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A Phase II Study of Gemcitabine, Vincristine, and Cisplatin As Second-Line Treatment for Patients With Advanced Soft Tissue Sarcoma

Zhiguo Luo, Xiaowei Zhang, Wei Peng, Xianghua Wu, Huijie Wang, Hui Yu, Jialei Wang, Jianhua Chang, and Xiaonan Hong

Abstract: Patients with advanced soft tissue sarcoma (aSTS) typically have a poor prognosis. Patients progressing to doxorubicin-based regimen have limited therapeutic options. Monotherapy with cytotoxic drugs appears to have only modest activity in the second-line setting. The purpose of this phase II study was to prospectively evaluate the safety and efficacy of combination regimen with gemcitabine, vincristine, and cisplatin (GVP) as a salvage treatment for patients with aSTS.

Eligible patients were female aged 18∼75 years, and had aSTS that had progressed after 1 prior anthracyclines-based chemotherapy regimen. Patients were treated with 1000 mg/m^2 gemcitabine intravenously (IV) on days 1 and 8, 1.4 mg/m^2 (max 2 mg) vincristine IV on day 1 and 25 mg/m^2 cisplatin IV on days 1 through 3 every 21 days until disease progression, unacceptable toxicity or up to 6 cycles. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), over response rate (ORR), and safety. This trial was registered with www.clinicaltrials.gov (no. NCT01192633).

A total of 26 patients with a median age 47 years (21–72) were recruited. ORR was 23.1% (1 complete response and 5 partial responses). The median PFS and OS were 4.8 (95% confidence interval [CI], 0.1–9.5) months and 15.0 (95% CI, 6.1–23.9) months, respectively. Grade 3/4 hematologic toxicities included neutropenia (34.6%), leukopenia (23.1%), thrombocytopenia (11.5%), and anemia (3.8%). No febrile neutropenia and grade 3/4 nonhematologic toxicities occurred. The most frequent nonhematologic toxicities were nausea/vomiting (50.0%), fatigue (30.8%), and fever (11.5%).

We conclude that GVP regimen is effective with a favorable safety profile as the second-line chemotherapy in aSTS patients, which warrants further investigation in a phase III study.

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Abbreviations: AE = adverse event, ANC = absolute neutrophil count, Asts = advanced soft tissue sarcoma, CR = complete response, CT = computed tomography, IV = intravenously, LMS = leiomyosarcoma, MFH = malignant fibrous histiocytoma, MRI = magnetic resonance imaging, ORRs = overall response rates, OS = overall survival, PFS = progression-free survival, PR = partial response, PS = performance status, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease, STSs = soft tissue sarcomas, ULN = upper limit of normal.

INTRODUCTION

Soft tissue sarcomas (STSs) are relatively rare and heterogeneous malignancies originating from mesenchymal cell with distinct clinical and pathological features. STSs account for <1% of all new cancer cases each year, but have an aggressive biologic behavior and poor prognosis.[1] More than 50 histological subtypes have been identified, including leiomyosarcoma (LMS), liposarcoma, synovial sarcoma, alveolar soft part sarcoma, angiosarcoma, fibrosarcoma, malignant fibrous histiocytoma (MFH), and pleomorphic undifferentiated sarcoma. Approximately, half of STS patients are diagnosed with advanced disease or will develop recurrent metastasis after surgery and/or chemotherapy.[2] In these patients not amenable to surgery, chemotherapy is almost the only available treatment with median survival estimated to be about 12 months from diagnosis of metastasis.[3] Until recently, a limited number of drugs have been available for these patients with advanced soft tissue sarcoma (aSTS). Doxorubicin and/or ifosfamide-based regimens with well-established activity constitute the standard treatment in the first-line setting. Patients progressing to these 2 drugs have limited therapeutic options.

A small number of drugs have been incorporated into the second-line treatment of sarcomas. Gemcitabine, temozolomide, ifosfamide, dacarbazine, vincristine, taxanes, platinums as well as trabectedin are promising cytotoxic drugs that have shown variable degrees of efficacy in phase II-III studies.[4] All these drugs appear to have only modest activity given as monotherapy. For example, the overall response rates (ORRs) of gemcitabine single agent in second-line treatment of aSTS have been reported from 6% to 22% with the progression-free survival (PFS) of about 3 months.[4] Therefore, it is necessary to identify new combinations to improve therapy for patients with aSTS. Previous preclinical study indicated that the drug combination (gemcitabine plus cisplatin, GP) produced a synergistic response (data not shown). Furthermore, vincristine has a different tumor suppression mechanism, which inhibits microtubule dynamics and is less likely to cause bone marrow suppression, which made the new regimen GP plus vincristine (GVP) worthy of being investigated. Here, we aimed to assess the safety and efficacy of combination regimen of GVP as a salvage treatment for patients with aSTS (ClinicalTrials.gov identifier, NCT01192633).

