ANTICANCER RESEARCH *25*: 2399-2406 (2005)

Caffeine-potentiated Chemotherapy for Metastatic Carcinoma and Lymphoma of Bone and Soft Tissue

MASAYUKI HAYASHI, HIROYUKI TSUCHIYA, NORIO YAMAMOTO, MICHIAKI KARITA, TOSHIHARU SHIRAI, HIDEJI NISHIDA, AKIHIKO TAKEUCHI and KATSURO TOMITA

Department of Orthopaedic Surgery, Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan

Abstract. *Background: We previously reported that caffeine-potentiated chemotherapy induced significantly good response in patients with musculoskeletal sarcomas. In that series, patients with metastatic carcinoma or lymphoma were treated with caffeine-potentiated chemotherapy. Patients and Methods: Five patients with metastatic carcinoma or lymphoma were treated with caffeine-potentiated chemotherapy. Results: Primary tumors were diagnosed as breast cancer, adenocarcinoma of the lung, clear cell adenocarcinoma of the vagina, diffuse large B-cell lymphoma and gastric cancer. Good responses (gross tumor shrinkage >30%, or histologically >90% necrosis) to chemotherapy were seen in all five patients. Survival time was >1 year in all patients, and three out of five patients presented no evidence of local recurrence or metastasis at the final follow-up. Conclusion: Caffeine-potentiated chemotherapy may be of benefit for malignant tumors other than musculoskeletal sarcoma.*

There are a number of strategies for the administration of chemotherapeutic drugs currently employed in cancer treatment. To improve survival, new cytotoxic agents or modifiers, which enhance the cytocidal effect of chemotherapeutic agents, have been developed. We previously introduced caffeine-potentiated chemotherapy in the treatment of high-grade bone and soft tissue sarcomas based on the ability of caffeine to enhance the cytocidal effects of anticancer drugs through a DNA-repair inhibiting effect (1-5). In clinical trials, we demonstrated that caffeine-potentiated chemotherapy induced a high rate of complete response in patients with osteosarcoma, as well as a high rate of good local response in patients with high-grade soft tissue sarcomas (1-5). In our studies, patients with metastatic carcinoma or lymphoma were initially suspected of having high-grade sarcoma and were treated with caffeine-potentiated chemotherapy. Here, we report five such patients and the significance of caffeine-potentiated chemotherapy for carcinoma and lymphoma.

Correspondence to: Hiroyuki Tsuchiya, M.D., Ph.D., Department of Orthopaedic Surgery, Graduate School of Medical Science, Kanazawa University, 13-1 Takara-Machi, Kanazawa 920-8641, Japan. Tel: +81-76-265-2374, Fax: +81-76-234-4261, e-mail: tsuchi@med.kanazawa-u.ac.jp

Key Words: Chemotherapy, caffeine, metastatic tumor, musculoskeletal sarcoma.

Patients and Methods

Two male and three female patients underwent caffeine-potentiated chemotherapy for metastatic cancer (Table I). Chemotherapy was performed according to the K2 protocol (Figure 1), which was modified for each patient based on past history of cytotoxic chemotherapy, general condition and renal or liver function. The K2 protocol consists of three to five courses of intra-arterial cisplatin, caffeine and doxorubicin at 3-week intervals as preoperative chemotherapy (2-4). 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.

Three of the five patients had histological results from biopsy specimens that initially suggested undifferentiated high-grade sarcoma. The other two patients were diagnosed with metastatic bone tumor at another institution. The primary tumors were finally diagnosed as cancer of the breast, adenocarcinoma of the lung, clear cell adenocarcinoma of the vagina, diffuse large B-cell lymphoma and gastric cancer. To assess the clinical response to caffeine-potentiated preoperative chemotherapy, we used the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [complete response (CR), the disappearance of all target lesions; partial response (PR), at least a 30% decrease in the sum of the longest diameter of target lesions; progressive disease (PD), at least a 20% increase in the sum of the longest diameter of target lesions; stable disease (SD), neither sufficient shrinkage to qualify

Table I. *Patient characteristics and treatment.*

					Chemotherapeutic effect		
Patient no.	Gender	Age	Site	Primary	Clinical response	Histological response	Outcome
1	Female	54	Pelvis	Breast cancer (adenocarcinoma)	PR	Grade III	DOD
2	Male	52	Femur	Lung cancer (adenocarcinoma)	PR	Grade III	NED
3	Female	50	Pelvis	Clear cell adenocarcinoma of the uterine cervix and vagina	PR	Grade II	NED
4	Female	71	Buttock	Diffuse large B-cell lymphoma	CR	No surgery	NED
5	Male	60	Sacrum	Gastric cancer (adenocarcinoma)	PR	No surgery	DOD

CR: complete response, PR: partial response, NED: no evidence of disease, DOD: dead of disease

