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Bodyweight change during the first 5 days of chemotherapy as an indicator of cisplatin renal toxicity

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To determine whether bodyweight (BW) loss, daily urine volume (UV) or furosemide use are associated with cisplatin nephrotoxicity, performance status, serum chemistries before treatment, average daily UV, maximum BW loss and use of furosemide on days 1–5 of chemotherapy were evaluated retrospectively in chemotherapy-naive patients with thoracic malignancies who had received 80 mg/m² cisplatin. Associations between these parameters and the worst serum creatinine levels (group 1, grade 0–1; and group 2, grade 2–3) during the first cycle were evaluated. Of the 417 patients (327 men and 90 women; median age, 59 years), 390 were categorized into group 1 and 27 were categorized into group 2. More women and older patients were observed in group 2 than in group 1 (11.1 *vs* 5.2%, $P = 0.044$, and 65 *vs* 59 years, $P = 0.041$, respectively). The median average daily UV was 3902 mL in group 1 and 3600 mL in group 2 ($P = 0.021$). A maximum BW loss ≥2.1 kg was noted in 4.4% of patients in group 1 and 18.5% of patients in group 2 ($P = 0.006$). Furosemide was used in 206 (49.4%) patients. The median total dose of furosemide in groups 1 and 2 were 0 mg and 26 mg, respectively ($P = 0.024$). A multivariate analysis showed that a maximum BW loss ≥2.1 kg and the total furosemide dose were significantly associated with group category. In conclusion, BW loss and total furosemide dose were associated with cisplatin nephrotoxicity. (*Cancer Sci* 2007; 98: 1408–1412)

Cisplatin alone or in combination with other chemotherapeutic agents has been the most frequently used chemotherapy regimen against a variety of solid tumors for 30 years because of its significant therapeutic effects.[1] In spite of intensive efforts to devise platinum analogs and the successful development of carboplatin, cisplatin remains a key agent in the treatment of germ cell tumors, head and neck cancer and bladder cancer, as shown in several randomized controlled trials comparing the two platinum agents.[2] In addition, cisplatin has a significant role in the treatment of lung and ovarian cancers, although carboplatin is becoming increasingly used against these cancers as an alternative chemotherapeutic agent.[3,4]

Cisplatin nephrotoxicity has been a major dose-limiting toxicity for this drug in most drug administration schedules.[5] Although the exact mechanism is unclear, high concentrations of platinum and widespread necrosis were observed in the proximal tubules of the kidney. This tubular impairment secondarily leads to a reduction in renal blood flow and glomerular filtration rate, potentiating primary tubular damage. This vicious circle causes a delayed deterioration in renal function, as an increase in the serum creatinine level typically appears 6–7 days after cisplatin administration in humans.[5,6] The standard prophylaxis for cisplatin nephrotoxicity is a normal saline infusion of 1–4 L with osmotic diuresis on the day of cisplatin administration.[5] Although this vigorous hydration diminishes life-threatening renal toxicity, 7–40% of patients still develop a mild to moderate increase in their serum creatinine levels, which influences subsequent cisplatin therapy.[7,8] For the prevention of cisplatin nephrotoxicity, the maintenance of good renal hemodynamics may be necessary for a week or longer after cisplatin administration, although indicators of hydration management on day 2 of chemotherapy and thereafter have not been reported. The purpose of this retrospective study was to evaluate bodyweight (BW) changes, daily urine volumes (UV) and use of furosemide on days 1–5 of chemotherapy as well as pretreatment patient characteristics in the hope of finding an association between these factors and nephrotoxicity during the first cycle of cisplatin-based chemotherapy.

Patients and Methods

Patient selection. Patients were selected retrospectively for the present study according to the following criteria: (1) a histological or cytological diagnosis of thoracic malignancy; (2) no prior chemotherapy; (3) a chemotherapy treatment regimen that included 80 mg/m² of cisplatin; and (4) treatment as an in-patient at the National Cancer Center Hospital. Patients were excluded if: (1) their pretreatment serum creatinine level was abnormal; or (2) no record of BW or daily UV on days 1–5 of chemotherapy was available.

