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Research Article

Real-life data of pazopanib usage in soft tissue sarcoma

Yumuşak doku sarkomunda pazopanib kullaniminin gerçek yaşam verisi

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Abstract

Aim: Soft tissue sarcomas are heterogeneous group of malignancies consisting of more than 50 subtypes. Although it is rare, it is usually resistant to chemotherapy and has a poor prognosis. In this study, we planned to investigate the efficacy, tolerability and side-effect profile of pazopanib in metastatic soft tissue sarcomas.

Material and Methods: Our study was a single-center retrospective study and included metastatic patients over the age of 18 who were treated with pazopanib. Data of 37 patients were obtained in retrospective medical records. In patients using pazopanib; tumor location, histological subtype, tumor grade, disease stage, the line at which pazopanib was used, efficacy, tolerability, and side-effect profile of pazopanib were examined.

Results: The mean age of the patients at the time of diagnosis was 49 years. Pleomorphic sarcoma was the most common subtype. The progression-free survival (PFS) of patients after first-line therapy was 18 weeks. The median overall survival (OS) of the patients was 20 months. The median PFS with pazopanip was 18 weeks. Any degree of thrombocytopenia was observed in 4 (10.8%) patients using pazopanib, any degree of anemia was observed in 18 (48.6%) patients, and any degree of neutropenia was observed in 7 (18.9%) patients. Hypothyroidism was observed in 5 (13.5%) patients using pazopanib, and hepatic dysfunction of any degree was observed in 10 (27%) patients.

Conclusion: The use of pazopanib in soft tissue sarcoma was found to be effective in terms of both PFS and OS. Side effects were tolerable and treatable. In our study, PFS of 32 weeks was obtained in patients with hypothyroidism and 16 weeks in patients without. In this respect, the development of hypothyroidism may be a predictive parameter for response.

Keywords: sarcoma, pazopanib, hypothyroidism, side effect

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Öz

Amaç: Yumuşak doku sarkomu 50'den fazla alt sınıftan oluşan heterojen bir malignite grubudur. Nadir görülmekle birlikte genellikle kemoterapiye dirençli olup, prognozu kötüdür. Çalışmamızda metastatik yumuşak doku sarkomlarında pazopanib kullanımının etkinliği, tolerabilitesi ve yan etki profilini araştırmayı planladık.

Gereç ve Yöntemler: Çalışmamız tek merkezli retrospektif bir çalışma olup, metastatik olan ve pazopanib alan 18 yaş üstü hastalar dahil edildi. Geriye yönelik dosya taramasında toplam 37 hastanın verisine ulaşıldı. Pazopanib kullanan hastalarda; tümörün yerleşim yeri, histolojik alt tipi, tümör derecesi, hastalığın evresi, pazopanibin hangi basamakta başlandığı, pazopanibin etkinliği, tolerabilitesi ve yan etki profili incelendi.

Bulgular: Hastaların tanı sırasında ortalama yaşı 49 idi. Pleomorfik sarkom en sık görülen alt tip idi. Birinci basamak tedavi sonrası hastaların progresyonsuz sağ kalımı (PFS) 18 hafta idi. Hastaların genel sağ kalımı (OS) 20 ay bulundu. Pazopanib ile ortanca PFS 18 hafta olarak saptandı. Pazopanib kullanan hastaların 4'ünde (%10,8) hastada herhangi bir derecede trombositopeni, 18 (%48,6) hastada herhangi bir derecede anemi ve 7 (%18,9) hastada herhangi bir derecede nötropeni gözlendi. Pazopanib kullanan 5 (%13,5) hastada hipotiroidi, 10 (%27) hastada herhangi bir derecede karaciğer fonksiyon bozukluğu gözlendi.

Sonuç: Yumuşak doku sarkomunda pazopanib kullanımı hem PFS hem OS açısından etkin bulundu. Yan etkiler tolere edilebilir ve tedavi edilebilir yan etkilerdi. Çalışmamızda hipotiroidi gelişen hastalarda 32 hafta, gelişmeyelerde ise 16 haftalık bir PFS elde edildi. Bu açıdan hipotiroidi gelişim yanıt için bir prediktif parametre olabilir.

