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ORIGINAL RESEARCH ARTICLE

Real-World Outcomes of Pazopanib Treatment in Korean Patients with Advanced Soft Tissue Sarcoma: A Multicenter Retrospective Cohort Study

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Abstract

Background Pazopanib is the only tyrosine kinase inhibitor approved for the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy, but there have been limited real-world data on pazopanib for the treatment of advanced STS.

Objective We aimed to evaluate clinical outcomes of pazopanib in patients with multiple histologic STS types in real-world settings.

Patients and Methods We retrospectively analyzed clinical data of Korean patients with advanced STS treated with pazopanib between 2008 and 2019. Outcomes of interest included treatment response, survival according to histologic subtypes, and adverse events.

Results The analysis included 347 STS patients. The disease control rate for all pazopanib-treated patients was 54.8% (95% confidence interval (CI) 49.5–60.0); 54 patients (15.6%) achieved a partial response and 136 (39.2%) had stable disease. Patients with alveolar soft-part sarcoma (ASPS; 90%), solitary fibrous tumor (SFT; 88.2%), synovial sarcoma (66.7%), leiomyosarcoma (61.1%), and undifferentiated pleomorphic sarcoma (59.6%) showed higher disease control rates than those with other STS subtypes. Overall, median progression-free survival (PFS) and overall survival (OS) were 5.3 months (95% CI 4.5–6.0) and 12 months (95% CI 10–14), respectively. Noticeable survival outcomes occurred in patients with ASPS and SFT, with a median PFS of 24.5 (95% CI 2.5–30.0) and 13.0 (95% CI 3.0–21.3) months, respectively. The median OS of patients with ASPS and SFT was 48 (95% CI 17–52) and 32 (95% CI 19–66) months, respectively. Adverse drug reactions occurred in 170 patients (49.0%) but were not life-threatening.

Conclusions This real-world data analysis showed acceptable efficacy and tolerability of pazopanib in patients pretreated with cytotoxic chemotherapy for advanced STS, with favorable treatment outcomes for ASPS and SFT.

Key Points

Pazopanib showed acceptable efficacy for advanced soft tissue sarcoma (STS) in a real-world setting.

Clinical outcomes varied according to the histologic subtypes of STS.

Remarkable outcome was observed in alveolar soft-part sarcoma and solitary fibrous tumor.

Chung Ryul Oh, Jung Yong Hong, and Jee Hung Kim contributed equally to this study.

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1 Introduction

Soft tissue sarcomas (STSs), a rare and heterogeneous group of tumors with mesenchymal origin, account for approximately 1% of all malignancies worldwide [1, 2]. In Korea, about 977 patients are diagnosed with STS yearly, 45% of whom have advanced disease [3]. STS comprises more than 50 different tumor entities that exhibit considerable differences in terms of genetic alterations, pathogenesis, and clinical manifestations [4]. STS can arise from almost any site of the body, including the extremities, internal organs, or soft tissues of the trunk. Because of its rarity and heterogeneity, there have been limited advancements in the development of novel therapeutic strategies for STS compared with other cancers [5].

Surgery is the main treatment for STSs diagnosed at an early stage; however, patients with relapsed or metastatic/unresectable disease are generally incurable and receive palliative systemic therapy [2]. Anthracycline-based chemotherapy is considered the standard first-line treatment for unresectable STS [6]. Pazopanib is the only multitarget tyrosine kinase inhibitor (TKI) approved by the US FDA for the treatment of multiple subtypes of pretreated advanced STS, based on the results of a randomized phase III trial that demonstrated a significant 3-month advantage in progression-free survival (PFS) in patients with advanced STS [7]; however, the study population consisted mainly of Caucasians and the clinical efficacy and tolerability of pazopanib in Asian patients with STSs have not been fully evaluated. Although several small cohort studies and case reviews have been reported, no large-scale multicenter research has assessed the efficacy of pazopanib in Korean patients with advanced STS.

The current study investigated the clinical outcomes of 347 Korean patients with advanced STS treated with pazopanib.

2 Material and Methods

2.1 Study Population

We retrospectively collected and reviewed the clinical data of patients with advanced STS treated with pazopanib between December 2008 and April 2019 at the Asan Medical Center, Samsung Medical Center, and Yonsei University of College of Medicine, Seoul, Republic of Korea.

