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LETTER TO THE EDITOR

Pazopanib in relapsed osteosarcoma patients: report on 15 cases

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Osteosarcoma is a rare bone tumor that occurs in young adults with a subsequent peak in the fifth decade. Neoadjuvant and adjuvant chemotherapy and surgery cure approximately 60% of patients with localized osteosarcoma [1]. Metastases occur in about 30–40% of patients, and are mainly localized in the lungs [1,2]. Survival in the metastatic setting is 20–25% at 5 years [1–3], and depends on metastatic site (lung versus other sites), number of metastases and disease-free interval [3,4]. Surgery is the preferred therapy if the metastases are resectable, and chemotherapy is an option when surgery is not feasible. The drugs used at relapse are usually gemcitabine and docetaxel [response rates (RR) 15–30%] [5–7], high-dose ifosfamide [RR 30–40%] [8,9] or etoposide.

As for many other orphan diseases, there is a limited development of new drugs for osteosarcoma, and new therapeutic principles often rely on repurposing of drugs originally developed for other indications. Pazopanib is an orally administered multi-target receptor tyrosine kinase inhibitor (TKI) approved for soft tissue sarcoma and renal cancer. It is an inhibitor of several kinases, including VEGF, PDGF, and cKIT. Its toxicity profile is quite favorable, but still about two-thirds of patients have to reduce dose for toxicity (e.g.,

hypertension, hypothyroidism, and hand-foot syndrome) [10].

So far only case reports have been published on pazopanib in advanced osteosarcoma. A Danish study [11] reported three patients with clinical benefit, and a Japanese report [12] demonstrated one out of three cases with prolonged response. There are also ongoing clinical trials and unreported completed trials with different TKIs where osteosarcoma patients are eligible, including pazopanib (NCT01759303), lenvatinib (NCT02432274), apatinib (NCT02711007), and regorafenib (NCT02389244).

Here, we report the results from two large sarcoma reference centers of pazopanib treatment in metastatic osteosarcoma patients after failure of conventional chemotherapy.

