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Therapeutic Efficacy and Dosage of Pazopanib for Metastatic or Unresectable Advanced Soft Tissue Sarcomas

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Abstract

Objective: The molecular targeted drug pazopanib is a selective oral tyrosine kinase inhibitor that exerts its effects on vascular endothelial growth factor receptors (VEGF-R) and inhibits angiogenesis. This study aimed to examine the therapeutic efficacy, incidence of adverse events (AEs), and dosage of pazopanib in Japanese patients with metastatic or unresectable advanced soft tissue sarcoma.

Methods: Subjects were 42 patients (16 men and 26 women) with a history of previous anti-cancer agent treatment, who were administered pazopanib for metastatic or unresectable soft tissue sarcoma between November 2012 and August 2014 at our hospital or affiliated hospitals. Pazopanib was administered at an initial dose of 800 mg/day in 25 patients, 600 mg/day in 7 patients, and 400 mg/day in 10 patients; dose was reduced by 200 mg when continuation of treatment was deemed difficult due to the occurrence of grade ≥ 2 AEs.

Results: After pazopanib treatment, 6-month and 1-year overall cumulative survival rates were 74.7% and 53.5%, respectively (median survival, 7.7 months). Progression-free survival rates after pazopanib administration were 47.7% at 6 months and 27.0% at 1 year (median survival, 5.0 months). With regard to tumor regression effects, 14 of 42 (33.3%) patients achieved a minor response or better, and the effects were evident even among undifferentiated pleomorphic sarcoma (UPS), malignant peripheral nerve sheath tumor (MPNST), angiosarcoma, and alveolar soft part sarcoma (ASPS). Though AEs due to pazopanib were acceptable, 7% developed grade 3-4 liver dysfunction. All of the 25 patients who started on an initial 800 mg/day dose ended up discontinuing or reducing the medication due to the occurrence of AEs after a mean duration of 34.4 days (median, 17 days).

Conclusion: Overall and progression-free median survival after pazopanib administration were 7.7 months and 5.0 months, respectively. Pazopanib proved effective even for UPS, MPNST, angiosarcoma, and ASPS, but continuation of an 800 mg/day dose was difficult among Japanese people.

Keywords: Pazopanib; Soft tissue sarcoma; Dosage; Efficacy; Adverse event; Molecular targeted drug; VEGF-R; Japanese patients

Introduction

Doxorubicin and ifosfamide were the two key drugs that had been widely used for unresectable advanced recurrent soft tissue sarcoma [1,2] until the recent approval of pazopanib, a molecular targeted drug, for public insurance coverage. The use of pazopanib is increasing worldwide [3]. Pazopanib is a selective oral tyrosine kinase inhibitor that acts on vascular endothelial growth factor receptors (VEGF-R) and inhibits angiogenesis [4]. Recently, it has been shown to exhibit inhibitory effects on platelet-derived growth factor receptors (PDGF-R) and a stem cell factor receptor (c-Kit) [5,6]. Moreover, pazopanib was shown to inhibit directly the proliferation of synovial sarcoma cells and block the PI3K-AKT pathway [7]. Clinically, pazopanib is effective against metastatic recurrent renal cell carcinoma [8] and ovarian cancer with high recurrence risk [9]. The efficacy of pazopanib for the treatment of soft tissue sarcoma has been demonstrated in a phase II study of advanced metastatic soft tissue sarcoma, with a reportedly improved progression-free survival at 12 weeks [10]. Subsequently, the efficacy of pazopanib for soft tissue sarcoma was confirmed by a placebo-controlled, multi-center, phase III study [3]. Moreover, a recent phase I study on pediatric soft tissue sarcoma will further provide evidence that verifies the efficacy of pazopanib [11]. However, no study has yet clarified the therapeutic efficacy and dosage of pazopanib in the Japanese population. The present study aimed to examine the tumor regression effects, incidence of adverse events (AEs), and dosage of pazopanib in Japanese patients who were treated with pazopanib for metastatic or unresectable advanced soft tissue sarcoma.

