RESEARCH ARTICLE

Efficacy and Safety of Endostar® Combined with Chemotherapy in Patients with Advanced Soft Tissue Sarcomas

Lu-Ping Zhang, Xing-Yun Liao, Yan-Mei Xu, Lv-Jun Yan, Gui-Fang Yan, Xin-Xin Wang, Yu-Zhong Duan, Jian-Guo Sun*

Abstract

**Background:** Soft tissue sarcomas (STS) are a heterogeneous group of tumors, and approximately 40-50% of patients with STS develop metastatic disease. The median overall survival of those patients was 12 months and their 5-year survival rate was 8%. Therefore, study on more effective treatment, especially the targeting therapies, is urgently needed. **Objective:** To evaluate the efficacy and safety of Endostar® combined with chemotherapy in patients with advanced STS. **Methods:** A retrospective case-series study was conducted in Cancer Institute of PLA, Xinqiao Hospital. A total of 71 patients suffering from advanced STS (IIB - IV) were included, of whom 49 cases treated with chemotherapy alone were defined as the control group and the rest 22 cases treated with the traditional chemotherapy combined with Endostar® were defined as the test group. The short-term therapeutic effects including objective response rate (ORR), disease control rate (DCR) and safety were evaluated in the two groups. In the follow-up, progression-free survival (PFS) and overall survival (OS) were also observed. **Results:** In the test and control groups, the ORR was 18.2% and 12.2%, respectively ($P=0.767$), and the DCR was 86.4% and 61.2%, respectively ($P=0.034$). The median time to progression in the test and control groups was 120 days and 70 days with significant difference ($P=0.017$), while the median overall survival was 452 days and 286 days without significant difference ($P=0.503$). The one-year survival rate in the test group and control group was 56.2% and 35.4%, respectively, while the two-year survival rate was 30.2% and 26.5%, respectively. No significant difference in the side effects was found between the two groups. **Conclusions:** Endostar® combined with chemotherapy resulted in a higher DCR and longer PFS in the patients with advanced STS, and the toxicity was tolerable.

**Keywords:** Soft tissue sarcomas (STS) - endostatin - antiangiogenic - survival analysis

Introduction

Soft tissue sarcomas (STS) are a group of rare solid tumors arising from the embryonic mesoderm. They constitute about 1% of all cancers. The annual incidence of STS in the United States in 2010 was estimated to be about 10,520 cases, with an overall mortality rate of approximately 3,920 cases (including adults and children) per year. Collectively, sarcomas account for approximately 1% of all adult malignancies and 15% of pediatric malignancies (Riedel, 2012). More than 50 different histological subtypes of STS have been identified, such as pleomorphic sarcoma, gastrointestinal stromal tumors (GIST), liposarcoma, leiomyosarcoma, synovial sarcoma and malignant peripheral nerve sheath tumors (Cormier et al., 2004). Depending on tumor grade, size, depth, site, and histological subtype, the overall 5-year survival rate for patients with STS is approximately 50-60% in adults and 75% in children (Riedel, 2012). However, 40-50% of patients with STS will develop metastatic disease (Italiano et al., 2011). For STS, the most common metastasis is to the lungs. When tumors arise in the abdominal cavity, the most common locations for metastasis are the liver and peritoneum. The prognosis for the patients with metastatic disease is poor, with a median overall survival of 12 months and an overall 5-year survival rate of 8% (Heuel et al., 2012). So far, the common treatments are still chemotherapy, radiation and surgery.

With the hypothesis that solid tumor growth is angiogenesis-dependent comes the realization that angiogenesis itself might be a potential therapeutic target. Angiogenesis inhibition may therefore represent a new approach to cancer therapy (Kaya et al., 2007). In addition to growth, invasion, and metastasis, neoplastic neovascularization was also a common characteristic of malignant tumors. STS with a tendency of systemic metastases is particularly prominent. Thus, the angiogenesis inhibition combined with chemotherapy could theoretically improve patients’ quality of life and prognosis.

