Cancer Chemother Pharmacol (2012) 69:635–642
DOI 10.1007/s00280-011-1742-5

ORIGINAL ARTICLE

Phase II study of weekly docetaxel and fixed dose rate gemcitabine in patients with previously treated advanced soft tissue and bone sarcoma

Eun Mi Lee · Sun Young Rha · Jeeyun Lee · Kyong Hwa Park · Jin-Hee Ahn

Received: 15 July 2011 / Accepted: 8 September 2011 / Published online: 30 September 2011
© Springer-Verlag 2011

Abstract
Purpose The purpose of this prospective multicenter phase II study was to evaluate the efficacy and toxicity of weekly docetaxel and fixed dose rate gemcitabine in patients with previously treated advanced soft tissue and bone sarcoma.
Methods Patients with advanced soft tissue or bone sarcoma, previously treated with ifosfamide and anthracycline-based chemotherapies, were treated with docetaxel (35 mg/m^2 over 60 min) and gemcitabine (1,000 mg/m^2 over 100 min) on days 1 and 8 of every 3-week cycle.
Results From September 2008 to August 2010, 30 patients were enrolled; 24 (80.0%) were men and median patient age was 45 years (range 17–70 years). The patients received a total of 136 cycles of therapy (median 4 cycles per patient; range 1–15 cycles). Of these 30 patients, none achieved complete response (CR) and 5 achieved a partial response (PR), making the overall response rate 16.7% (95% CI, 2.5–30.8%). Twelve patients had stable disease (SD), resulting in tumor control (CR or PR or SD) in 17 of 30 patients (56.7%). Median progression-free survival was 2.5 months (range 0.8–15.3 months), and median overall survival was 8.4 months (range 1.4–22.3 months). Grade 3 or 4 neutropenia, thrombocytopenia, and anemia were observed in 17 (56.7%), 13 (43.4%), and 4 (13.3%) patients, respectively. None of these patients, however, had febrile neutropenia or bleeding events, and all non-hematologic toxicities were manageable.
Conclusions The combination of weekly docetaxel and fixed dose rate gemcitabine was tolerable and may be an active regimen in patients with previously treated advanced sarcoma.

Keywords Weekly docetaxel · Gemcitabine · Sarcoma · Survival

E. M. Lee · J.-H. Ahn (✉)
Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Pungnap-Dong Songpa-Gu, Seoul 138-736, Korea
e-mail: drjiny@amc.seoul.kr

S. Y. Rha
Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea

J. Lee
Division of Hematology and Oncology, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

K. H. Park
Division of Hematology and Oncology, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea

Introduction

Soft tissue sarcomas (STS) are heterogeneous malignancies originated from mesenchymal tissues and account for less than 1% of all new cancers in the United States annually [1]. Anthracycline and ifosfamide, either alone or in combination, have served as the backbone of treatment for several decades [2]. Once advanced sarcoma becomes resistant to the first-line therapy with these two drugs, however, subsequent chemotherapeutic options are limited.

Docetaxel and gemcitabine as a single agent have been tested as a salvage therapy in patients with advanced STS [3–12]. Docetaxel, which is usually administered as a 1-h infusion once every 3 weeks, showed a 17% response rate as the second-line therapy in patients with advanced STS [9].

In a follow-up randomized phase II study, however, first- and second-line docetaxel did not show any response [11]. Nevertheless, angiosarcoma has been shown sensitive to taxanes, although most trials tested paclitaxel [13].

Gemcitabine remains a therapeutic option for patients with metastatic sarcoma, especially for those with leiomyosarcoma who cannot tolerate combination chemotherapy. A randomized phase II trial in patients with pancreatic cancer found that gemcitabine might have greater activity when given as a fixed dose rate (FDR) infusion (10 mg/m^2/min) than as a bolus infusion over 30 min, in that FDR infusion can maximize the amount of gemcitabine triphosphate that can accumulate intracellularly in a given time period [14]. A trial of FDR infusion of gemcitabine in patients with sarcoma showed that the pharmacodynamics of this agent were consistent with those observed in patients with pancreatic cancer [5].

Although docetaxel or gemcitabine as a single agent has minimal activity, their combination has been shown effective in patients with advanced sarcoma [15–19]. For example, the combination of FDR gemcitabine and docetaxel showed a 53% response rate and a median time to progression of 5.6 months in patients with metastatic leiomyosarcoma [15]. This combination regimen was also found to be active in other histological subtypes of sarcoma [16–19]. This combination, however, may be associated with significant toxicities, such as thrombocytopenia and neutropenia. The observed toxicity profile in patients given weekly docetaxel has been found to be more favorable, with a lower incidence of myelosuppression, than the standard 3-week cycle [20]. Little is known, however, about the toxicity profile of weekly docetaxel plus gemcitabine in patients with advanced sarcoma.

