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ORIGINAL ARTICLE

Assessment of Pazopanib-Related Heart Failure in Patients With Advanced Soft Tissue Sarcoma

— A Single Institute Analysis —

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Background: Heart failure (HF) is one of the potential adverse events of pazopanib treatment for soft tissue sarcoma (STS), but detailed reports of such HF cases are scarce. This study determined the incidence and risk factors of HF following pazopanib treatment for STS at our Institute and the clinical outcomes.

Methods and Results: This study retrospectively analyzed the cases of STS patients treated with pazopanib (n=151) between 2012 and 2020. HF occurred in 6 patients (3.9%) at the median onset of 137 (range 14–468) days after the treatment initiation. When their HF was diagnosed, pazopanib was interrupted in all 6 patients. No patients experienced HF-related death, and HF development was not a significant factor for poor overall survival. The cumulative doses of anthracyclines (>225 mg/m^2) before pazopanib initiation (83% vs. 37%, P=0.031), pazopanib initiation at age ≥60 years (83% vs. 35%, P=0.026), and the baseline B-type natriuretic peptide (BNP) concentration (≥50 pg/mL) before pazopanib (67% vs. 11%, P=0.002) initiation were predictive factors for post-pazopanib treatment HF.

Conclusions: The study findings highlight the effect of past anthracycline exposure and baseline BNP for pazopanib-associated HF. Although the study patients' clinical outcomes were generally favorable, periodic monitoring of cardiac function using ultrasonic echocardiography or serum markers is essential to detect events early and begin therapeutic intervention appropriately under a cardiologist's instructions.

Key Words: Cardio-oncology; Heart failure; Pazopanib; Soft tissue sarcoma; Tyrosine kinase inhibitor

Pazopanib is an antiangiogenic oral tyrosine kinase inhibitor (TKI) that targets the receptors of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), and it is currently approved for the treatment of metastatic soft-tissue sarcoma (STS) and renal cell carcinoma (RCC).[1,2] Pazopanib treatment is generally well tolerated, with common side-effects such as fatigue, hypertension, liver dysfunction, and gastrointestinal toxicity.[1] As increased numbers of patients are receiving TKI treatment, it has become known that heart failure (HF) following the administration of a TKI occurs in some patients. The onset mechanisms of these instances of HF are unknown, but it was suggested that the inhibition of VEGF receptor (VEGFR) and PDGF receptor (PDGFR) could induce cardiomyocyte apoptosis, and that the off-target inhibition of adenosine monophosphate (AMP)-activated protein kinase by a TKI could alter metabolic homeostasis in the heart.[3,4] It is also possible that TKI treatment induces HF by elevating blood pressure.

Two systematic reviews and a meta-analysis of >10,000 patients who were treated with VEGFR–TKIs, including pazopanib, revealed that the incidence of HF of any grade was 2.4% and 3.2%, respectively.[5,6] In a subgroup analysis of the meta-analysis, the HF risk was not significantly

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Table 1. Clinical Characteristics of the 151 Patients With STS Who Received Pazopanib Treatment

Variable	
Age (years), median (range)	52 (19–75)
Male	71 (47)
Female	80 (53)
Pathological subtype	
Leiomyosarcoma	27 (18)
Synovial sarcoma	15 (10)
Liposarcoma	25 (16)
Other histologies	84 (56)
ECOG PS	
0	88 (58)
1	58 (39)
≥2	5 (3)
Smoking history	49 (32)
Hypertension	30 (20)
Diabetes mellitus	12 (8)
History of heart disease	3 (2)
ACEIs/ARBs	11 (37)
CCBs	17 (57)
Diuretics	2 (7)
BBs	3 (10)
Baseline BNP before pazopanib treatment, (pg/mL), median (range)	(1–229)
Creatinine, mg/dL, median (range)	0.69 (0.32–1.64)
Creatine kinase, ng/dL, median (range)	74 (4–533)
Baseline EF (%) before pazopanib treatment, median (range)	67 (40–81)
Baseline EF (%) before doxorubicin treatment, median (range)	70 (59–86)

