Caffeine-potentiated chemotherapy for clear cell sarcoma: a report of five cases

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ORIGINAL ARTICLE

Caffeine-potentiated chemotherapy for clear cell sarcoma: a report of five cases

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Abstract
Background Clear cell sarcoma is a rare malignant tumor of soft tissue which is most commonly encountered in the extremities, especially in the foot and ankle. This tumor is slow-growing and looks like a benign tumor; it is therefore often treated inadequately and its high rate of recurrence and metastases results in a poor prognosis. Caffeine has been used as a chemotherapy potentiator that inhibits DNA damage repair and enhances the cytocidal effects of anticancer drugs. This study reports the effect of caffeine-potentiated chemotherapy for clear cell sarcoma in five patients.
Methods Caffeine-potentiated chemotherapy was administered to five patients with clear cell sarcoma. Three to five courses of intra-arterial chemotherapy using cisplatin, doxorubicin and caffeine were administered preoperatively, at 3-week intervals. Conservatively, wide margin surgery was performed following the preoperative chemotherapy. Intravenous cisplatin and doxorubicin with caffeine were administered three to six times to the patients who responded to the preoperative chemotherapy. This study evaluated the response to chemotherapy, recurrence, metastasis and the overall prognosis in these five patients.
Results Four of the eligible patients responded to preoperative chemotherapy. Local recurrence occurred in only one of the five patients. Distant metastasis newly developed in one patient. All five patients survive.
Conclusion Caffeine-potentiated chemotherapy can be effective treatment for clear cell sarcoma not only as initial therapy, but also as salvage therapy.

Keywords Clear cell sarcoma · Caffeine · Chemotherapy · Response

Introduction

Clear cell sarcoma is a rare malignant tumor of soft tissue that is most commonly encountered in the extremities, especially the foot and ankle [1]. Clear cell sarcoma was first described by Enzinger in 1965, [2] and is now a well accepted clinicopathological entity. Although it produces melanin [3] and is called malignant melanoma of soft tissue, it differs from conventional melanoma in several important respects. The specific chromosomal translocation t(12;22)(q13;q12) involving DNA transcription factors ATF-1 on chromosome 12 and the *EWS* gene on chromosome 22 has been detected in 60–75% of clear cell sarcomas [4, 5]. Clear cell sarcoma is slow-growing and looks like a benign tumor; it is therefore often treated inadequately and its high rate of recurrence (84%) [1] and metastases (60–70%) [6] results in a poor prognosis. Some previous reports showed that chemotherapy or radiotherapy was effective for clear cell sarcoma. However, these treatments have had little impact on the survival rate. This study reports the effect of caffeine-potentiated chemotherapy for clear cell sarcoma in five patients.

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Patients and methods

Caffeine-potentiated chemotherapy has been administered to five patients with clear cell sarcoma since 1997. Three patients were male and two female; their mean age was 35.8 years (range 15–50 years). The sarcoma was in the back in two patients and in the foot in three. Two patients were recurrent cases (site: back in one and foot in one) and one had multiple lung metastases after they had undergone treatment at other institutions. Two patients were stage II (musculoskeletal staging system by Enneking [7]) without metastasis and three were stage III with metastasis at the time of initial consultation at this institution. Chemotherapy was performed according to the K2 protocol for soft tissue sarcoma [8–10] (Fig. 1), which was modified for each patient based on their past history of cytotoxic chemotherapy, general condition and renal or liver function. The K2 protocol calls for the preoperative administration of three to five courses of intra-arterial chemotherapy using cisplatin (120 mg/m^2), doxorubicin (30 mg/m^2 × 3 days) and caffeine (1.5 g/m^2 × 3 days) at 3-week intervals. The effects of caffeine-potentiated chemotherapy were then evaluated radiologically after three courses of treatment. An additional two courses of chemotherapy were administered to responders. Nonresponders underwent surgery immediately or were given other drugs with caffeine-enhanced cytocidal effects, such as ifosfamide or etoposide. As postoperative chemotherapy, intravenous cisplatin and caffeine with doxorubicin were administered three to six times to those responding to preoperative treatment. The clinical and histological response to the chemotherapy, recurrence, metastasis and the overall prognosis were evaluated in the five patients. A complete response (CR) to the preoperative chemotherapy was defined as complete disappearance of a tumor in some radiological examinations for more than four weeks, partial response (PR) as more than 50% tumor shrinkage, stable disease (SD) as less than 50% and progressive disease (PD) as more than 25% tumor expansion [11]. The histological response to preoperative chemotherapy was evaluated by a grading system: grade I, no response to chemotherapy; grade II, 50–90% tumor necrosis; grade III, more than 90% tumor necrosis; and grade IV, no evidence of viable tumor cells.

