TABLE 3. CHARACTERISTICS OF CONFIRMED CASES AND CONTROLS (AS A REPRESENTATIVE SAMPLE OF THE STUDY COHORT)

	Cases ($n = 115$)	Controls ($n = 520$)	Gefitinib Control Sample ($n = 240$)	Chemotherapy Control Sample ($n = 280$)
Severity of preexisting interstitial lung disease on CT scan (CRB evaluation)				
No ILD	84 (73.0)	473 (91.0)	231 (96.3)	242 (86.4)
Mild	15 (13.0)	28 (5.4)	8 (3.3)	20 (7.1)
Moderate	12 (10.4)	14 (2.7)	1 (0.4)	13 (4.6)
Severe	4 (3.5)	5 (1.0)	0 (0.0)	5 (1.8)
Severity of preexisting pulmonary emphysema on CT scan (CRB evaluation)				
No emphysema	56 (48.7)	326 (62.8)	176 (73.3)	150 (53.8)
Mild	35 (30.4)	92 (17.7)	36 (15.0)	56 (20.1)
Moderate	18 (15.7)	59 (11.4)	16 (6.7)	43 (15.4)
Severe	6 (5.2)	42 (8.1)	12 (5.0)	30 (10.8)
Extent of normal lung on CT scan (CRB evaluation)				
Low (10–50%)	49 (42.6)	133 (25.6)	56 (23.3)	77 (27.5)
Normal (60–100%)	66 (57.4)	387 (74.4)	184 (76.7)	203 (72.5)

Definition of abbreviations: CRB = case review board; ILD = interstitial lung disease.
Values shown are numbers (%) of total subjects with available CRB data.

to date. For the first time, the risk of acute ILD events for a large and relatively unselected chemotherapy-treated NSCLC patient cohort in Japan was determined in clinical practice. The study also quantified the greater risk of developing acute ILD associated with gefitinib treatment than with conventional chemotherapy, mainly in the first 4 weeks after treatment initiation. The study confirmed and further defined risk factors for developing ILD with gefitinib or chemotherapy. The factors included older age, poor WHO PS, smoking, short duration since diagnosis of NSCLC, reduced normal lung on CT scan, preexisting ILD, and concurrent cardiac disease. Several of these factors, or related factors, had been reported previously in bivariate or multivariate analyses from other studies (8, 18, 19). These risk factors were the same for patients treated with gefitinib or chemotherapy in the study, and no treatment-specific risk factors were identified. In particular, patients with CT evidence of preexisting ILD (chronic) were at considerably elevated risk of developing acute ILD during treatment, but there were relatively few subjects with preexisting ILD and the data did not indicate a statistically significant difference in treatment-related risk depending on the preexisting ILD status. Of clinical relevance, some of these risk factors were just as strong as, or stronger than, gefitinib treatment, for example having a poor WHO PS (≥2) rather than a good PS (OR, 4.0; 95% CI, 1.85–8.75), implying that they can be used to identify patients at particular risk of ILD in clinical practice. The relationship between ILD and pharmacokinetic characteristics of gefitinib, as well as genetic polymorphisms and proteomics determined in

TABLE 4. MEASURES OF DISEASE OCCURRENCE FOR ACUTE INTERSTITIAL LUNG DISEASE ESTIMATED FROM THE COHORT DATA (INCIDENCE RATE, CUMULATIVE INCIDENCE)

	Gefitinib Cohort	Chemotherapy Cohort
Overall observed incidence rate 0–84 d		
No. of treatment periods at Day 0	1,872	2,551
Cases of ILD/person-weeks	79/17,740	43/25,224
Incidence rate per week (95% CI)	0.00445 (0.00347–0.00544)	0.00170 (0.00120–0.00221)
Overall observed incidence rate 0–28 d		
No. of treatment periods at Day 0	1,872	2,551
Cases of ILD / person-weeks	56/7,032	21/9,902
Incidence rate per week (95% CI)	0.00796 (0.00588–0.01005)	0.00212 (0.00121–0.00303)
Overall observed incidence rate 29–56 d		
No. of treatment periods at Day 29	1,596	2,284
Cases of ILD/person-weeks	11/5,797	15/8,392
Incidence rate per week (95% CI)	0.00190 (0.00078–0.00302)	0.00179 (0.00088–0.00269)
Overall observed incidence rate 57–84 d		
No. of treatment periods at Day 57	1,328	1,890
Cases of ILD/person-weeks	12/4,911	7/6,930
Incidence rate per week (95% CI)	0.00244 (0.00106–0.00383)	0.00101 (0.00026–0.00176)
Naive cumulative incidence after 84 d (first treatment periods only)		
Cases of ILD/no. of patients	59/1,482	35/1,677
Cumulative incidence (95% CI)	3.98% (3.04–5.11%)	2.09% (1.46–2.89%)
Kaplan-Meier cumulative incidence after 84 d (first treatment periods only)		
Cases of ILD/no. of patients	59/1,482	35/1,677
Cumulative incidence (95% CI)	4.50% (3.37–5.64%)	2.40% (1.61–3.20%)

Definition of abbreviations: ILD = interstitial lung disease; CI = confidence interval.

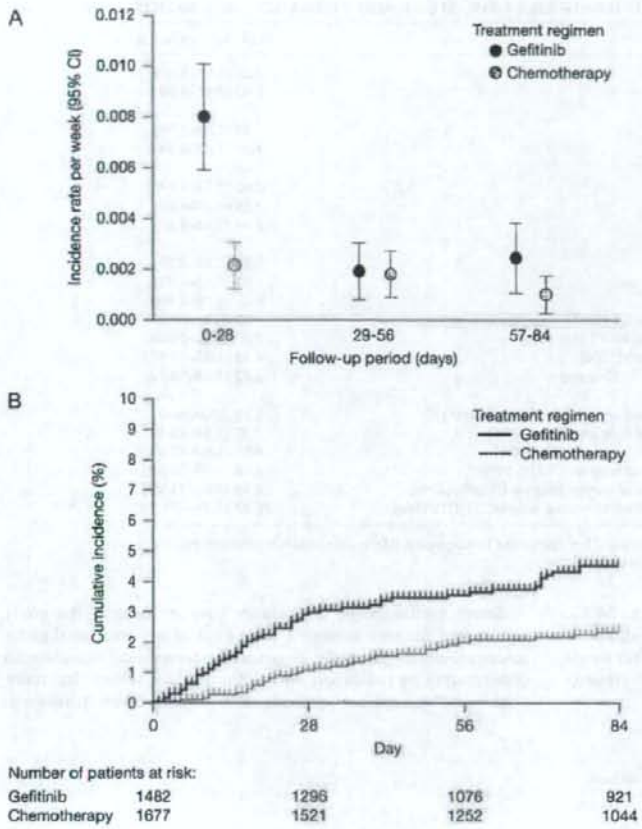


Figure 1. (*A*) Incidence rates of acute interstitial lung disease (ILD) in Japanese patients with non-small cell lung cancer for gefitinib and chemotherapy cohorts by 4-week period after treatment initiation. (*B*) Kaplan-Meier curves of risk of ILD to 12 weeks for the observed cohorts. CI = confidence interval.

study subjects, were also investigated as secondary and exploratory objectives in this study. These analyses are ongoing and results will be submitted for publication in due course.

Over the whole study follow-up, the average incidence rate for acute ILD events in patients treated with gefitinib was 3.2-fold higher relative to that seen with other chemotherapy treatments, adjusted for imbalances in other risk factors between treatments. The increased risk of ILD associated with gefitinib treatment was seen most clearly in the first 4 weeks after treatment initiation. Thus, increased physician awareness of risk factors and careful surveillance of Japanese patients during this period are indicated to manage risk. Such an approach is in line with current recommendations in Japan (20, 21). Beyond 4 weeks after treatment initiation, the risk of ILD associated with gefitinib treatment appears to fall.

ILD risk factors were found to be the same for both types of NSCLC therapy. Gefitinib is, however, a molecularly targeted agent. There is a significant body of evidence to indicate that gefitinib is a valid treatment option for some patients with NSCLC. In the IRESSA Survival Evaluation in Lung cancer (ISEL) study, a large phase III, placebo-controlled trial (n = 1,692), gefitinib was associated with some improvement in overall survival versus placebo, although this failed to reach statistical significance in the primary analysis of the overall population (22). Preplanned subgroup analyses from the study showed statistically significant differences in survival in favor of gefitinib in patients of Asian origin and those who had never smoked. Furthermore, tumor biomarker data suggest that patients with a high EGFR gene copy number, or an EGFR mutation, may be more likely to benefit (23, 24).

Therefore, the consideration of those patients more likely to benefit from the drug balanced with the better identification of these risk factors associated with ILD enables the physician to make careful judgment of the most appropriate therapy for the individual patient. Patients with several risk factors will generally be at more risk, and patients with risk factors may be at higher risk if gefitinib is used. This approach is facilitated by the fact that evidence to date suggests that subgroups less at risk of ILD tend to be those that respond well to gefitinib treatment (8).

