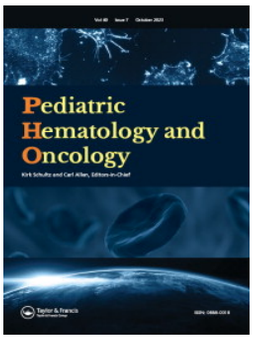

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Multicenter real-world experience of the clinical efficacy and tolerance of pazopanib in high-risk pediatric solid tumors (PazoPed)

Meziane Brizini[a], Lamia Naccache[b], Pauline Tibout[c], Catherine Goudie[d], Crystal Budd[e], Stéphanie Vairy[f], Marie-Claude Brisson[b], Thai Hoa Tran[c] and Raoul Santiago[b]

[a]Department of Pediatrics, CHU de Québec, Université Laval, Québec, Québec, Canada; [b]Department of Pediatrics, Division of Hematology-Oncology, CHU de Québec, Université Laval, Québec, Québec, Canada; [c]Department of Pediatrics, Division of Hematology-Oncology, CHU Sainte Justine, Université de Montréal, Montréal, Québec, Canada; [d]Department of Pediatrics, Division of Hematology-Oncology, Montreal Children's Hospital, McGill University Health Centre, Montréal, Québec, Canada; [e]Division of Hematology-Oncology, Montreal Children's Hospital, McGill University Health Centre, Montréal, Québec, Canada; [f]Department of Pediatrics, Division of Hematology-Oncology, CHU de Sherbrooke, Université de Sherbrooke, Québec, Canada

ABSTRACT

Pazopanib, a receptor tyrosine kinase inhibitor, exhibits anti-tumor activity in adult bone and soft-tissue sarcomas (STS), but has not yet been approved for pediatric tumors. The primary objective was to evaluate pazopanib efficacy when used alone or in combination with topotecan. This real-world multicenter retrospective study included patients with solid tumors, aged 25 years or less at the time of initial diagnosis, treated with pazopanib outside of a clinical trial. Nineteen patients were eligible for efficacy analysis: 14 bone tumors and 5 STS. At pazopanib initiation, the median age was 16.9 years, 18 patients had metastatic disease with a median of 2 prior therapeutic lines. With 6.2 months of median follow-up, no objective response was observed, but 10 patients (52.6%) had stable disease at 8 weeks and the 6-month disease control rate was 26.3%. The median progression free (PFS) and overall survival (OS) were 3.0 months and 6.2 months, respectively. Multivariate analysis showed an inverse relationship between the number of prior treatment lines and PFS and OS (hazard ratio = 1.73 ($p = 0.04$) and 1.76 ($p = 0.03$), respectively). Our study showed a potential tumor control activity of pazopanib in pediatric bone and soft tissue sarcomas. Further studies are warranted to determine the optimal timing and condition for pazopanib introduction to maximize the effect.

ABBREVIATIONS

AEs: Adverse events; CBR: Clinical benefit rate; CR: Complete response; COG: Children's Oncology Group; CHU: University hospital center; CHUL: University hospital center Laval; DC: Disease control rate; DSRCT: Desmoplastic small round cell tumors; ES: Ewing sarcoma ;

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CONTACT Raoul Santiago raoul.santiago@crchudequebec.ulaval.ca Department of Pediatrics, Division of Hematology Oncology, CHU de Québec, Université Laval, 2705 boulevard Laurier, suite A.0121.5, G1V 4G2, Québec, QC, Canada.

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HR: Hazard ratio ; LFT: Liver function test ; MTB: Molecular tumor board; NCI: National Cancer Institute; NGS: Next gene sequencing; PFS: Progression-free survival ; PR: Partial response ; OS: Overall survival; ORR: Overall response rate ; OST: Osteosarcoma ; REB: Research ethics board; RMS: Rhabdomyosarcoma; RTKi: Receptor tyrosine kinase inhibitor ; SD: Stable disease ; STS: Soft-tissue sarcoma; ToPaz: Topotecan and pazopanib combination

Background

Advances in chemotherapy have resulted in successful survival improvement of pediatric cancers over the past five decades, which has now reached a plateau with an overall survival around 80%, prompting the need for alternative novel therapies.[1,2] Next generation sequencing (NGS) technologies have facilitated extensive molecular profiling of tumors, accelerating the identification of actionable tumor alterations, thus paving the path for molecularly targeted therapies.[2–4] A large part of proto-oncogenes exhibits tyrosine kinase activity, and it represents the most frequent class of targetable alterations in pediatric tumors.[3–5] Based on this principle, several receptor tyrosine kinase inhibitors (RTKi) have been developed with successful anti-tumor activity and favorable toxicity profile leading to approval in many adult cancer types.[6]

Pazopanib is an ATP-competitive multi-specific RTKi targeting mainly the vascular growth factor receptors (VEGFR-1, −2, −3), platelet-derived growth factor receptors (PDGFR-α, - β) and c-KIT proto-oncogene, and to a lesser extent fibroblast growth factor receptor (FGFR-1, −3).[6–9] These pathways are important for angiogenesis and cell proliferation and represent recurrent oncogenic targets across different groups of tumors. Genetic alterations activating these pathways have been described in many pediatric solid tumors and represent one of the most dysregulated signaling pathways in childhood cancers.[2,10] Recent comprehensive NGS studies exploring the genomic landscape of pediatric tumors demonstrated therapeutically actionable alterations in 30% to 85% of pediatric cancers, depending on the study and the techniques used.[2–4,10–13] Mutations involving tyrosine kinase pathways are among the most frequently detected and, *FGFR1* and *PDGFRA* activations are over-represented in non-hematological tumors.[4,13] In an Australian study for molecular profiling of high-risk pediatric tumors, RTKi was the second most recommended targeted therapy[10] and, in the National Cancer Institute (NCI) - Children's Oncology Group (COG) MATCH study for pediatric malignancies, actionable mutations/fusions in *FGFR1* were present in 2.9% of cases, representing the 4th most frequent actionable alteration.[3] These observations suggest that pazopanib, or similar RTKi, could be an effective therapeutic opportunity for targeted treatment in selected pediatric tumors although, robust biomarkers to guide the utilization of such therapy are missing, as well as evidence for the best timing to introduce them.

