Caffeine-potentiated Chemotherapy for Patients with High-grade Soft Tissue Sarcoma: Long-term Clinical Outcome

AKIHIKO TAKEUCHI[1], HIROYUKI TSUCHIYA[1], NORIO YAMAMOTO[1], KATSUHIRO HAYASHI[1], KENSUKE YAMAUCHI[1], MASAMI KAWAHARA[2], KEN-ICHI MIYAMOTO[2] and KATSURO TOMITA[1]

[1]*Department of Orthopaedic Surgery, Kanazawa University Graduate School of Medical Science, Kanazawa;*
[2]*Department of Pharmacy, Kanazawa University Hospital, Kanazawa, Japan*

Abstract. *Background: Caffeine, which has a DNA-repair inhibiting effect, enhances the cytocidal effects of anticancer drugs and radiation. The present study was performed to assess the efficacy of caffeine-potentiated chemotherapy for high-grade soft tissue sarcoma (STS). Patients and Methods: A non-randomised prospective clinical trial was initiated for 90 patients with non-metastatic (stages II and III) or metastatic (stage IV) STS. Following doxorubicin or ifosfamide combined with caffeine, with or without radiotherapy, 88 patients were treated surgically. A radiographic and histological response to chemotherapy was assessed. Local-recurrence free, distant-metastasis free and overall survival were analyzed by multivariate analysis. Results: Radiographic and histological response rates were 57.8% and 42%, respectively. The local recurrence rate was 23.7% in stages II and III and 13.6% in stage IV. Lung metastases newly developed in 21 (35.6%) patients at stages II and III. With a median follow-up period of 52 months, the overall 5-year cumulative survival rate at stages II and III was 80.7%. Local recurrence-free survival for the histological responders and distant metastasis-free survival for the radiographic responders at stages II and III were significantly improved compared to the non-responders ($p=0.004$ and $p=0.034$). Overall survival for the radiographic responders at all stages was significant longer than for the non-responders ($p=0.009$). Conclusion: Caffeine-potentiated chemotherapy resulted in a favourable radiographic response and prolonged overall survival of the patients at all stages.*

.

Soft tissue sarcomas are rare malignant tumours that arise in mesenchymal tissues. Multiagent chemotherapy for patients with certain mesenchymal malignant tumours, such as osteosarcoma (1) or Ewing's sarcoma (2), has improved survival rate and limb function. Several studies have been performed to improve both the response to chemotherapy and survival rate of patients with high-grade soft tissue sarcoma (3-7). However, the precise role of chemotherapy in the management of patients with soft tissue sarcoma remains controversial. Previously, we reported that caffeine-potentiated chemotherapy improved the survival and enhanced the safety of limb-sparing surgery in the treatment of high-grade soft tissue sarcomas (8, 9). Caffeine-potentiated chemotherapy has been administered to patients with high-grade soft tissue sarcomas since 1989 on the basis of the ability of caffeine to enhance the cytocidal effects of anticancer drugs through an inhibitory effect on DNA repair (10-13).

The present study focused on evaluating the long-term disease-free and overall survival rates of patients with high-grade soft tissue sarcomas who were treated with caffeine-potentiated chemotherapy.

Patients and Methods

A nonrandomised prospective clinical trial was initiated for the treatment of non-metastatic (stage II and III) or metastatic (stage IV) STS (14, 15). Preoperative chemotherapy was performed in 98 patients from July 1989 to August 2005 at our institute; 90 of these 98 patients received more than 2 courses of preoperative chemotherapy and were enrolled in this study. The median age of the patients was 44.0 years (range, 7-77 years). Fifty-three patients were male and 37 were female. All the patients had high-grade sarcomas histologically confirmed by core needle or incisional biopsy. Twenty-four patients were at stage IV with lung metastasis on diagnosis and the remaining 66 were at stages II and III without metastasis. Seventy patients were considered to have primary tumours because they were untreated previously or had undergone only biopsy (incisional or excisional) at the time of presentation. The remaining 20 patients were defined as having locally recurrent disease (Table I). The trial was approved by the local ethical committee of Kanazawa University School of Medicine and Kanazawa University Hospital. After a full explanation of the study, written informed consent was obtained from each patient, or their guardian.

Correspondence to: Hiroyuki Tsuchiya, MD, Ph.D., Department of Orthopaedic Surgery, Kanazawa University Graduate School of Medical Science, 13-1 Takara-machi, Kanazawa 920-8641, Japan. Tel: +81 762652374, Fax: +81 762344261, e-mail: tsuchi@med.kanazawa-u.ac.jp

Key Words: Soft tissue sarcoma, caffeine, chemotherapy, clinical outcome, response.