A fatal outcome is the major concern with ILD as an SAE of drug treatment. In other large studies, fatality rates due to ILD in gefitinib-treated subjects of approximately 30% have been seen (8, 25), and a similar mortality was observed in this study in both gefitinib-treated and chemotherapy-treated ILD cases. The main predictors of a fatal outcome were older age (≥65 yr), smoking history, and preexisting ILD, as well as CT scan evidence of reduced normal lung (≤50%) or extensive areas adherent to pleura (≥50%). Because mortality is high among patients with NSCLC and the frequency of ILD in Japanese patients with NSCLC is low in comparison, ILD-related mortality impacted the overall survival at 12 weeks, for the cohort of

TABLE 5. RISK FACTORS FOR ACUTE ILD IDENTIFIED IN THE STUDY AND ESTIMATED ODDS RATIOS

Risk Factors	Odds Ratio (95% CI)
Treatment: gefitinib vs. chemotherapy	3.23 (1.94–5.40)
Age: ≥55 vs. ≤54 yr	1.92 (0.91–4.09)
WHO performance status	
1 vs. 0	1.57 (0.83–2.97)
2–3 vs. 0	4.02 (1.85–8.74)
Duration of NSCLC	
0.5 to <1 vs. <0.5 yr	0.65 (0.37–1.14)
≥1 vs. <0.5 yr	0.35 (0.20–0.62)
Concurrent cardiac disease: yes vs. no	2.44 (0.88–6.80)
Severity of preexisting pulmonary emphysema	
Mild vs. no	1.57 (0.89–2.79)
Moderate vs. no	1.04 (0.49–2.23)
Severe vs. no	0.47 (0.16–1.40)
Never-smoker and high extent of normal lung on CT (60–100%) (reference)	1.00 (reference)
Never-smoker and reduced extent of normal lung on CT (10–50%)	7.22 (2.52–20.64)
Smoker and high extent of normal lung on CT (60–100%)	4.43 (1.87–10.47)
Smoker and reduced extent of normal lung on CT (10–50%)	5.42 (2.08–14.12)
No preexisting ILD and high extent of normal lung on CT (60–100%) (reference)	1.00 (reference)
No preexisting ILD and reduced extent of normal lung on CT (10–50%)	7.22 (2.52–20.64)
Mild preexisting ILD and high extent of normal lung on CT (60–100%)	4.80 (1.83–12.63)
Mild preexisting ILD and reduced extent of normal lung on CT (10–50%)	6.08 (1.09–33.98)
Moderate–severe preexisting ILD and high extent of normal lung on CT (60–100%)	5.55 (1.40–21.99)
Moderate–severe preexisting ILD and reduced extent of normal lung on CT (10–50%)	25.27 (5.74–111.28)

Definition of abbreviations: CI = confidence interval; CT = computed tomography; ILD = interstitial lung disease; NSCLC = non–small cell lung cancer; WHO = World Health Organization.

gefitinib-treated patients, only to a limited extent (85.4 to 84%). Accordingly, there needs to be an appropriate individualized risk–benefit evaluation for patients also considering other treatments, many of which have their own problems with treatment-related mortality due to SAEs other than ILD.

Some methodologic issues may have influenced the study results and deserve comment. This kind of observational pharmacoepidemiologic study is generally considered sensitive to confounding by indication. Most often, it is assumed that more "sick" or "susceptible" patients will receive a new treatment,

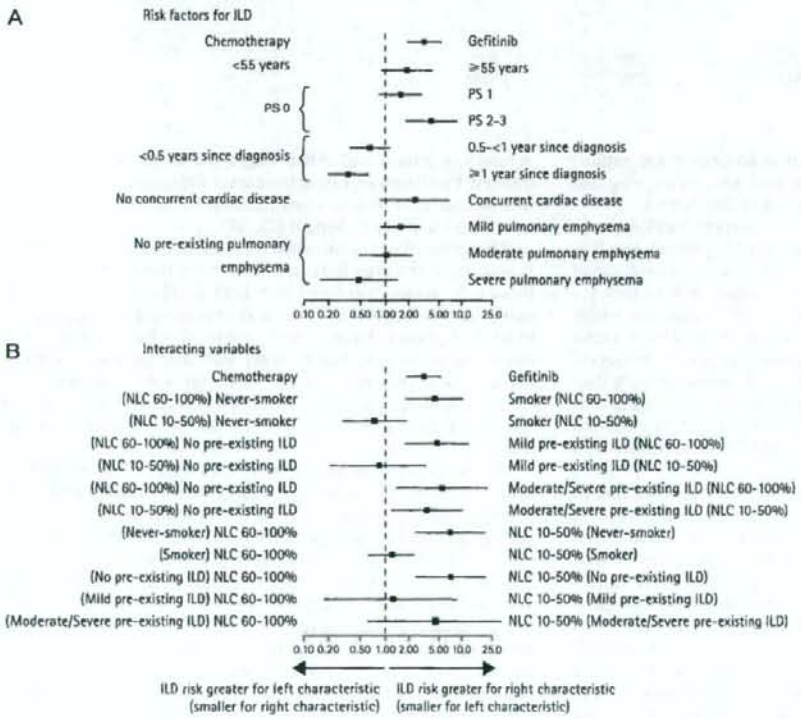
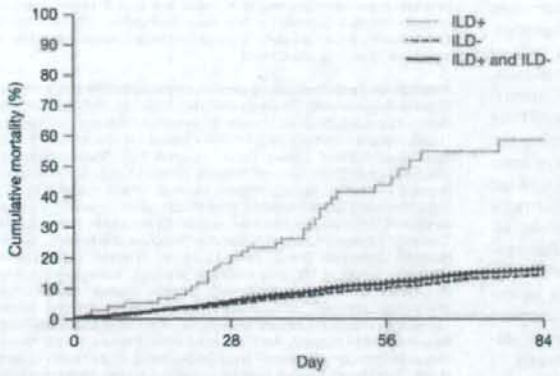


Figure 2. Adjusted odds ratios for risk factors for acute interstitial lung disease (ILD) in Japanese patients with non–small cell lung cancer from final logistic model. NLC = normal lung coverage (extent of normal lung on computed tomography scan); PS = World Health Organization performance status.



Number of patients at risk:

ILD+	78	64	22	11
ILD-	1771	1694	1416	1054
ILD+ and ILD-	1849	1758	1438	1065

Figure 3. Kaplan-Meier curves showing risk of death to 12 weeks in the gefitinib cohort overall and subdivided into those that developed interstitial lung disease (ILD+) and those who did not (ILD−).

leading to possibly more adverse effects in this group, even in the absence of a true relationship to treatment. Attempts to adjust for confounding using collected data would then push the adjusted estimate of effect closer to the null, but if sufficiently precise information on strong confounders cannot be collected, it may be impossible to remove all of the confounding. In conducting this study, the suspected adverse effect of ILD was recognized, and in the clinical setting, recommendations were in place to proceed with caution when treating some patients with suspected elevated baseline risk of ILD. This kind of selection would tend to produce the type of data pattern that was in fact observed in this study, a pattern of negative confounding that produces a more elevated OR when adjustment for confounders is performed. Thus, the results are well in line with what might be expected.

Misdiagnosis of ILD (outcome misclassification) is another concern, but it is expected that the stringent design features have minimized this problem in the present study (*see* online supplement for details). The diagnostic CRB review is a key feature, but it was still CT based, and biopsies—generally considered the gold standard for ILD diagnosis—were in most cases not taken. Overall, a sensitivity analysis suggested that, under reasonable assumptions about possible misclassification of ILD, the main result would remain similar and the conclusions from the study would not be greatly changed.

Random error is another consideration. However, although random error may be responsible for some bias in the point estimate, the confidence interval is reasonably narrow. The results are also consistent with other recent data. For example, as of January 2006, the estimated reporting rate of ILD-type events in Japan from the AstraZeneca Global Drug Safety Database of patients receiving gefitinib treatment was approximately 3.1% (26); from a retrospective study by the West Japan Thoracic Oncology Group (WJTOG), which studied 1,719 patients receiving gefitinib of whom 69 developed ILD, the frequency was 3.5% (95% CI, 2.8–4.5%) (8); from a postmarketing surveillance (PMS) study conducted by AstraZeneca KK Japan, which included 3,322 gefitinib-treated patients, it was 5.8% (25); whereas from the present study, the cumulative incidence at 12 weeks was 4.0% (95% CI, 3.0–5.1%).

These estimates are quite similar, even recognizing that the populations and selection of patients differ between these samples, and duration of follow-up, although similar, varies. In the present study, for the first time, an estimate of cumulative incidence of ILD after 12 weeks of treatment was obtained also from a chemotherapy-treated patient group; this frequency was 2.1% (95% CI, 1.5–2.9%), providing an estimate of this problem unrelated to gefitinib in patients with NSCLC in Japan.

The prognosis for gefitinib-treated patients who were diagnosed with ILD was also quite consistent with other studies. In the PMS study, ILD-related death among patients diagnosed with ILD was 38.6% (25); in the WJTOG study it was 44.3% (8); in the AstraZeneca Global Drug Safety Database as of January 2006, the proportion of ILD-type events with a fatal outcome in patients receiving treatment with gefitinib in Japan was 37.3% (AstraZeneca, data on file); and in the present study it was 31.6%. This proportion was quite similar to the chemotherapy-treated group, 27.9% (adjusted OR, 1.05; 95% CI, 0.4–3.2).

The factors associated with risk of acute ILD observed in this Japanese NSCLC population are largely different or even complementary to factors that predict better response to gefitinib. This would seem to support a hypothesis that the mechanism by which ILD occurs is distinct from the successful cancer response mechanism, offering a potential path toward selecting patients with optimal risk–benefit balance for gefitinib treatment.

