photon radiotherapy, and is deemed a feasible and effective treatment modality for curative high-dose irradiation to the tumor volume without any increase in normal tissue toxicity.[24] We therefore used proton radiotherapy in cases in which the potential for damage to surrounding critical organs with photon radiotherapy could not be ruled out. To facilitate prevention to surrounding critical organs, we adopted induction chemotherapy with ID for locoregional ONB. Thus, ID was followed by photon radiation therapy of 66 Gy in 2-Gy fractions in 1 of 7 locoregional ONB patients and by proton radiotherapy of 65 GyE in 2.5-GyE fractions in 6 patients. The patient receiving photon radiation achieved a CR, as did 4 of the 6 patients receiving proton radiotherapy, with the other 2 achieving PRs. At a median follow-up of 22.2 months, 6 of these 7 patients with locoregional ONB who received ID followed by definitive radiotherapy were still alive and the 2-year survival rate was 100%. These findings suggest that induction chemotherapy followed by definitive radiotherapy may be a promising nonsurgical treatment option for patients with locally advanced ONB.

In conclusion, chemotherapy with ID for both advanced and/or metastatic ONB was found to be safe and manageable. The response to ID was no better than expected, however, indicating that ONB requires a more active chemotherapy regimen. Induction chemotherapy followed by proton radiotherapy may be a promising treatment option for patients with locally advanced ONB and warrants further investigation.

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BRIEF COMMUNICATION

Outpatient management of low-risk febrile patients on paclitaxel and carboplatin for ovarian cancer

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Standard first-line chemotherapy for epithelial ovarian cancer consists of paclitaxel and carboplatin, given mainly in an outpatient setting in the USA and Europe, with interim clinic visits and blood tests. One serious potential complication of chemotherapy is febrile neutropenia as a manifestation of underlying infection. The purpose of this retrospective study was to evaluate the feasibility of outpatient management and risk assessment of febrile neutropenia by telephone interactions instead of clinic visits or blood tests.

Among 73 patients who underwent primary surgery for ovarian cancer at the National Cancer Center Hospital from 2005 to 2006, 38 were treated with paclitaxel (175–180 mg/m^2) and carboplatin (AUC5-6). Chemotherapy was administered intravenously every 21 days for up to 6 cycles. Adverse events occurring during therapy and up to 21 days after the last administration were graded according to the Common Terminology Criteria for Adverse Events (CTCA), version 3. Hematological and biochemical parameters were measured on day 1. Patients were educated regarding risk of fever prior to the first dose.

The Infectious Diseases Society of America (IDSA) neutropenic guidelines were followed for fever assessment and treatment [1]. Upon development of fever, a medical oncologist conducted a home telephone interview with the patient and assessed them using a scoring index from the Multinational Association of Supportive Care in Cancer (MASCC) used to stratify febrile neutropenia patients into risk categories [2]. The MASCC risk index includes burden of illness, blood pressure, chronic obstructive pulmonary disease, solid tumor diagnosis, previous fungal infection, dehydration, outpatient status, and age. If classified as low risk, ciprofloxacin was given empirically (1200 mg for 7 days). If high risk, patients were instructed to present to the clinic for evaluation and treatment. If fever persisted for longer than 3 days, the patients were reassessed by telephone. If patients were still febrile on day 8, they were again instructed to present to the clinic for evaluation.

A total of 207 treatment cycles were administered to 38 patients. Characteristics of the patients are presented in Table 1. Thirty-seven patients were treated with paclitaxel and carboplatin as first-line chemotherapy, and 1 patient with recurrent but platinum-sensitive disease was treated with paclitaxel and carboplatin as second-line therapy. The adverse events reported are presented in Table 2.

Three patients (8%) were determined to have low-risk fever; 2 had stage IC disease, and 1 had stage IV disease with pleural effusion preoperatively. All 3 had an MASCC risk index score less than 21 and were thus classified as low risk. Mean time to onset of febrile neutropenia was 12 days after chemotherapy (range, 7–19 days). All fevers resolved with ciprofloxacin and notably without granulocyte colony-stimulating factor (G-CSF) or office visit. Four patients required urgent hospitalization, with 3 cases due to ileus following surgery.

Prognosis in low-risk febrile neutropenia patients is generally good, particularly when the origin of the fever is unexplained. Between 70% and 80% of low-risk patients have fever of unknown origin

Table 1
Patient characteristics

Characteristics	No. of patients (n=38)
Age, median (range)	57 (37–73)
ECOG performance status	
0	29
1	6
2	2
3	1
Histology	
Serous	16
Endometrioid	5
Clear cell carcinoma	10
Mucinous	1
Mixed	2
Adenocarcinoma	4
Stage	
I	9
II	6
III	16
IV	6
Recurrent case	1

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Table 2
Toxicities experienced by patients given paclitaxel and carboplatin

Toxicity	No. of patients experiencing toxicities (n=38)			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic				
Neutropenia	7	8	8	3
Anemia	15	10	1	1
Thrombocytopenia	8	4	2	0
Non-hematologic				
Alopecia	0	38	–	–
Neuropathy				
Sensory	19	13	4	0
Motor	1	4	0	0
Arthritis	10	2	0	0
Myalgia	10	0	1	0
Hypersensitivity	10	0	1	0
Fatigue	7	2	0	0
Constipation	7	3	0	0
Nausea	6	2	0	0
Vomiting	2	0	1	0
Edema	4	0	0	0
Mucositis/stomatitis	3	0	0	0
Hepatitis	0	1	1	0
Anorexia	1	0	0	0

[2]. Consequently, it is important to stratify and define which patients are low risk. Elting et al. [3] determined that using a threshold of 21 or more for the MASCC risk index correctly identified patients who ultimately failed outpatient treatment and required hospitalization. In the present study, a threshold of 21 was also found to be reasonable to classify low risk patients.

Growth factors are not recommended for routine use to treat febrile or afebrile neutropenic patients in the 2002 IDSA guideline, because no study has demonstrated a decrease in infection-related mortality rates [1]. The incidence of febrile neutropenia with a paclitaxel and carboplatin regimen is generally reported to be less than 20%, thus failing to meet the criteria from American Society of Clinical Oncology guidelines for prophylactic growth factor use [4]. Consistent with this, in our study, 8% of patients with epithelial ovarian cancer receiving tri-weekly paclitaxel and carboplatin chemotherapy developed febrile neutropenia, with all cases of fever resolving with ciprofloxacin and without growth factors or clinic visit.

Hospital admission exposes patients to potential iatrogenic complications and drug-resistant nosocomial infections such as methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci. In fact, outpatient status is one of the positive characteristics in the scoring index for febrile neutropenia [2], and the risk of nosocomial infection with such bacteria would be reduced with outpatient management.

In the present study, none of the patients who underwent bowel resection or experienced ileus developed febrile neutropenia. Notably the incidence of ileus among 7 patients who underwent bowel resection (14%) was equivalent to patients who did not undergo bowel resection (10%). However, advanced ovarian cancer is frequently accompanied by peritoneal dissemination and ascites, which increases the risk and incidence of ileus. Risk assessment for ileus was included in the telephone evaluation, with specific inquiry for nausea, vomiting, and decreased oral intake.

Our results show that outpatient management of tri-weekly paclitaxel and carboplatin therapy appears to be safe and feasible for patients with epithelial ovarian cancer without clinic visits, blood tests, or routine administration of growth factors for neutropenia between courses. We emphasize the importance of close telephone contact with patients, patient education, and establishment of an emergency support system by hospital and medical staff.

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FROM THE ASCO-JSCO JOINT SYMPOSIUM

Isamu Okamoto

Overview of chemoradiation clinical trials for locally advanced non-small cell lung cancer in Japan

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Abstract The standard of care for unresectable stage III non-small cell lung cancer (NSCLC) is combined-modality therapy with both chemotherapy and thoracic radiation therapy (TRT). A phase III trial by the West Japan Lung Cancer Group revealed that the combination of mitomycin, vindesine, and cisplatin (MVP) with concurrent TRT yielded a median survival time of 16.6 months and a 5-year survival rate of 16% in patients with unresectable stage III NSCLC. Although evidence indicates that concurrent chemotherapy and TRT (chemoradiation) increases survival to a moderately greater extent than sequential therapeutic approaches, the optimal strategies for such concurrent treatment remain to be defined, and differ between full-dose systemic and low-dose radio-enhancing protocols. Two phase III trials have been initiated in Japan to address these issues and they have recently reported preliminary data. Early results of the Okayama Lung Cancer Study Group (OLCSG) trial, comparing chemoradiation based on divided docetaxel and cisplatin chemotherapy with MVP-based chemoradiation, have been reported. The West Japan Oncology Group (WJOG) is comparing the efficacy and toxicity of TRT and concurrent chemotherapy with either carboplatin-paclitaxel or carboplatin-irinotecan, followed by full-dose consolidation chemotherapy, with the efficacy and toxicity of MVP-based chemoradiation. Several phase I/II studies to test the optimal use of new agents such as S-1 (an oral anticancer drug combining tegafur, 5-chloro-2, 4-dihydroxypyridine, and potassium oxonate) and gefitinib (an inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor) are also ongoing. In addition, radiation dose intensification with three-dimensional planning approaches is currently under evaluation. A phase I clinical trial by WJOG to establish, prospectively, the maximum tolerated dose of three-dimensional hyperfractionated radiotherapy with concurrent weekly chemotherapy (carboplatin-paclitaxel) is thus currently under way. This overview of ongoing trials highlights new directions in the treatment of locally advanced NSCLC.