Table I. *Patient characteristics.*

Characteristics	No. of patients	%
Mean follow-up period:		
52 months (3-200 months)		
Mean age: 44.0 years (7-77 years)		
Gender		
Male	53	58.9
Female	37	41.1
AJCC/UICC TNM Classification		
IIA	16	17.8
IIB	6	6.7
III	44	48.9
IV	24	26.7
Location		
Extremity	62	68.9
Trunk	23	25.6
Retroperitoneum	5	5.6
Tumor status		
Primary	70	77.8
Recurrence	20	22.2
Histology		
Malignant fibrous histiocytoma	28	31.1
Liposarcoma	13	14.4
Synovial sarcoma	12	13.3
Leiomyosarcoma	10	11.1
Rabdomyosarcoma	6	6.7
Clear cell sarcoma	5	5.6
Malignant peripheral nerve sheath tumor	5	5.6
Epithelioid sarcoma	4	4.4
Extraskeletal chondrosarcoma	3	3.3
Alveolar soft part sarcoma	3	3.3
Angiosarcoma	1	1.1

A protocol for caffeine-potentiated chemotherapy (K1, 2 and 3-protocol) was developed based on our *in vitro* and *in vivo* studies with regard to the enhancement of the effects of anticancer drugs by caffeine (8, 9). Nineteen patients were treated by the K1-protocol with two to five courses of intra-arterial cisplatin (120 mg/m^2, for 1 day) and caffeine (1.5 g/m^2/day for 3 days continuously) at 2-week intervals from June 1989 to December 1991. Twenty patients were treated by the K2 protocol with two to five courses of cisplatin, caffeine and doxorubicin at 3-week intervals preoperatively from January 1992 to December 1995. Nineteen patients were treated by the K3 protocol with three to five courses of intra-arterial chemotherapy using cisplatin (120 mg/m^2, for 1 day) and caffeine (1.5 g/m^2/day for 3 days continuously) and doxorubicin (30 mg/m^2/day for 2 days) after radiation therapy (2 Gy/day for 5 days) at 3-week intervals from January 1996 to December 1998. Due to the side-effect of skin necrosis caused by radiotherapy, 40 patients were treated with the K2 protocol from January 1999. The serum level of caffeine was monitored at 24, 48 and 72 h after the start of continuous infusion at a dose of 1.5 g/m^2/day for 72 h. The appropriate infusion rate was calculated to avoid severe side-effects in the final phase of infusion using a one-compartment constant infusion model based on the serum levels measured at 24 and 48 h (16).

Following preoperative chemotherapy, conservative surgery (limb-sparing for extremities) aiming at a wide margin was performed. When a good response to chemotherapy was documented in terms of marked tumour shrinkage seen on MRI, the disappearance of tumour staining on angiograms, or the disappearance of abnormal accumulation on thallium-201 scintigrams, a marginal margin to preserve neurovascular bundles and important structures for function, such as ligament, tendon and muscle, was employed for selected cases.

Patients who achieved radiographic response were considered as clinical responders. For assessment of the clinical response to caffeine-potentiated preoperative chemotherapy, the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines were followed: complete response (CR), 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 for partial response nor sufficient increase to qualify for progressive disease (17). The histological response to preoperative chemotherapy was evaluated by a grading system: grade I, no response to chemotherapy; grade II, 50-90% tumour necrosis; grade III, >90% tumour necrosis; grade IV, no evidence of viable tumour cells.

Survival analysis was performed with the Kaplan-Meier method (18) and compared with the log-rank test. Survival was defined as the time from entry into the study until death or last contact. The local tumour recurrence rates were measured from the date of surgery. The distant metastasis-free survival rates were measured from the date of initiation of neoadjuvant chemotherapy. Data were analysed with SPSS II statistical software (version 11.0.1J, SPSS Inc., Chicago, IL, USA).

Results

The clinical response to preoperative chemotherapy was evaluated in 83 eligible patients. The remaining 7 patients were excluded for evaluation of clinical response to chemotherapy because they underwent excisional biopsy at other institutes prior to administration of chemotherapy. Nine patients (10.8%) showed a complete response and 39 patients (47.0%) showed a partial response. The total clinical response rate was 57.8% (Table II). The histological types of CR were as follows: 3 with rhabdomyosarcoma, 2 with MFH and clear cell sarcoma, and one each with leiomyosarcoma and liposarcoma (Figures 1 and 2). Table III shows the histological types and clinical response rates for the 83 patients.

