

Intra-Arterial Intervention Chemotherapy for Sarcoma and Cancerous Ulcer Via an Implanted Pump

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Abstract To observe the efficacy of intra-arterial chemotherapy with subcutaneously implanted pump for soft tissue sarcoma in extremities and cancerous ulcer. 31 patients with ulcerative skin squamous cell carcinoma or sarcoma in extremities who received treatment during the period from July 2003 to November 2011 at our hospital were recruited, including 15 male and 16 female patients, aging between 14 and 83 with average age of 49 years old. 10 patients had tumor in upper extremities and 21 patients in lower extremities. The pathological types of studied cases include 9 cases with skin squamous cell carcinoma, 6 cases with synovial sarcoma, 5 cases with malignant fibrous histiocytoma, 3 cases with liposarcoma, 3 cases with osteosarcoma, 2 cases with malignant melanoma, 2 cases with epidermoid sarcoma, and 1 case with protuberans. The main symptoms of cancerous ulcer were pain, infection and hemorrhage; All the studied patients were administrated with cisplatin and doxorubicin by intra-arterial chemotherapy pump, and the patients with squamous cell carcinoma were additionally applied with bleomycin and patients with malignant melanoma were additionally applied with dacarbazine. The chemotherapy efficiency was observed after at 3 cycles of intra-arterial chemotherapy. The total remission rate of pain (RR) was 87 %, and total remission rate of ulcer cicatrization (RR) was 71 %, with ulcer cicatrizing spontaneously in 9 cases and obvious homeostasis in 5 cases with bleeding ulcers. 19 patients underwent surgery after chemotherapy, in which 16 cases had limb-salvage surgery and 3 cases underwent lower leg amputation after chemotherapy, and 3 patients out of 16 cases had local

recurrence (19 %). The subcutaneous intra-arterial targeting chemotherapy could be applied to treat refractory sarcoma and cancerous ulcer in extremities to significantly increase the chemotherapeutic concentration at tumor area so as to effectively constrain the tumor rupture induced main symptoms including pain, infection and bleeding, which would help to make a decreased blood supplied and well defined tumor boundary to finally decrease the recurrence rate.

Keyword Sarcoma ulcer · Cancerous ulcer · Chemotherapy pump · Intra-arterial chemotherapy

As the progression of skin squamous cell carcinoma and bone and soft tissue sarcoma in extremities, the tumor can directly invades skin to form ulcers on skin surface combining with necrosis and infection to cause stench, pain and bleeding, especially those recurrent patients who have received operations or radiotherapy and chemotherapy. It is the crucial issue to figure out the next step treatment. In this study, we tried to apply arterial infusion chemotherapy to the nutrient blood vessels of the tumor to maintain chemotherapeutics at high concentration at tumor area by drug first-pass effect, which had good effects on controlling bleeding, infection and pain.

Materials and Methods

Material

Thirty-one patients with ulcerative skin squamous cell carcinoma or sarcoma in extremities who received treatment during the period from July 2003 to November 2011 at our hospital were recruited, including 15 male and 16 female patients, aging between 14 and 83 (with average age of 49 years old). 10 patients had sarcoma in upper extremities (3 cases at hand, 2 cases at forearms, 2 cases at armpits, 2 cases at scapular region, 1 case at subclavian region), and 21 patients had

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tumors in lower extremities (7 cases at thighs, 5 cases at lower legs, 4 cases at feet, 3 cases at groins, 2 cases at hips), in which 11 cases with lymph node metastasis did not show lung metastasis. The ulcer ranges from maximum around $30 \times 16 \times 12$ cm to minimum around $1.5 \times 1.5 \times 1.3$ cm.

In the studied cases, 13 cases had sever pain, 18 cases had moderate pain, 12 cases had anaerobic infection at ulcerated surface with stench, 6 cases had bleeding ulcer, 22 cases relapsed after post-surgery radiotherapy, chemotherapy, and other treatments at other hospitals including 7 out of 9 cases with skin squamous cell carcinoma relapsed after radiotherapy. Pathological types: skin squamous cell carcinoma in 9 cases, synovial sarcoma in 6 cases, malignant fibrous histiocytoma in 5 cases, liposarcoma in 3 cases, osteosarcoma in 3 cases, malignant melanoma in 2 cases, epidermoid sarcoma in 2 cases, protuberans in 1 case.

