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RESEARCH

The Significance of Preoperative Chemotherapy in Evaluation of Recurrent Soft Tissue Liposarcoma Necrosis

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Abstract To investigate the effect of preoperative induction chemotherapy on treatment of recurrent liposarcoma. 21 patients with recurrent liposarcoma received the treatment of preoperative intra-arterial chemotherapy and surgical resection. Intra-arterial chemotherapy was given by subcutaneous implantable drug delivery system with infusion of cisplatin and doxorubicin followed by caffeine. After treatment, patients were followed up for 39 months. The liposarcoma changes in CT imaging were observed in 18 cases and there were 15 cases with medium or severe pathological changes caused by chemotherapy. At the end of the postoperative follow-up of 39 months, liposarcoma reoccurred locally in 2 cases; pulmonary metastasis occurred in 1 case and death in 3 cases. Preoperative intra-arterial chemotherapy is effective for highly malignant tumors such as recurrent liposarcoma and the judgment of prognosis is based on the postoperative pathological changes of such tumor.

Keywords Implantable intra-arterial induction chemotherapy · Liposarcoma · Cisplatin · Doxorubicin · Caffeine

Introduction

Liposarcoma is the second-most common soft tissue sarcoma among adults. Its incidence was reported as 10–12% among soft tissue sarcomas [1]. Unfortunately, patients with liposarcomas continue to have a high rate of recurrence and poor overall survival. Despite aggressive surgical resection, the vast majority of these patients succumb to uncontrolled sarcomatosis [2–5]. The surgical treatment of soft tissue liposarcoma is a tough task because of the postoperative high recurrent rate (85%) [5]. Aggressive surgical resection followed by postoperative radiotherapy still can not prevent the recurrence of liposarcoma. In order to shrink the size of liposarcom, create a clear boundary for surgical resection and ultimately lower the recurrent rate, we employed the intra-arterial chemotherapy that infuses cisplatin and doxorubicin to assist the treatment of recurrent liposarcoma. In addition, we used caffeine, the DNA replication inhibitor, to reinforce the effect of these anticancer drugs and enhance the treatment effect in order to seek satisfactory clinical outcome.

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Methods

Subjects

There were 21 patients with recurrent liposarcoma received treatment from September 1995 to July 2006. These patients developed recurrent liposarcoma after first surgery and later discharging from the hospital. Some of them received radiotherapy and chemotherapy. There were 10 male and 11 female patients with age ranging from 22 to 83 years (mean, 54 years). The primary sites of these liposarcomas are thigh in 11, pelvis and fossa iliaca in 3 (with 2 in retroperitoneum), popliteal fossa in 1, leg in 2, the upper arm in 1, forearm in 1, hip in 1 and shoulder in 1. Among the 21 cases, 15 were myxiod liposarcomas, 3 were polymorphic, 2 were combined and 1 was dedifferentiated. The number of recurrence was 2 to 4 times (twice in 10 cases, three times in 8 and four times in 3).

The size of the tumors ranged from 7×8cm to 15×2with mean 12×15cm. For chemotherapy, 6 patients received twice, 12 received three times and 3 received 4 times. The postoperative follow up lasted from 4 months to 7 years plus 9 months and on average 39 months.

Methods

After the clinical diagnosis was confirmed by CT imaging, the subcutaneous intra-arterial drug delivery system was implanted and doxorubicin (30 mg) was given during implantation. Then, 100–120 mg/m^2 cisplatin (CDDP) and 90 mg/m^2 doxorubicin (AMD) was infused through the drug delivery system. After infusion, 1–1.5 g/m^2 caffeine and 5% glucose (or normal saline) 1,000 ml was infused via the implantable pump.

Observation and Evaluation Criteria

Three criteria were adopted in our study: the effect of relieving the pain caused by tumor oppression, the changes of tumor in CT imaging evaluated by WHO [6]. Evaluation of liposarcoma necrosis after chemotherapy was performed. The formula to calculate tumor cell necrosis rate was TCNR = (1-N/M)×100% . The grade of TCNR was divided to four degree: GradeI TCNR ≤50% ,GradeII 50% < TCNR ≤ 90%, GradeIII 90% < TCNR ≤99%, Grade IV=100% [7].

Results

Clinical Outcome

After surgical resection, liposarcomas in 2 patients recurred locally. Pulmonary metastasis occurred in 1 patient and death occurred in 3 patients.

Effect of Relieving the Pain

Compared with the situation prior to chemotherapy when 14 patients were in medium pain and 7 in severe pain, the pain was relieved with an overall effective rate 90.5% (i.e., 19/21). We found that the sustaining time of pain relief is related to the time of treatment, size of the tumor, the degree of tumor malignancy and the number of times that chemotherapy was performed.