Results

The mean follow-up interval was 58.8 months (range 27–103 months). The data on the five patients is shown in Table 1. Four patients were treated according to the K2 protocol, but one patient with tumor in the foot rejected the preoperative chemotherapy and underwent primary below-knee amputation and postoperative chemotherapy. It was

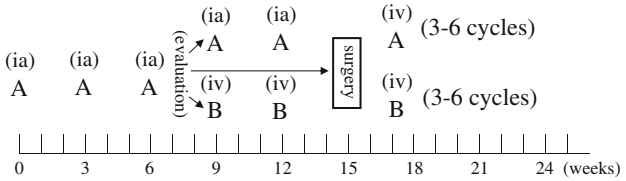

Fig. 1 K2 protocol of caffeine-potentiated chemotherapy. *A* cisplatin (120 mg/m^2/2–4 h) + doxorubicin (30 mg/m^2/24 h × 2 days) + caffeine (1.5 g/m^2/24 h × 3 days), *B* ifosfamide (3 g/m^2/bolus × 3 days) + etoposide (60 mg/m^2/bolus × 3 days) + caffeine (1.5 g/m^2/24 h × 3 days), *ia* intra-arterial infusion, *iv* intravenous infusion

therefore impossible to evaluate the response to the chemotherapy in that patient. Four of the eligible patients responded to preoperative chemotherapy (CR in two, PR in two). Local recurrence occurred in only one of the five patients. Distant metastasis newly developed in one patient. One patient with clear cell sarcoma in the back had undergone an initial intralesional excision and a secondary additional wide excision at another institution. Multiple lung metastases were detected and he presented to this institution. His metastases completely disappeared after caffeine-potentiated chemotherapy and no operation was necessary. The histological response to preoperative chemotherapy could therefore be evaluated in only three patients. One of the three patients responded histologically (grade IV). In addition, all four eligible patients showed radiological or histological responses to preoperative chemotherapy. Local recurrence occurred in only one of the five patients; this patient then underwent surgical tumor excision and no recurrence occurs. Lung metastasis newly developed in one patient. For this patient, metasectomy was performed and no evident metastasis has been found. All five patients survive.

Case presentation

Case 1

A 15-year-old female with clear cell sarcoma in the back had undergone an initial operation (tumor excision and skin graft) at another institution. Local recurrence was evident several months after the operation and she presented to this institution. She had no metastases (stage II). She immediately received five courses of intra-arterial caffeine-potentiated chemotherapy (cisplatin and doxorubicin with caffeine). The swelling on her back disappeared after chemotherapy (Fig. 2) and T2-weighted magnetic resonance imaging (MRI) revealed complete disappearance of the tumor (Fig. 3). She underwent a marginal excision of the lesion that appeared to contain necrotic change or scar tissue by T2-weighted MRI. The specimen after