Key words Non-small cell lung cancer · Locally advanced · Chemoradiation

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Introduction

Lung cancer remains the most common cause of cancer-related mortality worldwide.[1] Non-small cell lung cancer (NSCLC) is a heterogeneous disease that accounts for around 80% of lung cancer cases, and about one-third of individuals with newly diagnosed NSCLC present with locally advanced disease not amenable to curative resection.[2] The American Society of Clinical Oncology guidelines for the treatment of unresectable stage III NSCLC recommend combined-modality therapy with platinum-based chemotherapy and definitive thoracic radiation therapy (TRT), particularly for patients with good performance status.[3] Recent clinical trials and a metaanalysis have shown that concurrent chemotherapy and radiotherapy (chemoradiation) affords outcomes superior to those of sequential therapy in patients with unresectable stage III NSCLC. This review addresses the current status of Japanese chemoradiation trials for unresectable locally advanced NSCLC and outlines potential directions for future investigations in this important area of clinical research. Strategies that also include surgical treatment protocols are not covered in this article.

Randomized controlled trials of chemoradiation based on newer platinum-based drug regimens

Data from several randomized controlled trials comparing the sequential administration of chemotherapy and radiotherapy with up-front concurrent chemoradiation in patients with unresectable stage III NSCLC are now available. One

of the first studies to demonstrate a difference in outcomes between these two approaches was conducted by the West Japan Lung Cancer Group, which compared split-course radiotherapy concurrent with mitomycin (8 mg/m^2), vindesine (3 mg/m^2), and cisplatin (80 mg/m^2) (MVP) with a sequential regimen of MVP followed by non-split-course radiotherapy.[4] The median survival time was significantly longer in patients receiving concurrent therapy than in those receiving sequential therapy (16.6 versus 13.3 months; $P = 0.03998$). The 5-year survival rate was also higher for the concurrently treated patients (16%) than for those receiving the sequential therapy (9%). Similarly, the Radiation Therapy Oncology Group (RTOG) 9410 trial in the United States compared two different concurrent regimens (cisplatin and vinblastine with conventional radiotherapy or cisplatin and oral etoposide with hyperfractionated radiotherapy) with a sequential regimen of cisplatin and vinblastine followed by radiation.[5] The median survival time was again significantly longer for patients receiving concurrent therapy than for those receiving sequential therapy (17.0 versus 14.6 months; $P = 0.038$). The overall 4-year survival rate was also superior for patients on the concurrent arm (21%) compared with the rate for those on the sequential arm (12%). These studies together provide evidence that up-front concurrent cisplatin-based chemoradiation should be the standard of care for patients with inoperable stage III NSCLC who have a good performance status.

There are some limitations in the application of the results of these pivotal phase III trials to current daily clinical practice, however, because the studies used old-generation cisplatin-based chemotherapy regimens including vindesine, vinblastine, and etoposide. In the past decade several active drugs, such as docetaxel, paclitaxel, irinotecan, gemcitabine, and vinorelbine, have emerged, and combinations of platinum with these newer drugs have proved to be more effective than old-generation combination chemotherapy in metastatic NSCLC.[6,7] Although the data favor chemoradiation that is based on newer platinum-based regimens as the curative treatment of choice for patients with inoperable stage III NSCLC, phase III studies that convincingly demonstrate the benefit of newer drugs in chemoradiation are lacking. Whereas a full dose of the old-generation combination chemotherapy can be combined with concurrent radiotherapy,[4,5] a reduced-dose (weekly or daily administration) of new-generation chemotherapy must be used in combination with TRT.[8–11] Chemoradiation based on full-dose old-generation chemotherapy has not yet been directly compared with that based on reduced-dose new-generation chemotherapy. Well-designed multicenter clinical trials to determine how to integrate newer platinum-based regimens into chemoradiation protocols are thus urgently needed. Two Japanese phase III trials that address this issue are currently underway. The Okayama Lung Cancer Study Group (OLCSG) is conducting a phase III trial to compare the concurrent application of TRT and cisplatin and docetaxel with conventional MVP-based chemoradiation (Fig. 1).[12] On the basis of the corresponding previous phase I/II trial, the administration of both cisplatin (40 mg/m^2) and docetaxel (40 mg/m^2) is divided between

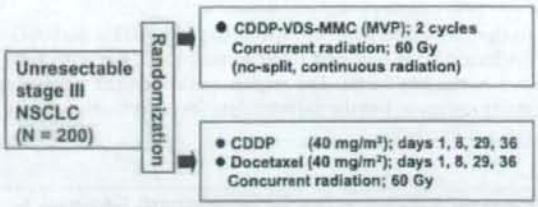

Fig. 1. Schema of the Okayama Lung Cancer Study Group (OLCSG) trial comparing chemoradiation regimens based on the administration of cisplatin (*CDDP*) and docetaxel, or based on *MVP* (mitomycin [*MMC*], vindesine [*VDS*], and cisplatin) in individuals with unresectable stage III non-small cell lung cancer (*NSCLC*)

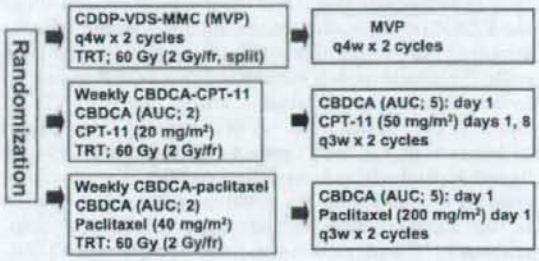

Fig. 2. Schema of the West Japan Oncology Group (WJOG) trial comparing chemoradiation regimens based either on the weekly administration of carboplatin (*CBDCA*) together with irinotecan (*CPT-11*) or paclitaxel, or based on MVP in individuals with unresectable stage III NSCLC. *TRT*, concurrent thoracic radiotherapy; *fr*, fraction; *w*, weeks

days 1 and 8.[13] Preliminary data from 199 patients enrolled in the phase III study were reported by Kiura et al.[12] at the 2006 Annual Meeting of the American Society of Clinical Oncology. The cisplatin-docetaxel arm appears to be associated with lower rates of grade 3 and 4 hematologic toxicities. The 2-year survival rate, the primary endpoint, was 60% for the cisplatin-docetaxel arm and 49% for the MVP arm. More long-term survival information is needed, however, before final conclusions can be drawn on the relative efficacy of the newer platinum-based regimen in chemoradiation therapy.

Another Japanese randomized controlled trial addressing this issue is being conducted by the West Japan Oncology Group (WJOG). This trial has conventional MVP-based chemoradiation as a standard arm, on the basis of results of a previous study,[4] and compares it with weekly carboplatin and either irinotecan or paclitaxel together with concurrent radiation (Fig. 2). All three treatment arms include up-front concurrent chemoradiation followed by systemic consolidation chemotherapy. Only the MVP arm has split-course radiation built into the protocol, which might hamper interpretation of the clinical findings because of a possible difference in efficacy between split-course and non-split-course radiotherapy. The primary endpoint of the study is overall survival. Preliminary results were presented at the 2007 Annual Meeting of the American Society of Clinical Oncology.[14] A total of 451 patients have been randomly assigned

to the three treatment arms, and the two weekly carboplatin-based arms manifest lower hematologic toxicities relative to the MVP arm. The response rates appear similar in the three arms, but the survival data for individual arms are not yet available.

Epidermal growth factor receptor (EGFR) inhibitors in combination with radiotherapy

Therapy targeted to the EGFR has been extensively evaluated in patients with various solid tumors, including NSCLC. Such therapy is based either on monoclonal antibodies, such as cetuximab, that target the extracellular domain of the EGFR or on small-molecule inhibitors of the tyrosine kinase activity of the receptor, such as gefitinib and erlotinib. Preclinical models have shown that EGFR inhibition by such antibodies or tyrosine kinase inhibitors (TKIs) enhances the antitumor activity of radiation.[15–18] Irradiation of tumor cells has been shown to activate the EGFR via ligand-dependent and ligand-independent mechanisms, possibly accounting for the radiation-induced acceleration of tumor cell repopulation and the development of radioresistance.[19,20] Such radiation-induced activation of EGFR-dependent processes provides a rationale for combined treatment with radiation and EGFR inhibitors. In a randomized phase III study, the addition of cetuximab to radiation therapy improved survival in patients with locally advanced, unresectable squamous cell carcinoma of the head and neck compared with the effect of radiation therapy alone.[21] There is, thus, justifiable interest in studying the effects of the incorporation of inhibitors of the EGFR signaling pathway into the treatment of locally advanced NSCLC with definitive chemoradiation.

