Managing pazopanib toxicity in the treatment of advanced soft tissue sarcoma

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Abstract

Background Pazopanib is a multikinase inhibitor registered for the treatment of advanced renal clear cell carcinoma (RCC) and as second or further-line therapy in advanced non-adipocytic soft tissue sarcoma (STS). It is a relatively well-tolerated compound, but, as with many other tyrosine kinase inhibitors (TKI), chronic toxicity may become a challenge that both patient and physician need to take into account when starting treatment. This retrospective study investigated toxicities and their management in STS patients treated with pazopanib in routine clinical practice in Italy.

Materials and Methods Data were collected between January 2013 and May 2016 at Candiolo Cancer Institute and Prato Medical Oncology Unit. The primary objective was to describe observed toxicities in a real-life setting, and use this information to inform strategies for adverse event management.

Results A total of 43 patients with advanced STS who received treatment with pazopanib were included. Median progression-free survival was 4 months and median overall survival was 18 months. The most common toxicities were fatigue (74.4%), hypertension (72%), hair hypopigmentation (74.4%) and diarrhea (60.5%). Liver toxicities occurred in less than one-third of patients. Severe adverse events, requiring drug interruption, were relatively rare.

Conclusions This study confirms the safety and efficacy of pazopanib in pretreated unresectable or metastatic soft tissue sarcoma, and highlights the importance of close follow-up and patient support to improve compliance and treatment duration.

Introduction

Pazopanib is a multikinase inhibitor targeting KIT, PDGFR, VEGFR and FGFR that is currently registered for the treatment of advanced renal clear cell carcinoma (RCC) and as second or further-line therapy in advanced non-adipocytic soft tissue sarcoma (STS) [1-2]. This drug was initially developed in RCC because it selectively binds VEGFR to inhibit angiogenesis [3]. However, the precise role of other tyrosine kinase receptor (TKR) inhibition is still not completely understood. Pazopanib has been studied in other indications, including gastrointestinal stromal tumors (GIST), because it also targets KIT and PDGFR [4-5].

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CANCER BREAKING NEWS 2016;4(3):30-35
DOI: 10.19156/cbn.2016.0026

Overall, pazopanib is a relatively well-tolerated compound but, as with many other tyrosine kinase inhibitors (TKI), chronic toxicity may become a challenge that needs to be considered by both the patient and their physician when starting treatment [6-8].

In fact, there is a good body of data data across several indications confirming that oral agents, and TKIs in particular, are demanding therapies. This is true for several reasons, but a long-term persisting adverse event may be more problematic overall than a more severe event that that only lasts a few days. This highlights the importance of patient motivation and education to facilitate early recognition and management of adverse events as a key element to establishing adequate compliance with treatment.

Therapeutic continuity is, therefore, a consequence of early and correct symptom management implemented by both patients and physicians [9-10].

For reasons that are not completely understood, the toxicity profile of pazopanib is slightly different in patients with RCC compared to those with STS. This might be related to the pattern of tumor progression but could also be a result of earlier therapies, which are very different between these two kind of tumors. This study in-

vestigated long-term toxicities in STS patients treated with pazopanib using data collected from two Italian institutions.

Methods

Patients

We retrospectively reviewed the clinical records of patients treated with pazopanib between January 2013 and May 2016 at Candiolo Cancer Institute and Prato Medical Oncology Unit. Inclusion criteria were: confirmed diagnosis of advanced STS, on-label treatment according to European Society of Medical Oncology guidelines, and toxicities clearly detailed in patient charts. Other information required were sex, age, performance status, comorbid diseases and previous therapies. Patients provided informed consent before treatment start.

Objective

The primary objective was to describe observed pazopanib-related toxicities in patients treated in a real-life setting, and to suggest how adverse events could be managed so that treatment success can be maximized.

Treatment

Pazopanib was administered orally twice daily. The usual starting dose was the recommended one of 400 mg twice daily. However, several patients were started at either 400 mg daily or 400 mg in the morning ± 200 mg in the evening.