Patients were included in this analysis if they (1) were aged ≥ 16 years; (2) had pathologically confirmed advanced STS; (3) had failed one or more lines of chemotherapy; (4) had measurable or evaluable lesion(s) according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 [8]; and (5) had available clinical data and treatment records. We excluded patients with concurrent malignancies and those without available imaging studies for pazopanib response evaluation. The following baseline clinicopathological variables were reviewed: age, sex, histologic type, grade, primary tumor site, extent of metastasis, Eastern Cooperative Oncology Group (ECOG) performance status, and treatment history. The study was approved by the Asan Medical Center Institutional Review Board (IRB No. 2017-1098).

2.2 Treatment Assessment

Tumor response was evaluated using computed tomography or magnetic resonance imaging according to RECIST version 1.1 criteria. Disease control rate was defined as the percentage of patients with the best tumor response of complete response (CR), partial response (PR), or stable disease (SD). Overall survival (OS) was measured from pazopanib initiation to death from any cause, and PFS was measured from pazopanib initiation to disease progression or death from any cause with censoring of patients lost to follow-up.

2.3 Statistical Analysis

Patient demographics were summarized as numbers (percentage) and means (range) for categorical and continuous variables, respectively. Survival curves for PFS and OS were represented using the Kaplan–Meier method. Independent prognostic factors were evaluated using the Cox proportional hazards regression model. Statistically significant variables in univariate analysis were subjected to multivariable Cox proportional hazard regression models. p values < 0.05 were considered statistically significant and all reported p values were two-sided. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3 Results

3.1 Patient Characteristics

A total of 347 patients with STS were included in the analysis. Table 1 shows their demographics and baseline characteristics. Among these patients, 170 (49.0%) were males and the median age was 51 years. The most common primary tumor site was the abdominopelvic cavity (47.8%), followed by the thorax (24.5%), extremities (21.9%), and others (5.8%). Most patients (80.7%) had an ECOG performance status of 0 or 1. Overall, 194 patients (55.9%) received only one prior line of chemotherapy, 92 (26.5%) received two lines, and 61 (17.6%) underwent three or more

Table 1 Baseline patient characteristics

Characteristics	No. of patients (%)
Mean age, years (range)	51 (16–89)
Sex	
Male	170 (49.0)
Female	177 (51.0)
Primary tumor site	
Extremities	76 (21.9)
Abdomen-pelvis	166 (47.8)
Thorax	85 (24.5)
Others	20 (5.8)
ECOG performance status	
0	39 (11.2)
1	241 (69.5)
2+	41 (11.8)
unknown	26 (7.5)
Histologic grade of tumor	
Low	19 (5.5)
Intermediate	66 (19.0)
High	143 (41.2)
Unknown	119 (34.3)
Patient status at pazopanib administration	
No. of lines of previous systemic chemotherapy	
1	194 (55.9)
2	92 (26.5)
3	40 (11.5)
4+	21 (6.1)
Primary site involvement	
No	151 (43.5)
Yes	196 (56.5)
Liver involvement	
No	266 (76.7)
Yes	80 (23.1)
Unknown	1 (0.3)

ECOG Eastern Cooperative Oncology Group

lines of conventional systemic therapy prior to pazopanib. Primary site involvement was found in more than half of the patients (56.5%), and 80 patients (23.1%) had liver involvement of the tumor.

Figure 1 shows the treatment regimens by lines of therapy. The combination of doxorubicin and ifosfamide (27.7%) was the most frequently used first-line chemotherapy regimen. Doxorubicin with or without other chemotherapeutic agents (25.1%) and ifosfamide-based combinations (23.6%) were also commonly used as front-line treatment.

Within the study population, the largest group of histologic subtypes was leiomyosarcoma (LMS; 95 patients, 27.4%). Undifferentiated pleomorphic sarcoma (UPS; 47 patients, 13.5%), angiosarcoma (44 patients, 12.7%), synovial sarcoma (SS; 24 patients, 6.9%), malignant peripheral nerve sheath tumor (MPNST; 20 patients, 5.8%), undifferentiated sarcoma (18 patients, 5.2%), solitary fibrous tumor (SFT, hemangiopericytoma; 17 patients, 4.9%), and alveolar soft-part sarcoma (ASPS; 10 patients, 2.9%) were also observed in this population.

