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ORIGINAL ARTICLE

Efficacy of Pazopanib in patients with metastatic uterine sarcoma: A multi-institutional study

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Summary

Purpose: *Uterine sarcoma accounts for 3-9% of uterine malignant tumors and has poor prognosis. Pazopanib is an oral multi-kinase inhibitor and the only tyrosine kinase inhibitor which has been approved for metastatic soft tissue sarcoma. In the present study we aimed to evaluate the efficacy of pazopanib in metastatic uterine sarcoma.*

Methods: *The data of 28 metastatic uterine sarcoma patients receiving pazopanib therapy, who were followed in four oncology centers in Ankara, Turkey between May 2013 and June 2018, were retrospectively analyzed. Patients over 18 years, ECOG performance status ≤ 2, receiving at least one line of chemotherapy for metastatic disease, measurable disease at diagnosis, and histologically proven uterine high grade sarcoma were the inclusion criteria. Progression-free survival (PFS), overall survival (OS), and response rates to pazopanib were retrospectively evaluated.*

Results: *The median age was 53 years (range, 26-76). The majority of the patients had uterine leiomyosarcoma (LMS) (n=25, 89.3%), 2 (7.1%) had undifferentiated uterine sarcoma (UUS), and 1(3.6%) had high grade endometrial stromal sarcoma (ESS). The most common site of metastasis was lung (n: 21, 75%). The median time for pazopanib therapy was 5 months (0.6-28.3). In 22 patients (78.5%), pazopanib was discontinued due to disease progression, while 2 patients (7.1%) quitted therapy owing to toxicity. Partial response was achieved in 4 patients (14.3%), while 17 (60.7%) had stable disease. Median PFS was 5.2 months (95% CI 2.8-7.5) and median OS was 11.4 months (95% CI 3.4-19.5).*

Conclusion: *In the present study aiming to assess the real-life outcome of pazopanib-treated patients, we found that pazopanib is efficient in metastatic uterine sarcoma, and our results correspond to the literature.*

Key words: *pazopanib, sarcoma, uterus, uterine sarcoma*

Introduction

Uterine sarcomas are a heterogeneous tumor group accounting for 3-9 % of all uterine malignant neoplasms [1], with an incidence of 0.36 per 100,000 woman-years in the United States [2]. This heterogeneous tumor originates from myometrium or connective tissue of the uterus. Compared to the endometrial carcinomas, uterine sarcomas have an aggressive course and poor prognosis. Uterine leiomyosarcoma (uLMS) is the most common histological type accounting for 60% of the uterine sarcomas, followed by endometrial stromal sarcoma (ESS), undifferentiated uterine sarcoma (UUS), and adenosarcoma [3].

Uterine sarcomas differ from endometrial carcinomas in terms of clinical behavior and therapeutic management. Uterine sarcoma, which is an aggressive tumor independent of the stage at diagnosis, is associated with high relapse and death risk [4].

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In patients with disease confined to the uterus, the risk for relapse is about 50-70% [5]. Docetaxel plus gemcitabine, doxorubicin-based regimens (doxorubicin plus ifosfamide or olaratumab), single-agent gemcitabine, doxorubicin, pegylated-liposomal doxorubicin, ifosfamide, trabectedin, and pazopanib are therapeutic agents in metastatic disease, with objective response rates ranging between 9.9 and 36% [6-15].

Pazopanib is a multi-targeted, orally active small molecule exerting its effects through inhibition of several tyrosine kinases, including vascular endothelial growth factor receptors (VEGFR-1, -2, -3), platelet-derived growth factor receptors (PDGFR-α and -β), fibroblast growth factor receptors (FGFR-1 and -3), and cytokine receptor (cKIT) [16].

Randomized controlled phase III PALETTE trial evaluated the efficacy of pazopanib monotherapy in patients with metastatic soft tissue sarcomas who showed progression on standard chemotherapy (CT). In the pazopanib group, progression-free survival (PFS) was significantly higher than that in placebo; however, there was no difference in terms of overall survival (OS). On the basis of this trial, pazopanib received Food and Drug Administration FDA approval in April, 2012. In the present retrospective study, we aimed to exhibit our real-life outcomes of patients with metastatic uterine sarcoma (mUS) receiving pazopanib treatment.