We therefore evaluated the efficacy and safety of weekly docetaxel plus FDR gemcitabine in patients with advanced soft tissue or bone sarcoma, who had been previously treated with chemotherapy regimens containing anthracycline and ifosfamide.

Patients and methods

Eligibility criteria

Patients with histologically confirmed recurrent, metastatic, or unresectable soft tissue sarcoma or bone sarcoma were enrolled. All patients had been previously treated and failed anthracycline and ifosfamide-based chemotherapies afterward; had unidimensionally measurable lesions; were >16 years; had a life expectancy ≥3 months; had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2; and had adequate hematologic (neutrophil ≥1,500/mm^3 and platelet ≥100,000/mm^3), renal (serum creatinine ≤1.5 mg/dl), and hepatic (bilirubin ≤2 mg/dl, transaminases ≤3 times the upper normal limit [UNL] or <5 times for patients with liver metastases, serum alkaline phosphatase <2.5 times the UNL, or <5 times if liver metastases were present, or <10 times if bone metastases were present) function. Patients were excluded if resectable lung metastasis was present, CNS metastasis was present, or they were pregnant or lactating.

Physical examination, ECOG PS, laboratory test, and echocardiography or multigated acquisition (MUGA) scan were performed in the screening visit. Initial work-up for metastases included chest radiography, chest and abdominal computed tomography (CT), and bone scan, if bone metastasis was clinically suspected.

The study was approved by the Institutional Review Board of each participating centers, and all patients provided written informed consent.

Study design

Patients received intravenous gemcitabine, 1,000 mg/m^2, and intravenous docetaxel, 35 mg/m^2, on days 1 and 8 every 21 days. Gemcitabine was administered at 10 mg/m^2/min, and docetaxel was administered as a continuous infusion over 1 h. Patients were premedicated with 8 mg of dexamethasone, starting the night before each docetaxel infusion and ending the evening of the day after chemotherapy, for a total of 6 doses per docetaxel infusion. All patients received full supportive care, including blood product transfusions, antibiotics, and antiemetics as appropriate. Use of the prophylactic hematopoietic growth factors may be allowed to prevent neutropenia. Treatment was continued until disease progression or unacceptable toxicities, or discontinuation by the patients.

Toxicities were evaluated before days 1 and 8 of each treatment cycle according to the National Cancer Institute of Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 3.0. The next treatment cycle could be started only when ANC was ≥1,500/mm^3, platelet was ≥75,000/mm^3, and all non-hematologic toxicities had been reduced to grade 1 or less. The doses of gemcitabine and docetaxel were reduced to 75% each in patients who experienced febrile neutropenia, grade 4 neutropenia lasting >7 days, grade 3 or 4 thrombocytopenia, or grade 3 or 4 non-hematologic toxicities, except for nausea, vomiting, and alopecia. Weekly doses of gemcitabine and docetaxel on day 8 were reduced to 75%, if ANC was between 1,000 and 1,500/mm^3 or platelet was between 50,000 and 75,000/mm^3, and doses of both were omitted when ANC was <1,000/mm^3 or platelet was <50,000/mm^3.

Complete blood counts (CBC) and blood chemistry tests were performed before days 1 and 8 of each treatment cycle, and physical examinations were carried out before

every cycle. Tumor size was measured radiologically every 2 cycles until disease progression. Tumor response was classified by Response Evaluation Criteria in Solid tumor (RECIST) guideline.

Statistical analysis

The primary end-point was response rate, with secondary end-points including toxicity profile, progression-free survival (PFS), and overall survival (OS). According to Simon's two-stage phase II design with α and β errors of 0.05 and 0.20, respectively, a minimum of 13 patients were required to terminate the study of the first stage as early as possible if the response rate was $\leq$5%. If $\leq$3 responses in 27 patients were observed by the end of second stage, then no further investigation would be warranted. Since we had expected non-compliance rate of 10%, the planned sample size was 30 patients.

The Kaplan–Meier method was used to estimate the survival, and differences were analyzed by the log-rank test. Progression-free survival (PFS) was measured from the first day of chemotherapy until disease progression or death. Overall survival (OS) was measured from the first day of chemotherapy until death of any cause. Patient characteristics and toxicities were evaluated by descriptive methods. All statistical analyses were performed using the SPSS software (version 14.0), and $P < 0.05$ was defined as statistically significant.