3.2 Pazopanib Treatment Outcomes

Among the 347 patients, 54 (15.6%) achieved a PR, 136 (39.2%) achieved SD, and 123 (35.4%) had progressive disease (PD) as best response. Overall, the disease control rate for all patients treated with pazopanib was 54.8% (95% confidence interval (CI) 49.5–60.0). Excluding relatively rare STS subtypes ($n < 10$), the highest disease control rates were observed in patients with ASPS (90%) and SFT (88.2%). Patients with SS (66.7%), LMS (61.1%), and UPS (59.6%) also demonstrated relatively favorable disease control rates (Fig. 2). The best overall responses for each histologic STS subtype are shown in electronic supplementary Table A.

Survival analysis showed a median overall PFS of 5.3 months (95% CI 4.5–6.0). The median PFS in patients with ASPS, SFT, angiosarcoma, LMS, UPS, and SS was 24.5, 13.0, 6.3, 6.0, 5.8, and 5.5 months, respectively. The median OS of the 347 patients was 12 months (95% CI 10–14), and the median OS for patients with ASPS, SFT, LMS, and SS was 48, 32, 16, and 14 months, respectively. Notably, patients with ASPS and SFT achieved outstanding survival outcomes compared with patients with other subtypes (Table 2; Figs. 3, 4).

A Cox univariate analysis showed that unfavorable prognostic factors for survival in patients with advanced STS who underwent pazopanib treatment were male sex and poor ECOG performance status (≥ 2). After adjusting for confounding variables by multivariate Cox regression analysis, poor ECOG performance status (≥ 2) and the number of lines of previous chemotherapy (three or more) were significant poor prognostic factors for patient survival (Table 3).

3.3 Dose and Toxicity Profile of Pazopanib Treatment

The daily average dose of pazopanib was approximately 700 mg among the study population. The mean relative dose intensity was 83.4% and the mean starting dose was 717 mg daily. Most patients (72.6%) started at a daily dose of 800 mg, but 48 patients (13.8%) started at daily doses $\leq 50\%$ of the standard recommended dose of 800 mg/day (Table 4); 113 patients (32.6%) experienced at least one dose modification.

Adverse events occurred in 170 patients (49.0%). The most common toxicities were diarrhea (77 patients, 22.2%), nausea (75 patients, 21.6%), and tumor pain (68 patients, 19.6%). Relatively rare adverse effects were also reported,