Interestingly, the issue of ILD in patients with NSCLC, after gefitinib or other treatments, appears to be a problem largely limited to Japan. From the AstraZeneca Global Drug Safety Database, the reporting rate of ILD-type events in patients receiving treatment with gefitinib was only 0.23% in the rest of the world excluding Japan, based on more than 215,000 patients worldwide estimated to have been exposed to gefitinib (26). Even for neighboring countries, the pattern differs from Japan: the rate for East Asian countries, including Korea and Taiwan but excluding Japan, was 0.17% (26). The proportion of ILD-type events with a fatal outcome was similar, however: 37% in Japan and 31% in the rest of the world. The reasons for this difference in incidence of ILD between Japan and other countries remain unclear, but may relate to both constitutional and environmental factors specific to Japan or Japanese patients. For other drug treatments, too, a higher incidence of ILD has been noted in Japan than elsewhere (12, 13).

Within the study, some exploratory analyses are still ongoing related to genetic and proteomic predictors for ILD in patients with NSCLC, to search for biomarkers for early recognition of ILD and hopefully individualized risk assessment. This may

help to shed light on why ILD appears to be a particular issue for Japanese patients and the possible underlying mechanisms.

The EGFR is expressed on a number of constituent cells of the lungs including epithelium, smooth muscle cells, fibroblasts, and endothelium (27). There have been a number of animal studies using bleomycin- and vanadium pentoxide–induced lung injury with EGFR–tyrosine kinase inhibitors to determine the role of EGFR in lung fibrosis. Gefitinib and AG1478 have been used in such studies of mice and, when administered in a range of therapeutic doses, show clear attenuation of both bleomycin- (28) and vanadium pentoxide–induced (29) lung fibrosis, although one study (30) has shown augmentation of bleomycin-induced fibrosis (when using a subtoxic dose of gefitinib). The similarity of study design and choice of animal strain in the bleomycin studies make it difficult to explain the discrepant results other than by the excessive dosing. This leaves uncertainty as to the underlying mechanism of lung fibrosis in patients with NSCLC receiving gefitinib.

In summary, the study appears to be of adequate validity to avoid serious systematic biases, random error does not seem to be the most likely explanation for the results, and the observed increased risk of ILD with gefitinib treatment relative to chemotherapy treatment in Japanese patients is consistent with previous studies. Although preexisting ILD was confirmed as an important determinant of developing acute ILD symptoms after treatment with gefitinib or chemotherapy, the results also suggested that risk of ILD may be generally affected by a variety of other factors that decrease the amount of normally functioning lung tissue or affect the capability of tissue repair and recovery. The study thus identified several risk factors apart from treatment, which included preexisting ILD, which were not treatment specific, and which were partly similar to risk factors for idiopathic or rheumatic pulmonary lung fibrosis. These findings taken together suggest that there may be a common etiology that gives some patients a greater susceptibility both to idiopathic or rheumatic pulmonary fibrosis and to acute drug-induced lung injury after various treatments.

Conflict of Interest Statement: S.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. H.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. Y.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. Y.I. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.Y. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. The Japan Thoracic Radiology Group does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. H.J. has been an AstraZeneca employee since 2001. Y.I. has been an AstraZeneca employee since 2000. A.A. is a full-time employee of AstraZeneca. C.W. has been a full-time employee at AstraZeneca since 2001 until present and owns shares in the company. T.H. is a full-time R&D scientist at AstraZeneca, UK, and received stock options. F.N. is a full-time employee of AstraZeneca and owns shares in the company.

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Clinical Studies

Irinotecan plus carboplatin for patients with carcinoma of unknown primary site

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Carcinoma of unknown primary site (CUP) is rarely encountered in clinical practice and optimal chemotherapy has not yet been established. This phase II study was conducted to evaluate the efficacy and toxicity of combined irinotecan + carboplatin therapy in chemotherapy-naive patients with CUP. Irinotecan was administered at 60 mg m^{-2} as a 90-min intravenous infusion on days 1, 8 and 15. Carboplatin was administered at an area-under-the curve of 5 mg ml^{-1} min as a 60-min intravenous infusion on day 1. This cycle was repeated every 28 days for up to six cycles. Forty-five patients were enrolled in the study. An intent-to-treat analysis revealed an objective response rate to the treatment of 41.9% (95% confidence interval, 27.0–57.9%). The median time to progression was 4.8 months and the median survival was 12.2 months. The 1- and 2-year survival rates were 44 and 27%, respectively. The most frequent grade 3 or more severe adverse events were leukopaenia (21%), neutropaenia (33%), anaemia (25%) and thrombocytopaenia (20%). Thus, the combination of irinotecan plus carboplatin was found to be active in patients with CUP. Therefore, the regimen may be one of the potentially available chemotherapeutic options for community standard of care in patients with a good performance status.
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Carcinoma of unknown primary site (CUP) represents a group of heterogeneous malignancies that is diagnosed based on the presence of a metastatic disease without an identifiable primary tumour at the time of presentation. Carcinoma of unknown primary site accounts for approximately 3–5% of all newly diagnosed patients with malignancies (Briasoulis *et al*, 2008b).

The prognosis of CUP is generally poor, with a median overall survival time (OS) of approximately 6–12 months. Some of these patients with favourable and unique clinical and/or pathologic features may show prolonged survival with specific treatment approaches (Pavlidis *et al*, 2003). However, most of the patients fit into the category of poor prognosis. Many investigators have made efforts to develop optimal chemotherapeutic regimens based on the empiric approach, and platinum-based combination chemotherapy is considered to be one of the suitable treatment options for a large proportion of these patients (Pavlidis *et al*, 2003).

Irinotecan is a potent inhibitor of DNA topoisomerase I. It exhibits excellent antitumour activity, not only against a broad spectrum of tumours in experimental models (Kano *et al*, 1992; Misawa *et al*, 1995). Carboplatin is an analogue of cisplatin, with less severe non-haematological toxicities (Briasoulis *et al*, 2000; Yonemori *et al*, 2005). No cross-resistance has been found between irinotecan and carboplatin, and a synergistic effect of irinotecan with carboplatin has been shown in *in vitro* studies (Kano *et al*, 1993).

In an earlier study conducted by us, although the combination of docetaxel plus cisplatin produced favourable results in patients with CUP, treatment discontinuation sometimes became necessary because of the renal toxicity induced by cisplatin (Mukai *et al*, 2003; Yakushiji *et al*, 2006). Carboplatin has proven to be as effective as cisplatin against chemosensitive CUP, with an additional advantage of being better tolerated and more convenient in clinical practice (Briasoulis *et al*, 2000). In this study, we report the results of a phase II trial conducted to evaluate the effect of irinotecan plus carboplatin in the treatment for CUP.

PATIENTS AND METHODS

Patients

Patients who had histologically confirmed metastatic carcinoma were eligible for enrollment in this study, if the following evaluations did not reveal a primary site: complete history, physical examination, blood counts and blood chemistry examinations, including serum α-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) as tumour markers in both sexes, carbohydrate antigen 125 (CA125) as a tumour marker in women, prostate-specific antigen (PSA) as a tumour marker in men, urinalysis, head and neck examination with pharyngeal

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endoscopy conducted by experienced head and neck surgeons, urologic examination conducted by experienced urologists, mammography in women, gynaecologic examination by experienced gynaecologists in women, chest X-ray, whole-body computed tomography, upper gastrointestinal endoscopy, lower gastrointestinal endoscopy or barium enema, bone scintigraphy and direct workup of any symptomatic area.

Patients were enrolled in the study if they fulfilled the following eligibility criteria: (1) diagnosed as having CUP, (2) chemotherapy naive, (3) age $\geqslant$20 years, (4) life expectancy of at least 3 months, (5) an Eastern Cooperative Oncology Group performance status of $\leqslant$2, (6) the presence of a measurable lesion as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) (Therasse *et al*, 2000) and (7) adequate organ function (total leukocyte count $\geqslant$3000 per μl or absolute neutrophil count $\geqslant$1500 per μl, platelet count $\geqslant$100 000 per μl, serum total bilirubin $\leqslant$1.5 mg dl^{-1}, serum alanine aminotransferase $\leqslant$2 times the upper limit of normal, serum creatinine $\leqslant$1.5 mg dl^{-1}). Patients with active infection, bowel obstruction, interstitial pneumonitis, uncontrolled severe heart disease, uncontrolled diabetes mellitus, pregnant or lactating women, symptomatic brain metastasis, severe coexistent medical illness or a past history of hypersensitivity to drugs were excluded from the study. Patients who had massive pleural effusion or ascites that required drainage or active concomitant malignancy were also excluded. Patient subgroups that were suitable for well-established treatments (i.e., men with blastic bone metastases showing features of adenocarcinoma and elevated PSA, women with axillary lymph nodes as the only site of disease showing features of adenocarcinoma, woman with papillary serous carcinoma of the peritoneum, patients with either cervical or inguinal lymph node involvement only with features of squamous cell carcinoma, patients with poorly differentiated carcinomas suggestive of germ cell tumour with elevated levels of AFP and/or β-HCG, patients with low-grade, well-differentiated neuroendocrine carcinoma and patients with carcinoma involving a single, potentially resectable site) were also excluded from the study. The protocol was approved by the institutional review board. All patients provided written informed consent before their enrollment.

