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SHORT REPORT

Efficacy and Safety of Apatinib in the Treatment of Postoperative Recurrence of Fibrosarcoma

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Objective: To evaluate the efficacy and safety of apatinib in patients with relapse after surgery for fibrosarcoma.

Methods: We reviewed the clinical data of 56 patients who experienced recurrence after fibrosarcoma resection and who received chemotherapy from September 2015 to September 2017 (no significant difference in general data of patients) ($p>0.05$). Differences in drug use and adverse effects were observed between patients who received monotherapy and those who received regular chemotherapy (MAID/AI).

Results: Compared with the regular chemotherapy group, patients in the apatinib monotherapy group exhibited an improved overall response rate (ORR) and disease control rate (DCR). In patients treated with apatinib, the incidence of adverse reactions was improved, and the symptoms were mild ($P<0.05$).

Conclusion: Apatinib is a single-drug regimen that can be used in cases of recurrence of fibrosarcoma with high expression of vascular endothelial growth factor receptor-2 (VEGFR-2); its short-term efficacy is excellent, and its side effects are minimal. This drug may be used as part of a regular chemotherapy program.

Keywords: fibrosarcoma, chemotherapy, apatinib, prognosis

Fibrosarcoma is a mesenchymal cell-derived malignant tumor whose pathological features include abnormal proliferation of poorly differentiated fibroblasts or spindle cells.[1] In principle, radical surgery is the preferred treatment approach, but the recurrence rate after simple resection is high; further, it is often necessary to combine local radiotherapy and chemotherapy. For patients with discomfort or postoperative recurrence, arterial chemotherapy can be used as the primary treatment method.[2] Doxorubicin (ADM) and ifosfamide (IFO) are the two most commonly used drugs in the first-line chemotherapy regimen currently used for fibrosarcoma, and no valid second-line chemotherapy exists for fibrosarcoma patients with first-line chemotherapy failure. Related research suggests[3] that the progression of this tumors type is closely related to the growth of microvessels within it. As a small-molecule drug that targets vascular endothelial growth factor receptor 2 (VEGFR-2), apatinib exhibits anti-tumor effects by inhibiting the activity of VEGFR-2 and tumor angiogenesis.[4] This study retrospectively analyzed the clinical data of 56 patients with postoperative recurrence of fibrosarcoma at our hospital and evaluated the short-term efficacy and side effects of apatinib in patients with recurrent fibrosarcoma. This study was reviewed and approved by the Ethics Committee of Chongqing University. And all patients gave written informed consent before participation in this study.

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Materials and Methods

Clinical Data

Case data of patients with recurrent fibrosarcoma who were admitted to the Chongqing University Cancer Hospital from September 2015 to September 2017 are presented in Table 1. The inclusion criteria were as follows: ①pathological diagnosis of fibrosarcoma; ②surgical treatment and progression after first-line chemotherapy (ADM+DTIC); ③more than 4 weeks before the previous treatment; ④physical status (ps) 0–2; ⑤did not receive other anti-angiogenic drugs or targeted anti-tumor drugs; ⑥patients had measurable lesions without radiotherapy; ⑦patients received apatinib for more than 2 months or more than 2 cycles of chemotherapy until tumor progression or intolerable adverse reactions occurred and treatment was replaced or stopped. A total of 56 eligible patients were enrolled in the study, including 28 patients in the apatinib group and 28 patients in the regular chemotherapy (MAID/AI) group. All 56 patients underwent genetic testing for vegfr-2 mutation from the tissue removed during surgery by PCR amplification, and only vegfr-2 mutation-positive patients were eligible for the apatinib group.

Treatment

For patients in the apatinib group, apatinib was administered orally in a 28-day treatment cycle: the initial dose of apatinib was 250 mg/day, which was adjusted to 500 mg per day from the fourth day, and the amount was reduced if an adverse reaction could not be tolerated. Standard chemotherapy was administered to patients in the regular chemotherapy group. The chemotherapy regimen was as follows: ADM+IFO (14 cases) and ADM+DTIC+IFO (14 cases) in a 21-day treatment cycle.