The Japan Clinical Oncology Group (JCOG) has initiated a safety and efficacy trial of cisplatin and vinorelbine followed by gefitinib and concurrent TRT in patients with unresectable, locally advanced NSCLC (Fig. 3). The eligibility criteria for enrollment in the trial were changed midway through the study because gefitinib-induced fatal interstitial lung disease (ILD) became a substantial problem in Japan. Data now suggest that never-smokers and patients

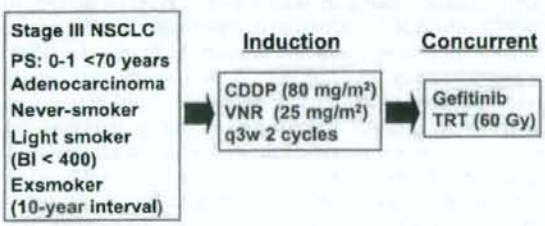

Fig. 3. Schema of the Japan Clinical Oncology Group (JCOG) 0402-MF trial evaluating the safety and efficacy of induction chemotherapy with cisplatin and vinorelbine (*VNR*) followed by concurrent administration of gefitinib and TRT in patients with unresectable stage III NSCLC (adenocarcinoma histology; never-smokers or history of light smoking). *PS*, performance status; *BI*, Brinkman index; *MF*, medical frontier

with adenocarcinoma are more likely to respond to gefitinib and are at a lower risk of developing gefitinib-induced ILD.[22] On the basis of these findings, eligibility for enrollment in the JCOG trial, which is still ongoing, has been limited to individuals with adenocarcinoma and either never-smokers or patients with a history of light smoking.

The recent discovery of somatic mutations in the tyrosine kinase domain of the EGFR and of the association of such mutations with a high response rate to EGFR-TKIs has had a profound impact on the treatment of advanced NSCLC.[23–25] Several phase II trials of EGFR-TKIs in patients positive for such EGFR mutations have yielded relatively reproducible and encouraging results.[26–30] A high response rate and good survival have thus been achieved in individuals with metastatic NSCLC. Clinical trials of these drugs in patients with EGFR mutation-positive stage III NSCLC are warranted.

Integration of a novel chemotherapy regimen into chemoradiation protocols

S-1 (Taiho Pharmaceutical, Tokyo, Japan) is an oral anticancer agent consisting of tegafur (FT), 5-chloro-2, 4-dihydroxypyridine (CDHP), and potassium oxonate, in a molar ratio of 1 : 0.4 : 1.[31] Tegafur is a prodrug that generates 5-fluorouracil (5-FU) in blood, largely as a result of its metabolism by cytochrome P450 in the liver. CDHP increases the plasma concentration of 5-FU through the competitive inhibition of dihydropyrimidine dehydrogenase, which catalyzes 5-FU catabolism. Oxonate reduces the gastrointestinal toxicity of 5-FU. A response rate of 22% and a median survival time of 10.2 months were obtained in a clinical trial of S-1 in patients with advanced NSCLC not previously subjected to chemotherapy.[32] Few severe gastrointestinal or hematologic adverse events were reported. Moreover, a phase II trial of S-1 plus cisplatin in NSCLC patients yielded a 47% response rate and an acceptable safety profile.[33] On the basis of these results, two groups in Japan are separately conducting phase II studies of cisplatin and S-1 with concurrent radiation in patients with unresectable stage III NSCLC. Patients are treated with cisplatin (60 mg/m^2) on day 1 and oral S-1 for 2 weeks together with concurrent radiation (60 Gy) administered over 6 weeks (Fig. 4). The primary endpoint of both trials is the response rate. Preliminary data for one of the two studies were presented at the 12th World Conference on Lung Cancer.[34] The response rate was more than 90% and toxicity was mild, justifying the enthusiasm for studying this regimen in the treatment of locally advanced NSCLC.

WJOG radiation dose-escalation trial

With the advent of improved radiation planning in patients with lung cancer, the WJOG initiated a radiation dose-escalation trial (WJTOG 3305) for individuals with unresectable stage III NSCLC. Patients receive weekly paclitaxel

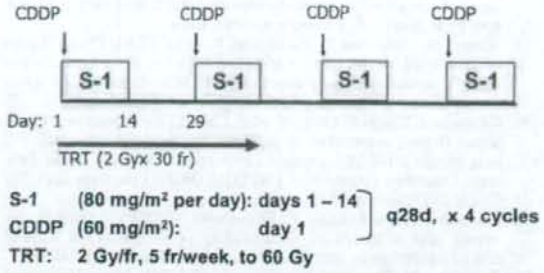

Fig. 4. Schema for treatment with cisplatin and S-1 combined with concurrent radiation in patients with unresectable stage III NSCLC. *d*, days

(40 mg/m^2) and carboplatin (area under the curve, 2), as well as concurrent hyperfractionated radiotherapy (1.5 Gy twice daily, from 54 to 72 Gy) with a three-dimensional planning approach. This trial is one of the first Japanese multi-institutional studies to test three-dimensional conformal radiotherapy (3D-CRT) for NSCLC. The planning target volume includes the primary tumor and involves lymph nodes that are defined on computed tomography or positron emission tomography scans. Elective nodal regions are not included in the planning target volume. The lung volume receiving more than 20 Gy (V20) is limited to less than 35%. Patient recruitment is currently ongoing.

Conclusions

Although it is clear that chemoradiation is the standard of care at the present time for patients with unresectable stage III NSCLC, questions remain to be answered with regard to the optimal chemotherapy regimens, including questions related to dose and duration. The integration of molecularly targeted agents such as inhibitors of EGFR and of the receptor for vascular endothelial growth factor into treatment regimens also remains to be worked out. The development of 3D-CRT techniques has also engendered efforts to determine whether dose-escalated radiation with concurrent chemotherapy is able to improve outcome. Japanese clinical trials focusing on these issues may lead to a new and better standard treatment for patients with unresectable stage III NSCLC.

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Pharmacokinetic Analysis of Carboplatin and Etoposide in a Small Cell Lung Cancer Patient Undergoing Hemodialysis

Ken Takezawa, MD, Isamu Okamoto, MD, PhD, Masahiro Fukuoka, MD, PhD, and Kazuhiko Nakagawa, MD, PhD

Cancer chemotherapy is not well established for patients on hemodialysis (HD). A 77-year-old man on HD presented with small cell lung cancer. He was treated with the combination of carboplatin and etoposide while the pharmacokinetics of the drugs were monitored. The patient showed a response with manageable toxicity and remained progression free for at least 8 months. The area under the concentration-time curve for each antitumor agent in the patient was within the therapeutic range achieved in individuals with normal renal function. Carboplatin and etoposide chemotherapy combined with HD thus allowed the drugs to achieve an appropriate area under the concentration-time curve and sufficient efficacy in a small cell lung cancer patient with chronic renal failure.

Key Words: Small cell lung cancer, Hemodialysis, Pharmacokinetics, Chemotherapy.

(*J Thorac Oncol.* 2008;3: 1073–1075)

The prognosis of patients with chronic renal failure has improved as a result of progress in hemodialysis (HD), and opportunities to treat malignant tumors that develop in such HD patients are increasing. However, little is known of the safety or efficacy of chemotherapy for malignant tumors in HD patients. We analyzed the pharmacokinetics of combination chemotherapy with carboplatin (CBDCA) and etoposide in a patient with small cell lung cancer (SCLC) undergoing HD.

CASE REPORT

A 77-year-old man with chronic renal failure due to diabetic nephropathy presented with a mass in the left hilar area in March 2007. The general condition of the patient, who had undergone HD, three times a week, was fair, with symptoms such as cough, weight loss, and fever being absent. His Eastern Cooperative Oncology Group performance status was 1. Computed tomography of the chest revealed a 45/33 mm mass in the lower left lobe as well as interstitial pneumonia in the lower left and lower right lobes. Histopathologic analysis of a transbronchial biopsy specimen revealed SCLC. No distant metastasis was detected on systemic examinations, and the patient was diagnosed with limited-stage SCLC. Laboratory testing revealed blood urea nitrogen and creatinine levels of 101 and 8.6 mg/dl, respectively. Other examined laboratory parameters were within normal limits, but subsequent evaluation of serum tumor markers revealed an increased level (18.2 ng/ml) of neuron-specific enolase, which is not affected by renal function.[1]

Radiotherapy was not appropriate for the patient because of his bilateral interstitial pneumonia. Given his good performance status and after obtaining informed consent, we treated the patient with the combination of CBDCA and etoposide (Figure 1). On day 1 of the treatment cycle, the patient received an intravenous injection of etoposide (50 mg/m^2) over 60 minutes followed by an intravenous injection of CBDCA (250–275 mg/m^2) also over 60 minutes. HD was initiated 60 minutes after completion of CBDCA administration and was performed for 4 hours. On day 3, etoposide (50 mg/m^2) was administered over 60 minutes and HD was performed for 4 hours beginning 2 hours after completion of etoposide injection. The doses of CBDCA and etoposide as well as the timing of HD were based on previous studies.[2–4] The treatment was well tolerated. Nonhematologic toxicities such as nausea, vomiting, and fatigue were not observed. The patient also did not experience neutoropenia or thrombocytopenia (Nadir neutrophil and platelet counts during 3 cycles of chemotherapy were 2200/μl and 15.5 × 10^4/μl, respectively). Prophylactic administration of granulocyte colony-stimulating was not carried out. After three cycles of chemotherapy, each separated by an interval of 3 weeks, the tumor had decreased in size and the serum neuron-specific enolase level had decreased to within normal limits (6.3 ng/ml). The patient remained progression free 8 months after the initiation of treatment.