Pazopanib has antitumor activity in some adult cancers and is approved by Health Canada for relapsed or refractory soft tissue sarcoma (STS) and metastatic renal cell carcinoma.[14,15] For example, in the randomized phase 3 PALETTE study, pazopanib demonstrated a survival advantage in progression-free survival (PFS) compared to

placebo for patients with STS who were previously exposed to chemotherapy.[16] Early-phase pediatric trials have established a recommended dose for pazopanib in children when used in monotherapy or in combination.[9,17,18] Phase 1 and 2 clinical trials for pazopanib, in monotherapy or in combination with topotecan, conducted in pediatric solid tumors have reported an anti-tumor activity with a disease control rate ranging from 19% to 40%.[18–20] Pazopanib is however not yet approved for cancers at pediatric ages.[14]

Based on these observations, pazopanib has been used off-label, often later in the courses of treatment, in pediatric patients with poor prognosis solid tumors for whom limited therapeutic options are available. This study aims to report the "real-world" experience of pazopanib use for pediatric solid tumors in the province of Quebec and to describe the efficacy and tolerance of this treatment in monotherapy and in combination.

Methodology

This study is an observational retrospective study describing the clinical efficacy and tolerance of pazopanib, in monotherapy or combination, when used off-label for pediatric solid tumors. All four pediatric oncology centers of the province of Quebec (University Hospital Center (CHU) Laval (CHUL), CHU Sainte-Justine, Montreal Children's Hospital, and CHU of Sherbrooke) participated in this study that was approved by the institutional research ethics boards (REB) of each participating center. In the context of the retrospective setting, the REB waived the requirement of informed consent.

Population and objectives

All patients with solid tumors aged 25 years or less at the time of initial diagnosis and treated with pazopanib (monotherapy or combination) initiated prior to January 1st, 2021, were eligible. Patients receiving pazopanib in the context of an active clinical trial were excluded. Patients treated in combination therapy were excluded from efficacy analysis to prevent bias, except for patients who received pazopanib in combination with oral topotecan, ToPaz,[18,21] or with a non-cytotoxic therapy.

The primary objective was to determine the efficacy of pazopanib-based treatment in pediatric solid tumors by evaluating overall response rate (ORR), defined as complete (CR) or partial response (PR) at any time of the treatment, and disease control rate (DCR), defined as a CR, PR or stable disease (SD) for more than 8 weeks (8-week DCR) and more than 6 months (6-month DCR), as suggested by COG recommendation,[9] after the initiation of pazopanib. The response evaluation followed RECIST 1.1 guideline.[22]

The secondary objectives were to assess of progression-free (PFS) and overall survival (OS), clinical benefit rate (CBR) and treatment related toxicity, according to the CTCAE v5.0.[23] The survival data were calculated from pazopanib initiation to disease progression, death or data censored for PFS, and to death or data censored for OS. CBR was defined as the percentage of patient who experienced a subjective

improvement in clinical symptoms, for a minimum of 8 weeks, as stated by the patients and objectified in medical charts.

Molecular profiling by whole exome and transcriptome sequencing, as previously described,[2] was performed for some patients through a research program but was not an inclusion criteria for our study. The efficacy and survival outcomes were compared depending on the molecular profiling and if molecular alterations were predicted, by our institutional molecular tumor board (MTB), potentially actionable by pazopanib. Toxicity was compared between those who received pazopanib as monotherapy and or in combination.

Data collection

Medical records were reviewed by co-investigators from each site to extract the following data: demographic data, disease evolution and treatment received prior to pazopanib initiation, molecular profiling and MTB recommendations (when applicable), clinical characteristics at the time of pazopanib introduction as well as patients' outcomes after the start of pazopanib. De-identified and coded data were captured by each institution in an online REDCap database (v10.6.26) and centralized in the host institution (CHUL) for analysis. The cutoff for data entry was on June 30th, 2021.

Statistics

The characteristics of the population were described by measures of central tendency and dispersion (means or median with 95% confidence intervals or range, as appropriate) for continuous variables and, percentage or proportion for categorical variables.

Comparisons were performed using the Chi-square test for categorical variables and with Student's *t* test or Wilcoxon Mann-Whitney test for quantitative variables. Survival curves were plotted by the Kaplan Meier method and compared with the Log-rank test. Cox regression models and hazard ratios were used to test the strength of correlation of 4 pre-identified predictors with response and survival (age at pazopanib initiation, molecular profiling, disease stage and number of prior treatments lines at pazopanib initiation).

The analyses were carried out with SAS 9.4 software, *p* values were two-sided and considered statistically significant when <0.05.