Anahtar kelimeler: sarkom, pazopanib, hipotiroidi, yan etki

Introduction

Sarcomas are a group of heterogeneous, malignant tumors originating from mesenchyme and constitute approximately 1% of adult malignancies (1,2). Around 80% of sarcomas originate from soft tissue while the remaining originate from the bone (1). The most common types of sarcoma include liposarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma, gastrointestinal stromal tumors and synovial sarcoma (3,4). Histological grade has prognostic importance in sarcomas; histological grading is performed according to differentiation, mitotic activity and necrosis rate of the tumor (5,6). In sarcoma cases with local disease at diagnosis, primary treatment is R0 resection which provides a safe surgical limit (7). Post-surgery radiotherapy (RT) and adjuvant - neoadjuvant chemotherapy may be added to the treatment depending on the tumor characteristics, tumor size and grade (8). Anthracycline-based chemotherapy is recommended as first-line therapy in patients with metastatic disease (9). Pazopanib, a multityrosine kinase inhibitor, is used in non-liposarcoma soft tissue sarcomas progressing after chemotherapy.

Pazopanib is a multityrosine kinase inhibitor which inhibits vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor (PDGFR) -α -β, fibroblast growth factor receptor (FGF)-1, FGF-3 and KIT (10). In pre-clinical studies, pazopanib was demonstrated to reduce angiogenesis and growth by inhibiting these growth factors (11). The method of administration and standard dose of pazopanib is 800 mg/day via oral route. In a study comparing pazopanib with placebo, it was observed that pazopanib was superior with a progression-free survival (PFS) of 4.6 months compared to 1.6 months with placebo (12). The most common side effects associated with pazopanib are predisposition to thrombosis, hypertension, bleeding, proteinuria, hypothyroidism, hepatotoxicity, cardiac toxicity, depigmentation and gastrointestinal irritation (13). Since pazopanib is eliminated through hepatic metabolism by CYP3A4, medicinal products that induce and inhibit CYP3A4 should be avoided.

In our study, we planned to investigate the efficacy, tolerability and side-effect profile of pazopanib use in non-liposarcoma soft tissue sarcomas. In patients using pazopanib; The location of the tumor, histological subtype, tumor grade, disease stage, the series in which pazopanib was used, the efficacy, tolerability and side-effect profile of pazopanib were examined.

In this study, the use of pazopanib in soft tissue sarcoma was found to be effective in terms of both PFS and OS. Side effects were tolerable and treatable. In the study, PFS of 32 weeks was obtained in patients with hypothyroidism and 16 weeks in patients without hypothyroidism. In this respect, the development of hypothyroidism may be a predictive parameter for response.

Material and Methods

It is a retrospective, single-center study including patients with metastatic soft tissue sarcoma who started to receive pazopanib in Dicle University Faculty of Medicine, Medical Oncology Outpatient Clinic between February 2015 and October 2018. The data of 37 patients were obtained by retrospective chart review in the study. The patients with non-liposarcoma soft tissue sarcoma between the ages 18-85 who were treated with pazopanib were included in this study. Patients with a subtype of liposarcoma, patients with secondary malignancies, and patients younger than 18 years and older than 85 years were excluded from the study. In patients diagnosed with non-liposarcoma soft tissue sarcoma who are receiving pazopanib; tumor localization, histological subtype, tumor grade, disease stage, treatment line in which pazopanib was used, the efficacy, tolerability and side effect profiles of pazopanib were investigated. Patients started to receive treatment at a standard dose of 800 mg/day. In cases where a side effect was developed, the dose was reduced to 200-400 mg/day. Tumor sizes were investigated using systemic imaging methods performed every three months in order to evaluate the efficacy of pazopanib. Response status was evaluated according to RECIST 1.1, and progression-free survival (PFS) and overall survival (OS) were calculated. The time from the starting date of pazopanib to the date of disease progression or death from any cause was calculated as PFS while the time from the starting date of pazopanib to death from any cause was calculated as OS. This study was granted ethical approval by Non-Interventional Clinical Trials Ethics Committee of Gazi Yasargil Training and Research Hospital (date and number of decision: 04.07.2019-324) and carried out in accordance with the principles of Declaration of Helsinki.

Statistical Analysis

Kaplan-Meier test was used to estimate the progression-free survival (PFS) and overall survival (OS) of pazopanib, and the variables were compared using the log-rank test. Descriptive statistics for variables were presented as mean, standard deviation, and minimum and maximum values. Categorical variables were expressed as numbers and percentages. Chi-square test was performed for categorical variables to find differences between groups. For numerical data, mean data were used for normally distributed values and median data were used for non-normally distributed values, while in independent data sets with non-normally-distributed numerical values, Mann-Whitney U test was used for the difference between two groups and Kruskall-Wallis test was used if there are more than two groups. For numerical data with normal distribution, Student T test was performed if there are two groups and ANOVA test was performed if there are more than two groups in independent data sets. Statistical significance level was set to 5% in the calculations. SPSS (IBM, version 18.0, USA) statistical software package was used for the analysis of our study.