Treatment. Cisplatin at a dose of 80 mg/m² was administered intravenously over 60 min on day 1 in combination with other chemotherapeutic agents. Hydration just before cisplatin administration consisted of 500 mL normal saline, 500 mL 5% glucose and 10 mL KCl over 4 h. Hydration just after cisplatin infusion consisted of 500 mL normal saline with 40 g mannitol over 2 h, followed by 500 mL normal saline, 1000 mL 5% glucose and 15 mL KCl over 6 h. On days 2–5, 1000 mL normal saline, 1000 mL 5% glucose and 20 mL KCl were administered over 8 h. Antiemetic prophylaxis consisted of a $5HT_3$ antagonist and 16 mg dexamethasone on day 1 followed by 8 mg dexamethasone on days 2 and 3, 4 mg on day 4 and 2 mg on day 5. Furosemide was given orally or intravenously if fluid retention was suspected based on an increased BW or a decreased UV. These treatments were repeated every 3–4 weeks.

Data collection and statistical analyses. The patients' baseline characteristics, including age, sex and performance status as well as serum albumin, Na, K, Ca and fasting blood sugar levels were analyzed. The modified Ca level was calculated using the following formula:

$$\text{modified Ca (mg/dL)} = \text{serum Ca (mg/dL)} + 4 - \text{serum albumin (g/dL)}.$$

The daily UV and BW at 0800 hours (before breakfast) and at 1600 hours (before dinner) were measured once a day on days

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Table 1. Patient demographics and pretreatment blood chemistry tests in groups categorized according to worst creatinine grade

		Group 1 (n = 390)		Group 2 (n = 27)		P-value
		n	%	n	%	
Sex	Male	310	94.8	17	5.2	0.044
	Female	80	88.9	10	11.1	
Age (years)	Median	59	(Range 18–77)	65	(Range 38–74)	0.041
Performance status	0	169	92.3	14	7.7	0.82
	1	218	94.3	13	5.6	
	2–3	3	100	0	0	
Serum albumin	≥3.7 g/dL	319	94.1	20	5.9	0.32
	≤3.6 g/dL	71	91.0	7	9.0	
Serum Na	≥138 mEq/L	341	93.2	25	6.8	0.43
	≤137 mEq/L	49	96.1	2	3.9	
Serum K	≤4.9 mEq/L	373	93.7	25	6.3	0.46
	≥5.0 mEq/L	17	89.5	2	10.5	
Modified Ca†	≤10.4 mg/dL	376	93.3	27	6.7	0.31
	≥10.5 mg/dL	14	100	0	0	
Fasting blood sugar	≤125 mg/dL	322	92.8	25	7.2	0.36
	≥126 mg/dL	54	96.4	2	3.6	
	Not done	14	100	0	0	

†Calculated using the equation: modified Ca (mg/dL) = serum Ca (mg/dL) + 4 − serum albumin (g/dL). Groups 1 and 2 were patients with worst creatinine grades of 0–1 and 2–3, respectively.

1–5 of the chemotherapy regimens. The BW at 0800 hours on day 1 was used as the baseline BW. During the chemotherapy course, blood chemistry was analyzed at least once a week. Data on furosemide use and the BW gain just before furosemide use during the first course of chemotherapy were obtained from medical charts.

The worst serum creatinine level during the first course of chemotherapy was graded (WCG) according to the National Cancer Institute (NCI) Common Toxicity Criteria, version 2.0. The patients were categorized into two groups according to their WCG: patients with WCG_{0-1} (group 1) and patients with WCG_{2-3} (group 2). The daily UV and BW changes, compared with the baseline BW, on days 2–5 of the chemotherapy regimens were noted, and differences in the averages of these measures between groups 1 and 2 were evaluated using repeated measures analyses of variance. Correlations between daily UV and BW changes were assessed using scatter diagrams and Pearson correlation coefficients.

The daily UV on days 1–5 and the maximum BW loss during days 1–5 of the first chemotherapy course were calculated for each patient. These parameters, the pretreatment parameters, the use of furosemide, and their associations with the two group categories were evaluated using χ-tests for categorical variables, Mann–Whitney tests for continuous variables, and logistic regression analyses for both types of variables. The total furosemide dose was calculated using the following formula:[9]

$$\text{total furosemide dose (mg)} = \text{intravenous dose (mg)} + 0.65 \times \text{oral dose (mg)}.$$

The Dr SPSS II 11.0 for Windows software package (SPSS Japan, Tokyo, Japan) was used for the statistical analyses.