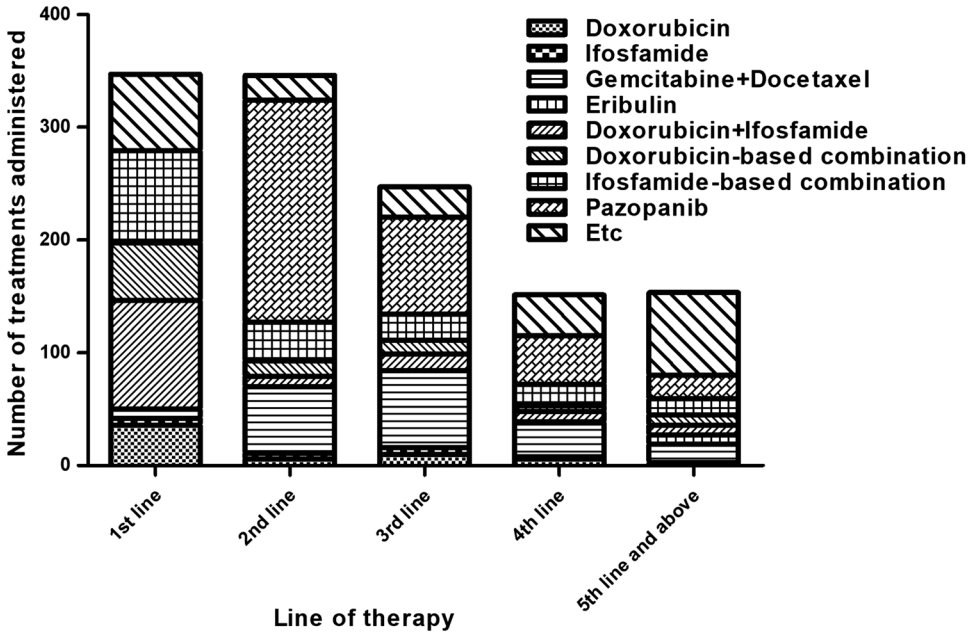

Fig. 1 Treatment regimens by line of therapy

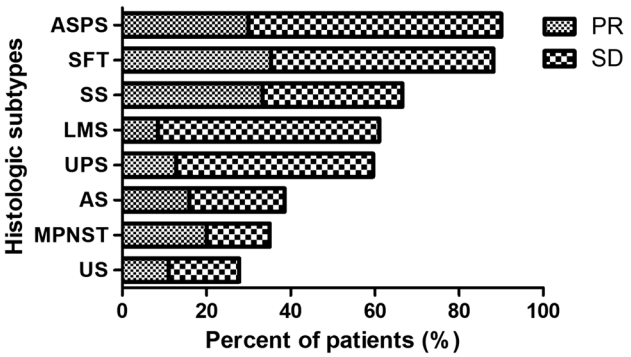

Fig. 2 Disease control rate for pazopanib treatment. *ASPS* alveolar soft-part sarcoma, *SFT* solitary fibrous tumor, *SS* synovial sarcoma, *LMS* leiomyosarcoma, *UPS* undifferentiated pleomorphic sarcoma, *AS* angiosarcoma, *MPNST* malignant peripheral nerve sheath tumor, *US* undifferentiated sarcoma, *PR* partial response, *SD* stable disease

including pneumothorax (9 patients, 2.6%), deep vein thrombosis (4 patients, 1.2%), pulmonary embolism (2 patients, 0.6%), and heart failure (2 patients, 0.6%); however, none of these adverse events were grade 4 or 5 according to the Common Terminology Criteria of Adverse Events (CTCAE) version 4.0. Grade 3 adverse events were observed in only 2.3% of patients (Table 5).

4 Discussion

The current multicenter, large-scale analysis of real-world data demonstrated that pazopanib is effective and can be administered safely in patients pretreated with cytotoxic chemotherapy for advanced STS. Additionally, our results showed that the efficacy of pazopanib treatment can vary according to the histologic STS subtype.

The PALETTE phase III clinical trial showed that pazopanib significantly increased the median PFS compared with placebo (4.6 vs. 1.6 months; hazard ratio [HR] 0.31, 95% CI 0.24–0.40; $p < 0.0001$). The median OS with pazopanib treatment in this trial was 12.5 months (95% CI 10.6–14.8). In terms of efficacy, our study results showed similar survival outcomes as those of the PALETTE trial. The median PFS and OS in all 347 patients were 5.3 months (95% CI 4.5–6.0) and 12 months (95% CI 10–14), respectively, in the present study. These results are also concordant with other previously published data [9–12].

Several studies have examined the efficacy and tolerability of pazopanib for the treatment of advanced STS in Asian patients. Yoo et al. studied 43 Korean patients and suggested that pazopanib seemed to have antitumor activity in patients who had been heavily pretreated for metastatic STS [9]. Another retrospective study that included 156 Japanese patients with relapsed STS reported acceptable survival outcomes. The researchers in this Japanese study also proposed differences in the clinical benefit of pazopanib among histologic STS types [10]. However, the relatively small sample sizes in these previous reports prevented profound investigations of the relationship between tumor histology and treatment outcomes. To our knowledge, our study is the largest retrospective study to assess the outcomes of pazopanib for the treatment of patients with various subtypes of advanced STS.

The results of the present study showed that the pazopanib treatment response and clinical outcomes varied

Table 2 Survival of STS patients with main histologic subtypes

Histology	No. of patients	Median PFS, months	6-Month PFS, %	Median OS, months	1-Year OS, %
LMS	95	6.0	47.1 (36.9–57.3)	16	67.8 (58.1–77.4)
SS	24	5.5	49.1 (28.8–69.4)	14	53.9 (32.7–75.1)
UPS	47	5.8	43.1 (28.3–57.8)	8	46.4 (31.8–61.1)
AS	44	6.3	51.5 (35.4–67.5)	6	28.5 (14.7–42.2)
MPNST	20	4.8	39.5 (16.9–62.1)	9	34.3 (13.2–55.4)
ASPS	10	24.5	80.0 (55.2–100.0)	48	100.0 (100.0–100.0)
SFT	17	13.0	58.8 (35.4–82.2)	32	87.8 (72.0–100.0)
US	18	2.8	17.7 (0.0–35.9)	7	34.7 (11.2–58.2)

