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Ifosfamide Dose-Intensification for Patients with Metastatic Ewing Sarcoma

Heather Magnan, MD[1], **Christine M. Goodbody, BA**[2], **Elyn Riedel, MA**[3], **Christine A. Pratilas, MD**[1], **Leonard H. Wexler, MD**[1], and **Alexander J. Chou, MD**[1]

[1]Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York, NY

[2]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

[3]Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY

Abstract

Background—Outcomes for patients with metastatic Ewing sarcoma (ES) remain poor. We investigated whether the intensification of ifosfamide improved survival for patients with metastatic ES.

Procedure—We conducted a retrospective chart review of 30 patients with metastatic ES treated with the MSKCC "EFT regimen". The regimen included an intensification of ifosfamide dosing from 1,800 mg/m^2/day × 5 days per cycle to 2,800 mg/m^2/day × 5 days per cycle.

Results—Twenty six of the 30 patients completed planned chemotherapy. Two patients experienced disease progression during therapy. There were no toxic deaths. One patient developed secondary leukemia. The 4-year event free survival (EFS) was 27% and the overall survival (OS) was 39%.

Conclusions—Intensification of ifosfamide was tolerated and did not increase toxicity in patients with metastatic ES. The intensification did not improve outcomes for these patients with metastatic disease.

Keywords

Ewing sarcoma; chemotherapy; outcomes

INTRODUCTION

Ewing sarcoma (ES) is the second most common primary bone tumor affecting children and young adults with an incidence of 3 cases per 1,000,000 per year in the United States. Approximately twenty five percent of new patients will present with metastatic disease [1]. The presence of metastatic disease at diagnosis confers a poor prognosis with an estimated

Correspondence to Heather Magnan, MD, Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. magnanh@mskcc.org. Fax: 212-717-3239. Phone: 212-639-7937.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

event free survival of 22–30% at five years [2–4]. Other prognostic factors associated with a poor prognosis include central/pelvic tumors[5, 6], large tumors[2, 6], age > 18 years [2], and an elevated serum lactate dehydrogenase (LDH) at diagnosis[7]. In patients with metastatic disease, those with metastases limited to the lungs have a better prognosis than those with metastases to the bone, bone marrow or a combination of bone and lung[5, 6].

In 2003 we reported the results of the MSKCC P6 trial for treatment of newly diagnosed patients with Ewing sarcoma. The trial included patients with both localized and metastatic disease. With this dose intense regimen the 4 year event free survival (EFS) and overall survival (OS) for patients with localized disease were excellent at 82% and 89% respectively. The results for patients with metastatic disease were disappointing with EFS and OS of 12% and 17.8% [8]. The MSKCC EFT regimen was developed as a further dose intensification of the P6 regimen. The cumulative dose of ifosfamide was increased from 27 grams/m^2 to 42 grams/m^2 to investigate whether further intensification could improve prognosis for patients with metastatic ES.

METHODS

Patients

From 2004 to 2012, 30 patients with newly diagnosed, previously untreated, metastatic Ewing sarcoma were treated according to a modified version of the P6 protocol. This treatment was renamed the “EFT regimen”. All patients were confirmed pathologically to have Ewing sarcoma. Pretreatment extent of disease evaluation included computed tomography (CT) and/or magnetic resonance imaging of the primary site and all sites of metastatic disease; CT of the chest, a technetium-99m bone scan; and bone marrow analysis by aspiration and biopsy. A retrospective chart review was conducted to analyze prognostic factors and outcomes of patients treated according to this regimen. Age, gender, site of primary disease, extent and site(s) of metastatic disease, primary tumor size, pre-treatment LDH, local control modality employed and events during or following therapy including recurrence, death and secondary malignancy were reviewed for all patients. The institutional review board at MSKCC approved the review of medical records for this analysis.

Therapy

The EFT regimen is a modified version of the P6 regimen [9]. The major modification was an increase in the dosing of ifosfamide from 1,800 mg/m^2/day × 5 days per cycle to 2,800 mg/m^2/day × 5 days per cycle. Other minor changes included a change in the ordering of cycles 6 and 7 and a change from continuous infusion doxorubicin 75 mg/m^2 with vincristine 2 mg/m^2 over 72 hours to the same dosing in two divided doses of doxorubicin on days 1 and 2 and one bolus dose of vincristine on day 1 of each cycle.