Data are presented as n (%) unless otherwise stated. ACEIs, angiotensin-converting inhibitors; ARBs, angiotensin receptor blockers; BBs, β-blockers; BNP, baseline B-type natriuretic peptide; CCBs, calcium channel blockers; ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction; PS, performance status; STS, soft tissue sarcoma.

different among tumor types or among the various VEGFR–TKIs used.[6] A Phase III trial comparing pazopanib with sunitinib treatment for patients with RCC described symptomatic cardiac dysfunction and a ≥15% decrease in the absolute left ventricular ejection fraction (LVEF) in 1% and 9% of the pazopanib-treated patients, respectively.[7] Detailed information about pazopanib-related HF is still insufficient.[8–12] In light of the potential lethality of pazopanib treatment, the early detection of HF and appropriate therapeutic intervention are essential. In this study, we present the clinical features of 6 patients with STS who developed HF after being treated with pazopanib.

Methods

Study Design and Patient Selection

We retrospectively reviewed the medical records of patients with STS who were treated with pazopanib at our Institute between December 2012 and February 2020. The initial daily dose of pazopanib was 800 mg in all patients. Baseline characteristics included sex, age at pazopanib start, pathological STS subtype, Eastern Cooperative Oncology Group (ECOG) performance status, pre-existing cardiovascular comorbidities (hypertension and diabetes mellitus), smoking history, body mass index (BMI), past history of any heart disease, and cumulative anthracycline dose before pazopanib initiation.

We extracted information about the patient cases who developed HF during pazopanib treatment and analyzed the incidence of HF and the clinical management for HF, which included symptomatic cardiac dysfunction, or an absolute LVEF <50% and a ≥10% absolute LVEF decrease based on a comprehensive decision, as described.[13] We used these evaluations based on the 2020 European Society for Medical Oncology (ESMO) consensus recommendations.[14] We determined clinical risk factors associated with HF by comparing the characteristics between patients with and without HF. The patients' cardiac function was assessed based on the LVEF shown by ultrasonic echocardiography (UCG) and the level of a serum cardiac marker (i.e., baseline B-type natriuretic peptide [BNP]). The BNP value was determined before pazopanib initiation in all but 1 of 150 patients. After pazopanib treatment, the BNP value was checked monthly. One-hundred and forty-seven patients underwent an echocardiography examination before pazopanib initiation. Thirty-nine patients underwent an echocardiography examination after the completion of their pazopanib treatment. The assessment interval in respective patients was decided based on the clinical judgement of the attending physician.

Pinkhas et al reported that the systolic blood pressure (SBP) of 75% of the patients in their study increased during pazopanib therapy,[15] and we thus analyzed the present study patients' SBP. Among the patients without pre-existing hypertension (HTN) in the Pinkhas et al study, the median time to incident HTN was 19 days (range 7–53 days).[15] In our present study, the SBP was first determined at day 14 after pazopanib initiation.

This study was approved by the Ethics Committee of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research.

Statistical Analyses

Differences in categorical variables between groups were analyzed by using Fisher's exact test. Survival curves were estimated by using the Kaplan-Meier method, and P values were calculated by using the log-rank test. Effects were considered significant if 2-sided P values were <0.05. All statistical analyses were performed using EZR ver. 1.53 (Saitama Medical Center, Jichi Medical University), which is based on R and R commander.[16]

Results

Patient Characteristics

The baseline characteristics of the 151 patients with STS treated with pazopanib at our institute during the study period (80 females, 71 males) are presented in **Table 1**. The median patient age was 52 years (range 19–75 years). Thirty-two percent of the patients had a current or past smoking history, 20% had hypertension, and 2% had a history of arrythmia (2 patients with atrial fibrillation [Af] and 1 patient with Wolff-Parkinson-White [WPW] syndrome).