As suggested, it was recommended that pazopanib was taken two hours before or after meals.

Statistical analysis

Overall survival (OS) and progression-free survival (PFS) data were collected from prospective databases at each institution. Survival was defined as the time from the initial administration of pazopanib to the date of either death or last follow-up. PFS was defined as the time from the initial administration of pazopanib to the date of progression, death or last follow-up, whichever occurred first. Disease progression was defined as radiological tumor progression according to Response Evaluation Criteria In Solid Tumors (RECIST version 1.1) or clinical progression, including death. Adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE version 4.0). OS and PFS were estimated by the Kaplan Meier method. Statistical associations of the clinicopathological observations were evaluated using the Mann-Whitney U test (for quantitative data) and the chi-square test (for qualitative data). Two-tailed $p<0.05$ was considered statistically significant. Statistical analysis was performed using the SPSS version 20 software (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 43 patients with advanced STS who were treated with pazopanib were included. All patients were deemed unresectable because of locally advanced or metastatic disease and had previously received chemotherapy. They had received an average of two prior lines of therapy (range 1–7). Demographic and clinical characteristics of the included patients at baseline are shown in Table 1. Median duration of exposure to pazopanib was 4 months (range 1–27 months). At the time of analysis, 4 patients were still receiving pazopanib.

Clinical outcomes

Median follow-up was 14 months (range 1–41) and the longest treatment duration was 27 months in a patient with leiomyosarcoma. Median PFS was 4 months (95% confidence interval [CI] 3.12–4.87) and median OS was 18 months (95% CI 12.45–23.54) (Figure 1). The overall response rate was 9.3% (Table 2), and median time to best response was 12 weeks.

Toxicity

Overall, dose reductions and/or treatment interruptions due to an adverse event were required in 13 patients (30.2%); mean time to the first dose reduction or treatment interruption because of an adverse event was 30 days. The main reasons for an interruption or reduction in pazopanib treatment were diarrhea (27.9% of cases), hypertension (23.3%), serum creatinine increase (18.6%), mucositis (9.3%), nausea (7%), arthralgia (9.3%) and liver toxicity (11.6%). More specific details of adverse events, and their consequences and management, are provided below.

The most common toxicities were fatigue (n=32, 74.4%), hypertension (n=31, 72%), hair hypopigmentation (n=32, 74.4%) and diarrhea (n=26, 60.5%). Grade 3 hypertension and diarrhea occurred in 6 (14%) and 2 (4.7%), respectively; management of these events required treatment interruption, with an average recovery of 10 days. Anorexia occurred in most patients (n=32, 74.4%), nausea in 15 (34.9%) and vomiting in 2 (4.7%). Dysgeusia and mucositis occurred in 11 (25.6%) and 7 (16.3%) patients, respectively.

Liver function test (LFT) abnormalities were common. Elevated alanine transaminase (ALT) and/or aspar-

Table 1. Patient demographics and clinical characteristics at baseline.

	Patients (n=43)
Age, years	57 (20-78)
Male, n (%)	12 (27.9%)
ECOG PS, n (%)	
0-1	38 (88.4)
2	5 (11.6)
Histology, n (%)	
Leiomyosarcoma	24 (53.5)
Solitary fibrous tumor	4 (9.3)
Pleomorphic sarcoma	6 (14.0)
Angiosarcoma	1 (2.3)
MPNST	2 (4.7)
Other	7 (26.3)
FNCLCC grade, n (%)	
1	1 (2.3)
2	4 (9.3)
3	38 (88.4)
Primary site, n (%)	
Limb	17 (39.5)
Uterus	14 (32.6)
Visceral	12 (27.9)
Site of metastasis, n (%)	
Lung	27 (6.28)
Liver	8 (18.6)
Other	8 (18.6)
N. of prior chemotherapy regimens, n (%)	
1	13 (30.2)
2	10 (23.3)
>2	20 (46.5)
N. of subsequent chemotherapy regimens, n (%)	
0	21 (48.8)
1	11 (25.6)
2	9 (20.9)
>2	2 (4.3)