Treatment

Irinotecan was administered at the dose of 60 mg m^{-2} dissolved in 100 ml saline as a 90-min intravenous infusion, followed by carboplatin at an area-under-the curve of 5 mg ml^{-1} min dissolved in 250 ml of saline or 5% dextrose as a 60-min intravenous infusion. Irinotecan administration was planned for days 1, 8 and 15 of each cycle, and that of carboplatin was planned for day 1 of each cycle. The Calvert formula was used to determine the carboplatin dose, based on the glomerular filtration rate calculated using the serum creatinine level, body weight, age and sex (Cockcroft and Gault, 1976; Calvert *et al*, 1989). Patients showing treatment response or stable disease were administered up to a total of six courses. Granisetron 3 mg and dexamethasone 8 mg were used routinely before the drug infusions as antiemetic agents on days 1, 8 and 15. Prophylactic granulocyte colony-stimulating factor was not used routinely.

Irinotecan and carboplatin were administered on day 1 if the leukocyte count was $\geqslant$3000 per μl or the neutrophil count was $\geqslant$1500 per μl, the platelet count was $\geqslant$75 000 per μl, serum total bilirubin was $\leqslant$1.5 mg dl^{-1}, serum alanine aminotransferase was $\leqslant$2 times the upper limit of normal, the serum creatinine was $\leqslant$1.5 mg dl^{-1} and any non-haematological toxicities, with the exception of alopaecia, were $\leqslant$grade 1. Patients who failed to improve to less than grade 2 in terms of the non-haematological toxicity even after withholding of the treatment for 2 weeks were withdrawn from the study.

Irinotecan was administered on day 8 or 15 if the leukocyte count was $\geqslant$2000 per μl or the neutrophil count was $\geqslant$1000 per μl, the platelet count was $\geqslant$75 000 per μl and any non-haematological toxicities, with the exception of alopaecia, were $\leqslant$grade 1. The dose on day 8 and/or day 15 was omitted entirely if the counts or toxicities did not satisfy the above criteria.

Dose modification of carboplatin from AUC 4 to AUC 5 was allowed if febrile neutropaenia or grade 4 thrombocytopaenia was observed, or if platelet transfusion was required.

Response and toxicity evaluation

All patients were re-evaluated for response after completion of two cycles of treatment, and the response categories were assigned based on the RECIST criteria (Therasse *et al*, 2000). Repeat scans at 8-week intervals were performed to confirm the response. The final response category assigned to these patients represented the best response obtained during the treatment course. Toxicities were evaluated according to the National Cancer Institute's Common Toxicity Criteria, Version 2.0, after every cycle and at the end of the study treatment.

Statistical analysis

The primary end point of this study was the objective response rate, defined as the proportion of patients with complete response or partial response in the intent-to-treat (ITT) population, in turn, defined as patients who had received at least one cycle of irinotecan and carboplatin. The secondary end points included safety and tolerability, time to tumour progression (TTP), OS, and the 1- and 2-year survival rates.

The sample size was determined using Simon's Minimax two-stage design for phase II studies. The response rates to chemotherapy of patients with CUP have been reported as approximately in the range of 20–40% (Briasoulis *et al*, 2000; Greco *et al*, 2000a, b; Dowell *et al*, 2001), so that the null hypothesis was that the true response rate was less than or equal to 30% (not considered to be clinically meaningful). The alternative hypothesis was that the true response rate was more than or equal to 50%. A total of 39 patients were required as the target sample to ensure results with 80% power and a type I error rate of 5%, for rejecting the null hypothesis that the true response probability was less than or equal to 30%. The enrollment of 45 patients was planned to fulfill the requirement of 39 patients, because some patients might need to be potentially excluded from the analysis because of failure to receive at least one cycle of irinotecan and carboplatin.

The objective response rate was reported as a percentage, along with the 95% confidence interval. The TTP and OS were determined by the Kaplan–Meier method. All the statistical analyses were performed using SPSS 12.0J (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Between May 2003 and November 2007, 45 patients were enrolled in this clinical trial. The patient characteristics are listed in Table 1. The median age was 59 years (range, 36–78 years), and the median performance status (PS) was 1 (range, 0–2). The median number of disease sites per patient was two (range, 1–7).

Twenty-three patients had lymph node involvement only. Serum tumour markers were assessed at the baseline pretreatment evaluation in 43 patients. The median number of tumour markers showing elevated serum levels was 5 (range, 0–10). Eighty-seven percent (N=39) of the patients showed elevated serum levels of tumour markers at the time of diagnosis (Table 2).

Table 1 Patient characteristics

Characteristics	No. of patients
No. of patients enrolled	45
Age (years)	
Median	59
Range	36–78
Sex	
Male	23
Female	22
ECOG performance status	
0	19
1	22
2	4
Histologic type	
Adenocarcinoma (well and moderately differentiated)	21
Poorly differentiated adenocarcinoma	9
Squamous cell carcinoma	7
Poorly differentiated carcinoma	5
Clear cell carcinoma	1
Small cell carcinoma	1
Undifferentiated carcinoma	1
No. of disease sites	
1	13
2	10
⩾3	22
Site of disease	
Lymph node	40
Lung	6
Bone	4
Liver	8
Adrenal	2
Malignant effusion	4
Soft tissue	3
Other	6
Prognostic index	
Culine *et al* (2002a)[a]	
Good risk	29
Poor risk	16
van der Gaast *et al* (1996)[b]	
Good risk	19
Intermediate risk	19
Poor risk	7

ECOG = Eastern Cooperative Oncology Group. [a]Good-risk patients had a performance status of 0 or 1 and normal serum lactate dehydrogenase (LDH) levels; poor-risk patients had a performance status of ⩾2 or elevated serum LDH levels. [b]Good-risk patients had a performance status of 0 and serum alkaline phosphatase (ALP) levels of < 1.25 × normal range (*N*); intermediate-risk patients had a performance status of ⩾1 or serum ALP levels of ⩾1.25 × *N*; poor-risk patients had a performance status of ⩾1 and serum ALP levels of ⩾1.25 × *N*.

Table 2 Elevated serum tumour marker levels at diagnosis

Markers	Normal range	No. of measured patients	No. of patients with elevated levels (%)
AFP	⩽10 ng ml^{-1}	42	2 (4.7)
β-HCG	⩽0.5 mIU ml^{-1}	42	22 (52.4)
Cyfra	⩽2.2 ng ml^{-1}	41	30 (73.2)
SCC	⩽1.5 ng ml^{-1}	41	7 (17.1)
NSE	⩽15 ng ml^{-1}	42	10 (23.8)
ProGRP	<46 pg ml^{-1}	41	8 (19.5)
PSA	⩽2.7 ng ml^{-1}	23	5 (21.7)
CEA	⩽5.0 ng ml^{-1}	43	19 (44.2)
SLX	⩽38 U ml^{-1}	41	21 (51.2)
STN	⩽45 U ml^{-1}	41	16 (39)
NCC-ST439	⩽4.5 U ml^{-1}	41	16 (39)
CA125	⩽35 U ml^{-1}	39	25 (64.1)
CA15-3	⩽28 U ml^{-1}	41	12 (29.3)
CA19-9	⩽37 U ml^{-1}	43	17 (39.5)
PIVKA-II	<40 mIU ml^{-1}	39	2 (5.1)
Elastase	⩽300 ng dl^{-1}	41	3 (7.3)

AFP = α-fetoprotein; CA125 = carbohydrate antigen 125; CA15-3 = carbohydrate antigen 15-3; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; Cyfra = cytokeratin 19 fragment; NCC-ST439 = national cancer center-ST439; NSE = neuron-specific antigen; PIVKA-II = protein induced by vitamin K absence-2; ProGRP = progastrin-releasing peptide; PSA = prostate-specific antigen; SCC = squamous-cell carcinoma antigen; SLX = sialyl-specific embryonic antigen; STN = sialyl TN antigen; β-HCG = β-human chorionic gonadotropin.

Efficacy

Forty-five patients were enrolled in this study. All the enrolled patients were included in the analysis for TTP and OS, and 43 patients who had received at least one cycle of irinotecan plus carboplatin were assessed for tumour response to treatment. Two patients who were withdrawn from the study because of the appearance of toxicity in cycle 1 were considered as not evaluable. Objective response was observed in 18 patients, including complete response in two and partial response in 16 patients. Stable disease was observed in 10 patients and progressive disease in 15 patients. The results of an ITT analysis revealed an objective response rate of 41.9% (95% confidence interval, 27.0–57.9%); the response rate was 41.3% in the 30 patients with well-to-poorly differentiated adenocarcinoma and 50.0% in the 23 patients with lymph node involvement only. The median TTP was 4.8 months, and the median OS was 12.2 months. The 1- and 2-year survival rates were 44 and 27%, respectively (Figure 1).

Toxicity

The toxicity data are listed in Table 3. Bone marrow suppression (leukopaenia, neutropaenia and thrombocytopaenia) and gastrointestinal toxicities, such as nausea, vomiting, diarrhoea and appetite loss, were the most frequent. There were no treatment-related deaths in this study.

