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Research Article

The Evaluation of Pazopanib Treatment Experience and Real-Life Data in Metastatic Soft Tissue Sarcoma

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Abstract

Objectives: We aimed to share real-life data of pazopanib in non-liposarcoma STS patients in soft tissue sarcoma (STS), which is rare among adult cancers.

Methods: Characteristics of adult patients treated with pazopanib for metastatic STS were recorded retrospectively. Response rate, survival and toxicity data related to pazopanib treatment were evaluated in SPSS program with appropriate statistical analysis.

Results: The median age of 50 patients in our study was 48.4 (17.1- 92.4) years. The most common histological subtype was leomyosarcoma (11 patients, 22.0%), and the most common primary tumor location was the intra-abdominal region (17 patients, 34.0%). The most common site of metastasis was the lung (35 patients, 70.0%). Forty three of the patients had received two or more lines while twenty-seven of the patients had received three or more line treatments. With pazopanib treatment, the overall response rate (ORR): 12%, median progression-free survival (mPFS): 5.8 months, and median overall survival (mOS): 8.6 months. Grade 3/4 toxicity was observed in a total of 5 (10.0%) patients in the entire group.The most common toxicity was fatigue (15 patients, 30.0%).

Conclusion: In our study, pazopanib treatment provided a PFS contribution similar to the literature and showed a tolerable toxicity profile in patients diagnosed with liposarcoma and non-GIST soft tissue sarcoma that progressed after anthracycline-based treatment.

Keywords: Soft tissue sarcoma, pazopanib, treatment

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Soft tissue sarcomas (STS) are a very heterogeneous group of tumors in terms of histological, molecular and biological features, constituting approximately 1% of adult cancers.[1] There are more than 50 subtypes according to the World Health Organization (WHO) classification.[2] STS are tumors of mesenchymal origin and are located in different parts of the body, especially in the extremities and retroperitoneum. Due to its unique characteristics, multidisciplinary follow-up and treatment of STS in centers specialized in this field is of great importance. In early stage localized disease, surgical treatment is the basic treatment model, and adjuvant radiotherapy and chemotherapy treatments are applied in addition to suitable patients according to risk characteristics. Unfortunately, more than 50% of patients with high-grade and high-risk features develop metastases and die because of this.[3] In metastatic disease, the prognosis is generally poor, and the median survival varies between 12-18 months.[4-12]

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The main treatment approach in STS patients with metastatic disease is chemotherapy, and various chemotherapeutic agents, especially doxorubicin and ifosfamide, have been used in the historical process. Although doxorubicin monotherapy is the standard in first-line treatment, ifosfamide/doxorubicin combination is also widely used. While a response of about 15% is obtained with the use of a single agent of doxorubicin, this rate increases to 25-30% in its combined use with ifosfamide, and the median progression-free survival (mPFS) and median overall survival (mOS) reach 7.4 months and 14.3 months, respectively.[13, 14] On the other hand, when it comes to second-line treatments, gemcitabine and docetaxel are the most widely used chemotherapeutic agents, and the response rate in the combined use of these two agents is reported to be 24% and mPFS: 6.3 months.[7, 15] In the next lines, various agents such as trabectedin and eribulin, especially pazopanib are used.[16]

Pazopanib is a multitargeted tyrosine kinase inhibitor and has inhibiting properties of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and c-KIT.[17-21] VEGF is overexpressed in many STS, and it has been reported that elevated VEGF is associated with high grade, large tumor size, aggressive histology, and poor prognosis.[21] Therefore, all these features also make pazopanib an attractive treatment option in the treatment of STS. The most comprehensive study evaluating the efficacy of pazopanib in the treatment of STSs was the PALETTE study,[22] in which patients with metastatic STS who had previously received up to four lines of treatment were randomized to either the pazopanib or placebo arms. 99% of the patients were received anthracyclines and 56% were patients who had received at least two lines of treatment. While synovial sarcoma, leomyosarcoma and other subtypes were included as histological types, patients with liposarcoma were excluded from the study. As a result, a significant improvement in mPFS was reported with pazopanib (mPFS: 4.6 months vs 1.6 months, HR: 0.31, p<0.001). After these results, pazopanib took its place as an important treatment option in the treatment of metastatic STS with its unique moderate toxicity profile.