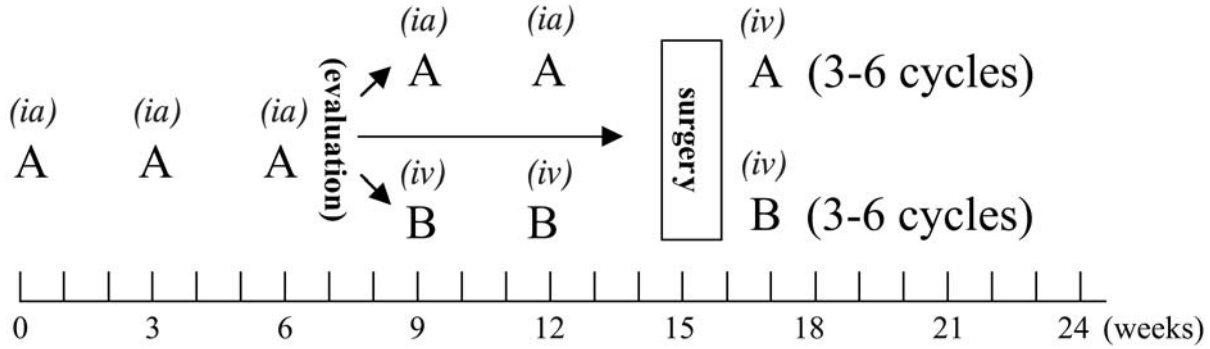

Figure 1. *K2 protocol of caffeine-potentiated chemotherapy. A: cisplatin (120 mg/m^2/2-4 h) + doxorubicin (30 mg/m^2/24 h x 2 days) + caffeine (1.5 g/m^2/24 h x 3 days), B: ifosfamide (3 g/m^2/bolus x 3 days) + etoposide (60 mg/m^2/bolus x 3 days) + caffeine (1.5 g/m^2/24 h x 3 days), ia: intra-arterial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

for partial response nor sufficient increase to qualify for progressive disease] (6). The histological response to preoperative chemotherapy was evaluated as follows: grade I, no response; grade II, 50% to 90% tumor necrosis; grade III, >90% tumor necrosis; and grade IV, no evidence of viable tumor cells.

Case Presentations

Case 1

A 54-year-old woman with a history of mastectomy for breast cancer and nephrectomy for left kidney metastasis 5 years earlier, presented right buttock pain lasting 6 months. She consulted a local doctor and, upon physical examination, a large mass was palpated in the right buttock. Radiographs showed a sclerotic lesion in the iliac bone, and magnetic resonance imaging (MRI) revealed a tumor of the ilium with a large soft tissue mass (Figure 2A). In addition, a thallium-201 scan revealed an area of high uptake limited to the pelvis. Since the tumor was diagnosed histologically as a high-grade undifferentiated sarcoma, the patient was referred to our institution. We administered caffeine-potentiated chemotherapy prior to surgery according to the modified K2 protocol (one course of intra-arterial caffeine, cisplatin and doxorubicin and two courses of intravenous caffeine, ifosfamide and etoposide) while monitoring renal function. After chemotherapy, MRI revealed marked shrinkage of the tumor extending into the soft tissue (Figure 2B). The soft tissue mass had decreased by 52% from its pre-chemotherapy size. The accumulation of thallium-201 had also decreased significantly. The response to chemotherapy was assessed as a partial response. We then performed a wide excision of the tumor with reconstruction using a frozen autograft (7). More than 90% tumor necrosis (grade III) was observed in a resected specimen. Histological findings were similar to a specimen resected 5 years previously, and the tumor was diagnosed as metastatic breast cancer. Three courses of postoperative chemotherapy consisting of

