Original Article

Efficacy of Pazopanib in Patients with Pretreated Advanced Stage Soft Tissue Sarcomas

Önceden Tedavi Edilmiş İleri Evre Yumuşak Doku Sarkomlu Hastalarda Pazopanib Etkinliği

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ABSTRACT

Background: Pazopanib acts as a multitargeted tyrosine kinase inhibitor. It has been shown to be effective in patients with advanced stage Soft Tissue Sarcomas (STSs). We aimed to evaluate survival times and significant side effects by making a retrospective evaluation of real-life data.

Materials and Methods: This study was carried out with a retrospective method. Clinical characteristics of adult patients with advanced STSs treated with the pazopanib were recorded in the hospital's patient registry database. Patients without medical records were excluded from the study. Objective response rate (ORR), Progression-free survival (PFS), overall survival (OS), and treatment-related pneumothorax and hypertension side effects were determined.

Results: Forty adult patients were included (males: 55%). The median age was 44.5 years (range: 20-88). Malignant mesenchymal tumor by histopathology was found in 32.5% of the sample. Eighty-eight percent of the sample had a Stage 3 or higher disease at the time of initial diagnosis. Seventy percent of the patients had lung metastases. Seventy percent of the patients received two or more lines of systemic chemotherapy prior to pazopanib. The ORR to the pazopanib was 45% for whole patients. Median PFS (IQR) was determined as 5.73 (2.67) months (95% Confidence Interval (CI) of 5.19 to 6.19 months). Median OS (IQR) was 8.54 (17.81) months (95% CI of 8.24 to 15.65 months). Pneumothorax was detected during pazopanib in twelve and a half percent of patients. Hypertension was detected during pazopanib in fifteen percent of patients.

Conclusion: Pazopanib led to significant survival in this pretreated population of patients based on real-life data. It also has a manageable side-effect profile.

Keywords: Sarcoma, Vascular endothelial growth factor receptor, Pazopanib

ÖZET

Amaç: Pazopanib, birden çok hedefli bir tirozin kinaz inhibitörü olarak çalışır. İleri evre Yumuşak Doku Sarkomlu (YDS) hastalarda etkinliği gösterilmiştir. Gerçek yaşam verilerinin retrospektif bir değerlendirmesini yaparak sağkalım sürelerini ve önemli yan etkilerini değerlendirmeyi amaçladık.

Materyal ve Metod: Bu çalışma retrospektif yöntemle gerçekleştirilmiştir. Pazopanib ile tedavi edilen ileri ever YDS'li yetişkin hastaların klinik özellikleri hasta kayıt veri tabanından kaydedilmiştir. Tıbbi kaydı olmayan hastalar çalışma dışı bırakılmıştır. Objektif yanıt oranı (ORR), Progresyonsuz sağkalım (PFS), genel sağkalım (OS), tedaviye bağlı pnömotoraks ve hipertansiyon yan etkiler değerlendirilmiştir.

Bulgular: Kırk yetişkin hasta dahil edildi (erkekler: %55). Ortanca yaş 44,5 (aralık: 20-88) olarak saptandı. Histopatolojik olarak malign mezenkimal tümör örneklemin %32,5'inde tespit edildi. Yüzde seksen sekiz hasta ilk tanı anında Evre 3 veya daha yüksek bir hastalığa sahipti. Hastaların yüzde yetmi-

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şinde akciğer metastazı vardı. Hastaların yüzde yetmişi pazopanib öncesinde iki veya daha fazla sıra sistemik kemoterapi almıştır. Pazopanib için ORR tüm hastalar için %45 olarak saptandı. Medyan PFS (IQR) 5,73 (2,67) ay olarak belirlendi (%95 Güven Aralığı (GA) 5,19-6,19 ay). Medyan OS (IQR) 8,54 (17,81) aydı (%95 GA 8,24- 5,65 ay arasında). Pazopanib sırasında hastaların %12'sinde pnömotoraks tespit edildi. Pazopanib sırasında hastaların %15'inde hipertansiyon saptandı.
Sonuç: Pazopanib, gerçek yaşam verilerine dayalı olarak önceden tedavi edilmiş bu hasta popülasyonunda anlamlı sağkalıma yol açmıştır. Ayrıca yönetilebilir bir yan etki profiline sahiptir.