Method

With complete clinical and imaging diagnosis, the patients were applied with arterial infusion chemotherapy pump implanted at subcutaneous tissue connected with catheter, among whom the patients with upper limb ulcer were implanted with chemotherapy pump at subclavian artery by selective retrograde intubation via brachial artery of affected limb, and the patients with lower limb ulcer were implanted with chemotherapy pump at external iliac artery by retrograde intubation via femoral artery of affected limb, and the epirubicin 20 mg was administered via the implanted chemotherapy pump during the operation. With the

implanted pump, all patients were treated with epirubicin (EADM) 50 mg/m^2 , cisplatin (CDDP) 120 mg/m^2 , the patients with squamous cell carcinoma were additionally applied with bleomycin (BLM) 15 mg, and patients with malignant melanoma were additionally applied with dacarbazine. After an interval of 2–3 weeks, chemotherapy enters the next cycle, and curative effects were observed after 2–3 cycles of intra-arterial chemotherapy. All treatment strategies and medication were approved by ethics committee of investigator's department. During chemotherapy, iodine gauze was applied on the ulcer with periodical dressing change. Among the studied cases, 9 cases underwent two cycles of chemotherapy, and 22 cases underwent three cycles of chemotherapy. Follow-up visit varied from 10 months to 9 years and 2 months, averaged at 67 months.

Observation Indexes and Evaluation

It referenced WHO standards for evaluating the objective curative effects of antineoplastic drugs [1]. When the ulcer surface completely heals in more than 1 month without ulcer re-rupture, it should be complete remission (CR); When the ulcer surface shrinks by more than 50 % without ulcer re-rupture in more than 1 month, it should be partial remission (PR); when the local ulcer shrinks by less than 50 % or enlarges by no more than 25 %, it should be stable disease (SD); when 1 or more ulcer enlarge by more than 25 % or new ulcers appear, it should be progress disease (PD). The total response rate (RR) was the percentage of sum of CR and PR.

Fig. 1 Malignant fibrous histiocytoma of left thigh combined with ulceration. **a** Before treatment: Ulcers pushing out the skin surface; **b** After two times of chemotherapy: Tumor boundary was clear gradually; **c** After four times of chemotherapy (Before operation): Boundary was very clear; **d** Tumor was complete resection and defects was covered by local flap



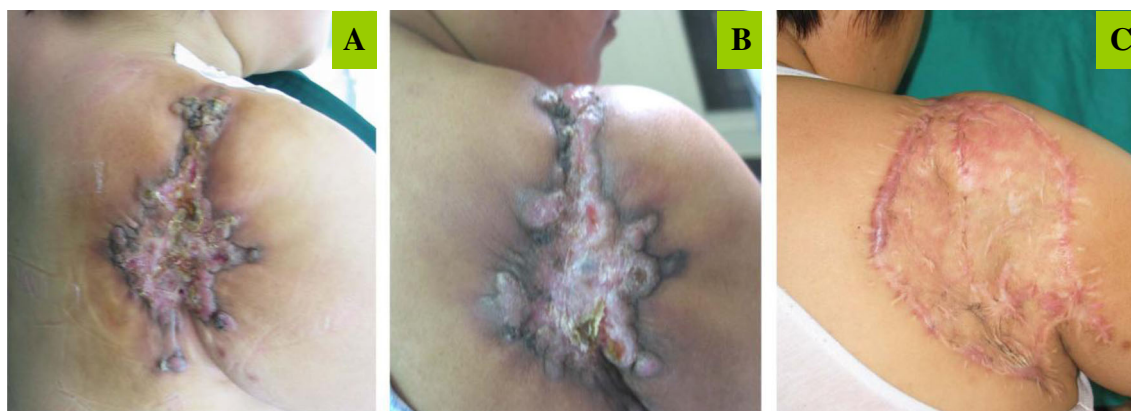


Fig. 2 Skin carcinoma fibrosarcoma of scapular site. **a** Before treatment; **b** After three times of chemotherapy; **c**: After operation

Pain Indexes and Evaluation

It refers to as followings [2]. 0 level should be painless, I level (slight) should be slight and endurable pain; II level (moderate) should be obvious pain with normal life and sleep significantly affected requiring analgesic to relieve pain, III level (severe) should be intense and unbearable pain accompanying vegetative nerve functional disturbance and passive position with normal life and sleep seriously interfered, requiring powerful analgesic. Pain palliation efficacy refers to as followings. 1) complete remission (CR) should be of completely no pain after treatment; 2) partial remission (PR) should be of significantly reduced pain after drug treatment, basically without interference of sleep and normal life; 3) mild remission (MR) should be of reduced pain compared with the pain before drug treatment, but still with obviously felt pain and disturbed sleep; 4) no curative effect (NC) should be of the pain neither changing nor intensifying after treatment. The total remission rate (RR) should be the percentage of sum of CR and PR.

