

Oncology

Recurrent retroperitoneal soft tissue sarcoma showing drastic reduction after pazopanib administration accompanied by severe liver dysfunction



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ABSTRACT

Pazopanib is an orally bioavailable tyrosine kinase inhibitor anticancer drug approved worldwide for the treatment of metastatic renal cell carcinoma and advanced soft tissue sarcoma. Here we report the case of a patient whose recurrent retroperitoneal soft tissue sarcoma showed a drastic reduction immediately after pazopanib administration accompanied by severe liver dysfunction. His liver function was restored conservatively by giving him hepatoprotectors and having him stop taking pazopanib. The recurrent tumor disappeared but by 4 months later had regrown.

Introduction

Soft tissue sarcomas (STSs) are rare malignant tumors of mesenchymal origin found in fat, blood vessels, lymphatic tissue, muscles, and nerves. Pazopanib is an orally available receptor tyrosine kinase inhibitor targeting the vascular endothelial growth factor receptors (VEGFRs) 1–3, and c-kit and also targeting platelet-derived growth factor receptors (PDGFRs) alpha and beta, and it is effective in the treatment of soft tissue sarcoma.

Here we report a patient whose recurrent STS showed drastic reduction after a short pazopanib treatment that was accompanied by severe liver dysfunction.

Case presentation

A 75-year-old male who six years ago underwent surgical resection of a retroperitoneal tumor surrounding the right kidney, the histological diagnosis of which was undifferentiated/unclassified sarcoma, came to our hospital for annual follow up. Magnetic resonance imaging (MRI) showed a high-intensity lesion in the right iliopsoas muscle (Fig. 1A). The lesion was highly suggestive of recurrent STS, so he was started on a course of oral pazopanib at 800 mg per day. Two weeks later he showed signs of liver dysfunction (elevated serum levels of liver enzymes) appeared and the pazopanib treatment was stopped (Fig. 2). After 1 week he was restarted on pazopanib at a reduced dosage, 400 mg per day. Six days later he visited our hospital complaining of fever, general malaise, fatigue, and appetite loss. Biochemical examination of his blood showed severe liver dysfunction (elevated liver enzymes and bilirubin) (Fig. 2), so he was admitted to our hospital immediately and

treated by giving him hepatoprotectors and stopping his pazopanib. Liver biopsy confirmed drug-induced hepatitis, and he was additionally treated with prednisolone. After administration of these drugs, he recovered from drug-induced hepatitis and was discharged from the hospital. MRI performed during his hospital stay showed that the tumor had completely disappeared (Fig. 1B). Four months later, however, MRI showed a small high-intensity lesion in the right iliopsoas muscle, suggesting tumor regrowth (Fig. 1C). We recommended anthracycline chemotherapy, but he chose not to receive any further anticancer treatment and instead be followed up serially.

Discussion

Malignant fibrous histiocytoma is the most common type of STS and is now classified as undifferentiated/unclassified sarcoma.¹ Surgical resection remains the mainstay of the treatment of STSs and it is important for clinical outcome to obtain negative margins by excising the tumor and surrounding tissues. But with retroperitoneal tumors it is very difficult to obtain negative margins because of the many critical organs around them. The 5-year survival rate of patients with unresectable tumors is < 10%.² New agents for treating recurrent STSs systemically have therefore been needed.

Pazopanib is an oral tyrosine kinase and has approved as the 1st line therapy for advanced and metastatic RCC, and it has also been approved for recurrent and/or metastatic STSs treatment according to the multicenter phase 3 trial conducted by the European Organization for Research and Treatment of Cancer (EORTC), the EORTC 62072—PALETTE study.³ The PALETTE study included only patients who had previously received at least one regimen of chemotherapy