Patients and Methods

Patients

This retrospective study examined 45 patients with a prior history of anti-cancer agent treatment, who were administered pazopanib for metastatic or unresectable soft tissue sarcoma at our hospital or other affiliated hospitals between November 2012 and August 2014. Of these, two patients who could not be followed for more than one month due to rapid exacerbation of their disease, and one patient who was missing detailed data regarding medication, were excluded. The remaining 42 subjects included 16 men and 26 women, with a mean age of 55.0 years (range, 20-88 years) at the time of treatment initiation, and a mean observation period of 10.1 months (range, 1-23 months). Histological types included liposarcoma (7 cases), undifferentiated pleomorphic sarcoma (UPS) (6 cases), leiomyosarcoma (6 cases), malignant peripheral nerve sheath tumor (MPNST), Ewing sarcoma, alveolar soft part sarcoma (ASPS) (3 cases each), synovial sarcoma, rhabdomyosarcoma, solitary fibrous tumor (SFT), myxofibrosarcoma, angiosarcoma (2 cases each), epithelioid sarcoma, extraskeletal myxoid chondrosarcoma, extraosseous osteosarcoma, and desmoplastic small round cell tumor (DSRCT) (1 case each). As shown in Table 1, prior treatment mainly involved the use of ifosfamide, doxorubicin, carboplatin, and etoposide, with the number of regimens ranging from 0 to 4 (mean 1.6) Pazopanib was administered at an initial dose of 800 mg/day in 25 patients, 600 mg/day in 7 patients, and 400 mg/day in 10 patients. When continuation of treatment was deemed difficult due to the occurrence of grade ≥ 2 AEs, dose was reduced by 200 mg. The tumor regression effects, cumulative survival, progression-free survival, incidence of AEs, and dosage of pazopanib were examined.

	All patients (42)
Age, year	
Median (range)	55 (20-88)
Sex, n	
Men	16
Women	26
Histology, n	
Liposarcoma	7
UPS	6
Leiomyosarcoma	6
Others	23
Site of primary disease, n	
Peritoneum	9
Thigh	8
Pelvis	4
Others	21
Number of previous chemotherapy regimens, n	
0	5
1	16
2	14
3-4	7
Previous chemotherapy, n (overlapped)	
Ifosfamide+Doxorubicin	14
Ifosfamide+Carboplatin+Etoposide	9
Carboplatin+Etoposide	8
Doxorubicin	4
Docetaxel	4
Ifosfamide+Etoposide	3
Gemcitabine+Docetaxel	3
Others	14
Disease extent, n	
Mtastastic disease	37
Locally advanced disease	5
Starting dose of pazopanib, n	
400 mg/day	10
600 mg/day	7
800 mg/day	25
Mean dose (mg/day)	671
Dose of pazopanib at final follow-up, n	
Discontinue	30
400 mg/day	7
600 mg/day	4
800 mg/day	1
Mean dose (mg/day)	500
Dose of pazopanib prior to discontinuation	
200 mg/day	1
400 mg/day	12
600 mg/day	11
800 mg/day	6
Mean dose (mg/day)	547
UPS: Undifferentiated Pleomorphic Sarcoma	

Table 1: Characterristics of patients.

Statistical variables and analysis

Computed tomography or magnetic resonance image scans were used to assess the lesions. In accordance with the response evaluation criteria in solid tumors (RECIST) [12], complete response (CR) was

defined as the disappearance of all target lesions, and partial response (PR) and progressive disease (PD) were defined as a ≥ 30% decrease and a ≥ 20% increase, respectively, in the sum of the longest diameter (LD) of target lesions, relative to that prior to treatment initiation. In addition to the RECIST assessment, minor response (MR) was defined as a ≥ 10% and <30% decrease in the sum of the LD, and stable disease (SD) was defined as all other situations (i.e., other than CR, PR, MR, or PD). Response rate was shown as the rate of patients who had MR, PR, and CR to pazopanib. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, version 4.0. Statistical processing of cumulative and progression-free survival rates was performed using the Kaplan-Meier method. Informed consent was obtained from all patients who were administered pazopanib. The Ethics committee of our hospital approved the study.