Following preoperative chemotherapy, conservative surgery (limb-sparing surgery for lesions in the extremities) was performed except in one case of angiosarcoma in the lower leg. Although high-dose caffeine administration sometimes caused palpitations, nausea and sleeplessness, these complications were resolved in most patients with concomitant use of a major tranquilliser and had no influence on either surgical procedures or clinical outcome.

Table II. *Responses to preoperative chemotherapy of individual stages in 83 eligible patients.*

		Radiographic response			
AJCC/UICC stage	No. of patients	CR	PR	SD	PD
IIA	10	2	4	3	1
IIB	5	1	1	3	0
III	44	4	26	14	0
IV	24	2	8	12	2
Total	83	9 (10.8%)	39 (47.0%)	32(38.6%)	3 (3.6%)
Response rate:		48 (57.8%)			
		Histological response (grade)			
AJCC/UICC stage	No. of patients	I	II	III	IV
IIA	11	4	3	2	2
IIB	5	3	0	1	1
III	43	14	10	13	6
IV	22	5	8	5	5
Total	81	26 (32.1%)	21 (25.9%)	21 (25.9%)	13 (16%)
Response rate:		34 (42.0%)			
Overall response rate:		53 (63.9%)			

Table III. *Response to preoperative chemotherapy of individual histological diagnosis in 83 eligible patients.*

		Response		
Histology	No. of patients	Radiographic (n=83)	Histological (n=81)	Objective (n=83)
MFH	27	14	9	17
Liposarcoma	12	8	5	8
Leiomyosarcoma	10	6	4	6
Synovial sarcoma	8	5	4	5
Rhabdomyosarcoma	6	4	6	6
MPNST	5	3	3	3
Clear cell sarcoma	5	4	1	4
Epithelioid sarcoma	3	1	1	1
Extraskeletal chondrosarcoma	3	2	1	2
Alveolar soft part sarcoma	3	0	0	0
Angiosarcoma	1	1	0	1
Total	83	48 (57.8%)	34 (42.0%)	53 (63.9%)

MFH: malignant fibrous histiocytoma; MPNST: malignant peripheral nerve sheath tumor.

Surgical margins were wide for 62 patients, marginal for 18 patients and intra-lesional for 8 patients. Two patients did not undergo surgical treatment because one patient with multiple lung metastases with clear cell sarcoma achieved complete remission of the tumour after chemotherapy and the other with multiple lung metastases with MPNST was not suitable for surgical treatment due to their clinical status.

Histological response to preoperative chemotherapy was evaluated in 81 of the 88 patients who underwent surgery. The histologically identified response to this preoperative treatment consisted of grade I in 26 cases, grade II in 21 cases, grade III in 21 cases, and grade IV in 13 cases (Table II). The remaining 7 patients were excluded for evaluation of histological response to chemotherapy because they underwent excisional biopsy at other institutes prior to administration of chemotherapy. Additional wide excision was performed in these cases after preoperative chemotherapy and no tumour cells were seen in any resected surgical specimens.

The patients who showed clinical or histological responses were considered to be objective responders to preoperative chemotherapy. A total of 53 (63.9%) patients responded to caffeine-potentiated chemotherapy while 30 showed no response (Table II).

Local recurrence occurred in 17 of the 88 patients who underwent surgical tumour excision (19.3%; 14 patients in stage II and III and 3 in stage IV) during follow-up. Twelve patients were judged as histological non-responders in stages II and III, and 1 as a responder in stage IV. The remaining 1 patient belonged to the group that was excluded from histological evaluation because they had undergone excisional biopsy at other institutes before administration of chemotherapy. Local recurrence-free survival periods for the histological responders (n=25) in stages II and III were significantly longer than those of non-responders (n=34) ($p=0.004$) (Figure 3). All of the patients who showed local recurrence underwent additional surgery. Nine patients remain alive, six died due to metastatic disease and 2 died due to other causes.

Distant metastasis newly developed in 5 patients with stage II and 16 with stage III, respectively. Fourteen patients died due to the metastatic disease within 3 years. Eleven patients remain alive after metastasectomy. Distant metastasis-free survival period for clinical responders (n=38) in stages II and III was significantly longer than that for clinical non-responders (n=21) ($p=0.034$); the mean metastasis-free survival was 123.3 months (95% confidence interval (CI), 103.4-143.25 months) *vs.* 61.7 months (95% CI, 43.28-80.15 months), and the estimated 5-year distant metastasis-free survival rate was 75.5% *vs.* 42.3% (Figure 4).