Pharmacokinetic analysis of CBDCA and etoposide was performed for the first and third courses of chemotherapy. Serial blood samples were collected 0, 1, 2, 3, 4, 5, 6, 24, 37, 41, 42, 49, 53, and 54 hours after completion of CBDCA administration as well as 0, 2, 3, 4, 5, 6, 7, 25, 48, 50, 52, 54, 55, and 73 hours after completion of the first etoposide administration. Each blood sample was analyzed for free

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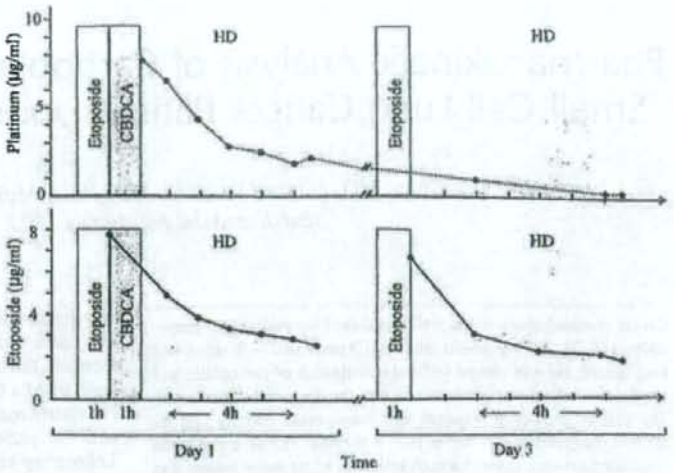

FIGURE 1. Chemotherapy and hemodialysis schedule as well as the plasma concentrations of free platinum and etoposide for the proband. Data are for the first of three cycles of chemotherapy. HD, hemodialysis; CBDCA, carboplatin.

platinum and etoposide (Figure 1) as described previously.[5] In the first cycle, the area under the concentration-time curve (AUC) was 4.10 minutes mg/ml for free platinum and 4401 and 3612 minutes μg/ml for etoposide on days 1 and 3, respectively. In the third course of chemotherapy, for which the CBDCA dose was increased from 250 to 275 mg/m^2, the AUC of free platinum was 4.16 minutes mg/ml. The maximal concentration and half-life of free platinum were 7.7 μg/ml and 2.51 hours in the first cycle and 9.4 μg/ml and 1.93 hours in the third cycle.

DISCUSSION

Many lung cancer patients undergoing HD as a result of impaired renal function may be "undertreated" because chemotherapy regimens are not well established for such individuals. The lack of pharmacokinetic data for most cytotoxic agents in HD patients makes it difficult to administer chemotherapy effectively. Given his old age, bilateral interstitial pneumonia, and renal dysfunction, the present patient might have been considered too high a risk for chemotherapy and recommended to receive best supportive care. However, taking into account the sensitivity of SCLC to platinum combination chemotherapy, we treated him with CBDCA and etoposide while monitoring the pharmacokinetics of these antitumor agents.

CBDCA is a less emetic and less nephrotoxic analog of cisplatin and is preferred over cisplatin for use in patients with renal insufficiency. The desired AUC for CBDCA can be individualized with the use of Calvert's formula on the basis of individual renal function.[6] In previous studies of CBDCA-based chemotherapy in patients undergoing HD, a CBDCA dose of 100 to 150 mg/body was chosen according to this formula, with the glomerular filtration rate set to zero because of the absence of renal function (Table 1).[7–10] In these studies, HD was performed 16 to 24 hours after completion of CBDCA administration, resulting in an AUC of 4.43 to 6.9 minutes mg/ml. More recently, administration of a relatively high dose (300 mg/m^2) of CBDCA with initiation of HD 0.5 to 1.5 hours after completion of drug injection has been shown to be feasible and effective in lung cancer patients undergoing HD.[2–4] However, the AUC of CBDCA in these latter studies was not determined. In the present study, we found that a CBDCA dose of 250 to 275 mg/m^2 administered completely 1 hour before HD gave rise to an AUC for free platinum of 4.10 to 4.16 minutes mg/ml, a therapeutic blood level, consistent with the antitumor efficacy observed

TABLE 1. Previous Studies of Carboplatin-Based Chemotherapy in Cancer Patients on Hemodialysis

	Disease	No. of Patients	Carboplatin Dose	Interval Between Carboplatin Infusion and Hemodialysis (h)	AUC (min mg/ml)
Watanabe et al.[7]	Ovarian cancer	1	125 mg	16	4.43
Jeyabalan et al.[8]	Ovarian cancer	1	125 mg	24	N.D
Chatelut et al.[9]	Ovarian cancer	1	150 mg	24	6.06–6.70
Motzer et al.[10]	Germ cell tumor	2	100 mg/m^2	24	6.7–6.9
Inoue et al.[2]	SCLC	3	300 mg/m^2	1	N.D
Yanagawa et al.[3]	NSCLC/epipharynx ca	2	300 mg/m^2	0.5	N.D
Haraguchi et al.[4]	SCLC	1	300 mg/m^2	1.5	N.D

N.D, not determined; NSCLC, non-small cell lung cancer.

in the previous studies[2–4]. Our presented study supports that relatively high dose administration of CBDCA with initiation of HD 1 hour after drug injection would be an alternative strategy for patients with HD -dependent renal insufficiency.

Etoposide is active against various types of malignant tumors, but its membrane permeability in HD remains unclear. The AUC range for etoposide in 13 patients with normal renal function treated with this drug at a dose of 100 mg/m^2 was previously shown to be 2291 to 6832 minutes μg/ml (Ref. [11]). The present patient was treated with etoposide at 50 mg/m^2 on days 1 and 3, with HD being initiated 2 hours after completion of the drug injection. The AUC of etoposide was 3612 to 4401 minutes μg/ ml, values that are within the range achieved in patients with normal renal function. Indeed, the combination chemotherapy in the proband induced a tumor response that persisted for at least 8 months. Administration of etoposide at 100 mg/m^2 on days 1, 3, and 5 in combination with cisplatin at 80 mg/m^2 was shown to be acceptable in 4 lung cancer patients with renal dysfunction.[12] In the previous study, HD was performed soon after drug administration, resulting in an AUC for etoposide of 4800 to 6204 minutes μg/ml. Data from the previous studies and our present patient thus indicate that etoposide can be administered safely in HD patients.

The present case shows that CBDCA and etoposide chemotherapy combined with HD resulted in AUCs for these drugs within the therapeutic range in a SCLC patient with chronic renal failure. Although further studies are needed, our findings suggest that this regimen of combination chemotherapy can be administered to lung cancer patients with renal insufficiency.

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Phase 1 trial of denosumab safety, pharmacokinetics, and pharmacodynamics in Japanese women with breast cancer–related bone metastases

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Denosumab, a fully human monoclonal antibody to receptor activator of nuclear factor–kappa B ligand (RANKL), suppresses bone resorption. This open-label, multicenter, phase 1 study evaluated the safety, pharmacodynamics, and pharmacokinetics of denosumab in Japanese women with breast cancer–related bone metastases. Patients (n = 18; median age, 57 years) received a single subcutaneous injection of denosumab 60 mg or 180 mg or three doses of denosumab 180 mg on days 1, 29, and 57 (every 4 weeks) and were followed for ≥ 141 days. No major safety concerns related to denosumab were noted in any cohort. All patients experienced at least 1 adverse event (AE); most were mild (grade ≤ 2). One patient reported grade 4 myositis and grade 3 anemia, malaise, and dysphagia that the investigator deemed treatment-related; other treatment-related AE were grade ≤ 2. No antidenosumab antibodies or clinically significant changes in laboratory findings, vital signs, or electrocardiograms were observed. Pharmacokinetics were approximately dose-linear. Denosumab caused rapid, substantial, and sustained suppression of urinary N-telopeptide corrected for creatinine (uNTx/Cr) across all doses; at day 85, the median change from baseline uNTx/Cr ranged from −61.9% to −90.8%. No dose-limiting toxicity was observed at any dosage. Coupled with pharmacokinetic and pharmacodynamic data, these results were consistent with those observed in non-Japanese populations. (*Cancer Sci* 2008; 99: 1237–1242)

Bone is a common site of metastasis in breast cancer. An estimated 75% of women with advanced breast cancer will develop bone metastases,[1–3] which are characterized by pain, fracturing, and spinal cord compression that cause morbidity for many patients. Receptor activator of nuclear factor–kappa B ligand (RANKL) is a key mediator of the 'vicious cycle' of bone destruction in metastatic cancer. RANKL is a critical mediator of osteoclast differentiation, function, and survival.[4–6] Within the bone microenvironment, tumor cells secrete factors that stimulate stromal cells and osteoblasts to express and secrete RANKL, which binds to its cognate receptor RANK on the surface of precursor and mature osteoclasts. Osteoclast-mediated bone resorption releases growth factors that further stimulate tumor growth, resulting in a propagation of bone destruction and tumor cell proliferation.[7] RANKL has recently been shown to promote migration of RANK-expressing tumor cells to bone.[8]

Patients with bone metastases often have increased bone turnover that can be measured using biochemical markers of bone resorption and formation, such as urinary N-telopeptide (uNTx) and bone-specific alkaline phosphatase (BSAP). Elevated levels of bone turnover markers are correlated with an increased risk of skeletal complications, disease progression, and death.[9–12] A key objective in the management of bone metastases is to minimize skeletal morbidity by re-establishing the homeostasis of bone metabolism. If excessive osteolysis is inhibited, skeletal complications caused by bone metastases may be prevented or delayed.