Overall, 180 treatment cycles were administered and the median number of cycles per patient was four (range, 1–6). Of the 180 cycles, in 9.4% (17 episodes), the day-8 administration of irinotecan was withheld because of neutropaenia (11.8%), anaemia (5.9%), thrombocytopaenia (35.3%) or non-haematological toxicity (41.1%), including two episodes of fatigue, three episodes of nausea, two episodes of infection and one episode of palpitation. Furthermore, in 27.2% of the cycles, the day-15 administration of irinotecan was withheld because of neutropaenia (14.3%), thrombocytopaenia (65.3%), non-haematological toxicity (16.3%), including one episode of appetite loss, one episode of nausea, two episodes of diarrhoea, four episodes of febrile neutropaenia and patient refusal for personal reasons (two instances). The day-8 or day-15 irinotecan was withheld at least once in 24 (53%) patients. Five patients (11.1%) with anaemia required red blood cell transfusion and four patients (8.9%) with thrombocytopaenia required platelet transfusion. Dose modification of carboplatin was necessary in 15.5% of the patients (seven patients).

DISCUSSION

Recently published trials, in the literature, of regimens containing platinum agents for CUP have reported objective response rates in the range of 13–55% and median OS in the range of 6.0–16.2

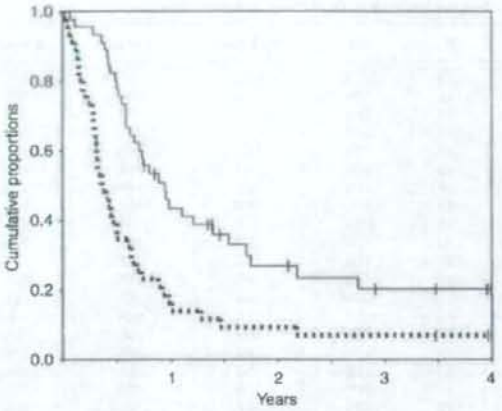

Figure 1 Kaplan–Meier analysis to determine the time to progression (dotted line) and overall survival (solid line).

Table 3 Toxicity profiles (frequency > 10%)

Profile	Frequency (%)	No. of grade 3 (%)	No. of grade 4 (%)
Haematologic toxicity			
Leukopaenia	75.6	6 (13.3)	4 (8)
Neutropaenia	80	6 (13.3)	9 (20)
Anaemia	93.3	8 (17.8)	3 (6.7)
Thrombocytopaenia	68.9	7 (15.6)	2 (4.4)
Non-haematologic toxicity			
Fatigue	60	0 (0)	0 (0)
Appetite loss	46.7	0 (0)	0 (0)
Nausea	82.2	1 (2.2)	0 (0)
Vomiting	26.7	1 (2.2)	0 (0)
Diarrhoea	57.8	4 (8)	0 (0)
Constipation	42.2	0 (0)	0 (0)
Skin rash	20	0 (0)	0 (0)
Febrile neutropaenia	13.3	5 (11.1)	1 (2.2)

months (Table 4). In two of these trials conducted to evaluate the activity of first-line platinum-based combination chemotherapy, the treatment regimen included irinotecan (Culine *et al*, 2003; Briasoulis *et al*, 2008a). According to one, the combination of irinotecan plus cisplatin yielded an objective response rate of 38% and median OS of 6 months (Culine *et al*, 2003). In another study limited to poor-prognosis patients, irinotecan plus oxaliplatin yielded an objective response rate of 13% and median survival time of 9.5 months, with 40% of the patients still alive at 1 year (Briasoulis *et al*, 2008a). The patient background, especially the prognostic characteristics, may have an influence on the treatment outcome. Two-thirds of the patients in this study were prognostically good-risk patients, with a low percentage of patients having liver metastasis and a large percentage of patients with the disease extent being limited to the lymph nodes; in contrast, in most of the recently published series, the majority of the patients were prognostically poor-risk patients and/or had liver metastasis. Therefore, potential bias would make a reliable comparison of the results of the present and previous studies difficult.

Interestingly, the Kaplan–Meier analysis in this study revealed a 2-year survival rate of 27%, with some patients even showing long-term survival (Figure 1). The results of chemotherapy in a total of 1515 patients enrolled in 45 trials including 10 patients or more conducted between 1964 and 2002 showed that survival of the patients beyond 2 years was rare and that there were no cases of disease-free survival beyond 3 years (Pavlidis *et al*, 2003; Greco and Hainsworth, 2008). However, more recent studies have reported long-term survival in a small percentage of patients (Table 4). Long-term follow-up of the 396 patients enrolled in the five most recent studies revealed 1-, 2-, 3-, 5-, 8- and 10-year survival rates of 38, 19, 12, 11, 8 and 8% (Greco and Hainsworth, 2008). Although the reasons for the recent increase in long-term survival are uncertain, it is noteworthy that long-term survival was obtained with the combination of platinum agents and new agents.

The emergence of new non-platinum agents after 1995, including taxanes, gemcitabine, vinorelbine and irinotecan, has enabled the development of platinum-based combination chemotherapy for patients with CUP (Pavlidis *et al*, 2003). However, no definitive conclusions have been reached, because there is still no evidence based on randomised clinical trials to prove the superiority of the aforementioned combination chemotherapies over single-agent platinum therapy. In addition, the clinical benefits and risks of doublet and triplet combination chemotherapies are still uncertain. An attempt was made by European investigators to compare the effect of single-agent cisplatin with that of combined therapy with gemcitabine plus cisplatin on survival in good-risk patients with CUP. Although the results of this prospective trial were expected to clarify the role of combination chemotherapy in good-risk patients with CUP, the trial was stopped due to insufficient accrual, and the result showed a non-significantly higher survival with gemcitabine plus cisplatin as compared to that with cisplatin alone (Gross-Goupil *et al*, 2008).

Recently, standard chemotherapeutic regimens with or without molecular-targeting agents have been established for many cancers. Thus, there is a great demand to optimise the chemotherapeutic regimen for each patient with CUP. The approach based on the genomic characteristics may come to represent one of the breakthroughs in the proper use of chemotherapies tailored to individual patients.

In addition, the advances in the development of many molecular-targeted agents provide opportunities to explore various new combination therapies containing both cytotoxic and molecular-targeted agents for patients with CUP. Several studies have demonstrated the immunohistochemical expression of relevant molecular targets at high frequencies in tissue specimens (Massard *et al*, 2007). A phase II trial of bevacizumab plus erlotinib revealed substantial activity of this combination in patients treated previously or patients who had not received treatment because of the presence of poor-prognostic features (Hainsworth *et al*, 2007). In a preliminary study, treatment with paclitaxel plus carboplatin used in combination with bevacizumab plus erlotinib yielded an objective response rate of 48% ($N = 19$ out of 40) and was well tolerated as first-line chemotherapy for patients with CUP (Greco *et al*, 2008). After first-line platinum-based combination chemotherapy, the approach of empiric second-line chemotherapy has shown little promise, with extremely low response rates (Hainsworth *et al*, 2001, 2005). Therefore, tailor-made first-line chemotherapy by genomic typing or addition of molecular-targeted drugs may be important in the treatment of CUP, which includes heterogeneous cancers, rather than the development of second-line chemotherapy.

In this study, the most frequently encountered toxicity was haematological toxicity and some patients needed blood transfusion or dose reduction of carboplatin. The dose delivery was fairly smooth in the chemotherapy-naive patients with CUP as compared with that in our earlier phase I study of combined irinotecan plus carboplatin in patients with heavily treated ovarian cancer (Yonemori *et al*, 2005). Among the advantages of this regimen are

Table 4 Clinical trials of first-line regimens containing platinum agents reported in the literature from 2000

Group	Reference	Regimen	N	RR	MST (m)	1 year[a]	2 year[b]
Doublet	Briasoulis et al (2000)	Carbo–P	77	38.7%	13.0	NA	NA
	Voog et al (2000)	Cis–E	22	32%	8.0	NA	NA
	Greco et al (2000a)	Cis–D	26	26%	8.0	40%	28%
		Carbo–D	47	22%	8.0	33%	28%
	Dowell et al (2001)	Carbo–E	17	19%	8.3	26%	NA
	Saghatchian et al (2001)	Cis–E→Cis–E–B–I	30	40%	9.4	NA	28%
		Cis–F	18	44%	16.1	NA	39%
	Culine et al (2002b)	Dx–Cy⇒Cis–E	82	39%	10.0	NA	NA
	Culine et al (2003)	Cis–G	39	55%	8.0	NA	NA
		Cis–Ir	40	38%	6.0	NA	NA
	Park et al (2004)	Cis–P	37	42%	11.0	38%	11%
	El-Rayes et al (2005)	Carbo–P	22	23%	6.5	27%	NA
	Pittman et al (2006)	Carbo–G	51	30.5%	7.8	26%	12%
	Briasoulis et al (2008a)	Ox–Ir	47	13%	9.5	40%	NA
	Pentheroudakis et al (2008)	Carbo–D	47	32%	16.2	NA	NA
	This study	Carbo–Ir	45	41.9%	12.2	44%	27%
Triplet or more	Pamis et al (2000)	Cis–F–Ep	43	23%	5.8	NA	NA
	Greco et al (2000b)	Carb–P–E	71	48%	11.0	48%	20%
	Guardiola et al (2001)	Cis–Dx–Cy	22	50%	10.7	NA	NA
	Macdonald et al (2002)	Cis–F–Mit	31	27%	7.7	28%	10%
	Greco et al (2002)	Carbo–G–P	113	25%	9.0	42%	23%
	Balaña et al (2003)	Cis–G–E	30	36.6%	7.2	26%	NA
	Piga et al (2004)	Carbo–Dx–E	102	26.5%	9.0	35.2%	18.1%
	Greco et al (2004)	Carbo–P–E→G–Ir	111	33%	9.1	35%	16%
	Palmeri et al (2006)	Cis–G–P	33	48.5%	9.6	NA	NA
		Cis–G–V	33	42.3%	13.6	NA	NA
	Schneider et al (2007)	Carb–G–Cape	33	39.4%	7.6	35.6%	14.2%
	Greco et al (2008)	Carbo–P–Bv–Er	51	48%	11.3	NA	NA

