Surgical Resection and Pazopanib Treatment for Recurrent Cardiac Angiosarcoma

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ABSTRACT: Cardiac sarcoma treatment is challenging for surgeons because of frequent tumor recurrence and poor prognosis. In addition, optimal management of recurrences is not well established. The multi-targeted tyrosine kinase inhibitor, pazopanib, was recently approved for soft-tissue sarcoma. Herein, we present a case involving recurrent cardiac angiosarcoma where the patient survived for 2 years with complete remission of disease after repeated surgical resection and treatment with oral pazopanib. Based on our experience, aggressive surgical resection combined with pazopanib may be a valid treatment for recurrent cardiac angiosarcoma to improve patient survival.

KEYWORDS: cardiac angiosarcoma, pazopanib, angiogenesis

Introduction

Cardiac angiosarcoma is a rare but life-threatening disease because of its rapid growth and resistance to existing therapies. Although complete surgical excision reportedly results in the highest cure rate, total cardiac sarcoma removal is difficult because of tumor inaccessibility, the proximity of vital cardiac structures, and the frequent requirement of emergency surgery. Incomplete cardiac angiosarcoma resection frequently results in tumor recurrence, but the optimal management of disease recurrence is not well established. Pazopanib is a multi-targeted tyrosine kinase inhibitor with activity against vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α, PDGFR-β, and c-kit. A randomized, double-blinded, placebo-controlled, phase III trial demonstrated the clinical efficacy of oral pazopanib in patients with metastatic soft-tissue sarcoma. Herein, we present a case involving recurrent cardiac angiosarcoma where the patient survived without significant disease progression after repeated surgical resections and treatment with pazopanib.

Case Description

A previously healthy 54-year-old man presented with respiratory distress. His echocardiogram showed pericardial effusion and a 45-mm tumor in the right atrium (RA; Figure 1A). Positron emission tomography–computed tomography (CT) with fluorodeoxyglucose (FDG) showed high FDG uptake in the tumor (Figure 1B) without evidence of metastasis. There were no significant physical and laboratory findings in the preoperative period. Thus, we planned complete tumor resection. Our surgical observations included pericardial effusion and a tumor localized in the free wall of the RA, which invaded only to the pericardium (Figure 1C). After establishing cardiopulmonary bypass and cardiac arrest, we resected the entire mass and reconstructed the RA free wall using a bovine pericardial patch. Intraoperative pathological examination revealed no malignant cells in the resected specimen margins. Postoperative immunohistochemical studies of the specimen were positive for cluster of differentiation 31 (CD31) and erythroblast-transformation–specific–related gene (ERG), and the histological findings were consistent with cardiac angiosarcoma (Figure 2A to C).

The patient’s postoperative course was uneventful. Postoperative adjuvant chemotherapy using paclitaxel was performed for 6 months; however, follow-up CT demonstrated cardiac angiosarcoma recurrence in the residual RA near the right coronary artery (RCA; Figure 2D) 10 months postoperatively. Immunohistochemical evaluation revealed that the resected cardiac angiosarcoma was positive for several pazopanib targets, including VEGFR-3, c-kit, PDGFR-α, and PDGFR-β (Figure 3). Therefore, we initiated oral pazopanib (400 mg/day) for the treatment of recurrent cardiac angiosarcoma. After pazopanib treatment for 5 months, a follow-up CT showed that the diameter of the recurrent tumor near the RCA had reduced (Figure 2E); however, the recurrent tumor remained. Other examinations demonstrated no significant evidence of cardiac angiosarcoma progression and metastasis. Given these findings, we suspected that the tumor still remains and achieving complete remission not only by oral pazopanib but also by secondary surgical resection is necessary to improve the prognosis. We stopped the administration of pazopanib 1 week prior to the surgery and performed a second surgical procedure to remove the recurrent cardiac angiosarcoma 15 months after the first surgery. The recurrent angiosarcoma invaded the RA and RCA and adhered to the left atrium (LA), right pulmonary vein, right upper lobe of the...
lung, and the aortic root. We resected the tumors and their surrounding structures including the RCA, LA, superior vena cava, right pulmonary vein, and the right upper lobe under cardiopulmonary bypass and cardiac arrest; we then reconstructed them with a bovine pericardial patch and coronary artery bypass grafting to the RCA using a saphenous vein graft. Macroscopic examination of the surgical specimen showed that the central portion of the resected tumor was necrotic and partially scarred. The patient’s postoperative course was uneventful.

Oral pazopanib was resumed a month after the second surgery because postoperative pathological examination revealed that malignant cells in the resection margin near the aortic root were present. During a 24-month follow-up after the second surgery, the patient was doing well and had continued pazopanib since discharge. His follow-up CT showed no recurrence of cardiac angiosarcoma. The patients did not have any significant side effect of pazopanib throughout the administration period.

Comment
Herein, we described a 54-year-old man with recurrent cardiac angiosarcoma successfully treated with surgery and pazopanib. Angiosarcomas constitute most of the cardiac sarcomas among...
malignant primary cardiac tumors, and patients with angiosarcomas have poorer survival rates than those with other types of cardiac sarcoma. Several studies have indicated that surgical resection is the mainstay of treatment in primary cardiac sarcoma and complete resections led to superior outcomes compared with microscopically incomplete resections. Therefore, microscopically negative margins are crucial for long-term survival. In our case, cardiac angiosarcoma recurred after the first surgery despite microscopically negative margins being confirmed via evaluation of multiple surgical sections. This may indicate that microscopically negative margins do not always guarantee non-recurrence of cardiac sarcomas and patients should receive intensive postoperative follow-up even after an apparently complete surgical resection.

Li et al. reported that repeated surgical interventions were ideal for recurrent or metastatic cardiac sarcoma in cases amenable to resection. Several series suggested that multi-modal therapy prolonged survival in patients with inoperable cardiac sarcoma and cases of incomplete resection. In our case, treatment with oral pazopanib reduced the tumor size after the first surgery and also prevented recurrence after the second surgery. Schur et al. also reported patients with primary metastatic cardiac angiosarcoma who responded well to treatment with oral pazopanib. Therefore, we suspect that pazopanib may demonstrate a tumor reduction effect on cardiac angiosarcoma, which may be difficult or impossible to perform complete surgical resection. Ravi et al. reported that angiosarcoma has genomic alterations in VEGFR family members, especially VEGFR-3, and pazopanib showed potent antitumor activity against angiosarcomas. In our case, immunohistochemistry demonstrated that the resected cardiac angiosarcoma in the first surgery was positive for multiple angiogenic targets of pazopanib, including VEGFR-3, and necrotic change was observed in the cardiac angiosarcoma resected during the second surgery. These findings indicate that impeding angiogenesis of angiosarcoma by pazopanib may induce tumor necrosis, resulting in longer patient survival without progression and recurrence. Therefore, pazopanib may become a therapeutic option for cardiac angiosarcoma.

In conclusion, aggressive surgical resection combined with pazopanib may be a potential therapeutic option for recurrent cardiac angiosarcoma, of which the immunohistochemical assessment is positive for multiple angiogenic targets of pazopanib, to improve patients’ long-term survival.

AUTHOR CONTRIBUTIONS
All authors were involved in the diagnosis and clinical care of the patient. YN and HH drafted the manuscript. YS supervised the manuscript. All authors contributed to the manuscript revision.

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