Denosumab is a fully human monoclonal antibody that binds and inhibits RANKL, thus inhibiting osteoclast-mediated bone destruction. Results from clinical trials in non-Japanese women with breast cancer-related bone metastases showed that denosumab suppressed bone turnover, and the incidence of adverse events was similar in the denosumab and control groups.[12,13] The objectives of this trial were to evaluate the safety, pharmacokinetics, and pharmacodynamics of denosumab in Japanese women with bone metastases associated with breast cancer and to compare the results of this trial with those from a similar study in an analogous population of non-Japanese women (NCT00091832, Clinical Trials.gov).[12,13,14]

Materials and Methods

This study was conducted according to the principles of the Japanese Ministry of Health, Labour, and Welfare, and the International Conference on Harmonisation regulations and guidelines. Institutional Review Boards at each clinical site approved the protocol and all amendments. An Efficacy and Safety Evaluation Committee monitored patient safety during the study as needed. Patients provided appropriate written informed consent.

Study design. In this phase 1 open-label, multicenter, dose-ascending single, and multiple dose study, patients were sequentially enrolled in one of three cohorts. Patients in the first cohort received a single 60-mg subcutaneous injection of denosumab. If no safety signals were observed in the first cohort after 8–10 days, patients were enrolled in the second cohort and received a single 180-mg subcutaneous injection of denosumab. After an 8- to 10-day period for observation of safety of the second dose, patients were enrolled in the third cohort and received three 180-mg subcutaneous injections of denosumab at 4-week intervals (Q4W) on days 1, 29, and 57. Doses were chosen to be comparable with those administered in a study in non-Japanese women with breast cancer and bone metastases.[12] Although no formal stopping rules were specified in the protocol, safety signals that were considered when making dose escalation decisions included adverse events (AE), vital signs, and serum chemistry and hematology values.

Endpoints. The primary endpoint of the study was the subject incidence of AE, including physical findings, changes in laboratory values, vital signs, and 12-lead electrocardiogram

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(ECG) data. Adverse events were classified using the Common Terminology Criteria for Adverse Events version 3.0. Secondary endpoints included serum denosumab levels (pharmacokinetics); the maximum observed serum concentration (C_{max}), time at which C_{max} was reached (T_{max}); the area under the concentration-time curve (AUC_{tz}); the accumulation ratio (AR, for cohort 3 only), the beta-phase half-life ($t_{1/2\beta}$, for cohorts 1 and 2 only) after administration of the first dose (pharmacokinetics); the presence of serum antidenosumab antibodies; and the percent change in the bone turnover marker urinary N-telopeptide corrected for creatinine (uNTx/Cr) from baseline to study day 85 (pharmacodynamics). Exploratory endpoints included pharmacokinetic parameter estimates following the last dose; the percent change in uNTx at study day 141 in cohort 3; the percent change in additional bone turnover markers (serum type I collagen cross-link C telopeptide [sCTx], bone-specific alkaline phosphatase, and osteocalcin) from baseline at study day 85 (all cohorts) and day 141 (cohort 3 only); and the proportion of patients experiencing skeletal-related events (SRE), defined as bone fracture, surgery or radiation therapy to bone, and spinal cord compression.

Patient eligibility. Patients were non-pregnant Japanese women with histologically or cytologically confirmed breast cancer and radiographic evidence of at least one bone metastasis, enrolled at three centers in Japan. Eligible patients were 20–74 years of age, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 and adequate organ function. Concurrent chemotherapy or hormonal therapy was allowed as long as the regimen did not change within 13 days before or after administration of the denosumab dose. Patients with prior SRE were eligible to participate in the study except for those who had evidence of an impending fracture in weight-bearing bones; major surgery to bone within 4 weeks before the first dose of denosumab; radiation therapy to bone within 2 weeks before the first dose of denosumab; or treatment with radioisotopes directed to bone within 8 weeks before the first dose of denosumab. Other exclusion criteria included cytotoxic chemotherapy within 13 days before denosumab administration; unresolved toxicities > grade 2 from previous chemotherapy regimens; central nervous system metastasis that was symptomatic or required treatment; or prior administration of osteoprotegerin or denosumab or administration of calcitonin, parathyroid hormone-related peptides, mithramycin, gallium nitrate, or strontium ranelate within 6 months; or systemic corticosteroid treatment during the study. Patients were also excluded if they reported or had evidence of disorders that could affect bone metabolism; prior malignancies (excluding the targeted breast cancer, basal cell carcinoma, or cervical cancer *in situ*) within 3 years; uncontrolled systemic disease; major surgery or traumatic injury within 4 weeks; HIV infection; bisphosphonate use within 4 weeks of the first dose of denosumab; or an organic or psychiatric disorder that might prevent the patient from completing the study.

Study procedures. Patients in the 60 mg and 180 mg single-dose cohorts received a single subcutaneous injection of denosumab in the anterior abdominal wall on study day 1. These patients were scheduled to have a total of nine study visits (study days 1, 2, 4, 8, 15, 22, 29, 57, and 85). Patients in the 180 mg Q4W cohort received a subcutaneous injection in the anterior abdominal wall on study days 1, 28, and 57. Patients in this cohort were scheduled to have a total of 12 study visits (study days 1, 8, 15, 22, 29, 57, 64, 71, 78, 85, 113, and 141). Screening assessments included medical and medication histories, physical examination including height and weight measurements, assessment of ECOG PS, hematology, serum chemistry, urinalysis, pregnancy tests, and spinal X-ray imaging. Existing SRE were noted. Throughout the study, physical examinations, monitoring of vital signs, weight measurements, electrocardiograms, and collection of urine and blood were performed periodically. Adverse events, laboratory values, and concomitant medications were recorded and assessed at all study visits. Patients did not receive calcium or vitamin D supplementation in this study.

Statistics and data analysis. The study planned to enroll six patients in each of three treatment cohorts for a total sample size of 18 patients. The safety analysis subset included all patients who received at least 1 dose of denosumab. The pharmacokinetic (PK) analysis subset included all patients in the safety subset who had an evaluable serum denosumab concentration-time profile. Pharmacodynamic evaluations were conducted among patients in the safety subset. Data were reviewed for safety before each dose escalation. Demographics and other baseline characteristics (values obtained 1 week before the first dose administration) were summarized using descriptive statistics. For continuous data, descriptive statistics included mean, median, standard deviation or standard error; and number of subjects, minimum, and maximum. Frequencies and percentages were presented for nominal categorical variables, including the number and percent of subjects.

Results

Patients. The first patient was enrolled on 22 November 2004 and the last patient visit occurred on 26 October 2005. A total of 19 patients were enrolled, including six in each cohort; a seventh patient in the 180 mg single-dose cohort withdrew at the physician's discretion before receiving denosumab because of disease progression; this patient was not included in any results. All patients were Japanese women. The overall median age was 57 years (range, 28–67 years) (Table 1). Patients in the 60 mg and 180 mg Q4W cohorts were of similar ages; patients in the 180 mg single-dose cohort had a median age of 47 years (range, 28–61 years). All women had an ECOG PS of 0 or 1. The median time since the original diagnosis was 6.2 years (range, 0.1–19.1), and the median time since the diagnosis of bone metastasis was 0.31 years (range, 0–5.6). Prior to the study, eight patients (44%) had never experienced an SRE, six patients (33%) had experienced only one SRE, and four patients (22%) had experienced two or more SRE (Table 1).

Safety

Adverse events. No deaths occurred during the study, and no patients withdrew from the study because of AE. All 18 patients who received at least one dose of denosumab experienced at least one AE during the study, most of which were mild. The most common AE were fatigue, anorexia, headache, malaise, and nausea (Table 2).

Two patients, both in the 180 mg single-dose group, reported serious AE (Table 2). One of these patients reported grade 4 myositis and grade 3 anemia, dysphagia, and malaise that were deemed by the investigator to be treatment-related; she also experienced grade 4 metastatic brain cancer and depression and grade 3 herpes zoster infection and liver disorder that were not treatment-related. The other patient experienced febrile neutropenia (absolute neutrophil count < 1.0×10^9/L, temperature ≥ 38.5°C), which was not deemed treatment-related and was resolved with outpatient treatment. Two patients experienced mild, asymptomatic hypocalcemia (grades 1 and 2) that was deemed treatment-related. Nine patients reported other grade 1 or 2 AE that were deemed by investigators to be treatment-related (blurred vision, nausea, chest pain, fatigue, decreased white blood cell count, hyperkalemia, arthropathy, muscle spasms, pain in extremity, hypoesthesia, seborrheic dermatitis, and hot flush). No SRE occurred during the study.

Laboratory findings, vital signs, and ECG results. No clinically significant changes were observed in laboratory findings or vital signs except for the anemia, neutropenia, and liver disorder described above. Abnormal findings in ECGs were observed in four patients in the 60 mg cohort after dosing with denosumab.