Results

Study population

Twenty-three patients were included in this study and were evaluated for the toxicity analysis and 19 patients were eligible for the efficacy analysis (pazopanib alone, off-study ToPaz or combination with a non-cytotoxic agent) (Figure 1).

The patients included in the efficacy analysis (11 males, 8 females) had a diversity of bone and soft tissue sarcomas: 7 Ewing sarcomas (ES) (36.8%), 6 osteosarcomas (OST) (31.6%), 2 rhabdomyosarcomas (RMS) (10.5%), 2 desmoplastic small round cell tumors (DSRCT) (10.5%) and 2 others (10.5%). In other cancers, one had a liposarcoma pleomorphic mixed with high-grade OST and the other an extra-skeletal myxoid

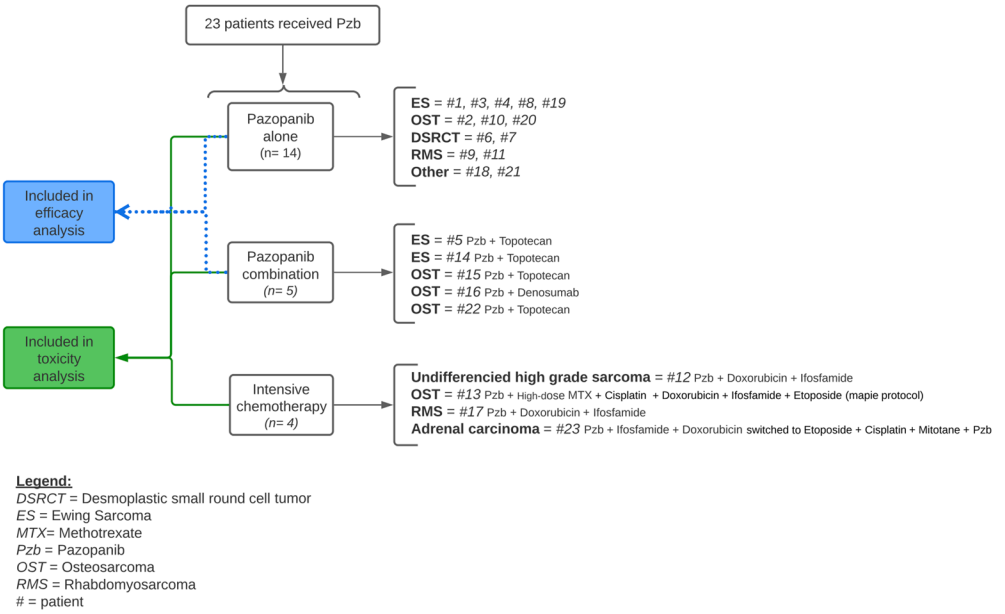


Figure 1. Patient distribution.

chondrosarcoma. The median age at diagnosis was 15.2 years old (y.o) [range: 4.0 – 22.5]. Two patients had significant comorbidities: Li-Fraumeni syndrome with a previous treated cerebral choroid plexus carcinoma, Duchenne muscular dystrophy with obstructive sleep apnea syndrome and arterial hypertension.

At initial diagnosis, 11 patients (57.9%) had metastatic disease involving bones (n = 4), lungs (n = 2) or lymph nodes (n = 5). One patient had refractory disease and 18 patients had relapsed disease. The median number of relapses was 2 [range: 1–4] and the median number of previous lines of treatment was 2 [range: 1–5] prior to pazopanib introduction.

At initiation of pazopanib, 18 patients (94.7%) had metastatic disease and all but one (94.1%) had a Karnosky/Lansky score ≥70 (2 had missing information). Pazopanib was administered in monotherapy for 14 patients (73.7%) and in combination for 5 patients (26.3%): 4 patients with topotecan (ToPaz) and 1 with the osteoclast inhibitor, denosumab (RANKL inhibitor). The Table 1 summarizes the clinical characteristics of the patients included in the efficacy analysis.

Molecular profiling data

Within the 19 patients included in the efficacy analysis, 12 had NGS molecular profiling of their tumor. Table 1 compares the patients who did and did not undergo molecular profiling. No significant differences were noted between the characteristics of both groups. Figure 2 lists all the molecular alterations identified in patients who underwent molecular profiling and classifies them according to the pathway involved and their predicted sensitivity to pazopanib as defined by the report of our institutional MTB. Fifty-six alterations were identified and classified by pathways. Alterations in

Table 1. Clinical characteristics of patients included in the efficacy analysis.