Results

Between November 2000 and May 2006, 427 patients met the four inclusion criteria. Of these, six patients were excluded because their pretreatment serum creatinine levels were elevated, and four patients were excluded because no data on their daily UV or BW were available. Thus, a total of 417 patients were analyzed in the present study. The subjects comprised 327 men and 90 women, with a median age of 59 years (range 18–78 years) (Table 1). Non-small cell lung cancer was the most common tumor type, noted in 338 patients, followed by small cell lung cancer in 71 patients, thymic cancer in four patients, malignant mesothelioma in three patients, and tracheal cancer in one patient. Thirty-two patients with stage I–II diseases received chemotherapy as an adjuvant therapy after surgery. The remaining 385 patients with stage III–IV diseases or postoperative recurrent diseases received chemotherapy for the treatment of locally advanced or metastatic diseases.

All of the patients received cisplatin at a dose of 80 mg/m^2 in combination with other agents. The chemotherapy regimens were cisplatin and vinorelbine (n = 200), cisplatin and etoposide (n = 77), cisplatin, vindesine and mitomycin (n = 48), cisplatin and irinotecan (n = 41), cisplatin and gemcitabine (n = 41), and cisplatin and docetaxel (n = 10). The WCG was evaluated in all of the patients, with 390 patients categorized into group 1 and 27 patients categorized into group 2.

The average daily UV during days 1–5 of the chemotherapy regimens showed that the UV on day 1 did not differ between groups 1 and 2, but the daily UV on days 2–5 in group 2 were lower than those in group 1 (Fig. 1A, P = 0.042). The average changes in BW on days 2–5 showed that patients gained BW on days 2–3 and lost BW on days 4–5 (Fig. 1B). The line plotting the changes in BW in group 2 was always below that for group 1 (P = 0.036). Thus, the patients in group 2 retained less water than the patients in group 1. Furthermore, the patients in group 2 may have developed dehydration on day 5, as their average BW dropped to below the baseline level (Fig. 1B). Scatter diagrams comparing the average UV on days 1–2 and the BW change on day 3, and the average UV on days 1–4 and the BW change on day 5 showed no correlation between the UV and BW changes (data not shown), suggesting that the reduction in fluid intake may have caused the BW loss.

The development of renal toxicity was associated with some patient demographics. The percentage of women was higher in group 2 than in group 1 (11.1 *vs* 5.2%, P = 0.04). The median age of the patients in group 1 was 59 years (range 18–77 years), whereas that for group 2 was 65 years (range 38–74 years) (P = 0.041). None of the pretreatment chemistry parameters differed between the groups (Table 1). The frequency of renal toxicity did not differ according to chemotherapy regimen but was associated with a decreased average daily UV during days

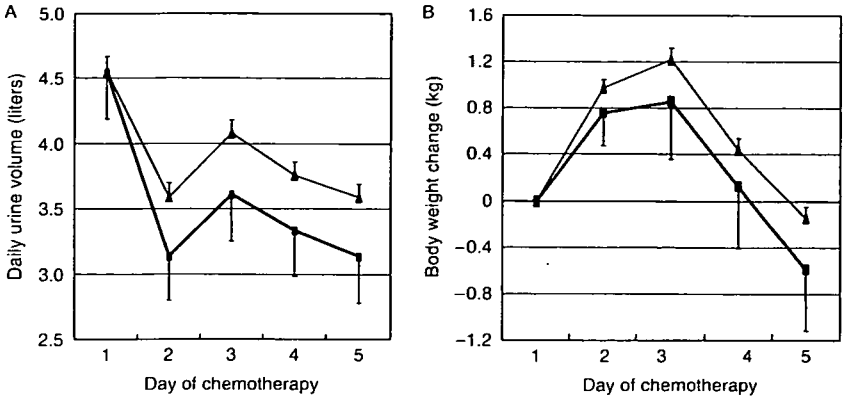

Fig. 1. (A) Average daily urine volumes during days 1–5 of chemotherapy. The differences were statistically significant ($P = 0.042$, repeated measures analysis of variance). (B) Average bodyweight changes on days 1–5 of chemotherapy. The differences were statistically significant ($P = 0.036$, repeated measures analysis of variance). Thin line with closed triangles: group 1, patients with a worst creatinine grade of 0–1 ($n = 390$); thick line with closed squares: group 2, patients with a worst creatinine grade of 2–3 ($n = 27$). Error bars show the 95% confidence intervals.

