Case Report

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Excellent Response to Apatinib for Residual Tumor in Recurrence Retroperitoneal Malignant Peripheral Nerve Sheath Tumor: A Case Report And Review of The Literature

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1. Abstract

1.1. Background:
Malignant peripheral nerve sheath tumor (MPNST) is a rare and aggressive sarcoma with a high rate of recurrence and metastasis, and the current treatments for MPNST have limited effectiveness. Apatinib is a novel and potent tyrosine kinase inhibitor that specifically targets the intracellular domain of vascular endothelial growth factor receptor 2 (VEGFR-2). In this case study, we report the successful treatment of a patient with retroperitoneal MPNST using apatinib. Our findings suggest that apatinib may be a promising therapeutic option for MPNST patients, and further studies are warranted to investigate its efficacy and safety in this population.

1.2. Case presentation:
A female patient, aged 43, was admitted to our department with a diagnosis of retroperitoneal MPNST. Unfortunately, the patient experienced recurrence after the second surgery, and radiotherapy left her with residual tumor. We consulted with multiple disciplinary teams in our department to determine the best course of action. After receiving approval from the institutional ethics committee, we administered oral apatinib at a dose of 250 mg/day. The patient responded well to the treatment, achieving partial response (PR) in the first few months. The treatment was continued and evaluated as stable disease (SD) thereafter.

1.3. Conclusion:
In this case report, we present a rare case of recurrent retroperitoneal malignant peripheral nerve sheath tumor and its successful treatment with apatinib. Our findings suggest that apatinib may be a promising treatment option for MPNST, with potential for improving patient outcomes.

2. Keywords:
Malignant peripheral nerve sheath tumor (MPNST), recurrence, retroperitoneal, treatment, apatinib

3. Background

MPNST is a challenging diagnosis, often presenting as a mass and requiring surgical resection as the main treatment. While radiotherapy can improve local control, it has not shown to improve overall survival rates[1]. Unfortunately, the 5-year survival rate for MPNST remains low, ranging from 20% to 50%[2]. Chemotherapy, including agents such as dacarbazine, doxorubicin, and epirubicin, may benefit metastatic disease and downstage unresectable primaries when used as neoadjuvant treatment. Despite these options, there is currently no optimal targeted therapy for MPNST[3,4]. Previous studies have explored imatinib, tipifarnib, sorafenib, bevacizumab, everolimus, nilotinib, sunitinib, and selumetinib, but only imatinib showed a 17% response rate[5-8]. In this article, we report a case of recurrent MPNST and its successful treatment with apatinib, a novel tyrosine kinase inhibitor targeting VEGFR-2.

4. Case presentation

A 43-year-old Chinese woman with a history of left retroperitoneal malignant peripheral nerve sheath tumor (MPNST) presented to our radiotherapy department with recurrence 9 months after undergoing two surgical treatments and radiotherapy. The first surgery, “retroperitoneal tumor resection+left nephrectomy,” was performed on February 1, 2018. Postoperative pathology confirmed the presence of malignant peripheral nerve sheath tumor (MPNST) in the retroperitoneum (number 1800893). The second surgery, “laparotomy+retroperitoneal tumor resection+left hemicolectomy,” was performed on September 25, 2018. Postoperative pathology (number 1808570) revealed MPNST with partial necrosis. The

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tumor was mainly located in the intestinal wall muscular layer and had not invaded the mucosal surface. Surgical margins were clean. The patient presented with left back pain, and a CT scan on April 8, 2019, revealed a recurrence of the MPNST in the surgical area and a left posterior abdominal wall mass measuring 4.5 cm × 3.8 cm. She underwent locoregional radiotherapy from April 22, 2019, to May 27, 2019, with a total dose of 50 Gy in 25 fractions using a 6 MV linear accelerator. An abdomen CT scan on May 10, 2019, revealed tumor enlargement measuring 5.1 cm × 4.2cm during radiation therapy. A half month after radiotherapy, a CT scan on June 16, 2019, revealed the tumor had reduced in size, measuring 4.6 cm × 3.6 cm, and the efficacy evaluation of radiotherapy was stable disease (SD). The patient had a history of allergy to penicillin and cephalosporins, and no family history of similar cancer. The remaining medical history, family history, and psychosocial history were unremarkable.

Following multiple disciplinary discussions in our department, the patient was advised to continue treatment with an anti-VEGF targeting drug due to the presence of residual tumor. After considering various factors, including budgetary and physical constraints, the patient decided to proceed with apatinib treatment. Following approval from the institutional ethics committee and after refusing chemotherapy, the patient was administered a continuous dose of 250mg of apatinib per day. On July 4, 2019, the patient's tumor showed significant shrinkage in the first six months of treatment. The patient underwent periodic reviews at intervals of 2-3 months, which showed a marked decrease in tumor size from 4.6cm × 3.3 cm on August 1, 2019, to 2.3cm × 2.1 cm on January 17, 2020, thus achieving partial response according to RECIST 1.1 criteria. Subsequent re-examinations every three months have shown that the tumor remains stable, with the evaluation of efficacy being stable disease (SD).In addition, the patient's chest CT and tumor marker have shown no significant abnormalities. (Figure7) Throughout the course of apatinib treatment, the patient did not experience hypertension, proteinuria, or hand-and-foot syndrome.

