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RESEARCH

Comprehensive Treatment Based on Intra-arterial Chemotherapy for Distal Femur Neoplasms

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Abstract To investigate the clinical efficacy of intra-arterial chemotherapy by subcutaneous implantable delivery system (SIDS) in the treatment of distal femur neoplasm. From March 2002 to December 2009, 51 patients were treated with SIDS intra-femoral artery chemotherapy, followed by customized prosthetic reconstruction, including 45 patients of osteosarcoma and 6 malignant fibrous histiocytoma in distal femur. The average follow-up period was 64 months (ranging between 24 and 116 months) to track on the efficacy of chemotherapy, which shows that 96.1 % of patients got pain relief, 70.6 % of patients had significant radiological change, and 82.4 % of paitents with medium to severe pathological variation responded to the chemotherapy. Local recurrence happened in 4 cases, 3 cases are alive with disease, 4 cases died because of pulmonary metastases and other 40 patients are free of local recurrence or distant metastasis. SIDS intra-femur artery chemotherapy can improve clinical outcome of DFN, and provide effective method for treatment of DFN when combined with customized prosthetic reconstruction.

Keywords Intra-arterial chemotherapy · SIDS · Distal femur · Bone neoplasms

Distal femur is the most common occurrence site for primary bone tumor especially osteosarcoma. According to the features of such tumor's blood supply, we placed subcutaneous chemotherapy pump into femoral artery for neoadjuvant chemotherapy. After favorable chemotherapy response of tumor was observed, extensive excision at the edge of tumor and functional reconstruction were performed. Good clinical results were obtained following such treatment strategy.

Of 51 patients in our study, 27 were male and 24 were female. Their age ranging between 5 and 64 with averaged as 25. Tumor of distal femur was identified in all patients. Forty-five cases were osteosarcoma and 6 cases were malignant fibrous histocytoma (MFH). SIDS intra-femur artery chemotherapy was performed on all patients. Before resection of the tumor, interventional chemotherapy was performed for 3–5 times according to tumor response of chemotherapy. After the operation, chemotherapy was performed for over 3 times.

Pre-operative chemotherapy: after complete clinical and imaging diagnosis, biopsy of tumor tissue was performed via longitudinal incision. Then SIDS arterial infusion chemotherapy equipment (chemotherapy pump) was placed in patients by retrocatherization to femoral artery of the affected side. The 8–15 cm long catheter reached external iliac artery, and was connected to chemotherapeutic pump subcutaneously implanted near the incision. Twenty mg of epirubicin was intraoperatively administered. After implantation, 50 mg/m^2 epirubicin (EADM) and 120 mg/m^2 cisplatin was administered via chemotherapy pump for 3 days, and at the same time hepatoprotective, myocardial nutrient, and diuretic medicine were given balance the treatment., The next cycle of chemotherapy was repeated 2–3 weeks later, and therapeutic effect was observed to determine subsequent therapy.

Subsequent therapies in all patients: amputation for 4 patients, inactivated reimplantation with preservation of epiphysis for 3 patients, conservative therapy dominated by interventional chemotherapy for 2 patients who refused surgery, extensive excision at the edge of tumor followed by customized prosthesis replacement for the rest patients.

Post-operative intra-arterial cisplatin chemotherapy was performed after incision recovery and stitch removal. If chemotherapeutic effect was pathologically proven to be

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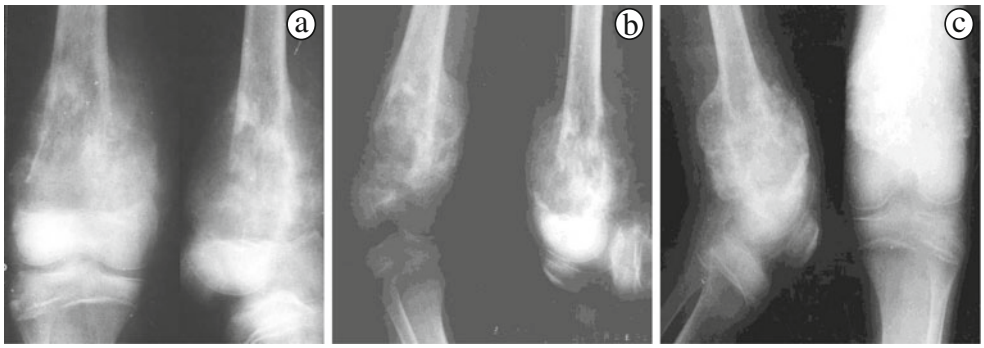