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From the Department of Medical Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, shanghai, China.
Correspondence: Xiaonan Hong, Department of Medical Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, No. 270 Dong'an Rd, Shanghai 200032, China (e-mail: xnhong@126.com).
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PATIENTS AND METHODS

Patients

The main inclusion criteria were unresectable or metastatic STS with previous treatment with anthracyclines-based regimen, 18 to 75 years of age, at least 1 extracranial measurable lesion by MRI or CT according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1), Eastern Cooperative Oncology Group performance status of 0 to 2, $\leq$1 prior regimen of chemotherapy for advanced disease, no anticancer treatment for at least 4 weeks before enrollment in the study, a life expectancy $\geq$3 months, adequate hematologic, renal, and hepatic function, as indicated by hemoglobin $\geq$8 g/dL, absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ cells/L, platelet count $\geq 80 \times 10^9$ cells/L, total serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), aspartate transaminase/alanine transaminase $\leq 2.5 \times$ ULN ($\leq 5 \times$ ULN if hepatic disease involvement present), alkaline phosphatase $\leq 2.5 \times$ ULN ($\leq 5 \times$ ULN if hepatic disease involvement present and $\leq 10 \times$ ULN if bone disease involvement present), serum creatinine $\leq 1.25 \times$ ULN, or calculated creatinine clearance $\geq$65 mL/min.

Patients with primitive neuroectodermal tumor, Ewing sarcoma, embryonal rhabdomyosarcoma, chondrosarcoma, osteosarcoma, and gastrointestinal stromal tumor were not eligible. Other exclusion criteria included prior exposure to gemcitabine, vincristine, or cisplatin, known CNS metastases, participation in any other clinical trials within 28 days of enrollment, previous or concomitant malignant disease (with the exception of cervical carcinoma in situ and cutaneous basal cell carcinoma), grade $\geq$2 peripheral neuropathy, uncontrolled severe infections, significant cardiac disease, and pregnant or lactating women.

Independent ethics committees of Fudan University Shanghai Cancer Center approved the study protocol. We did the study in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Treatment

Patients were treated with 1000 mg/m^2 gemcitabine intravenously (IV) on days 1 and 8, 1.4 mg/m^2 (max 2 mg) vincristine IV on day 1 and 25 mg/m^2 cisplatin IV on days 1 through 3 every 21 days until disease progression, unacceptable toxicity or up to 6 cycles (Supplementary Figure 1, http://links.lww.com/MD/A470). Patients were required to have an adequate absolute neutrophil ($\geq 1.5 \times 10^9$/L) and platelet count ($\geq 75 \times 10^9$/L) before day 1 of each cycle. The following recommendations for chemotherapy dose reductions were applied. In patients who experienced grade 4 haematological, grade 3/4 non-haematological, or other protocol-specified toxicities, gemcitabine, vincristine, and cisplatin treatment was interrupted. When the toxicity resolved to grade $<$2, the dose of gemcitabine and cisplatin was restarted at 75% of the original dose at the first appearance of the respective toxicity and at 50% of the starting dose at the second appearance. Vincristine was reduced only when grade 3/4 nonhematological toxicities occurred. If whole blood count was low, day 8 gemcitabine could be postponed for at most 7 days to allow recovery, otherwise it would be cancelled. Maximum delay for GVP regimen was 14 days. Treatment was permanently discontinued if dose modification of greater than twice was required. Patients would discontinue only 1 drug if 1 specific severe adverse event (AE) was judged to be related to that particular drug. Administration of prophylactic G-CSF was not permitted in the study.

Assessment

Pretreatment assessment included a detailed medical history, physical examination, routine laboratory tests, and performance status. Laboratory evaluation included a routine blood count, biochemistry including electrolytes, renal and liver function tests, and urinalysis. AEs and concomitant medications were recorded at the end of each cycle throughout the study period until 30 days after the last dose of a study treatment was administered. Toxicity was evaluated and graded according to National Cancer Institute Common Terminology Criteria for AEs, version 4.0.

