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A Pilot Study of Vincristine, Ifosfamide, and Doxorubicin in the Treatment of Pediatric Non-Rhabdomyosarcoma Soft Tissue Sarcomas

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Background. Standard therapy for pediatric nonrhabdomyosarcoma soft tissue sarcomas (PNRSTS) consists of surgical resection with or without radiotherapy. The role of chemotherapy in the treatment of these tumors has not yet been defined. We investigated the efficacy and toxicity of an ifosfamide-based regimen in controlling disease in children with high-risk PNRSTS.

Patients and Methods. Between January 1992 and June 1994 at St. Jude Children's Research Hospital, we treated 11 children and young adults with PNRSTS who were at high risk for treatment failure by using a combined modality regimen that comprised aggressive surgery, radiotherapy, and chemotherapy including vincristine, ifosfamide, and doxorubicin (VID). Nine of these patients had grade 3 disease and one had grade 2 tumor; due to insufficient tissue, the disease grade of the remaining patient could not be established. Metastases were present at diagnosis in 2 children.

Results. Therapy was generally well tolerated, with minimal morbidity and no mortality. The most common toxicity was grade 4 neutropenia, which occurred in 51% of evaluable courses. Among 4 patients evaluable for response to chemotherapy alone, 1 child attained a partial response and 3 had stable disease. One child had a response to chemotherapy and concurrent irradiation. At a median follow-up of 30 months, 10 of 11 patients are alive; 8 of 11 patients are alive without evidence of disease.

Conclusion. Aggressive multimodality therapy for PNRSTS is well tolerated, despite frequent and profound neutropenia. Although adjuvant chemotherapy for this group of cancers remains unproved, the rate of tumor control achieved in this pilot study encourages further investigation in a multi-institutional setting. Med. Pediatr. Oncol. 30:210–216, 1998.

Key words: sarcoma; soft tissue neoplasms; antineoplastic agents, combined; combined modality therapy; clinical trials; adolescence; child

INTRODUCTION

Soft tissue sarcomas (STS) comprise 7% of pediatric malignancies. They occur at an annual rate of 9 new cases per million children (under the age of 15 years), resulting in about 740 new cases per year in the United States [1]. Most (50–70%) pediatric STS are rhabdomyosarcomas (RMS); the remainder are known collectively as the pediatric nonrhabdomyosarcoma soft tissue sarcomas (PNRSTS). There are important differences between RMS and PNRSTS. RMS is sensitive to chemotherapy, which plays an important role in its treatment. The role of chemotherapy in the treatment of pediatric as well as adult STS has not been clearly defined and remains investigational [2–9].

The optimal approach to treating PNRSTS has not been established. Surgical resection with or without radiation therapy has been used to treat successfully many of these tumors in adults and children. The challenge in the treatment of STS is therapy for high-grade (grade 3) tumors, which are most commonly associated with morbidity and mortality [4,10]. Patients with high-grade sar-

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comas frequently have large, unresectable lesions. In addition, many present with metastatic disease at diagnosis, with many more eventually failing at a distant site [6,11,12]. These patients cannot be cured by local therapy alone and are the ones most likely to benefit from chemotherapy [13–15]. Agents active in STS include ifosfamide, doxorubicin, dacarbazine, cyclophosphamide, melphalan, dactinomycin, and vincristine [5,7,16–28]. Some studies have shown a benefit from chemotherapy with an improvement in the percentage of patients achieving complete remission (CR) or partial remission (PR) or a prolonged median time to progression or median survival [7,24,25].

We developed an aggressive ifosfamide-based treatment approach to children with PNRSTS in an effort to improve outcome. We treated 11 children with high-risk PNRSTS between 1992 and 1994 at St. Jude Children's Research Hospital.

PATIENTS AND METHODS

Between January 1992 and June 1994, 11 children younger than 21 years of age who had high-risk PNRSTS were treated at St. Jude Children's Research Hospital with a multimodality approach that included VID chemotherapy. Patients were determined to be high-risk in light of high-grade histology and/or the presence of metastatic or unresectable disease. Tumor group was assigned at diagnosis according to the Intergroup Rhabdomyosarcoma Study Clinical Grouping (CG) system: CG I, completely resected tumor; CG II, microscopic residual disease in tumor bed and/or regional lymph nodes; CG III, gross residual disease with or without regional lymph node involvement; and CG IV, distant metastases.