	Molecular profile			
	All patients (N = 19)	No (N = 7)	Yes (N = 12)	*p*-value[1]
Sex Male: Female Ratio	11:8	6:1	5:7	0.15
Median age at Dx- (y.o.) [range]	15.2 [4.0 – 22.5]	16.2 [9.5 – 22.5]	12.9 [4.0 – 21.5]	0.12[2]
Significant comorbidity- n (%)	2 (10.5%)	0 (0.0%)	2 (16.7%)	0.62
Karnosky/Lansky score[4]- n (%) <70	1 (5.9%)	1 (14.3%)	0	0.41
Type of cancers- n (%)				
Osteosarcoma	6 (31.6%)	1 (14.3%)	5 (41.7%)	0.33
Rhabdomyosarcoma	2 (10.5%)	1 (14.3%)	1 (8.3%)	1.00
Ewing sarcoma	7 (36.8%)	4 (57.1%)	3 (25.0%)	0.33
Desmoplastic small round cell tumor	2 (10.5%)	1 (14.3%)	1 (8.3%)	1.00
Other cancers	2 (10.5%)	0	2 (16.7%)	0.51
Metastases at diagnosis- n (%)	11 (57.9%)	6 (85.7%)	5 (41.7%)	0.15
Brain- n	0	0	0	
Lungs- n	2	2	0	
Liver- n	0	0	0	
Kidneys- n	0	0	0	
Others[5]- n	10	5	5	
Type of 1st line treatment- n (%)				
Chemotherapy	18 (94.7%)	7 (100%)	11 (91.7%)	1.00
Radiotherapy (primary site)	11 (57.9%)	6 (85.7%)	5 (41.7%)	0.15
Surgery (primary site)	12 (63.2%)	4 (57.1%)	8 (66.7%)	1.00
Negative margin- n	9	3	6	
Treatment for metastasis	3 (15.8%)	1 (14.3%)	2 (16.7%)	1.00
Median of prior COTx line- [Range]	2 [1–5]	2 [1–5]	2.5 [1–5]	0.62[2]
Median number of relapses- [range]	2 [1–4]	2 [2–4]	2 [1–4]	0.92[3]
Status disease at initiation- n (%)				
Localized Disease	1 (5.3%)	0	1 (8.3%)	1.00
Metastatic Disease	18 (94.7%)	7 (100%)	11 (91.7%)	1.00
Treatment administration- n (%)				
Monotherapy	14 (73.7%)	7 (100%)	7 (58.3%)	0.11
Combination[5]	5 (26.3%)	0	5 (41.7%)	

[1] Based on an Exact Pearson Chi Square Test, unless otherwise specified.
[2] Based on Student t-test with correction (C) for inequality of variances when appropriate.
[3] Based on Wilcoxon Mann Whitney Test.
[4] Missing 2 values.
[5]4 patients in combination with topotecan (topaz regimen) and 1 patient in combination with an osteoclast inhibitor.
[6] Others = Lymphatic nodes, bones, peritoneal or retroperitoneal.
Dx = diagnosis, y.o. = years old, COTx = chemotherapy.

the VEGF, tumor suppressors, and other pathways were the most frequent, accounting for up to 66.1%. The other pathways altered in our population are listed in Figure 2. Overall, 21 of the alterations were considered to be potentially sensitive to the RTKi and 16 were predicted to be specifically targetable by pazopanib, representing 28.6% of all molecular alterations identified (Figure 2 and Table S5).[24]

Efficacy

For the 19 patients included in the efficacy analysis, the median follow-up was 6.2 months [range: 0.8–26.0]. No objective response was observed, but 10 patients had a SD at

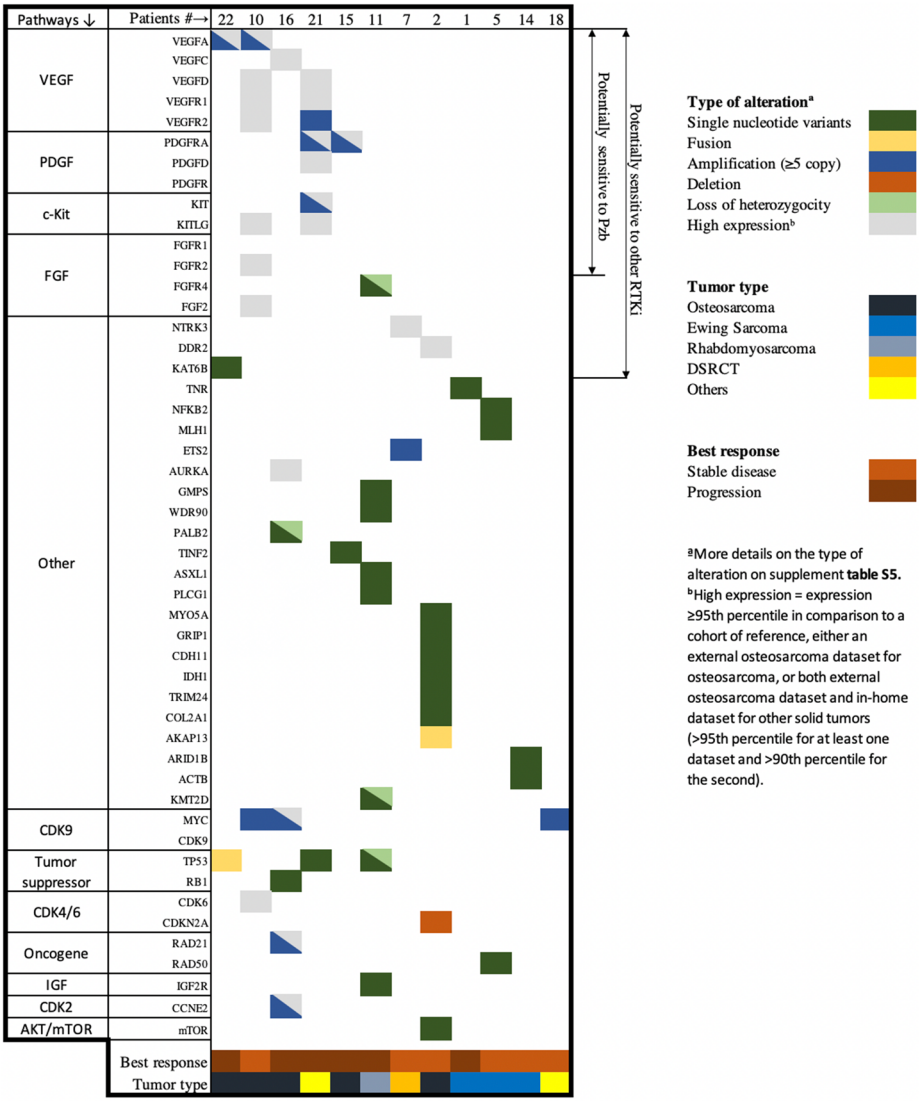


Figure 2. Somatic alterations identified on tumor molecular profiling performed by RNA and whole exome sequencing. Genomic waterfall plot displaying the alterations, their variant type and the pathways involved. Each column represents a patient and each line a gene.