Results

Patient characteristics

From September 2008 to October 2009, 30 patients were enrolled. Their characteristics are summarized in Table 1. Sixteen patients (53.3%) were initially diagnosed with metastatic disease, and 14 (46.7%) with recurrent disease. Median age at the start of chemotherapy was 45 years old (range 17–70 years). PS at the time of chemotherapy was ECOG 0 in 10 patients (33.3%), ECOG 1 in 18 (60.0%), and ECOG 2 in 2 (6.7%). Seven patients had Ewing's sarcoma or primitive neuroectodermal tumor (PNET), 4 had leiomyosarcoma, 3 each had liposarcoma, fibrosarcoma, and angiosarcoma, 2 each had osteosarcoma, synovial sarcoma, and pleomorphic sarcoma, and 1 each had malignant fibrous histiocytoma (MFH), rhabdomyosarcoma, hemangiopericytoma, and high-grade undifferentiated sarcoma. Primary tumors were located in the extremity/trunk of 12 patients and in the retroperitoneum/abdomen of 16. Of the 4 leiomyosarcomas, 3 originated from the retroperitoneum and 1 from visceral organs. The most common metastatic site was lung ($n = 18$, 60%), followed by the liver ($n = 10$, 33.3%), lymph nodes ($n = 8$, 26.7%), peritoneum ($n = 4$, 13.3%), and pleura ($n = 4$, 13.3%). All patients had previously received at least first line of chemotherapy containing anthracyclines and ifosfamide, separately or together. Anthracycline and ifosfamide had been used as adjuvant and/or neoadjuvant chemotherapy in 11 patients.

Table 1 Patient characteristics

Characteristics	No. of patients (%)
Soft tissue/bone sarcoma	27 (90.0)/3 (10.0)
Age, years [median (range)]	45 (17–70)
Gender male/female	24 (80.0)/6 (20.0)
ECOG PS 0/1/2	10 (33.3)/18 (60.0)/2 (6.7)
Histology	
Ewing' sarcoma/PNET	7 (23.3)
Leiomyosarcoma	4 (13.3)
Liposarcoma	3 (10.0)
Fibrosarcoma	3 (10.0)
Angiosarcoma	3 (10.0)
Osteosarcoma	2 (6.7)
Synovial sarcoma	2 (6.7)
Pleomorphic sarcoma	2 (6.7)
Others*	4 (13.3)
Primary tumor site	
Extremities/trunk	12 (40.0)
Retroperitoneum/abdomen	16 (53.5)
Others	2 (6.7)
No. of metastatic site 1/2/3	14 (46.6)/9 (30.0)/7 (23.3)
Lung metastasis	18 (60.0)
Liver metastasis	10 (33.3)
Previous chemotherapy	
Line of chemotherapy regimen 1/2/≥3	12(40.0)/11 (36.7)/7(33.3)

ECOG Eastern Cooperative Oncology Group, *PS* performance status, *PNET* primitive neuroectodermal tumor

* Others included 1 patient each with malignant fibrous histiocytoma, rhabdomyosarcoma, hemangiopericytoma, and high-grade undifferentiated sarcoma

Treatment and toxicity

The 30 patients received a total of 136 cycles of chemotherapy (median 4 cycles, range 1–15 cycles). Four patients received only 1 cycle of chemotherapy each due to disease progression. The relative dose intensities per cycle were 83.1% for both gemcitabine (554 mg/m^2/week) and docetaxel (20 mg/m^2/week). None received prophylactic hematopoietic growth factor.

Toxicity profiles are shown in Table 2. The most common grade 3 or 4 toxicity was neutropenia (56.7%). However, febrile neutropenia was not observed. Rates of

Table 2 Maximal toxicity profile per patient (according to NCI-CTCAE ver. 3.0) [*n* (%)]