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Table 1. Baseline patient demographics and disease characteristics

	60 mg SC (single dose) ($n = 6$)	180 mg SC (single dose) ($n = 6$)	180 mg Q4W (3 doses) ($n = 6$)	Total ($n = 18$)
Sex – (%)				
Female	6 (100)	6 (100)	6 (100)	18 (100)
Race – *n* (%)				
Japanese	6 (100)	6 (100)	6 (100)	18 (100)
Age – years				
Median (min, max)	58 (52, 66)	47 (28, 61)	60 (47, 67)	57 (28, 67)
ECOG PS – *n* (%)				
0	3 (50)	3 (50)	4 (67)	10 (56)
1	3 (50)	3 (50)	2 (33)	8 (44)
Hormone receptor status – *n* (%)[1]				
Negative	4 (67)	0 (0)	0 (0)	4 (22)
Positive	2 (33)	5 (83)	6 (100)	13 (72)
Unknown	0 (0)	1 (17)	0 (0)	1 (6)
Time since original diagnosis – years				
Median (min, max)	6.4 (0.9, 10.4)	3.3 (0.1, 12.8)	7.4 (1.6, 19.0)	6.2 (0.1, 19.0)
Time since bone metastases – years				
Median (min, max)	0.38 (0.0, 3.8)	0.32 (0.1, 2.5)	0.25 (0.1, 5.6)	0.31 (0.0, 5.6)
Total number of previous SRE – *n* (%)				
0	1 (17)	4 (67)	3 (50)	8 (44)
1	3 (50)	1 (17)	2 (33)	6 (33)
2	1 (17)	1 (17)	0 (0)	2 (11)
3	1 (17)	0 (0)	0 (0)	1 (6)
>3	0 (0)	0 (0)	1 (17)	1 (6)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; Q4W, every 4 weeks; SC, subcutaneous; SRE, skeletal-related events.
[1]Tumors were screened for expression of the estrogen receptor (ER) or progesterone receptor (PR).

Table 2. Adverse events summary

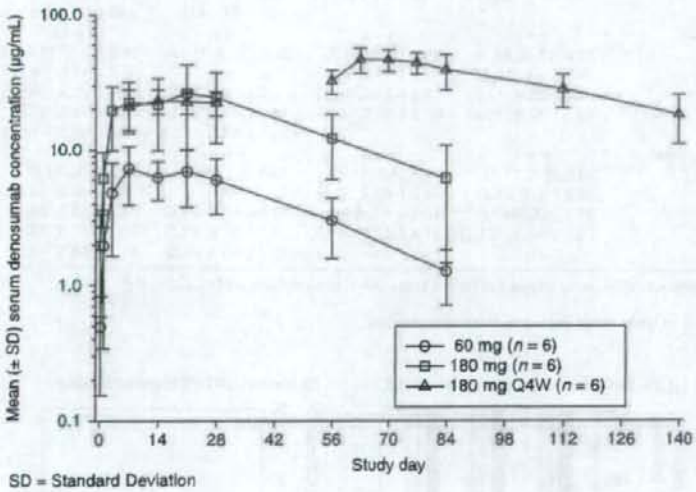
Event – *n* (%) (patients)	60 mg SC (single dose) ($n = 6$)	180 mg SC (single dose) ($n = 6$)	180 mg Q4W (3 doses) ($n = 6$)	Total ($n = 18$)
All AE	6 (100)	6 (100)	6 (100)	6 (100)
Serious AE	0 (0)	2 (33)[1]	0 (0)	2 (11)
Treatment-related AE	3 (50)	3 (50)	3 (50)	9 (50)
Serious treatment-related AE	0 (0)	1 (16.7)[2]	0 (0)	1 (5.6)
Deaths on study	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events occurring in 2 or more patients				
Fatigue	2 (33)	1 (17)	2 (33)	5 (28)
Anorexia	2 (33)	1 (17)	1 (17)	4 (22)
Headache	2 (33)	0 (0)	2 (33)	4 (22)
Malaise	1 (17)	3 (50)	0 (0)	4 (22)
Nausea	1 (17)	2 (33)	1 (17)	4 (22)
Arthralgia	2 (33)	0 (0)	1 (17)	3 (17)
Constipation	1 (17)	1 (17)	1 (17)	3 (17)
Diarrhea	2 (33)	0 (0)	1 (17)	3 (17)
Metastases to bone	1 (17)	1 (17)	1 (17)	3 (17)
Edema	1 (17)	1 (17)	1 (17)	3 (17)
Shoulder pain	1 (17)	1 (17)	1 (17)	3 (17)
Stomatitis	2 (33)	1 (17)	0 (0)	3 (17)
Alopecia	2 (33)	0 (0)	0 (0)	2 (11)
Chest pain	1 (17)	1 (17)	0 (0)	2 (11)
Hot flush	0 (0)	1 (17)	1 (17)	2 (11)
Hypoesthesia	0 (0)	0 (0)	2 (33)	2 (11)
Hypocalcemia	1 (17)	1 (17)	0 (0)	2 (11)
Insomnia	0 (0)	2 (33)	0 (0)	2 (11)
Metastases to liver	0 (0)	1 (17)	1 (17)	2 (11)
Nasopharyngitis	1 (17)	1 (17)	0 (0)	2 (11)
Neutrophil count decreased	2 (33)	0 (0)	0 (0)	2 (11)
Pain in extremity	1 (17)	1 (17)	0 (0)	2 (11)
White blood cell count decreased	2 (33)	0 (0)	0 (0)	2 (11)

[1]Includes 1 patient with grade 4 myositis and 1 patient with grade 3 febrile neutropenia.
[2]Includes 1 patient with grade 4 myositis.
AE, adverse events; SC, subcutaneous.

Table 3. Pharmacokinetic parameters following denosumab administration

Dose	Number of doses	C_{max} mean (SD) (μg/L)	T_{max} median (range) (day)	AUC_{0-t} mean (SD) (μgday/L)	$t_{1/2,\beta}$ mean (SD) (day)
60 mg	Single	7.73 (3.13)	8.0 (7.0–28)	351.0 (144.0)	24.7 (2.44)
180 mg	Single	31.10 (14.9)	10 (4.0–28)	1320.0 (640.0)	29.1 (7.15)
180 mg Q4W	1	24.10 (5.13)	18 (7.0–28)	545.0 (123.0)	NA
	3	48.0 (9.34)	14 (7.0–21)	1210.0 (240.0)	NA

C_{max} = Maximum observed serum concentration.
T_{max} = Time at which C_{max} was observed.
AUC_{0-t} = Area under the concentration-time curve from time zero to the time of the last observation (which corresponds to AUC_{0-84} for cohorts 1 and 2, and AUC_{0-28} for cohort 3).
$t_{1/2,\beta}$ = Beta-phase half-life.
NA, not applicable.



SD = Standard Deviation

Fig. 1. Denosumab demonstrated approximately dose-linear pharmacokinetics. Serum concentration-time profiles were biphasic, with an absorption phase and a beta phase that immediately followed peak concentrations. Mean half-life values associated with the beta phase ($t_{1/2,\beta}$) were comparable between the two single-dose cohorts (25–29 days).

The findings included transient sinus tachycardia, supraventricular extrasystole, transient ST elevation; one patient with previously documented atrioventricular (AV) block experienced transient first-degree AV block. None of these were considered as AE although the AV block was considered clinically significant by the investigator. No antidenosumab antibodies were observed.

Pharmacokinetics. Denosumab demonstrated approximately dose-linear pharmacokinetics over the dose range investigated. Absorption of denosumab appeared to be rapid, with maximal exposures observed in median times of 8–10 days after a single dose and 14–18 days after Q4W dosing. In the 180 mg Q4W cohort, an approximate 2.2-fold accumulation was observed from the first dose to the third dose. The serum denosumab concentration increased in an approximately dose-proportional manner, with a four-fold increase in mean C_{max} and 3.8-fold increase in AUC_{0-t}-values (Table 3). Serum concentration-time profiles were biphasic, with an absorption phase and a beta phase that immediately followed peak concentrations. Mean half-life values associated with the beta phase ($t_{1/2,\beta}$) were comparable between the two single-dose cohorts (25–29 days) (Fig. 1).

Pharmacodynamics. The suppression of uNTx/Cr was rapid, substantial, and sustained (Table 4). At day 85, the median percent changes from uNTx/Cr values at baseline were –91% (range, –23% to –93%) in the 60 mg single-dose group, –62% (range, –74% to +54%) in the 180 mg single-dose group, and –85% (range, –69% to –98%) in the 180 mg Q4W group. These values exclude five patients (two in the 180 mg single-dose group, three in the 180 mg Q4W group) whose baseline values were below quantifiable limits (BQL). By day 2, the median change in uNTx/Cr was –70% (range, –85% to +10%) in the 60 mg group and –70% (range, –80% to –65%) in the 180 mg single-dose group. In the 180 mg Q4W group, by week 2 (the first visit after administration of denosumab), uNTx/Cr changed a median of –64% (range, –10% to –96%). At day 141, the median percent change in uNTx/Cr in the 180 mg Q4W group (three patients) was –63% (range, –60% to –96%).

