Case Report

Treatment of Retroperitoneal Well-Differentiated Liposarcoma with Combination of Penpulimab and Anlotinib: A Case Report and Literature Review

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Received: 23-Nov-2023;
Revision: 11-Jun-2024;
Accepted: 16-Dec-2024;
Published: 17-Mar-2025

ABSTRACT

To observe the efficacy of combination therapy with Penpulimab and Anlotinib in the treatment of retroperitoneal well-differentiated liposarcoma. Retrospective analysis of clinical data of a patient with retroperitoneal well-differentiated soft tissue sarcoma admitted to Shaoxing People's Hospital, and review of relevant literature. The patient is a young male who experienced recurrence of retroperitoneal well-differentiated liposarcoma after two surgeries. After first-line treatment with Anlotinib combined with Penpulimab, the patient achieved almost complete remission with a progression free survival period of about 16 months. The first-line treatment of retroperitoneal well-differentiated soft tissue sarcoma using Anlotinib combined with Penpulimab resulted in a good prognosis.

KEYWORDS: *Anlotinib, penpulimab, soft tissue sarcoma*

Soft tissue sarcoma (STS) is a rare mesenchymal tumor that can originate from any connective tissue such as muscle, fat, blood vessels and cartilage,[1] accounting for 1% of adult tumors. Based on its origin, histological appearance, and molecular characteristics, STS covers over 100 histological subtypes.[2] In STS, 15% occurred in the retroperitoneum, and the most common histological subtypes of retroperitoneal STS include well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), leiomyosarcoma (LMS), solitary fibrous tumor (SFT), and malignant peripheral nerve sheath tumor (MPNST).[3,4] WDLPS as the most common type of liposarcoma, has a relatively good prognosis.[2]

Remote metastasis of retroperitoneal liposarcoma is rare, but it is prone to local recurrence.[2] The main treatment method for retroperitoneal liposarcoma is surgical resection. Chemotherapy is the primary systemic treatment for advanced STS patients, and immunotherapy is only effective for some subtypes of STS. Tyrosine kinase inhibitors, represented by Pazotinib and Anlotinib, are the main targeted therapies and have been explicitly recommended as second-line treatments for non-specific soft tissue sarcoma.We have achieved good results in the first-line treatment of a case of recurrent STS after two surgeries using the combination of arotinib and Penpulimab monoclonal antibody. The following is a report.

Case Data

The patient, male, 39 years old, was admitted to Shanghai Changhai Hospital in January 2014 due to the retroperitoneal mass. After exclusion of contraindications, the retroperitoneal tumor resection was performed. Postoperative pathological examination showed liposarcoma and no postoperative radiotherapy or chemotherapy was performed. In August 2018, a retroperitoneal MR examination revealed that after

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How to cite this article: Jin X, Ji R, Wu Y, Wang J, Chen X. Treatment of retroperitoneal well-differentiated liposarcoma with combination of Penpulimab and Anlotinib: A case report and literature review. Niger J Clin Pract 2025;28:128-33.

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_817_23

surgery for a retroperitoneal tumor, there was a perimesenteric mass located in front of the left psoas major muscle, which increased compared to August 6, 2017. Therefore, recurrence is considered. On January 18, 2019, abdominal ultrasound showed a left retroperitoneal heterogeneous mass (9.7*5.0cm) with unclear boundaries. After ruling out relevant contraindications, on January 21, 2019, a retroperitoneal tumor resection, left nephrectomy resection, and colon resection and anastomosis were performed under general anesthesia at Changhai Hospital of Naval Medical University. During the operation, it was found that there were extensive and severe intestinal adhesions in the abdominal cavity, then extensive intestinal adhesions being released. A tumor occupying the left retroperitoneum and around the kidney was visible, enveloping and invading the left colon. There was severe adhesion to the left kidney, accompanied by invasion of the left psoas major muscle, and compression of the left ureter. Postoperative pathology showed (retroperitoneal) well differentiated liposarcoma. Immunohistochemistry results: VI (+) CD34 (+) S-100 (-) MDM2 (+) ABC (+/-) CDK4 (+) SOX-10 (-) P16 (+) SMA (-) Ki-67 (3%).