	1	2	3	4
Hematologic				
Anemia	6 (20.0)	16 (53.3)	3 (10.0)	1 (3.3)
Leucopenia	3 (10.0)	9 (30.0)	6 (20.0)	6 (20.0)
Neutropenia	1 (3.3)	4 (13.3)	9 (30.0)	8 (26.7)
Thrombocytopenia	1 (3.3)	9 (30.0)	8 (26.7)	5 (16.7)
Febrile neutropenia	0	0	0	0
Non-hematologic				
AST/ALT elevation	7 (23.3)	0	0	0
Hyperbilirubinemia	1 (3.3)	0	1 (3.3)	0
Nausea	7 (23.3)	0	0	0
Vomiting	2 (6.7)	0	0	0
Anorexia	8 (26.7)	5 (16.7)	0	0
Mucositis/stomatitis	6 (20.0)	0	0	0
Fatigue/weakness	9 (30.0)	4 (13.3)	0	0
Myalgia	7 (23.3)	0	0	0
Alopecia	6 (20.0)	5 (16.7)	0	0
Diarrhea	3 (10.0)	2 (6.7)	1 (3.3)	0
Edema	4 (13.3)	2 (6.7)	1 (3.3)	0
Peripheral neuropathy	6 (20.0)	2 (6.7)	1 (3.3)	0
Hemorrhage	2 (6.7)	0	1 (3.3)	0
Infection	0	1 (3.3)	1 (3.3)	0
Fever	4 (13.3)	0	0	0
Nail change	1 (3.3)	2 (6.7)	0	0
Rash	1 (3.3)	1 (3.3)	1 (3.3)	0

NCI-CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

grade 3 or 4 anemia and thrombocytopenia were 13.3 and 43.4%, respectively. Grade 3 non-hematologic toxicities included hyperbilirubinemia (3.3%), diarrhea (3.3%), edema (3.3%), peripheral neuropathy (3.3%), hemorrhage (3.3%), infection (3.3%), and rash (3.3%). Dose reduction was required in seven patients due to severe and prolonged cytopenia and in one patient due to grade 3 edema and diarrhea. Following dose reductions, severe toxicities were uncommon and the next cycle of chemotherapy was generally tolerable. One patient discontinued chemotherapy due to grade 3 neuropathy and edema. Treatment-related death occurred in one patient, who may have died of pneumonia, but it was not associated with neutropenia.

Response evaluation

Of the 30 patients, 26 were evaluable for response after 2 cycles, whereas four patients received only 1 cycle of chemotherapy each because of disease progression. None of these patients had shown complete response (CR), although 5 had shown partial response (PR), for a total response rate of 16.7% (95% confidence interval [CI], 2.5–30.8%). All patients who achieved PR had been administered 8 or more cycles of chemotherapy (8 cycles in 4 patients and 9 in 1). Of these 5 patients, 4 had only lung metastases and 1 had lung and pleural metastases. In addition, 12 patients had stable disease (SD), making the tumor control rate (CR + PR + SD) 56.7% (95% CI, 38.7–75.5%). Of the 12 patients with SD, 3 had received 10 or more cycles of chemotherapy (10 cycles in 2 patients and 15 in 1). Responses according to histological subtypes are listed in Table 3. Two patients with angiosarcoma and 1 each with osteosarcoma, Ewing's sarcoma, and hemangiopericytoma achieved PR. Of the 3 patients with angiosarcoma, 2 achieved PR and 1 had SD. All 4 patients with leiomyosarcoma had SD.

Survival

The 30 patients had median PFS of 2.5 months (range 0.8–15.3 months). The progression-free rates (PFR) at 3 and 6 months were 47 and 20%, respectively (Fig. 1a). At a median follow-up of 13.9 months (range, 10.1–22.3 months), median OS was 8.4 months (range 1.4–22.3 months), and the 1-year survival rate was 33% (Fig. 1b). Survival was significantly correlated with response to treatment. Median PFS and OS were 4.8 months (range 2.5–15.3 months) and 15.9 months (range 5.7–22.3 months),

Table 3 Tumor response per histological subtype by RECIST

Histology	No. of patients	PR	SD	PD	NE
Ewing's sarcoma/PNET	7	1	2	2	2
Leiomyosarcoma	4	0	4	0	0
Liposarcoma	3	0	2	1	0
Fibrosarcoma	3	0	0	2	1
Angiosarcoma	3	2	1	0	0
Osteosarcoma	2	1	0	1	0
Synovial sarcoma	2	0	1	1	0
Pleomorphic sarcoma	2	0	1	1	0
MFH	1	0	1	0	0
Rhabdomyosarcoma	1	0	0	0	1
Hemangiopericytoma	1	1	0	0	0
High-grade undifferentiated sarcoma	1	0	0	1	0
Total	30	5	12	9	4

RECIST Response evaluation criteria in solid tumor, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *PNET* primitive neuroectodermal tumor, *MFH* malignant fibrous histiocytoma