8 weeks (8-week DCR = 52.6%) and 5 for more than 6 months (6-month DCR = 26.3%). Interestingly, at least one patient of each tumor type obtained a SD: 2/2 in DSRCT, 4/7 in ES, 2/6 in OST, 1/2 in each RMS and *others*. The median PFS and OS were 3.0 months [95%-CI: 1.1–5.8] and 6.2 months [95%-CI = 2.8–13.6], respectively (Table 2, Figure 3a). Nine patients (47.4%) reported subjective clinical benefit (pain or dyspnea improvement, increased energy, return to school), all of them also had SD.

A swimmer plot (Figure 4) summarizes the disease evolution after pazopanib introduction for each patient. Two patients in second relapse of metastatic DSRCT (#6) and OST (#10) were still on pazopanib at data cutoff, on pazopanib for 11.7 and

Table 2. Efficacy analysis for patients treated with pazopanib alone, ToPaz or combination with a non-cytotoxic agent.

	Molecular profile			
	All patients (N = 19)	No (N = 7)	Yes (N = 12)	*p*-value[1]
ORR - Overall response rate (%)	0	0	0	
CBR - Clinical benefit rate (%)	9 (47.4%)	3 (42.9%)	6 (50.0%)	1.00
DCR - Disease control rate (%)				
-At 8 weeks	10 (52.6%)	4 (57.1%)	6 (50.0%)	1.00
-At 6 months	5 (26.3%)	1 (14.3%)	4 (33.3%)	0.60[2]
Median PFS (months) [95%-CI][3]	3.0 [1.1 – 5.8]	3.0 [0.9 – 5.8]	3.0 [0.8 – 6.7]	0.73[3]
Median OS (months) [95%-CI][3]	6.2 [2.8 – 13.6]	6.1 [0.9 – 7.6]	9.4 [1.4 – 25.8]	0.25[3]
Median follow-up (months) [range]	6.2 [0.8 – 26.0]	6.1 [0.9 – 11.7]	7.1 [0.8 – 26.0]	0.22[2]
Status at last follow up:				
Death- n (%)	16 (84.2%)	6 (85.7%)	10 (83.3%)	
Alive- n (%):	3 (15.8%)	1 (14.3%)	2 (16.7%)	1.00
Alive in remission- n	0	0	0	
Alive with active disease- n	3	1	2	

[1] Based on an Exact Pearson Chi-Square Test, unless otherwise specified.
[2] Based on Student t-test with correction (C) for inequality of variances when appropriate.
[3] Median PFS and OS were obtained with Kaplan-Meier analysis. There p-value was obtained with Logrank test.
ToPaz = pazopanib combined with metronomic topotecan, PFS = progression-free survival, OS = overall survival.

7.9 months, respectively. Another patient with OST had pazopanib-actionable alteration in *VEGFR*, *FGF* and *KITLG*, and had sustained SD at data cutoff.

In 10 patients, a medical decision was made to continue the treatment with pazopanib beyond objectified disease progression (more than two weeks after progression). The median duration for treatment beyond progression was 2.8 months [range: 0.8–19.2]. Three patients received pazopanib for more than 6 months after progression. A patient with osteosarcoma in third metastatic relapse (#2) progressed on pazopanib after 6.6 months, the treatment was maintained, and the patient survived more than two years (25.7 months) on pazopanib. The tumor molecular profiling did not reveal any alteration targetable by pazopanib, for this patient. Patients with an extra-skeletal myxoid chondrosarcoma (#18) and an OST (#22) in 3rd and 4th metastatic relapse, respectively, also had prolonged treatments beyond progression. They progressed at 6.9 and 2.8 months on pazopanib and ToPaz, respectively, but continued their treatments and survived for more than a year in total. Both tumors harbored molecular alterations targetable by pazopanib (in PDGFR and in VEGF pathways, respectively).

Biomarker analysis

Treatment efficacy was compared between the patients who had a tumor molecular profiling or not, and according to the predicted sensitivity to pazopanib for the molecular alterations that were found. No difference in terms of objective response or survival were observed depending on whether the patient had a tumor molecular profiling or not (Table 2, Figure 3b). In the 12 patients who had a molecular profiling, when