Cancer Institute of PLA, Xinqiao Hospital, Third Military Medical University, Chongqing, China  *For correspondence: sunjg09@aliyun.com
Endostatin was first isolated from the culture supernatant of a murine hemangioendothelioma cell line. And it is an endogenous angiogenesis inhibitor with strong anti-angiogenic activity that can inhibit the growth of a wide variety of tumors and prevent the progression of pulmonary metastasis (Olsson et al., 2004; Li et al., 2010). Endostar® is a novel recombinant human endostatin. With an additional nine-amino acid sequence at the N terminus, Endostar® is more stable than conventional endostatin (Jiang et al., 2009) and strongly inhibits the growth of a variety of murine and xenotransplanted human tumors by suppressing the neovascularization (Tsukagoshi, 2010). It has been demonstrated that Endostar® combined with first-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) can improve overall and progression-free survival (Wang et al., 2005). However, there were few studies of Endostar® used for STS. We therefore conducted this study to observe the efficacy and safety of Endostar® combined with chemotherapy in advanced STS.

Materials and Methods

Samples
A retrospective case-series study was conducted in Cancer Institute of PLA, Xinqiao Hospital, from May 2007 to November 2012 with the approval of the Ethics Committee of the Third Medical University. A total of 71 eligible patients with STS were included. All the patients with at least one measurable tumor lesion were no longer amenable to surgical treatment or even relapsed after surgery. And all the patients were pathologically confirmed with IIB-IV stage STS according to American Joint Committee on Cancer (AJCC) Staging System for STS (7th Ed, 2010). Other criteria included being at least 18 years old, the Karnofsky performance status (KPS) ≥70 points, and life expectancy ≥ 3 months. Their blood routine, liver and kidney function, and electrocardiogram (ECG) were confirmed to be normal before the trial.

Treatment
The control group received the traditional chemotherapy while the test group was administered Endostar® in each chemotherapy cycle. The chemotherapeutics to the two groups were mainly docetaxel, gemcitabine, doxorubicin, ifosfamide, cisplatin, vincristine and temozolomide. Endostar® was given daily at the dosage of 15 mg day 1 through day 14 and repeated 7 days later. Endostar® dissolved in 500 ml normal saline was administered by intravenous infusion for 4 hours. When patients were receiving the infusion of Endostar®, heart rate, blood pressure, pulse oxygen saturation and electrocardiogram were continuously monitored using an intelliVue MP20 patient monitor (Royal Philips Electronics, the Netherlands).

The observation indexes
The indexes to be observed and monitored are clinical symptoms and signs, adverse reaction, and blood routine every week. Blood chemistry and ECG were performed in every cycle, and computed tomography (CT) or magnetic resonance scanning was conducted every two cycles. Patients’ response was classified, according to the Response Evaluation Criteria in Solid Tumors (RECIST), as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The disease control rate (DCR) was defined as the percentage of patients with CR, or PR, or SD, and the overall response rate (ORR) was defined as the percentage of patients with CR or PR. Overall survival (OS) was the time from first treatment to death while progression-free survival (PFS) was calculated from the initiation of treatment to disease progression. The duration of survival was counted until the last day of follow-up.

Statistical analysis
All the statistical analyses were performed using the SPSS 18.0 statistical package for Windows. X² test was used to compare short-term efficacy and side effects of the two groups. The differences in KPS were examined using t test. The PFS survival curves were estimated by the GraphPad prism. Survival curves were drawn by Kaplan-Meier method. Log-rank test was used to compare the survival rates of the two groups. Statistical significance was set at P<0.05.

Results

Patient characteristics
The patients were divided into two groups, the control group with 49 patients (29 men and 20 female) and the test group with 22 patients (16 men and 6 female). The age of the test group ranged from 18 to 67 and that of the control group from 18 to 70. The number of patients with IIB stage STS in the test group and the control group was 7 vs 32 and stage IV 15 vs 35, respectively. There was no significant difference in age, gender and clinical stage between the two groups (all P>0.05, Table1). Actually, the patients in stage IIB/III were 7 vs 32 and stage IV 15 vs 17 in the test group and control group, respectively. The stage in the test group was worse than the control group (P=0.009, data not shown).