Age is reported as median (range); all other values are number of patients (%).
ECOG PS: European Cooperative Oncology Group Performance Status; FNCLCC: French Federation of Cancer Centers Sarcoma Group; MPNST: Malignant Peripheral Nerve Sheath Tumors.

tate transaminase (AST) levels were documented in 10 (23.3%) and 13 (30.2%) patients, respectively. Gamma glutamyl transpeptidase (γGT) and alkaline phosphatase (ALP) were increased in 8 (18.6%) and 6 (14%) patients, respectively, while bilirubin was elevated in 2 cases (4.7%). Grade 3/4 liver toxicities occurred in 2

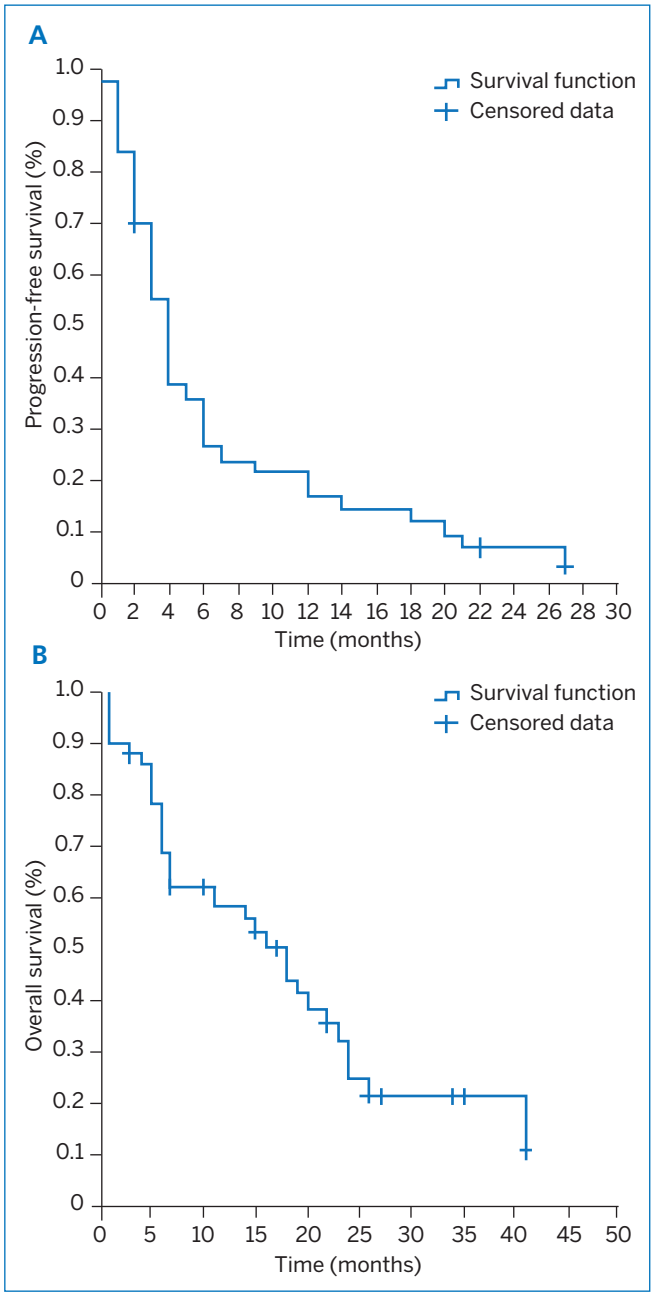

Fig. 1. Kaplan-Meier curves for (A) progression-free survival and (B) overall survival.

patients (4.7%). One of these events was not reversible and the patient had to discontinue pazopanib. A thorough work-up for alternate causes of acute hepatotoxicity and chronic underlying liver pathology failed to identify any

Table 2. Objective responses.

Best response	Patients, n (%)
Complete response (CR)	0 (0%)
Partial response (PR)	4 (9.3%)
Stable disease	21 (48.8%)
Progressive disease	18 (41.9%)
Objective response rate (CR + PR)	4 (9.3%)

other possible causes of liver failure in both patients. A liver biopsy demonstrated mild active hepatitis with both cholestasis and inflammation, mostly in the portal tracts, consistent with the hypothesis of iatrogenic damage caused by pazopanib.