Anahtar Kelimeler: Sarkom, Vasküler endotelyal büyüme faktörü reseptörü, Pazopanib

Introduction

Sarcomas are a rare but heterogeneous group of malignancies of mesenchymal origin. Whole sarcomas constitute less than one percent of all adult cancers [1-3]. Soft tissue sarcomas (STSs) constitute eighty-five percent of the entire sarcoma patient population [3]. STSs most commonly originate from the extremities [4,5].

Primary treatment of STSs consists of surgery and radiotherapy. However, local recurrence is observed in 5-30% of patients and recurrence with clinically detectable distant organ metastasis in approximately 25% of patients [6,7]. There is a poor prognosis for relapsed/refractory STSs. While the median overall survival is less than 12 months with conventional chemotherapy in metastatic sarcomas, in recent years the survival time has increased to longer than 12 months due to developments in the typing of sarcomas and the use of new treatments [8,9].

Angiogenesis and invasion are critical for tumor growth and distant metastasis [10]. Pazopanib is a potent receptor tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 and is approved for the treatment of heavily pretreated STS [11]. Studies demonstrating the efficacy of pazopanib in real life for relapsed/refractory STSs are relatively lacking.

In this study we aimed to demonstrate the efficacy of the pazopanib protocol on survival and disease control endpoints in relapsed/refractory STS.

Methods and Materials

Study Design

This study has a retrospective design. It is a single center study. Study data were collected using the medical records of patients followed for relapsed/refractory STSs at a tertiary care clinic between January 2017 and August 2021. Inclusion criteria were age ≥ 18 years, histologically confirmed advanced STSs, and imaging-proven metastases of this condition. Among the patients with these characteristics, those followed by the oral pazopanib treatment protocol were included in the study. Exclusion criteria were age <18 years and insufficient clinical follow-up data. Oral pazopanib treatment was administered as 1x800 mg. Radiological response evaluation was performed at three-month intervals. Ethical approval was obtained from the local clinical research ethics committee (Desicion number: 2021/97 Date: 02 March 2022). This study was conducted in accordance with the 1964 Declaration of Helsinki and subsequent amendments or comparable ethical standards.

Patients

The age, gender, localization, histology, and stage of the primary malignancy at diagnosis were recorded in the study database. Within the scope of the study, lung, liver, bone, soft tissue, lymph node, and brain metastasis status were evaluated before the pazopanib protocol. The following information was recorded: number of systemic treatment protocols used by the patients before pazopanib, best response with pazopanib treatment, dose

Table 1. Demographic and clinical characteristics of the patients

Features	n: 40
Age, median (range)	44.5 (20-88)
Gender	
Male, n (%)	22 (55)
Primary origin of tumor, n (%)	
Extremities	21 (52.5)
Intraabdominal	17 (42.5)
Head and neck	2 (5)
Histopathology, n (%)	
Malignant mesenchymal tumor	13 (32.5)
Synovial sarcoma	10 (25)
Leiomyosarcoma	9 (22.5)
Rhabdomyosarcoma	5 (12.5)
Fibrosarcoma	3 (7.5)
Stage at Diagnosis, n (%)	
≤ Stage 2	6 (15)
≥ Stage 3	34 (85)
Site of Metastases, n (%)	
Lung	28 (70)
Lymph nodes	25 (62,6)
Liver	13 (32,5)
Bone	17 (42,5)
Soft tissue	23 (57,5)
Brain	2 (5)
Number of systemic lines before pazopanib, n (%)	
< 2 lines	12 (30)
≥ 2 lines	28 (70)