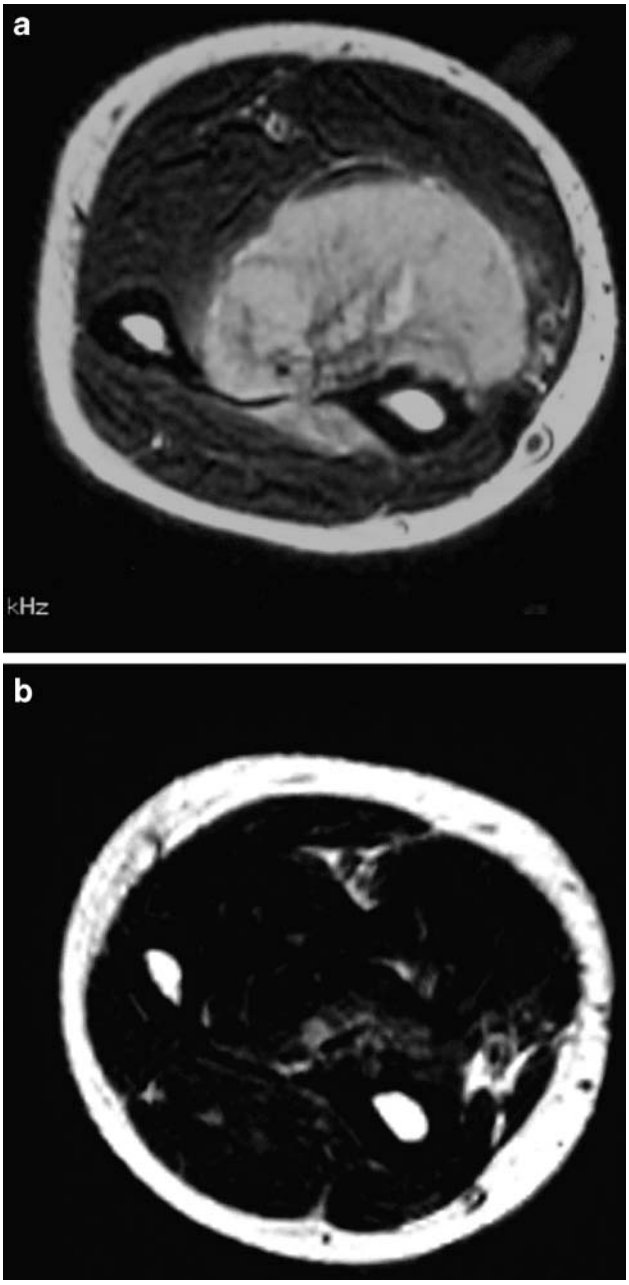

Figure 1. *A 12-year-old girl with a rhabdomyosarcoma of the right forearm (a) showed complete disappearance of the tumour on MR images (T2 weight image) after five courses of caffeine-potentiated chemotherapy (b).*

All 90 eligible patients at all stages were included in the survival analysis using the Kaplan-Meier technique. The cumulative survival rates were 80.16% at 5 years and 66.9% at 10 years in stages II and III. In stage IV, the 5-year survival rate was 15.5% (Figure 5a). There were significant differences between the cumulative survival rates of clinical responders (n=48) and non-responders (n=35) at all stages (p= 0.009) (Figure 5b).