LMS leiomyosarcoma, *SS* synovial sarcoma, *UPS* undifferentiated pleomorphic sarcoma, *AS* angiosarcoma, *MPNST* malignant peripheral nerve sheath tumor, *ASPS* alveolar soft-part sarcoma, *SFT* solitary fibrous tumor, *US* undifferentiated sarcoma, *PFS* progression-free survival, *OS* overall survival

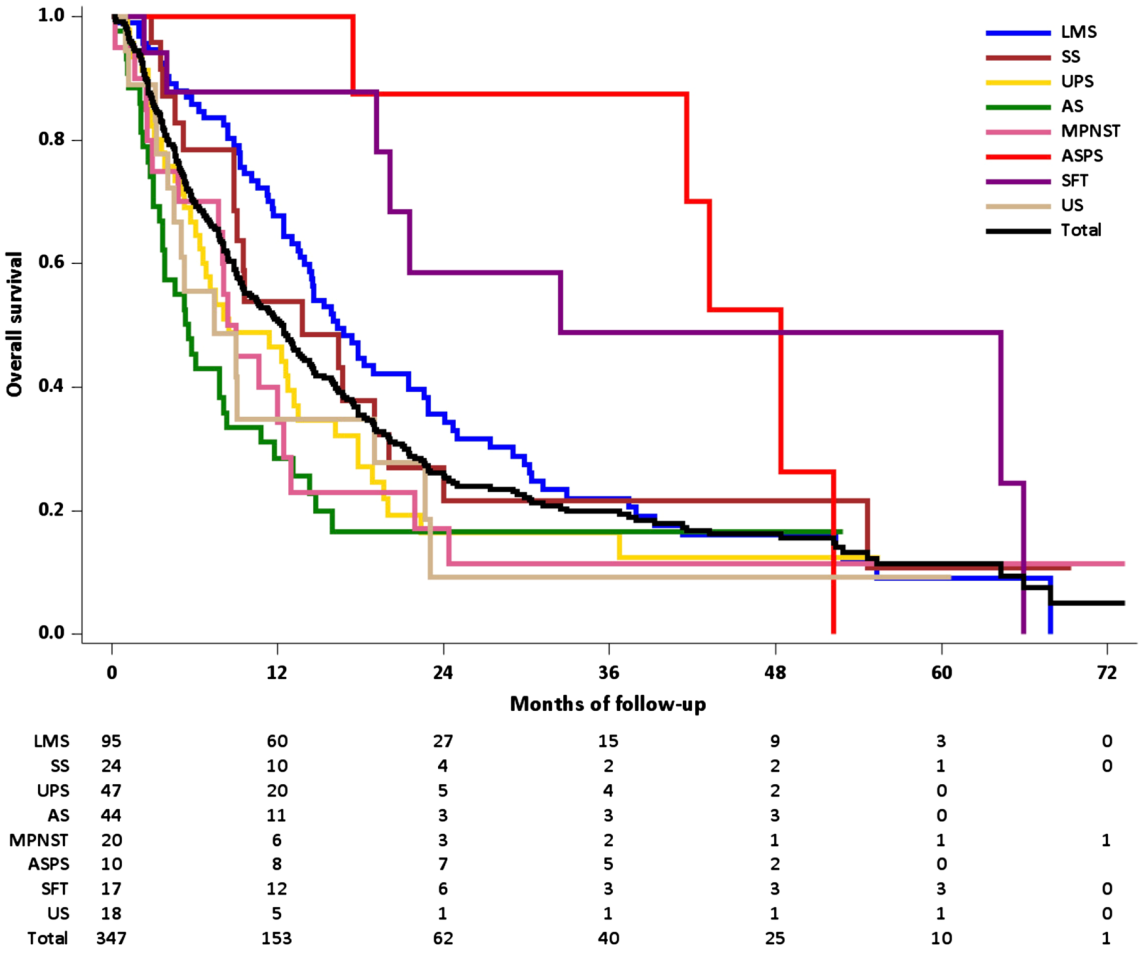

Fig. 3 Kaplan–Meier analysis of progression-free survival according to histologic subtypes. *LMS* leiomyosarcoma, *SS* synovial sarcoma, *UPS* undifferentiated pleomorphic sarcoma, *AS* angiosarcoma, *MPNST* malignant peripheral nerve sheath tumor, *ASPS* alveolar soft-part sarcoma, *SFT* solitary fibrous tumor, *US* undifferentiated sarcoma