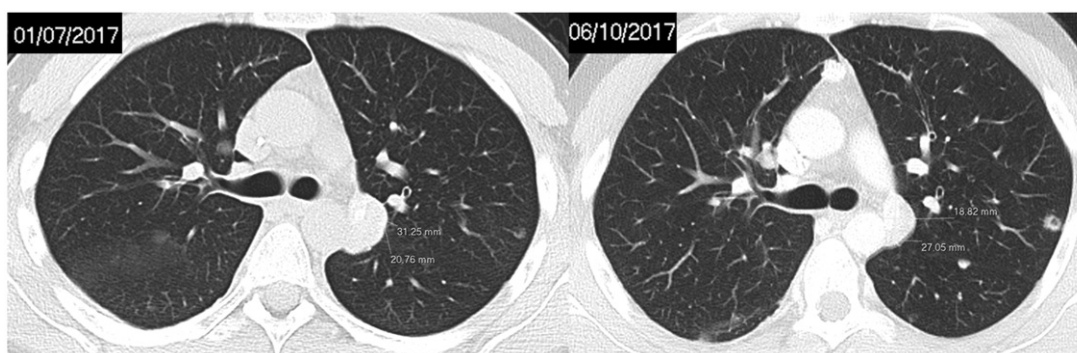
Material and methods

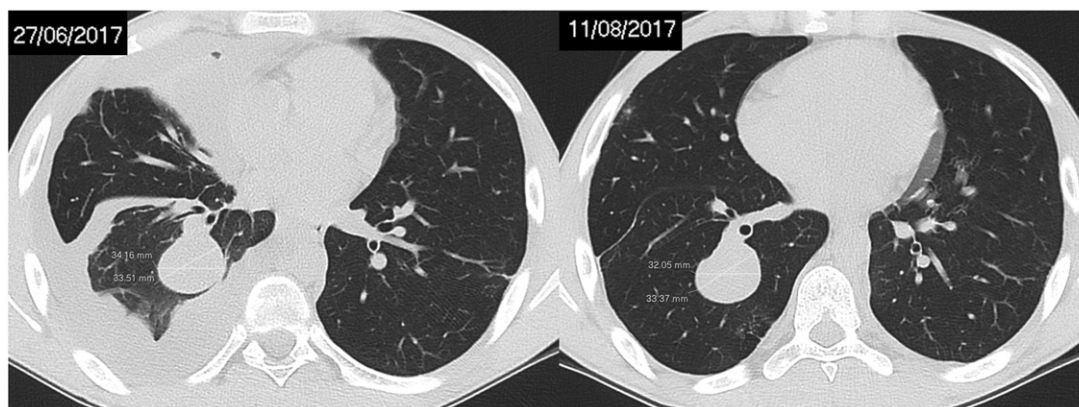
All patients with metastatic osteosarcoma treated with pazopanib at Rizzoli Orthopedic Inst, Bologna (Italy) and at Oslo University Hospital (Norway) were included. In Bologna, a compassionate use permit was obtained from the hospital

Table 1. Cases of metasatatic osteosarcoma treated with name-based pazopanib.

PTS ID	Center	Sex	Age	M site	Previous CT for met dis.	PZP response	PFS, ms	OS 31 May 2018, ms	Toxicity	Status	Comment
1	IOR	M	20	Lung	GD	SD	8	12	pnx, lipotimia	AWD	Non-RECIST reduction of target lesion, cavitation
2	IOR	M	18	Lung	HDIFO, GD, VP16	RP	6	15	Hand-foot s.G3	AWD	RECIST PR
3	IOR	M	16	Lung	HDIFO/GD	SD	5	8	Hand-foot s.G2	Dead	Resolution of pleural effusion stable lung nodules
4	IOR	F	31	Lung	HDIFO/GD	SD	6	12	Diarrhea G2	AWD	
5	IOR	M	47	Lung	HDIFO/MTX/GD	SD	4	7	HTN G2	Dead	
6	IOR	F	25	Lung, bone	HDIFO, GD	SD	2	8	PLT G4	Dead	
7	IOR	F	53	Lung	GD/HDIFO/VP16	NV	NV	7	HTN G4	AWD	Interruption after 35 days for brain hemorrhage
8	IOR	M	17	Lung	HDIFO/ADM/MTX/GD/VP16	PD	2	3	PLT3/pnx	Dead	
9	IOR	F	12	Lung	GD/ADM/VP16	PD	2	6	NauseaG2	Dead	
10	IOR	M	18	Lung	GD	SD	2	2	PLT2, HTN2, hyperbil, pnx	AWD	
11	Oslo	M	11	Lung, bone		SD	7	7	Perianal abscess G3, pnx	AWD	
12	Oslo	M	69	No metastases, inoperable primary	ADM/IFO	PD	3	5	No G3/4 tox	Dead	
13	Oslo	M	55	Lung, soft tissue	GD, Pembro	PD	2	2	No G3/4 tox	Dead	
14	Oslo	F	44	Lung, soft tissue	GD	SD	10	13	No G3/4 tox	Dead	Reduction in target lesions, non-RECIST
15	Oslo	M	55	Lung, peritoneum	HD-IFO, Pembro	PD	2	2	Anemia G3	Dead	

GD: gemcitabine + docetaxel; HDIFO: high-dose ifosfamide; VP16: etoposide; MTX: methotrexate; ADM: Adriamycin; Pembro: pembrolizumab; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable; pnx: pneumothorax; HTN: hyperthension; PLT: platelet, AWD: alive with disease.





drug commission and from the patient or relative. In Oslo, pazopanib was prescribed off-label and approved by regional health authorities or the hospital administration.

All patients underwent evaluation with computer tomography (CT) scan of the metastatic sites prior to start of pazopanib. Patients were then evaluated every 2 months using CT. Radiological response was evaluated by radiologist and oncologist using RECIST v1.1 (<http://recist.eortc.org>, 2009). Dose reduction was performed according to hematologic and non-hematological toxicity (CTCAE v4.0) (NCI- NIH, USA 2009).