In this study, we aimed to retrospectively evaluate the results of patients treated with pazopanib in our center where STS patients were evaluated as multidisciplinary.

Methods

Patient Characteristics

In this study, patients who were followed up and treated in Dokuz Eylul University Faculty of Medicine, Department of Medical Oncology between January 01, 2013 and December 31, 2020 and who received pazopanib therapy for metastatic soft tissue sarcoma were evaluated retrospectively. Demographic characteristics, hematological and biochemical laboratory parameters, clinicopathological characteristics of the tumor and information about the treatments they received were recorded from the file records of the patients. Patients with adequate medical records, living longer than 3 months, receiving pazopanib therapy for at least 2 months or more were included in the study. While many subtypes included in the PALETTE study[22] were taken as histological subtypes; liposarcoma, embryonal rhabdomyosarcoma, chondrosarcoma, osteosarcoma, Ewing tumors, primitive neuroectodermal tumor, gastrointestinal stromal tumor, dermatofibrosarcoma protuberans, inflammatory myofibroblastic sarcoma, malignant mesothelioma, and mixed mesodermal subtypes of the uterus were excluded from the study.

Pazopanib Treatment

Information about the starting dose of pazopanib treatment, which line of treatment was started, whether dose reduction or postponement was made were recorded. In general, pazopanib treatment was continued until progression or severe intolerance.

Response and Toxicity Assessment

Tumor staging was performed according to the "Eighth Edition of American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) TNM stage classification".[23, 24] Response assessments. It was done according to "Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines".[25] Toxicity assessments were made according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC).[26]

Statistical Analysis

Descriptive and frequency analyzes were used for patient data. Parametric data were presented as mean±standard deviation, non-parametric data as median (minimum-maximum) and categorical data as percentages. Objective response rate was defined as complete response + partial response. As progression-free survival (PFS), the time from the start of pazopanib therapy to the date of progression; The overall survival time (OS) was taken from the start of pazopanib treatment to death/last follow-up date. Kaplan-Meier method and Log-rank test were used for survival analysis. All data were analyzed using SPSS (v24.0) package program. Statistical significance was accepted as $p<0.05$ (bidirectional).

Results

Patient Characteristics

A total of 50 patients who received pazopanib treatment with the diagnosis of metastatic STS were evaluated retrospectively. Twenty-six of the patients were male while twenty-four of the patients were female and the median age was 48.4 (17.1-92.4) years. The most common histological subtypes were leomyosarcoma (n=11, 22.0%), pleomorphic sarcoma (n=8, 16.0%), and synovial sarcoma (n=6, 12.0%), respectively. When the patients were evaluated according to the primary tumor localization, it was intraabdominal in seventeen (34.0%) patients, lower extremities in eleven (22.0%) and trunk in ten patients (20.0%). When evaluated according to metastasis sites, it was determined that the most common metastasis site was the lung (n=35, 70.0%), followed by the liver (n=16, 32.0%) and lymph nodes (n=16, 32.0%). Surgery for the primary tumor was performed in thirty-nine (78.0%) patients. The findings regarding the demographic characteristics of the patients are shown in Table 1.

Previous Systemic Treatments

Of the fifty patients, twenty-two (44.0%) of patients had previously received adjuvant chemotherapy and five of patients (10.0%) had received neoadjuvant therapy. While 21 (42.0%) of the patients were de novo metastatic, twenty-nine of patients had early stage disease and later metastatic. Forty three (86.0%) of all patients had two or more lines; twenty-seven (54.0%) received three lines or more of treatment. The most common chemotherapy regimen was ifosfamide+doxorubicin combination (n=16, 32.0%). Twenty two (n=11) percent of the all patients were able to receive systemic treatment after pazopanib treatment. The findings regarding the systemic treatments received by the patients in the pre-pazopanib period are shown in Table 2.

Pazopanib Treatment

Pazopanib treatment was started at a dose of 800 mg/day and continued until progression or development of intolerance. Of the 50 patients with metastatic STS, sixteen (32.0%) patients received pazopanib as second-line therapy, Nineteen (38.0%) patients received as third-line therapy, and eight (16%) patients received as fourth-line therapy and beyond. Seven (14%) patients received pazopanib as first-line therapy due to ECOG PS, age and cardiac comorbidities.

