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VIP (etoposide, ifosfamide, and cisplatin) in patients with previously treated soft tissue sarcoma

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Abstract

We retrospectively reviewed outcomes of treatment with VIP (combination of etoposide, ifosfamide, and cisplatin) in patients with previously treated soft tissue sarcoma (STS).

We analyzed the medical records of patients with advanced or relapsed STS who had undergone VIP treatment as second-line or more chemotherapy between January 2000 and December 2015. The patients were treated with a combination of etoposide (100 mg/m^2 for 5 days), ifosfamide (2000 mg/m^2 for 2 days), and cisplatin (20 mg/m^2 for 5 days) once every 4 weeks. Treatment response, progression-free survival (PFS), and overall survival (OS) were analyzed in all patients and between responder and nonresponder groups (responders showed a tumor response to any prior systemic chemotherapy before VIP).

Twenty-four patients with a median age of 50 years (range: 20–68 years) were treated with VIP. Eleven (45.8%) patients were male and 7 (29.2%) received 2 or more chemotherapy regimens before VIP. Median PFS was 3.7 months (95% confidence interval [CI], 1.3–6.1 months) and median OS was 10.0 months (95% CI, 6.6–13.5). The overall response rate was 37.5%, and the disease control rate was 50%. The responder group showed better PFS (7.7 months vs 3.0 months; $P=0.101$) and significantly improved OS (11.0 months vs 8.8 months; $P=0.039$) compared to those of nonresponders. All patients reported some grade of hematological toxicity. The most frequently encountered hematological toxicity was neutropenia (any grade, 77.7%; grade 3 or 4, 74.0%).

VIP might be effective in patients with previously treated STS.

Abbreviations: AD = adriamycin, dacarbazine, AI = adriamycin, ifosfamide, ANC = absolute neutrophil count, BCD = bleomycin, cyclophosphamide, dactinomycin, CI = confidence interval, CR = complete response, CTCAE = Common Terminology Criteria for Adverse Event, CYVADIC = cyclophosphamide, vincristine, adriamycin, dacarbazine, EP = etoposide, cisplatin, GD = gemcitabine, docetaxel, HR = hazard ratio, IE = ifosfamide, etoposide, IP = ifosfamide, cisplatin, MAID = mesna, adriamycin, ifosfamide, dacarbazine, NOS = not otherwise specified, OR = objective response, OS = overall survival, P = paclitaxel, PCb = paclitaxel, carboplatin, PD = progressive disease, PFS = progression-free survival, PR = partial response, R = recurrence, RECIST = Response Evaluation Criteria in Solid Tumor, RT = radiotherapy, SD = stable disease, STS = soft tissue sarcoma, VAC = vincristine, adriamycin, cyclophosphamide, VIP = etoposide, ifosfamide, cisplatin.

Keywords: chemotherapy, cisplatin, etoposide, ifosfamide, soft tissue sarcoma

1. Introduction

Soft tissue sarcomas (STS) are rare, accounting for 1% of all malignant tumors, and are a group of mesenchymal neoplasms that have traditionally been managed by wide excisional surgery and radiotherapy. Chemotherapy has been reserved for advanced disease.[1–3] However, approximately 40% of patients experience tumor recurrence and median overall survival (OS) <12 months.[4]

STS has been classified into over 50 subtypes, which differ in terms of treatment response and prognosis.[2] For example, angiosarcomas respond to paclitaxel,[5–7] and uterine leiomyosarcomas show a good response to gemcitabine combined with docetaxel.[8] The profound heterogeneity of sarcoma subtypes complicates clinical trials and interpretation of their results. Thus, systemic treatment options for STSs remain relatively limited, although the therapeutic choices for many solid tumors have expanded over the last decade.[9]

Doxorubicin- and/or ifosfamide-based regimens are the gold standard treatment for advanced STS.[4,10] A combination of both drugs as a first-line therapy accounts for an objective response (OR) of 23% to 48%.[10–13] The combination of doxorubicin, ifosfamide, and dacarbazine has a 47% response rate.[14] However, after failure of conventional first-line doxorubicin-based cytotoxic chemotherapy, available treatment options are limited because of the high risk-to-benefit ratio in terms of patient tolerability and survival.