The GTNM designation was assigned according to the International Union Against Cancer modification of the American Joint Committee Staging System for Soft Tissue Sarcomas [29]. Review of the operative notes provided details of tumor invasiveness (T1, non-invasive; T2, invasive). Scans provided data on tumor size, which were used to assign tumor stage (a, <5 cm in diameter; b, ⩾5 cm), as well as information regarding nodal involvement and the presence of distant metastases. Adapted from a scheme described by Costa et al. [10,11,30], the Pediatric Oncology Group system was used to determine tumor grade. In this system, grade 3 tumors (high-grade) are poorly differentiated, highly anaplastic lesions having >10% necrosis and ⩾5 mitoses per 10 high-power fields [10].

We initiated therapy after obtaining informed consent from the patient and/or guardian. In general, surgical resection or biopsy was followed by two cycles of VID chemotherapy and G-CSF. Local control was instituted at week 7 or 8 and comprised a second attempt at gross total resection (if feasible) and the start of radiation therapy. Details of therapy for each patient are presented in Table 1; the chemotherapy schedule is illustrated in Figure 1. Patients were considered evaluable for response to chemotherapy if: (1) residual disease (confirmed by imaging studies) remained after the initial surgical procedure, (2) radiation therapy had not been administered to these lesions(s), and (3) at least 2 courses of chemotherapy had been delivered. Toxicity was evaluated following each course of chemotherapy and quantitated according to criteria published by the National Cancer Institute.

RESULTS

Table I summarizes the patient characteristics, tumor features, treatment, and outcome of the 11 children treated for PNRSTS. The 3 male and 8 female patients ranged from 3.0 to 18.7 years of age at diagnosis (median, 12.9 years); 9 patients were white and 2 were black. Non-invasive lesions were found in 6 patients (three T1a and three T1b), and 5 patients had invasive disease (one T2a and four T2b). Nine patients had grade 3 tumors. A single patient had a grade 2 tumor, and grade could not be determined in the remaining case because of the paucity of tissue obtained at diagnosis; these children received VID chemotherapy because of unresectable or metastatic disease, respectively.

Surgery

The initial surgery led to wide local excision with negative margins in the 3 patients (nos. 1, 2, and 3). Microscopic residual disease was demonstrated after surgery in 3 patients (nos. 4, 5, and 6), and 3 patients had gross residual disease (nos. 7, 8, and 9). Two patients had metastatic disease; one (no. 11) underwent gross total resection of her primary tumor followed by thoracotomy to render her disease-free, and surgical resection was not attempted in the other (no. 10).

Radiotherapy

Of the 11 patients, 8 received radiation therapy [either brachytherapy and/or external beam therapy (standard or hyperfractionated)]. One of the 3 patients with CG I disease received radiation therapy in light of negative but close margins. Seven of the 8 patients with CG II-IV disease received radiation therapy; the patient who did not (no. 10) had CG IV disease with numerous bony metastases and an early response to chemotherapy. Local field therapy only (55 to 66 Gy) was given to 5 patients (nos. 5–9), and 2 (nos. 1 and 11) received both brachytherapy and local field external beam radiation (total doses, 55 Gy and 70 Gy, respectively). The remaining patient (no. 4) received 50 Gy brachytherapy only.