The median duration of treatment in the whole group was 5.4 (2.1-36.1) months, and the relative dose intensity was 97.0%. Dose reduction was performed in six (12.0%) patients, and treatment was discontinued in three (6.0%) patients due to toxicity.

Table 1. Clinicopathological Characteristics of the Patients

Characteristics	% (n)
Histological Subtype	
Leomyosarcoma	22 (11)
Pleomorphic cell sarcoma	16 (8)
Synovial sarcoma	12 (6)
Malignant fibrous solitary tumor	10 (5)
Angiosarcoma	8 (4)
Fibrosarcoma	8 (4)
Rhabdomyosarcoma	6 (3)
Undifferentiated round cell sarcoma	6 (3)
Alveolar soft part sarcoma	4 (2)
Malignant peripheral nerve sheath tumor	4 (2)
Other	4 (2)
Primary Tumor Location	
Intraabdominal	34 (17)
Lower extremity	22 (11)
Body	20 (10)
Retroperitoneal	10 (5)
Upper extremity	6 (3)
Head-neck	6 (3)
Testis	2 (1)
Metastasis at Diagnosis Tıme	
No	58 (29)
Yes	42 (21)
Metastasis Site	
Lung	70 (35)
Lymph node	32 (16)
Liver	32 (16)
Bone	12 (6)
Pleura	8 (4)
Peritoneal carcinomatosis	6 (3)
Cranial	6 (3)
Leptomeningeal	2 (1)
Local Recurrence	
No	50 (25)
Yes	50 (25)

Activity

The objective response rate (ORR) achieved with pazopanib in the whole group was 12%, and all responses were partial responses. In addition, stable disease was obtained in twenty-seven (54.0%) patients in the whole group.

The median follow-up time was 17.9 months, and the median PFS obtained with pazopanib was 5.8 months (2.4–9.1) and median OS: 8.6 months (4.0–13.1) in the whole group. When the survival results were evaluated according to the order in which pazopanib was administered, the median PFS was 7.1 months, 4.4 months and 4.2 months in the group in which pazopanib was administered as the second, third, fourth line and after treatment,

Table 2. Characterics of Pazopanib Treatment

Characaterics	% (n)
Pazopanib Treatment Selection Line	
1st Line	14 (7)
2nd Line	32 (16)
3rd Line	38 (19)
4th Line	10 (5)
5th Line	6 (3)
Pazopanib Treatment Response	
Partial Response	10 (5)
Stable Response	20 (10)
progression	34 (17)
Unknown	36 (18)
Treatment Pre-Pazopanib	
Ifosfamide-doxorubicin	32 (16)
Gemcitabine-docetaxel	22 (11)
Ifosfamide-etoposide	10 (5)
ICE	6 (3)
Paclitaxel	4 (2)
Mtx	2 (1)
Unknown	24 (12)
Treatment Post-Pazopanib	
Gemcitabine-docetaxel	14 (7)
Ifosfamide -etoposide	2 (1)
ICE	2 (1)
Oral cyclofosfamide	2 (1)
Vinorelbine	2 (1)
Unknown	78 (39)

ICE: Ifosfamide, carboplatin, and etoposide; Mtx: Methotrexate.

respectively. Median OS was 8.1 months, 8.0 months and 5.5 months in the group in which pazopanib was administered as the second, third, fourth line and after treatment, respectively. Survival outcomes are shown in Figure 1a and 1b.

Toxicity

Grade 3/4 toxicity was observed in a total of 5 (10.0%) patients in the entire group. The most common toxicities in all grades were fatigue (n=15, 30.0%), diarrhea (n=8, 16.0 %) and hepatotoxicity (n=8, 16.0%). The toxicities occurring in the whole group are shown in Table 3. Dose reduction was performed in six (12.0%) patients due to toxicity, while treatment was discontinued in three (6.0%) patients. The main reasons for dose reduction were fatigue and diarrhea. Of the patients who progressed while using pazopanib therapy, 11 (22.0%) were able to receive next-line therapy.

Discussion

In this study, in which patients treated with pazopanib for the diagnosis of metastatic STS were evaluated retrospectively, we found ORR: 12%, mPFS: 5.8 months, and mOS: 8.6 months in the whole group. We also found that pazopanib exhibited a reasonable and manageable toxicity profile in this patient group, where the majority of patients had received at least two lines of systemic therapy before.