Hypothyroidism was diagnosed in 4 patients (9.3%), all of whom were successfully treated with levothyroxine. Asymptomatic grade 1/2 elevations of serum amylase and lipase levels were observed in 2 (4.6%) and 1 (2.3%) patients, respectively. None of the patients experienced proteinuria of any grade. Increased creatinine levels were of grade 1 severity in 5 patients (11.6%) and grade 2 in 5 (11.6%); this abnormality was seen more often in elderly patients (age >75 years), but the comparison with rates in younger patients was not statistically significant (p=0.065).

Six (30.2%) patients experienced arthralgia while receiving pazopanib; in one patient this was severe enough (grade 3) to necessitate dosage reduction. The incidence of myalgia was 14% (4.7% grade 2 and 9.3% grade 1). None of the 43 patients experienced serious hand and foot skin reactions. Drug-induced QT interval prolongation occurred in 2.3% of cases and one patient experienced heart failure.

Hematologic toxicity was not a significant complication of pazopanib treatment. Leukopenia, neutropenia, anemia and thrombocytopenia each occurred in less than one-third of patients (14%, 20.9%, 20.9% and 11.6% of patients, respectively). These toxicities were not related to patient age, gender or number of previous treatments (p>0.05).

Two patients (4.3%) with lung metastases developed a symptomatic pneumothorax during pazopanib treatment and required chest drain insertion.

The most serious case was a spontaneous bilateral pneumothorax in a 57-year-old woman with high-grade undifferentiated pleomorphic sarcoma with multiple lung lesions. About two months after starting pazopanib the patient experienced severe dyspnea and hypotension. A chest x-ray revealed a bilateral pneumothorax (Figure 2). The patient required chest-tube placement and had to discontinue pazopanib.

Other serious adverse events were rare, but did require short treatment interruption and hospitalization. Specifically, these were grade 3 thromboembolic events in 3 patients, grade 3 hemorrhagic complications in 1 patient and intestinal perforation in 1 patient. No pazopanib-related mortality or neutropenic fever was identified. Overall, there were no statistically significant association between any toxicities and age, sex, number of previous treatment lines and histology.

Discussion

Pazopanib is the only targeted therapy approved for the treatment of advanced STS. The phase III PALETTE trial demonstrated that this new drug improved PFS compared with placebo, by a median of 3 months [2]. In terms of efficacy, our study showed similar PFS and OS outcomes to the PALETTE trial. Most of our patients had been heavily pretreated with at least two prior chemotherapy regimens and more than half received other