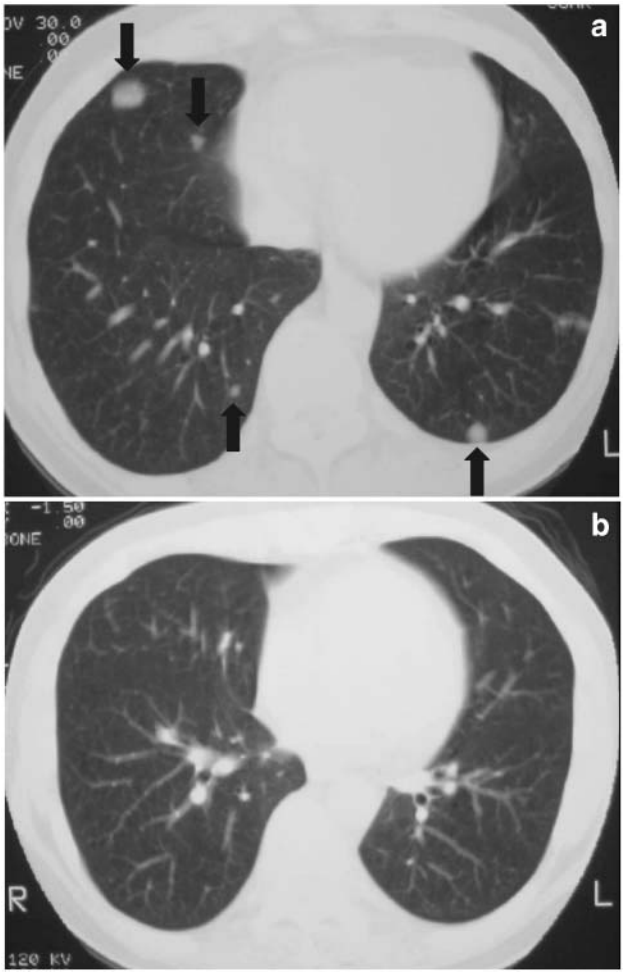

Figure 2. *A 56-year-old man with multiple lung metastases of clear cell sarcoma (a, black arrows) showed complete disappearance of the tumor on CT images after five courses of caffeine-potentiated chemotherapy (b).*

Discussion

Caffeine, which is a xanthine analogue, has a biochemical modulating effect as an inhibitor of DNA repair and may inhibit post-replication repair of sublethally damaged DNA (19, 20). Our previous experimental studies revealed that caffeine-enhanced cytotoxicity caused by anticancer agents depended on the degree of lethal or sublethal effects (12, 13, 21). The enhancement by caffeine also increased in a time-dependent manner by facilitating cell cycle progression before the recovery of DNA damage. In previous *in vitro* studies, caffeine was shown to enhance the cytocidal effects of cisplatin, doxorubicin, cyclophosphamide and mitomycin C on human osteosarcoma and fibrosarcoma cells (12, 13, 21). We have administered doxorubicin, cisplatin and ifosfamide-based caffeine combined chemotherapy in patients with osteosarcoma since 1989 on the basis of these

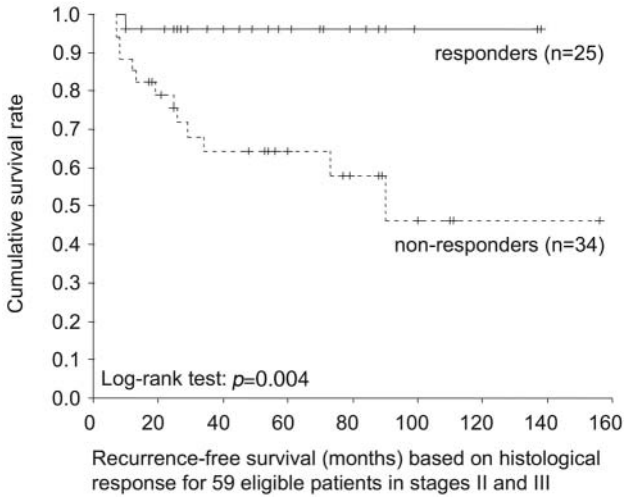

Figure 3. *Kaplan-Meier analysis of recurrence-free survival based on histological response for 59 eligible patients in stages II and III. Local recurrence-free survival periods for the histological responders (solid line, n=25) in stages II and III were significantly longer than those of non-responders (dotted line, n=34) (p=0.004).*

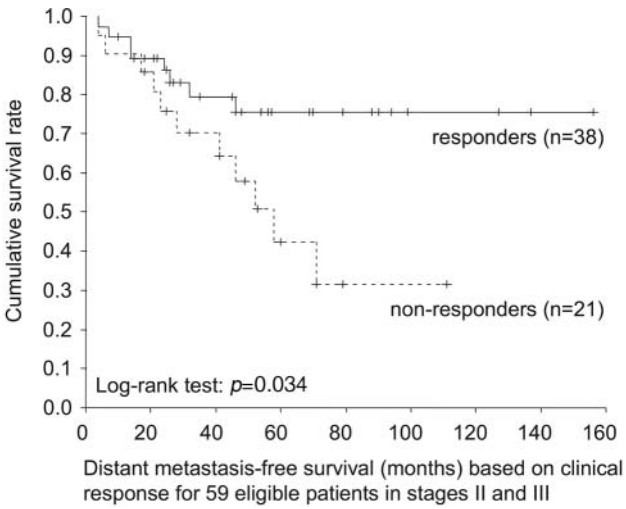

Figure 4. *Kaplan-Meier analysis of distant metastasis-free survival based on clinical response for 59 eligible patients in stages II and III. Distant metastasis-free survival for clinical responders (solid line, n=38) in stages II and III was significantly longer than that for clinical non-responders (dotted line, n=21) (p=0.034); the mean metastasis-free survival was 123.3 months (95% CI, 103.4-143.25 months) vs. 61.7 months (95% CI, 43.28-80.15 months), and the estimated 5-year distant metastasis-free survival rate was 75.5% vs. 42.3%.*