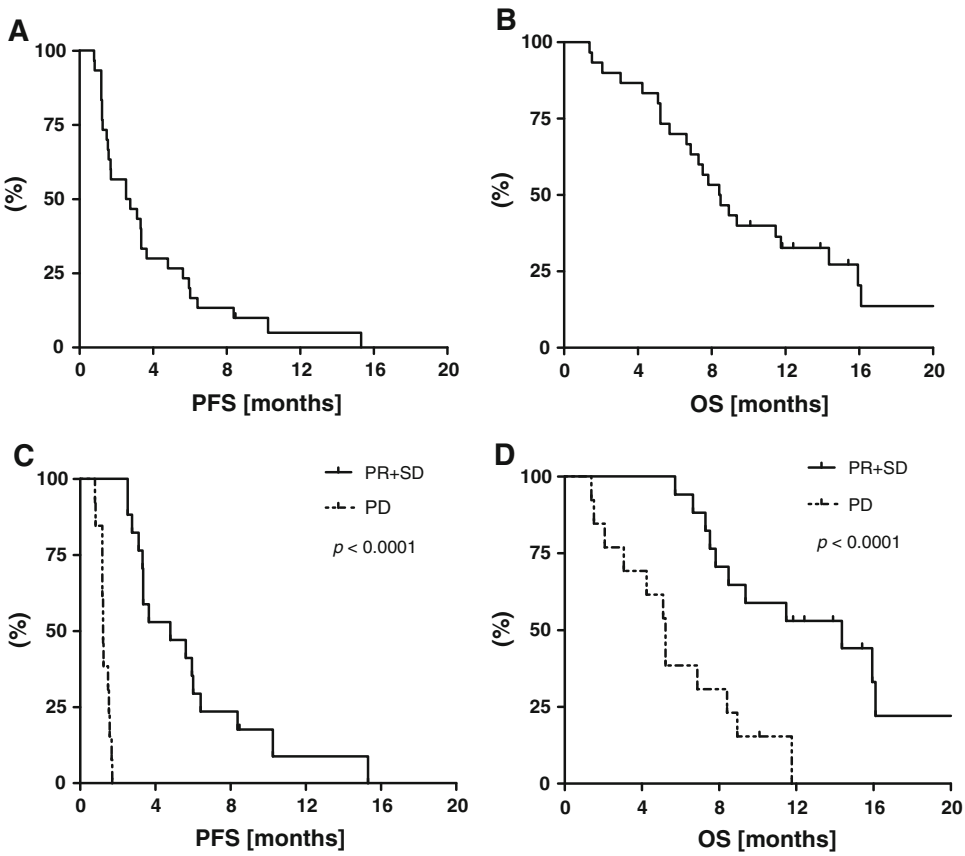

Fig. 1 Kaplan–Meier estimates of survival. **a** PFS of all patients. **b** OS of all patients. **c** PFS in patients with PR + SD versus PD. **d** OS in patients with PR + SD versus PD

respectively, in patients achieving disease control (CR + PR + SD), compared with 1.2 months (range 0.8–1.7 months) and 5.2 months (range 1.4–11.8 months), respectively, in those not achieving disease control (Fig. 1c, d; $P < 0.001$). ECOG PS, age, and lung metastases were not correlated with either PFS or OS. Of the 4 patients with leiomyosarcoma, 3 survived at least 12 months.

Discussion

The current standard chemotherapy regimens for advanced or metastatic sarcoma include anthracycline and/or ifosfamide, but therapeutic options are limited for patients with tumors refractory to anthracycline and ifosfamide. This prospective phase II trial showed that the combination of weekly docetaxel and fixed dose rate gemcitabine as a

salvage therapeutic option had an overall response rate of 16.7% and a tolerable toxicity profile.

The combination of FDR gemcitabine and docetaxel has been shown to be highly active in patients with uterine leiomyosarcoma [15, 21, 22]. For example, a phase II randomized trial of FDR gemcitabine and docetaxel in 34 patients with unresectable leiomyosarcomas predominately originated from uterus yielded a surprising response rate of 53% [15]. Several subsequent studies had showed that combinations of gemcitabine and docetaxel had antitumor activities, with response rates of 43% in patients with uterine leiomyosarcoma and 15–18% in patients with various subtypes of sarcoma [16–19]. We observed a response rate of 16.7%, although none of our patients had uterine leiomyosarcoma.