Results

Maximum therapeutic efficacy of pazopanib was as follows: CR, 0 cases (0%); PR, 2 cases (5%); MR, 12 cases (28%); SD, 20 cases (48%), and PD, 8 cases (19%). Fourteen of the 42 patients (33%) achieved tumor regression. According to histological type, 2 of 2 angiosarcomas (100%), 2 of 3 MPNSTs (67%), 2 of 6 UPSs (33%), 2 of 6 leiomyosarcomas (33%), 1 of 3 ASPSs (33%), 1 of 7 liposarcomas (14%), and 4 of 15 other sarcomas (27%) showed tumor regression (Table 2). At final observation, 24 patients were alive with disease, and 18 had died of disease. After pazopanib treatment, 6-month and 1-year cumulative survival rates were 74.7% and 53.5%, respectively. The mean cumulative survival was 10.1 ± 7.3 months, with a median of 7.7 months (Figure 1a). The 6-month and 1-year cumulative progression-free survival rates were 47.7% and 27.0%, respectively, and the mean progression-free survival was 6.7 ± 5.8 months, with a median of 5.0 months (Figure 1b). The incidences of main AEs were as follows: 28 cases of diarrhea (67%), 22 cases of anorexia (52%), 22 cases of fatigue (52%), 21 cases of hypertension (50%), 19 cases of liver dysfunction (45%), 18 cases of hair hypopigmentation (43%), 13 cases of nausea (31%), 10 cases of eczema (24%), and 7 cases of proteinuria (17%). Among these, grade 3 AEs included liver dysfunction (2 cases, 5%), proteinuria (1 case, 2%), fever (1 case, 2%), melena (1 case, 2%), and ileus (1 case, 2%). One patient developed liver dysfunction (2%) that was judged to be grade 4 AE, but recovered quickly upon discontinuation of pazopanib along with continuous infusion and administration of liver supporting agents (Table 3). All 25 patients who started on 800 mg/day subsequently discontinued treatment or reduced doses due to AEs, which occurred at a mean duration of 34.4 ± 44.4 days (median, 17.0 days) after treatment initiation. At final observation, 12 patients were continued on pazopanib at a mean dose of 500 mg/day (400 mg/day in 7 patients, 600 mg/day in 4, and 800 mg/day in 1). The remaining 30 patients had discontinued treatment due to AEs or aggravated condition; dosage at the time of the last observation prior to discontinuation was 200 mg/day in 1 patient, 400 mg/day in 12 patients, 600 mg/day in 11 patients, and 800 mg/day in 6 patients, with a mean dose of 547 mg/day (Table 1).

Histology	No.	CR	PR	MR	SD	PD	Response rate* (%)
Liposarcoma	7	0	0	1	5	1	14
UPS	6	0	1	1	2	2	33
Leiomyosarcoma	6	0	0	2	2	2	33
MPNST	3	0	0	2	1	0	67
ASPS	3	0	0	1	2	0	33
Ewing sarcoma/PNET	3	0	0	0	2	1	0
Synovial sarcoma	2	0	0	0	2	0	0
Rhabdomyosarcoma	2	0	0	0	2	0	0
SFT	2	0	0	1	1	0	50
Myxofibrosarcoma	2	0	0	0	1	1	0
Angiosarcoma	2	0	1	1	0	0	100
Epithelioid sarcoma	1	0	0	1	0	0	100
Extraskeletal chondrosarcoma	1	0	0	1	0	0	100
DSRCT	1	0	0	0	0	1	0
Extraskeletal osteosarcoma	1	0	0	1	0	0	100
Total	42	0	2	12	20	8	33

* Response rate shows the rate of patients who had a minor response (MR) or better.

UPS: Undifferentiated Pleomorphic Sarcoma; MPNST: Malignant Peripheral Nerve Sheath Tumor; ASPS: Alveolar Soft Part Sarcoma; PNET: Primitive Neuroectodermal Tumor; SFT: Solitary Fibrous Tumor; DSRCT: Desmoplastic Small Round Cell Tumor

Table 2: Response rates to pazopanib by sarcoma subtype.

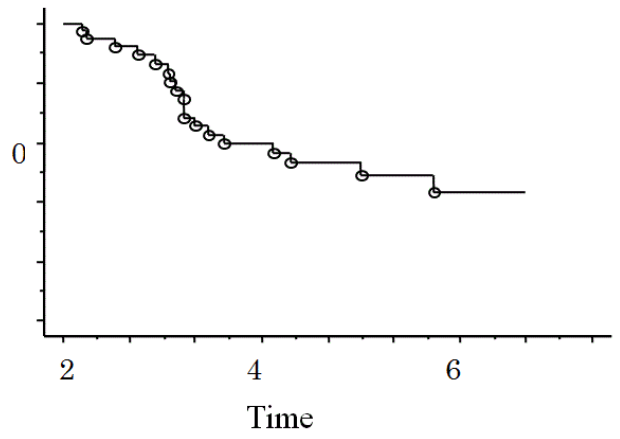

Figure 1a: Kaplan-Meier curve shows overall survival after pazopanib administration. The 6-month and 1-year cumulative survival rates were 74.7% and 53.5%, respectively.