The expression and microsatellite status of programmed death receptor ligand 1 (PD-L1) are unknown. Regular outpatient follow-up was conducted afterwards. On February 26, 2021, in another hospital contrast-enhanced CT of the retroperitoneum showed patchy irregular low-density shadows in the surgical area, with a range of approximately 12.2*9.6cm. The enhanced scan showed mild enhancement and recurrence was considered. On April 5, 2021, enhanced CT scan of the entire abdomen revealed postoperative follow-up of retroperitoneal tumors. The left kidney was absent after surgery, and there was a large abnormal density shadow in the left upper abdomen, indicating a possibility of recurrence. The patient received targeted therapy with 12 mg of arotinib for 1-14 days and q3w starting from April 16, 2021. During the follow-up period, CT scan of the entire abdomen showed stable condition. Starting from October 15, 2021, the combination therapy of Amplizumab 200mgd1 + Anlotinib 12mgqdd1-14 and q3w targeted immunotherapy was administered. During the treatment process, secondary hypothyroidism occurs, and symptomatic treatment with Euthyrox is given. During the treatment period, on March 30, 2022, a full abdominal contrast-enhanced CT scan was performed: there was a mass shadow in the left upper abdomen, accompanied by multiple enlarged lymph nodes in the mesentery, abdominal aorta, and retroperitoneum. The lesion was significantly reduced compared to February 14, 2022. After regular follow-up CT scans, the tumor continued to shrink. On June 9, 2023, a full abdominal CT scan showed almost no tumor (as shown in the Figure 1).

Discussion

Soft tissue sarcoma (STS) is a rare but heterogeneous group of malignant tumors originating from mesenchymal tissue, comprising 1% of all adult malignant tumors and more than 50 histopathological changes.[5,6] Nearly 40000 new cases are diagnosed annually in China. Although surgery and/or radiotherapy are considered as the standard treatment for most local STS, more than 30% of high-risk STS patients will still experience tumor recurrence and metastasis after active treatment.[7] Generally speaking, because of the deep and hidden location of retroperitoneal STS, the survival outcomes and prognosis of patients with recurrent or metastatic retroperitoneal STS are lower than those of in other parts.[3] The 5-year and 10-year disease specific survival rates (DSS) of primary retroperitoneal sarcoma (RPS) are 50% and 35%, respectively. The poor prognosis of RPS is mainly due to the higher local recurrence rate.[4,8] However, the differences in prognosis between STS and RPS patients are not only related to location, but also to the major histological subtypes of RPS.

Since 1974, doxorubicin had been widely used in the trentment of soft tissue sarcoma. Its single agent chemotherapy and ifosfamide combination chemotherapy are still prescribed as the first line standard chemotherapy regimen for advanced or metastatic soft tissue sarcoma. However, the actual treatment effect is far from expected effect.[9,10] The objective response rate (ORR) is 5%-20%, the median progression free survival (PFS) is 4.2 months, and the median overall survival (OS) is 14 months.[7] According to previous studies, the therapeutic effect of chemotherapy or radiotherapy on WDLPS and ddlps was unsatisfactory.[11,12] For second-line treatment of STS, FDA approved pazopanib is usually used. In recent years, new treatment methods have been developed for the second line treatment of STS, including eribulin, trobertinine, and pazopanib. However, these drugs have not yet been approved for the treatment of STS in China. The specific efficacy and scope of application still need further research and clinical trials. In addition, due to the rarity and numerous subtypes of this type of disease, it is difficult to obtain a large amount of data for treatment guidance.[13,14] Aniotinib has shown good efficacy in the second-line treatment of STS. It is a novel small molecule multi target tyrosine kinase inhibitor (mTKI) independently developed by Chinese pharmaceutical companies. It plays an anti-tumor

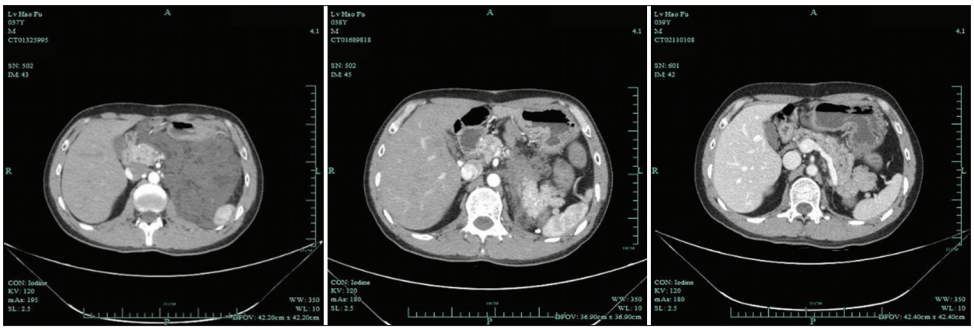

Figure 1: Postoperative follow-up of retroperitoneal tumors with enhanced CT scan of the entire abdomen

angiogenesis and inhibiting tumor growth inhibition role byinhibiting the activity of vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor (PDGFR), fibroblast growth factor and stem cell growth factor receptor and other kinases.