Except for uterine leiomyosarcoma, it is not clear which specific histological subtypes of sarcoma are more sensitive to this combination regimen. Although our study included 4 patients with leiomyosarcoma, none of these tumors was of uterine origin; rather, they originated from the retroperitoneum and visceral GI tract. It is also unclear if non-uterine leiomyosarcomas are as sensitive to the combination of gemcitabine and docetaxel as uterine leiomyosarcomas. All 4 of our patients with leiomyosarcoma showed SD, with 2 maintaining SD for over 6 months. In current study, PR was achieved by patients with angiosarcoma, Ewing's sarcoma/PNET, osteosarcoma, and hemangiopericytoma. Of the 3 patients with angiosarcoma, 2 achieved PR and 1 had SD, comparable to finding that 3 of 4 patients with angiosarcoma achieved PR [16] and suggesting that angiosarcoma is sensitive to the combination of gemcitabine and docetaxel. It is unclear, however, whether this sensitivity is due to the synergistic effect of the combination regimen, because angiosarcoma has been reported to be relatively sensitive to taxanes [13, 23, 24].

Although overall response was considered as the effective end-point, evaluations of tumor response by volume reduction in soft tissue sarcomas are limited. Because tumor tissue may be replaced by necrotic or fibrotic tissue, a substantial reduction in viable tumor cell volume may not result in a marked decrease in overall tumor volume [25]. Disease stabilization seems to be relevant in patients with advanced sarcoma because patients who exhibit prolonged SD often have similar clinical outcomes as those who achieve PR [25–27]. We observed that the disease stabilization rate, the combination of SD, PR, and CR, was 56.7%. Three patients who never achieved PR showed prolonged disease stabilization over 6 months and received 10 or more cycles of chemotherapy, suggesting that disease stabilization is beneficial, at least in some types of advanced soft tissue sarcoma. Treatment with FDR gemcitabine and docetaxel may be continued in patients with good disease control, whereas the duration of anthracycline-based treatment is limited by the cumulative risk of cardiotoxicity.

Progression-free rate (PFR) may be a more reliable endpoint in phase II studies of non-cytotoxic agents or in situations where a low response rate is expected [28]. That study suggested that a 3-month PFR $\geq$ 40% for second-line therapy would be indicative of drug activity. We found that the 3-month PFR in our patients was 47%. The median OS we observed, 8.4 months, was lower than the almost 12 months observed in other studies [16, 17, 19]. However, few of our patients had a subsequent therapeutic option after failure of this combination regimen, because all of these patients had previously failed treatments with anthracycline and ifosfamide.

The optimal dose schedules for gemcitabine plus docetaxel combination chemotherapy have not been determined yet. Weekly docetaxel is well tolerated in patients with other tumor types, with minimal myelosuppression and the added benefit of maintaining dose intensity [20, 29, 30]. In a randomized phase III trial in lung cancer patients, the rate of febrile neutropenia was significantly lower in patients treated with weekly than with 3 weekly docetaxel (0.8% vs. 7.8%) [20]. Our patients were regarded as being at high risk for severe neutropenia because all had been previously treated with more than 2 myelotoxic agents. We, therefore, administered FDR gemcitabine 1,000 mg/m^2 and docetaxel 35 mg/m^2, on days 1 and 8 of every 21-day cycle, a regimen shown safe and effective in a phase I study of patients with pancreatic cancer [31].

We found that this regimen had an acceptable toxicity profile, with rates of grade 3 or 4 neutropenia and thrombocytopenia of 56.7 and 43.3%, respectively, and no cases of febrile neutropenia. In previous trials, the rate of febrile neutropenia with this regimen was 0–6% [15, 18, 21, 22]. While patients in other such studies routinely received prophylactic hematopoietic growth factor, our patients were not so treated. We also found that the non-hematologic toxicity profile of this regimen was manageable, with only 1 patient requiring a dose reduction due to grade 3 edema and diarrhea. Severe pulmonary toxicity has also been reported in patients treated with the combination of gemcitabine and docetaxel [32]. Of our 30 patients, 1 patient died during treatment, possibly due to pneumonia. Chest radiographs of this patients showed diffuse ground glass opacities on both lungs, suggesting that pneumonia in this patient was consistent with underlying chemotherapy-induced lung injury.

In conclusion, we found that the combination of gemcitabine and weekly docetaxel was active in patients with advanced sarcomas refractory to anthracyclines and ifosfamide. This regimen also showed a good toxicity profiles, with low rates of myelosuppression and non-hematologic

toxicities. However, survival remains still poor, indicating the need for novel treatment options to improve the outcome of patients with advanced sarcoma.