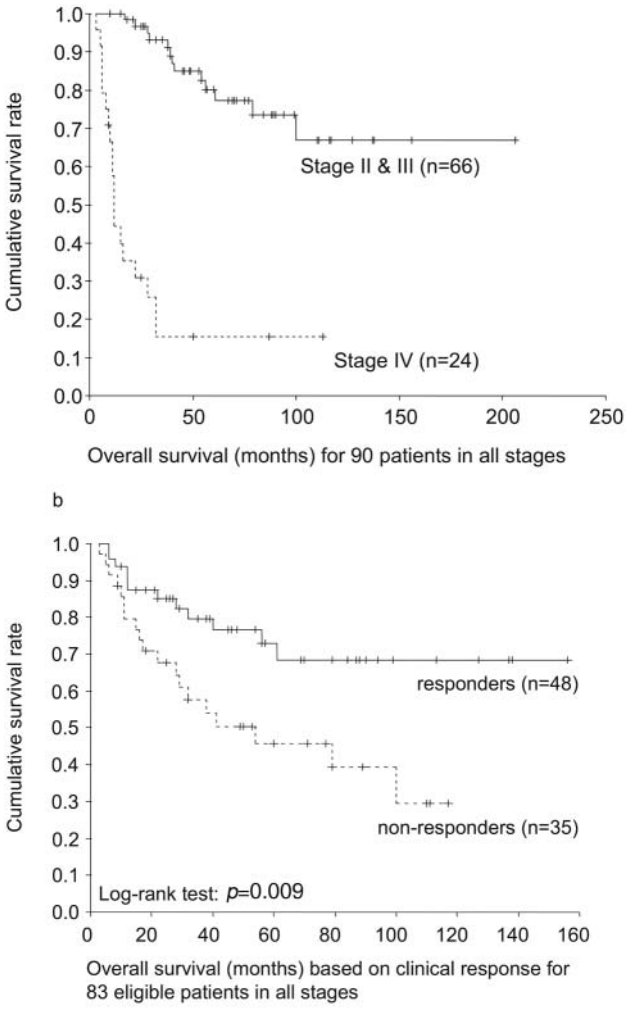

Figure 5. *a) Kaplan-Meier analysis of overall survival for 90 patients in all stages. The cumulative survival rates were 80.16% at 5 years and 66.9% at 10 years in stages II and III (solid line, n=66). In stage IV, the 5-year survival rate was 15.5% (dotted line, n=24). b) Overall survival based on clinical response for 83 eligible patients in all stages. There were significant differences between the cumulative survival rates of clinical responders (solid line, n=48) and non-responders (dotted line, n=35) at all stages (p=0.009).*

experimental studies. As a result, caffeine-potentiated chemotherapy demonstrated a complete response in more than 70% of the patients with osteosarcoma (86% in patients with non-metastatic osteosarcoma) (23-25). Moreover, we have also applied this regimen for high-grade STS since 1989. In previous reports, we showed that patients with high-grade soft tissue sarcomas (n=36 in K1 and K2 protocol, n=17 in K3 protocol) had a favourable response to caffeine-potentiated chemotherapy (73% of overall objective response rate in K1 and 2, 71% in K3 protocol), and had a beneficial effect on overall survival at 5 years (81% of stage II patients in K1 and 2 protocol) (8, 9). We also observed the efficacy of caffeine-potentiated chemotherapy in five cases of metastatic carcinoma and lymphoma of bone and soft tissue (25). These were breast, lung and gastric cancer, clear cell adenocarcinoma and diffuse large B-cell lymphoma.

There have been many reports of trials of adjuvant or neoadjuvant chemotherapy using different combinations of drugs for treatment of high-grade STS. Eilber *et al.* (7) treated patients with high-grade STS with neoadjuvant chemotherapy using five different protocols (adriamycin-based chemotherapy either intra-arterially or intravenously, combined with preoperative radiation therapy). Although the local recurrence rate increased in the initial treatment group with reduced doses of radiation, their subsequent protocol with the addition of cis-platinum demonstrated a further reduction in local recurrence. Their final protocol with the addition of high-dose ifosfamide showed greater benefit. The percentage of histological response increased to 48% with the addition of ifosfamide as compared with 13% in all other protocols (7). They concluded that histological response is an independent predictor of both local recurrence and overall survival. This result coincides with our experience that histological response was a good predictor of the local recurrence rate. Meric *et al.* (5) treated high-grade STS using six different doxorubicin-based protocols. Their treatments obtained a partial response (PR) rate of 34% in radiographic response (5). They concluded that the radiographic response predicted improved local tumour control and overall survival rate. Their data also agreed with our results that clinical response was a predictor of improvement of overall survival. On the other hand, recent randomised trials using doxorubicin- or ifosfamide-based chemotherapy have explored the benefits of these protocols, but found no improvements in survival (26, 27).