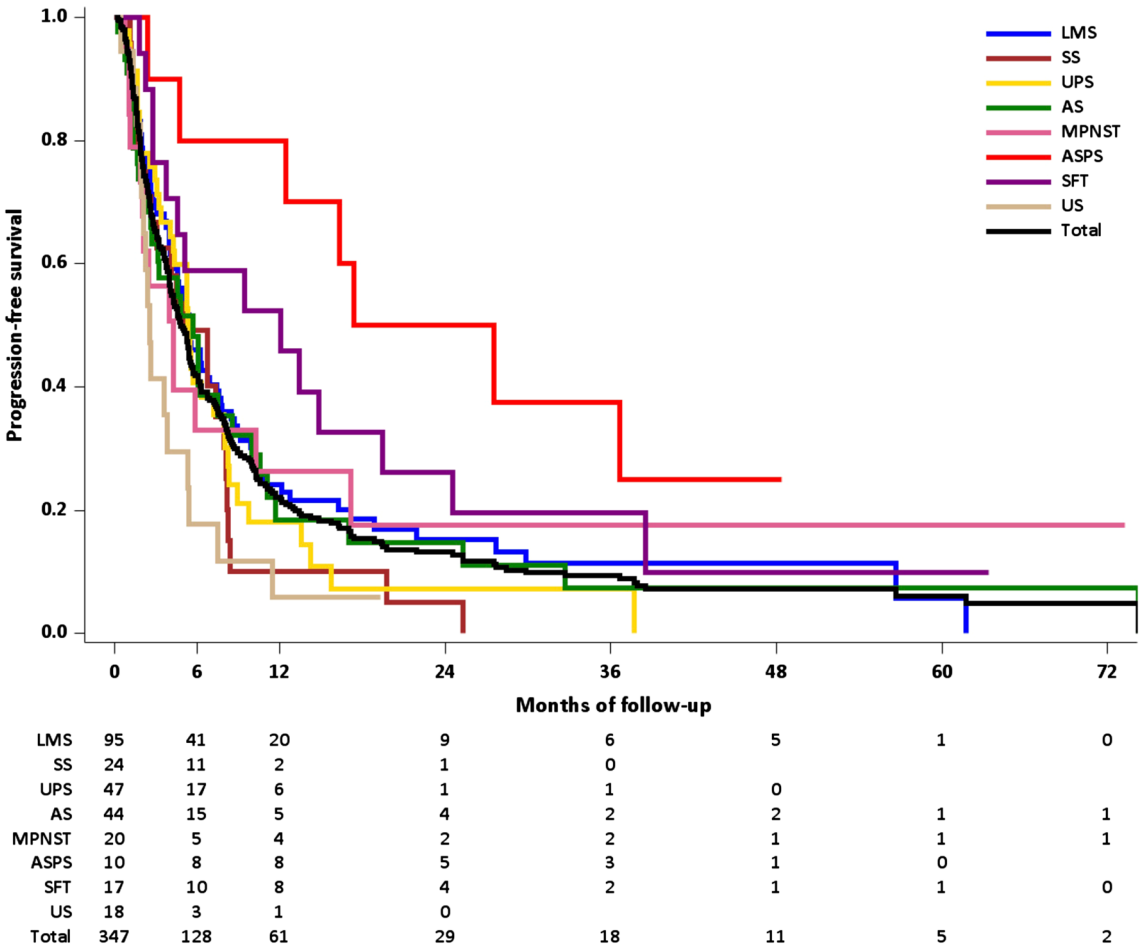

Fig. 4 Kaplan–Meier analysis of overall survival according to histologic subtypes. *LMS* leiomyosarcoma, *SS* synovial sarcoma, *UPS* undifferentiated pleomorphic sarcoma, *AS* angiosarcoma, *MPNST* malignant peripheral nerve sheath tumor, *ASPS* alveolar soft-part sarcoma, *SFT* solitary fibrous tumor, *US* undifferentiated sarcoma