Soft Tissue Sarcomas are generally a heterogeneous group of tumors with different histological, molecular and biological characteristics, and it is of great importance that their follow-up and treatment be carried out in centers specialized in this field, in accordance with the principles of multidisciplinary approach. Our center is a center where patients have been evaluated in this context for nearly thirty years. Accordingly, 78% of the patients in our study underwent surgery for their primary tumors, and 44% consisted of patients who received adjuvant chemotherapy.

The prognosis is poor in metastatic STS, and the median survival ranges between 12-18 month.[4, 5, 7, 10] These results may vary according to the histological subtype and according to the changing treatment paradigms over time. Due to the relatively low incidence and highly heterogeneous sub-

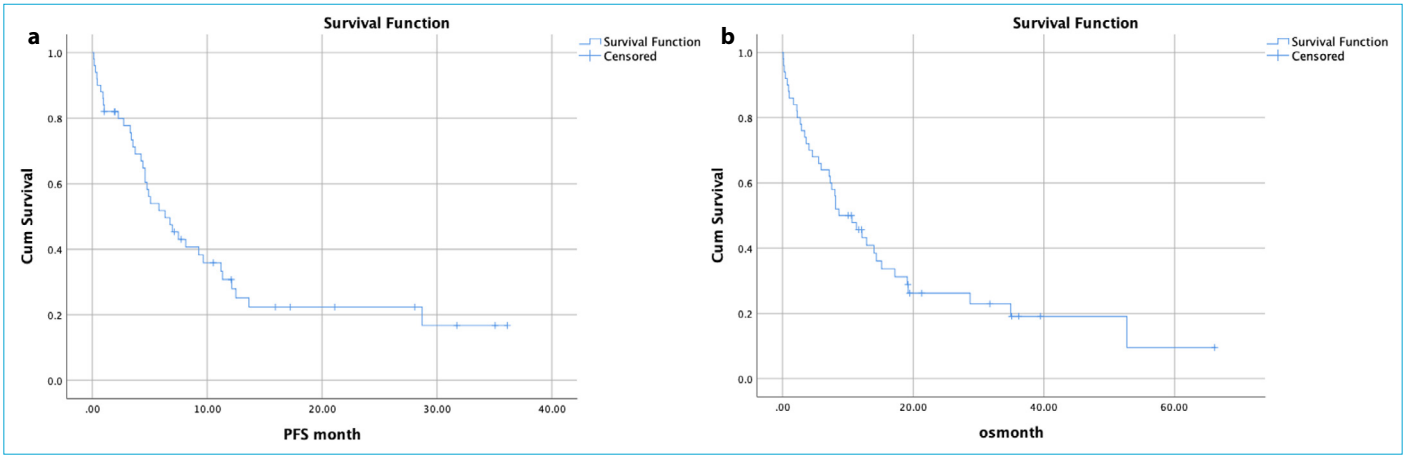

Figure 1. (a) Curve of Progression-Free Survival (Kaplan Meier Analysis). **(b)** Curve of Overall Survival (Kaplan Meier Analysis).

Table 3. Treatment-related side effects

Characteristic	Grade % (n)			
Side Effects	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Fatigue	28 (14)		2 (1)	
Diarrhea	10 (5)	4 (2)	2 (1)	
GGT level increases	10 (5)	6 (3)		
ALT level increases	6 (3)	2 (1)	4 (2)	
Hypertension	10 (5)			
AST level increases	8 (4)		2 (1)	
Nausea	8 (4)			
QTc prolongation	8 (4)			
Weight loss	6 (3)			
Hypothyroidism		4 (2)		
Hair hypopigmentation	6 (3)			

ALT: Alanine transaminase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; QTc: QT corrected.

types, the introduction of new treatment options in this tumor group is less frequent and slower than in other tumor types. This situation complicates the work of medical oncologists who treat and manage these patients. Although anthracyclines are generally used in the first-line treatment of metastatic STS, regardless of histology, the combination of ifosfamide plus anthracycline is also widely used. In our study, combination of ifosfamide plus anthracycline was the most frequently preferred treatment regimen (32.0%). On the other hand, when it comes to second-line therapy, histological subtype-based approach is mostly preferred and combination of gemcitabine plus docetaxel, trabectedin and pazopanib are frequently used.