Our trials of caffeine-potentiated chemotherapy for soft tissue sarcoma demonstrated a favourable clinical response (57.1%). In particular, patients with clear cell sarcoma showed a clinical response rate of 80%. The histological responders in stage II and III showed beneficial effects on local recurrence-free survival compared to non-responders ($p=0.004$). There was a significant difference in the distant metastasis-free survival in stage II and III between clinical responders and non-responders ($p=0.019$). Our overall survival rate of 80.1% at 5 years in stage II and III compares favourably with those reported for adjuvant chemotherapy for soft tissue sarcoma (3, 4, 6). The overall survival rate in clinical responders was significantly superior to that in non-responders at stage II and III ($p=0.014$). It is expected that the radiographic response is predictive of improved overall survival and distant tumor control. The histological response is also expected to be a predictor of improved local tumor control.

The limitation of this study was that the number of patients was small, and this was a nonrandomised prospective clinical study that did not include a control arm involving chemotherapy alone without caffeine. Therefore, it is difficult to assess whether caffeine definitively improved the survival of the patients who responded to caffeine-potentiated chemotherapy. Our results demonstrated the favourable response rate to chemotherapy and cumulative survival in stages II and III compared with those reported in any adjuvant chemotherapy for high-grade soft tissue sarcoma. However, further investigations and continued clinical trials – ideally, a randomised prospective study – are necessary to evaluate whether caffeine-potentiated chemotherapy contributes to improvement of the survival rate in patients with high-grade soft tissue sarcoma.

Conclusion

Caffeine-potentiated chemotherapy resulted in a favourable radiographic response and prolonged survival of patients at stages II and III. The radiographic response is predictive of improved distant tumour control at stages II and III and overall survival at all stages. The histological response is predictive of local tumour control at stages II and III. Further investigations and continuous clinical trials are needed and, if possible, should be performed with individual histology in a multi-institutional setting.

References

1 Eilber F, Giuliano A, Eckardt J, Patterson K, Moseley S and Goodnight J: Adjuvant chemotherapy for osteosarcoma: a randomized prospective trial. J Clin Oncol *5*: 21-26, 1987.

2 Jurgens H, Exner U, Gadner H, Harms D, Michaelis J, Sauer R, Treuner J, Voute T, Winkelmann W and Winkler K: Multidisciplinary treatment of primary Ewing's sarcoma of bone. A 6-year experience of a European Cooperative Trial. Cancer *61*: 23-32, 1988.

3 Pezzi CM, Pollock RE, Evans HL, Lorigan JG, Pezzi TA, Benjamin RS and Romsdahl MM: Preoperative chemotherapy for soft-tissue sarcomas of the extremities. Ann Surg *211*: 476-481, 1990.

4 Pisters PW, Patel SR, Varma DG, Cheng SC, Chen NP, Nguyen HT, Feig BW, Pollack A, Pollock RE and Benjamin RS: Preoperative chemotherapy for stage IIIB extremity soft tissue sarcoma: long-term results from a single institution. J Clin Oncol *15*: 3481-3487, 1997.

5 Meric F, Hess KR, Varma DG, Hunt KK, Pisters PW, Milas KM, Patel SR, Benjamin RS, Plager C, Papadopoulos NE, Burgess MA, Pollock RE and Feig BW: Radiographic response to neoadjuvant chemotherapy is a predictor of local control and survival in soft tissue sarcomas. Cancer *95*: 1120-1126, 2002.

6 Gortzak E, Azzarelli A, Buesa J, Bramwell VH, van Coevorden F, van Geel AN, Ezzat A, Santoro A, Oosterhuis JW, van Glabbeke M, Kirkpatrick A and Verweij J: A randomised phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma. Eur J Cancer *37*: 1096-1103, 2001.

7 Eilber FC, Rosen G, Eckardt J, Forscher C, Nelson SD, Selch M, Dorey F and Eilber FR: Treatment-induced pathologic necrosis: a predictor of local recurrence and survival in patients receiving neoadjuvant therapy for high-grade extremity soft tissue sarcomas. J Clin Oncol *19*: 3203-3209, 2001.