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In 2000, an open-label, phase II trial with a combination of etoposide, ifosfamide, and cisplatin (VIP) as first-line treatment was reported for patients with locally advanced (inoperable) or metastatic STS with an overall response rate of 46% and manageable toxicity profiles.[15] In addition, another retrospective study reported that the VIP combination was active in patients with recurrent/refractory Ewing sarcoma family of tumors, with acceptable toxicity. In that study, a complete response (CR) was obtained in 4% of cases, and a partial response (PR) in 30%, with an overall response rate of 34%.[16] Therefore, based on these reports, it would be reasonable to expect a clinical benefit of VIP in previously treated patients with STS, for whom there is no established standard treatment.

Here, we present a retrospective analysis of VIP and treatment outcomes in patients with previously treated STS.

2. Methods

2.1. Patients

We collected and reviewed the medical records of patients diagnosed with STS treated with VIP from January 2000 to December 2015 at Chungnam National University Hospital, Daejeon, Republic of Korea.

We included patients ≥18 years of age with histologically proven STS and treated with VIP. Other inclusion criteria were having more than 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1); Eastern Cooperative Oncology Group performance score ≤2; treated with one or more prior systemic chemotherapies; white cell count >4000/mm^3; platelet count >100,000/mm^3; and creatinine clearance >50 mL/min. We excluded patients diagnosed with alveolar soft part sarcoma, clear cell sarcoma, and chondrosarcoma. This study was approved by the Institutional Review Board of Chungnam National University Hospital.

2.2. Treatment

The patients were treated with etoposide (100 mg/m^2 for 5 days), ifosfamide (2000 mg/m^2 for 2 days), and cisplatin (20 mg/m^2 for 5 days). Mesna (sodium-2-mercapto-ethansulfonate) was added to prevent ifosfamide-induced toxicity (Table 1). The 3 drugs were infused separately and cycles were repeated every 28 days. Cycles were delayed if the absolute neutrophil count (ANC) was <1500/mm^3 and/or platelet count was <100,000/mm^3 on the proposed day of treatment. All patients received prophylactic medication for chemotherapy-induced nausea/vomiting. Granulocyte colony stimulating factor was administered in patients with ANC <500/mm^3 or febrile neutropenia. Chemotherapy was continued until disease progression, unacceptable toxicity, or patient refusal.

Table 1

VIP dose and schedule.

Agent	Dose, mg/m^2/d	Schedule
Etoposide	100	Days 1–5
Ifosfamide	2000	Days 1–2
Cisplatin	20	Days 1–5
Mesna	1200	Days 1–2

VIP = etoposide, ifosfamide, cisplatin.

2.3. Response assessment

Response evaluations were made by clinical assessment and imaging studies after alternate cycles in the absence of overt progression. The treatment response was classified as CR, PR, stable disease (SD), or progressive disease (PD) according to the RECIST criteria[17] and toxicity was evaluated based on Common Terminology Criteria for Adverse Event (CTCAE v4.0; http://www.eortc.be/services/doc/ctc).

2.4. Statistical analysis

Basic descriptive statistics included medians with/without ranges. Differences between the 2 groups were tested using the *t* test or Wilcoxon rank-sum test for continuous variables and the Chi-square test for categorical variables. OS was defined as the time from initiating VIP treatment to the date of death or last follow-up. Progression-free survival (PFS) was defined as the time from initiating VIP treatment to the date of documented disease progression or death from any cause. PFS and OS were estimated by the Kaplan–Meier method with the log-rank test. A P-value < 0.05 was considered significant. SPSS for Windows software (ver. 22; SPSS, Inc., Chicago, IL) was used for all statistical analyses.

3. Results

3.1. Patient population

Twenty-four patients with advanced or relapsed STS were treated with VIP as an at-least second-line chemotherapy between January 2000 and December 2015. The characteristics of the

Table 2

Baseline patient characteristics.

Characteristics	N (%)
Total number	24
Gender	
Male	11 (45.8)
Female	13 (54.2)
Age (y; median, range)	50 (20–68)
Stage at initial diagnosis*	
I	6 (25.0)
II	3 (12.5)
III	6 (25.0)
IV	8 (33.3)
No. of prior systemic treatments	
1	17 (70.8)
≥2	7 (29.2)
Histology	
Myxofibrosarcoma	8 (33.3)
Liposarcoma	1 (4.2)
Leiomyosarcoma	5 (20.8)
Rhabdomyosarcoma	1 (4.2)
Synovial sarcoma	3 (12.5)
Ewing sarcoma	1 (4.2)
Angiosarcoma	2 (8.3)
Sarcoma NOS	3 (12.5)
Cumulative dose of VIP (%)	
100	7 (29.2)
75	15 (62.5)
50	2 (8.3)
Response status to prior systemic treatment	
Responder	13 (54.2%)
Nonresponder	11 (45.8%)

NOS = not otherwise specified, VIP = etoposide, ifosfamide, cisplatin.
* One patient was excluded due to missing data.