The Liposarcoma Lesion Change Revealed by CT

After chemotherapy, CT imaging revealed the shrinkage of soft tissue liposarcoma and the trend of repair—part of liposarcoma was liquefied and false membrane surrounding the tumor was formed which made the tumor boundary clear (see Figs. 1 and 2). The changes in CT imaging were: complete relief (CR) in 7 cases, partial relief (PR) in 11 cases, none relief (SD) in 3 cases and overall relative relief (RR) in 18.

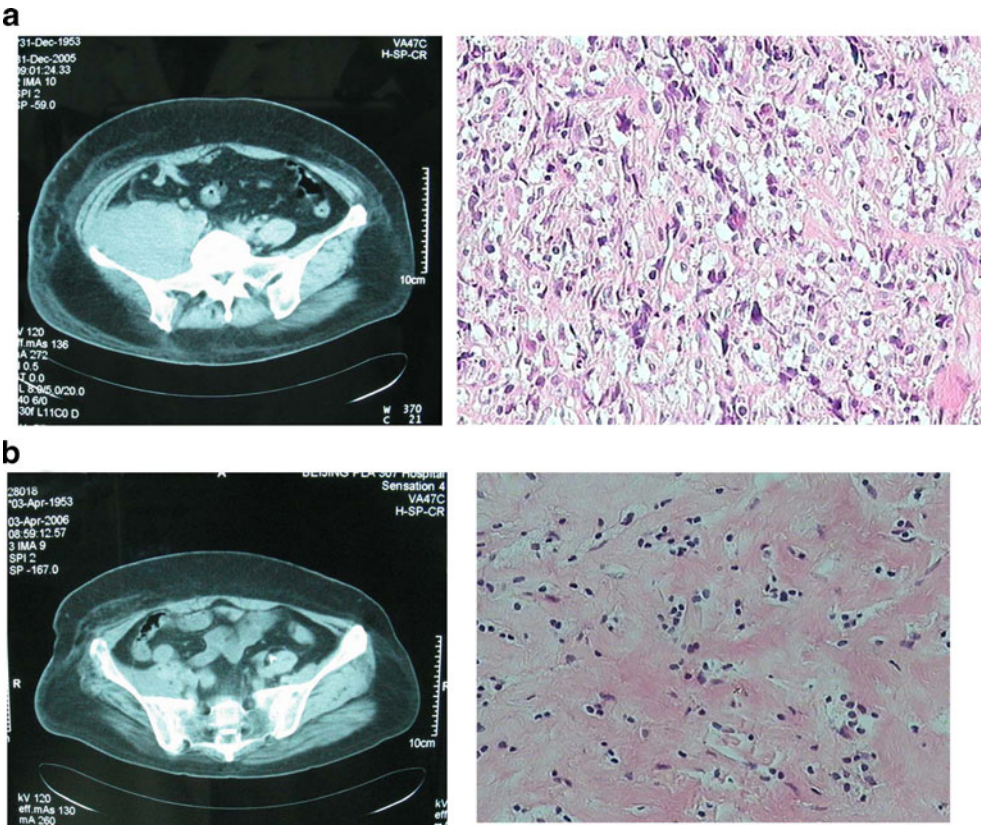

Fig. 1 Liposarcoma case 1: A female with a large myxoid liposarcoma in pelvic. After chemotherapy 3 times, the tumor shrinked. (**a**) CT and pathological image before chemotherapy; (**b**) CT and pathological image after chemotherapy