Pazopanib is an important treatment option in patients progressed with anthracycline therapy and advanced high-grade STS (except for liposarcoma). Pazopanib, a multikinase inhibitor, has antiangiogenic properties as well as inhibition of PDGF and c-KIT. In the EORTC 62043 study, a phase II study, pazopanib was used at a dose of 800 mg/day in 142 patients who had received up to two lines of chemotherapy or were unable to receive chemotherapy, and the PFS rate at 12th week was 44%, 49%, and 39% in leomyosarcoma, synovial sarcoma, and other sarcomas, respectively. It has been reported that all of the responses obtained are partial responses.[27] In our study, similar to the results in the phase II study, all of the responses obtained were in the form of partial responses.

In the subsequent phase III PALETTE study, 369 patients with advanced sarcoma subtypes other than liposarcoma that progressed after first-line therapy were randomized 2:1 to the pazopanib or placebo arms. 99% of the patients had received anthracyclines and 56% of patients had received at least two lines of treatment. As a result of this study, whose primary end-point was PFS, a significant improvement in mPFS was obtained with pazopanib (mPFS: 4.6 months vs 1.6 months, HR: 0.31, p<0.001), while the improvement in OS did not reach statistical significance (mOS 12.5 months vs 10.7 months HR: 0.86, p=0.25).[22] In our study, mPFS was 5.8 months, which was consistent with the PALETTE study and even slightly higher. Although the rate of patients who received at least two lines or more of treatment in our study was higher than the rate in the phase III study (56% vs 86%), we think that the mentioned 5.8-month mPFS result is remarkable. Similarly, the ORR rate (12%) obtained in our study was found to be higher than the rate of 6.0% in the phase III study in the literature. Our stable disease rate is 54%, which is minimally lower than the 67.0% rate in the PALETTE study. Since in general, targeted therapies provide stable disease as well as complete or partial response, it is more recommended to consider stable disease rates and accordingly PFS rates in the evaluation of the efficacy of such therapies. On the other hand, our overall survival results (mOS: 8.6 months) were lower than the PALETTE study. In the discussion of the PALETTE study, it is stated that the mOS results of the control group were higher than expected at the time of design of the study, and that more post-progression treatments were applied in the placebo arm compared to the pazopanib arm (49% vs. 63%).[22] In addition, both the heterogeneity of histological subtypes and the order in which pazopanib is administered may also play a role. We think that the ORR and PFS results obtained in our study better reflect the efficacy of pazopanib, since PFS is one of the parameters that best demonstrate the effectiveness of a treatment and post-protocol treatments also play a role in OS.

As in many oncological treatments, the clinical and pathological features of pazopanib treatment that will better predict efficacy have been investigated. Until now, it has been stated that the single most important indicator is the histological type.[12, 21, 22, 27] On the other hand, in a phase II study, good performance status (PS), intermediate histological grade, and normal hemoglobin levels were reported to be factors that positively affect survival.[27] We think that the good performance of the majority of the patients in our study (ECOG 0-1: 84%) may also have an impact on these survival outcomes.

When the toxicities observed with pazopanib treatment were evaluated in our study, we found that the most common side effect was fatigue and was observed at rates similar to the literature (49.0% vs 42.3%).[22] On the other hand, our rate of dose reduction was lower compared to the literature (12.0% vs 39.0%).[22, 27] This may be due to the fact that the majority of patients are patients with good PS.

In addition, it has been reported that pneumothorax is an important problem in patients with pulmonary metastases receiving pazopanib therapy in recent years.[28] Although the patient population in our study consisted of patients with pulmonary metastases at a high rate of 70%, pneumothorax was not observed in any of the patients.

The limitations of our study include the relatively small number of patients, its retrospective nature, the lack of quality of life analysis, and the limited experience of a single center.

Conclusion

In conclusion, the data we obtained from our study support that pazopanib treatment contributes to PFS in patients diagnosed with non- liposarcoma and non-GIST soft tissue sarcoma that progressed after anthracycline-based treatment and has a tolerable toxicity profile, similar to the literature. Since it is an easily applicable, oral treatment option, it should be considered in the treatment of patients in such heterogeneous sarcoma group.

Disclosures

Ethics Committee Approval: The study was approved by the Dokuz Eylül University Faculty of Medicine Non-Invasive Research Ethics Committee (Date: 05.01.2022 Decision No: 2022/01-35).

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Conflict of Interest: None declared.

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