Efficacy
In the control group: CR 0 case, PR 6 cases, and SD 24 cases. In the test group: CR 0 case, PR 4 cases, and SD 15 cases. The difference in overall response rate (CR+PR) between the two groups was insignificant (X²= 0.088, P=0.767). However, the disease control rates

<table>
<thead>
<tr>
<th>Table 1. The General Condition of the Two Groups</th>
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<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Gender</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Age</td>
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<td></td>
</tr>
<tr>
<td>TNM stage</td>
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</table>
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Table 2. Early Efficacy in the Two Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>ORR</th>
<th>DCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>49</td>
<td>0</td>
<td>6(12.2%)</td>
<td>24(49.0%)</td>
<td>19(38.8%)</td>
<td>6(12.2%)</td>
<td>30(61.2%)</td>
</tr>
<tr>
<td>Test</td>
<td>22</td>
<td>0</td>
<td>4(18.2%)</td>
<td>15(68.2%)</td>
<td>3(13.6%)</td>
<td>4(18.2%)</td>
<td>19(86.3%)</td>
</tr>
</tbody>
</table>

Table 3. Comparison of Toxic Effects in the Two Groups

<table>
<thead>
<tr>
<th>Toxic effect</th>
<th>Test group</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0  I  II   III  IV</td>
<td>0  I  II  III  IV</td>
<td></td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>8  5  4    4  1</td>
<td>18  9  14  8   8  0</td>
<td>0.892</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3  9  7    3  0</td>
<td>6  22  11  10  0  0</td>
<td>0.890</td>
</tr>
<tr>
<td>Heart Poison</td>
<td>14 5  2    1  0</td>
<td>35 14  0  0   0  0</td>
<td>0.332</td>
</tr>
</tbody>
</table>

Figure 1. The Difference of the Median PFS Between the Control Group and the Test Group was Statistically Significant (P<0.05)

Progress Free Survival

Figure 2. The Difference of the Overall Survival Between the Two Groups was Statistically Insignificant (P>0.05)

Safety

No significant difference in the toxic effects between the groups was observed (Table 3). All the 71 patients were assessed for safety. A majority of them were mild to moderate in intensity and manageable. Main toxic effects included fatigue, vomiting, diarrhea, and myelosuppression. One case in the test group had IV grade myelosuppression, but recovered after the injection of recombinant human granulocyte colony-stimulating factor and recombinant human interleukin-11. There were no treatment-related deaths.

Discussion

STS is a heterogeneous group of tumors that are highly malignant. This group of tumors have different sensitivity to treatment such as chemotherapy and radiotherapy. Their optimal treatment requires a multidisciplinary approach based on their histologic grade, the tumor size and depth, and the presence of distant or nodal metastases. Despite enhancements in local control rates achieved by wide local resections and radiation therapy, metastasis and death remain a significant problem for some advanced patients with unresectable neoplasm. These patients are faced with especially high rates of recurrence and poor overall survival. To solve the problem that few options exist for the treatment of advanced sarcomas, researchers are doing intensive work in this field. Because of the hypersensitivity of STS, targeted therapies with better tolerance and less side effects are quite promising (Shukla et al., 2011; Purohit et al., 2011).

In the last decade, research has been conducted to identify specific molecules or mutations within tumors that could be exploited as therapeutic targets. Drug treatment of tumor is undergoing a major transition from the previous pregenomic cytotoxic era to the new postgenomic targeted era. New cancer drugs that target tumor cells instead of normal healthy cells are just about to reshape the cancer treatment. There are some examples of drugs targeting neoplasm. Some EGFR inhibitors, including small molecule tyrosine kinase inhibitors (TKIs) and monoclonal antibodies such as erlotinib, crizotinib, gefitinib, cetuximab and bevacizumab have been approved by the U.S. Food and Drug Administration (FDA), and many of them have already been recommended by the National Comprehensive Cancer Network (NCCN) as the first or second line systemic therapy for NSCLC patients (Cohen et al., 2010; Sasaki et al., 2011; Brand et al., 2011). Now, many new drugs are available for
cancers, such as bevacizumab for vascular endothelial growth factor (VEGF) in colorectal cancer, trastuzumab for her2/neu over-expressing metastatic breast cancer, cetuximab for EGFR over-expressing metastatic colorectal cancer, imatinib for bcr/abl-positive chronic myelogenous leukemia, and rituximab for non-Hodgkin’s lymphoma, gemtuzumab for acute myelogenous leukemia, alemtuzumab for chronic lymphocytic leukemia, and bortezomib for proteasome in multiple myeloma.