Acknowledgments This study was supported by sanofi-aventis Korea and Chong Kun Dang Pharm with the sample (Docetaxel and Gemcitabine) supply.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ (2009) Cancer statistics, 2009. CA Cancer J Clin 59(4):225–249
2. Clark MA, Fisher C, Judson I, Thomas JM (2005) Soft-tissue sarcomas in adults. N Engl J Med 353(7):701–711
3. Merimsky O, Meller I, Flusser G, Kollender Y, Issakov J, Weil-Ben-Arush M, Fenig E, Neuman G, Sapir D, Ariad S, Inbar M (2000) Gemcitabine in soft tissue or bone sarcoma resistant to standard chemotherapy: a phase II study. Cancer Chemother Pharmacol 45(2):177–181
4. Spath-Schwalbe E, Genvresse I, Koschuth A, Dietzmann A, Grunewald R, Possinger K (2000) Phase II trial of gemcitabine in patients with pretreated advanced soft tissue sarcomas. Anticancer Drugs 11(5):325–329
5. Patel SR, Gandhi V, Jenkins J, Papadopolous N, Burgess MA, Plager C, Plunkett W, Benjamin RS (2001) Phase II clinical investigation of gemcitabine in advanced soft tissue sarcomas and window evaluation of dose rate on gemcitabine triphosphate accumulation. J Clin Oncol 19(15):3483–3489
6. Svancarova L, Blay JY, Judson IR, van Hoesel QG, van Oosterom AT, le Cesne A, Keizer HJ, Hermans C, van Glabbeke M, Verweij J, Hogendoorn PC, Nielsen OS (2002) Gemcitabine in advanced adult soft-tissue sarcomas. A phase II study of the EORTC soft tissue and bone sarcoma group. Eur J Cancer 38(4):556–559
7. Okuno S, Ryan LM, Edmonson JH, Priebat DA, Blum RH (2003) Phase II trial of gemcitabine in patients with advanced sarcomas (E1797): a trial of the Eastern Cooperative Oncology Group. Cancer 97(8):1969–1973
8. Hartmann JT, Oechsle K, Huober J, Jakob A, Azemar M, Horger M, Kanz L, Bokemeyer C (2006) An open label, non-comparative phase II study of gemcitabine as salvage treatment for patients with pretreated adult type soft tissue sarcoma. Invest New Drugs 24(3):249–253. doi:10.1007/s10637-005-3537-1
9. van Hoesel QG, Verweij J, Catimel G, Clavel M, Kerbrat P, van Oosterom AT, Kerger J, Tursz T, van Glabbeke M, van Pottelsberghe C (1994) Phase II study with docetaxel (Taxotere) in advanced soft tissue sarcomas of the adult. EORTC Soft Tissue and Bone Sarcoma Group. Ann Oncol 5(6):539–542
10. Edmonson JH, Ebbert LP, Nascimento AG, Jung SH, McGaw H, Gerstner JB (1996) Phase II study of docetaxel in advanced soft tissue sarcomas. Am J Clin Oncol 19(6):574–576
11. Verweij J, Lee SM, Ruka W, Buesa J, Coleman R, van Hoessel R, Seynaeve C, di Paola ED, van Glabbeke M, Tonelli D, Judson IR (2000) Randomized phase II study of docetaxel versus doxorubicin in first- and second-line chemotherapy for locally advanced or metastatic soft tissue sarcomas in adults: a study of the European organization for research and treatment of cancer soft tissue and bone sarcoma group. J Clin Oncol 18(10):2081–2086
12. Kostler WJ, Brodowicz T, Attems Y, Hejna M, Tomek S, Amann G, Fiebiger WC, Wiltschke CH, Krainer M, Zielinski CC (2001) Docetaxel as rescue medication in anthracycline- and ifosfamide-resistant locally advanced or metastatic soft tissue sarcoma: results of a phase II trial. Ann Oncol 12(9):1281–1288
13. Fury MG, Antonescu CR, Van Zee KJ, Brennan MF, Maki RG (2005) A 14-year retrospective review of angiosarcoma: clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. Cancer J 11(3):241–247
14. Tempero M, Plunkett W, Ruiz Van Haperen V, Hainsworth J, Hochster H, Lenzi R, Abbruzzese J (2003) Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 21(18):3402–3408
15. Hensley ML, Maki R, Venkatraman E, Geller G, Lovegren M, Aghajanian C, Sabbatini P, Tong W, Barakat R, Spriggs DR (2002) Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol 20(12):2824–2831
16. Leu KM, Ostruszka LJ, Shewach D, Zalupski M, Sondak V, Biermann JS, Lee JS, Couwlier C, Palazzolo K, Baker LH (2004) Laboratory and clinical evidence of synergistic cytotoxicity of sequential treatment with gemcitabine followed by docetaxel in the treatment of sarcoma. J Clin Oncol 22(9):1706–1712
17. Bay JO, Ray-Coquard I, Fayette J, Leyvraz S, Cherix S, Piperno-Neumann S, Chevreau C, Isambert N, Brain E, Emile G, Le Cesne A, Cioffi A, Kwiatkowski F, Coindre JM, Bui NB, Peyrade F, Penel N, Blay JY (2006) Docetaxel and gemcitabine combination in 133 advanced soft-tissue sarcomas: a retrospective analysis. Int J Cancer 119(3):706–711. doi:10.1002/ijc.21867
18. Maki RG, Wathen JK, Patel SR, Priebat DA, Okuno SH, Samuels B, Fanucchi M, Harmon DC, Schuetze SM, Reinke D, Thall PF, Benjamin RS, Baker LH, Hensley ML (2007) Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. J Clin Oncol 25(19):2755–2763
19. Ebeling P, Eisele L, Schuett P, Bauer S, Schuette J, Moritz T, Seeber S, Flasshove M (2008) Docetaxel and gemcitabine in the treatment of soft tissue sarcoma—a single-center experience. Onkologie 31(1–2):11–16
20. Camps C, Massuti B, Jimenez A, Maestu I, Gomez RG, Isla D, Gonzalez JL, Almenar D, Blasco A, Rosell R, Carrato A, Vinolas N, Batista N, Giron CG, Galan A, Lopez M, Blanco R, Provencio M, Diz P, Felip E (2006) Randomized phase III study of 3-weekly versus weekly docetaxel in pretreated advanced non-small-cell lung cancer: a Spanish lung cancer group trial. Ann Oncol 17(3):467–472
21. Hensley ML, Blessing JA, Degeest K, Abulafia O, Rose PG, Homesley HD (2008) Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a gynecologic oncology group phase II study. Gynecol Oncol 109(3):323–328
22. Hensley ML, Blessing JA, Mannel R, Rose PG (2008) Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a gynecologic oncology group phase II trial. Gynecol Oncol 109(3):329–334
23. Fata F, O'Reilly E, Ilson D, Pfister D, Leffel D, Kelsen DP, Schwartz GK, Casper ES (1999) Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. Cancer 86(10):2034–2037
24. Isogai R, Kawada A, Aragane Y, Tezuka T (2004) Successful treatment of pulmonary metastasis and local recurrence of angiosarcoma with docetaxel. J Dermatol 31(4):335–341
25. Verweij J (2008) Other endpoints in screening studies for soft tissue sarcomas. Oncologist 13(Suppl 2):27–31
26. Blay JY, van Glabbeke M, Verweij J, van Oosterom AT, Le Cesne A, Oosterhuis JW, Judson I, Nielsen OS (2003) Advanced soft-tissue sarcoma: a disease that is potentially curable for a subset of patients treated with chemotherapy. Eur J Cancer 39(1):64–69