TABLE I. Patient Characteristics, Treatment and Outcome

Pt. no.	Age (yr)	Sex	Race	Diagnosis and site of primary tumor	IRS group	GTNM staging	Therapy (response)	Outcome
1	14.8	F	W	MPNST, trunk	I	$G_3T_{1A}N_0M_0$	(1) WLE, margins negative (CR) (2) Brachytherapy ^{192}Ir 20 Gy (NE) (3) 50 Gy local field during course 1 (NE) (4) VID × 8 (NE)	NED, 44 months
2	12.9	M	W	Fibrosarcoma, trunk	I	$G_3T_{1B}N_0M_0$	(1) WLE, margins negative (CR) (2) VID × 8 (NE)	NED, 54 months
3	18.7	F	B	Liposarcoma, extremity	I	$G_3T_{1B}N_0M_0$	(1) WLE, margins negative (CR) (2) VID × 6 (NE)	NED, 22 months
4	4.3	F	W	ASPS, head and neck	II	$G_3T_{1A}N_0M_0$	(1) GTR, margins positive (PR) (2) Brachytherapy ^{125}150 Gy (NE) (3) VID × 5 (NE)	NED, 25 months
5	3.0	F	W	Mesenchymoma, retroperitoneal	II	$G_3T_{2B}N_0M_0$	(1) GTR, margins positive (PR) (2) 55 Gy hemi-abdomen during course 3 (NE) (3) VID × 3 (NE) (4) VIE × 3 (NE)	NED, 26 months
6	4.0	M	B	MPNST, trunk	II	$G_3T_{1B}N_0M_0$	(1) GTR, margins positive (PR) (2) VID × 3 (NE) (3) 60 Gy local field (NE) (4) VID × 2 (NE)	NED, 29 months
7	17.5	M	W	Hemangio-pericytoma, extremity	III	$G_3T_{2B}N_1M_0$	(1) biopsy (2) 60 Gy local field during course 1 (NE) (3) VID × 5 (NE) (4) VI × 2 (NE)	NED, 36 months

TABLE I. (*Continued*)

Pt. no.	Age (yr)	Sex	Race	Diagnosis and site of primary tumor	IRS group	GTNM staging	Therapy (response)	Outcome
8	12.6	F	W	MPNST, head and neck	III	$G_3T_{2A}N_0M_0$	(1) VID × 2 (SD) (2) STR (PR) (3) 60 Gy local field (SD) (4) IE × 3 (SD) (5) VID × 2 (SD)	relapse to lungs, 21 months; AWD, 23 months
9	13.5	F	W	MPNST abdomen	III	$G_2T_{2B}N_0M_0$	(1) VID × 2 (SD) (2) STR (PR) (3) 66 Gy local field (PD)	DOD, 8 months
10	11.2	F	W	Epithelioid hemangio-endothelioma, trunk	IV	$G_XT_{2B}N_XM_1$	(1) biopsy (2) VID × 6 (PR)	AWD, 30 months
11	5.0	F	W	ASPS, extremity	IV	$G_3T_{1A}N_0M_1$	(1) GTR, margins negative (PR) (2) Brachytherapy ^{192}Ir 25 Gy (NE) (3) 30 Gy local field during course 1 (NE) (4) VID × 6 (SD) (5) VIE × 2 (SD) (6) Thoracotomy (CR)	NED, 30 months

ASPS, alveolar soft part sarcoma; B, black; CR, complete response; D, doxorubicin; DOD, died of disease; E, etoposide; Gy, Gray; GTR, gross total resection; I, ifosfamide; MPNST, malignant peripheral nerve sheath tumor; NE, not evaluable; NED, no evidence of disease; PD, progressive disease; PR, partial response; SD, stable disease; STR, sub-total resection; V, vincristine; W, white; WLE, wide local excision.

Chemotherapy

All patients received multi-agent chemotherapy with vincristine, ifosfamide, and doxorubicin (Fig. 1). During radiation therapy, three patients received etoposide instead of doxorubicin because of concerns that doxorubicin might increase radiotoxicity; these cycles were administered after the efficacy of chemotherapy was evaluated and therefore were not included in the response evaluation. In addition, these cycles were excluded from the toxicity evaluation. Of the 11 patients, 10 received daily G-CSF after chemotherapy for at least 7 days, until the absolute neutrophil count exceeded 10,000. The one patient who did not receive G-CSF had no treatment-related neutropenia. Patients received a median of 6 courses of chemotherapy (range, 2–8 courses).

Toxicity

Including the 8 courses in which etoposide was substituted for doxorubicin (which were excluded from the toxicity analysis), 67 courses of chemotherapy were delivered to the 11 patients. Of 39 courses of VID chemotherapy for which complete blood counts were available, 29 (74%) were associated with grade 3 or 4 hematologic toxicity. In addition, 11 of these 29 courses led to both grade 3 or 4 neutropenia and thrombocytopenia. Grade 4 neutropenia was documented in 20/39 (51%) courses and grade 4 thrombocytopenia in 4/39 (10%).