Methods

The data of patients with mUS receiving oral pazopanib, who were followed in four oncology centers in Ankara/Turkey between May 2013 and June 2018, were analyzed retrospectively. Clinicopathological characteristics including age, menopausal status, Eastern Cooperative Oncology Group (ECOG) performance status, histological subtypes, tumor grades, stage at diagnosis, primary cytoreductive surgery, presence of adjuvant CT, previous lines of CT given for the metastatic disease, and the sites of metastasis were analyzed.

The therapeutic decisions of the patients were made by their primary oncologist. The patients participated in clinical trials were excluded. Patients over 18 years, ECOG performance status ≤2, patients who received at least one line of CT for metastatic disease, those with a measurable disease at diagnosis, and patients with histologically proven uterine high grade sarcoma were included. Prior to the treatment, detailed anamnesis, physical examination, basal imaging, echocardiography, and blood tests including complete blood counts and serum chemistry panel were performed. Exclusion criteria were defined as follows: insufficient bone marrow reserve, impairment in liver or kidney functions, central nervous system metastasis, a second primary malignancy, history of cardiac disease, poor performance status due to certain comorbidities, and histological subtypes that were excluded in phase III PALETTE trial. All patients received pazopanib 800 mg PO daily. A total of 28 patients were analyzed.

Treatment was continued until disease progression (according to Response Evaluation Criteria In Solid Tumors (RECIST), version 1.0), or unacceptable toxic effects, or refusal by the patient [17]. To determine the treatment response, CT or MRI was performed every 2 months. Treatment response was evaluated according to the RECIST, version 1.0 [17].

Statistics

Statistical analyses were performed using Statistics Package for the Social Sciences (SPSS) software (version

Table 1. The clinicopathological characteristics of patients

	Number (n=28) *n (%)*
Age, Median (Min-max)	53*(26-76**)
Menopausal status	
Premenopausal	12 (42.9)
Postmenopausal	16 (57.1)
ECOG performance status	
0	6 (21.4)
1	22 (78.6)
Histopathology	
LMS	25 (89.3)
High grade ESS	1 (3.6)
UUS	2 (7.1)
Stage at diagnosis	
I	15 (53.6)
II	1 (3.6)
III	3 (10.7)
IV	9 (31.1)
Primary cytoreductive surgery	
Present	27 (96.4)
Absent	1 (3.6)
Adjuvant CT	
Present	12 (42.9)
Absent	16 (57.1)
Number of prior CT lines***	
1	16 (57.1)
2	10 (35.7)
3	2 (7.1)
The sites of metastasis	
Lung	21 (75)
Liver	7 (25)
Bone	2 (7.1)
Pelvic mass	14 (50)

*Median, **Min-max: Minimum-maximum, ***For metastatic disease, LMS: leiomyosarcoma, ESS: endometrial stromal sarcoma, UUS: undifferentiated uterine sarcoma, CT: chemotherapy

17, SPSS, Inc., Chicago, 11). While continuous variables were reported as median and range, binary variables were expressed as counts and percentages. The PFS, OS, and response rates for pazopanib therapy were determined retrospectively. PFS was defined as the time from administration of pazopanib to either first disease progression or death from any cause. OS was defined as the time interval from the date of commencing pazopanib to death due to any cause. Last control date was accepted as the death date for the patients that are alive at the time of evaluation.

The Kaplan-Meier method was used to generate survival curves. A p value < 0.05 was accepted as statistically significant.

Results

A total of 28 patients with mUS treated with pazopanib between May 2013 and June 2018 were included. The baseline clinicopathological characteristics of patients were presented in Table 1. Median age was 53 years (range, 26-76). At diagnosis, 42.9% (n: 12) of patients were premenopausal. Of the patients, 78.6% (n: 22) had ECOG performance status of 0 and 21.4 % (n: 6) had ECOG performance status of 1. As for histopathological types, 25 patients had uterine LMS (89.3%), 2 (7.1%) had UUS, and 1(3.6%) had high grade ESS. Stages of patients at diagnosis were as follows: stage 1 in 15 patients (53.6%), stage 2 in 1 patient (3.6%), stage 3 in 3 patients (10.7%), and stage 4 in 9 patients (31.1%). Except for one patient, all had undergone surgery for the primary tumor. Twelve (42.9%) patients had received adjuvant CT. Prior to pazopanib treatment; all patients had received at least one line of CT for the metastatic disease. Sixteen patients (57.1%) had received one line of CT, while 12 patients (42.8%) had received two or more lines of CT. Twenty-three patients (82.1%) had received doxorubicin-based regimen (with or without ifosfamide), 19 (67.8%) had received gemcitabine plus docetaxel for either metastatic disease or adjuvant setting. The most frequent site of metastasis was lung. Twenty-one (75%) patients had lung metastasis.