Fig. 1 X-ray of osteosarcoma patients before and after the chemotherapy. **a** X-ray image before chemotherapy; **b** X-ray image after twice chemotherapy; **c** X-ray image after 4 cycles of chemotherapy. Before chemotherapy, sclerotin was extensively damaged due to tumor infiltration in the lower segment of femur with blurred boundary and obviously damaged bone cortex at the leading edge. After effective chemotherapy, the boundary of tumor can be clearly seen with less damaged sclerotin, and part of the damaged bone cortex is recovered with gradual disappearance of periosteal reaction. Obvious calcification occurs in tumor with less swollen surrounding soft tissues

good (necrosis rate>90 %), then the original therapy strategy would be kept, otherwise, such chemotherapeutics as methotrexate and ifosfamide for osteosarcoma patients as well as ifosfamide and dacarbazine for malignant fibrous histiocytoma were intravenously administered.

Result

Follow-up visits lasted for 24–116 months, averaging 64 months. Chemotherapeutic effect was evaluated by clinical symptoms, imaging diagnosis and intra-operative pathology.

1. Clinical pain relief: Before chemotherapy, 29 cases had moderate pain (56.9 %) and 22 cases had serious pain (43.1 %). After 1–3 times of chemotherapy, the pain was significantly relieved. 41 cases were completely relieved (CR) (80.4 %); 8 cases were partially relieved (PR) (15.7 %); 2 cases were no change (NC) (3.9 %). Total effective rate was 96.1 %. The duration of pain relief was associated with onset time, tumor size, malignancy and chemotherapy cycles. Pain relief was usually accompanied with increased appetite, better mood and improved general conditions.
2. Radiological imaging for bone lesion: After over 3 times of chemotherapy, 36 patients showed positive radiological changes. X-ray and CT results showed clear image of tumor and surrounding tissues. Soft tissue tumor shrank, and bone tumor reduced with more calcification and plerosis. The tumor exhibited a recovery trend with the scope of periosteal reaction reduced to show a trend of recovery, the clear boundary between tumor and surrounding tissues, and liquefaction and calcification in some parts wrapped with pseudocapsule (Figs. 1 and 2).

Complete biopsy results before chemotherapy and pathological data of removed tumor after chemotherapy were available for all 51 cases. 4 cases were low sensitivity to chemotherapy, 20 cases were median sensitivity to chemotherapy (39.2 %) and 27 cases were high sensitivity to chemotherapy (52.9 %). Median to high sensitivity to chemotherapy accounted for 92.2 % of all cases (Table 1). Denaturation, necrosis, fibrosis and hyaline degeneration of varying degrees were observed in tumor tissues. Typical tumor cells were not identified in most cases (Figs. 3 and 4).

In subsequent therapies, 4 patients received amputation. Among them, 2 patients were 7 and 9 years old respectively, with huge tumor and poor conditions of local soft tissues, and the other 2 patients were diagnosed with stage III tumor which affected local vascular and nerves, therefore they had to receive amputation. Three cases with epiphyseal plate not exceeded by tumor in imaging diagnosis received inactivated reimplantation with preservation of epiphysis. Two cases received conservative therapy (chemotherapy) as they refused

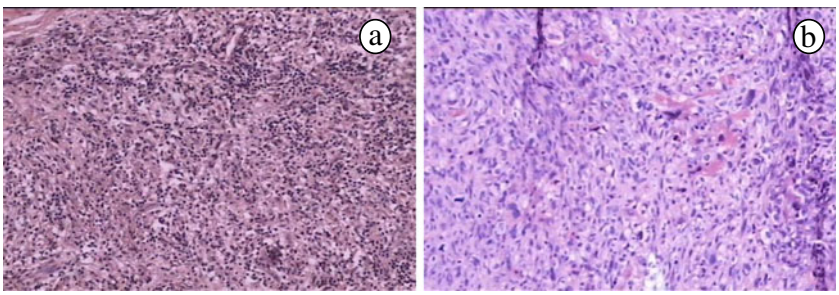

Fig. 2 Pathological changes before and after chemotherapy for osteosarcoma. **a** Large quantity of atypical cells before chemotherapy; **b** Necrosis and fibrosis of tissues after chemotherapy considered as stage II chemotherapy reaction

Table 1 Chemotherapeutic effect of intra-arterial chemotherapy by subcutaneous implantable delivery system (SIDS)

		Chemotherapeutic Effect					
		Pain Relief			Sensitivity to Chemotherapy		
		NC	PR	CR	Low	Median	High
Moderate Pain	Radiological Changes (+)	20	3	–	–	4	19
	Radiological Changes (−)	4	2	–	–	5	–
Serious Pain	Radiological Changes (+)	11	2	–	–	5	8
	Radiological Changes (−)	6	1	2	3	6	–

