT
76	F	Primary	2/24/89	9/25/95	CR	RT to primary
21	F	Metastatic	1/2/90	5/2/96	PR	Necrotic pulmonary met resected

Ewing's: Ewing's sarcoma; M: male; F: female; PR: partial response; RT: radiotherapy; ANR: no evaluation, assumed no response; mets: metastases; CR: complete response; PCR: pathologic CR.

penia expected in the majority of patients and the emergence of a subset of patients with long term, disease free survival would most likely justify their use.

Thus MAID chemotherapy is an active regimen in adults with advanced or metastatic Ewing's sarcoma and RMS. Although there was no direct comparison with a doxorubicin and cisplatin-based regimen, the response rate and survival in patients with osteosarcoma suggests that doxorubicin and cisplatin-based chemotherapy would remain the accepted initial chemotherapy regimen. In RMS and Ewing's sarcoma, 10–20% of patients remained disease free at 5 years.

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