Table 1 The General Patient Information

Age (Mean)		**Apatinib Group**	**Regular Chemotherapy Group**	**P-value**
		63.46	**63.21**	**0.908**
Gender	Male Female	18 10	14 14	0.289
Tumor staging	IIIb V	2 26	3 25	0.647
Drug grading	Second line Third line	4 24	6 22	0.494
Genetic Testing	Positive Negative	28 0	26 2	0.155

Efficacy Evaluation

After the completion of 2 treatment cycles, the clinical efficacy in each group of patients was evaluated according to the World Health Organization (WHO) Response Evaluation Criteria in Solid Tumors (RECIST), and the treatment effect was divided into the following: complete remission (CR): lesion elimination; partial remission (PR): lesion diameter reduced by more than 30%; stable disease (SD): lesion between PR and PD; progressive disease (PD): lesion increased by more than 20%. The objective response rate (ORR) is defined as (CR+ PR)/total number of cases x 100%, and the disease control rate (DCR) is defined as (CR + PR + SD)/total number of cases x 100%. The treatment effect was evaluated every two cycles.

Adverse Reactions

According to the World Health Organization's anti-tumor adverse drug evaluation criteria, the adverse reactions were divided into five levels (0–IV degrees). The higher the level, the more serious the adverse reaction. During treatment, routine examinations such as blood tests and liver and kidney function tests, among others, were performed as a result of the adverse reactions.

Statistical Methods

SPSS 18.0 software was used for the statistical analysis. The chi-square test was used to analyze the general data and short-term efficacy of the two patient groups. The K–S test was used to analyze the adverse reactions in the two patient groups after treatment. When $p<0.05$, the difference was considered statistically significant.

Results

Fifty-six patients completed more than 2 courses of treatment, and after treatment in the apatinib group, the clinical efficacy was determined to be: CR, 0 cases; PR, 7 cases (25.00%); SD, 16 cases (57.14%); PD, 5 cases (17.86%). The overall response rate was 25.00%, and the disease control rate was 82.14%. After treatment in the regular chemotherapy group, the clinical efficacy was determined to be: CR, 0 cases; PR, 5 cases (17.86%); SD, 15 cases (53.57%); PD, 8 cases (28.57) %). The overall response rate was 17.86%, and the disease control rate was 71.43% (Table 2).

The common adverse reactions in the apatinib group and the regular chemotherapy group were feebleness and

Table 2 The Comparison of the Short-Term Efficacy Between Groups

Short-Term Efficacy	CR	PR	SD	PD	ORR	DCR
Apatinib group	0	7	16	5	25.00%	82.14%
Regular chemotherapy group	0	5	15	8	17.86%	71.43%

Notes: Objective response rate (ORR): (CR+PR)/total number of cases x 100%; disease control rate (DCR): (CR+PR +SD)/Total number of cases x 100%.
Abbreviations: CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

anorexia (39.29%; 89.29%), vomiting and diarrhea (35.71%; 85.71%), liver damage (3.57%; 14.29%), myelosuppression (0.00%; 92.86%), hypertension (71.43%; 7.14%), proteinuria (14.29%; 7.14%), and hand-foot syndrome (100.00%; 0.00%). The adverse reactions to chemotherapy in both groups were mostly grade 1~2 (82.43%; 83.13%), and a few were 3~4 (17.57%; 16.87%) (Table 3). The 3–4 grade adverse reactions of the apatinib group were as follows: 1 case of vomiting and diarrhea and 9 cases of hand-foot syndrome, which improved after the dosage was adjusted; 2 cases of hypertension, which improved after a hypotensive agent was given; 1 case of proteinuria, the symptoms of which were relieved after drug withdrawal. The 3–4 grade adverse reactions in the regular chemotherapy group were as follows: 3 cases of feebleness and anorexia, 3 cases of vomiting and diarrhea, 3 cases of liver damage, and 7 cases of myelosuppression. Symptoms were relieved after the dosage was reduced.

Discussion

Fibrosarcoma, which is a sarcoma formed by fibroblasts and collagen fibers, is typically invasive. Related literature reports[5] that the recurrence rate of adult fibrosarcoma is approximately 50%; the current primary treatment for fibrosarcoma is surgical resection, but for cases of postoperative recurrence, the existing second- and third-line chemotherapy regimens are only effective for some cases, and the remission time is short. In the absence of significant improvement in efficacy, patients also need to experience adverse reactions that are difficult to tolerate with regular chemotherapy.[6]

Since the 1970s, some scholars have reported that tumor progression depends on the formation of blood vessels inside them. The invasion and infiltration by solid tumors also depend on the establishment of new blood vessel networks induced by those tumors.[7] The imbalance in angiogenic factors and anti-angiogenic factors causes the formation of microvessels in the tumor, and the formation of new blood vessels promotes the further growth and metastasis of the tumor, which involves proliferation, apoptosis as well as the degradation of the basement membrane and the integration of various cells through the membrane.[8] Interfering with one or more of the aforementioned processes may have an effect on the formation of blood vessels in the tumor, thereby inhibiting the progression and invasiveness of the tumor.[9] The establishment of this hypothesis provides a theoretical basis for the application of targeted anti-angiogenic drugs for the treatment of solid tumors with a rich blood supply. Targeted anti-angiogenic drugs currently used in clinical work include blockers of the vascular endothelial growth factor pathway (bevacizumab and sorafenib) and inhibitors of vascular endothelial growth factor production (recombinant human endostatin).[10] The results of Phase II and III clinical studies by Kasper et al suggest that, for patients with refractory sarcoma who failed multiline therapy, the median PFS was 20 weeks in the targeted anti-angiogenic drug treatment group, whereas the median PFS in the