The EFT regimen consists of seven cycles of chemotherapy planned every 21 days. Patients must have recovered from the toxicities of the prior cycle and have an absolute neutrophil count of 500/μL or higher and a platelet count of 75,000/μL or higher before proceeding with each cycle. Cycles 1, 2, 3, and 7 consist of cyclophosphamide 2,100 mg/m^2/day × 2 days, doxorubicin 37.5 mg/m^2/day × 2 days and vincristine 2 mg/m^2/dose to maximum of 2

mg on day 1. Cycles 4, 5, and 6 consist of ifosfamide 2,800 mg/m^2/day × 5 days and etoposide 100 mg/m^2/day × 5 days. Cyclophosphamide and ifosfamide are given with vigorous intravenous hydration and an equivalent daily dose of mesna continuously over 24 hours. Dexrazoxane 375 mg/m^2/dose is given 15 minutes prior to each dose of doxorubicin. Filgrastim or peg-filgrastim is given for neutrophil support with each cycle.

For those patients in whom gross total resection of the primary tumor was feasible, surgical local control was performed following recovery from cycle 3 of chemotherapy. If radiation therapy was used for primary local control it was administered concurrent with cycles 4–6 of chemotherapy. Local control of metastatic sites of disease, including whole lung irradiation for pulmonary disease, was performed following cycle 7 of chemotherapy.

Statistics

Event free survival (EFS) and overall survival (OS) were calculated for all patients from the time of treatment initiation. For EFS, events included recurrence, second malignancy or death. Prognostic factors for EFS and OS were evaluated using the log-rank test. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Toxicity

Outpatient clinic notes, inpatient admission and discharge summaries, and laboratory reports were reviewed for assessment of toxicity. Acute toxicities were documented from the start of the first cycle of the EFT regimen through recovery from the final administered cycle of this regimen. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

RESULTS

Patient Characteristics

Thirty patients with newly diagnosed, previously untreated, metastatic Ewing sarcoma were treated according to the EFT regimen. The characteristics of all patients are described in Table I. Five (17%) of these patients had a primary tumor in an extremity, 13 (43%) in the pelvis and the remainder in other locations in the axial skeleton. Twelve patients had metastatic disease in the lungs only (40%); the remainder had metastases to other sites or a combination of lung and other sites. Three patients had disease in the bone marrow.

Outcomes

Twenty six of the 30 patients completed planned chemotherapy. One patient progressed after 4 cycles of chemotherapy. This patient had a 5 week delay in starting cycle 4 as a surgical plan was made and cancelled. A second patient progressed after cycle 5 of chemotherapy. He had not received chemotherapy in almost 8 weeks due to thrombocytopenia associated with a large radiation field. A third patient was changed to a regimen with a lesser risk of cytopenias to allow for continued administration of therapy while healing from Grade 3 hemorrhagic cystitis. The fourth patient to not complete planned chemotherapy elected to return to his home country after 4 cycles and was lost to follow-up.

For local control of the primary site, 3 patients were treated with surgery, 16 with radiation therapy and 10 with a combination of surgery and radiation therapy. The patient who progressed after cycle 4 did not receive local control to the primary site until after progression. Twenty four (80%) patients received local control (radiation therapy in all cases) to all sites of metastatic disease. Two patients with pulmonary disease did not receive whole lung irradiation (WLI) because the pulmonary disease recurred or progressed prior to initiation of WLI. In 3 patients the boney lesions were too numerous to deliver RT to all sites of disease. One patient elected to discontinue RT.

The four year EFS and OS are 27% (95% CI: 12–45%) and 39% (95% CI: 22–57%) respectively (Figure 1). Ten patients remain in a continuous first remission. Twelve patients were alive at the time of last follow-up; two having received several lines of additional therapy for recurrent disease. The median follow-up for survivors is 58 months (range 0.6–95). None of the patients who did not receive local control to all sites of metastatic disease survived event free though two were alive (one in remission) at the time of last follow-up. All patients with bone marrow disease (n=3) died. There were no toxic deaths. All deaths were attributed to progressive Ewing sarcoma.

Toxicity

Two hundred and one cycles of chemotherapy, 85 of them ifosfamide/etoposide cycles, were assessed for toxicity. Common toxicities are summarized in Table III. The “other” infections included a peri-rectal abscess that required incision and drainage, 2 urinary tract infections (UTIs)- one associated with a Foley catheter, the other with ureteral stents, and a herpes zoster infection. The perirectal abscess and one UTI were associated with ifosfamide/etoposide cycles.

Eighty eight percent of ifosfamide/etoposide cycles were associated with Grade 3 or 4 thrombocytopenia. Only 8 of these cycles were given without concurrent radiation therapy.