Progression-free survival (PFS) was calculated from date of start of pazopanib therapy till radiological progression of disease according to RECIST v1.1. Patients without progression were censored at the date of last CT scan. Overall survival was calculated from start of pazopanib till death or date of last follow-up.

Results

Patients

From December 2016 to May 2018, ten patients from Rizzoli Institute and five patients from Oslo University Hospital received pazopanib. Median age was 25 years (range 11–69 years). There were ten male and five female patients: nine patients had only lung metastases, two patients had lung and bone metastases, two had soft tissue and lung metastases, one had inoperable locally advanced disease, and one had metastases to lung and peritoneum. The median number of previous lines of chemotherapy for metastatic disease was 2 (range 0–5).

Toxicity

Thirteen patients (>16 years old) started with 800 mg/d, and two patients (aged 11 and 12 years) started with 400 mg/d. The 11-year-old, 65-kg boy had few side effects and increased the dose to 800 mg/d after 4 weeks. Dose reduction was necessary in 11/13 patients who started with 800 mg/d. A 53-year-old patient who had hypertension before pazopanib experienced a brain hemorrhage due to

uncontrolled hypertension after 35 days of treatment. Four patients experienced a pneumothorax, of whom two needed a chest tube. Two patients (both reported an objective response, Case 2 and 3) had hand–foot syndrome (Grade 2 and 3, respectively), three patients experienced thrombocytopenia (Grade 2, 3 and 4), one had Grade 3 anemia, and three patients had hypertension. Nausea, diarrhea, and hyperbilirubinemia were other side effects reported in three patients. One patient had a perianal abscess.

Response to treatment

Three patients with only lung metastases had a reduction of target lesions: one patient had a partial response (PR; Case 2), and two patients did not meet the criteria for PR (Case 1 and 3). Six other patients also had stable disease (SD) as their best response. A clinical benefit, defined as SD or PR, was thus observed in nine patients (60%). Median PFS was 6 months (range 2–10). Two patients are still receiving treatment. Nine patients were dead from osteosarcoma at the time of data analysis. Median overall survival was 7 months (range 2–15).

Case reports

Case 1. A 20-year-old male with lung metastases started pazopanib 800 mg/d in May 2017. After 3 weeks, a unilateral pneumothorax was diagnosed, and pazopanib was discontinued until resolution of the pneumothorax. Pazopanib was restarted in July 2017 at 800 mg/d. After 1 month, he had a hand–foot syndrome and the pazopanib dose was reduced to 600 mg/d. Response evaluation after 1 month showed a reduction of targets lesions and cavitation of other lung metastases and no new lesions, but he did not meet the criteria for PR. In September 2017, he had repeated episodes with loss of consciousness, but MRI and EEG were negative. A dose reduction to 400 mg/d was performed. He continued with pazopanib 400 mg/d with stable disease until February 2018 when an increase of lung metastases and bilateral pneumothorax was detected. He is alive with disease as of May 2018.

Case 2. An 18-year-old male started pazopanib 800 mg/d in February 2017 after progression of bilateral lung metastases on

gemcitabine/docetaxel and high-dose ifosfamide. After 3 months, pazopanib was reduced to 400 mg/d due to hand–foot syndrome, but increased to 600 mg/d 2 months thereafter. Response evaluation in April 2017 and June 2017 showed a PR according to RECIST. Late August 2017, a progression of disease (PD) was noted after a duration of response of 6 months. The patient started lenvatinib in November 2017 and had a new PR that lasted until May 2018.

Case 3. A 16-year-old male with a large right diaphragmatic mass, right pleural effusion, and bilateral lung metastases started pazopanib 800 mg/d in June 2017. A new CT scan in August 2018 showed disappearance of the pleural effusion, a slight decrease of one lesion and otherwise SD. Due to Grade 2 hand–foot syndrome, a dose reduction to 400 mg/d was performed. His performance status improved significantly, and he could resume his soccer practice. No pleural drainage was necessary. In November 2017, progression of lung metastases was detected and he died of disease in February 2018.

