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CASE REPORT

Prolonged clinical response is possible with regorafenib in refractory osteosarcoma: A case report

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ABSTRACT

Background: Treatment options for metastatic unresectable osteosarcoma are limited, and there is no standard approach after the failure of first-line chemotherapy. Conventional chemotherapy in the second and subsequent lines typically yield a median progression-free survival (PFS) of less than 4 months, with objective response rates ranging from 3 to 29%. The activity of anti-vascular endothelial growth factor receptor multi-tyrosine kinase inhibitors (TKIs) in bone sarcomas has been demonstrated. We present a case of metastatic osteosarcoma exhibiting a durable response to regorafenib treatment.

Case: We discuss a 30-year-old male with metastatic osteosarcoma who had extensive bone and lung metastases and was ineligible for metastasectomy. The patient had received all active chemotherapy regimens in the early and metastatic stages except ifosfamide. Next generation sequencing analysis of resected tumor tissue revealed a possibly pathogenic missense mutation (P.G472E) in NOTCH1 gene. Due to the presence of heart failure with a reduced ejection fraction, chemotherapy was not considered, and regorafenib was initiated. After four cycles of regorafenib, a partial metabolic response was achieved. The patient was followed up without progression under regorafenib for 15 months, without requiring dose reduction. Unfortunately, the treatment had to be interrupted for an extended period due to challenges with recurrent tumor infection and the necessity for repeated surgeries. Following successful wound site control, we restarted full-dose regorafenib and achieved a metabolic partial response again.

Conclusion: To our knowledge, this case represents the longest achieved PFS with regorafenib in metastatic osteosarcoma. TKIs can provide a durable clinical response in metastatic osteosarcoma patients. Clinical and molecular biomarkers are required to determine which patients are most likely to benefit from these treatments.

Keywords: osteosarcoma, regorafenib, multi-TKIs

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INTRODUCTION

Even with successful surgery and potent multiagent chemotherapy, recurrence occurs in 30-50% of patients with localized osteosarcoma [1]. Complete resection of all metastatic sites may provide long-term survival but patients not amenable to surgery have a poor prognosis [2]. The 5-year overall survival (OS) rate for patients ineligible for metastasectomy is between 28-32% [3].

Chemotherapeutic agents like doxorubicin, cisplatin, high-dose methotrexate (HD-MTX), and ifosfamide exhibit antitumor activity against osteosarcoma [4-6]. However, treatment of recurrent metastatic osteosarcoma is extremely tough since these patients have already received the most effective chemotherapy during the neo/adjuvant or first-line metastatic setting. Second-line and subsequent therapies have shown limited efficacy. Objective response rates with high-dose ifosfamide, cyclophosphamide and etoposide or gemcitabine plus docetaxel typically range from 3% to 44% and a median progression-free survival (PFS) of less than 4 months [7-9].

Similar to various cancer types, osteosarcoma exhibits overexpression of vascular endothelial growth factor receptor (VEGFR)-mediated angiogenesis [10]. Multi-tyrosine kinase inhibitors (TKIs) that

target VEGFR and other kinases; such as regorafenib, cabozantinib and sorafenib have demonstrated limited activity in advanced osteosarcoma [11-14].

We report a case of metastatic osteosarcoma that had a partial response with regorafenib and was followed for fifteen months without disease progression.

CASE

In 2006, a 13-year-old male patient underwent complete surgical resection for a mass in his left distal femur and was subsequently diagnosed with conventional osteosarcoma. Following limb sparing surgery, adjuvant multi-institutional osteosarcoma study chemotherapy regimen (bleomycin [15 mg/m^2], cylophosphamide [600 mg/m^2], actinomycin-D [0.6 mg/m^2]; high dose methotrexate with leucovorin rescue; doxorubicin [30 mg/m^2] and cisplatin [100 mg/m^2] and doxorubicin [50 mg/m^2]) was administered. In 2013, after seven years of disease free follow-up, a recurrent lump up to 1.5 cm in size was found in the proximal diaphysis of the right femur. Surgical resection of the mass revealed a recurrence of conventional osteosarcoma. Subsequently, the patient received three cycles of cisplatin and doxorubicin; followed by radiotherapy delivering a dose of 3,000 Gy to the tumor site. The patient's informed consent was obtained for the case report.