Table 2. Treatment-related characteristics of the patients

Features	n:40
Best Objective Response, n (%)	
Complete Response	- (0)
Partial Response	18 (45)
Stable Disease	10 (25)
Progressive Disease	12 (30)
PFS, median (IQR), months	5,73 (2,67)
OS, median (IQR), months	8,54 (17,81)
Side Effects	
Dose reduction, n (%)	13 (32,5)
Pneumothorax, n (%)	2 (5)
Hypertension, n (%)	6 (15)
Liver enzymes elevation, n(%)	7 (17,5)
LVEF reduction, n(%)	- (0)

PFS: Progression free survival;OS: Overall survival; IQR: Interquartile range

reduction status during pazopanib treatment, and pneumothorax and hypertension adverse events during pazopanib treatment. After scanning the files for the study, eighty-two patients were identified. Forty patients who met the inclusion criteria were included in the study.

Treatment/response evaluation

Objective response rate (ORR) was determined as the sum of the complete response and partial response received. Progression-free survival (PFS) was defined as the time from the onset of pazopanib to the first documented disease progression or death from any cause. Overall survival (OS) was calculated as the time from the onset of pazopanib to the patient's last appearance or date of death.

Statistics

Statistical analyzes were performed using IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Descriptive data were expressed as a percentage of the total. The normality of continuous variables was determined using the Kolmogorov-Smirnov test. Normally distributed continuous data were expressed as mean ± standard deviation (SD) and non-normally distributed median [interquartile range (IQR)]. Kaplan Meier analysis analysis was performed for survival analysis. While evaluating the statistical significance of the results obtained, $p<0.05$ level and 95% confidence interval were taken as basis.

Results

The final sample included 40 patients (males: 55%). The median age was 44.5 years (range: 20-88). The primary tumor site was in the extremities of 52.5% of study participants. Malignant mesenchymal tumor by histo-pathology was found in 32.5% of the sample. The subtype of patients with rhabdomyosar-

coma is embryonal rhabdomyosarcoma in all patients. Eighty-eight percent of the sample had a Stage 3 or higher disease at the time of initial diagnosis. Seventy percent of patients had lung metastases. Seventy percent of patients received two or more lines of systemic chemotherapy prior to pazopanib. The characteristics of the patients are presented in Table 1.

ORR to the pazopanib was forty-five percent. Median PFS (IQR) was determined as 5.73 (2.67) months (95% Confidence Interval (CI) of 5.19 to 6.19 months). Median OS (IQR) was 8.54 (17.81) months (95% CI of 8.24 to 15.65 months). Dose reduction was required in 32.5% of the patients. Pneumothorax and hypertensin were detected at a rate of 12.5% and %15 during pazopanib. The median follow-up (IQR) was 25.64 (31.14) months. Treatment side effects and responses to treatment are presented in Table 2, Figure 1, and Figure 2.

Discussion

Forty patients were evaluated retrospectively in our study. Although pazopanib was approved in the STSs group in those who progressed after initial systemic therapy, 70% of patients in our study sample used this treatment agent after the second line. Despite heavily pretreated patients, the contribution of PFS and OS is acceptable for this line. In this sense, we can say that it is a treatment option with significant antitumor activity. An acceptable level of side-effect profile was observed. Dose reduction was also not needed in most patients.

Sarcomas constitute a rare tumor group encountered. Sarcomas actually consist of a group of diseases that include many subtypes. STSs constitute 75-80% of this group [12,13]. There are also more than 40 malignant histological subtypes of STSs, which constitute one of the most heterogeneous groups of oncological diseases [13,14]. This heterogeneity brings with it difficult treatment, especially in the advanced stage. The treatment process is difficult because of the low success of known systemic chemotherapy protocols. However, clinical and pathological features, which are important in all advanced malignancies, also contribute to determining survival. Among these, performance status, clinical stage, and therefore lymph node metastasis or distant metastasis, and histopathological subtype can be counted [14,15]. Surgery, radiotherapy and systemic treatment options can always be considered during the course of the disease [16]. Systemic therapy in the form of relapsed, refractory, or directly metastatic disease also plays an important role for STSs. While there is no suitable performance or contraindication for almost all tumors in the STSs family, chemotherapy protocols containing ifosfamide and anthracycline can be used initially [15,16]. Although the treatment options are needed in the second and later stages vary according to the subtypes for this heterogeneous tumor group, there is actually a lack of standard systemic treatment with accepted efficacy [17].