Table 2. Treatment-related parameters and groups categorized according to worst creatinine grade

		Group 1 ($n = 390$)		Group 2 ($n = 27$)		*P*-value
		n	%	*n*	%	
Agents combined with cisplatin	Vinorelbine	184	92.0	16	8.0	0.83
	Etoposide	74	96.1	3	3.9	
	Vindesine + mitomycin	45	93.8	3	6.2	
	Gemcitabine	39	95.1	2	4.9	
	Irinotecan	39	95.1	2	4.9	
	Docetaxel	9	90.0	1	10.0	
Average daily urine volume (mL)[†]	Median	3902	(Range 2058–6680)	3600	(Range 1700–5020)	0.021
	≤3000	41	87.2	6	12.8	0.054
	3001–4000	185	92.5	15	7.5	
	≥4001	164	96.5	6	3.5	
Maximum bodyweight loss (kg)[‡]	Median	0.2	(Range 0–3.9)	0.4	(Range 0–4.6)	0.11
	0	172	95.0	9	5.0	0.006
	0.1–2.0	201	93.9	13	6.1	
	≥2.1	17	77.3	5	22.7	
Total furosemide dose[§]	Median	0	(Range 0–160)	26	(Range 0–360)	0.024
	0	201	95.2	10	4.7	0.015
	1–30	87	94.6	5	5.4	
	31–60	70	93.3	5	6.7	
	61–90	11	91.7	1	8.3	
	≥91	21	77.8	6	22.2	

[†]The average daily urine volume on days 1–5 of chemotherapy. [‡]Maximum body weight loss during days 1–5 of chemotherapy. [§]Total furosemide dose (mg) = intravenous dose (mg) + 0.65 × oral dose (mg). Groups 1 and 2 were patients with worst creatinine grades of 0–1 and 2–3, respectively.

1–5 of the chemotherapy regimens (Table 2). In addition, only 5–6% of the patients with a maximum BW loss of 2 kg or less were classified as $WCG_{2\text{-}3}$, whereas 23% of the patients with a maximum BW loss of more than 2 kg were classified as $WCG_{2\text{-}3}$ ($P = 0.006$). Furosemide was administered to 206 of the 417 patients (49.4%). Of these patients, 198 did not complain of any symptoms whereas eight developed mild edema in the lower extremities or face, which disappeared after a few days. The difference in the frequencies of renal toxicity among patients who received furosemide and those who did not (8.3 *vs* 4.7%, respectively; $P = 0.14$) was not large enough to be statistically significant. Administration route (intravenous or oral), day of use (day 1, day 2 or days 3–8), or BW gain just before use of furosemide (0–1.4, 1.5–2.9 or ≥3.0 kg) did not influence the frequency of renal toxicity. The total dose of furosemide, however, differed between groups 1 and 2 (median, 0 mg; range, 0–160 mg *vs* median, 26 mg; range, 0–360 mg, respectively; $P = 0.024$). In particular, 22% of the patients who received more than 90 mg of furosemide were classified as $WCG_{2\text{-}3}$ (Table 2).

A multivariate analysis showed that the maximum BW loss (odds ratio, 1.77; 95% confidence interval, 1.08–2.90) and the total furosemide dose (odds ratio, 1.21; 95% confidence interval, 1.11–1.33) were significantly associated with the $WCG_{2\text{-}3}$ category. Associations with sex and the daily UV were marginally significant (Table 3).

Discussion

The present study showed that the maximum BW loss during days 1–5 of chemotherapy was associated with the development of cisplatin renal toxicity. In particular, 23% of patients with a maximum BW loss of more than 2 kg were classified as $WCG_{2\text{-}3}$. Because dehydration amounting to as little as a 2% loss in BW results in impaired physiological and performance responses,[10] the BW loss and dehydration observed in the present study may be enough to aggravate cisplatin nephrotoxicity. No correlation was noted between the UV and BW changes, suggesting that the dehydration was attributable to a reduced oral intake by patients as a result of cisplatin-induced emesis. BW measurements are

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Table 3. Multivariate analysis of pretreatment and treatment-related parameters and groups categorized according to worst creatinine grade

Parameter		Odds ratio (95% confidence interval†)	*P*-value
Sex	Male	1	0.082
	Female	2.34 (0.90–6.10)	
Age	10-year increments	1.55 (0.91–2.64)	0.11
Average daily urine volume†	100-mL increments	0.94 (0.88–1.00)	0.073
Body weight loss	1-kg decrements	1.77 (1.08–2.90)	0.024
Total furosemide dose	10-mg increments	1.21 (1.11–1.33)	<0.001

†The average daily urine volume on days 1–5 of chemotherapy.

a simple and useful indicator of the hydration status of these patients.