Table 1 Data on the five patients

Patient no.	Gender	Age (years)	Site	Surgical stage	Surgery	Chemotherapeutic effect			Follow-up	
						Clinical response	Histological response	Outcome	Interval (months)	Recurrence
1	Female	15	Back	IIb (recurrent)	Marginal excision	CR	Grade IV	CDF	90	–
2	Male	47	Back	IIIb (lung metastases)	No surgery	CR	No surgery	NED	62	–
3	Male	50	Foot	IIb (recurrent)	Wide excision	PR	Grade I	NED	41	+
4	Female	37	Foot	IIIb (primary, LN metastasis)	Amputation (before CTX)	Impossible	Impossible	CDF	22	–
5	Male	30	Foot	IIb (primary)	Wide excision	PR	Grade I	CDF	14	–

LN lymph node, *CTX* chemotherapy, *CR* complete response, *PR* partial response, *CDF* continuous disease free, *NED* no evidence of disease

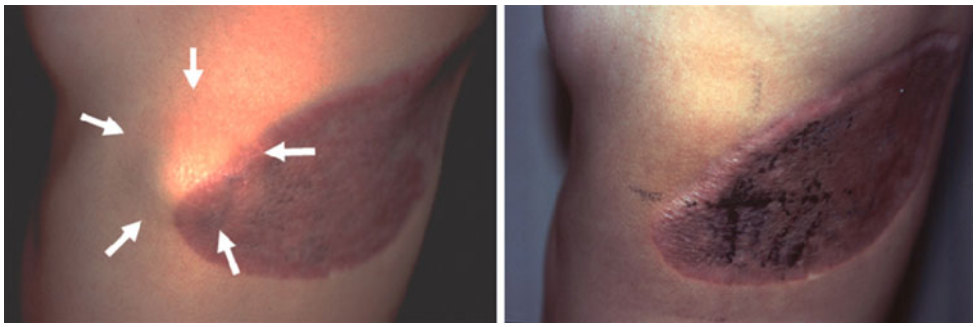

Fig. 2 Disappearance of swelling on patient's back after chemotherapy

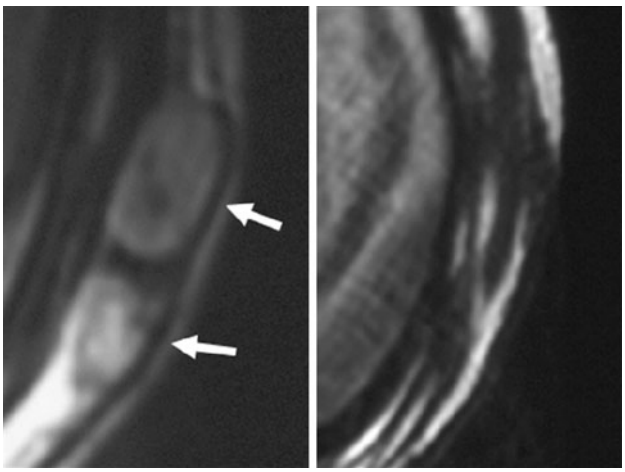

Fig. 3 T2-weighted MRI reveals the disappearance of the tumor after chemotherapy

chemotherapy contained no viable tumor cells and the tissue had total necrosis, so the histological response was grade IV (Fig. 4). She has had no evidence of either recurrence or metastasis for 90 months.

Case 2

The patient was a 47-year-old male with clear cell sarcoma on the right back. The lesion was initially diagnosed as an atheroma and was curetted by a dermatologist. The final diagnosis of the surgical specimen was clear cell sarcoma, and local recurrence occurred 1 month after the first operation. He therefore underwent a wide excision and skin grafting by dermatologists in this institution. Computed tomography of the chest demonstrated multiple lung metastases at that time (Fig. 5) and, as a result, he presented at this department to receive postoperative chemotherapy. Intravenous caffeine-potentiated chemotherapy was initiated using cisplatin and doxorubicin with caffeine. The cancer agents were changed after two courses of the chemotherapy because he developed renal dysfunction. He then received five courses of intravenous chemotherapy using ifosfamide and etoposide with caffeine. The lung metastases all disappeared on computed tomography following seven courses of the chemotherapy (Fig. 5). No signs of local recurrence and metastasis have been detected in the 6 years after the chemotherapy.

