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The Short-Term Efficacy and Safety of Anlotinib Combined With Chemotherapy in Treatment of Advanced Soft Tissue Sarcoma

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Abstract

Soft tissue sarcoma has a strong tendency of local recurrence and metastasis, and the treatment results after metastasis are not ideal. Alonitide, as a newly developed oral small molecule RTK inhibitor, has good results on STS. This article aims to summarize the results of anlotinib combined with chemotherapy in the treatment of advanced soft tissue sarcoma, and to provide indications for subsequent treatment.

Keywords: Anlotinib; Advanced Soft Tissue Sarcoma; Chemotherapy

1 INSTRUCTION

Soft tissue sarcoma (STS) is a heterogeneous group of rare tumors with heterogeneous mesenchymal origin, covering approximately 70 different entities [1]. The natural history of these aggressive diseases is characterized by a strong tendency for local recurrence and metastatic spread, and despite the best initial treatment strategy, it still occurs in 10% to 30% and 30% to 40% of patients, respectively. Lungs are the most common site for STS metastases, and lung metastasis is the standard treatment for patients with certain lung diseases. For metastatic patients who are not suitable for surgery, chemotherapy still plays the most important role in disease control. Despite the progress made over the past few decades, the prognosis for patients with metastases remains poor, with a median overall survival (OS) reported to be 14-17 months [2-4]. This article summarizes the results of anlotinib combined with chemotherapy in the treatment of advanced soft tissue sarcoma, and provides indications for subsequent treatment.

2 BASIC THEORY OF ANLOTINIB

Anlotinib (1-[[[[4- (4-fluoro-2-methyl-1H-indole-5-yloxy) -6-methoxyquinolin-7-yl] oxy] methyl] ring Alanine dihydrochloride) is a newly developed oral small molecule RTK inhibitor that targets VEGFR1, VEGFR2 / KDR, VEGFR3, c-Kit, PDGFR-α and fibroblast growth factor receptors (FGFR1, FGFR2 and FGFR3). In addition, it can inhibit tumor angiogenesis and tumor cell proliferation [3, 4]. Anlotinib inhibits more targets than other RTK inhibitors, including sorafenib, sunitinib, and pazopanib.

Preclinical studies have shown that anlotinib inhibits VEGF / PDGF-BB / FGF-2-induced cell migration and capillary-like formation in endothelial cells. In addition, alotinib significantly inhibited VEGF / PDGF-BB / FGF-2-induced angiogenesis in vitro and in vivo. Studies of possible mechanisms have shown that alotinib inhibits the activation of VEGFR2, PDGFRβ and FGFR1 and downstream ERK signaling. Anlotinib has stronger antiangiogenic activity than three other antiangiogenic drugs, including sunitinib, sorafenib, and nintedanib [5]. Another study showed that alotinib binds to the ATP-binding pocket of VEGFR2 tyrosine kinase and inhibits VEGFR2 with high selectivity (IC50 <1 nmol / L), thereby inhibiting VEGF-stimulated human umbilical vein endothelial cells (HUVEC) proliferation. In addition, alotinib inhibits HUVEC migration, tube formation and microvascular growth in vitro, and reduces blood vessel density in vivo. Compared with sunitinib in vivo, anlotinib has a broader and better antitumor effect [3]. In a cell line expressing the mutated FGFR2 protein, alotinib reduced the number of cells. However, similar to other oral RTK inhibitors, the combination of anlotinib with carboplatin and paclitaxel seems to be more effective than anlotinib alone [6].

3 Research Status

In recent years, more and more targeted drugs have shown good clinical efficacy in patients with certain types of advanced STS. These drugs include multi-target kinase inhibitors, such as pazopanib, imatinib, sunitinib, and sorafenib; ALK inhibitors, such as crizotinib and ceritinib; anti-PDGFR, such as anti-PDGFR PDGFRα monoclonal antibody olaratumab; and anti-angiogenic drugs, such as bevacizumab [7-15]. However, pazopanib is by far the only small molecule TKI approved by the FDA for second-line STS treatment.

Judson et al. [16] reported that doxorubicin combined with ifosfamide can increase the ORR (26.5% vs 13.6%) of patients with advanced STS compared with ifosfamide alone, and delay the progression-free time of the median disease. survival, PFS; 7.4 months vs. 4.6 months, HR = 0.74, P = 0.003), but adverse reactions increased significantly, and overall survival benefit was not significant (14.3 months vs 12.8 months, P = 0.076). There is no standard protocol for advanced STS second-line chemotherapy, and chemotherapeutics such as dacarbazine, gemcitabine, temozolomide, vincristine, cyclophosphamide, and paclitaxel can be selected according to the pathological type and individual circumstances, but the overall efficacy is poor. In recent years, the research of molecular targeted drugs has made rapid progress [17], and has shown satisfactory curative effects in certain types of STS. Angiogenesis plays an important role in the growth, invasion and metastasis of STS. Anti-angiogenesis therapy targeting VEGF or VEGFR has become a research hotspot in the treatment of STS, including monoclonal antibodies (such as bevacizumab) and small cells. Molecular tyrosine kinase inhibitors (such as sorafenib, perazopanib, sunitinib, and anlotinib, etc.). Studies [18] have shown that anlotinib can treat multiple STS subtypes, especially can prolong PFS, increase ORR and DCR in patients with synovial sarcoma, leiomyosarcoma, and alveolar soft part sarcoma (ASPS) Good safety. Further research [19] showed that anti-angiogenesis therapy combined with cytotoxic chemotherapy can effectively overcome chemotherapy resistance and help inhibit tumor growth. In some early clinical studies, antiangiogenic drugs, including bevacizumab and sorafenib, in combination with chemotherapy have shown some efficacy and good tolerance in advanced STS. In a phase I b study by Verschraegen et al. [20], bevacizumab combined with gemcitabine and docetaxel were used to treat 36 patients with advanced STS, with an ORR of 31%, including 4 CR, 6 PR, and 18 patients The median PFS was 6 months. In a phase II clinical trial reported by the Spanish Sarcoma Research Group [21], sorafenib combined with ifosfamide was used to treat 35 patients with advanced STS, and their 3-month and 6-month progression-free survival rates were 66%. (95% CI 48-81) and 37% (95% CI 22-55), with a median PFS of 4.8 months and a median overall survival (OS) of 16.2 months, indicating that sorafenib combined with chemotherapy is clinical Benefits are clear, but no randomized controlled trial results confirm this.。

Because of the excellent therapeutic efficacy of Anlotinib in STS, the results of these two clinical studies have been presented in the oral presentation section of the American Society of Clinical Oncology (ASCO) Annual Meeting. Anlotinib may be approved for the treatment of STS in China in the future.

4 Conclusion

In summary, anlotinib combined with chemotherapy is a new strategy for the treatment of advanced STS. Its short-term efficacy is better than the first-line treatment options for STS reported in the previous literature. The adverse reactions have not increased and the patient is well tolerated. Follow-up treatment and survival follow-up are ongoing. However, this study is a single-center clinical study with a small sample size, and the clinical background of patients in first- and second-line treatments is very different, and the chemotherapy drugs used are inconsistent. Therefore, it is necessary to further conduct randomized controlled clinical studies to explore the value of anlotinib combined with different chemotherapy regimens in the treatment of advanced STS of different pathological types.

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