Results

The mean age of the patients included in our study was 49.3 years (18.8 - 80.2) at diagnosis. Among all patients, 24 were female and 13 were male. The most frequently observed subtypes were pleomorphic sarcoma 35.1% (13/37) and leiomyosarcoma 32.4% (12/37). When the cases were evaluated in terms of grade, 37.8% (14/37) of the patients had grade 4, 29.7% (11/37) of the patients had grade 3 and 21.6% (8/37) of the patients had grade 2 disease. At diagnosis, the disease stage was determined as stage 4 in 45.9% (17/37) and stage 3 in 35.1% (13/37) of the patients. General characteristics of the patients were shown in Table 1. A total of 3 patients (8.1%) received neoadjuvant chemotherapy and 10 patients (27.2%) received adjuvant chemotherapy. In the first-line therapy of metastatic stage disease, 16 patients received IMA (ifosfamide + mesna + adriamycin), 11 patients received docetaxel + gemcitabine and 6 patients received pazopanib. The median progression-free survival (PFS) of the patients receiving first-line therapy was 18 weeks (14-21 weeks) (figure 1 A) while the PFS was 19 weeks (figure 1 B) for 28 patients receiving second-line therapy. Overall survival (OS) of the patients was calculated to be 20 months (4.3-25.6 months) (figure 1 C). The med ian duration of pazopanib treatment was 16.7 weeks (1 -164.2 weeks).

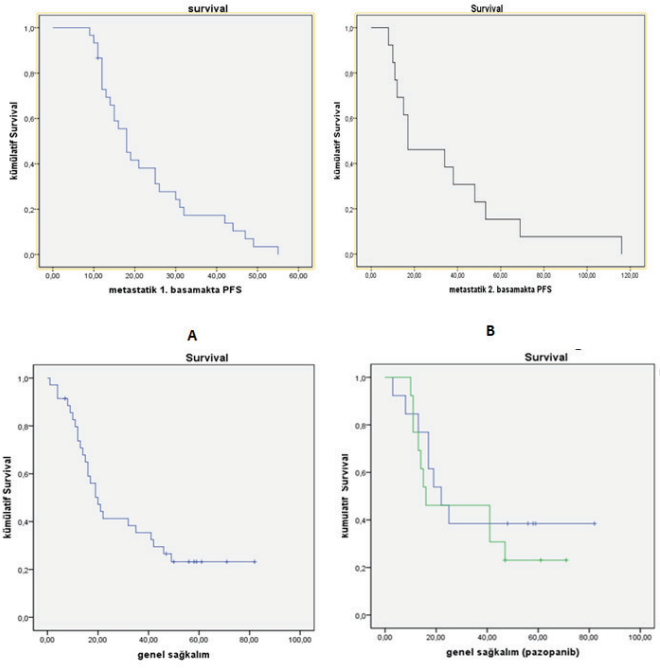

Figure 1: Overall survival and progression-free survival values of the patients

A: Progression-free survival for 1st-line therapy in patients with metastatic disease

B: Progression-free survival for 2nd-line therapy in patients with metastatic disease

C: Overall survival of all patients

D: Comparison of overall survival for pazopanib given as 2rd vs. 3rd-line of therapy

Table 1: Patient characteristics

Patient characteristics (n:37)		
	Number (n)	Percentage (%)
Gender		
Female	24	64.9
Male	13	35.1
Histological subtypes		
Pleomorphic sarcoma	13	35.1
Leiomyosarcoma	12	32.4
Fibrosarcoma	4	10.8
Synovial sarcoma	3	8.1
Other types	5	13.5
Primary tumor location		
Extremities	15	40.5
Head and neck	1	2.7
Abdomen	15	40.5
Thorax	6	16.2
Grade		
Grade 2	8	21.6
Grade 3	11	29.7
Grade 4	14	37.8
Unknown	4	10.8
Stage at diagnosis		
Stage 2	7	18.9
Stage 3	13	35.1
Stage 4	17	45.9
Line of treatment in which pazopanib was given		
1st line	1	2.7
2nd line	18	48.6
3rd line	14	37.8
4th line	4	10.8
Response to pazopanib		
Partial regression	7	18.9
Stable disease	7	18.9
Progression	19	51.4
Not evaluable	4	10.8
Dose reduction		
No	32	86.5
Yes	5	13.5