The median absolute neutrophil count nadir for evaluable courses of VID leading to grade 3 or 4 neutropenia was 138/mm^3 (range, 0–810/mm^3). The median duration of grade 4 neutropenia was 4.5 days (range, 2–10 days). The median platelet nadir for evaluable courses of VID associated with grade 3 or 4 thrombocytopenia was 26,000/mm^3 (range, 8,000–48,000/mm^3). The median duration of grade 4 thrombocytopenia was 2 days (range, 2–3 days).

Seven patients (nos. 2, 4, 5, 6, 8, 10, and 11) were admitted for 1 to 5 episodes of fever and neutropenia; 1

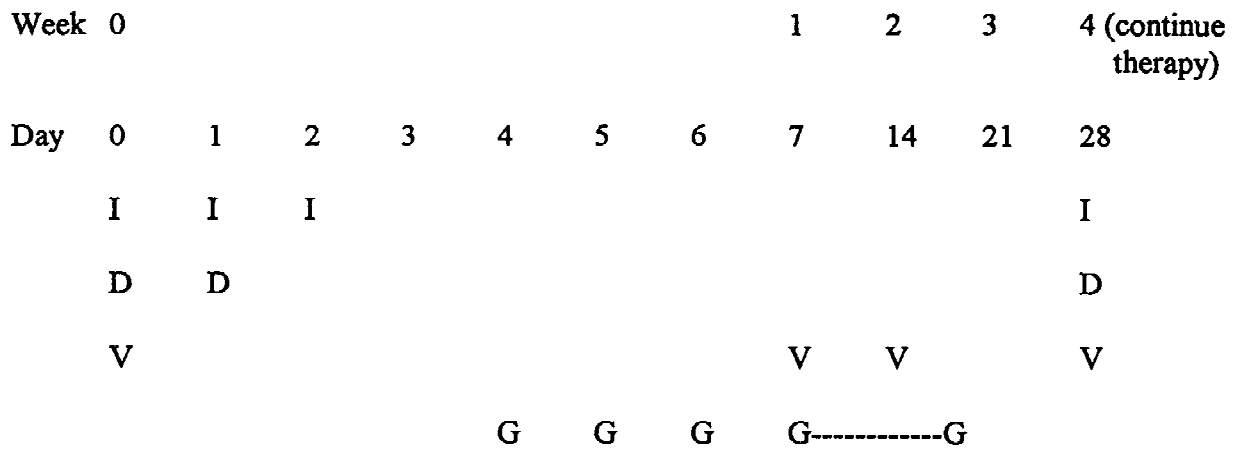

Fig. 1. Schedule of VID chemotherapy for PRNSTS. Each cycle lasts 4 weeks, and eight cycles are scheduled. Local control (including an attempt at gross total resection, if appropriate) is initiated at week 7 and is followed by radiation therapy. I, ifosfamide (3 g/m^2 IV) plus MESNA (750 mg/m^2 IV × 4 doses); D, doxorubicin (30 mg/m^2 IV); V, vincristine (1.5 mg/m^2 IV, maximum dose = 2 mg); G, G-CSF (5 to 10 μg/kg subcutaneously daily for 14 days).

patient (no. 11) had mild hypotension concurrently with his febrile episode. There were 4 instances of grade 2 vincristine neuropathy, 3 occurrences of mild metabolic abnormalities, and 1 case each of hemorrhagic cystitis, hypertension secondary to steroids, poor wound healing at an irradiated resection site, grade 3 radiation-induced dermatitis, radiation enteritis, and radiation pneumonitis. One child had a catheter-related infection, and another experienced a transient decrease in cardiac shortening fraction (identified by echocardiography) after the first cycle of chemotherapy. The shortening fraction subsequently normalized, and doxorubicin was successfully reintroduced. Five patients required nutritional support because of weight loss ⩾10%; 3 of these patients received supplemental feeds through a nasogastric tube for 1, 3, or 4 cycles, and the remaining 2 children required total parenteral nutrition for 1 or 4 cycles.