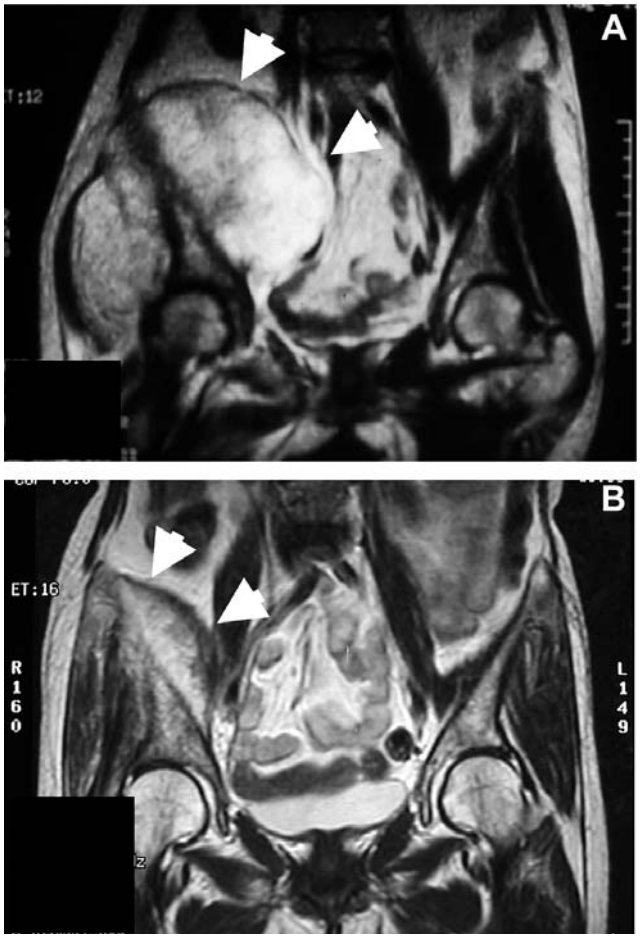

Figure 2. *Magnetic resonance imaging (MRI) findings before and after chemotherapy. A. Bone tumor of the ilium with a large soft tissue mass. B. Marked tumor shrinkage after three courses of chemotherapy. Arrows indicate the soft tissue mass.*

caffeine, cisplatin and doxorubicin were administered intravenously. Fifteen months after resection, the patient was able to walk outdoors using a T-cane. However, she died of multiple lung metastases 33 months after the operation.

Case 2

A 52-year-old man presented with left thigh pain at a nearby hospital. Radiographs revealed destructive change in the cortex of the femur. The patient was referred to our institution where MRI revealed a bone tumor extending into the soft tissue of the femur. Angiography revealed intense vascularity in the tumor (Figure 3A). A thallium-201 scan also showed strong accumulation limited to the femur (Figure 4A). The initial diagnosis was malignant bone tumor, possibly metastatic; however, no additional lesion was identified other than a lung bulla. We gave three courses of caffeine-potentiated chemotherapy consisting of intra-arterial caffeine, cisplatin and doxorubicin after histological study of a biopsy specimen suggested high-grade sarcoma. Following chemotherapy, MRI indicated 50% shrinkage of the tumor. By angiography, a tumor-related area of hypervascularity had disappeared (Figure 3B). A thallium-201 scan no longer showed high uptake (Figure 4B). The response to chemotherapy was assessed clinically as a partial response. We performed wide excision of the tumor and reconstruction with a frozen autograft, followed by three courses of postoperative chemotherapy consisting of intravenous cisplatin, caffeine and doxorubicin. The histological response to preoperative chemotherapy was evaluated as grade III (>90% necrosis). During the course of treatment, lung cancer was detected in relation to the bulla, and the patient underwent lobectomy. Since the histological findings from the lung cancer were similar to those of the femoral tumor, the patient was diagnosed with metastatic adenocarcinoma of the lung. This patient has maintained good limb function with no evidence of recurrence or metastasis for 71 months.

Case 3

A 50-year-old woman with a history of clear cell adenocarcinoma of the uterine cervix and vagina consulted a gynecologist because of right buttock pain. MRI revealed metastatic tumor of the pelvis (Figure 5A). She underwent chemotherapy consisting of irinotecan and mitomycin C; however, after 3 cycles, the clinical response to chemotherapy was defined as progression of disease. She was referred to our hospital for limb-saving surgery. Because reduction in the size of the tumor was needed for safe excision, caffeine-potentiated neoadjuvant chemotherapy was administered intravenously. Since the patient had previously been treated with cisplatin-containing chemotherapy, we used ifosfamide and etoposide in combination with caffeine. After 5 cycles, more than 60% tumor shrinkage was seen on MRI (Figure 5B). Postoperative chemotherapy, consisting of intravenous caffeine, ifosfamide and etoposide, was given in two courses. The histological response to preoperative chemotherapy was grade II (50% to 90% necrosis). No signs of recurrence or metastasis have been detected 15 months after the operation.

Case 4

A 71-year-old woman consulted a nearby hospital because of right buttock pain which was caused by a huge soft tissue tumor (Figure 6A). She was referred to our hospital. Since histological examination of a biopsy specimen disclosed a small round cell sarcoma, we carried out caffeine-assisted chemotherapy consisting of intravenous caffeine, cisplatin and doxorubicin. After one course, the tumor was no longer evident on MRI, representing a complete response (Figure 6B). Since the previous pathological diagnosis of the biopsy