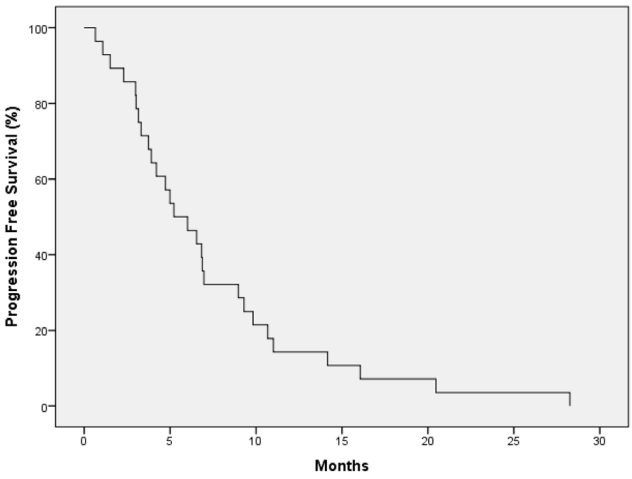

Figure 1. Progression-free survival.

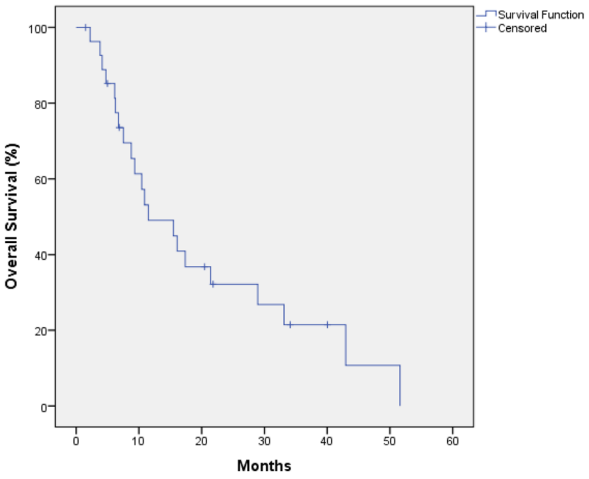

Figure 2. Overall survival.

As for response rates, 4 patients (14.3%) achieved partial response, 17 (60.7%) had stable disease, and 7 (25%) had progressive disease. Disease control rate (partial response + stable disease) was 75%. None of the patients achieved complete response.

As for the survival outcome, median PFS was 5.2 months (% 95 CI 2.8-7.5, Figure 1) and median OS was 11.4 months (% 95 CI 3.4-19.5, Figure 2).

Median time for staying at pazopanib therapy was 5 months (range, 0.6-28.3). Treatment was discontinued in 22 (78.5%) patients due to progression and in 2 patients (7.1%) due to toxicity (cardiac toxicity in 1 patient, hepatotoxicity in 1 patient). Median follow-up time was 10.7 months (range, 1.5-51.6). At the time of data analysis (August 2018), 21 patients died and 7 were alive, among whom 4 patients were still on pazopanib therapy.

Discussion

In the present retrospective study we evaluated the data of 28 patients with mUS treated with pazopanib. Because of the heterogeneity of soft tissue sarcomas (STS), we aimed to evaluate the efficacy of pazopanib in a more homogeneous group of sarcomas by including high grade uterine sarcomas. We found a median PFS of 5.2 months and median OS of 11.4 months. Disease control rate (partial response + stable disease) was 75%. We consider that our results are compatible with the literature.

STS have more than 50 histological subtypes, with distinct features of clinical behavior, response to treatment, and prognostic aspect [18]. Although

these tumor groups were handled and treated in the same way in the past, it is recommended to individualize the treatment in these patients, considering factors such as histological subtype, tumor grade, biological behavior, performance status, and patient preference. Uterine sarcomas are rare tumors with poor prognosis and the treatment of recurrent disease is usually similar to metastatic non-uterine STS. Uterine LMS is the most common histological type of uterine sarcomas and associated with high risk of relapse and death, independent of the stage at diagnosis [4]. Although there is no consensus to guide the CT agent or regimen due to its rarity and histopathological diversity, it is recommended to use CT in mUS [19]. It has been shown that CT improved survival in metastatic disease [20]. Gemcitabine + docetaxel combination and doxorubicin-based regimens (with ifosfamide or olaratumab) are the most widely used first-line regimens [6-8,21]. Olaratumab is an IgG1 monoclonal antibody that binds specifically to PDGFR- α and inhibits receptor activation [22]. In a randomized phase II trial, it was shown that doxorubicin plus olaratumab combination increased OS compared to doxorubicin monotherapy in anthracycline-naive metastatic STS patients (26.5 months versus 14.7 months, p=0.0003) [8]. Owing to the survival advantage provided in this study, olaratumab + doxorubicin combination gained an accelerated approval in the first-line treatment and led to a treatment alteration in metastatic STS after many years.