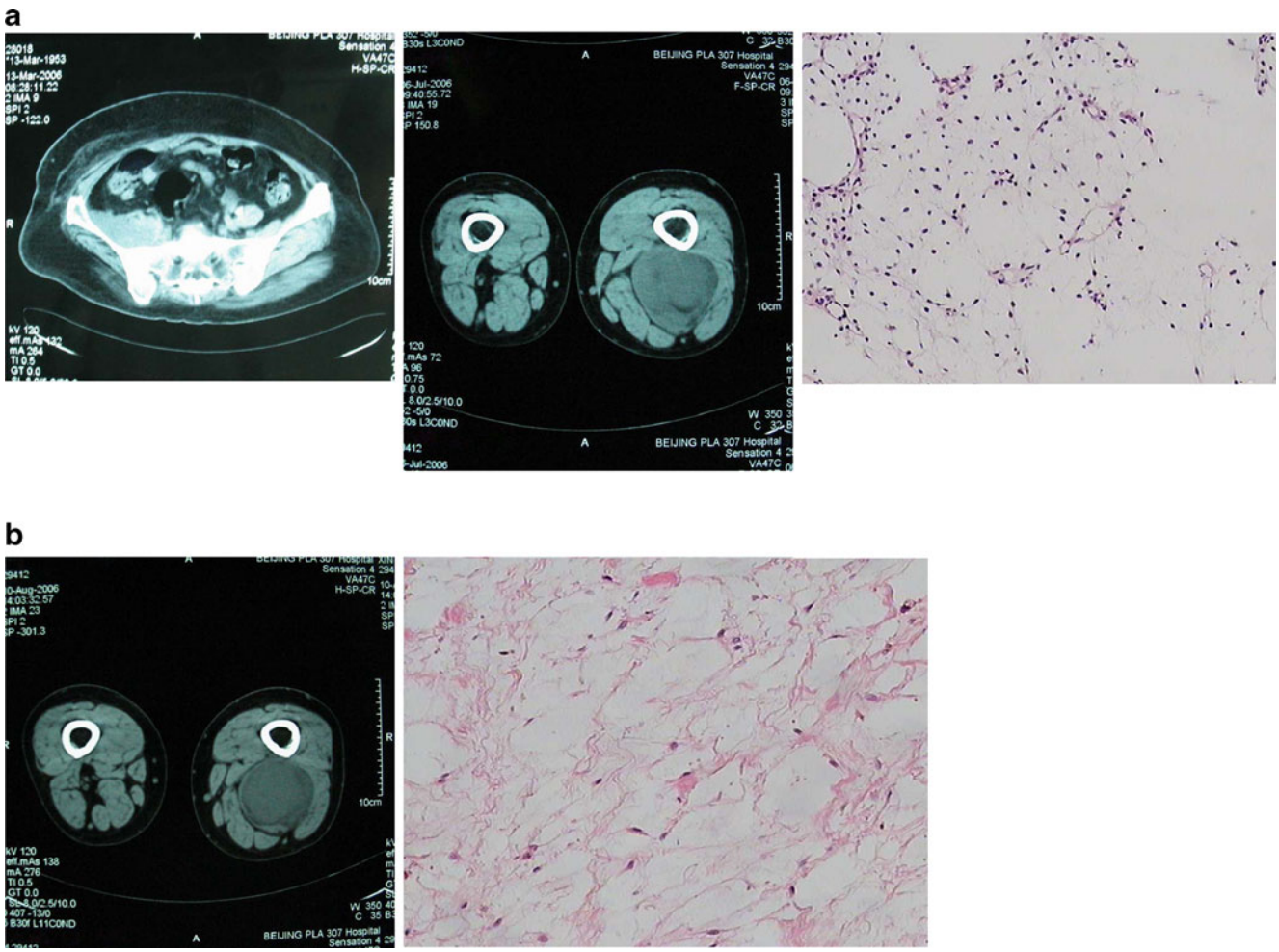

Fig. 2 Liposarcoma case 2: A female with a myxoid liposarcoma in the right thigh. The boundary of the tumor is unclear and adhering to surrounding tissue. After chemotherapy 3 times, a chemo-responding zone was formed around the tumor and the tumor tissue became fiber-like. (**a**) CT and pathological image before chemotherapy; (**b**) CT and pathological image after chemotherapy

Tumor Cell Necrosis Rate Evaluation

There were 3 patients with light response to chemotherapy (GradeI), 9 with medium response(GradeII) and 6 with severe response(Grade III, IV). The tumor tissue showed different degrees of degeneration, necrosis, fibration and glass-like change with few typical cancer cells and there was obvious necrosis in cancer cells (Fig. 3).

Discussion

Liposarcoma is a malignant tumor consisting of adipocytes with various degrees of differentiation and heteromorphosis. It accounts for 9.8% to 16.0% of all soft tissue sarcoma [5]. In order to suit clinical applications, liposarcomas were classified into dedifferentiated, myxoid, pleomorphic and combined liposarcoma according to histological appearance and genetic features of liposarcoma cells and molecules in 2002. Liposarcomas could occur in every part of the body and are most frequently localized in deep-seated lower limbs and retroperitoneum. The common treatment of liposarcoma is aggressive surgical resection. For high-grade malignant liposarcoma, complete excision is usually performed to seek radical cure. Radiotherapy and chemotherapy are sometimes employed as adjuvant treatment to liposarcoma. However, the prognoses of liposarcoma seem to be poor. For example, pleomorphic liposarcoma, a high-grade pleomorphic sarcoma containing multivacuolated lipoblasts, has a poor prognosis. It occurs in about 10% of liposarcoma cases and has a 45% local recurrence rate and 42.5% metastatic rate [2, 3]. Five-year overall, metastasis-free, and local recurrence-free survival was 57%, 50%, and 48% respectively [4].