In STS, imatinib has been shown to provide a high level of clinical efficacy. In patients with advanced gastrointestinal stromal tumors (GIST), it has a median PFS of 19 to 26 months and an OS approaching 5 years (Blay et al., 2012). The application of imatinib in GIST has become the paradigm of molecularly targeted therapies for cancers (Reichardt et al., 2011). Some researchers have found that OSU-03012 inhibited tumor cell viability, induced apoptosis in tumor cells, and did not induce detectable apoptosis in normal human cells. So, in the treatment of rhabdomyosarcoma, the novel OSU-03012 compound may be a more potent inhibitor of PDK-1/AKT pathway than the current potent inhibitor of PI3-K/AKT, LY294002 (Cen et al., 2007). In addition, the mammalian target of rapamycin (mTOR) inhibitors has been proven to have promising antitumor activity in patients with metastatic sarcoma (Vinceci et al., 2011). Large phase II and III trials of mTOR inhibitor used in STS have led to favorable results (Judson, 2010). Angiogenic inhibition is also a potential therapeutic target. The recombinant of murine endostatin can inhibit the murine primary tumors growing in mice and a wide variety of human tumors. These results about experimental mouse models provide forces to initiate clinical trials, and several clinical trials using recombinant human endostatin have already begun (Kaya et al., 2007).

As new approaches, the angiogenesis inhibitors for the treatment of cancer are based upon Folkman’s theory proposed in 1971 (Folkman, 2002). To add 9 amino acids to the N-end of Endostatin peptide chain, Endostar® can improve the function and efficacy. JiaY et al. have found that Endostar® can suppress not only the angiogenesis but also lymphangogenesis and lymph node metastasis. Because of this, the nutrition supply of tumor cell is blocked and the tumor cell proliferation and migration are suppressed. Endostar® can also inhibit human lung adenocarcinoma cell line SPC-A4. In addition, in in vitro experiments, results have showed that Endostar® can suppress the migration of HHEC, the formation of Tube, and the angiogenesis of Chorio Allantioc Membrane, and it can also suppress mouse tumor models (S180 sarcoma, H22 liver cancer) and human xenograft tumor models (SPC-A4 lung adenocarcinoma, SGC7901 gastric cancer, HeLa cervical cancer, SMMC-7721 liver cancer and BEL7402 liver cancer) (Jia et al., 2012; Ke et al., 2012). In 2007, Endostar® became the first-line drug in the treatment of NSCLC. No death related to Endostar® has been reported. Its main adverse effects are heart reactions, gastrointestinal reactions, and allergy of skin and limbs.

Our study explored the efficacy and tolerance of Endostar® combined with chemotherapy for STS. In our study, the ORR of the test group was 18.2%, insignificantly different from that of the control group (12.2%). However, the difference in the DCR and PFS was significant ($X^2 = 4.487$, $P = 0.034$, $X^2 = 5.652$, $P = 0.017$). It means that the DCR of the test group is significantly higher than that of the control group, and the PFS of the former is also significantly longer than that of the latter. Another important value, the overall survival of the two groups, has no significant difference. These results might be explained by the small sample size. On the whole, Endostar® combined with chemotherapy for advanced soft tissue sarcomas results in a higher DCR and longer PFS, and the adverse effects are acceptable. Studies using a larger number of cases still need to be conducted in the future.

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References