Outcome

All of the 6 patients who had CG I or II disease are alive, off therapy, and free of disease. Of the 5 patients diagnosed with CG III and IV disease, 2 are off therapy, alive, and disease-free. Another 2 of these patients are alive with stable disease 23 months and 30 months after diagnosis; these children had distant failures at 7 and 21 months, respectively. The remaining patient died due to progressive local disease 8 months after diagnosis. Overall, 10 of 11 patients survive at a median of 30 months (range, 22–54 months).

All 6 patients with CG I or II disease were free of disease (confirmed by imaging) after resection at diagnosis and therefore could not be evaluated for response to chemotherapy. One CG III patient (no. 7) received radiation therapy during his first cycle of chemotherapy; response to chemotherapy could not be evaluated for this child. He remains alive and well, with no evidence of disease. The remaining 4 CG III and IV patients were evaluable for response to chemotherapy, 3 (nos. 8, 9, and 10) for response at the primary site and 1 (no. 11) for response at metastatic sites. Of these patients, 3 (nos. 8, 9, and 11) had stable disease and 1 (no. 10) had a partial response.

DISCUSSION

High-grade STS are aggressive locally infiltrative neoplasms. Tumor grade in PNRSTS (and in STS in general) is highly predictive of biological behavior, morbidity, and mortality [31]. In a review of prognostic factors influencing survival in PNRSTS [11], Rao et al. found that among 52 children with high-grade (grade 3) lesions treated with chemotherapy and/or radiotherapy, 38 patients (73%) had progressive disease despite therapy. Only 31% of the 41 patients with grade 1 or 2 lesions had progressive disease after therapy.

Improvements in the local control of high-risk sarcomas has done little to help decrease the morbidity and mortality from high-grade sarcomas. The inability to control distant metastatic disease continues to be a major cause of treatment failures, and previous attempts to limit distant treatment failures through chemotherapy have had little success. A report from the Pediatric Oncology Group describing the therapy of patients with CG I or II PNRSTS confirmed the poor prognosis associated with grade 3 PNRSTS and the marginal efficacy of chemotherapy. In addition, most of the failures among the patients with grade 3 lesions were distant (disease metastatic to lung), highlighting the importance of improving the chemotherapy regimen [32]. The 3-year event-free survival (EFS) in those patients with grade 3 lesions was

61%. A companion protocol that enrolled patients with high-risk CG III or IV PNRSTS demonstrated a 4-year EFS of approximately 20% (Charles Pratt, personal communication).

Few pediatric trials have attempted to deliver intensive multi-agent chemotherapy to decrease metastatic disease while using aggressive surgery and radiation therapy to control local disease [12,13]. Our treatment regimen combines dose-intensive ifosfamide-based chemotherapy with aggressive surgical resection and radiation therapy to treat high-risk patients with PNRSTS. Ifosfamide has significant activity against sarcomas [26,33,34] and is more effective in the treatment of sarcomas when used in a multi-agent regimen, especially when combined with doxorubicin in a dose-intensive fashion [7,9,26,34–38]. Vincristine was included because of its activity against pediatric sarcomas, relative lack of myelosuppression, and potential for greater efficacy using a weekly schedule of administration [39]. Granulocyte colony stimulating factor (G-CSF) was administered daily after chemotherapy to decrease the morbidity associated with this treatment [40–42].

Although 10 of our 11 patients remain alive at 30 months after diagnosis, the efficacy of this adjuvant chemotherapy in treating high-risk sarcomas remains unproved. The therapy was generally well tolerated. The most common toxicity was grade 4 neutropenia (51% of evaluable courses). Despite frequent and profound neutropenia, none of our patients had any sepsis or other serious infections.

In summary, the use of VID chemotherapy was frequently associated with moderate to profound cytopenias. However, the primarily hematologic toxicities were usually well tolerated and reversible, and generally not associated with morbidity. Although the value of adjuvant chemotherapy for children with high-risk PNRSTS remains unproved, we are encouraged by the rate of tumor control in this pilot study and plan to investigate the potential benefits of VID chemotherapy with a prospective multi-institutional trial.

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