according to STS histologic subtypes. In our study population, 54 patients (15.6%) achieved PR and 136 (39.2%) had SD, corresponding to a disease control rate of 54.8% and objective response rate of 15.6%. Patients with ASPS (90%), SFT (88.2%), SS (66.7%), LMS (61.1%), UPS (59.6%), and epithelioid sarcoma (57.1%) had satisfactory disease control rates following pazopanib treatment. In terms of objective response rate, pazopanib demonstrated acceptable efficacy in patients with advanced SFT (35.3%), SS (33.3%), and ASPS (30.0%). Better survival outcomes were observed in patients with ASPS, SFT, LMS, and SS than in patients with other types of STS.

Pazopanib showed remarkable efficacy in patients with advanced ASPS and SFT. ASPS is a rare STS subtype representing < 1% of all STSs [13]. Given the extreme rarity of the disease, available clinical data are not sufficient, although ASPS has greater metastatic potential and poorer long-term outcomes than other STSs. Several reports have suggested its sensitivity to the effect of vascular endothelial growth factor receptor (VEGFR)-predominant TKIs [14–17]. A retrospective review of data of 44 patients with advanced ASPS by Stacchiotti et al. confirmed the activity of pazopanib in the treatment of advanced ASPS, with a 27% overall response rate by RECIST, a median PFS of 13.6 months, and 59% of patients progression-free at 12 months [16]. In our study, the median PFS of 10 patients with ASPS was 24.5 months and the overall response rate was 30%. In a recently published randomized phase II trial, cediranib, a TKI with a similar spectrum of activity, was also shown to have significant clinical activity in this disease [18]. The results of this trial provide the strongest evidence of the effectiveness of TKIs in ASPS patients. The utility of angiogenesis inhibitors such as VEGFR blockers, including pazopanib or cediranib can be explained by the fact that ASPS cells use lactate as an energy source, with consequent upregulation of hypoxia-inducible factor (HIF)-1α and VEGF, resulting in angiogenesis, cell proliferation, metastasis, and myogenic differentiation [18–21].

Table 3 Prognostic factors for survival: hazard ratios and *p* values

	Crude HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
Median age, years				
< 52	Ref		Ref	
≥ 52	1.17 (0.92–1.50)	0.2026	1.20 (0.92–1.57)	0.1738
Sex				
Female	Ref		Ref	
Male	1.29 (1.01–1.65)	0.0414	1.14 (0.88–1.47)	0.3301
ECOG performance status				
0	Ref		Ref	
1	1.29 (0.86–1.92)	0.2171	1.22 (0.81–1.86)	0.3389
2+	3.78 (2.30–6.21)	< 0.0001	3.67 (2.20–6.15)	< 0.0001
No. of lines of previous chemotherapy				
1	Ref		Ref	
2	1.04 (0.78–1.38)	0.8130	1.01 (0.74–1.37)	0.9596
3+	1.38 (0.98–1.94)	0.0614	1.56 (1.08–2.27)	0.0184
Liver metastasis				
No	Ref		Ref	
Yes	1.20 (0.90–1.60)	0.2108	1.18 (0.86–1.61)	0.2988

HR hazard ratio, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group, *Ref* reference group

Table 4 Pazopanib mean daily dose and relative dose intensity

	N = 347
Mean daily dose (mg)	669.8
Mean relative dose intensity (%)	83.4
Mean starting dose (mg)	716.9
Starting dose (mg) [*n* (%)]	
200	3 (0.9)
400	45 (13.0)
600	44 (12.7)
800	252 (72.6)
Unknown	3 (0.9)