The two patients who experienced hemorrhagic cystitis following administration of ifosfamide were both concurrently receiving radiation therapy to large pelvic masses. One of these patients later received an additional cycle of ifosfamide without incident supported by double dosing of mesna and continuous bladder irrigation during the week of chemotherapy. The second patient was changed to an alternate chemotherapy regimen. One patient experienced significant Fanconi syndrome following his final cycle of ifosfamide. This patient had presented with acute renal failure at the time of diagnosis due to ureteral obstruction by a large pelvic mass. The renal imaging findings at diagnosis were thought consistent with longstanding obstruction and resultant nephron loss.

One patient developed secondary AML (monosomy 7) 2 years and 10 months from completion of the EFT regimen. Prior to development of tAML this patient was also treated with 26 cycles of irinotecan/temozolomide and 3 cycles of cyclophosphamide/topotecan for recurrent Ewing sarcoma.

Prognostic Features

Of the various prognostic features examined (patient age, disease site, tumor size, pre-treatment LDH and site of metastatic disease) the only variable found to be significant in predicting poorer EFS was tumor size. Those patients with a tumor size >8 cm (n = 19 patients) had an EFS of 9% (95% CI: 1–33%) compared with 39% (95% CI: 4–61%) for patients with tumors less than or equal to 8 cm (p= 0.03). The OS for these patients was 18% (95% CI: 3–44%) versus 49% (95% CI: 23%–71%) with a p-value of 0.07. As demonstrated in Table II, patients under age 18, patients with an LDH less than or equal to 200 and patients with metastatic disease limited to the lungs had improved OS; however, none of these factors reached statistical significance.

DISCUSSION

Several studies have demonstrated that increasing dose intensity of chemotherapy improves outcomes for patients with localized ES [8, 10]. An increase in dose intensity can be achieved by interval compression as in the most recently completed Children's Oncology Group (COG) trial for patients with localized ES (AEWS0031) [10] or by an escalation of dose as in the P6 protocol [8]. Both approaches increase the planned dose per unit time-mg/m^2/week [11]. For more than 20 years we have treated patients at MSKCC with a short-duration (21 week), dose-intensified chemotherapy regimen. The mg/m^2/week dose of cyclophosphamide is more than double the dosing used in COG studies and the doxorubicin and ifosfamide dosages/m^2/week are comparable to those used in AEWS0031, Regimen B (interval compressed arm). Excellent outcomes were described for patients with localized ES treated on the P6 protocol while results for patients with metastatic disease remained poor [8]. While the current study was not prospective, further intensification of ifosfamide does not appear to have improved outcomes. It is notable though that our cohort of patients included a disproportionate number of older patients (median age 19 years) and few patients with primary tumors located in the extremities (17%).

As the number of patients evaluated was 30 our ability to determine prognostic factors was limited. The data did confirm tumor size greater than 8 cm as predictive of poorer EFS with a trend to the same for OS. Similar to observations made by other groups [5, 6, 12], patients with metastases limited to the lungs seemed to fare better than those with metastases to other sites.

The intensification of ifosfamide did not increase apparent toxicity as compared with the P6 regimen; there were no toxic deaths and one case of secondary cancer. The majority of patients were able to receive local control as planned without delays related to excess toxicity. New therapies are desperately needed to treat patients with metastatic ES. Intensification of therapy alone has not proven to be the answer but as we consider the addition of new active drug combinations to the current standard 5 chemotherapy agents, this EFT regimen could serve as a backbone that delivers dose density and intensity without toxicity greater than expected.