The current study also showed that the total furosemide dose was associated with the development of renal toxicity. Vigorous fluid infusion and diuresis with mannitol or furosemide have been used widely for the prevention of cisplatin nephrotoxicity.[11,12] These interventions are thought to reduce the cisplatin concentration in the renal tubules and the time during which this drug and the tubular epithelial cells are in contact.[5] However, numerous experimental studies have provided conflicting results regarding the renal protective effects of these diuretics; cisplatin nephrotoxicity was reduced in some studies but was enhanced in others.[5] A randomized trial of cisplatin at a dose of 100 mg/m^2 and hydration with or without mannitol in patients with malignant melanoma showed that this regimen prevented nephrotoxicity during the first treatment course.[13] Another randomized trial of cisplatin hydration with mannitol or furosemide in patients with advanced solid tumors showed that a serum creatinine elevation of more than 2 mg/dL was observed in 28% of the courses in the mannitol-treated group and 19% of the courses in the furosemide-treated group.[14] A third randomized trial of cisplatin at a dose of 75 mg/m^2 and hydration alone, hydration with mannitol, or hydration with furosemide showed that creatinine clearance did not change before or after cisplatin treatment in the hydration alone and the furosemide-treated groups, but decreased in the mannitol-treated group.[15] However, these randomized trials included only small numbers of patients and therefore are not conclusive. Thus, no reports have convincingly shown any advantage of diuretics in preventing cisplatin nephrotoxicity. These studies differed from the current study, in which furosemide was administered only when fluid retention was suspected based on an increased BW or a decreased UV. Although an association between renal toxicity and the total furosemide dose was observed in this study, patients with fluid retention may be more prone to develop renal toxicity. Another explanation is that furosemide may have a direct toxic effect on the kidney. Thus, the administration of furosemide may be inevitable in some cases to prevent fluid overload during aggressive hydration, but its frequent use should be avoided.

Because renal function decreases physiologically with aging,[16] cisplatin use in elderly patients remains controversial. Some authors of clinical studies for patients aged 70 years or older have concluded that the use of cisplatin at moderate doses (60–100 mg/m^2) should be encouraged in these patients, just as it is in younger patients.[17–19] Studies that evaluated risk factors for cisplatin nephrotoxicity in more than 400 patients showed that an older age was a significant risk factor in two studies[7,20] but not in a third study.[8] In the current study, age was not a risk factor for renal toxicity according to a multivariate analysis, probably because 80 mg/m^2 of cisplatin was administered only to selected elderly patients. In our practice, many elderly patients are treated with cisplatin at a dose of 25 mg/m^2 on three consecutive days or weekly; these patients were excluded from the present study.

In the present study women were more likely to suffer from cisplatin nephrotoxicity than men. Another study also showed that women had a twofold increased risk for renal toxicity compared with men.[7] Although the reason for this difference is not definitely known, it may be explained, at least in part, by a 15% lower unbound cisplatin clearance in women than men,[7,21] because pharmacokinetics of unbound cisplatin have been repeatedly shown to be correlated with cisplatin nephrotoxicity.[22–24]

Although intravenous fluid infusion on the day of cisplatin administration is a well established treatment for preventing nephrotoxicity, the use of subsequent fluid infusions has not been reported. Because the present study showed that dehydration progressed on day 5 in many cases and an elevated serum creatinine level appeared thereafter, maintaining the total body water level during days 1–5 of chemotherapy seems to be important for the prophylaxis of cisplatin nephrotoxicity. For this purpose, a BW measurement carried out before breakfast would be a simple and useful indicator; if oral intake is found to be insufficient, vigorous infusion therapy on days 2–5 may be effective.

In conclusion, the maximum BW loss during days 1–5 of chemotherapy and the total furosemide dose were associated with the development of cisplatin renal toxicity. Maintaining total body water levels during this period seems to be important, and measuring BW would be a simple and useful indicator for this purpose.