NC no change; *CR* completely relieved; *PR* partially relieved

surgery, and lung metastasis was found respectively in 2 and 4 years later. All the remaining 42 patients received prosthesis replacement among whom adjustable prosthesis was applied in 5 patients at growth period, radioactive particle I^{125} and artificial joint recombination were applied in 10 cases, including 4 patients with pre-operative fracture, and prosthesis replacement with customized artificial knee joint with femoral shaft was applied to the rest 27 patients,. Local recurrence was identified in 4 cases, among which 2 cases received local excision and chemotherapy; 2 cases received amputation; 3 cases were alive with lung metastasis during the follow-up visit; and 4 cases died of lung metastasis. The rest 40 cases were alive without tumor (Table 2).

Forty-two patients who received prosthesis replacement were evaluated by Enneking staging system in 6 aspects: pain on the preserved limb; movement; satisfaction degree; weight bearing; walking ability and gait. Twenty-seven cases were excellent (64.3 %); 12 cases were good (28.6 %) and 3 cases were poor (7.1 %) with local infection.

Discussion

Chemotherapy can extend the survival time of bone tumor patients, and pre-operative chemotherapy could further facilitate the application of limb salvage treatment. So far, 85 %–90 % patients with malignant tumor are suitable for limb salvage treatment through neo-adjuvant chemotherapy.

We believe that intra-arterial chemotherapy is more effective than intravenous chemotherapy with the following advantages. (1) Markedly increased drug concentration at tumor area. Drug concentration in intra-arterial chemotherapy is over 4–6 times as much as that in intravenous chemotherapy. Chemotherapeutics especially concentration-dependent cisplatin used in intra-arterial chemotherapy can significantly improve therapeutic effects [1]. For tumor of distal femur, tumor blood flow is supplied by deep femoral artery or popliteal artery, both of which are branches of femoral artery, therefore, the interventional chemotherapy via femoral artery is a specific treatment. (2) Without being inactivated in liver as administrated intravenously, the intra-arterially administrated chemotherapeutic drug keeps high concentration to act on tumor cells with its original molecular structure. (3) Local intra-arterial chemotherapy could shorten the interval between two chemotherapy cycles with less adverse effects than systematic administration when using the same dose of chemotherapeutic drug. (4) SIDS intra-arterial chemotherapy could maintain the chemotherapeutic drug at high concentration for relative long time in tumor blood supplying area; (5) SIDS make it easy to perform pre-operative and post-operative interventional chemotherapy by keeping a long-term route for multiple intra-arterial chemotherapy with lower costs and less pain for patients as well [2].

Distal femur is the site where malignant tumors mostly happen. Most of the cases are adolescent, and early pains can be easily ignored. Misdiagnosis and mistreatment are

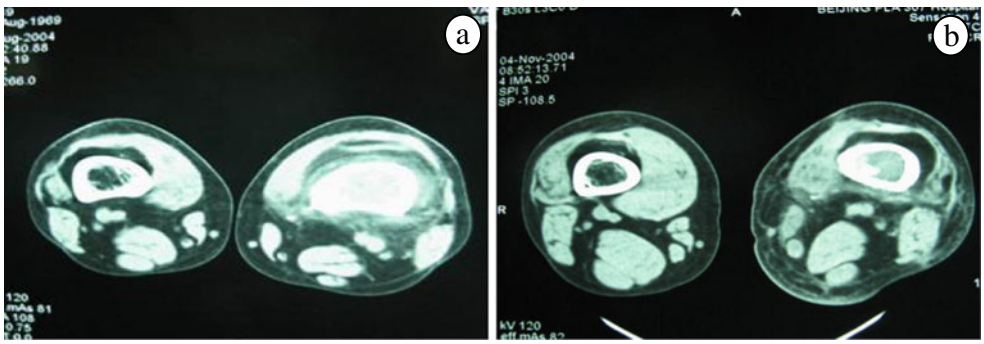

Fig. 3 Malignant fibrous histocytoma in the lower segment of left femur. **a** Irregular damaged bone area at metaphysis before chemotherapy with eccentric sclerotin damages and evident intramedullary invasion, local irregular osteoproliferation & hardening, and soft tissue lump at the rear with blurred boundary; **b** Shrinked tumor after chemotherapy with clear boundary and reappearance of medullary cavity