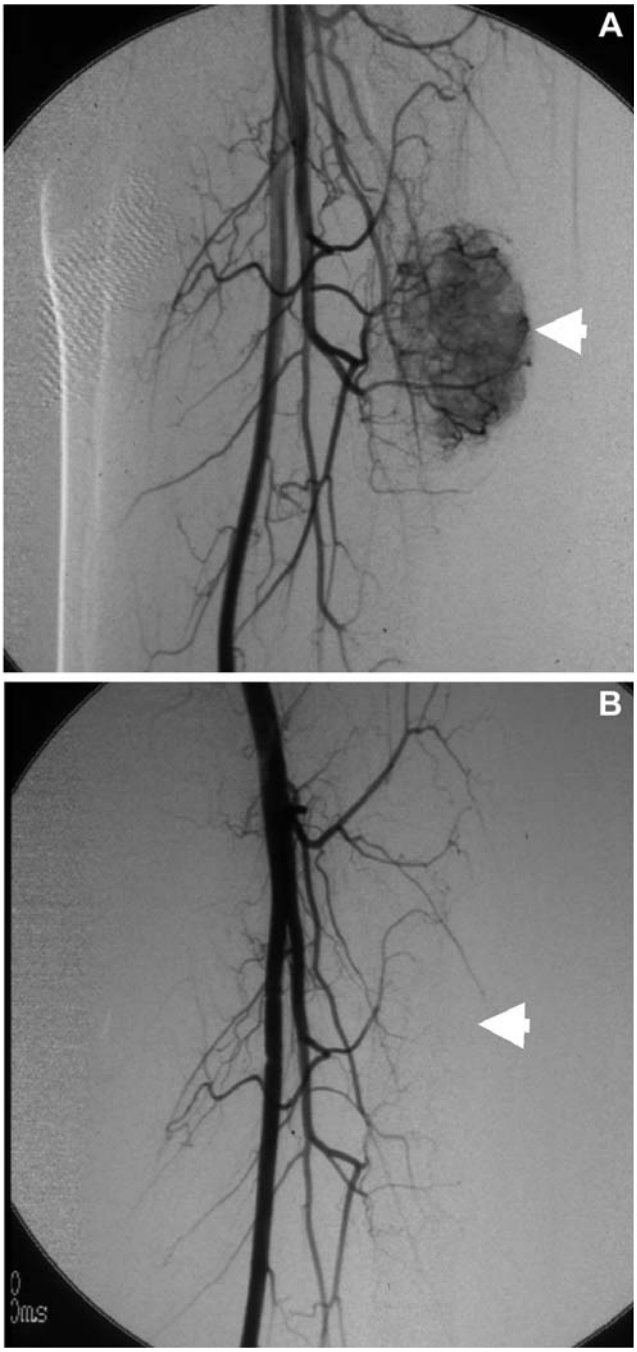

Figure 3. *Angiography before and after chemotherapy. A. Hypervascular area (white arrow) in the femur. B. The hypervascular area disappeared after three courses of chemotherapy.*

specimen suggested B-cell lymphoma, the patient was referred to a hematologist. Although the patient received only one course of chemotherapy, we interpreted the clinical response as complete. No signs of recurrence have been detected 12 months after the chemotherapy.

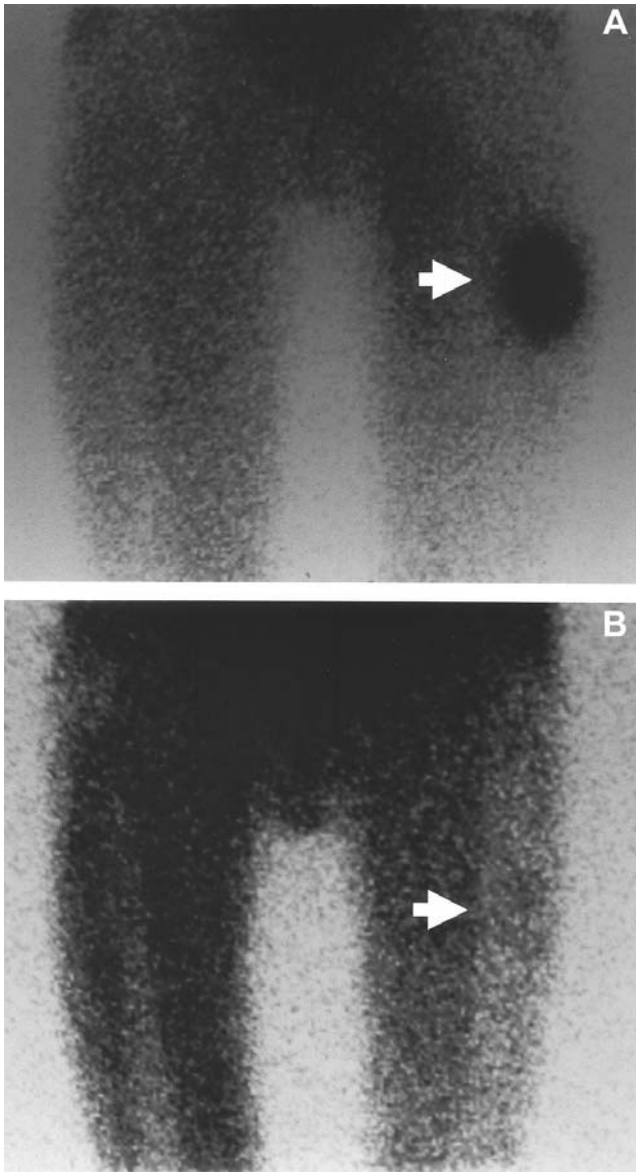

Figure 4. *Thallium-201 scan before and after chemotherapy. A. Strong accumulation (white arrow) in the femur alone. B. High uptake ceased after three courses of chemotherapy.*