Table 3

Summary of patient characteristics.

Patient no.	Gender/age, y	Type	Primary site	Stage at initial diagnosis	Previous therapy	No. of prior chemotherapies	VIP treatment	
							Best response	Cycles
1	F/60	Synovial sarcoma	Inguinal area	IV	AI	1	PD	2
2	F/68	Myxofibrosarcoma	Thigh	IV	MAID → pazopanib	2	PR	6
3	F/54	Sarcoma NOS	Uterus	IB	IP → PCb → MAID	3	PR	6
4	F/59	Sarcoma NOS	Thigh	IB	BCD → (R) → MAID → RT → IE	3	PD	4
5	F/64	Myxofibrosarcoma	Heart	IA	MAID	1	SD	6
6	M/20	Ewing sarcoma	Thigh	IIB	VAC → EP	2	PR	5
7	M/54	Myxofibrosarcoma	Rectum	IA	MAID → RT → (R)	1	CR	2
8	F/34	Myxofibrosarcoma	Intraabdomen	IIB	MAID	1	PR	6
9	M/61	Myxofibrosarcoma	Knee	III	MAID	1	PD	2
10	F/47	Leiomyosarcoma	Uterus	IB	RT → (R) → CYVADIC	1	PD	3
11	M/40	Synovial sarcoma	Thigh	IIB	RT → MAID → (R)	1	PR	6
12	M/51	Angiosarcoma	Heart	IV	MAID	1	PR	4
13	M/36	Myxofibrosarcoma	Thigh	III	RT → MAID → (R)	1	PR	6
14	M/36	Liposarcoma	Inguinal area	III	RT → MAID → (R)	1	PD	3
15	F/62	Leiomyosarcoma	Uterus	*	AI → GD	2	PD	2
16	M/20	Rhabdomyosarcoma	Prostate	III	VAC	1	SD	3
17	F/48	Leiomyosarcoma	Stomach	IV	MAID	1	PD	2
18	M/49	Myxofibrosarcoma	Buttock	IV	MAID	1	PD	1
19	F/41	Synovial sarcoma	Inguinal area	III	RT → AI	1	PD	1
20	M/65	Myxofibrosarcoma	Trunk	IV	MAID	1	PD	2
21	F/51	Angiosarcoma	Heart	IV	P → AI	2	PD	2
22	F/45	Sarcoma NOS	Scalp	IV	AI	1	SD	2
23	F/48	Leiomyosarcoma	Uterus	IB	(R) → AI	1	PD	2
24	54/M	Leiomyosarcoma	Retroperitoneum	III	RT → (R) → AD → pazopanib → GD	3	PR	3

AD = adriamycin, dacarbazine, AI = adriamycin, ifosfamide, BCD = bleomycin, cyclophosphamide, dactinomycin, CR = complete response, CYVADIC = cyclophosphamide, vincristine, adriamycin, dacarbazine, EP = etoposide, cisplatin, GD = gemcitabine, docetaxel, IE = ifosfamide, etoposide, IP = ifosfamide, cisplatin, MAID = mesna, adriamycin, ifosfamide, dacarbazine, NOS = not otherwise specified, P = paclitaxel, PCb = paclitaxel, carboplatin, PD = progression disease, PR = partial response, R = recurrence, RT = radiotherapy, SD = stable disease, VAC = vincristine, adriamycin, cyclophosphamide, VIP = etoposide, ifosfamide, cisplatin.

* Missing data.

patients are listed in Table 2, and Table 3 shows the main features of each patient.

Median age was 50 years (range: 20–68 years), and 11 (45.8%) patients were male. The distribution of histological subtypes was as follows: myxofibrosarcoma (n = 8), liposarcoma (n = 1), leiomyosarcoma (n = 5), rhabdomyosarcoma (n = 1), synovial sarcoma (n = 3), Ewing sarcoma (n = 1), angiosarcoma (n = 2), and sarcoma not otherwise specified (NOS) (n = 3). All patients had previously received at least 1 cytotoxic chemotherapy regimen before the VIP treatment, and 7 (29.2%) had been heavily pretreated with at least 2 previous cytotoxic regimens. The VIP dose was reduced in 70.8% of patients (n = 17). Thirteen (54.2%) patients showed at least PR to prior systemic chemotherapy (responders) and 11 (45.8%) patients did not achieve any response to prior chemotherapy (nonresponders).