Among all patients receiving pazopanib, 18 (48.6%) had stage 2 disease, 14 (37.8%) had stage 3 disease and 4 (10.8%) had stage 4 disease at diagnosis. The median PFS was detected to be 18 weeks with pazopanib. According to tumor grade, PFS was 17 weeks in grade 2 tumors, 19 weeks in grade 3 tumors, 13 weeks in grade 4 tumors and there was no statistical difference between the groups in patients with pazopanib administered(p>0.05) . The PFS was 32 weeks in patients who developed hypothyroidism and 16 weeks in patients who did not develop hypothyroidism. The treatment of pazopanib either in second or third-line therapy did not make difference to overall survival (figure 1D). The median OS was 22 months in patients receiving pazopanib who had stage 2 disease at time of diagnosis while it was 16 months in patients with stage 3 disease (p>0.05) at time of diagnosis. Likewise, the median PFS was 19 weeks in patients receiving pazopanib who had stage 2 disease at diagnosis and then had metastasis while it was 12 weeks in patients with stage 3 disease (p>0.05). During pazopanib use, a total of 22 (59.4%) patients had a history of proton pump inhibitor (PPI) use, 14 (37.8%) patients did not have a history of PPI use. While using pazopanib, any degree of thrombocytopenia was observed in 4 (10.8%) patients, any level of anemia was observed in 18 (48.6%) patients and any level of neutropenia was observed in 7 (18.9%) patients. Hypothyroidism was developed in 5 (13.5%) patients while using pazopanib. Any degree of hepatic dysfunction was observed in 10 (27%) patients, increased bilirubin levels in 11 (29.7%) patients and increased creatinine levels in 5 (13.5%) patients.

Pazopanib dose was reduced in 4 patients as part of our study. Pazopanib dose was reduced in two patients due to cardiac failure, one patient due to hypertension and one patient due to diarrhea.

Discussion

In phase 3 PALETTE study pazopanib was compared with placebo,while PFS was 1.6 months in the placebo arm it was 4.6 months in the pazopanib arm (12). In another study PFS was 3 months in patients who received pazopanib (14). In our study, the PFS was calculated to be 18 weeks and found to be consistent with the literature. It is known from previous studies that patients who developed hypothyroidism due to pazopanip usage had better treatment responses than who did not develop hypothyroidism(15). In our study, PFS was 32 weeks in patients who developed hypothyroidism and 16 weeks in those who did not develop hypothyroidism and there was a significant numerical superiority. In a study performed by Mannavola et al (16), it was detected that the inhibition of iodine intake was associated with the etiology of hypothyroidism induced by tyrosine kinase inhibitors and the mechanism of tyrosine kinase inhibitors to develop hypothyroidism is not entirely known (17). We think that it may be used in the future as a predictive parameter for pazopanib response in patients who develop hypothyroidism compared to those who do not.

The most common side effects were fatigue (65%), diarrhea (58%), nausea (54%), weight loss (48%) and hypertension (41%) in PALETTE study while the most common side effects were anemia (48.6%), hepatic dysfunction (29.7%) and neutropenia (18.9%) in our study. Abnormal hepatic function test is a common side effect observed with pazopanib use (18). In our study, any degree of hepatic dysfunction was observed in 11 patients (29.7%), which is consistent with the literature.

Since impaired hepatic function test is a common side effect, routine hepatic function tests and follow-ups should be performed in patients while using pazopanib.

Since clinical studies were conducted in selected patient groups, the results obtained here should be supported by real-life data. Our study had some limitations such as being single-center, retrospective design, and small number of patients. Due to the small number of patients, subgroup analyzes could not be performed sufficiently. Another limitation of the study is that it was not randomized due to the retrospective nature of the study and the small number of patients. The efficacy and safety of pazopanib should be evaluated as part of multicenter, prospective studies.

Conclusion

Soft tissue sarcomas are a heterogeneous group of malignancies and treatment options are limited. In our single-center, observational study investigating the efficacy of pazopanib in soft tissue sarcomas, pazopanib was found to be effective. In our study, pazopanib showed similar features with other clinical studies in terms of efficacy and side-effect profile. No life-threatening side effects were observed with the use of pazopanib. Side effects associated with pazopanib were acceptable and manageable compared to standard chemotherapies. The development of hypothyroidism associated with pazopanib use may be a predictive marker for response.

Ethics approval

This study was granted ethical approval by Non-Interventional Clinical Trials Ethics Committee of Gazi Yasargil Training and Research Hospital (date and number of decision: 04.07.2019-324) and carried out in accordance with the principles of Declaration of Helsinki.

Conflict of interests

Authors have declared no conflict of interest for this article.

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Authors' contributions

O. K. and Y.S. in concept and design, S. İ. and H. Y. in collecting and processing data, M.Ü. in literature screening.

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