Results

Pain Palliation Efficacy

The studied cases including 18 patients with moderate pain and 13 patients with sever pain were relieved in pain after

chemotherapy, among whom 19 cases were evaluated as CR, 8 cases as PR, and 4 cases as MR. The total remission rate of pain (RR) was 87 %. The patients were usually relieved in pain and could sleep normally without taking analgesic after one cycle of chemotherapy, and the pain palliation efficacy became increasingly obvious with more cycles of chemotherapies. Only 4 cases still had mild pains after three cycles of chemotherapies. The duration of pain palliation related to the tumor size, the malignant degree, the time of treatment and chemotherapy cycles.

Ulcer Cicatrization

The ulcers in 7 patients had complete remission (CR), 15 patients had partial remission (PR), 9 patients had no curative effect (NC) after chemotherapy, and the total remission rate of ulcer cicatrization (RR) was 71 %. The ulcer cicatrization efficiency was related to the ulcer size and tumor's sensitivity to chemotherapy, and the cicatrization efficiency of squamous cell carcinoma and epithelioid sarcoma was relatively better than that of other types of tumors. 12 patients who had obvious ulcers with stench had ulcers reduced in exudate and stench after treatment, then the ulcers completely healed with local flap operation after chemotherapy, (Figs. 1 and 2), among whom the small ulcers of 9 patients cicatrized spontaneously (Fig. 3). 6 cases with bleeding ulcer as the main symptom bled less after chemotherapy in 5 cases, and the bleeding completely

Fig. 3 Epithelioid sarcoma of left upper arm. **a** Before treatment; **b** After two times of chemotherapy



Fig. 4 Synovial sarcoma of right hand. **a** Before treatment; **b** After three times of chemotherapy



stopped after 3 to 4 cycles of chemotherapy (Fig. 4). 8 cases out of 11 patients with lymph node metastasis had the lymph node metastases disappeared, and 3 out of 11 patients had tumor obviously shrank.

Among 31 studied cases, 19 patients underwent tumor resection when tumor shrank after chemotherapy, in which 16 patients had limb-salvage surgery. The pathological examination of excised tissues after surgery indicated mild chemotherapy reaction in 5 patients, moderate chemotherapy reaction was observed in 10 patients, and severe chemotherapy reaction in 4 patients, and different degree of degeneration, necrosis, fibrosis, hyaline change in tumor tissues were observed, and in some patients tumor necrosis was so obvious that even typical tumor cells could hardly be identified. 3 patients out of 16 cases who had limb-salvage surgery had local recurrence (3/16). 3 out of 31 cases underwent lower leg amputation after chemotherapy. The rest 12 cases received other conservative treatments after ulcer remission. No obvious adverse reactions in chemotherapy with chemotherapy pump were observed except the skin malnutrition of affected limb

compared to the healthy limb, and the toxic and side effects, such as gastrointestinal reaction, bone marrow suppression and visceral damage, were milder than those of traditional chemotherapy. The overall treatment status were summarized according to different criteria (Table 1).

Discussion

Sarcomas and cancerous ulcer were relatively rare in bone and soft tissue tumors, which only accounts for 6 % (31 cases) of the 517 patients with the bone and soft tissue malignant tumors treated in the same period in our department. The characteristics of cancerous ulcer include 1) the ulcers locate in the center of the protrudent part of tumor with brittle tissues and rich blood supplies, accompanying severe pain with the tumor invading the sensory nerves; 2) haemorrhage is usually caused by vascular rupture as tumor blood vessels lack contraction when the tumor progressively enlarges to make ulcer expand; 3) stenches is caused by anaerobic bacteria infection at

Table 1 The overall therapeutic reaction of cancerous ulcer

			Remission degree after chemotherapy			Chemotherapy reaction		
			CR	PR	MR/CN	Mild	Moderate	Severe
Operation	Moderate pain	Ulcer + stenches	1	2	2	1(local recur)	3	1
		Bleeding Ulcer	1					1
		Ulcer + lymph node metastasis	1	2	2	1	4	
	Severe pain	Ulcer + stenches		1	1	1(local recur)		1
		Bleeding Ulcer		2	1	1(local recur)	1	1
		Ulcer + lymph node metastasis	1	2		1	2	
Conservative treatment	Moderate pain	Simple ulcer	1	1		N/A	N/A	N/A
		Ulcer + stenches		2	1	N/A	N/A	N/A
		Bleeding Ulcer	1	1		N/A	N/A	N/A
	Severe pain	Ulcer + lymph node metastasis	0			N/A	N/A	N/A
		Ulcer + stenches		1	1	N/A	N/A	N/A
		Bleeding Ulcer	0			N/A	N/A	N/A
		Ulcer + lymph node metastasis	1	1	1	N/A	N/A	N/A

ulcer surface; 4) chemotherapy is usually ineffective to such patients who mostly have taken surgery and chemotherapy previously and are apt to be resistant to chemotherapy. It is very intractable to figure out the effective clinical treatment for such kind of patients.