Due to the misguided impact of the traditional thinking that chemotherapy is ineffective, patients often lose the

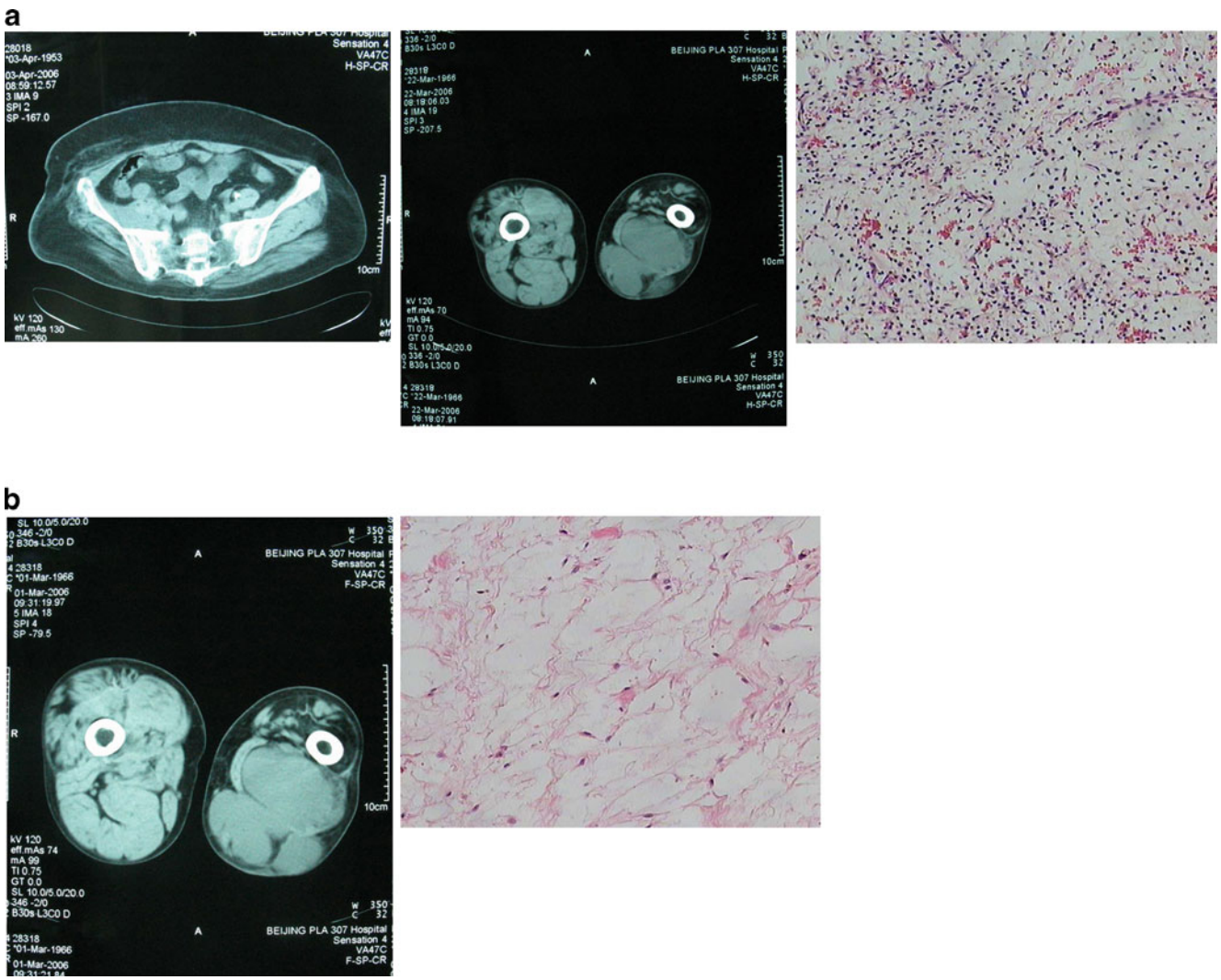

Fig. 3 Liposarcoma case 3: A male with a myxoid liposarcoma in the leg thigh. After chemotherapy twice, chemo-response zone was form around the tumor and tumor tissue necrosis. (**a**) CT and pathological image before chemotherapy; (**b**) CT and pathological image after chemotherapy

opportunity to try the treatment option of chemotherapy. In fact, it is difficult to cure liposarcomas located in pelvis or restroperitoneum by surgical resection and complete resection is hard to achieve even though for liposarcomas with single site occurrence. Hence, it is important to treat liposarcomas with adjuvant treatment that concerns both the primary site of the tumor and the whole body. However, there is severe disagreement in the treatment of liposarcoma with chemotherapy. To date, except for the chemotherapy on pediatric striated muscle sarcoma that has been proved effective, chemotherapy on other soft tissue sarcomas is still controversial [8–15]. Chemotherapy is preferably given before surgery, in order to assess tumour response and thus modulate the length of treatment [16].