Three years later, in 2016 a local recurrence with a diameter of 6.5 cm was noted in the medial metaphysis of the left distal femur and tumor resection and reconstruction with prosthesis was performed. Three additional cycles of HD-MTX and cisplatin were administered. A year following the end of chemotherapy in 2018, bilateral multiple lung metastases were detected. The multidisciplinary tumor board decided to proceed with bilateral sequential lung metastasectomy for the patient. The pathology of all lung metastases was reported as conventional osteosarcoma.

The patient was followed without any treatment for another year. In February 2020, sub-centimetric lung metastases and recurrence in the distal 1/3 of the left femur were identified. Throughout this time, the patient was hospitalized due to a severe COVID-19 infection and subsequently developed heart failure with a reduced ejection fraction (%30-%35). Heart failure treatment was immediately initiated. For one more year, the patient did not apply to the hospital for an oncological treatment plan.

In February 2021, restaging PET-CT showed local and systemic metabolic progression (part a in **Figure 1**). No further local treatment was planned for the patient and regorafenib (160 mg once daily on days 1 to 21 of a 28-day cycle) was started with close cardiological follow-up in March 2021. After four cycles of regorafenib, a partial metabolic response was achieved (part b in **Figure 1**). Regorafenib did not lead to a deterioration in myocardial function. A stable disease response was achieved by the 10th month of treatment. The patient continued to receive 160 mg of regorafenib, and no dose reduction was required because of grade 3 or persistent grade 2 adverse events.

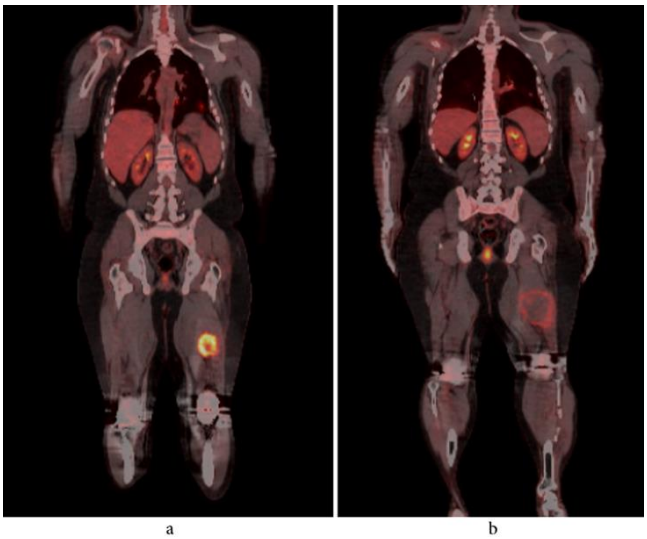

Figure 1. Regorafenib images-1: (a) Baseline imaging before regorafenib–Focal pathological activity in the middle lower part of the left femur (SUVmax: 13.4) and nodular lesion in the left lung and left hilus (SUVmax:8.1) & (b) Four months after starting regorafenib–The size of the existing lesion in the femur increased but the pathological activity decreased (SUVmax: 5.7) and the metabolic activity of nodules in the left lung and hilus has decreased (SUVmax: 4.5) (reprinted with permission of patient)

In the 15th month of regorafenib, an infection developed in the recurrent tumor around the prosthesis on the left distal femur. Regorafenib was interrupted due to grade 3 tumor infection. Unfortunately, long-term hospitalization was required, and wound healing could not be achieved. As a result, the patient underwent left total hip disarticulation. At the same time, NGS revealed a missense mutation (P.G472E) in NOTCH1 gene (Qiagen GeneRead), no targetable mutation was detected. Throughout these perioperative and postoperative periods, he could not receive regorafenib treatment.

In October 2023, restaging PET-CT showed that there were several new bone metastases as well as progressive lung metastases (part a in **Figure 2**). Given the patient's prior long-term response to regorafenib treatment, it was decided to restart same TKI. In February 2024, a partial response was observed in the 16th week of regorafenib again (part b in **Figure 2**).