Radiographic scans (CT scan or MRI) for efficacy evaluation were conducted at baseline and every 2 treatment cycles until disease progression according to RECIST 1.1. The best overall response was reported. Survival status was assessed every 2 months after disease progression.

Statistical Methods

The primary endpoint was PFS defined as the time from the date of enrollment to progression or death from any cause. Secondary endpoints included overall survival (OS, time from enrollment to death from any cause), ORR (complete response and partial response), and safety.

The sample size was based on testing the hypothesis that GVP given for aSTS pretreated with anthracyline-based chemotherapy may be superior to single agent gemcitabine given to comparable set of patients. The median PFS for patients receiving gemcitabine was assumed to be 3.0 months.[5,6] Therefore, the null hypothesis of PFS of $\leq$3.0 months was tested against the alternative hypothesis of a true PFS of 4.8 $\geq$months with GVP regimen. The sample size was calculated as 26 patients, with a 2-sided alpha-level of 0.05 and 70% power (48 months' enrollment duration, 12 months follow-up duration after enrollment).

All statistical analyses were carried out using SPSS 19.0 (SPSS, Inc, Chicago, IL). Statistical analysis of 2×2 contingency tables of categorical variables was carried out using the Pearson χ^2 test (or Fisher exact test when appropriate). Time-to-event variables were summarized using the Kaplan-Meier method.

RESULTS

Patients

Between March 2009 and July 2013, 26 patients with a STS were recruited. Patient characteristics are listed in Table 1. The median age was 47 years (range: 21–72). Six (23.1%) had LMS, 3 (11.5%) liposarcoma, 3 (11.5%) alveolar soft part sarcoma, 2 (7.7%) angiosarcoma, and 12 (46.2%) other histologic types. Only 2 patients (7.7%) had locally advanced disease, and the remainder had relapsed or metastatic diseases. The majority (73.1%) of tumors were histologically grade 3. All patients had been exposed to anthracyclines-based regimen regimens.

Efficacy

The median number of treatment cycles was 4 (range: 1–6 cycles). The outcome of the patients treated with GVP as salvage chemotherapy was presented in Table 2. Of the 26 patients, 1 (3.8%) achieved complete response (CR), 5 (19.2%) partial response (PR), and 11 (42.3%) stable disease (SD) with the ORR of 23.1% and disease control rate of 65.4%. Both the 2 patients with angiosarcoma who had progressed to MAID (mesna, anthracycline, ifosfamide, and dacarbazine) regimen responded to GVP (1 CR and 1 PR). Of the 8 patients with

TABLE 1. Patient Characteristics at Baseline

Characteristics	No. (%)
Patients enrolled	26
Male	11 (42.3)
Female	15 (57.7)
Age, y	
Median (range)	47 (21–72)
ECOG performance status	
0	13 (50.0)
1	12 (46.2)
2	1 (3.8)
Histologic type	
Leiomyosarcoma	6 (23.1)
Liposarcoma	3 (11.5)
Alveolar soft part sarcoma	3 (11.5)
Angiosarcoma	2 (7.7)
Fibrosarcoma	1 (3.8)
Synovial sarcoma	1 (3.8)
Clear cell sarcoma	1 (3.8)
Sarcoma epithelioides	1 (3.8)
Malignant fibrous histiocytoma	1 (3.8)
Undifferentiated sarcoma	1 (3.8)
Other or unclassified	6 (23.1)
Grade of malignancy	
1	1 (3.8)
2	6 (23.1)
3	19 (73.1)
Site of the primary tumor	
Extremity/superficial trunk	10 (38.5)
Retroperitoneal/intra-abdominal	4 (15.4)
Fossa axillaris	2 (7.7)
Buttocks	2 (7.7)
Head/Neck	1 (3.8)
Breast	1 (3.8)
Esophagus	1 (3.8)
Lung	1 (3.8)
Uterus	1 (3.8)
Ovary	1 (3.8)
Seminal vesicle	1 (3.8)
Others	1 (3.8)
Disease status	
Locally advanced	2 (7.7)
Relapsed or metastatic	24 (92.3)

ECOG = Eastern Cooperative Oncology Group, No = number.

primary extremity sarcomas, 2 (25.0%) achieved PR and 5 (62.5%) achieved SD. After a median follow-up of 22.6 months, the median PFS and OS were 4.8 (95% CI, 0.1–9.5) months and 15.0 (95% CI, 6.1–23.9) months, respectively (Fig. 1).