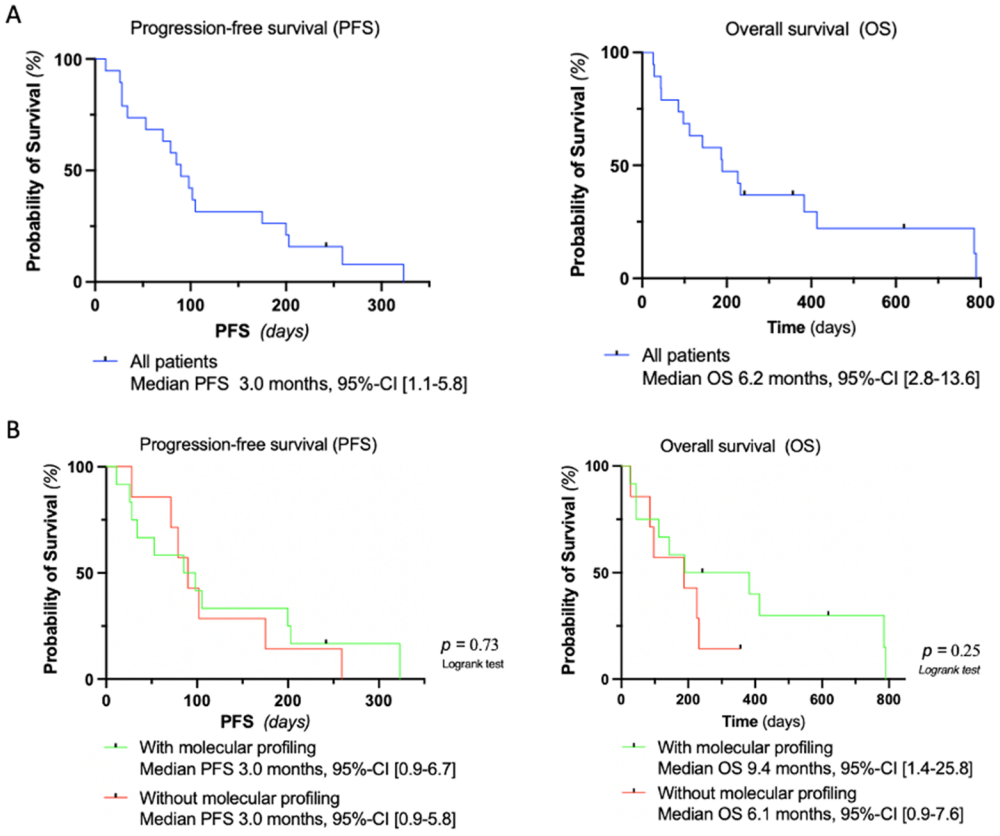
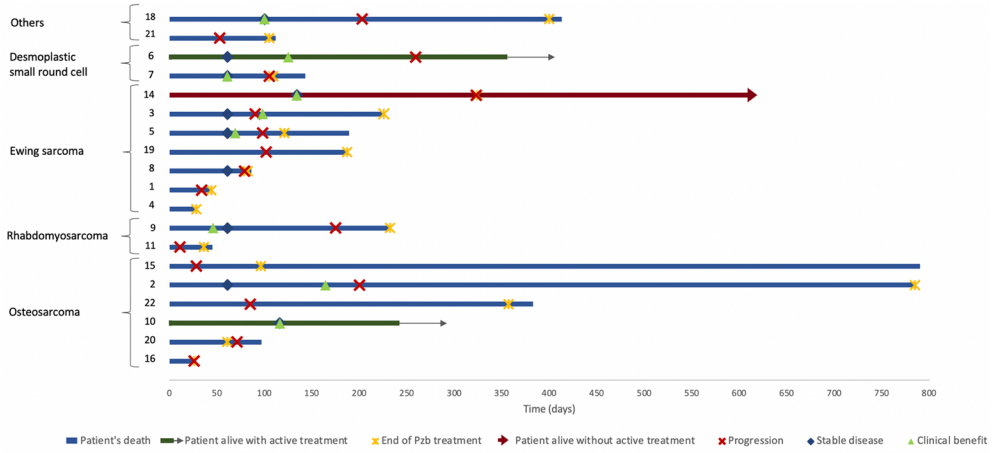


Figure 3. Survival curves (a) for all the patients included in the efficacy analysis and (b) comparing the patients who had a molecular profiling of the tumor or not.



** Patients 12-13-17-23 were excluded from efficacy analysis.*

Figure 4. Swimmer plot summarizing the clinical evolution on pazopanib for every patient included in the efficacy analysis (each line represents a patient).

subdividing by molecular alterations and predicted pazopanib sensitivity, there was no significant difference in disease control rate or survival (Tables S1 and S2).

A multivariate analysis tested predictors for response and survival. There was an inverse relationship between the number of prior therapeutic lines and PFS (hazard ratio (HR) = 1.73, ($p = 0.04$)) and OS (HR = 1.76, $p = 0.03$), meaning that the patients with fewer prior treatments had an improved survival on pazopanib (Table S3). When disease control rate was tested, multivariate analysis did not identify any clinical predictor (data not shown).

Toxicity

All 23 patients (100%) were included in the toxicity analysis. The population was divided according to monotherapy (n = 14) versus combination therapy with pazopanib (n = 9, including 4 patients receiving a combination with polychemotherapy regimens) (Table S4).

Eighteen adverse events (AEs) in 12 patients (52.2%) were reported, including 4 AE's greater than grade 3: increase in liver function test (LFT), neutropenia, pain and weakness. Two patients were hospitalized for a toxicity-related issue (once and twice respectively), both for pneumothorax. Four patients (17.4%) required at least a cycle delay (median of 1, range [1–3]) for ≥2 weeks because of toxicity and 10 patients (43.5%) had a dose reduction. Pazopanib was discontinued for potential toxicities in 5 patients (21.7%), after a median of 2.0 months [range: 0.9–7.4]. There was no pazopanib-related death. Reason for treatment discontinuation were increased LFT (n = 1), recurrent pneumothorax (n = 1) and unspecified (n = 1) in the monotherapy group, and increased LFT (n = 1) and gastrointestinal hemorrhage (n = 1) for combination therapies. For patients receiving combination therapies, no AEs greater than grade 3 were observed and they did not necessitate any hospitalization for treatment toxicity. There was no significant difference in toxicity between patients who received pazopanib monotherapy or in combination (Table 3).