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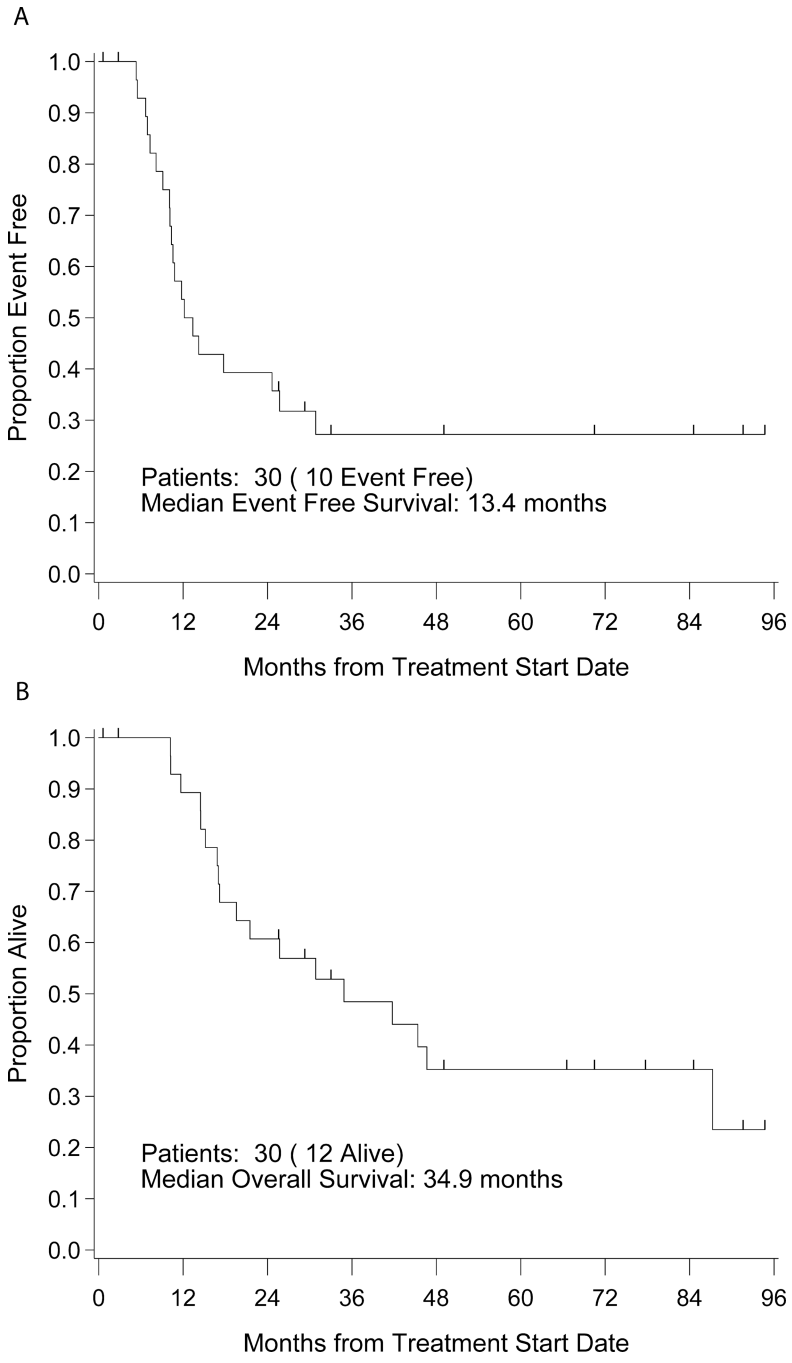

Figure 1.

A. Event free survival of all patients. **B.** Overall survival of all patients.

Table I

Patient Characteristics (n = 30)

Gender	
Male	22
Female	8
Age, years	
Median	19
Range	10–38
Primary Tumor Location	
Pelvis	13
Extremity	5
Other axial skeleton	12
Site of Metastasis	
Lung Only	12
Other	18
LDH at diagnosis, Units/L	
Median (range)	305 (234–436)
Less than/equal to 200	7
Greater than 200	23
Size of primary tumor	
Less than/equal to 8 cm	11
Greater than 8 cm	19
Local Control of primary site	
Surgery	3
Irradiation	16
Both	10

Table II

Prognostic Factors

		Overall Survival			Event Free Survival		
		Events	**4 year estimate (95% CI)**	**p-value**	**Events**	**4 year estimate (95% CI)**	**p-value**
Age	<18 years	4	54 % (13–82)	0.27	4	43% (10–73)	0.54
	≥18 years	14	29 % (11–50)		16	23% (8–43)	
Site	Central	15	37% (17–56)	0.67	17	26% (11–45)	0.47
	Extremity	3	27% (1–69)		3	30% (1–72)	
Size	≤8 cm	9	49% (23–71)	0.07	10	39% (16–61)	0.03
	>8 cm	9	18% (3–44)		10	9% (1–33)	
LDH	≤200	3	57% (17–85)	0.17	5	29% (4–61)	0.88
	>200	15	26% (9–48)		15	26% (9–47)	
Metastatic Site	Lung	6	53% (21–77)	0.28	6	45% (17–71)	0.16
	Other	12	23% (6–47)		14	16% (3–37)	

Table III

Toxicity

	Ifosfamide/Etoposide Cycles		Entire Regimen	
Toxicity	**No. of cycles**	**%**	**No. of cycles**	**%**
Infection				
Febrile Neutropenia	31	36	115	57
Sepsis-ICU admission	0	0	1	0.5
Central line infection	5	6	16	8
Other Infection	2	2.4	4	2
Neutropenia-Grade 4	85	100	201	100
Thrombocytopenia				
Grade 3	14	16	49	24
Grade 4	50	59	117	58
Encephalopathy	1	1.2	1	0.5
Fanconi Syndrome	1	1.2	1	0.5
Hemorrhagic Cystitis	2	2.4	2	1
Acute kidney injury				
Grade 2	1	1.2	1	0.5
Grade 3	0	0	0	0