In the randomized, double-blind, placebo-controlled multicenter clinical study of phase IIB (study Alter0203), 233 late stage STS patients who failed anthracycline therapy were enrolled, covering multiple pathological subtypes and liposarcoma. The results showed that the mPFS of arotinib reached 6.27 months, which was significantly longer from 1.47 months in the placebo group, and the risk of disease progression decreased by 67%.[15] Further subgroup analysis showed that the PFS of arotinib was more significant in synovial sarcoma, leiomyosarcoma, ASPS and other pathological subtypes, and there was also a certain degree of response in liposarcoma.[16] Therefore, it has also become the first second-line treatment for STS after anthracycline therapy failure, and has been recommended by CSCO guidelines. At the 2021 ASCO annual meeting, a small sample Phase II study on maintenance therapy of arotinib was reported, which included 30 patients with advanced STS who were treated with epirubicin combined with arotinib for 6 cycles, and then continued to use arotinib maintenance therapy until disease progression or intolerance.

The results showed that the ORR was 13.3%, the disease control rate was 80%, and the median PFS was 11.5 months at 18 weeks of treatment, with good safety.[17] For patients with advanced STS, it is suggested to consider using anti angiogenic small molecule TKIs as a maintenance therapy. The exceptions are DDLPS and WDLPS, both of which are the main tumors with MDM2-CDK4 mutations and typically coexist in patients with primary and recurrent liposarcoma.[18] Both WDLPS and DDLPS contain huge chromosomes in their karyotypes. The megachromosome contains the gene sequence of chromosome 12 and is genetically characterized by repeated 12q13-q15 amplification. MDM2 is located at 12q13 and is induced to be highly expressed and amplifyed in almost all cases, serving as a major carcinogen for WDLPS and DDLPS.[19] As an E3 ubiquitin ligase, MDM2 is responsible for targeting p53 protein and degrading it, which is a challenging target from a molecular perspective. Nutlin-3 is an MDM2 antagonist with a narrow therapeutic window and high toxicity.[20] Therefore, alternative methods of targeted molecular therapy, such as immunotherapy, may be a suitable choice.

The application of immunotherapy, mainly using immune checkpoint inhibitors ICIs, in soft tissue sarcomas is receiving increasing attention. However, currently ICI has shown therapeutic effects in some sarcomas (undifferentiated multilinear sarcoma, undifferentiated liposarcoma) (SARC028 clinical trial), while its efficacy is not ideal in other sarcomas. Immunotherapy has higher response in tumors with TMB (a large number of mutated genes) or MMR defects (leading to high TMB).[21,22] Although the genetics of sarcomas are indeed complex and have histological diversity, overall, the TMB is of sarcomas is often lower compared to other types of cancer.[23-26] There are many histological types of retroperitoneal tumors, but most common retroperitoneal histological types are not classified as high TMB, and WDLPS has the lowest TMB among all subtypes. The SARC028 trial (NCT02301039) is the first trial to evaluate the efficacy of ICI in patients with sarcoma. This is a multicenter, dual cohort, open label, phase 2 pembrolizumab monotherapy trial involving 40 patients with STS and 40 patients with osteosarcoma. STS subtypes include LMS, UPS, DDLPS, and synovial sarcoma. The main endpoint of overall remission was not achieved, but 40% of UPS patients, 20% of DDLPS patients, and 0% of LMS patients experienced remission.[27] In the final analysis of the extended queue, DDLPS showed an ORR of 10% (4/39 patients).[28] Subsequent correlation analysis found that patients with PD-1 positivity and elevated TAM activated T cell density were more likely to experience reactions.[29] Anti angiogenic therapy can

remodel the immune microenvironment, enhance antigen presentation, and promote immune cell recruitment to promote immune activation.[30,31] Meanwhile, cytological and zoological studies have shown that immune checkpoint inhibitors can promote tumor vascular normalization, reduce metastasis, and have synergistic effects with anti angiogenic drugs.[32] Therefore, the combination therapy of anti angiogenic small molecule inhibitor TKIs and immunotherapy has synergistic effect in theory.