Toxicity

Toxicity profile of the combination was acceptable and manageable. The most common AEs were presented in Table 3. Grade 3/4 hematologic toxicities included neutropenia (34.6%), leukopenia (23.1%), thrombocytopenia (11.5%), and anemia (3.8%). No grade 3/4 nonhematologic toxicities occurred. The most frequent nonhematologic toxicities were nausea/vomiting (50.0%), fatigue (30.8%), and fever (11.5%). Dose adjustment due to AEs occurred in 11 patients (42.3%). There were no treatment-related deaths.

DISCUSSION

The primary purpose of therapy for aSTS is palliation.[7,8] Current treatment for unresectable or metastatic STS is not only dictated by the histological subtype of sarcoma, but also by location of metastatic sites, tumor size, and the pathological grade.[7–9] Cytotoxic chemotherapy is still the main systemic treatment, with little dedicated biological agents currently available. According to the European Society for Medical Oncology and the National Comprehensive Cancer Network treatment guidelines, anthracycline monotherapy or anthracycline-based regimen (mainly combined with ifosfamide) was recommended as the first-line regimen for most subtypes of aSTS.[8,10] However, after treatment failure of doxorubicin and/or ifosfamide, no standard recognized therapeutic options exist.

The combination of gemcitabine, vincristine, and cisplatin may have a relatively important role for patients with aSTS who have failed to doxorubicin-based regimens. In our study, this regimen has shown a total response rate of 23.1%, a disease control rate of 65.4%, a median PFS of 4.8 months, and a median OS of 15.0 months in an unselected cohort of patients with aSTS including different histological subtypes. Both the PFS and OS were particularly promising and these results could be decisive for second-line treatment of patients with pretreated aSTS.

As a limitation, it should be noted that the range of different tumor types included in this study was relatively wide. However, the results of the study suggested which subtypes might better respond to GVP regimen and require further confirmation. Actually, the subtypes comprising the group of STSs differ strongly in their sensitivity to the different drugs or combinations. Selection of cytotoxic chemotherapy for patients with different types of aSTS is increasingly driven by histological subtype considerations.[11–13] Prior experience indicated that LMS and MFH are relatively responsive to gemcitabine-docetaxel (GD) chemotherapy. However, in our study, angiosarcoma was the most sensitive subtype to the treatment of GVP (ORR 100%). On the contrary, no response was found in patients with LMS or MFH when salvage GVP was administered. The reason why angiosarcoma responded better to this combination is unknown. Hence, this subtype should be separately tested in future clinical trials.

GD or GD-based regimens[13–23] had been widely investigated as the salvage treatment for patients with aSTS. The ORR and PFS in our study were almost comparable with those with GD-based regimens; however, the side effect results of our study were relatively lower. In our study, the most common hematologic and nonhematologic toxicities were neutropenia (34.6%) and nausea/vomiting (50.0%), respectively. There was no toxicity-related death. The toxicity profile of GVP was as expected, generally self-limiting, and well manageable, with no new safety observations.

Recently, in the Phase III PALETTE study, pazopanib, a new oral selective tyrosine kinase inhibitor for the treatment of aSTS (excluding GIST, liposarcoma and other subtypes), has successfully demonstrated significant PFS prolongation compared with placebo (4.6 vs 1.6 months, $P < 0.001$).[24] However, it is not commercially available in China and salvage chemotherapy still remains the standard therapy. The traditional

TABLE 2. Summary of Efficacy

	CR, N (%)	PR, N (%)	SD, N (%)	PD, N (%)	*P*
All patients (N = 26)	1 (3.8)	5 (19.2)	11 (42.3)	9 (34.6)	
Histologic type					0.165
Leiomyosarcoma	0	0	4 (66.7)	2 (33.3)	
Liposarcoma	0	0	1 (33.3)	2 (66.7)	
Alveolar soft part sarcoma	0	0	2 (66.7)	1 (33.3)	
Angiosarcoma	1 (50.0)	1 (50.0)	0	0	
Malignant fibrous histiocytoma	0	0	1 (100.0)	0	
Others	0	4 (36.4)	3 (27.3)	4 (36.4)	
Grade					0.860
1	0	0	1 (100.0)	0	
2	0	1 (16.7)	3 (50.0)	2 (33.3)	
3	1 (5.3)	4 (21.1)	7 (36.8)	7 (36.8)	
Site of the primary tumor					0.493
Extremity/Superficial trunk	0	3 (30.0)	5 (50.0)	2 (20.0)	
Retroperitoneal/Intra-abdominal	0	1 (25.0)	2 (50.0)	1 (25.0)	
Fossa axillaris	0	1 (50.0)	0	1 (50.0)	
Buttocks	0	0	0	2 (100.0)	
Others	1 (12.5)	0	4 (50.0)	3 (37.5)	