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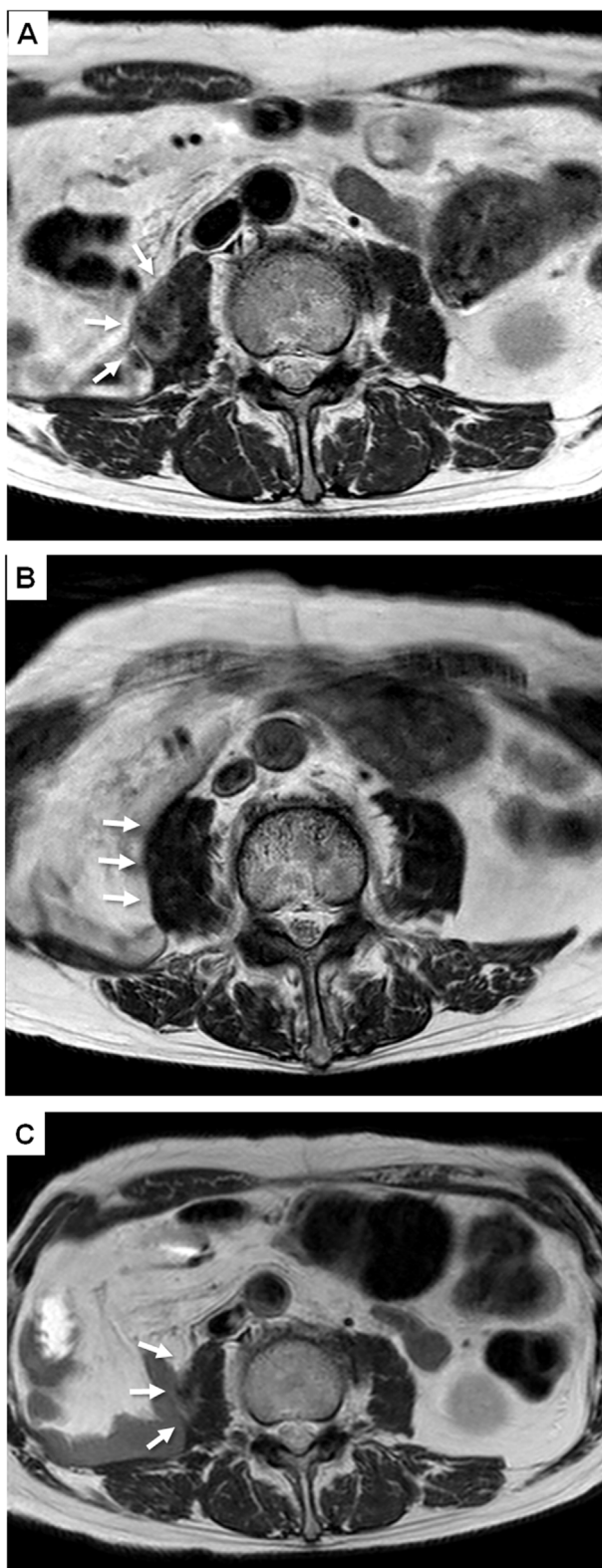


Fig. 1. MRI before and after treatment. T2-weighted MR images showing recurrent tumor before and after treatment with pazopanib. Pretreatment image shows a mass with heterogenous intensity in right iliopsoas muscle (A, arrows). Image 2 months after administration of pazopanib shows no tumor (B). Image 4 months after cessation of pazopanib shows that the tumor reappeared (C).

containing anthracycline and had received no more than four previous lines of chemotherapy. The histopathological diagnosis of the primary site in the present case was undifferentiated/unclassified sarcoma,

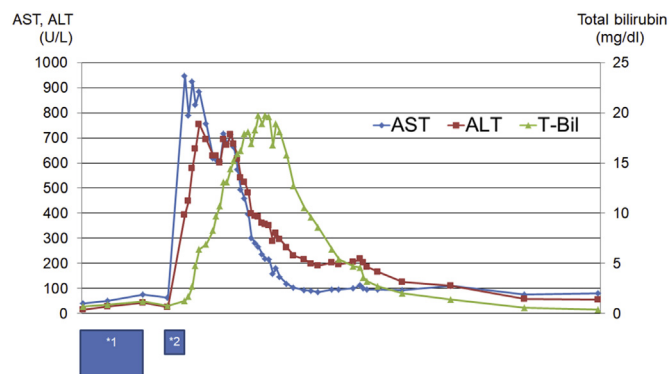


Fig. 2. Clinical course of biochemical examinations. Sequential changes of liver enzymes and total bilirubin during pazopanib treatment. *1: 800 mg per day. *2: 400 mg per day.

which in the PALETTE study was classified as “other sarcoma.” To the best of our knowledge, this is the first report of recurrent STS that showed complete response after administration of pazopanib for only 2 weeks. One of the reasons for the prompt response to pazopanib in our case might be that the patient had previously taken no other anticancer drug.

Despite the marked antitumor effect in this case, the patient had to stop taking pazopanib due to severe hepatotoxicity. Some studies based on the clinical trials have demonstrated that pazopanib is associated with a significantly increased risk of liver toxicity.⁴ Liver toxicity has also been associated with other tyrosine kinase inhibitors such as sunitinib, sorafenib, and axitinib, but it is clear that the rate of high-grade liver toxicity is significantly higher with pazopanib.⁴ The different liver toxicities of different tyrosine kinase inhibitors may be due to different receptor affinities, liver metabolisms, and target differences. It has been suggested that the occurrence of adverse events such as hypertension and/or hypothyroidism after taking tyrosine kinase inhibitors is associated with improved antitumor efficacy and that these events might be markers of a drug's antitumor activity.⁵ The association between liver toxicity and antitumor activity remains unclear and clinical meta-analysis will be needed to elucidate their association.

In the present case, we also proposed to the patient surgical resection of the recurrent tumor before taking pazopanib. He chose to receive pazopanib and forgo surgical resection because of the risk of post-surgical complications such as walking disorder due to intraoperative nerve injury and the risk of incomplete resection. This case suggests that pazopanib is effective against STSs but that we must pay attention to the risk of liver toxicity with it. Awareness of this risk could lead to appropriate intervention reducing the morbidity and mortality due to pazopanib's liver toxicity, thereby leading to a more beneficial effect of pazopanib.

Conclusion

We experienced a case in which recurrent STS showed drastic reduction after a short pazopanib treatment that was accompanied by severe liver dysfunction.

Conflicts of interest

We have no conflict of interest to declare.

Consent

Written informed consent was obtained from the patient for publication of this case report.

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