Discussion

The treatment of relapsed osteosarcoma is challenging due to few effective treatment options. Surgery of isolated lung metastases or stereotactic radiotherapy are usually performed if possible, but only a fraction of patients with relapsed osteosarcoma are eligible for this treatment, and relapse after local therapy occurs frequently [13,14].

TKIs have recently emerged as a treatment option in osteosarcoma and in other pediatric solid tumors [15]. A phase II study with sorafenib in 35 metastatic osteosarcoma patients showed a median PFS of 4 months [16]. Apatinib was reported to have activity in a non-randomized study from China [17]. Results from a phase II study with lenvatinib in children and young adults showed that 5 of 15 (33%) evaluable patients were progression-free at 4 months, with one PR and 7 SD [18]. In a placebo controlled study with regorafenib in patients >10 years 17/26 (65%) patients treated with regorafenib reached 8-week PFS compared to 0/12 in the placebo arm [19]. Furthermore, combining TKI with other drugs have also shown promising results, including sunitinib and nivolumab in a cohort of bone and soft tissue sarcoma [20], and pazopanib and topotecan in a cohort of 17 osteosarcoma patients, where an 88% clinical benefit rate was reported [21]. Our data show that pazopanib gives a clinical benefit in approximately half of the patients, but the duration of benefit was relatively short, with a median PFS of 6 months. Radiological responses were infrequent, and only one patient had a confirmed response according to RECIST. The results of the present study are comparable with the other trials using other TKIs in metastatic osteosarcoma summarized above. The different TKIs have never been compared in a randomized study, and there are thus no data to support the optimal order of targeted therapy in metastatic osteosarcoma. Finally, a phase II study on pazopanib in metastatic osteosarcoma (NCT01759303) was terminated due to low accrual, and the results of this study are awaited.

The toxicity was manageable. Hand–foot syndrome was noted in two patients who had a dimensional response to pazopanib. Similar findings have previously been reported with the EGFR inhibitor gefitinib, suggesting that skin toxicity is associated with efficacy for certain TKIs [22]. Pneumothorax due to cavitation of metastases was a frequent complication in our patients. This has also been noted in other studies in soft tissue sarcoma patients, with a rate of 14% in one case series [23], and also in osteosarcoma patients treated with other TKIs [17].

Conclusions

Few new drugs are available for advanced metastatic osteosarcoma. In the present study, pazopanib showed interesting activity and a tolerable toxicity profile comparable to other TKIs. We believe that pazopanib could be considered as a treatment option when no conventional chemotherapy is available. Further randomized studies are necessary to evaluate the activity of pazopanib alone or in combination with other drugs.

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LETTER TO THE EDITOR

Bone sarcoma during pregnancy: an example of personalized multidisciplinary care

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The presentation of a bone sarcoma during pregnancy is very rare and a challenging situation for all parties involved. Here, we describe a case of a patient who was diagnosed with bone sarcoma during pregnancy and received a tailored multidisciplinary treatment.

A 31-year-old previously healthy Caucasian woman, G2P1, was diagnosed with a high-grade pleomorphic undifferentiated spindle cell sarcoma of the distal femur at 22 weeks of gestation. No metastases were found on a whole-body fluorodeoxyglucose (FDG)-positron emission tomography (PET)-scan combined with low-dose computerized tomography (CT)-scan. Given the clinicopathological characteristics of the

tumor, an osteosarcoma protocol was applied. A multidisciplinary team was formed, consisting of a medical oncologist, gynecologist-obstetrician, orthopedic oncologist, pharmacologist and specialized adolescent and young adults (AYA) nurse. After thorough counseling, the patient decided to maintain the pregnancy. The usual neoadjuvant schedule of chemotherapy (cisplatin, doxorubicin and methotrexate) [1] was adjusted in close collaboration with the pharmacologist to minimize the risk of teratogenic effects. Cisplatin and doxorubicin can be used safely, though with caution, from the second trimester of pregnancy [2,3]. Since limited data are available on the administration of the high dose of

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