Despite new systemic treatments, overall survival is at the level of 11-12 months when evaluated in the second line and after. Taxanes in patients with angiosarcoma and gemcitabine-docetaxel combination in patients with leiomyosarcoma contributed to a slight improvement in overall survival [18,19]. Tyrosine kinase inhibitors such as sunitinib and imatinib have significantly contributed to survival for some STSs, especially gastrointestinal stromal tumors [20,21].

The mean age in the study group was 44.5 years. Yoo KH et al. reported the median age as 54 in a similar number of study samples that had previously received multiple-line therapy [22]. STSs are common in a relatively young age group.

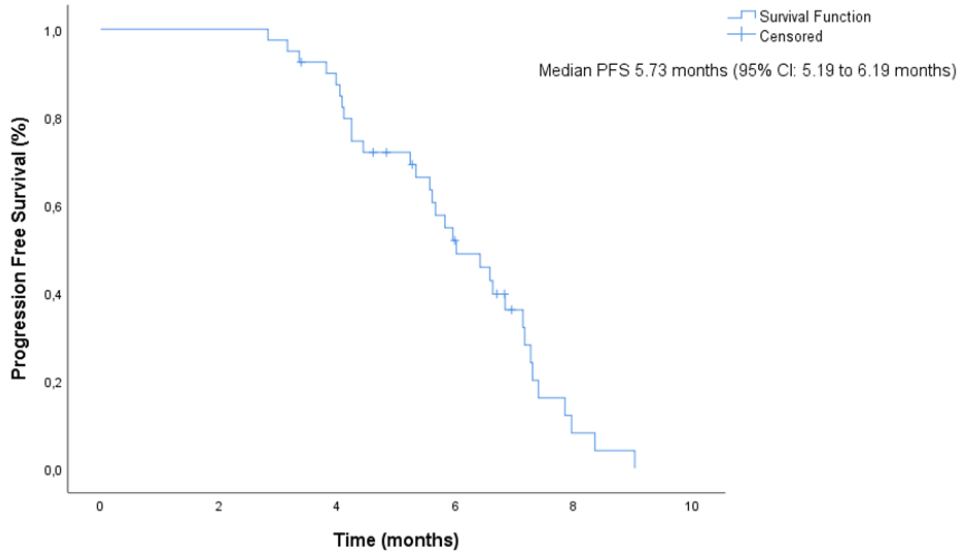

Figure 1: Median progression-free survival curve in patients with metastatic STSs