27. Le Cesne A, Blay JY, Judson I, Van Oosterom A, Verweij J, Radford J, Lorigan P, Rodenhuis S, Ray-Coquard I, Bonvalot S, Collin F, Jimeno J, Di Paola E, Van Glabbeke M, Nielsen OS (2005) Phase II study of ET-743 in advanced soft tissue sarcomas: a European organisation for the research and treatment of cancer (EORTC) soft tissue and bone sarcoma group trial. J Clin Oncol 23(3):576–584
28. Van Glabbeke M, Verweij J, Judson I, Nielsen OS (2002) Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. Eur J Cancer 38(4):543–549
29. Hainsworth JD, Burris HA, Erland JB, Thomas M, Greco FA (1998) Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. J Clin Oncol 16(6):2164–2168
30. Burstein HJ, Manola J, Younger J, Parker LM, Bunnell CA, Scheib R, Matulonis UA, Garber JE, Clarke KD, Shulman LN, Winer EP (2000) Docetaxel administered on a weekly basis for metastatic breast cancer. J Clin Oncol 18(6):1212–1219
31. Meyer F, Lueck A, Hribaschek A, Lippert H, Ridwelski K (2004) Phase I trial using weekly administration of gemcitabine and docetaxel in patients with advanced pancreatic carcinoma. Chemotherapy 50(6):289–296
32. Dunsford ML, Mead GM, Bateman AC, Cook T, Tung K (1999) Severe pulmonary toxicity in patients treated with a combination of docetaxel and gemcitabine for metastatic transitional cell carcinoma. Ann Oncol 10(8):943–947