B = bleomycin; Bv = bevacizumab; Cape = capecitabine; Carbo = carboplatin; Cis = cisplatin; Cy = cyclophosphamide; D = docetaxel; Dx = doxorubicin; E = etoposide; Ep = epirubicin; Er = erlotinib; F = 5-FU; G = gemcitabine; I = ifosfamide; Ir = irinotecan; m = months; Mit = mitomycin C; MST = median survival time; NA = not available; Ox = oxaliplatin; P = paclitaxel; RR = response rate; V = vinorelbine. [a]1 year = 1-year survival rate. [b]2 year = 2-year survival rate.

that it is easy to adjust the irinotecan dose during each chemotherapy cycle according to the individual toxicity profiles and to manage the chemotherapy on an outpatient basis without prophylactic use of granulocyte-stimulating factor or erythropoietin.

In conclusion, combined irinotecan plus carboplatin chemotherapy appears to exert satisfactory activity and to be reasonably well tolerated in patients with CUP. Many conventional chemotherapies have been reported as the community standard of care for patients with CUP. This regimen was moderately well tolerated and may become established as one of the treatment options in patients with a good PS.

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Conflict of interest

Katsumata N: Honoraria (Sanofi-aventis, Pfizer, Nippon Kayaku, Kyowa Hakko Kogyo, Zeneca). His family members have no financial interest or conflict of interest in relation to this study. None of the authors or their immediate family members have any financial interest or conflict of interest in relation to this study.

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CASE REPORT

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Leptomeningeal metastasis from ovarian carcinoma successfully treated by the intraventricular administration of methotrexate

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Abstract A 60-year-old woman with a history of ovarian carcinoma and complaining of gait instability, dizziness, nausea, and a right temporal headache visited a neurologist. A diagnosis of leptomeningeal metastasis was made, based on the results of a cerebrospinal fluid examination. After the administration of intrathecal methotrexate, her neurological complaints disappeared. An Ommaya intraventricular reservoir was inserted, and methotrexate administration was continued for 11 months, until another recurrence was found in her pelvis. Although uncommon, the possibility of leptomeningeal metastasis from ovarian carcinoma should be considered; in such cases, treatment with intraventricular methotrexate may be effective and feasible and should be considered as a treatment strategy.

Key words Leptomeningeal metastasis · Ovarian carcinoma · Intrathecal chemotherapy · Methotrexate

Introduction

Metastasis to the central nervous system (CNS) from ovarian carcinoma is uncommon, and leptomeningeal metastasis is even more uncommon. The reported incidence of CNS metastasis from ovarian carcinoma ranges between 0.29% and 4.5%,[1–4] and the number of reported cases of leptomeningeal metastasis is less than 30.

In this report, we describe the case of a 60-year-old woman with a leptomeningeal metastasis from an ovarian carcinoma; this patient was successfully treated by the intraventricular administration of methotrexate.

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Case report

A 60-year-old woman visited a neurologist's office in November 2004; she complained of dizziness, nausea, a right temporal headache and gait instability, with a tendency to lean to the left. She had a history of right ovarian carcinoma, diagnosed in June 2003, and identified by adenocarcinoma cells obtained from peritoneal lavage (Fig. 1A). Her tumor had been classified as stage IV, based on a positive cytology result in right pleural fluid. Her serum carbohydrate antigen (CA) 125 level was 2680 U/ml. Because of massive ascites and hypoxia arising from pleural effusion, she underwent chemotherapy with a combination of carboplatin at an AUC (area under the concentration-time curve) of 6 on day 1, plus paclitaxel (80 mg/m^2) on days 1, 8, and 15 every 3 weeks; this regimen had been used in a clinical study by the Japanese Gynecologic Oncology Group (JGOG trial 3016). The regimen was repeated four times in our patient, and her ascites and pleural effusion completely disappeared. Her serum CA125 level also decreased, to 29 U/m. The treatment efficacy was rated as a partial response. The patient subsequently underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and an omentectomy as part of cytoreductive surgery, resulting in residual tumors of less than 1 cm. The histologic diagnosis was serous adenocarcinoma. Following the surgery, three courses of chemotherapy (the same regimen as that described above) were administered, ending in December 2003. Her serum CA125 level at that time was under 10 U/ml. Her clinical course had been followed and she had shown no signs of reoccurrence.

At the time of her visit to the neurologist, the results of a general physical examination were entirely within the normal limits. Upon neurological examination, however, she was found to have sensory neuropathy in her extremities (which had previously appeared after the postoperative

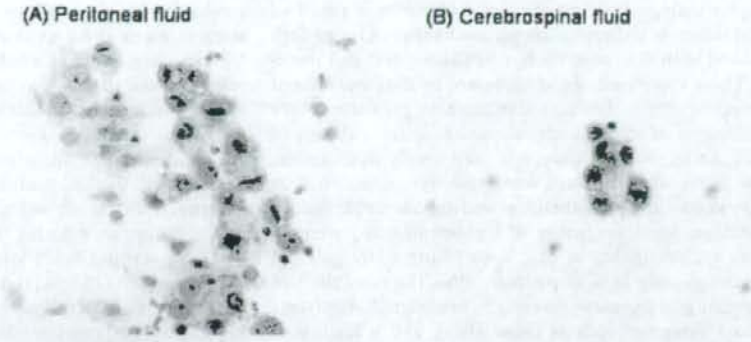

Fig. 1A,B. Cytology of **A** peritoneal lavage and **B** cerebrospinal fluid. **A** Numerous malignant cells with hyperchromatic nuclei and vacuolar degeneration, derived from ovarian carcinoma; **B** agglomeration of cells that resemble the adenocarcinoma cells in the peritoneal lavage

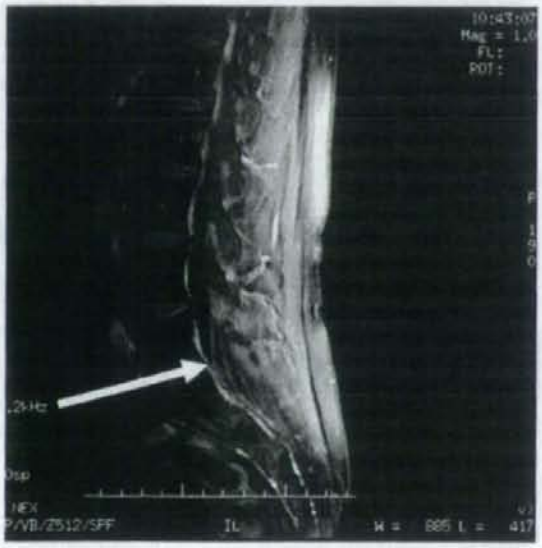

Fig. 2. Gadolinium-enhanced magnetic resonance imaging (MRI) of the spine (T1-weighted image); the nerve roots of the cauda equina are enhanced (*arrow*)

chemotherapy), a wide-based gait, and difficulty standing with her feet placed together – regardless of whether her eyes were open or closed. She was afebrile with no visible signs of malaise, and she did not have a stiff neck.

Further diagnosis workup was done by the neurologist. Magnetic resonance imaging (MRI) of the brain revealed no evidence of metastasis. MRI of the spine revealed an enhancement along the nerve roots of the cauda equina (Fig. 2). An examination of her cerebrospinal fluid was done on the same day, and revealed malignant cells (15 cells per µl) with the same characteristics as the serous adenocarcinoma cells in the peritoneal lavage derived from the ovarian cancer (Fig. 1B). Thus, a diagnosis of leptomeningeal metastasis was confirmed. She was then referred to our hospital for further management.

The patient's clinical screening results, complete blood count, urinalysis results, chest X-ray, and bone scan were normal. A computed tomography (CT) examination of her abdomen disclosed no evidence of recurrent malignancy. Her serum CA125 level was elevated (90 U/ml).

The patient was given intrathecal methotrexate at the dose of 10 mg/kg of body weight per day for one day. She developed nausea as an adverse event, but her symptoms were alleviated after the intrathecal administration of 20 mg prednisolone. The intrathecal methotrexate treatment was repeated three times, at intervals of 5 days. Her neurological complaints disappeared, and so an Ommaya intraventricular reservoir was inserted, without any complications. The dosing interval was gradually extended, but when it was tapered off to a dosing interval of once in 2 months, lumbago and weakness of the lower limbs appeared. Therefore, we reverted to once-monthly administration and continued this treatment for a total of 19 times (190 mg/kg of body weight). The cerebrospinal fluid cytology results remained positive, but the number of cells decreased during the treatment. Her serum CA125 level returned to within the normal limit after the third administration, but gradually increased once again after June 2005, when the sixteenth administration was performed.