A single arm phase II study explored the efficacy of acitinib combined with pabolizumab in patients with advanced treated STS. This study enrolled a total of 33 patients with various pathological subtypes of sarcoma, including 12 cases of ASPS. The results showed that the 3-month PFS rate (PFSR 3m) of the total population was 65.6%, the median PFS was 4.7 months and the ORR was 25%, indicating that this efficacy was not superior to the that of anti angiogenic small molecule TKIs combined with chemotherapy.[33] Subgroup analysis showed that in ASPS and non ASPS patients, the PFSR 3m was 72.7% and 61.9%, respectively, median PFS was 12.4 and 3.0 months, and ORR was 54.5% and 9.5%, respectively, indicating that the overall efficacy of the population depends more on ASPS, a subtype that is highly sensitive to targeted therapy and immunotherapy. In addition, compared with previous research reports, the ORR of single drug anti angiogenic small molecule TKIs drug sunitinib in the treatment of ASPS was 40.0%~62.5%, and the median PFS was 13-19 months,[34,35] indicating that anti angiogenic small molecule TKIs combined with immunotherapy did not bring about the improvement of curative effect. At the 2021 ASCO annual meeting, the results of a single arm phase II study on the treatment of advanced STS with programmed cell death protein 1 ligand 1 antibody Devalumab combined with pezopanib were reported. Among the 46 enrolled patients, 1 had complete remission (2.2%), 13 had partial remission (28.3%), and 27 had stable disease (58.7%), the overall ORR was 30.4%, the disease control rate was 89.1%, and the median PFS could reach 8.6 months.[36] Existing studies have shown that the anti angiogenic small molecule TKIs combined with immunotherapy may be effective for some patients in some cases, but the overall efficacy is not satisfactory, how to select the beneficiaries is a dilemma that needs to be overcome in future combined therapy.

Sun *et al*.[37] explored the therapeutic effect of alotinib combined with ICIs in the treatment of metastatic sarcoma previously treated. In a small sample size, the ORR was 34.4%. You *et al*.[38] found that TKI-ICI therapy has anti-tumor activity in soft tissue sarcoma, and in the dedifferentiated liposarcoma (DDLPS) subgroup, the ORR was good with 36.6%. Although most patients are well toleranced with this treatment, it is still necessary to explore the clinical effect through a large number of samples of retroperitoneal sarcoma. Li *et al*.[39] evaluated the function of anlotinib in the treatment of locally recurrent or metastatic WDLS/DDLS. This study involved the collection and analysis of baseline and observational indicators. The estimated median PFS was 27.9 weeks, the 24 week PFS rate was 58.8%, the OS was 56.6 weeks, and the disease control rate was 64.7%. No complete or partial remission was detected. Level 3/4 adverse events occurred in 4 cases and were managed. This present study suggests that anlotinib is a potential treatment option for unresectable locally recurrent or metastatic WDLS/DDLS. Panapril monoclonal antibody is currently the only new PD-1 monoclonal antibody using IgG1 subtype and undergoes FC segment modification, which completely eliminating the ADCC/ADCP/CDC effect while reducing the ADCR effect. Compared with other marketed products, immunotherapy has a systemic effect, good cancer cell killing effect and less adverse reactions. We chose to treat this patient with combination of antiprolizumab and arotinib as the first line treatment, and the PFS time reached 16 months, which was longer than the single drug treatment. This combination has been applied to other types of cancer and has achieved good therapeutic effects.[40] The mechanism may be that vascular endothelial growth factor (VEGF) has an inhibitory effect on anti-tumor T cells, thereby weakening the attack effect of immune on tumors and the VEGF inhibitory effect of arotinib can enhance T cell function. Therefore, immune checkpoint inhibitors can enhance the anti-tumor therapeutic effect.[41] During the treatment period, the patient experienced symptoms of grade 1 hypothyroidism, which may be an adverse reaction of paclitaxel monoclonal antibody. In conclusion, this patient with advanced well differentiated retroperitoneal sarcoma attempted the first-line treatment regimen of combination of clopidogrel and arotinib, and obtained a PFS time of 16 months. The combination therapy of clopidogrel and arotinib may be an optional for advanced well differentiated retroperitoneal sarcoma. The combination of anti angiogenic drugs and immunotherapy may achieve “de chemotherapy” in this population. However, the current study only preliminarily explored the effect of this treatment strategy in specific patient groups and in the future, larger sample sizes and higher-level studies are needed to further confirm its efficacy and safety in patients with different types and stages of tumor.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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