Case 5

A 60-year-old man with a history of gastric cancer suffered sciatic pain. MRI revealed a metastatic tumor of the sacrum (Figure 7A). He was referred to our hospital for surgery. We administered three courses of caffeine-potentiated chemotherapy consisting of intravenous caffeine, cisplatin and doxorubicin before the operation. After three courses of chemotherapy, the tumor extending into the soft tissue had disappeared on MRI; thus, a marked response was detected (Figure 7B). Because the sciatic pain disappeared after chemotherapy, he refused the operation. Though no

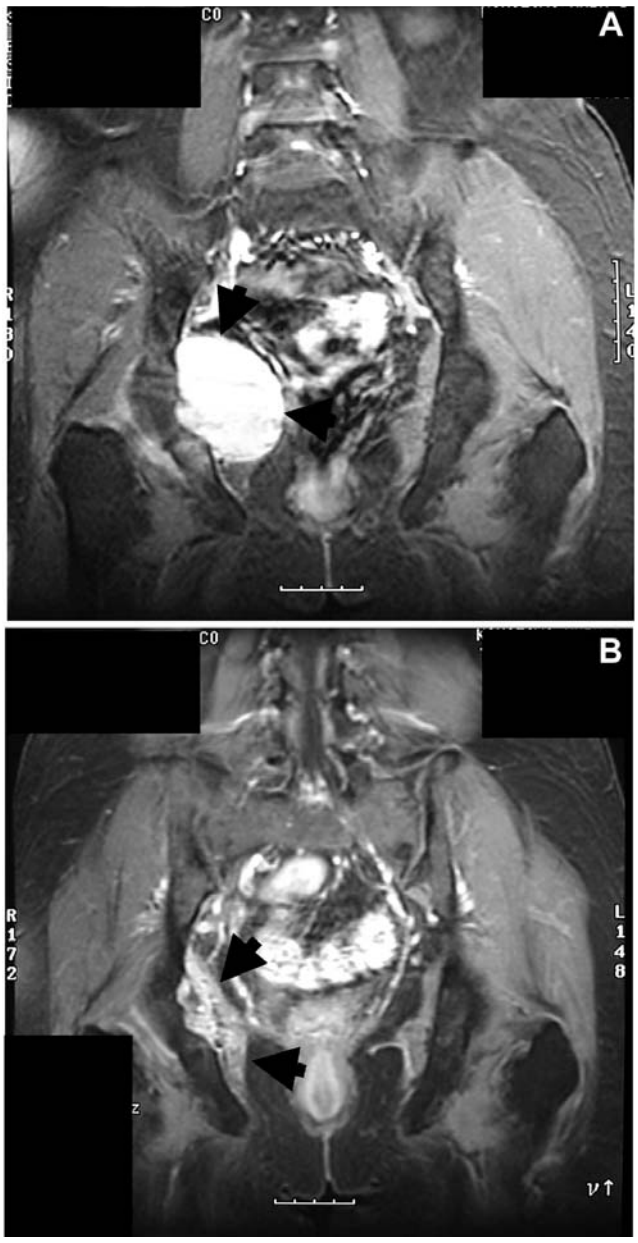

Figure 5. *MRI findings before and after chemotherapy. A. Bone tumor of the acetabulum with a large soft tissue mass. B. Marked tumor shrinkage after five courses of chemotherapy. Arrows indicate the soft tissue mass.*

sign of local recurrence had been detected, he died of multiple metastases 24 months after chemotherapy.