Age ≥60 Years at Pazopanib Initiation, >50 pg/mL Baseline BNP Concentration, and Cumulative Doxorubicin (ADR) Dose >225 mg/m² Were Significantly Higher in the HF Group

The results of the comparison of background characteristics between the patients with HF (n=6) and those without HF

Table 2. Comparison of the Baseline Characteristics of Patients With STS Who Received Pazopanib Treatment, Categorized by HF and No HF

Characteristic	HF (n=6)	Non-HF (n=145)	P value
Gender			0.69
Male	2	69	
Female	4	76	
Age at pazopanib initiation (years)			0.03
≥60	5	51	
<60	1	94	
PS			1
0	4	85	
≥1	2	60	
BMI ≥25	2	34	0.63
Hypertension	1	30	1
DM	0	12	1
Smoking history	0	48	0.18
History of heart disease	0	3	1
Cumulative ADR dose (mg/m^2)			
>180	5	73	0.21
>225	5	53	0.03
Baseline EF before pazopanib treatment (%)			
≥50	6	138	1
≥60	6	126	1
Baseline BNP >50 pg/mL pre-pazopanib treatment	4	14	0.002

Differences in categorical variables between groups were analyzed using Fisher's exact test. ADR, doxorubicin; BMI, body mass index; HF, heart failure. Other abbreviations as in Table 1.

(n=145) are given in **Table 2**. As has been reported, age ≥60 years tended to be a predictor of a pazopanib-related cardiovascular adverse event,[17] and we also used age (≥60 years vs. <60 years) for the logistic regression analysis in this study. The percentages of patients whose age at pazopanib initiation was ≥60 years and those who had a baseline BNP concentration that was >50 pg/mL were significantly higher in the HF group (83% vs. 35%, P=0.026; 67% vs. 11%, P=0.002, respectively). The HF group also had a significantly higher percentage of a cumulative ADR dose >225 mg/m^2 (83% vs. 37%, P=0.031). No significant between-group difference was observed concerning BMI ≥25, smoking history, hypertension, and diabetes mellitus.

The survival curves of the total series of 151 STS patients are shown in **Figure**. The 1-year overall survival (OS) rate in the entire cohort was 49%, and the OS was not significantly different between the HF and non-HF groups (1-year OS rate 67% vs. 48%, P=0.21). No significant difference in SBP was observed between the HF and non-HF groups before pazopanib initiation (126±18 mmHg vs. 132±11 mmHg; P=0.68) or at 14 days after pazopanib initiation (135±18 mmHg vs. 136±18 mmHg; P=0.19). The maximum elevation of SBP during pazopanib treatment was also similar in the 2 groups (142±20 mmHg vs. 153±16 mmHg; P=0.31).

Detailed Information of the 6 Patients Who Experienced HF

The clinical data of the 6 patients who developed HF are summarized in **Table 3**. The occurrence of any clinical symptom was observed in 4 patients. The baseline LVEF at pazopanib initiation was >60% (i.e., within the normal range) in all 6 patients. At the time point of the appearance of HF, the absolute LVEF was <50% in 5 of the 6 patients, and an absolute decline in LVEF >10% from baseline was observed in 5 patients.

Overall, 5 of the 6 patients had an increased BNP level (≥200 pg/mL) at the time point at which their HF developed. No patients had elevated creatine kinase (CK), CK-MB, or troponin I levels at the diagnosis of their HF. The median cumulative ADR dose before the diagnoses of HF was 368 mg/m^2 (range 0–450 mg/m^2). The duration (days) from the final ADR administration or the pazopanib initiation to the diagnosis of HF was 348 days (range 178–523 days) and 137 days (range 14–468 days), respectively. HF occurred during pazopanib treatment in 4 patients (67%) and after the end of the treatment in 2 patients. Notably, 2 patients developed HF within 14 days of pazopanib initiation (Patients 1 and 4), and 1 patient without anthracycline exposure (Patient 5) had a striking LVEF decline (from 62% to 28%) at 251 days after the final pazopanib treatment.

Following the instructions of a cardiologist, pazopanib treatment was interrupted in all 6 patients when HF was observed, and 5 patients received treatment with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), a β-blocker (BB) (n=5), and diuretics (n=3). At HF development, Patient 6 was diagnosed with Af, and direct oral anti-coagulant (DOAC) edoxaban treatment was initiated. Overall, 4 of the 6 patients recovered from HF, whereas the other 2 patients (Patients 3 and 5) maintained a decreased LVEF (30% and 35%) even after the therapeutic intervention. And 1 of the 6 patients had an increased BNP level (≥200 pg/mL) after the completion of pazopanib intervention. Pazopanib treatment was not reintroduced for any of the patients.