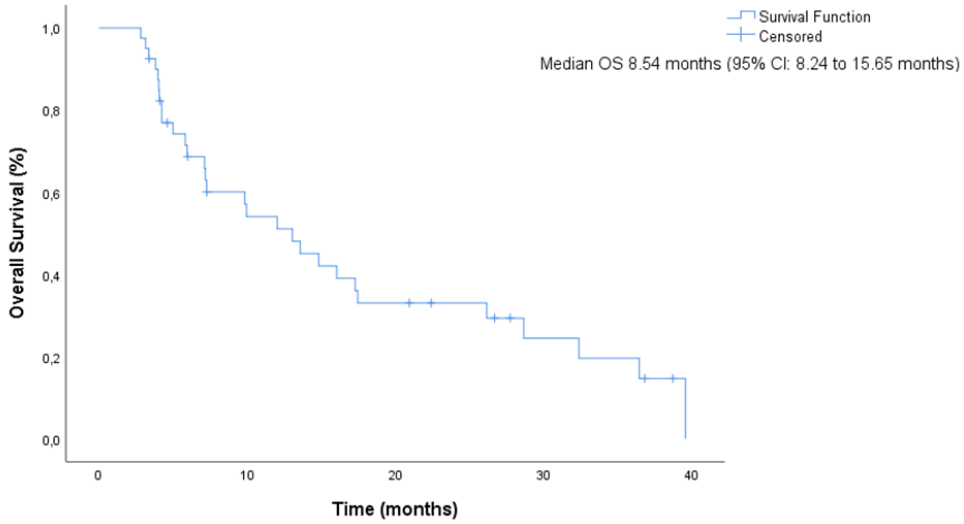

Figure 2: Overall survival curve in patients with metastatic STSs

Lung was the most common site for metastases in our study group. Liver metastases were observed in around 30%. Yoo KH et al. reported lung metastasis as 74% and liver metastasis as 27% [22]. The rates of lung metastases in the SPIRE study were similar to those in our study [23]. In the PALETTE study, which is at the forefront of the pivotal studies for pazopanib, liver metastases are in 30% of patients [24]. The frequent observation of visceral metastases in patients who need second-line and post-treatment therapy is already an indicator of a poor prognosis for this group of patients.

The same cannot be said for pazopanib, although survival times decrease as the

number of systemic treatment steps increases for patients who were previously heavily treated. There are a significant number of patients in our sample with two or more systemic treatments prior to pazopanib. In the study reported by Yoo KH et al., the number of patients who received two or more systemic treatment lines was around 80% [22]. We can state that our study populations are close to each other in this sense. In the PALETTE study, this rate was reported as 56% [24]. The PFS detected in our study is close to that reported by Yoo KH et al. Pazopanib has a significant survival effect in a population heavily exposed to systemic therapy. In contrast, it is difficult to maintain similar statements for OS. Overall survival was reported at around one year in the PALETTE study. In our study, this period is around eight months. The reason for this may be that the patients in our study were exposed to more severe systemic treatment. In this sense, we can deduce the idea that pazopanib should be used in earlier systemic treatment lines.

In our study, the partial response rate was found to be 45%. This rate is higher than the PALETTE study. The reason for this may be that the tumor burden of the patients in the study population is lower than that of PALETTE or their performance is better. In addition, data on the continued use of pazopanib in our study group are limited. This may be the reason why PFS and OS are found to be similar. Since we conducted a retrospective study, it is not possible to evaluate patients in this sense.

The choice of systemic treatments includes their manageable side-effect profiles and the survival advantage. This situation is directly related to patient compliance. It is also a parameter that directly concerns dose reduction. High compliance and the ability to continue without reducing the dose both directly affect success of the treatment. There are many side effects reported with pazopanib. However, we examined the effects on dose reduction, pneumothorax, and hypertension in our study. We found dose reduction rates similar to the PALETTE study, in which pneumothorax was reported at 3% [24]. This rate is around 2% in the SPIRE study [23]. In our sample, this rate was found to be 5%. Hypertension was detected in around 15% of our sample, which is lower than the PALETTE study [24].

In our study, liver enzyme elevation was found at a rate of 17.5%. But because of this, there is no patient whose treatment was stopped. There have been previous reports of pazopanib liver toxicity. This toxicity rate varies between 12-60% [25,26]. Also, we did not find any heart failure-related treatment discontinuation. In the PALETTE study, %11 of patients receiving pazopanib developed heart failure. A significant proportion of these patients had previously used anthracyclines [24].

This paper has several limitations. First, the number of patients was low, limiting the generalizability of the findings to different populations. Second, retrospective design of the study raises the possibility of errors in data quality. Third, since the analysis was cross-sectional, the results cannot be assumed to be causal. Finally, follow-up times and interval cannot be controlled in retrospective analyzes.

In conclusion, pazopanib is a good agent with survival benefit, even in pretreated patients. Demonstrating real-life data consistent with clinical studies is significant in terms of treatment success. Identifying subgroups that will benefit more from pazopanib in the STSs patient group may lead to a better clinical benefit in this sense.

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