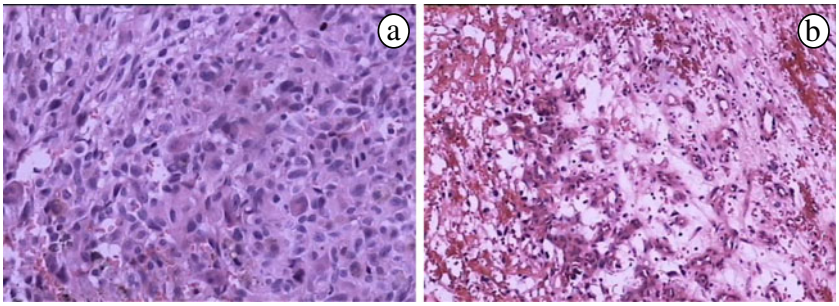

Fig. 4 Pathological changes in patients with malignant fibrous histiocytoma before and after chemotherapy. **a** Large quantity of atypical fibrohistiocytic cells before chemotherapy, with Touton cells and karyokinesis. **b** Obvious necrosis and fibrosis of tumor tissues after chemotherapy

not uncommon as the tumor is usually concealed by developed quadriceps femoris muscle. As the most common bone tumor, around 60 % osteosarcoma is anatomically positioned at distal femur, which is a problem usually confronted by surgeons. Coincident with abroad researches, our results indicated that pre-operative interventional chemotherapy could effectively alleviate local pain, drive tumor necrosis and reduce tumor volume & surrounding reaction area, which increase the chances to perform extensive excision and limb salvage and thus reduce local recurrence rate. Abe et al. found that tumor became smaller with clear boundary after patient with stage IIB osteosarcoma around knee received, intra-arterial chemotherapy, which made extensive excision possible [3]. Wilkins took cisplatin and doxorubicin as chemotherapeutic drugs for limb osteosarcoma, in which cisplatin was administered by intra-arterial perfusion. Kaplan-Meier survival analysis indicated that 10-year survival rate of patients receiving chemotherapy achieved as high as 92 %; disease free survival rate was 84 % [4]. In our study, survival rate during at least 3 years of follow-up visit was 85 %; disease free survival rate was 79 %. Large sample analysis indicated that by intra-arterially administrated cisplatin, arterial blood supply to tumor was reduced by over 90 % in over 86 % of patients, and positive histological response was observed in 82 % of patients by intra-operative pathology [5].

Surgery is the basic treatment for distal femur tumors following pre-operative chemotherapy. The 2 patients who only received chemotherapy with clear effectiveness but refused surgery were found lung metastasis in 2 and 4 years respectively, which indicate the significance of surgery from different angles. Adjustable prosthesis was applied in 5 patients at growth period to meet the demands of growth [6], among whom limb lengthening was performed in 4 cases by extending 4–5 cm 2 to 3 years after surgery with excellent limb function and without neurovascular complications. Radioactive particle I^{125} and artificial joint recombination were applied in 6 patients with high risk of local recurrence (pathological fracture, limb amputation on the opposite side due to osteosarcoma) [7], without local recurrence observed after surgery. Both the relative literatures and our experiences indicated that good therapeutic effect could be achieved by applying limb salvage in combination with chemotherapy to patients with pathological fracture [8]. Surrounding diseased tissues should be excised as much as possible, without influencing soft tissue coverage and prosthesis stability. Even when knee joint became less stable with too much excision, good therapeutic effects still can be obtained by musculocutaneous flap reconstruction [9].

Intra-arterial chemotherapy is recommended as mean of post-operative chemotherapy, which, based on existing

Table 2 Prognostics with subsequent therapies after intra-arterial chemotherapy by subcutaneous implantable delivery system (SIDS)

			Prognostics			
			Alive without Tumor	Alive with Tumor		Died of Lung metastasis
				Local Recurrence	Lung Metastasis	
Subsequent Therapies	Amputation		3	–	–	1
	Inactivated Reimplantation		2	–	1	–
	conservative therapy			–	–	2
	prosthesis replacement	Method 1	23	2	2	
		Method 2	4	1	–	
		Method 3	8	1	–	1

Method 1: prosthesis replacement with customized artificial knee joint with femoral shaft

Method 2: adjustable prosthesis replacement

Method 3: radioactive particle I^{125} and artificial joint recombination

researches, can reduce local recurrence and effectively control primary tumor compared with intravenous chemotherapy [10].

In conclusion, SIDS neo-adjuvant chemotherapy is eutherapeutic on distal femur malignant tumor treatment by relieving pain, reducing tumor volume and surrounding reaction areas and increasing the chances to perform extensive excision therefore to lower local recurrence rate, which was demonstrated to be significantly correlated with prognosis and distant metastasis[11]. Our study here only involved small number of cases with short term follow-up visit, and more cases are needed to be involved with long term follow-up visit to further confirm the eutherapeutic effects of SIDS on distal femur malignant tumor treatment.

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