In October 2005, a CT examination showed a new tumor in her left pelvic region, and her serum CA125 level was elevated to 119 U/ml. Based on this evidence, we diagnosed a recurrence of the disease and started systemic treatment with six cycles of docetaxel and carboplatin, producing a good clinical response. However, in May 2006, a meningeal metastasis became apparent on a head MRI examination. One week later, she developed rapidly progressive consciousness disturbance and died.

Discussion

Herein, we have reported a rare case of leptomeningeal metastasis from an ovarian carcinoma that was successfully treated by the intrathecal administration of methotrexate. Although metastases to the CNS from ovarian carcinomas are uncommon, the incidence of such metastases might increase with the prolongation of survival associated with improved primary treatment.[5] This phenomenon has also been reported in some other types of tumors, such as breast cancer.[6]

Leptomeningeal metastasis can manifest as a result of several different pathophysiologic mechanisms. Our patient presented with dizziness, nausea, headache, and gait instability. These symptoms can be explained by the involvement of the nerve root and increased intracranial pressure. Other possible signs of leptomeningeal metastasis are a change in mental status, seizure, dementia, autonomic dysfunction, cranial nerve abnormalities, and spinal symptoms such as limb weakness and paresthesia, as well as bowel and bladder dysfunction. Signs suggestive of leptomeningeal irritation, such as nuchal rigidity or pain upon lifting a straightened leg, occur in only 15% of patients;[7] thus, the possibility of leptomeningeal metastasis should be considered in patients with any symptom such as those above and a history of malignant disease. Imaging findings, such as an MRI examination of the head or spinal root, and positive spinal fluid samplings are helpful for making a diagnosis. MRI is probably more sensitive than a single spinal fluid cytology,[8] but its specificity is low. In our patient, although a spinal MRI showed abnormal findings, the findings were not sufficient to arrive at a definitive diagnosis of metastasis.

Because reports of leptomeningeal metastasis from ovarian carcinoma are scarce, strategies for treatment should be drawn from experiences with other tumors. Although the prognosis after leptomeningeal metastasis depends on the type of the primary cancer, the goals of treatment remain the palliation of symptoms, the improvement or stabilization of neurological function, and, if possible, the prolongation of survival. Intrathecal chemotherapy is a mainstay of treatment, although its effectiveness may be limited and its superiority over systemic treatment has still not been established in randomized trials. Currently, methotrexate, liposomal cytarabine, and, less commonly, thiotepa are used for intrathecal chemotherapy;[7] methotrexate is the most commonly used agent and the only one available in Japan. While its beneficial effect in the treatment of hematologic malignancies has been well established, its effect against solid tumors, with the exception of breast tumors,[9,10] remains unknown.

Gordon et al.[11] reported the first successfully treated case of a leptomeningeal metastasis from ovarian carcinoma. Their patient was treated with intrathecal methotrexate at a dose of 15 mg/m^2. After her neurological symptoms had been alleviated and results of cytologic examination of her spinal fluid had reverted to normal, systemic chemotherapy was administered. She survived for at least 7 months after the diagnosis of leptomeningeal metastasis, but her subsequent course was not mentioned. In our patient, the administration of intrathecal methotrexate was also effective for alleviating the clinical symptoms. We were unable to discontinue the treatment, however, because her neurological complaints recurred when the frequency of the drug administration was reduced. We did not start systemic chemotherapy even after her neurological symptoms had disappeared, because we believed that the goal of the treatment of her ovarian cancer was the palliation of symptoms, for which the intrathecal methotrexate was sufficient.

The meticulous assessment of response to therapy is essential for validating the continued use of aggressive treatments such as intrathecal chemotherapy. However, no suitable method for evaluating the disease progression of leptomeningeal metastasis has been established. We mostly relied on the patient's symptoms, the alleviation of which was the main goal of treatment. Spinal fluid cytology results were also evaluated. Generally, two consecutive samples are required to exclude a false-negative cytologic result with confidence.[12] We had planned to stop the intrathecal administration if this result was achieved, but the malignant cells never disappeared during the treatment. We further monitored the serum CA125 level as a supplementary measure. The serum CA125 level is a reliable marker for the evaluation of ovarian carcinoma.[13] Although its use as an indicator in patients receiving intrathecal chemotherapy has not been evaluated, in our patient, the CA125 level was elevated at the time of diagnosis and decreased to within the normal limits after treatment. It also became elevated again at the time of disease progression. While further experience is needed, the serum CA125 level may play an important role in evaluating the efficacy of intrathecal chemotherapy or in assessing the disease progression of leptomeningeal metastasis from an ovarian carcinoma.

One of the major issues in the treatment of our patient was whether we should have started the systemic chemotherapy earlier. The treatment-free interval was long enough, and good response was expected from systemic chemotherapy. However, it is impossible to give systemic chemotherapy concurrently with intrathecal chemotherapy. And because the purpose of the treatment, palliation, was well achieved by intrathecal methotrexate, and discontinuation was not feasible, we decided not to start systemic treatment instead of the intrathecal treatment. We chose to start systemic chemotherapy only after we found the new pelvic mass, which progression had a strong possibility to reduce her quality of life.

In summary, we have presented a case of leptomeningeal metastasis from an ovarian carcinoma in which intraventricular methotrexate chemotherapy was both effective and feasible. Although uncommon, there is a possibility of leptomeningeal metastasis from ovarian carcinoma, and treatment using intraventricular methotrexate should be considered if the patient is otherwise in good condition. Also, the serum CA125 level may be useful for evaluating the efficacy of the treatment.

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SHORT COMMUNICATION

Logistic regression analysis for febrile neutropenia (FN) induced by docetaxel in Japanese cancer patients

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Abstract
Purpose Fever occurring in a neutropenic patient remains a common life-threatening complication of cancer chemotherapy, and febrile neutropenia (FN) is recognized as a dose-limiting factor (DLF) in cancer chemotherapy. The aim of this study is to evaluate the significant covariate associated with the risk of FN occurrence in Japanese patients.
Methods A stepwise logistic regression was conducted using data from Japanese cancer patients treated with docetaxel. Based on those results, an equation was established which predicts the probability of FN occurrence.
Results From the result of a stepwise multivariate logistic regression analysis, performance status factor (PS*), which is set to 1 if performance status factor is 2 or 3, and to 0 otherwise and area under the plasma concentration versus time curve (AUC) were selected as covariates significantly associated ($p < 0.05$) with FN occurrence. The obtained equation to predict the probability (P) of docetaxel-induced FN occurrence is $P = 1/[1 + \exp\{-(1.29 \times \mathrm{AUC} + 1.41 \times \mathrm{PS}^* - 3.52)\}]$. A receiver operating characteristic (ROC) curve analysis revealed that the best cut-off value of FN probability to differentiate between the presence and absence of FN was 0.61.
Conclusions An equation was developed to predict the probability of FN occurrence for Japanese patients treated with docetaxel. It was found that FN may not occur when the probability of FN occurrence calculated by the predictive equation is less than 0.61. Therefore, the predictive equation for FN occurrence may be used for selecting the appropriate dose to avoid the occurrence of FN.

Keywords Docetaxel · Febrile neutropenia · Logistic regression analysis · Neutrophils · Japanese cancer patients

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Introduction

Fever occurring in neutropenic patients remains a common life-threatening complication of cancer chemotherapy [1]. Febrile neutropenia (FN) requires treatment with broad-spectrum antibiotics [2–7], and the standard setting of care has been patient hospitalization with close monitoring until fever resolution and recovery from neutropenia. Therefore, FN is recognized as a dose-limiting factor (DLF) of cancer chemotherapy.

Docetaxel is a widely used anticancer agent that is active against breast, non-small cell lung, ovarian, head and neck, gastric, and prostate cancers [8–13]. FN is a common complication of docetaxel therapy [14]. Bruno et al. [14] reported that α_1-acid glycoprotein (AGP) and clearance of docetaxel (CL) are significant covariates associated with the risk of FN occurrence, using a stepwise

logistic regression analysis for subjects enrolled in Phase 2 studies in Europe and United State. However, in clinical studies for the development of anticancer drugs, particular patients with moderate to severe liver dysfunction or poor performance status are commonly excluded, and there have been several studies for chemotherapy-induced FN occurrence [15, 16]. However, there have been no studies except for the study of Bruno et al. [14] which evaluated the significant covariate associated with the risk of docetaxel-induced FN occurrence. Therefore, in this study, a stepwise logistic regression analysis was conducted using data from Japanese cancer patients treated with docetaxel including patients with liver failure or poor performance status, who should fall within the exclusion criteria in conventional clinical studies for new drug development. The population pharmacokinetic (PK) part of this study has already been reported [17], where a three-compartment open model fitted well with the observed data.

Materials and methods

Patient selection

Two hundred patients were enrolled into the present clinical research of docetaxel (as single agent or combination chemotherapy), which was conducted at the hospitals of National Cancer Center Hospital East in Japan. The eligibility criteria included histologically or cytologically confirmed solid cancers against which docetaxel is active, age $\geq$20 years, Eastern Cooperative Oncology Group performance status 0–3, at least 3 weeks since the last chemotherapy (6 weeks for mitomycin and nitrosoureas), and adequate hematological values (white blood cells $\geq$3,000/μL, platelet count $\geq$75,000/μL). The exclusion criteria were active infection, severe heart disease, uncontrolled hypertension or diabetes mellitus, pregnant/nursing women, or seropositive for human immunodeficiency virus, hepatitis C virus, hepatitis B surface antigen or syphilis. Patients who received granulocyte colony stimulating factors after docetaxel administration were excluded from this analysis. This study was approved by the Institutional Review Board of the National Cancer Center Hospital East, Japan, and all patients gave their written informed consent.