In the past the treatments to cancerous ulcer include 1) externally-applied chemotherapeutics and antibiotics to kill the tumor cells [3]; 2) local spray of interferon to enhance the cytotoxicity and antiviral effects of NK cells [4]; 3) external application of traditional Chinese medicine with detoxification, stasis-removing, detumescent and analgesic effects [5]; 4) CO₂ laser-radiation therapy [6]; 5) topical therapy through surgery [7]. All above traditional topical treatments have certain curative effects, but are not effective enough when the tumors are relative large, especially when combined with lymph node metastasis, and the traditional chemotherapy's curative effects are far from ideal with sever toxic and side effects.

In recent years, chemotherapy has been playing a key role in treating soft tissue sarcoma, which could significantly narrow down excision scope when applied before the surgery. We adopted arterial infusion chemotherapy via subcutaneously implanted pump connected with arterial catheterization in tumor affected limb to enable the concentration of chemotherapeutics 4 to 6 times higher at tumor affected limb than that of the healthy limb by drug first-pass effect when administering chemotherapeutics through the pump, so as to effectively improve the physical diffusion ability of drugs from interstitial liquid to tumor cells, and thus enhance the cytotoxicity of chemotherapeutics on tumor cells. As we known, the efficacy of the chemotherapeutics would increase by 10 times when the drug concentration doubles. Intra-arterial chemotherapy with subcutaneously implanted pump changes drug delivery route to make its toxic and side effects lower than those of the same dose intravenously administrated chemotherapy, as it avoids the degradation and deactivation of drugs in liver, which shorten the interval between cycles of chemotherapy. With single pump implantation, the drug can be administered repeatedly to maintain the chemotherapeutics at high concentration in plateau phase in tumor region to further enhance chemotherapy efficacy [8–10].

The effects of intra-arterial chemotherapy with subcutaneously implanted pump on blood vessels when treating sarcoma and cancerous ulcer include: 1) When first passing through limb's blood vessels, high concentration of chemotherapeutics causes vessels contracting, vascular endothelium swelling and vessel lumen narrowing to reduce blood supply in the tumor area. 2) compared to normal tissues, chemotherapeutics maintain at higher concentration in tumor area via blood "back-flow" to tumor area thereby effectively killing tumor cells, as blood vessels in tumor are unable to normally contract due to lack of muscular layer. Therefore, intra-arterial chemotherapy with subcutaneously implanted pump could effectively relieve

patients of pains, and reduce the blood supply in tumor area to alleviate tumor bleeding and infection on clinic.

The efficacy of intra-arterial chemotherapy with subcutaneously implanted pump varies on different pathological types of tumors, ranking in descending order from fromsquamous cell carcinoma, epithelioid sarcoma, liposarcoma [11], malignant fibrous histiocytoma, bone sarcoma, to synovial sarcoma. In our research group, 16 out of 31 patients underwent limb-salvage surgery after more than 3 cycles of chemotherapy, among whom 3 patients were found tumor recurrence after surgery (19 %). According to our observation, the tumor recurrence is mainly related to the tumor size, pathological types and the tumor's response to chemotherapy. In order to enhance limb salvage rate and decrease tumor recurrence rate, it would be beneficial to do more researches on chemotherapy instead of just sticking to cycles of chemotherapy, including the observation of skin temperature at tumor area after chemotherapy, the active degree of tumor and normal tissues, imaging data of color ultrasound and computed tomography (CT) to verify whether the tumor boundary is clear and the blood supply is reduced or not, which, we believe, are crucial for next step therapy resorting to surgery or further chemotherapy.

Combined with some other drugs as preoperative treatment according to tumor's pathological features, large dose of cisplatin and epirubicin was applied by intra-arterial chemotherapy with subcutaneously implanted pump to treat sarcoma and cancerous ulcers, which effectively alleviated pains and controlled tumor rupture induced infection and hemorrhage, then surgery would be performed after the tumor shrank to expose well defined infiltrating boundary. The above applied therapies obviously decrease local tumor recurrence rate, and effective on treating sarcoma and cancerous ulcer, though the case number in this studied was not numerous enough, and further clinical observation and follow-up in a large quantity are needed to enrich our study.

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