3.2. Tumor responses

CR was obtained in 1 (4.2%) patient and PR in 8 (33.3%) patients. The overall response rate was 37.5%, and the disease control rate was about 50% (Table 4). Although the response profile was not different between the 2 groups, responders showed more favorable results (overall response rate, 53.9% vs 18.2%, $P = 0.210$) (Table 5).

3.3. Survival outcomes

Median PFS was 3.7 months (95% confidence interval [CI], 1.3–6.1) (Fig. 1), and median OS was 10.0 months (95% CI, 6.6–13.5) (Fig. 2).

Responders showed a better median PFS (7.7 months vs 3.0 months; $P = 0.101$; hazard ratio [HR], 0.46; 95% CI, 0.17–1.18) (Fig. 3), and median OS improved significantly in responders compared to that in nonresponders (11.0 months vs 8.8 months; $P = 0.039$; HR, 0.35; 95% CI, 0.13–0.98) (Fig. 4). The estimated PFS and OS rates at 1 year were 9.8% and 36.5% for all patients, 17.1% and 46.2% for responders, 0% and 27.3% for nonresponders, respectively.

3.4. Laboratory toxicity

A total of 81 treatment cycles were administered (median 3 cycles/patient; range: 1–6 cycles/patient). Seven (29.2%) patients were treated with the target scheduled dose. All patients reported some grade of hematological toxicity. The most frequently encountered toxicity was neutropenia, which was estimated at 77.7% of any grade and 74.0% of grade 3 or 4 cases. Anemia was estimated at

Table 4

Best response to VIP.

Response	No. (%)
CR	1 (4.2)
PR	8 (33.3)
SD	3 (12.5)
PD	12 (50.0)

CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease, VIP = etoposide, ifosfamide, cisplatin.

Table 5

Best response to VIP according to response status to prior systemic treatment.

Response	Nonresponder No. (%)	Responder No. (%)	*P*
CR	0 (0)	1 (7.7)	
PR	2 (18.2)	6 (46.2)	
SD	1 (9.1)	2 (15.4)	
PD	8 (72.7)	4 (30.8)	0.210

CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease, VIP = etoposide, ifosfamide, cisplatin.

67.9% of any grade and 27.1% of grade 3 or 4 cases, and thrombocytopenia was estimated at 62.9% of any grade and 46.9% of grade 3 or 4 cases. Thirteen (16.0%) patients developed febrile neutropenia. The nonhematological toxicities were relatively tolerable, with increased creatinine in 11.1% of grade 1 or 2 cases, and increased alanine aminotransferase in 7.4% of grade 1 or 2 and 1.2% of grade 3 or 4 cases (Table 6).

4. Discussion

Surgery with or without radiotherapy is the best option for curing STS in the absence of metastatic disease. The 5-year survival rate of patients with operable disease is about 60%. However, median OS is <1.5 years in patients with inoperable disease.[18,19] Surgery to salvage a limb may be useful for locally recurrent disease, and radiotherapy may allow substantial control of symptoms in patients with inoperable localized symptomatic disease. Adjuvant chemotherapy generally does little to influence the natural history of the disease, except for rhabdomyosarcomas and Ewing sarcomas.[18] Although some STS subtypes are sensitive to chemotherapy, the outcome of therapeutic chemotherapy is unsatisfactory overall.[9]

Doxorubicin and ifosfamide, either alone or in combination, are the gold standard chemotherapy for advanced STS. Beyond standard systemic treatment, commonly used second-line regimens include gemcitabine or gemcitabine plus docetaxel. The combination of gemcitabine and docetaxel demonstrates in vitro synergism in sarcoma cell lines,[20] suggesting that this combined regimen is promising in patients with STS who have failed doxorubicin- and ifosfamide-based therapy. In a phase II study, a fixed-dose rate of gemcitabine plus docetaxel was evaluated as second-line chemotherapy in patients with metastatic uterine leiomyosarcoma.[21] The OR rate was 27%, and median OS was 14.7 months. In addition, another phase II study reported that the gemcitabine-docetaxel combination showed superior PFS and OS (6.2 and 17.9 months) compared to gemcitabine alone (3.0 and 11.5 months).[22] In contrast, Pautier et al[23] reported no benefit of the combined regimen, as median PFS was 5.5 months for gemcitabine alone versus 4.7 months for gemcitabine plus docetaxel in patients with uterine leiomyosarcomas, and 6.3 months versus 3.8 months in patients with nonuterine leiomyosarcomas. Hence, these agents have not been officially approved to treat advanced STS, and the response may differ in histological subsets.