Treatment and follow-up

Docetaxel was infused intravenously over 1 h every 3 weeks. Most patients received the approved dose in Japan of 60 mg/m^2, but attending physicians were allowed to reduce the dose depending on liver function, performance status (PS), or the extent of prior chemotherapy. The physical examination and toxicity assessment included blood chemistry and complete blood cell counts with differential counts as well as platelet counts, and were performed before treatment and repeated at least weekly during the first course. Dexamethasone (8 or 16 mg) was administered before the docetaxel regimen to prevent emesis. The data obtained during the first course were used for an analysis in the present study.

Drug quantification

Blood sampling for drug quantification was carried out before and 30 min during the docetaxel infusion, at the end of the infusion, and 0.17, 1, 5, 10 and 24 h after the end of infusion. Heparinized blood was centrifuged immediately, and plasma samples were frozen at −80°C until analysis. The concentration of docetaxel in plasma was determined using a high-performance liquid chromatography (HPLC) as previously reported [18].

Population pharmacokinetic analysis

Pharmacokinetic parameters for individual patients were calculated using the Bayesian estimation after the population pharmacokinetic parameters were estimated in the entire population. These calculations were carried out using nonlinear mixed-effect modeling software, NONMEM (version V, level 1.1; GloboMax, Ellicot City, MD, USA). A method of first-order conditional estimation (FOCE) with an INTERACTION option was employed. NONMEM was running with a Compaq Visual FORTRAN 6.6 compiler (Hewlett–Packard Company, Palo Alto, CA, USA), on a Pentium 4 central processing unit, under the Windows XP operating system (Microsoft Corporation, Redmond, WA, USA). A three-compartment open model with zero-order administration (i.e. constant intravenous infusion) and first-order elimination (ADVAN 11 and TRANS 4) was used to describe the plasma concentration-time course of docetaxel in the entire population. The PK model was parameterized in terms of clearance (CL), the volume of the central compartment (V_1), inter-compartment clearance between the central and peripheral-1 compartments (Q_2), the volume of the peripheral-1 compartment (V_2), inter-compartment clearance between the central and peripheral-2 compartments (Q_3) and the volume of the peripheral-2 compartment (V_3). The interindividual variability was modeled assuming a log-normal distribution for interindividual variability of these pharmacokinetic parameters. For example, for clearance,

$$CL_j = \widehat{CL} \cdot \exp(\eta_{jCL}) \quad (1)$$

where CL_j and $\widehat{CL}$ are the estimated values in an individual j and the population mean for clearance, respectively, and η_{jCL} is the individual random perturbation from the population mean. Intrapatient residual variability was also described by a proportional model. The AUC was calculated as dose/CL in each patient.

Statistical analysis

FN was defined as a fever of greater than 38°C, which required antibiotics. The variables included for statistical analysis are as follows: age, sex, performance status (PS), regiment of prior chemotherapy, radiotherapy, albumin, α_1-acid glycoprotein, alanine aminotransferase, hemoglobin, pretreatment absolute neutrophil counts, the area under the plasma concentration vs. time curve (AUC), and peak concentration at the end of infusion (Cmax). To identify the factors associated with FN, continuous variables were compared between patients with and without FN using the Mann–Whitney's U test, and differences in the distribution of dichotomized variables were evaluated with the Fisher's exact test. Subsequently, factors that were significant ($p \leq 0.05$) were evaluated as potential covariates of categorical end-point (i.e., absence and presence of FN) in a stepwise multivariate logistic regression with backward selection. The backward selection model started with all candidate variables in the model. At each step, a variable that is not significant ($p > 0.05$ by a likelihood ratio test) was removed. This process continued until no non-significant variables remained. Statistic analyses were performed using statistics software, the Statistical Package for Social Systems (version 15J, SPSS Japan Corporation, Tokyo, Japan) and S-plus Professional Edition (version 6.2, Insightful Corporation, WA, USA).

Validation of the model

Since 200 patients is a small sample to develop a predictive model, the multivariate logistic regression model was validated using the technique of bootstrap resampling [19]. This technique is efficient and provides nearly unbiased estimates of the predictive accuracy of the model [20]. 200 samples were drawn at random with replacement, which have same numbers of successes and failures as original sample, then, a backward selection model which was applied to original dataset was fitted repeatedly to the 200 samples. The criterial statistics of model validation are mean and coefficient of variance (CV%) of area under a receiver operating characteristic (ROC) curve obtained from samples, which were calculated normally.

Results

The characteristics of the 200 patients treated in the present study are summarized in Table 1. FN occurred in 9 patients. Almost 90% of the patients had good PS (0 or 1), and 14% had previously received more than 3 regimens of chemotherapy. The Japanese standard dose of docetaxel is 60 mg/m^2, but some patients received reduced doses because of poor PS, liver dysfunction, or extensive prior treatments.

When the characteristics of the patients who did or did not develop FN were compared, the distribution of performance status factor (PS*), which is set to 1 if PS is 2 or 3, and to 0 otherwise, was significantly different, and pretreatment serum levels of albumin (ALB) in patients with FN was significantly lower than in those without (Table 2). Among the pharmacokinetic parameters, AUC was significantly lower in patients with FN. To investigate whether these variables are significantly associated with FN occurrence, a stepwise logistic regression with backward selection was

Table 1 Patient characteristics and the dose of docetaxel

Characteristic	Median and range or No.
Age (years)	57 (21–86)
Sex: female/male (*n*)	114/86
Disease: BC/NSCLC/H-N/Others (*n*)	79/68/31/22
Performance status: 0/1/2/3 (*n*)	46/131/17/6
Combination chemotherapy: Cisplatin/doxorubicin/irinotecan (*n*)	66/6/31
Regimens of prior chemotherapy (*n*)	
<3	172
≥3	28
Radiotherapy (*n*)	
Yes	65
No	135
Albumin (g/dL)	3.7 (1.3–4.6)
α_1-Acid glycoprotein (mg/dL)	97 (19–259)
Alanine aminotransferase (IU/L)	19 (5.0–255)
Hemoglobin (g/dL)	12 (7.5–16)
Pretreatment absolute neutrophil counts (per μL)	3910 (1023–15650)
Dose per body surface area (*n*)	
≥60 mg/m^2	37
≥40 to <60 mg/m^2	69
≥20 to <40 mg/m^2	77
<20 mg/m^2	17

carried out. AUC ($p < 0.001$) and PS* ($p < 0.001$) were selected among the variables listed in Table 2, with CV (%) of 13.5 and 22.1, respectively.

Table 3 shows the coefficients of covariates. Therefore, an equation was implemented which predicts the probability (P) of FN occurrence using these coefficients of significant covariates as follows:

$$P = \frac{1}{1 + \exp[-(1.29 \cdot \mathrm{AUC} + 1.41 \cdot \mathrm{PS}^* - 3.52)]} \quad (2)$$

A solid curve in Fig. 1 represents the probability of FN predicted from Eq. 2 at various AUC when PS* was set at 0. A dotted curve in Fig. 1 represents the probability of FN predicted from Eq. 2 at various AUC when PS* was set at 1.

Figure 2 shows an ROC curve for the probability of FN occurrence, which was predicted from the Eq. 2. The ROC curve indicates that the cut-off value at approximately 0.61 gives the best score of sensitivity and 1-specificity, and the area under an ROC curve is 0.85.

Table 4 shows a contingency, which compares the predicted and observed FN occurrences at the cut-off value of 0.61.

As a result of the model validation using a bootstrap method which created 200 samples of the original dataset,

Table 2 Characteristics and pharmacokinetic parameters of docetaxel in patients with or without febrile neutropenia

	Fever (+)	Fever (−)	p
Patients (n)	9	191	
Age (years)			
Median	59	57	0.470
Range	48–67	21–86	
Sex (n)			
Female	7	107	0.305
Male	2	84	
Performance status (n)			
0–1	5	172	0.0120
2–3	4	19	
Regimens of prior chemotherapy (n)			
0–2	6	165	0.116
≥3	3	25	
Radiotherapy (n)			
Yes	3	62	1.00
No	6	129	
Albumin (g/dL)			
Median	3.5	3.8	0.0280
Range	1.3–3.8	2.6–4.6	
α_1-Acid glycoprotein (mg/dL)			
Median	98	97	0.568
Range	57–241	19–259	
Alanine aminotransferase (IU/L)			
Median	26	19	0.667
Range	8–188	5–255	
Hemoglobin (g/dL)			
Median	11.6	12.2	0.188
Range	8.2–13.7	7.5–16.1	
Pretreatment absolute neutrophil counts (per μL)			
Median	3720	3920	0.795
Range	2270–7310	1023–15650	
Area under the plasma concentration vs. time curve (AUC) (mg*h/L)			
Median	3.03	1.78	0.00100
Range	1.99–4.29	0.451–7.58	
Peak concentration at the end of infusion (Cmax) (mg/L)			
Median	13.7	8.96	0.0830
Range	5.56–17.1	3.73–24.2	