Discussion

This is one of the largest-scale retrospective studies to focus

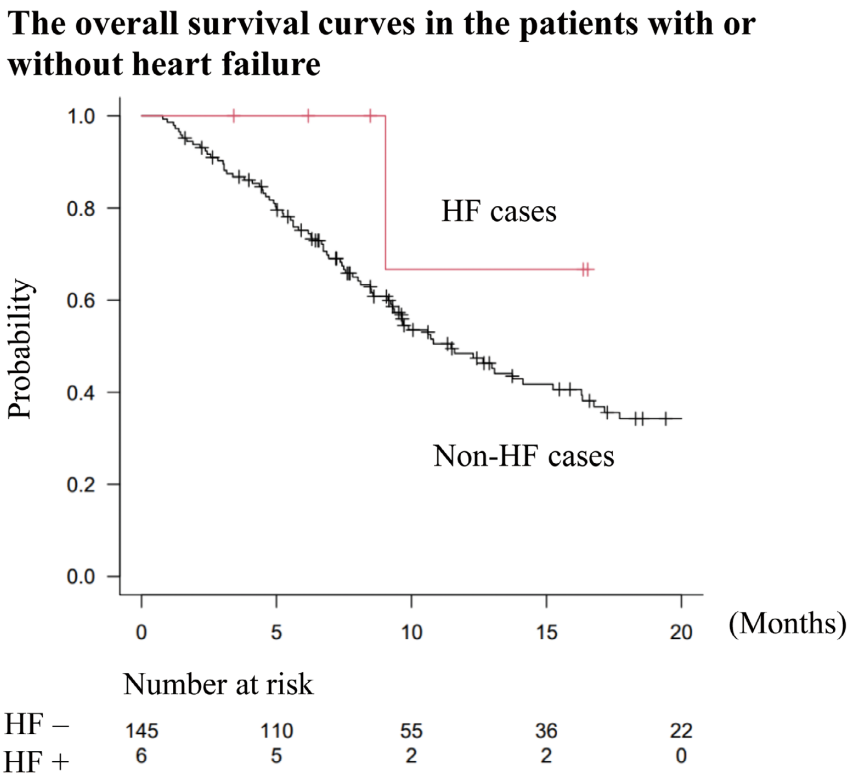

Figure. Overall survival (OS) curves for patients who developed heart failure (HF) and those who did not. The OS was calculated from the initiation of pazopanib treatment.

Table 3. Detailed Information of the 6 Patients Who Experienced HF Following Pazopanib Treatment

Case number	1	2	3	4	5	6
Sex	F	F	M	F	M	F
Age (years)	67	72	76	71	49	76
Pathological diagnosis	Spindle cell sarcoma	Leiomyosarcoma	MPNST	Leiomyosarcoma	Spindle cell sarcoma	Leiomyosarcoma
Clinical symptoms	Fatigue	Exertional, dyspnea	Breathless, peripheral edema	None	None	Dyspnea, palpitation
EF at baseline/HF diagnosis, %	69/68	61/46	73/28	66/49	62/28	66/45
Absolute EF decrease, %	1	15	45	17	34	21
EF, % (post-interruption)	68 (2 months)	50 (2 months)	35 (2 weeks)	64 (2 months)	30 (1 month)	57 (2.5 months)
BNP at baseline/HF diagnosis, pg/mL	79/219	45/449	61/1,370	128/471	6/25	75/258
BNP, pg/mL (post-interruption)	72 (2 months)	119 (2 months)	53 (1 month)	41 (2 months)	54 (1 month)	243 (2.5 months)
CK at HF diagnosis, ng/mL	24	72	108	101	NA	163
CK-MB at HF diagnosis, ng/mL	NA	NA	4	NA	NA	7
Troponin-I at HF diagnosis, pg/mL	NA	19.5	1	35.7	4.1	10.7
Cumulative ADR dose, mg/m^2	375	300	450	450	0	360
Days from final ADR to HF	523	294	178	245	NA	501
Days from pazopanib initiation to HF	14	112	83	14	468	132
Days from final pazopanib to HF	0	0	0	0	251	119
ACEI/ARB	Yes	Yes	Yes	No	Yes	Yes
BB	Yes	Yes	No	Yes	Yes	Yes
Diuretics	Yes	Yes	Yes	No	No	No
Intervention by a cardiologist	Yes	Yes	Yes	Yes	Yes	Yes