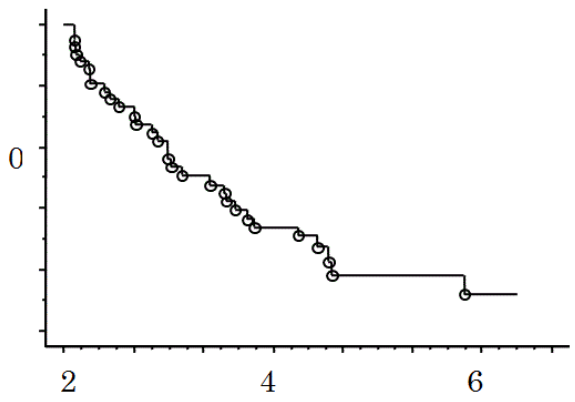

Figure 1b: Kaplan-Meier curve shows progression-free survival after pazopanib administration. The 6-month and 1-year cumulative progression-free survival rates were 47.7% and 27%, respectively.

	All grades		Grade 1-2		Grade 3		Grade 4	
	Number	Rate (%)	Number	Rate (%)	Number	Rate (%)	Number	Rate (%)
Diarrhea	28	67	28	67	0	0	0	0
Anorexia	22	52	22	52	0	0	0	0
Fatigue	22	52	22	52	0	0	0	0
Hypertension	21	50	21	50	0	0	0	0
Liver dysfunction	19	45	16	38	2	5	1	2
Hair hypopigmentation	18	43	18	43	0	0	0	0
Nausea	13	31	13	31	0	0	0	0
Eczema	10	24	10	24	0	0	0	0
Proteinurea	7	17	6	14	1	2	0	0
Abdominal pain	6	14	6	14	0	0	0	0
Nasal bleeding	5	12	5	12	0	0	0	0
Hyper bilirubinemia	3	7	3	7	0	0	0	0
Fever	3	7	2	5	1	2	0	0
Melena	1	2	0	0	1	2	0	0
Ileus	1	2	0	0	1	2	0	0

Table 3: Adverse events related to pazopanib.

Case presentation

Case: A 67-year-old man had an UPS in the right thigh, which had metastasized to the lungs and bones. Five months after pazopanib treatment, his tumor decreased in diameter from 13 mm to 8 mm (37 reduction), achieving a PR. He was initially started on 800 mg/day, but the dose was reduced to 600 mg/day after one month and 400 mg/day after 2 months due to AEs; he has been continued on 400 mg/day thereafter (Figure 2).

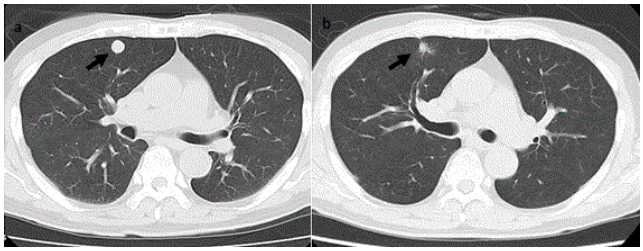

Figure 2: The CT scan findings of a 67-year-old male with lung metastases from UPS in the right thigh: **a**) before pazopanib treatment, and **b**) 5 months after pazopanib treatment. The therapeutic efficacy was PR.

Discussion

We examined the tumor regression effects, incidence of AEs, and dosage of pazopanib in Japanese patients who were treated with pazopanib for metastatic or unresectable advanced soft tissue sarcoma. The therapeutic efficacy of pazopanib has been demonstrated in a phase II study (i.e., the EORTC study 62043) [10], with a 12-week progression-free rate of 26% for liposarcoma, 44% for leiomyosarcoma, 49% for synovial sarcoma and 39% for other sarcomas [10]. In a phase III study (i.e., the PALETTE study) [3], response rates were 6% (PR), 67% (SD), and 23% (PD) in the pazopanib group, with a significantly improved progression-free period of 4.6 months compared to the placebo group (i.e., 1.6 months). In the present study, response rates were 5% (PR), 28% (MR), 48% (SD), and 19% (PD). Fourteen of 42 (33%) patients showed tumor regression, and the 6-month and 1-year progression-free rates after pazopanib treatment were 47.7% and 27.0%, respectively, with a median progression-free survival of 5.0 months.