Discussion

Our study describes the clinical efficacy and toxicity of pazopanib used off-label, for hard-to-treat pediatric solid tumors. With a median follow-up of 6.2 months, we observed a disease control rate of 52.6% and an overall survival exceeding 6 months in this heavily pretreated population. There was no difference in response or in survival when pazopanib treatment was guided or not by molecular profiling. Multivariate analysis showed an inverse relationship between the number of prior therapeutic lines before pazopanib and survival (PFS and OS), which gives an insight into the potential benefit of initiating pazopanib at an earlier timepoint in hard-to-treat solid tumors.

Adult studies were the first to show the antitumor activity of pazopanib in advanced soft tissue sarcomas. A phase 2 EORTC study of pazopanib in 142 adults with STS reported an ORR of 6% (PR) and prolonged PFS and OS compared to historical controls.[25] Following this encouraging result, the PALETTE randomized study demonstrated superiority in PFS of pazopanib over placebo in relapsed/refractory STS, with a median

Table 3. Toxicity analysis for all patients according to administration therapy.

	Monotherapy (N = 14)		Combination (N = 9)[5]		*p*-value[1]
Any problem related to Pzb- *n (%)*	7 (50.0%)		5 (55.6%)		1.00
Hospitalization- *n (%)*	2 (14.3%)		0 (0.0%)		0.50
Median hospitalization *[Range]*	1.5 [1–2]		0		
Patient with ≥1 toxicity- *n (%)*	7 (50.0%)		5 (55.6%)		1.00
Patient with ≥1 cycle delayed- *n (%)*	2 (14.3%)		2 (22.2%)		1.00
Median cycles *[Range]*	1 [1–1]		2 [1–3]		
Death caused by Pzb- *n (%)*	0 (0.0%)		0 (0.0%)		
D/c because of toxicity- *n (%)*	3 (21.4%)		2 (22.2%)		1.00
Patient with a dose reduction linked to toxicity- *n (%)*	6 (42.9%)		4 (44.4%)		
Median time *[Range]*	1 [1–1]		1 [1–2]		1.00
Toxicities identified- *n*					
Hepatic	1	- Gr 3. Increase LFT	1	- Gr 2. Increase LFT	1.00
Renal	0		0		
Hematology[2]	2	- Gr 3. Neutropenia	1		1.00
Cardiac[3]	0		2	- Gr 2. Decreased myocardial function	0.14
Pulmonary/Pleural	2	- Gr 2. PTX - Gr 2. PTX	0		0.50
Metabolic	0		0		
Skin	1	- Gr 1. Delayed pressure ulcer healing	0		
Others[3]	7	- Gr 1. Change hair color - Gr 2. HypoT4 - Gr 2. HypoT4 - Gr 2. MSK pain - Gr 3. Pain - Gr 3. Weakness	1	- Gr 2 G-I hemorrhage	0.63

[1] Based on an exact pearson chi square test.
[2] Grades were missing for 2 AEs.
[3] Grade was missing for 1 AE.
[5] 3 patients received pazopanib in combination with doxorubicin and ifosfamide (one was switched to etoposide, cisplatin and mitotane combined with pazopanib), one patient in combination with high-dose methotrexate, cisplatin, doxorubicin, ifosfamide and etoposide (mapie protocol), 4 patients in combination with topotecan (topaz regimen) and 1 patient in combination with an osteoclast inhibitor.
Pzb = pazopanib, D/c = discontinuation, G-I = gastro-intestinal, Gr = grade, Hypot4 = hypothyroidism, LFT = liver function test, MSK = musculoskeletal, PTX = pneumothorax.

PFS of 4.6 months.[16] Real-world experiences broadly reproduced this data with a DCR of 38% and a 3-month PFS in adult STS and bone sarcomas.[26]

In the pediatric setting, the clinical experience with pazopanib is still limited with only few early phase clinical trials completed, totaling less than 150 patients (83 in published article). A phase 1 trial conducted by COG on 51 pediatric patients with refractory solid tumors established the recommended dose for pazopanib monotherapy. In this study, 19% of the patients had a controlled disease including two prolonged PR (DSRCT and hepatoblastoma) and 15% had a prolonged SD superior to 6 months, for a 6-month DCR of 19%.[9] A COG phase 2 pediatric study for pazopanib monotherapy in solid tumors was started but enrolled only 57 patients on the 154 planned patients. Preliminary results are available on https://clinicaltrials.gov but the final results are still pending.[20] Only one patient with RMS had an objective response (PR) and

the 16-week DCR was 19%. More recently, a phase 1 study of pazopanib in combination with metronomic topotecan (ToPaz) in children with recurrent or refractory solid tumors achieved a 40% of SD as best response (10/25 patients), with a median duration of 6.1 months, without any objective response.[18]