5. Discussion

Malignant peripheral nerve sheath tumors (MPNSTs) are a rare and highly aggressive type of malignancy, accounting for only 5 to 10% of all malignant soft tissue sarcomas[9]. Their incidence is 1:100,000[10]. MPNSTs have poor survival rates, with 40% of patients experiencing local recurrence and 40%-60% developing metastatic disease within one year after the initial resection[11]. MPNSTs can appear in various locations, including the head, neck, and extremities. Early radical surgery is the most effective treatment for MPNSTs, as they are insensitive to radiotherapy and chemotherapy, and the disease tends to progress rapidly, leading to a poor prognosis and high mortality rate. Recent translational research on MPNSTs has identified potential therapeutic targets, including the NF1-Ras, Raf-MEK-ERK, PI3K-AKT-mTOR, and Wnt signaling pathways, as well as abnormalities in apoptotic proteins, the loss of polycomb repressive complex 2 (PRC2), the upregulation of the HDAC family, and various microRNAs. Clinical trials targeting these pathways may provide valuable information for MPNST-targeted therapy. In our case, the patient had a residual lesion after secondary surgery and radiotherapy. Due to budgetary and physical reasons, the patient chose a target therapy drug (apatinib). Ongoing treatment led to a partial response on January 17, 2020, and has since stabilized to a "SD" state. In recent years, a number of targeted therapies have shown promising results in treating certain histologic types of advanced or metastatic soft tissue sarcomas (STS). One such therapy is pazopanib, a multitargeted tyrosine kinase inhibitor (TKI) that targets the vascular endothelial growth factor receptor (VEGFR). By inhibiting angiogenesis, pazopanib has demonstrated single-agent activity in patients with advanced STS subtypes, except for liposarcoma adipocytic sarcoma (LPS)[12-15]. In a phase III study (EORTC 62072), 369 patients with metastatic non-lipogenic STS who had failed at least one anthracycline-based chemotherapy regimen were randomized to receive either pazopanib or placebo. Pazopanib significantly prolonged median progression-free survival (4.6 months vs. 1.6 months for placebo; $P < .0001$), and there was also a trend toward improved overall survival (12.5 months and 11 months, respectively; $P = 0.25$), although it was not statistically significant[16]. Current guidelines recommend pazopanib as a palliative therapy option for patients with progressive, unresectable, or metastatic non-lipogenic STS. These findings suggest that anti-VEGFR agents may be effective in treating non-lipid-derived STS.

Apatinib (Hengrui Pharmaceutical Co., Ltd., Shanghai, China) is a small-molecule tyrosine kinase inhibitor with multi-target activity that selectively inhibits vascular endothelial growth factor receptor-2 (VEGFR-2) and blocks tumor neovascularization, thereby suppressing tumor growth. Apatinib has demonstrated a specific anti-tumor effect in various types of cancer in clinical studies[17-19]. However, its effectiveness and safety in treating patients with malignant peripheral nerve sheath tumors (MPNST) have not been reported previously. Therefore, this case report aims to investigate the safety and efficacy of apatinib in MPNST. MPNST is characterized by complex molecular genetic changes that dysregulate key signaling pathways involved in cell proliferation, growth, and apoptosis. Genomic studies indicate that NF1 inactivation is the initial event leading to neurofibroma formation, followed by CDKN2A/B deletion, leading to the progression to atypical neurofibroma, and functional inactivation of polycomb repressive complex 2 (PRC2), eventually resulting in the formation of MPNST. Other signal channel modifications found in MPNST include PTEN, BMP2-SMad1/5/8, WNT, STAT3, and SMARCB1 gene inactivation. The downstream factor of STAT3 is involved in tumor angiogenesis, which is critical for tumor growth and metastasis. Anti-angiogenesis agents have been shown to effectively treat solid tumors[20], as they can prevent the provision of oxygen, nutrition, and growth factors to tumors. Apatinib is a small-molecule tyrosine kinase inhibitor that selectively binds and strongly inhibits VEGFR-2, decreasing VEGF-mediated endothelial cell migration, proliferation, and tumor microvascular formation[21].

It has been approved as a third-line treatment for advanced gastric and gastroesophageal junction adenocarcinoma in China and has shown

excellent potential in various solid tumors, including non-small cell lung cancer[22], breast cancer[23], hepatocellular carcinoma[24], pancreatic cancer[25], and ovarian cancer[26]. Adverse reactions to apatinib include hypertension, hand-foot syndrome, albuminuria, fatigue, anorexia, and elevated transaminase levels, most of which are of grade 1-2 and can be relieved by drug withdrawal or reduction[27]. Here, we report a patient with advanced MPNST who showed an encouraging response to apatinib, which was well-tolerated by the patient. Apatinib is a suitable choice for long-term maintenance treatment, and adverse effects can be controlled by dose reduction, interruption, and symptomatic treatment. Based on this patient's treatment process and relevant literature reports, we recommend administering the drug dose according to the patient's body weight and age. A medium dose is recommended initially, which can be increased if the patient tolerates it well. Conversely, if the adverse reaction is severe, the dose can be reduced to maintain the long-term curative effect. This case report has several limitations that should be acknowledged. As a retrospective observational study with a small sample size, the level of evidence generated is relatively low. Therefore, any conclusions drawn from these data should be considered preliminary and further clinical trials are necessary to validate these findings.

6. Conclusions

To the best of our knowledge, this is the first report demonstrating a rapid clinical response to apatinib in the treatment of recurrent retroperitoneal malignant peripheral nerve sheath tumors. The results of this case suggest that apatinib may be a promising treatment option for recurrent retroperitoneal malignant peripheral nerve sheath tumors. However, due to the limited nature of this case report, further clinical trials are needed to confirm the effectiveness of apatinib in this context, elucidate the underlying mechanisms of its action, and identify suitable patients who may benefit from this therapy.

7. Data Availability Statement

All datasets generated for this study are included in the article/ supplementary material.

8. Ethics Statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Hubei Cancer Hospital and Tongji Medical College, Huazhong University of Science. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

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