CK, creatine kinase; MPNST, malignant peripheral nerve sheath tumor; NA, not applicable. Other abbreviations as in Tables 1,2.

Table 4. Previous Case Reports About Pazopanib-Associated HF

No.	Age	Sex	Disease	EF at baseline, %	EF at HF development, %	BNP at HF development, pg/mL	Cumulative ADR dose, mg/m^2	Initial pazopanib dose, mg/day	Days from pazopanib initiation to HF	Clinical management	Outcome	Ref.
1	27	M	Leiomyosarcoma	NA	20–25	NA	450	800	28	Maximal supportive treatment including hemodynamic and ventilatory support	Dead	8
2	49	M	Spindle cell sarcoma	NA	10–15	NA	NA (3 cycles)	NA	10	BB and ACEI	Alive	9
3	50	F	Leiomyosarcoma	60	25	NA	NA (6 cycles)	800	60	BB, ACEI and diuretics	Dead	10
4	51	F	Thoracic sarcoma	75	10	5,000	NA (Yes)	600	15	Maximal supportive treatment	Dead	11
5	70	M	Renal cell carcinoma	40–45	15–20	2,685	0	600	10	Maximal supportive treatment including ventilatory support and catecholamines	Alive	12

F, female; M, male; NA, not available. Other abbreviations as in Tables 1,2.

on the development of HF in sarcoma patients treated with pazopanib. The incidence of HF in the present series of 151 patients was 3.9%, which is similar to the finding of the above-mentioned meta-analysis.[5,6] Our literature search revealed case reports of pazopanib-associated HF in 5 patients;[8–12] the patients' clinical features are summarized in **Table 4**. The duration from pazopanib initiation to HF development was <4 weeks in 4 of the 5 patients. At the time of HF diagnosis, all patients had an LVEF <30% shown by UCG, and 2 patients died due to HF, regardless of maximal supportive treatment. Our present study patients (6 in total) have slightly different features, as follows.

Three of the six patients developed HF at >3 months after pazopanib initiation. The LVEF at HF diagnosis was >40% in 4 of the patients, and HF symptoms recovered without maximal supportive treatment in all 6 cases. HF did not have an adverse impact on the patients' OS. Regarding the severity of HF, the first possible explanation is that our analysis included mainly low cardiovascular-risk cases. As shown in **Table 2**, the percentages of patients who had a history of hypertension, diabetes mellitus, or heavy smoking (Brinkman index >400) were low. In addition, the most important factor is the optimal and timely intervention by a cardio-oncology team. For all 6 patients, therapeutic intervention was conducted under the instructions of cardio-oncologists immediately when the symptomatic cardiac dysfunction appeared or abnormal UCG findings and lab data were observed by a laboratory technician.

For the prevention and the mitigation of HF development, appropriate screening of patients' cardiac function before and during their treatment is indispensable. The American Society of Clinical Oncology (ASCO) practice guideline for cancer survivors recommends regular monitoring by UCG and the measurement of serum cardiac biomarkers, although a uniform schedule and duration for this monitoring have not been established.[18] The ESMO guidelines concerning cardiac disease in cancer patients state that patients with a baseline LVEF >50% are suitable candidates for chemotherapy.[19] Those guidelines also recommend a temporary withholding of treatment with cardioprotective therapy (an ACEI/ARB or BB) when the absolute LVEF decreases by >10% and an absolute LVEF <50% is detected. Consistently, our 6 patients had baseline LVEF values ≥60%, and they received an ACEI/ARB or BB for the treatment of their HF.