New agents, such as pazopanib, a multitargeted tyrosine kinase inhibitor, have been assessed for treating metastatic non-

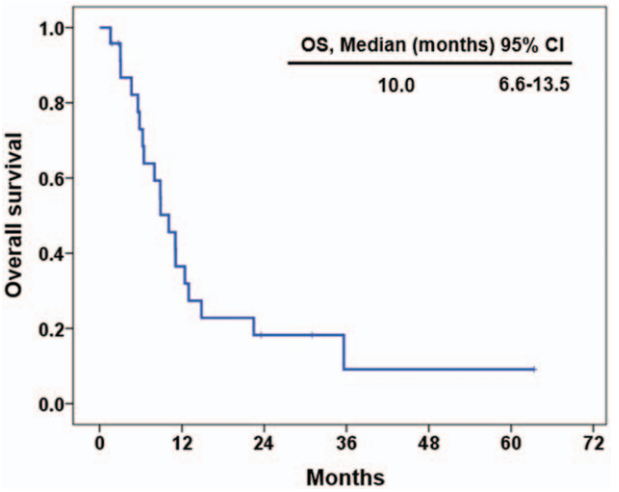

Figure 2. Overall survival for all patients (n = 24).

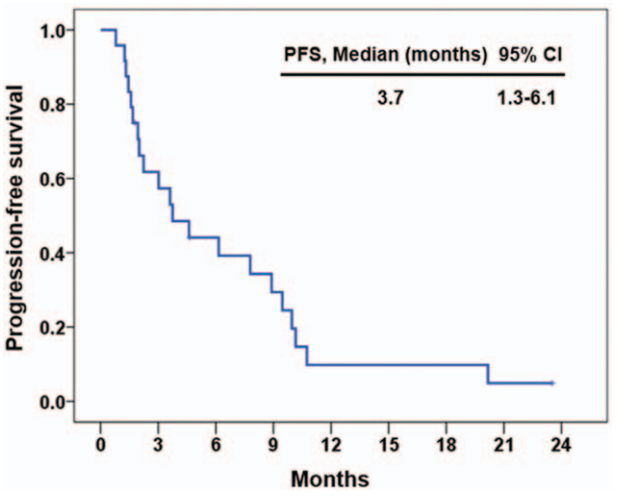

Figure 1. Progression-free survival for all patients (n = 24).

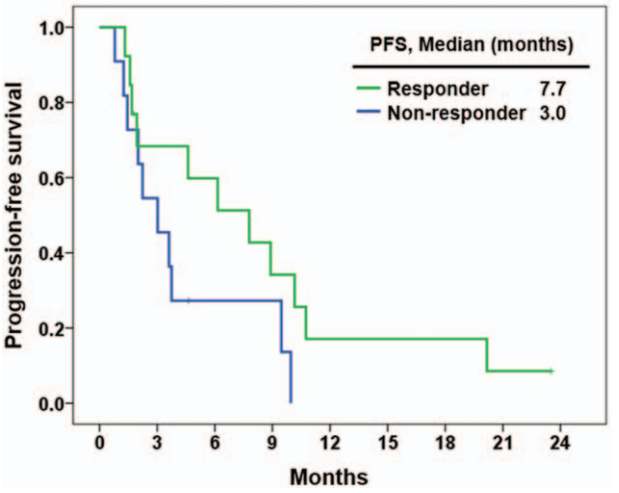

Figure 3. Progression-free survival between responder (n = 13) and non-responder (n = 11) groups.

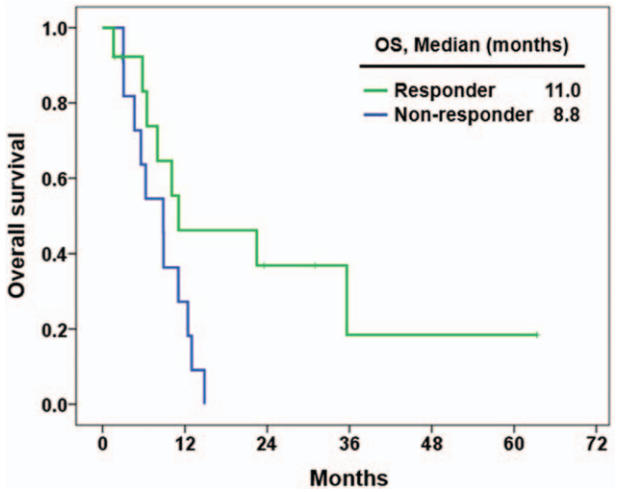

Figure 4. Overall survival between responder (n = 13) and nonresponder (n = 11) groups.