At day 85, the median percent change from baseline sCTx values was –89% (range, –68% to –97%) in the 60 mg group, –76% (range, –84% to +206%) in the 180 mg single-dose group, and –80% (range, –90% to +53%) in the 180 mg Q4W group (Table 4). These results reflect the exclusion of two patients in the 180 mg Q4W group because of missing data and a baseline BQL value. At day 141, the median percent change in sCTx in the 180 mg Q4W group was –80% (range, –62% to –93%). Effects of denosumab therapy on bone turnover markers are summarized in Table 4.

Comparison with results in non-Japanese women. In a randomised, phase 2, dose-ranging study in women with breast cancer (study NCT00091832, Clinical Trials.gov),[2] five denosumab dosing regimens were evaluated in 212 non-Japanese women with breast cancer and bone metastases who were bisphosphonate-

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Table 4. Denosumab effects: Changes from baseline in bone turnover markers

Bone turnover marker	60 mg SC (single dose)	180 mg SC (single dose)	180 mg Q4W (3 doses)	Total
	$n = 6$	$n = 4$	$n = 3$	$n = 13$
uNTx/Cr (nmol/mmol) – median percentage change (min, max)[1]				
Baseline	109 (19, 233)	55 (21, 60)	29 (20, 389)	60 (19, 389)
Day 2	-70 (-85, 9)	-70 (-80, -65)	–	-69 (-85, 9)
Week 2	-82 (-94, -40)	-75 (-90, -9)	-64 (-96, -10)	-77 (-96, -9)
Day 85	-91 (-93, -23)	-62 (-74, 54)	-85 (-98, -69)	-85 (-98, 54)
Day 141	–	–	-63 (-96, -60)	-63 (-96, -60)
sCTx (ng/mL) – median percentage change (min, max)[1]	$n = 6$	$n = 6$	$n = 4$	$n = 16$
Baseline	0.5 (0.2, 1.8)	0.3 (0.1, 0.9)	0.2 (0.2, 1.7)	0.3 (0.1, 1.8)
Day 2	-69 (-83, -54)	-63 (-75, -8)	–	-65 (-83, -8.1)
Week 2	-81 (-93, -69)	-77 (-85, -31)	-77 (-92, -50)	-80 (-93, -31)
Day 85	-89 (-97, -68)	-76 (-84, 206)	-80 (-90, 53)	-82 (-97, 206)
Day 141	–	–	-80 (-93, -62)	-80 (-93, -62)
BSAP (U/L) – median percentage change (min, max)	$n = 6$	$n = 6$	$n = 6$	$n = 18$
Baseline	30.4 (25.0, 44.3)	29.8 (17.9, 63.7)	26.9 (15.3, 114.4)	29.0 (15.3, 114.4)
Day 2	-0.8 (-7.8, 14.7)	1.9 (-11.8, 9.5)	–	-0.2 (-11.8, 14.7)
Week 2	0.4 (-25.4, 12.1)	3.3 (-23.9, 10.3)	0.7 (-18.4, 16.5)	1.7 (-25.4, 16.5)
Day 85	-48.3 (-60.0, 35.6)	-42.9 (-78.5, -9.5)	-34.3 (-63.2, 23.5)	-45.6 (-78.5, 35.6)
Day 141	–	–	-53.4 (-68.5, -12.5)	-53.4 (-68.5, -12.5)
Osteocalcin (ug/L) – median percentage change (min, max)	$n = 6$	$n = 6$	$n = 6$	$n = 18$
Baseline	13.8 (7.2, 17.6)	9.6 (4.2, 13.3)	10.9 (4.1, 30.5)	12.2 (4.1, 30.5)
Day 2	13.6 (-5.3, 21.6)	-3.2 (-40.2, 50.0)	–	1.4 (-40.2, 50.0)
Week 2	21.1 (9.5, 34.1)	12.5 (-4.0, 84.4)	22.9 (-15.9, 79.0)	18.2 (-15.9, 84.4)
Day 85	-28.0 (-50.3, -21.7)	-31.6 (-57.1, -18.8)	-7.7 (-57.9, 63.9)	-29.1 (-57.9, 63.9)
Day 141	–	–	-41.7 (-63.5, -1.5)	-41.7 (-63.5, -1.5)

BSAP, bone-specific alkaline phosphatase; SC, subcutaneous; sCTx, serum type I collagen cross-link C-telopeptide; uNTx/Cr, urinary N-telopeptide corrected for creatinine.
[1]Patients whose baseline values were below quantifiable limits were excluded from this analysis.

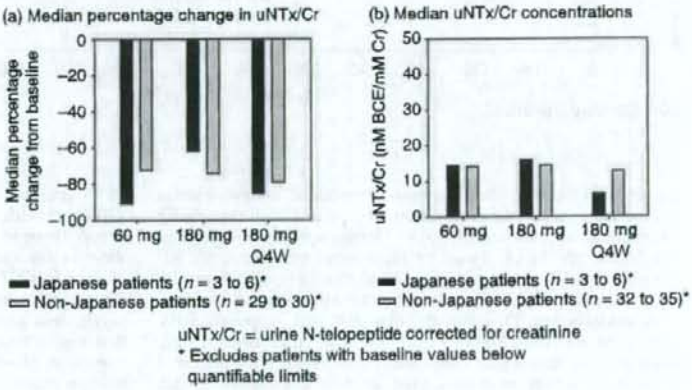

Fig. 2. At comparable dosing levels, results of Japanese patients were similar to those of non-Japanese patients for the median percent change from the baseline in (a) uNTx/Cr and (b) median uNTx/Cr concentrations. Q4W, every 4 weeks; uNTx/Cr, urine N-telopeptide corrected for creatinine.

uNTx/Cr = urine N-telopeptide corrected for creatinine
* Excludes patients with baseline values below quantifiable limits

naive. At comparable dosing levels after excluding patients with baseline BQL levels of uNTx/Cr, results in the current study were similar to those in the non-Japanese study for the median percent change from baseline for uNTx/Cr (Fig. 2) and the median uNTx/Cr concentrations (Fig. 2b). No marked differences were seen in safety profiles or in serum concentrations or other PK parameters between Japanese and non-Japanese patients.

Discussion

As expected, the adverse event profile in this study was similar to that observed in advanced cancer patients undergoing systemic therapy, with no dose-limiting toxicities observed. In a phase 2 study of non-Japanese women with metastatic breast cancer, denosumab treatment was not associated with any severe or serious treatment-related adverse events or with any dose-dependent increase in adverse events.[12] The only grade 4 AE that was deemed treatment-related by the investigator was myositis, although the investigator considered paraneoplastic syndrome to be the primary possible etiology of the myositis. This patient, who had active metastatic disease, exhibited substantially elevated levels of creatine phosphokinase (CPK) at baseline. She developed a further elevation in CPK levels and proximal muscular weakness with myalgia in the extremities on day 29. The histological findings indicated non-specific myositis with no apparent evidence of neurogenic change, collagen disorder, or viral infection. The patient was taking three concomitant medications (goserelin acetate, tamoxifen citrate,

and loxoprofen sodium) that the investigator considered to be potentially suspect. Because of these factors, it is difficult to establish the role of denosumab in the development of myositis. This event was resolved after treatment with steroids.

The pharmacokinetics of denosumab with respect to dose and time were consistent in this population with results observed in analogous non-Japanese populations. The range of baseline uNTx/Cr values observed in this study (19–389 nmol/mmol) was within the range observed in the phase 2 study of non-Japanese patients with breast cancer (5 nmol/mmol to 942 nmol/mmol),[12] and baseline variability among patients was similar in the two studies. Median percent changes in uNTx/Cr were also similar in both Japanese and non-Japanese populations regardless of the median baseline uNTx/Cr levels. No relationship was observed between baseline uNTx/Cr levels and the median percent change in uNTx/Cr.[12] In this study, the suppression of the bone turnover marker uNTx/Cr was rapid (occurring within 24 h), substantial (≥60%), and sustained (up to 12 weeks). These results are comparable to those seen in non-Japanese patients, in which median reductions were ≥70%.[12,13,14] The safety, pharmacokinetic, and pharmacodynamic profiles in denosumab-treated Japanese women were not markedly different from those in non-Japanese populations.[12,13,14] These results demonstrate that the 120 mg Q4W regimen identified in a phase 2 study of non-Japanese patients[13] is appropriate for Japanese as well as non-Japanese patients, a conclusion supported by the Japanese investigators in the current study. This study supports further investigation of denosumab for treatment of bone metastases and the prevention and treatment of SREs in Japanese patients with breast cancer. Multiple global phase 3 trials of denosumab are in progress for patients with advanced cancer and bone metastases; underlying malignancies include breast cancer (including Japanese patients), prostate cancer and other solid tumors, and multiple myeloma.

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Phase III trial of docetaxel plus gemcitabine versus docetaxel in second-line treatment for non-small-cell lung cancer: results of a Japan Clinical Oncology Group trial (JCOG0104)

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Background: This trial evaluated whether a combination of docetaxel and gemcitabine provides better survival than docetaxel alone in patients with previously treated non-small-cell lung cancer (NSCLC).