Discussion

In 1981, Byfield *et al.* (8) summarized studies on methylated xanthines as antitumor agents. Caffeine, which is a xanthine analog, has a biochemical modulating effect as a DNA-repair inhibitor and may inhibit postreplication repair of

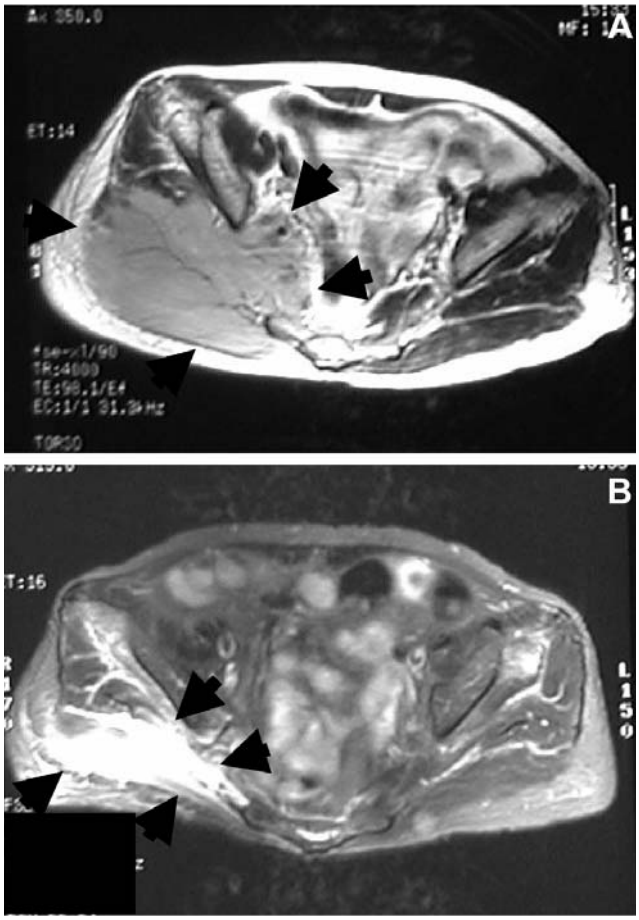

Figure 6. *MRI findings before and after chemotherapy. A. Large soft tissue tumor is found in the right buttock. B. The tumor mass disappeared after one course of chemotherapy. Arrows indicate the soft tissue tumor.*

sublethally damaged DNA (8, 9). According to our experimental studies, caffeine-enhanced cytotoxicity depends on the degree of lethal or sublethal effects caused by the anticancer agents (10-12). When human osteosarcoma and fibrosarcoma cells were exposed to caffeine, enhancement increased in a time-dependent manner by facilitating cell cycle progression before recovery from DNA damage. *In vitro* studies have demonstrated that caffeine enhances the cytocidal effects of cisplatin, doxorubicin, cyclophosphamide and mitomycin C on human osteosarcoma and fibrosarcoma cells (10-12). Based on these studies, we introduced chemotherapeutic caffeine into osteosarcoma chemotherapy in 1989. In our clinical trials, we demonstrated that caffeine-potentiated chemotherapy induced a complete response in more than 70% of patients with osteosarcoma (86% in patients with non-metastatic osteosarcoma) (2, 4). There also was a high rate (>70%) of good local response in patients with high-grade soft tissue sarcoma (3, 5).