adipocytic STS after failure of standard chemotherapy. In a phase III trial, pazopanib significantly improved PFS compared with placebo (4.6 months vs 1.6 months; $P < 0.001$); however, OS was not different (12.5 months vs 10.7 months; $P = 0.25$).[19] Therefore, available standard treatment options remain limited after failure of first-line doxorubicin- and/or ifosfamide-based cytotoxic chemotherapy.

Cisplatin is a widely used antineoplastic drug with broad clinical activity. A small trial of cisplatin in patients with metastatic STS, who failed 2 previous chemotherapy regimens, reported an overall response rate of about 30%.[24] Another phase II trial with cisplatin as second-line treatment for advanced or recurrent uterine leiomyosarcoma reported an overall response rate of about 5%.[25] Therefore, cisplatin monotherapy was insufficient for palliative chemotherapy in patients with STS. A phase II study conducted a few years later reported that the combination of ifosfamide and cisplatin showed a 50% response rate in patients with Ewing sarcoma.[26] In addition, a few trials have reported that VIP shows favorable outcomes in patients with recurrent solid tumors and hematological malignancies.[27,28] Based on these results, further studies are needed to investigate the VIP regimen in patients with STS. A phase II trial of VIP for previously untreated patients with inoperable/metastatic STS demonstrated an overall response rate of 46% (CR, 10% and PR, 36%), and mean OS was 8 months.[15] A retrospective study reported that VIP for recurrent/refractory Ewing sarcoma family of tumors has an overall response rate of 34% (CR, 4% and PR, 30%), PFS of 6.6 months, and OS of 12.8 months.[16] Based on these studies, VIP appears promising to treat patients with STS who failed first-line systemic chemotherapy.

Table 6

Laboratory toxicities (total 81 VIP cycles).

Toxicity	Grade 1 or 2 No. of cycles (%)	Grade 3 or 4 No. of cycles (%)
Hematologic		
Neutropenia	63 (77.7)	60 (74.0)
Anemia	55 (67.9)	22 (27.1)
Thrombocytopenia	51 (62.9)	38 (46.9)
Febrile neutropenia	—	13 (16.0)
Nonhematologic		
Creatinine increased	9 (11.1)	0
Alanine aminotransferase increased	6 (7.4)	1 (1.2)

VIP = etoposide, ifosfamide, cisplatin.

This is the first report demonstrating a clinical benefit of the VIP regimen in patients with previously treated STS. In this study, we report a 37.5% overall response (which was comparable to a previous report of VIP treatment in patients with the recurrent/refractory Ewing sarcoma family of tumors), median PFS of 3.7 months and median OS of 10.0 months. In addition, patients who responded to previous chemotherapy before VIP showed better PFS and significantly improved OS compared with those of nonresponders.

We evaluated laboratory toxicities because of the retrospective nature of this study. All patients reported some grade of hematological toxicity; 74.0% had grade 3/4 neutropenia, 27.1% had grade 3/4 anemia, 46.9% had grade 3/4 thrombocytopenia, and 16% had febrile neutropenia. This result is higher than previously reported toxicity results for this combined treatment. We assumed that this was because the majority of our patients had already been heavily treated.

Several potential limitations of the present study should be considered. First, it was a single-institution, retrospective, observational analysis which has the potential for selection biases. Second, the small sample size could preclude strong conclusions and a response assessment based on the different histological subtypes was not possible. Furthermore, the heterogeneity of treatment regimens before and after VIP may have affected the treatment outcomes, even if all of the patients received doxorubicin-based chemotherapy as first-line treatment. The heterogeneity of conservative treatments may also have influenced the difference in outcomes. Hence, a prospective, well-designed controlled trial is strongly needed, particularly in patients with a homogenous histological type of STS.

In conclusion, although the small number of patients and retrospective nature of the study are major limitations, the VIP combination might be active in patients with previously treated STS. Notably, it is reasonable to use VIP in patients showing at least a PR to prior chemotherapy. However, hematological toxicity must be considered.

Acknowledgments

The patient data reported herein were derived from a follow-up study approved by the Institutional Review Board of Chungnam National University Hospital, and patients signed appropriate informed consent forms for therapy.

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