8 Tsuchiya H, Tomita K, Yamamoto N, Mori Y and Asada N: Caffeine-potentiated chemotherapy and conservative surgery for high-grade soft-tissue sarcoma. Anticancer Res *18*: 3651-3656, 1998.
9 Tsuchiya H, Yamamoto N, Asada N, Terasaki T, Kanazawa Y, Takanaka T, Nishijima H and Tomita K: Caffeine-potentiated radiochemotherapy and function-saving surgery for high-grade soft tissue sarcoma. Anticancer Res *20*: 2137-2143, 2000.
10 Tsuchiya H and Tomita K: The combined effect of anti-tumor agents with caffeine or calcium channel blockers on sarcoma cells by clonogenic assay. Nippon Gan Chiryo Gakkai Shi *22*: 1003-1012, 1987 (in Japanese).
11 Tsuchiya H and Tomita K: The combined effect of cisplatin and caffeine on human sarcoma cells *in vitro*. Gan To Kagaku Ryoho *14*: 3125-3130, 1987 (in Japanese).
12 Tomita K and Tsuchiya H: Enhancement of cytocidal and antitumor effect of cisplatin by caffeine in human osteosarcoma. Clin Ther *11*: 43-52, 1989.
13 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.
14 Greene FL, Page DL, Fleming ID, Fritz AG, Balch ChM, Haller DG and Morrow M (eds.): American Joint Committee on Cancer Staging Manual (6th ed.). Philadelphia: Springer, 2002.
15 Sobin LH and Wittekind Ch (eds.): TNM Classification of Malignant Tumors (5th ed.). New York: John Wiley & Sons Inc., 1997.
16 Kawahara M, Kagiyama H, Kanazawa Y, Tsuchiya H, Tomita K, Yokogawa K and Miyamoto K: Rapid determination method of caffeine and application to monitoring of caffeine-assisted chemotherapy. Biopharm Drug Dispos *25*: 61-67, 2004.
17 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: 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.
18 Kaplan EL and Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc *53*: 457-481, 1958.
19 Byfield JE, Murnane J, Ward JF, Calabro-Jones P, Lynch M and Kulhanian F: Mice, men, mustard and methylated xanthines: the potential role of caffeine and related drugs in the sensitization of human tumours to alkylating agents. Br J Cancer *43*: 669-683, 1981.
20 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.
21 Yasutake H, Tsuchiya H, Tomita K, Matsunaga T, Nikaido O and Mori T: Inhibitory effect of caffeine on potentially lethal damage repair in cisplatin-treated human osteosarcoma cells. Anticancer Res *15*: 831-837, 1995.
22 Tsuchiya H, Tomita K, Mori Y, Asada N, Morinaga T, Kitano S and Yamamoto N: Caffeine-assisted chemotherapy and minimized tumor excision for nonmetastatic osteosarcoma. Anticancer Res *18*: 657-666, 1998.
23 Tsuchiya H, Tomita K, Mori Y, Asada N and Yamamoto N: Marginal excision for osteosarcoma with caffeine assisted chemotherapy. Clin Orthop Relat Res *358*: 27-35, 1999.
24 Kanazawa Y, Tsuchiya H, Nonomura A, Takazawa K, Yamamoto N and Tomita K: Intentional marginal excision of osteosarcoma of the proximal fibula to preserve limb function. J Orthop Sci *8*: 757-761, 2003.
25 Hayashi M, Tsuchiya H, Yamamoto N, Karita M, Shirai T, Nishida H, Takeuchi A and Tomita K: Caffeine-potentiated chemotherapy for metastatic carcinoma and lymphoma of bone and soft tissue. Anticancer Res *25*: 2399-2405, 2005.
26 Frustaci S, Gherlinzoni F, De Paoli A, Bonetti M, Azzarelli A, Comandone A, Olmi P, Buonadonna A, Pignatti G, Barbieri E, Apice G, Zmerly H, Serraino D and Picci P: Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. J Clin Oncol *19*: 1238-1247, 2001.
27 Petrioli R, Coratti A, Correale P, D'Aniello C, Grimaldi L, Tanzini G, Civitelli S, Marsili S, Messinese S, Marzocca G, Pirtoli L and Francini G: Adjuvant epirubicin with or without Ifosfamide for adult soft-tissue sarcoma. Am J Clin Oncol *25*: 468-473, 2002.

Received March 20, 2007
Revised May 29, 2007
Accepted June 4, 2007