Pazopanib is a multi-targeted, orally active small-molecule tyrosine kinase inhibitor that targets VEGFR and PDGFR. It is the only tyrosine kinase inhibitor approved in the treatment of mUS. In a phase II study on different STS subtypes including leiomyosarcoma, synovial sarcoma, and other eligible STS, its efficiency as a single agent was demonstrated. However, its activity in liposarcoma did not meet the primary endpoint [23]. Afterwards, the phase III randomized, double blind, placebo-controlled PALETTE trial compared pazopanib and placebo in advanced STS. A total of 369 patients with various STS subtypes (except liposarcoma and gastrointestinal stromal tumor) who had received at least one line of CT were included. Median PFS was 4.6 months (95% CI 3.7–4.8) in the pazopanib arm and 1.6 months (range, 0.9–1.8) in the placebo arm. (Hazard Ratio [HR] 0.31, 95% CI 0.24–0.40; p< 0.0001). OS did not differ significantly (12.5 versus 10.7 months, HR 0.86, 95% CI 0.67-1.1). Of the patients in the pazopanib group, 6% achieved partial response and 67% had stable disease. None of the patients achieved complete response. Leiomyosarcoma patients comprised 43% of this trial. Cox-regression analysis, which was performed to evaluate any PFS superiority among histological subtypes, did not reveal significant difference [14]. On the basis of this study results, pazopanib was approved by the FDA in 2012 for the treatment of advanced STS that progressed on standard CT. In this study which presents our real-life data, we can declare that our results are compatible with the phase III PALETTE trial. In our study, we had a more homogeneous histologic profile that consisted of 90% of leiomyosarcoma subtype. Since there were only 3 patients with non-leiomyosarcoma histology, we could not conduct an analysis to determine the differences according to subtypes. However, we can conclude that our results reflect the outcome of leiomyosarcoma histology. Benson et al evaluated the data of EORTC phase II and phase III (PALETTE) trials retrospectively to search whether response to pazopanib in uterine and non-uterine sarcomas differed. They compared the outcomes of uterine (n: 44) and non-uterine sarcoma (n: 299) patients treated with pazopanib by subgroup analyses and they concluded that pazopanib had similar efficacy in uterine and non-uterine STS [24].

Kim et al enrolled 35 patients in a single-center retrospective study. They analyzed the efficacy of pazopanib as a salvage therapy in heavily-treated patients with mUS. Median PFS was reported as 5.8 months (95% CI=3.8–8.1 months) and OS was 20.0 months (95% CI=11.6–28.4 months). The response rate was 29%, including complete response in one patient. Despite not reaching statistical significance, they stated that leiomyosarcoma subtype responded to pazopanib better than other subtypes [25].

The most important limitation of our study is the lack of data regarding tolerability of pazopanib.

We failed to attain adverse effect records of all our patients, hence we could not analyze tolerability data. Nevertheless, we can say that 2 (7.1%) patients quitted therapy due to toxicity and 22 (78.5%) patients due to disease progression. Of the two patients who discontinued treatment due to toxicity, one had cardiac toxicity (decrease in left ventricle systolic functions, ejection fraction in echocardiography: 35%), and one experienced hepatotoxicity. The lack of data regarding dose reduction, the small number of patients, and the lack of central radiographic assessment were the other weak parts of the study. However, our study represents the real-life experience, with treatment decisions made by patients and physicians, multi-institutional design, exclusion of clinical trial participants, and not having selection criteria similar to clinical trials. Furthermore, our study comprises a more specific patient group than those in the largest retrospective series of metastatic uterine sarco-

ma patients in the literature. We consider our study will contribute to the literature and enlighten the daily practice.

As a consequence, in this study which assessed the real-life outcomes of pazopanib in metastatic uterine sarcoma patients who had received prior chemotherapy, we found that pazopanib is efficient and our results correspond to the literature.

Conflict of interests

The authors declare no conflict of interests.

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