Discussion

Clear cell sarcoma is a rare tumor accounting for only 1% of all soft tissue sarcomas. It is relatively small and slow-growing and looks like a benign tumor. Clear cell sarcoma is therefore often treated by inadequate surgery such as curettage, intra-lesional excision or marginal excision.

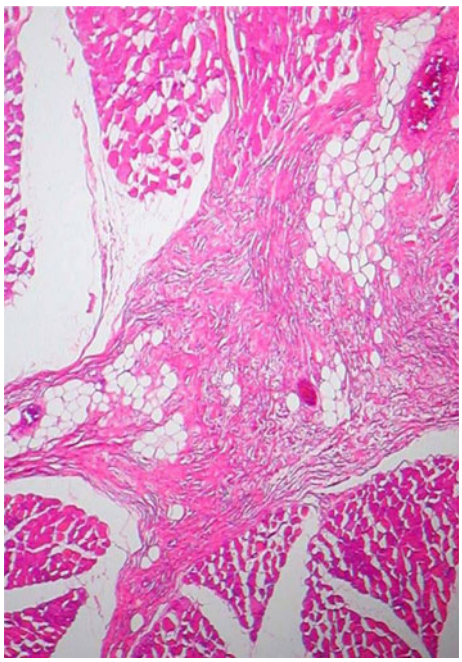

Fig. 4 Specimen contains no viable tumor cells and the tissue has total necrosis (grade IV) (H&E, ×200)

Enzinger [1] showed that survival in patients treated by wide excision or amputation was longer than those treated by marginal excision. In addition, the incidence of local recurrence following primary surgical treatment for clear cell sarcoma is very high.

Some previous reports have described the use of either chemotherapy or radiotherapy for treating clear cell sarcoma. However, the response rate to chemotherapy was 0–25% in these reports and the 5-year overall survival rate ranged from 55 to 68%, so these treatments had little impact [12–16] (Table 2).

Some sporadic case reports indicate that chemotherapy is effective for clear cell sarcoma; chemotherapy with doxorubicin and cisplatin was used in one report, bleomycin and vincristine in a second [17] and interferon-α_{2b} in a third [18]. However, it is generally thought that chemotherapy results in poor response and survival rates.

Caffeine has been used as a chemotherapy potentiator that inhibits DNA damage repair and enhances the cytocidal effects of anti-cancer drugs [8–10, 19–26]. The patients who showed radiological (PR and CR) or histological (grade III and IV) responses were considered to be