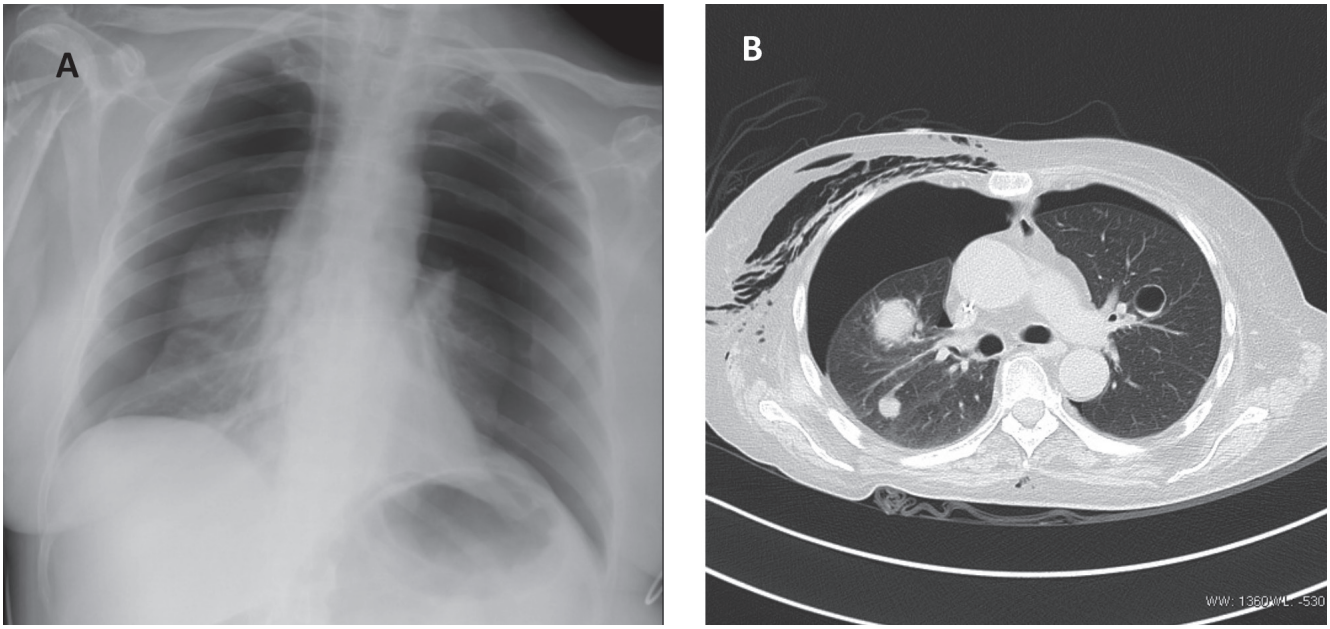

Fig. 2. (A) Chest X-ray showing bilateral pneumothorax, and (B) computed tomographic scan showing bilateral pneumothorax and multiple lung lesions.

treatments after pazopanib failure. Regarding toxicity profile, despite the retrospective nature of our study, doses given and requirements for dose reduction were similar to those used in the PALETTE trial. However, we did identify differences in the safety profile, possibly due to the small population in our retrospective analysis and differences in patient characteristics. Our population had a slightly higher median age (57 *vs* 55 years) and, more importantly, most of our patients had one or more comorbidities. Nevertheless, we demonstrated that pazopanib is a feasible option with an acceptable toxicity profile and antitumor activity in heavily pretreated patients.

In general, pazopanib was well-tolerated, and dose reduction or temporary interruptions limited serious toxicities and meant that adequate compliance could be maintained. The most common adverse events (hypertension, liver abnormalities, gastrointestinal complaints and increased creatinine) generally improved with dose reduction and symptomatic therapy; severe adverse events (pneumothorax, embolic events, heart failure and intestinal perforation) were rare. Nevertheless, patients should be adequately informed about these potential risks. Indeed, early recognition of potentially life-threatening situations can limit drug-related morbidity. In these cases, physicians need to discontinue treatment to manage the event and carefully evaluate the appropriate time to resume pazopanib, if indicated. In our experience in this study, it was important to limit the duration of treatment interruption to prevent disease progression.

The oral delivery of pazopanib requires patients to comply with the treatment schedule. To achieve this, patient education and involvement are important. Physicians should provide patients with clear, written directions to manage pazopanib therapy, encouraging them to take the drug at the same time each day, and record in a diary the exact time they took the pills and how many. Education about potential adverse events and when to contact the healthcare team is crucial for minimizing and treating toxicities. Dose modification and treatment interruption, along with supportive care measures (e.g. antiemetics and dietary strategies), are useful for preventing and managing pazopanib-induced side effects.

Conclusions

The results of this retrospective study of pazopanib in patients with STS are consistent with those of the prospective phase III clinical trial and other published observations.

They confirm the safety and efficacy of pazopanib in pretreated unresectable or metastatic STS, and highlight the importance of close follow-up and patient support to improve compliance and treatment duration.

Acknowledgments

The authors thank Nicola Ryan, an independent medical writer, who provided native English editing and journal styling on behalf of HPS. This editorial assistance was funded by PharmaMar, Spain.

Conflicts of Interest

GG has participated in an advisory board for Novartis. All other authors state that they have no conflicts of interest to declare.

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