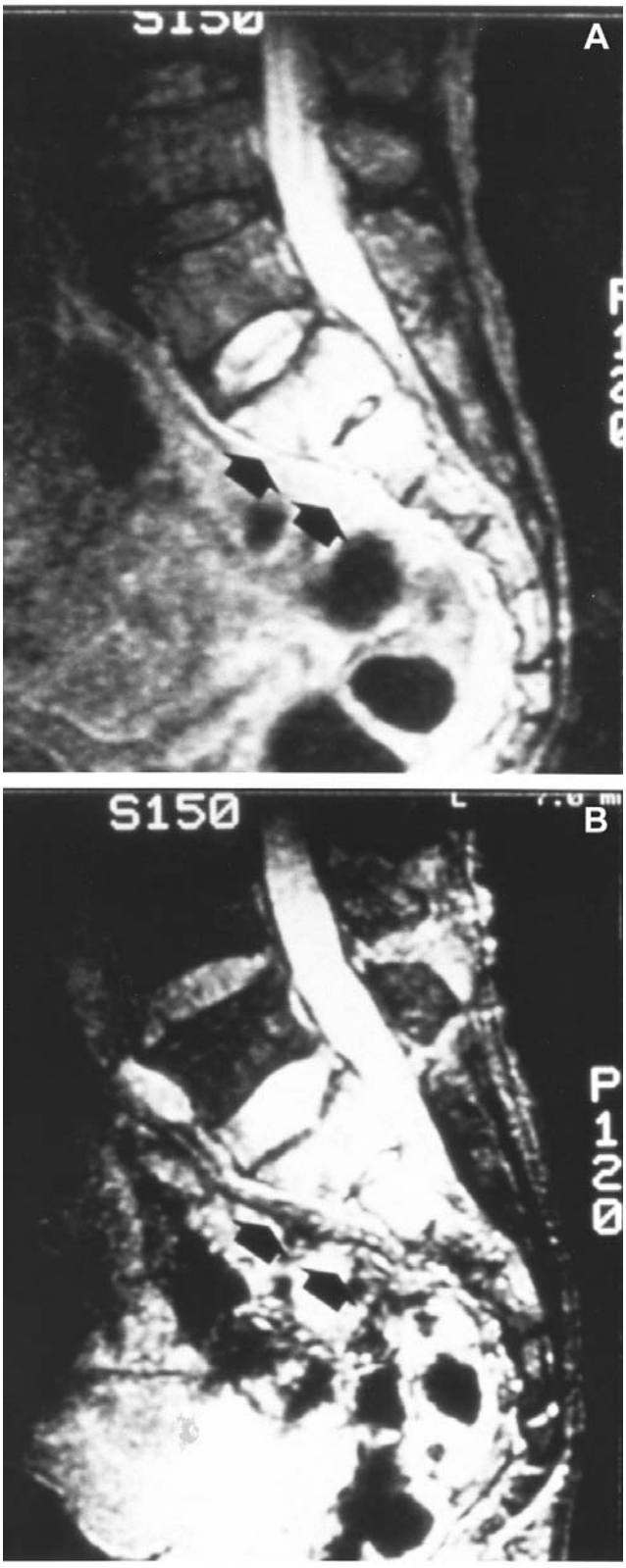

Figure 7. *MRI findings before and after chemotherapy. A. Tumor of the sacrum with a soft tissue mass. B. The soft tissue mass disappeared after three courses of chemotherapy. Arrows indicate the soft tissue mass.*

Regarding cancers other than musculoskeletal sarcoma, some investigators have reported caffeine enhancement of cytotoxicity with *in vitro* and *in vivo* models (13-19). Boike *et al.* (13) reported significant caffeine enhancement of cisplatin-induced cytotoxicity against a human ovarian and cervical cancer cell line. Takahashi *et al.* (18) examined the combined effect of cisplatin and caffeine against a human gastric cancer cell line *in vivo* and found that caffeine enhanced the effect of cisplatin. Concerning lung cancer, there are some reports of caffeine-enhanced chemosensitivity in human non-small cell lung cancer *in vitro* (17, 19). In clinical studies, there have been trials involving combination chemotherapy using caffeine for malignant melanoma (20), glioblastoma (21), and pancreatic cancer (22, 23). Unfortunately, chemotherapeutic caffeine had no impact on local recurrence or survival in these studies, most probably because the caffeine was administered orally, subcutaneously, or intramuscularly, and the dosage was lower than that used in our protocol. Intra-arterial or intravenous continuous administration is recommended to increase the efficacy of chemotherapeutic caffeine. Though high-dose caffeine administration sometimes causes palpitations and sleeplessness, these side-effects were found to be tolerable for most patients with concomitant use of a major tranquilizer. No symptomatic cardiac or neurological, side-effects attributable to caffeine were observed in our study (2).

In the five cases presented here, we confirmed a radiographically complete response in one patient and a partial response in four. Significantly, the patient with lymphoma who received only one course of chemotherapy achieved a complete response. In three of the five patients, we performed tumor excision and evaluated the histological response to preoperative chemotherapy. The histological response was grade II in one case and grade III in two cases. Good responses to chemotherapy (complete or partial clinical response, or histologically >90% necrosis by histological examination) were seen in all five patients. Though four patients had advanced metastatic cancer, survival time was more than 1 year in all patients. Three out of five patients have had no evidence of local recurrence or metastasis for 12, 15 and 71 months. The patient with lung cancer and skeletal metastasis has been alive for more than 5 years after operation without local recurrence or metastasis, despite an advanced stage. Caffeine-potentiated chemotherapy may possibly improve the survival rate even in cancers other than musculoskeletal sarcoma. However, a randomized prospective study is necessary to examine whether caffeine-potentiated chemotherapy definitively improves the survival rate of patients with malignant tumors other than musculoskeletal sarcoma.

In conclusion, caffeine-potentiated chemotherapy produced a good response in metastatic carcinoma and lymphoma. Though the number of patients who have undergone caffeine-

potentiated chemotherapy is limited, caffeine-potentiated chemotherapy may be of great benefit for patients with malignant tumors other than musculoskeletal sarcoma.

References

1 Tsuchiya H, Yasutake H, Yokogawa A *et al*: Effect of chemotherapy combined with caffeine for osteosarcoma. J Cancer Res Clin Oncol *118*: 567-569, 1992.

2 Tsuchiya H, Tomita K, Mori Y *et al*: Caffeine-assisted chemotherapy and minimized tumor excision for nonmetastatic osteosarcoma. Anticancer Res *18*: 657-666, 1998.

3 Tsuchiya H, Tomita K, Yamamoto N *et al*: Caffeine-potentiated chemotherapy and conservative surgery for high-grade soft-tissue sarcoma. Anticancer Res *18*: 3651-3656, 1998.