Patients and methods: Eligibility included pathologically or cytologically proven NSCLC, failure of one platinum-based regimen, performance status of zero or one, 20–75 years old, and adequate organ function. Patients received docetaxel 60 mg/m^2 (day 1) or docetaxel 60 mg/m^2 (day 8) and gemcitabine 800 mg/m^2 (days 1 and 8), both administered every 21 days until disease progression.

Results: Sixty-five patients participated in each arm. This trial was terminated early due to an unexpected high incidence of interstitial lung disease (ILD) and three treatment-related deaths due to ILD in the combination arm. Docetaxel plus gemcitabine compared with docetaxel-alone patients experienced similar grade and incidence of toxicity, except for ILD. No baseline factor was identified for predicting ILD. Median survival times were 10.3 and 10.1 months (one-sided $P = 0.36$) for docetaxel plus gemcitabine and docetaxel arms, respectively.

Conclusion: Docetaxel alone is still the standard second-line treatment for NSCLC. The incidence of ILD is higher for docetaxel combined with gemcitabine than for docetaxel alone in patients with previously treated NSCLC.

Key words: docetaxel, gemcitabine, non-small-cell lung cancer, platinum-refractory, second-line chemotherapy

introduction

Lung cancer is the most common cancer worldwide, with an estimated 1.2 million new cases globally (12.3% of all cancers) and 1.1 million deaths (17.8% of all cancer deaths) in 2000 [1]. The estimated global incidence of non-small-cell lung cancer (NSCLC) in 2000 was ~1 million, which accounted for ~80% of all cases of lung cancer [1]. Treatment of advanced NSCLC is palliative; the aim is to prolong survival without leading to deterioration in quality of life [2]. The recommended first-line treatment of advanced NSCLC currently involves up to four cycles of platinum-based combination chemotherapy, with no single combination recommended over others [3]. Although this treatment improves survival rates, a substantial proportion of patients do progress and should be offered second-line treatment. With unsurpassed efficacy compared with other chemotherapeutic regimens or best supportive care [4, 5], docetaxel alone is the current standard as second-line chemotherapy for advanced NSCLC. The recommended regimen of docetaxel 75 mg/m^2 given i.v. every 3 weeks as second-line therapy has been associated with median survival times of 5.7–7.5 months [4, 5] and is also associated with better quality-of-life outcomes compared with best supportive care [2]. Docetaxel monotherapy for recurrent NSCLC after platinum-based chemotherapy has several limitations, however, including low response rates (7–11%), brief duration of disease control, and minimal survival advantage [4, 5].

Gemcitabine is also active against recurrent NSCLC after platinum-based chemotherapy [6]. Gemcitabine 1000 mg/m^2 once a week for 3 weeks every 28 days produced a 19% response rate in a phase II trial, and it shows significant activity mainly

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in patients previously responsive to chemotherapy [6]. Single-agent gemcitabine has a low toxicity profile and is well tolerated [6].

Docetaxel and gemcitabine have distinct mechanisms of action and nonoverlapping toxic effects except for neutropenia. Many studies of the combination of docetaxel and gemcitabine have been conducted in first- and second-line settings [7–16]. The following doses and schedule have been adopted in most studies: docetaxel 80–100 mg/m^2 on day 1 or 8 and gemcitabine 800–1000 mg/m^2 on days 1 and 8 or on days 1, 8, and 15. Furthermore, most studies required use of prophylactic granulocyte colony-stimulating factor (G-CSF) support.

In Japan, however, the recommended dose of docetaxel is 60 mg/m^2 every 3 weeks [17, 18]. Several studies to confirm the dose and schedule of this combination without prophylactic G-CSF support have been conducted in Japan [19–21]. Two studies recommended docetaxel 60 mg/m^2 on day 8 and gemcitabine 800 mg/m^2 on days 1 and 8, and another study recommended docetaxel 50 mg/m^2 on day 8 and gemcitabine 1000 mg/m^2 on days 1 and 8, without prophylactic G-CSF support, every 3 weeks. These studies demonstrated the consistent promising efficacy of this combination regimen. An objective response was observed in 28%–40% of patients, with a median survival time of 11.1–11.9 months and a 1-year survival rate of 41%–47%.

We conducted a multicenter, randomized, phase III trial to evaluate whether the combination regimen of docetaxel and gemcitabine provides better survival than docetaxel alone in patients with previously treated NSCLC.

patients and methods

patient selection

Eligible patients were 20–75 years of age, with histologically or cytologically confirmed stage IIIB (with malignant pleural effusion or contralateral hilar lymph node metastases) or stage IV NSCLC who had failed one platinum-based chemotherapy regimen previously. Patients who had received gemcitabine or docetaxel were excluded. Additional inclusion criteria included a Eastern Cooperative Oncology Group performance status of zero to one, and adequate organ function as indicated by white blood cell count ≥4000/μl, absolute neutrophil count ≥2000/μl, hemoglobin ≥9.5 g/dl, platelets ≥100 000/μl, aspartate aminotransferase (AST)/alanine amonotransferase (ALT) ≤2.5 times the upper limit of normal, total bilirubin ≤1.5 mg/dl, serum creatinine ≤1.2 mg/dl, and PaO_2 in arterial blood ≥70 torr. Asymptomatic brain metastases were allowed provided that they had been irradiated and were clinically and radiologically stable. Prior thoracic radiotherapy was allowed provided that treatment was completed at least 12 weeks before enrollment. Patients were excluded from the study if they had radiologically and clinically apparent interstitial pneumonitis or pulmonary fibrosis. All patients provided written informed consent, and the study protocol was approved by Japan Clinical Oncology Group (JCOG) Clinical Trial Review Committee and the institutional review board of each participating institution.

treatment plan and dose modifications

Eligible patients were centrally registered at JCOG Data Center and were randomly assigned to either docetaxel 60 mg/m^2 as a 60-min i.v. infusion on day 1 or docetaxel 60 mg/m^2 as a 60-min i.v. infusion on day 8 plus gemcitabine 800 mg/m^2 as a 30-min i.v. infusion on days 1 and 8, using a minimization method with institutions and response to prior chemotherapy (progressive disease or not) as balancing factors. Patients receiving docetaxel were administered standard dexamethasone premedication (8 mg orally at the day before, on the day, and the day after docetaxel administration) as previously reported [7] and 50 mg of diphenhidramine 30 min before docetaxel administration. Recombinant human G-CSF was not given prophylactically. Chemotherapy cycles were repeated every 3 weeks until disease progression. Docetaxel was given before gemcitabine in the docetaxel plus gemcitabine regimen.

Dose adjustments were based mainly on hematologic parameters. The doses of docetaxel and gemcitabine were reduced by 10 and 200 mg/m^2, respectively, in subsequent cycles if chemotherapy-induced febrile neutropenia, grade 4 anemia, grade 4 thrombocytopenia, grade 4 leukopenia, or grade 4 neutropenia lasting for >3 days occurred in the absence of fever. Dose reductions were maintained for all subsequent cycles. Patients requiring more than one dose reduction were off-protocol treatment.

baseline and follow-up assessments

Pretreatment evaluation included a complete medical history and physical examination, a complete blood count (CBC) test with differential and platelet count, standard biochemical profile, electrocardiogram, chest radiographs, computed tomographic scans of the chest, abdomen, and brain, magnetic resonance imaging, and a whole-body bone scan. During treatment, a CBC and biochemical tests were carried out weekly. A detailed medical history was taken and a complete physical examination with clinical assessment was carried out weekly to assess disease symptoms and treatment toxicity, and chest radiographs were done every treatment cycle. Toxicity was evaluated according to the National Cancer Institute Cancer—Common Toxicity Criteria Version 2 [22].

All patients were assessed for response by computed tomography scans after every two cycles of chemotherapy. Response Evaluation Criteria in Solid Tumors (RECIST) were used for the evaluation of response [23].

The progression-free survival (PFS) was calculated from the day of randomization until the day of the first evidence of disease progression or death. If the patient had no progression, PFS was censored at the day when no clinical progression was confirmed. Overall survival (OS) was measured from the day of randomization to death.

Disease-related symptoms were evaluated and scored at baseline and 6 weeks after the start of treatment with the seven-item Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy-Lung version 4 [24], which were translated from English to Japanese. The questionnaire entries were listed as follows: 'I have been short of breath', 'I am losing weight', 'My thinking is clear', 'I have been coughing', 'I have a good appetite', 'I feel tightness in my chest', and 'Breathing is easy for me'. Patients scored using a five-point Likert scale (0–4) by themselves. The maximum attainable score of the LCS was 28, where the patient was considered to be asymptomatic.

statistical analysis

The primary endpoint was OS; secondary endpoints were PFS, the overall response rate, disease-related symptoms, and toxicity profile. Based on previous trials evaluating the docetaxel [4, 5] and docetaxel plus gemcitabine [19–21] regimens, the present study was designed to detect a 12% difference of 1-year survival rate. To attain an 80% power at a one-sided significance level of 0.05, assuming 1-year survival of docetaxel arm as 35% with 1 year of follow-up after 2 years of accrual, 284 patients (142 per each arm) were required. Analyses were to be carried out with all randomized patients. Both the OS and PFS were estimated with the Kaplan–Meier method. The comparisons of OS and PFS between arms were assessed by the stratified log-rank test with a factor used at randomization, response to prior chemotherapy. Two interim analyses were planned after half of the patients were registered and the end of registration.