These results were consistent with those of the PALETTE [3] study, and demonstrate the efficacy of pazopanib for advanced recurrent soft tissue sarcoma in our patient population. With regard to the therapeutic effects according to histological type, Kasper et al. [13] reported that 31 of 137 leiomyosarcoma cases (23%), 10 of 68 synovial sarcoma cases (15%), 4 of 9 angiosarcoma cases (44%), 4 of 7 ASPS cases (57%), 4 of 7 SFT cases (57%), and 2 of 6 DSRCT cases (33%) achieved a long-term response. Thus, responses were observed even among those for whom chemotherapy had not proven very effective, such as angiosarcomas, ASPS, SFT, and DSRCT. Recently, the efficacy of pazopanib has also been confirmed empirically using a clear cell sarcoma cell line [14]. In the present study, 2 of 2 angiosarcoma cases, (100%), 2 of 3 MPNST cases (67%), 2 of 6 UPS cases (33%), 2 of 6 leiomyosarcoma cases (33%), 1 of 3 ASPS cases (33%), and 1 of 7 liposarcoma cases (14%) showed tumor regression; thus, pazopanib was effective even for MPNST, UPS, angiosarcoma, and ASPS. Conventionally, the therapeutic effects of anti-cancer agents have not been readily observed in cases of MPNST, UPS, angiosarcoma, and ASPS [1,2,15]. Therefore, our finding that pazopanib is also effective for those sarcomas will expand the range of future therapeutic options for malignant soft tissue sarcomas. While a variety of histological types appear in malignant soft tissue sarcomas, many overexpress VEGF [16-19], as well as other angiogenic factors such as PDGF and c-Kit, regardless of their histological types [20-22]. Pazopanib was shown to be effective, even for sarcomas that present difficulty in achieving adequate therapeutic effects with conventional anti-cancer agents, possibly due to its inhibitory action on various tyrosine kinases, including VEGF-R and PDGF-R. The PALETTE study reported AEs including fatigue (65%), diarrhea (58%), nausea (54%), hypertension (41%), anorexia (40%), hair hypopigmentation (38%), eczema (18%), and liver dysfunction (13%) [3]. Similarly in the present study, diarrhea, anorexia, fatigue, hypertension, and liver dysfunction were among those that occurred with a high incidence (Table 3). All AEs improved after discontinuation or dose reduction, although one patient developed grade 4 liver dysfunction, requiring caution [23]. Moreover, although it was not noted in the present study, the occurrence of pneumothorax during pazopanib treatment for lung metastases has been previously reported [24], suggesting that careful observation over time is required in the treatment of lung metastases. The recommended pazopanib dose is 800 mg/day, according to a phase I clinical study [25] performed in the United States to assess multiple dose regimens; this dose was also selected in a phase II study [10] and phase III study [3]. However, patients in the present study had difficulty continuing on the 800 mg/day initial dose after a mean duration of 34 days (median, 17days), and had to reduce their doses. Moreover, among the 12 patients who were continued on pazopanib at the final observation, the mean dose was 500 mg/day. Furthermore, among those who discontinued treatment, the final mean dose prior to discontinuation was 547 mg/day. Pazopanib is metabolized primarily in the liver by its main metabolic enzyme CYP3A4 [26]. In a clinical study of trabectedin (i.e., another drug mainly metabolized by CYP3A4), the optimal dose was reportedly 1.5 mg/m^2 among Western patients. However, a phase I study targeting Japanese patients reported that this dose (i.e., 1.5 mg/m^2) caused severe AEs, and recommended that a 1.2 mg/m^2 dose, which was sufficient to maintain an adequate blood concentration [27], would be appropriate. These results suggest that for Japanese patients, an initial dose of 400-600 mg/day might be adequate, with a possible dose increase in a gradual manner. There are several limitations to this study, including the overall small sample size, retrospective design, and variation in the number of patients by histological type. However, to date, few studies have examined the therapeutic efficacy and dosage of pazopanib in a Japanese population. The findings of this study will provide valuable information regarding the efficacy, incidence of AEs, and dosage of pazopanib in Japanese patients with metastatic or unresectable advanced soft tissue sarcoma.

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