Our study reports the clinical efficacy of real-world (and off-label) use of pazopanib in 19 patients with pediatric solid tumors, in monotherapy or in combination with oral topotecan. We decided to include ToPaz regimen in the efficacy analysis as its superiority to pazopanib alone is not demonstrated.[18] The 8-week DCR in our population was 52.6% and 47.4% of patients experienced clinical benefit, which is an important outcome for a palliative treatment. Five patients had prolonged stable disease for a 6-month DCR of 26.3%, which slightly surpasses the results of prior reports in pediatric cancers.[18–20] The 3-month PFS observed in our cohort is similar to what was observed in the real-world experience in adult[26] but slightly inferior to the PALETTE study.[16] However, inclusion criteria, histological cancer types and response evaluation differ between the studies limiting the ability for comparison. There is no comparison yet for OS and PFS in pediatric solid tumors treated with pazopanib or ToPaz regimen as this information was not reported by prior clinical trial. These outcomes were included in the secondary objectives of the COG phase 2 study and should become available soon.[20] We also illustrated that continuing pazopanib beyond progression was sometimes associated with prolonged survival, exceeding 1 year in three patients and even 2 years in a patient with OST. This strategy is usually not allowed in clinical trials but can be favored when no other viable alternative exists to prevent disease flare at RTKi discontinuation. However, more research is needed to confirm the benefit of this approach.

The validation, in the real-world setting, of observations made in clinical trials is critical as restricted inclusion criteria may sometimes preclude the reproducibility of the results when tested in the overall population.[27] Our study argues in favor of clinical activity of pazopanib in pediatric STS and bone sarcoma in real-world settings.

For toxicity analysis, we included all patients receiving pazopanib in monotherapy, ToPaz combination or combination with poly-chemotherapy regimen. The toxicity profile of pazopanib did not identify unexpected toxicities in the pediatric population compared to what was observed in adults[9] and, the association with topotecan did not demonstrate additional toxicities.[18] The main toxicities reported in pediatric studies were gastro-intestinal toxicity, liver and pancreatic enzyme elevation, fatigue, proteinuria and hypertension. Rare cutaneous and cardiac AEs were observed but restricted to low-grade.[9] Few pediatric studies have tested pazopanib treatment in combination with poly-chemotherapy.[17,28] A randomized phase 2 study for pediatric and adult unresected STS investigated neoadjuvant pazopanib in combination with ifosfamide, doxorubicin and radiotherapy.[17] More adverse events and treatment discontinuation were recorded in the pazopanib group; however, there were no excessive or unexpected drug-related toxicities. In addition, this study highlighted a better pathological response in the pazopanib group when compared to placebo with a tolerable safety profile. A retrospective review of pediatric patients treated with pazopanib in association of vincristine and irinotecan for relapsed/refractory STS and bone sarcoma showed a good efficacy and safety profile without treatment discontinuation for toxicity.[28]

In our study, most toxicities were limited to grade 3 or lower. We did not observe any significant difference between pazopanib monotherapy and combination therapy

groups but, of note, only 9 patients received combination therapy (with only 4 receiving poly-chemotherapy regimens). Five patients had to discontinue pazopanib because of toxicity. Our study argues in favor of pazopanib safety in patient with hard-to-treat tumors, however, even with low-grade toxicity, some patients did not tolerate the treatment and had to discontinue for AEs. We did not observe an increased toxicity when pazopanib was combined with polychemotherapy in 9 patients.

Pazopanib has been so far approved based on histology-based criteria and it remains challenging to predict patients who will benefit from its treatment. No biomarkers based on molecular profiling have been identified so far and our study did not reveal any association between molecular testing and clinical outcome.

In the PALETTE study, clinical prognostic factors were assessed. A lower number of prior therapeutic lines (<2) was associated with an improved outcome in univariate analysis, but in multivariate analysis, only a better performance status and lower tumor stage correlated with improved outcome.[16] In our study, multivariate analysis showed that a lower number of prior lines of therapy was associated with a better progression-free and overall survival. Our study results give an insight that earlier introduction of pazopanib in the arsenal of therapies for relapsed STS or as maintenance therapy for high-risk patients in first remission may further improve outcome and warrant prospective evaluation in clinical trials. A neoadjuvant study of pazopanib added to chemotherapy backbone in primary STS proved that pazopanib increased tumor necrosis, but the correlation to clinical outcome has yet to be demonstrated.[17] In ovarian and small cell lung cancers, two randomized studies showed that pazopanib maintenance, after completion of first-line therapy, prolonged disease-free survival.[29,30] A similar study has not been performed for pediatric cancer. However, a study of regorafenib maintenance therapy is ongoing in pediatric and adult patients with bone sarcoma after completion of first-line therapy.[31] Alternatively, clinical trials should aim to determine biomarkers to identify the patients that are more likely to benefit from RTKi treatment.

Our study is mainly limited by its retrospective design, the small sample size with a heterogeneous population and the lack of good comparator due to the differences in inclusion criteria and response assessment across studies. Also, the clinical benefit was self-reported improvement in symptoms and there was no formal objective measure by standardized questionnaire. Finally, the biomarker analysis was hindered by the scarcity of patients with molecular profiling, thus precluding the ability to identify molecular predictors of efficacy. Our study emphasizes the need for well-documented large prospective registry of patients treated with novel off-label therapies with standardized response and AEs evaluation to learn more from the real-world experience.

Conclusion

Our study reports a real-world experience of pazopanib used off-label in high-risk pediatric solid tumors. We illustrated a favorable antitumor activity of pazopanib for refractory or relapsed pediatric STS and bone sarcoma, with a disease control rate exceeding 50% at 8 weeks and 25% at 6 months, and a median OS of over 6 months. A lower number of prior therapeutic lines was associated with an improved survival,

thus raising the interest of possibility introducing RTKi earlier in the disease course or for maintenance therapy to optimize outcome. However, further studies are warranted to determine the best timing for RTKi and to identify biomarkers of efficacy.

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