CR = complete response, OS = overall survival, PD = progressive disease, PFS = progression free survival, PR = partial response, SD = stable disease.

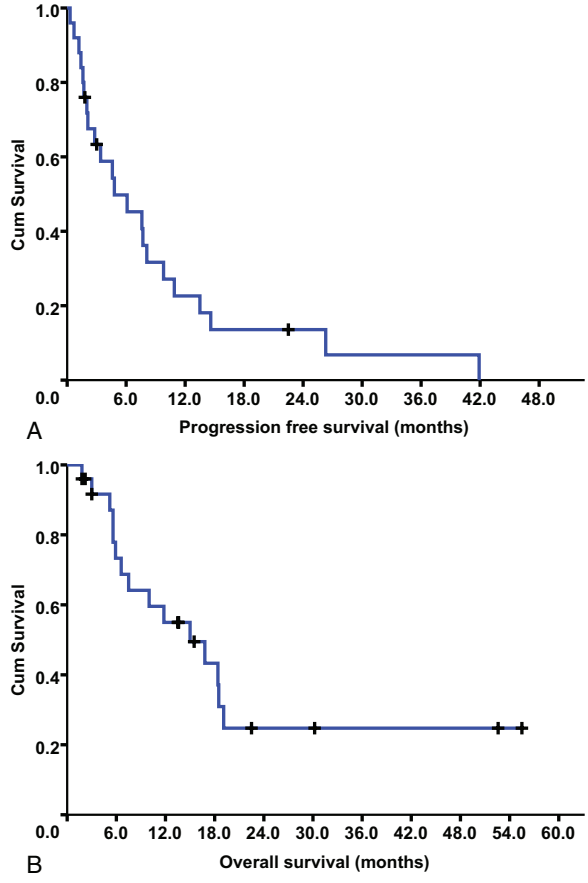

FIGURE 1. Kaplan-Meier estimates of progression-free survival (PFS) (A) and overall survival (OS) (B).

TABLE 3. Adverse Events

Description of Toxicity	Any No. (%)	Grade 3 No. (%)	Grade 4 No. (%)
Hematologic			
Leukopenia	6 (23.1)	2 (7.7)	4 (15.4)
Neutropenia	8 (30.8)	4 (15.4)	5 (19.2)
Thrombocytopenia	10 (38.5)	2 (7.7)	1 (3.8)
Anemia	1 (3.8)	1 (3.8)	0
Nonhematologic			
Nausea/vomiting	13 (50.0)	0	0
Fatigue	8 (30.8)	0	0
Fever	3 (11.5)	0	0
Anorexia	2 (7.7)	0	0
Increased ALT/AST	2 (7.7)	0	0
Rash	1 (3.8)	0	0
Constipation	2 (7.7)	0	0
Musculoskeletal pain	1 (3.8)	0	0
Peripheral neuropathy	1 (3.8)	0	0

ALT = alanine transaminase, AST = aspartate transaminase.

cytotoxic drugs commonly induce hematological toxicities, whereas grade 3/4 toxicities seen with pazopanib included fatigue, elevated liver enzymes, and hypertension. The safety profiles of both approaches (chemotherapy versus pazopanib) appear to be distinct and discontinuations due to AEs appear more frequent with pazopanib; this is of particular relevance when discussing the toxicity/benefit ratio with patients.

In conclusion, the GVP combination regimen given as second-line therapy for patients with aSTS resulted in better PFS when compared with the historical data for gemcitabine

single agent, an observation meeting the primary endpoints of our study. Future work could include the validation in a phase III study, expanding the information of our GVP regimen on prespecific histological subtype (such as angiosarcoma), and the identification of predictive markers for treatment with GVP for patients with aSTS.

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