Table 5 Adverse events of special interest while receiving pazopanib therapy

AESI category	Severity (CTCAE grade)			
	Grade 1	Grade 2	Grade 3	Total
Diarrhea	41 (11.8)	33 (9.5)	3 (0.9)	77 (22.2)
Nausea	57 (16.4)	17 (4.9)	1 (0.3)	75 (21.6)
Vomiting	18 (5.2)	8 (2.3)	1 (0.3)	27 (7.8)
Tumor pain	54 (15.6)	13 (3.7)	1 (0.3)	68 (19.6)
Pneumothorax	5 (1.4)	2 (0.6)	2 (0.6)	9 (2.6)
Heart failure	–	2 (0.6)	–	2 (0.6)
PTE	2 (0.6)	–	–	2 (0.6)
DVT	1 (0.3)	3 (0.9)	–	4 (1.2)

AESI adverse events of special interest, *CTCAE* Common Terminology Criteria for Adverse Events, *PTE* pulmonary thromboembolism, *DVT* deep vein thrombosis

SFT, another rare subtype of STS, has limited responsiveness to cytotoxic chemotherapy [22–24]. For this reason, several researchers have investigated targeted therapies for the treatment of patients with advanced SFT, and multiple TKIs, including pazopanib, have been studied for the treatment of SFT [25–27]. Most recently, the results of a phase II trial evaluating pazopanib for the treatment of advanced SFT have been reported [28]. Of 35 evaluable patients, 18 (51%) had achieved PR, 9 (26%) had SD, and 8 (23%) had PD. The median PFS of all patients was 5.57 months (95% CI 4.29–6.84). Our findings regarding the outstanding efficacy of pazopanib therapy in patients with SFT are in line with these recent results.

The spectrum of adverse events was generally consistent with the known safety profile of pazopanib; however, fewer adverse events were reported in the current study than in the PALETTE trial. In particular, grade 4 and 5 adverse events were not observed and grade 3 adverse events occurred in 2.3% of patients. This finding may be related to lower relative dose intensity compared with the PALETTE trial and the retrospective nature of the present study as not all adverse events might be completely documented in the medical records.

Clinical research for STS is somewhat challenging because of its low incidence and heterogeneity [29]. Although we included a considerable number of patients with STS, the study population was not sufficiently large to identify a significant association between tumor histology and clinical outcomes in patients receiving pazopanib treatment. In addition, given the retrospective nature of

this study design, the results might be affected by selection or recall biases. Nevertheless, our study demonstrated the efficacy and tolerability of pazopanib for the treatment of advanced STS in real-world settings. The outcomes from these real-world data provide valuable insight into the effectiveness and safety of the drug in clinical practice.

5 Conclusions

This large-scale, real-world data analysis evaluated the treatment outcome of pazopanib in patients with pretreated advanced STS. Pazopanib had acceptable efficacy and tolerability for the treatment of advanced STS, and noticeable differences were observed in the activity of pazopanib therapy among STS subtypes. A remarkable response to pazopanib was observed in patients with ASPS and SFT. Further prospective studies for each STS subtype and biomarker investigation for pazopanib are strongly recommended.

Author Contributions Study concept: Jeong Eun Kim and Tae Won Kim. Study design: Jeong Eun Kim. Data acquisition: Jeong Eun Kim, Jung Yong Hong, Jee Hung Kim, Hyo Song Kim, and Jin-Hee Ahn. Quality control of the data and algorithms: Jeong Eun Kim. Data analysis and interpretation: Jeong Eun Kim, Ji Sung Lee, and Chung Ryul Oh. Statistical analysis: Ji Sung Lee. Article preparation: Chung Ryul Oh and Jeong Eun Kim. Article editing: Chung Ryul Oh. Article review: Jeong Eun Kim, Jung Yong Hong, Jee Hung Kim, and Hyo Song Kim.

Compliance with Ethical Standards

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Conflict of interest Chung Ryul Oh, Jung Yong Hong, Jee Hung Kim, Ji Sung Lee, Hyo Song Kim, Tae Won Kim, Jin-Hee Ahn, and Jeong Eun Kim declare they have no conflicts of interest that might be relevant to the contents of this manuscript.

Consent for publication The authors declare that the manuscript has not been published previously, in whole or in part, and is not under consideration for publication elsewhere. All authors have approved the manuscript and consent to its publication.

Ethics approval This study was approved by the Asan Medical Center Institutional Review Board (IRB No. 2017-1098).

Availability of data and material The data contain potentially identifiable patient information and cannot be shared publicly due to ethical and legal restrictions.

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