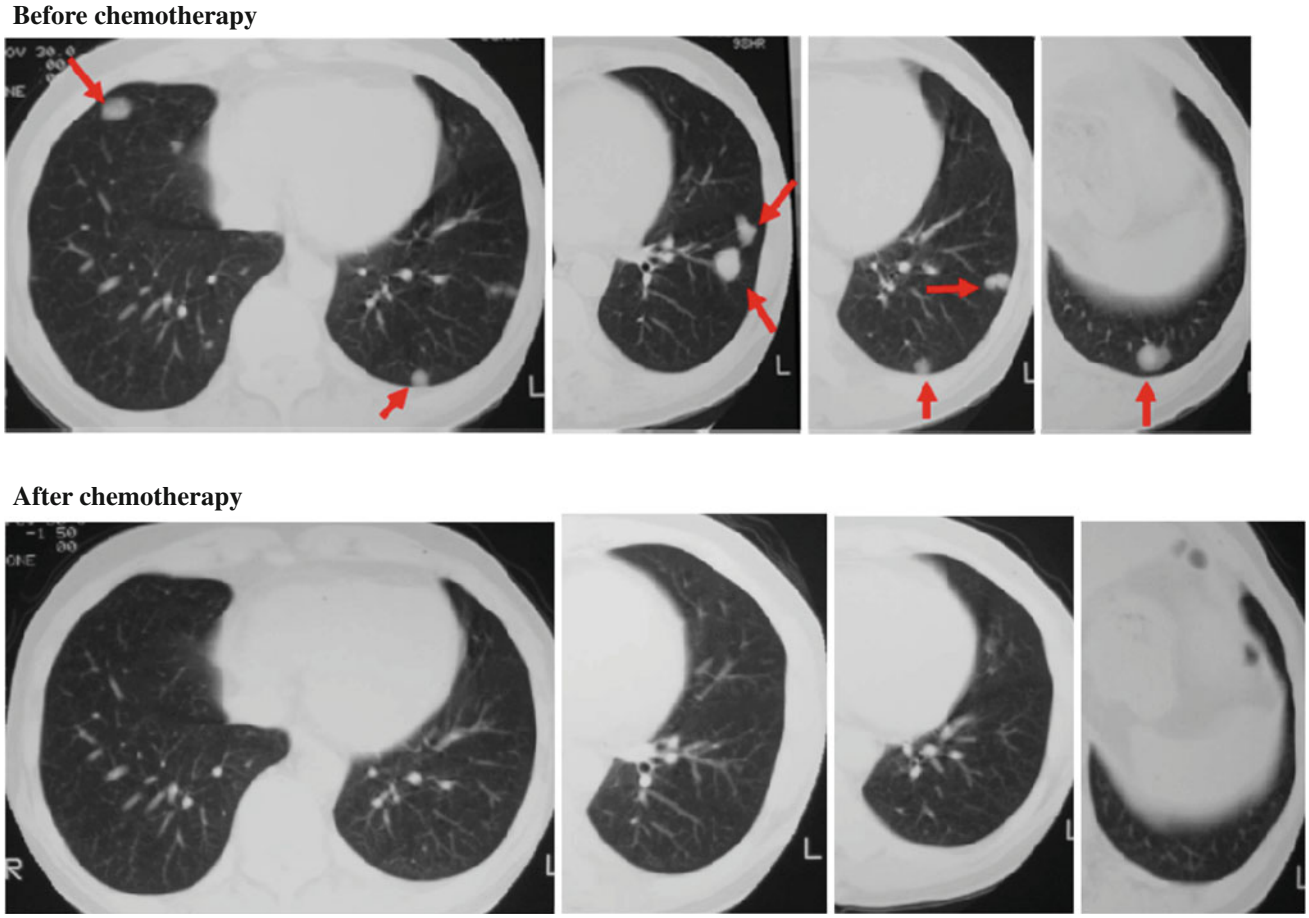

Fig. 5 Computed tomography of the chest following seven courses of chemotherapy reveals that the lung metastases have all disappeared

Table 2 Outcome for clear cell sarcoma in the other reports

References	Cases	Response rate of chemotherapy	5-year overall survival rate (%)
Jacobs et al. [12]	8	0% (0/3)	68
Kuiper et al. [13]	8	25% (1/4)	–
Ferrari et al. [14]	28	14% (1/7)	66.40
Finley et al. [15]	8	–	55
Lucas et al. [16]	35	–	67

objective responders to preoperative chemotherapy. A high response rate of 63.9% for 90 patients with high-grade soft tissue sarcoma was achieved with caffeine-potentiated chemotherapy in our institution [27]. In particular, the response rate for clear cell sarcoma was 100%. Moreover, both the recurrence rate and the metastatic rate were reduced, in addition to a higher survival rate.

There is no obvious explanation for the efficacy of caffeine-potentiated chemotherapy. The clinical effect of anti-cancer agents for clear cell sarcoma is low, but DNA may be damaged in many clear cell sarcoma cells by anti-cancer agents. If so, the anti-cancer effect for clear cell sarcoma can be enhanced by caffeine, which inhibits repair of DNA in cells treated by anti-cancer agents [19, 20]. Further study is thus required to determine the mechanism of caffeine-potentiated chemotherapy in clear cell sarcoma.

Conflict of interest No author has any conflict of interest.

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