Table 3 The Comparison of Toxicities Between Groups

Toxicities	Apatinib Group			Regular Chemotherapy Group			P-value
	L0	L1–L2	L3–L4	L0	L1–L2	L3–L4	
Feebleness	17	11	0	3	22	3	0.000
Vomiting	18	9	1	4	21	3	0.000
Liver damage	27	1	0	24	3	1	0.159
Myelosuppression	28	0	0	2	19	7	0.000
Hypertension	8	18	2	26	2	0	0.000
Proteinuria	24	3	1	26	2	0	0.376
Hand-foot syndrome	0	19	9	28	0	0	0.000

Notes: Level 0 (L0): Asymptomatic; Level 1 (L1): Mild symptoms, clinical or diagnostic observations only, intervention not indicated; Level 2 (L2): Moderate symptoms, local or noninvasive intervention indicated; Level 3 (L3): Medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; Level 4 (L4): Severe symptoms, life-threatening consequences, urgent intervention indicated.

regular control group was only 8 weeks.[11] Additionally, and some special subtypes of sarcoma have also shown good results after treatment with targeted anti-vascular drugs.[12]

Apatinib is a small molecule tyrosine kinase inhibitor that is administered orally. Its primary targets are VEGFR-2 and e-KIT, which can selectively inhibit VEGFR and prevent VEGF from binding to its receptor. Subsequent autophosphorylation inhibits the formation of vascular endothelium, which in turn reduces the microvessel density in tumors.[13] Related case reports[14] have confirmed that the application of apatinib in patients with advanced sarcoma has achieved a relatively good therapeutic effect. Similarly, other studies have suggested that the application of apatinib can reduce the incidence of tumor cell resistance to chemotherapy drugs.[15]

Recently, apatinib has been used to treat a variety of solid tumors, and its use in recurrent fibrosarcoma is also evolving. In this trial, our department used apatinib to treat 28 cases of postoperative recurrent fibrosarcoma. After 2 cycles of treatment, 7 cases achieved partial remission, the objective response rate was 25.00%, and the disease control rate was 82.14%, which was better than what was observed in the control group (administered regular chemotherapy only). Moreover, in this study, significant differences were observed in the occurrence of adverse reactions between the two groups. Adverse reactions, such as vomiting and diarrhea, feebleness and bone marrow suppression, were more common in the regular chemotherapy group, and several patients experienced more serious adverse reactions. Twenty-six of 28 patients had symptoms of myelosuppression, of which 7 were grade 3–4. More than 80% of patients exhibited obvious symptoms of fatigue (25/28 cases) and nausea and vomiting (24/28 cases); the dose was adjusted for a small number of patients due to intolerable gastrointestinal symptoms or liver function damage caused by chemotherapy. The most common adverse reactions in the apatinib group were feebleness, hypertension, and hand-foot syndrome: 11 patients had feebleness and anorexia in grade 1–2, and the treatment plan did not require special adjustment; 20 patients reported secondary hypertension. Significant blood pressure control was achieved after the patients were given anti-hypertensive medication. The patients in all groups showed different degrees of hand-foot syndrome. Among them, this adverse reaction was resolved in 19 patients without treatment and in 9 patients after adjusting the dosage. Studies have shown that,[16] when apatinib is applied to the clinical treatment of tumors, hypertension, hand-foot syndrome and other adverse reactions are positively correlated with the treatment efficacy. Patients with these adverse reactions can continue to receive better treatment benefits, but the specific mechanism should be further identified and studied.

The results of this study suggest that, for the treatment of fibrosarcoma with high expression of vegfr-2, the application of apatinib in patients with postoperative recurrence can result in a good short-term effect. The results also suggest that apatinib could reduce the incidence of adverse reactions, and the level of symptoms of apatinib are better than those of regular chemotherapy, which can be further verified in the clinic. It is also expected that a larger sample of clinical data will be collected to summarize more objective and powerful clinical experiences.

Data Sharing Statement

No additional unpublished data are available.

Disclosure

The authors report no conflicts of interest in this work.

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