4 Tsuchiya H, Tomita K, Mori Y *et al*: Marginal excision for osteosarcoma with caffeine assisted chemotherapy. Clin Orthop *358*: 27-35, 1999.

5 Tsuchiya H, Yamamoto N, Asada N *et al*: Caffeine-potentiated radiochemotherapy and function-saving surgery for high-grade soft-tissue sarcoma. Anticancer Res *20*: 2137-2144, 2000.

6 Therasse P, Arbuck SG and Eisenhauer EA: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst *92*: 205-216, 2000.

7 Tsuchiya H, Wann SL, Yamamoto N *et al*: Reconstruction using an autograft containing tumor treated by liquid nitrogen. J Bone Joint Surg Br *87*: 218-225, 2005.

8 Byfield JE, Murnane J, Ward JF *et al*: Mice, men, mustard and methylated xanthines: the potential role of caffeine and related drugs in the sensitization of human tumors to alkylating agents. Br J Cancer *43*: 669-683, 1981.

9 Van Den Berg HW and Roberts JJ: Inhibition by caffeine of post-replication repair in Chinese hamster cells treated with cis platinum (II) diamminedichloride: the extent of platinum binding to template DNA in relation to the size of low molecular weight nascent DNA. Chem Biol Interact *12*: 375-390, 1976.

10 Tomita K and Tsuchiya H: Caffeine enhancement of the effect of anticancer agents on human sarcoma cells. Jpn J Cancer Res *80*: 83-88, 1989.

11 Tomita K and Tsuchiya H: Enhancement of cytocidal and antitumor effect of cisplatin by caffeine in human osteosarcoma. Clin Ther *11*: 43-52, 1989.

12 Yasutake H, Tsuchiya H, Tomita K *et al*: Inhibitory effect of caffeine on potentially lethal damage repair in cisplatin-treated human osteosarcoma cells. Anticancer Res *15*: 831-837, 1995.

13 Boike GM, Petru E, Sevin BU *et al*: Chemical enhancement of cisplatin cytotoxicity in a human ovarian and cervical cancer cell line. Gynecol Oncol *38*: 315-322, 1990.

14 Gude RP, Menon LG and Rao SG: Effect of caffeine, a xanthine derivative, in the inhibition of experimental lung metastasis induced by B16F10 melanoma cells. J Exp Clin Cancer Res *20*: 287-292, 2001.

15 Kyriazis AP, Kyriazis AA and Yagoda A: Enhanced therapeutic effect of cis-diamminedichloroplatinum (II) against nude mouse grown human pancreatic adenocarcinoma when combined with 1-beta-D-arabinofuranosylcytosine and caffeine. Cancer Res *45*: 6083-6087, 1985.

16 Janss AJ, Levow C, Bernhard EJ *et al*: Caffeine and staurosporine enhance the cytotoxicity of cisplatin and camptothecin in human brain tumor cell lines. Exp Cell Res *243*: 29-38, 1998.

17 Ogasawara H, Nishio K, Ishida T *et al*: *In vitro* enhancement of antitumor activity of a water-soluble duocarmycin derivative, KW-2189, by caffeine-mediated DNA-repair inhibition in human lung cancer cells. Jpn J Cancer Res *88*: 1033-1037, 1997.

18 Takahashi M, Yanoma S, Yamamoto Y *et al*: Combined effect of CDDP and caffeine against human gastric cell line *in vivo*. Anticancer Res *18*: 4399-4401, 1998.

19 Tsai CM, Perng RP, Chen MH *et al*: Greater enhancement of chemosensitivity by caffeine in high-p185neu-expressing human non-small-cell lung cancer cell lines. J Natl Cancer Inst *86*: 1018-1020, 1994.

20 Cohen M, Schoenfeld D and Wolter J: Randomized trial of chlorpromazine, caffeine, and methyl-CCNU in disseminated melanoma. Cancer Treat Rep *64*: 151-153, 1980.

21 Stewart DJ, Benoit B, Hugenholtz H *et al*: Cisplatin, arabinofuranosylcytosine and caffeine before radiation for glioblastomas. *In:* Biology of Brain Tumors (ed. 1) (Walker MD, Thomas DT, eds). Boston, Martinus Nijhoff, pp. 393-398, 1986.

22 Al-Sukhun S, Zalupski MM, Ben-Josef E *et al*: Chemoradiotherapy in the treatment of regional pancreatic carcinoma: a phase II study. Am J Clin Oncol *26*: 543-549, 2003.

23 Kelsen D, Hudis C, Niedzwiecki D *et al*: A phase III comparison trial of streptozotocin, mitomycin, and 5-fluorouracil with cisplatin, cytosine arabinoside, and caffeine in patients with advanced pancreatic carcinoma. Cancer *68*: 965-969, 1991.

Received March 9, 2005
Accepted April 4, 2005