The results of our analyses demonstrate that the observation of a cumulative dose of anthracyclines (ADR >225 mg/m^2) before pazopanib induction and an elevated baseline BNP level (≥50 pg/mL) could each be useful for predicting the potential risk of HF development. Swain et al showed that the rate of ADR-associated HF was elevated depending on the ADR dose (5% at a cumulative dose of 400 mg/m^2, 16% at a dose of 500 mg/m^2, 26% at a dose of 550 mg/m^2, and 48% at a dose of 700 mg/m^2).[20] The standard dose of ADR for STS patients is 75 mg/m^2 per cycle; the cut-off value of our analysis of the cumulative ADR (i.e., 225 mg/m^2) indicates 3 cycles of ADR. There were 10 patients in the present series whose cumulative ADR treatment dose was between 225 and 250 mg/m^2, which is the cut-off value used by the ASCO guideline. For our Patient 5, with no history of ADR, a direct association with pazopanib was indicated. A similar case was reported by Wang et al, as HF developed in their patient shortly after pazopanib initiation.[12]

BNP is a type of cardiac marker reflecting the degree of ventricular burden.[20,21] According to the 2017 Japanese Circulation Society/Japanese Heart Failure Society (JCS/JHFS) guidelines, the upper normal limit for BNP is 18.4 pg/mL.[13] Patients with a BNP level 40–100 pg/mL are likely to develop mild HF (NYHA class II or greater), and the cut-off value that we identified (46 pg/mL) is within this range. It should be noted that the BNP levels differ among individuals and assessments are necessary by a time series.

Another important discussion concerns the potential reintroduction of pazopanib after a patient has recovered from HF symptoms. Under no definite recommendations, van Marcke et al reported the case of a patient who died due to HF after pazopadnib resumed, and they noted that discontinuation of pazopanib treatment might be best.[11] Further clinical data are warranted to test this hypothesis.

Study Limitations

This study has some limitations to address. Cardiac catherization and coronary CT are not routinely performed at our institution, and the possibility of other causes of HF such as coronary artery disease and cardiomyopathy thus

cannot be excluded. In 5 of the 6 patients, cardiologists comprehensively denied the involvement of ischemia based on the patients' cardiac biomarker levels, the results of physiological function evaluations (ECG and UCG), and clinical symptoms. In Patient 3 (who suffered from chest tightness), cardiac catheterization and cardiac MRI were performed, and the results excluded acute myocardial infarction.

Most of our patients with HF had a past history of ADR exposure, and it is difficult to exclude the effect of ADR when assessing pazopanib-associated HF. Due to the retrospective nature of this study, the intervals used for UCG and BNP monitoring varied among the patients. Multiple ultrasound technicians assessed the patients' LVEF values, which complicates the validation of the measurement results. In addition, the UCG was conducted based on each clinician's decision, and this might have missed the existence of asymptomatic cases who had decreased cardiac function. In addition, this study focused solely on systolic cardiac function in UCG, and the assessment of diastolic function would be insufficient. The parameter of global longitudinal strain (GLS), which exhibits longitudinal shortening as a percentage, is known to be excellent for detecting subclinical cardiac dysfunction at an early phase.[22] In the present series, the baseline GLS was measured in only 2 patients (Patient 4: −11.8% and Patient 5: −4.0%).

Conclusions

Our findings suggest that the cumulative dose of anthracycline and an increased baseline BNP value might be important factors for evaluating HF after pazopanib treatment with the limited data. To prevent cardiac dysfunction, oncologists should pay attention to clinical symptoms such as dyspnea and edema, and provide careful monitoring of the patients' LVEF with UCG. Also, monitoring the BNP level is important not only before pazopanib introduction but also during and after the treatment. Oncologists should consult cardiologists to manage the cardiovascular problems of their patients at as early a time point as possible.

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Disclosures

None of the authors have any potential conflicts of interest associated with this research to declare.

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IRB Information

The Ethics Committee of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (Reference number: 2020GA1312) approved this study.

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