Picci et al. reported the results of the Rizzoli randomized study performed in the 1980s, together with the results of the new Italian randomized study (closed in 1996) and confirmed the advantage of adjuvant chemotherapy in overall survival in very select groups of high-grade sarcomas of the extremities [17]. Patel et al. reported chemotherapy on 21 myxiod liposarcoma (18 received ADM and dacarbazine (DTIC) in addition to cyclophosphamide (CTX), 1 received CR and 7 received PR) among 44 liposarcoma patients and the overall effective rate is 44% [18]. Recently, preoperative and postoperative chemotherapy has played an important role in the treatment of soft tissue sarcoma. For example, preoperative chemotherapy reduces the size of liposarcoma and thus the region of surgical resection. Mankin et al. applied preoperative chemotherapy with MAID formula (the anticancer agents include mesna, doxorubicin, ifosfamide, dacarbazine) [19] to 196 liposarcomas, the survival rate was 78.1%, recurrent rate was 4.1% and death rate was 8.2%. For well-differentiated liposarcoma with large size, preoperative chemotherapy is very effective. It reduces the recurrence and metastasis rate, and improves the survival rate.

Due to the advantages of intra-arterial infusion chemotherapy (including high local concentration, powerful anticancer effect, evitable liver degradation, less toxic and side effect than infusion via vein, shortened duration between chemotherapy and continuous drug delivery), we employed it as a preoperative procedure. Caffeine intervened the life cycle regulation of cancer cells and causes the death of cancer cells.

In our study, the 21 patients all had postoperative local recurrent liposarcoma that were deep-seated in (thigh, pelvis, etc.) muscle or retropentoneum with large size (7×8cm–15×21cm, on average 12×15cm). It is very difficult to perform total resection in consecutive surgeries. Even, it is hard to amputate the limb of recurrent liposarcoma for these patients. If not take an effective way to shrink and reduce liposarcoma, surgery alone easily leads to recurrent liposarcoma.

The pathological classification of liposarcomas in our study is as follows. 15 myxiod liposarcomas and 3 polymorphic liposarcomas account for the majority, which are highly malignant and less differentiated liposarcoma. Among the 21 patients who received 2–4 times preoperative chemotherapy, 15 had severe chemo-response, 2 could not receive further surgery and 1 died of pulmonary metastasis. For the 3 polymorphic liposarcomas, all had severe chemo-response; but for the 1 lipoma liposarcoma, there was no chemo-response. This indicates that highly malignant and less differentiated liposarcomas easily have medium and severe chemo-response. However, since the sample of this study is not large enough, we can not yet draw any conclusion with statistical meaning.

The effectiveness of the new adjuvant chemotherapy is revealed in the whole treatment process of liposarcoma including preoperative chemotherapy, surgical resection and postoperative examination of chemo-response for sample tissues which forms a feedback-guided loop. For liposarcoma with medium and severe chemo-response, the scheme of chemotherapy can be kept after surgery; but little chemo-response suggests that the scheme of chemotherapy should be modified to make it effective, or alternatively, radiotherapy may be considered.

The boundary of recurrent liposarcoma after surgical resection is unclear and contracted adhering to nerves and blood vessels. The risk is high for consecutive surgical resection and liposarcoma recurrence. Hence, it is necessary to use adjuvant treatment such as chemotherapy to clarify the surgical boundary.

Liposarcomas especially myxoid liposarcomas are deep-seated in the body and infiltrating normal tissue in a gruel form with unclear boundary. Aggressive resection may cause high recurrence rate. However, effective chemotherapy can confine liposarcoma to certain boundary and form the membrane response zone of liposarcoma after chemotherapy, which is beneficial to surgical resection.

In summary, we applied subcutaneous implantable intra-arterial infusion of high dose cisplatin and doxorubicin combined with caffeine to preoperative chemotherapy in the treatment of recurrent liposarcoma. This method inhibits the infiltration of tumor, shrinks tumor boundary, reduces tumor local recurrence rate and improves survival rate. It is an effective method that aids the treatment of liposarcoma.

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