DISCUSSION AND CONCLUSION

The management of relapsed osteosarcoma is challenging due to limited effective systemic treatment options. However, recognizing the critical role of angiogenic activity in osteosarcoma has opened up novel therapeutic pathways. Here, we shared a case of metastatic osteosarcoma

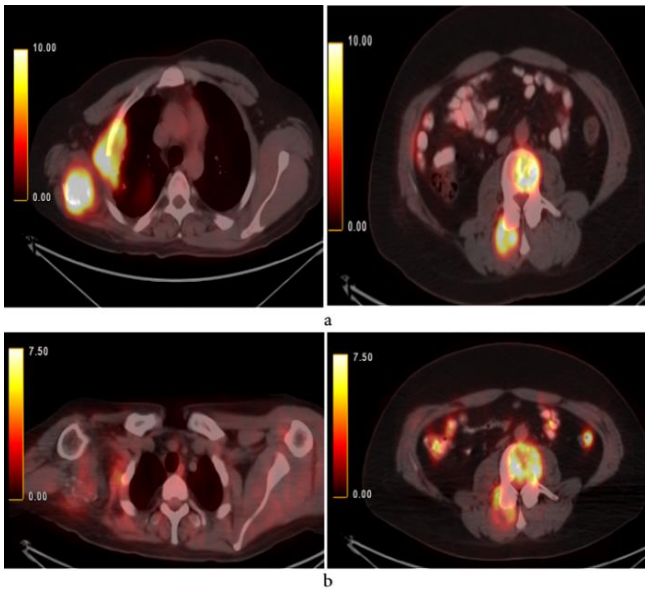

Figure 2. Regorafenib images-2: (a) Before restarting regorafenib–Right axillar and lung metastases and L4 vertebra metastasis & (b) Four months after restarting regorafenib–Decrease in pathological metabolic activity in the axilla and vertebra metastases (reprinted with permission of patient)

with more than one year PFS under regorafenib treatment. To our knowledge, this case represents the longest PFS achieved with regorafenib in metastatic osteosarcoma.

Regorafenib is a TKI targeting VEGFRs 1, 2, and 3 (VEGFR 1-3), as well as RET, KIT, platelet-derived growth factor receptor beta (PDGFR-β), involved in regulating tumor angiogenesis, oncogenesis, and the tumor microenvironment(14).

Regorafenib along with cabozantinib, sorafenib, and lenvatinib (in combination with etoposide and ifosfamide) have shown limited activity in the treatment of advanced osteosarcoma [10-13, 15]. The REGOBONE study enrolled 38 patients with metastatic osteosarcoma after failure of one or two lines of treatment. In the regorafenib arm, the median PFS was 16.4 weeks (95% confidence interval [CI] 8.0-27.3), and the OS was 11.3 months (95% CI 5.9-23.9). Another randomized, placebo-controlled phase II study SARC024, demonstrated similar activity. Median PFS and OS with regorafenib were 3.6 (95% CI 2.0-7.6) and 11.1 (95% CI, 4.7-26.7) months [11]. These two studies indicated that regorafenib may not be tolerated at the full dose of 160 mg per day, as dose reduction rates due to adverse events were 38% and 54%, respectively. However, regoragenib was well tolerated in our patient and no dose reduction was required.

Meta-analyses have indicated the utility of 18F-FDG PET-CT in the diagnosis, staging, and monitoring of patients with osteosarcoma [16]. Given the patient's several bone and lung metastases, PET-CT was utilized for restaging and monitoring treatment response and initial response to regorafenib was noted as a partial metabolic response. The early metabolic response detected by 18F-FDG PET-CT could be a promising biomarker for predicting the benefits of treatment with TKIs in advanced osteosarcoma [12]. Further studies are required to validate these finding.

Recent NGS studies have identified several frequently mutated genes and tumor-specific copy number alterations in osteosarcoma tissues [17]. In our case, likely pathogenic missense mutation in the NOTCH1 gene was detected. NOTCH pathway is activated and highly expressed in osteosarcoma and is closely related to metastasis, drug resistance, and recurrence [18]. In addition, NOTCH signaling plays an important role in angiogenesis [19]. But the exact role of NOTCH1 mutations in osteosarcoma pathogenesis is still under investigation.

As a conclusion, in patients with metastatic osteosarcoma who are ineligible for metastasectomy and have previously received active chemotherapy regimens, regorafenib can provide a durable clinical response. Clinical and molecular markers are needed to identify patients who are most likely to benefit from TKIs.

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Ethics statement: The authors stated that the patient's informed consent was obtained for the case report.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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