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Serum Total Bilirubin as a Predictive Factor for Severe Neutropenia in Lung Cancer Patients Treated with Cisplatin and Irinotecan

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Objective: To clarify the association between pre-treatment total bilirubin (PTB) level and severe toxicity in patients receiving cisplatin and irinotecan.
Methods: We analyzed retrospectively the relationships of grade 4 neutropenia or grade 3–4 diarrhea and clinical variables including PTB and pre-treatment neutrophil counts (PNC) using a logistic regression model.
Results: One hundred and twenty-seven patients (93 men, 34 women; median age: 61 years; range: 24–74 years) received cisplatin (60 or 80 mg/m^2) on day 1 and irinotecan (60 mg/m^2) on days 1 and 8 every 3 weeks or on days 1, 8 and 15 every 4 weeks. Grade 4 neutropenia occurred in 29 patients (23%) and grade 3–4 diarrhea occurred in 13 patients (10%). Grade 4 neutropenia was associated with a higher PTB level (odds ratio: 4.9; 95% confidence interval: 1.4–17.7), a higher cisplatin dose (2.8, 1.0–7.8) and a lower PNC (1.5, 1.0–2.3). Grade 3–4 diarrhea was associated with liver metastasis (11.2, 2.2–57.4), a higher cisplatin dose (5.0, 1.2–21.3) and a lower PNC (2.0, 1.1–3.6).
Conclusions: PTB level was associated with the severity of neutropenia caused by cisplatin and irinotecan.

Key words: irinotecan – toxicity – lung cancer

INTRODUCTION

Although irinotecan is an active agent against several solid tumors, it sometimes exhibits serious adverse effects, the most common being bone marrow toxicity, in particular leucopenia and neutropenia, and ileocolitis, which leads to diarrhea (1–4). The severity of these toxicities varies greatly between individuals, and thus identifying pre-treatment factors that predict an increased risk for severe toxicities is a critical issue in the treatment of cancer patients undergoing chemotherapy.

Irinotecan needs to be activated by systemic carboxylesterases to SN-38 to exert its anti-tumor activity, which is mediated by the inhibition of topoisomerase I (5). Glucuronidation of SN-38 (SN-38G) by UDP-glucuronosyltransferase (UGT) 1A1 during biliary excretion is the primary route of detoxification and elimination. A higher ratio of plasma SN-38 to SN38-G has been correlated with severe diarrhea, suggesting that the efficiency of SN-38 glucuronidation is an important determinant of toxicity (6–8).

Genetic polymorphisms of the UGT 1A1 gene, such as the number of TA repeats in the TATA box that are associated with reduced transcriptional efficiency and functional activity, have been reported previously (7). Some studies have demonstrated an association between UGT1A1 polymorphisms and the risk for severe toxicity from irinotecan (6, 8–11).

The UGT1A1 enzyme is also responsible for hepatic bilirubin glucuronidation. Serum bilirubin levels, therefore, may reflect UGT1A1 activity and may also be associated with irinotecan activity and toxicity. The pre-treatment serum total bilirubin (PTB) level has been shown to be related to

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severe neutropenia in patients receiving 350 mg/m^2 of irinotecan (8). We extended this observation in patients receiving cisplatin and irinotecan to clarify the association between PTB and severe toxicity, including neutropenia and diarrhea, in these patients.

PATIENTS AND METHODS

Treatment Schedule

The subjects consisted of consecutive lung cancer patients who had received cisplatin and irinotecan therapy at the National Cancer Centre Hospital between February 1999 and May 2004. Irinotecan, diluted in 500 ml of normal saline, was given intravenously over 90 min at a dose of 60 mg/m^2 on days 1 and 8 or on days 1, 8 and 15. Cisplatin was given intravenously over 60 min after the irinotecan infusion at a dose of 60 or 80 mg/m^2 on day 1 with at least 2500 ml of hydration. The first phase I trial of irinotecan and cisplatin showed that 80 mg/m^2 of cisplatin on day 1 and 60 mg/m^2 of irinotecan on days 1, 8, and 15 were the recommended dose for phase II trials (12), and this dose schedule was used for subsequent phase II and phase III trials of non-small cell lung cancer (NSCLC) (13,4,14). The second phase I trial of this combination showed that 60 mg/m^2 of cisplatin on day 1 and 80 mg/m^2 of irinotecan on days 1, 8, and 15 were the recommended dose (15). A phase II trial for small cell lung cancer, however, showed that this dose schedule was too toxic, and thereafter the dose of irinotecan was reduced from 80 to 60 mg/m^2 (16). From the above, we used 80 mg/m^2 of cisplatin and 60 mg/m^2 of irinotecan for patients with NSCLC, and 60 mg/m^2 of cisplatin and 60 mg/m^2 of irinotecan for the other patients. Administration of irinotecan was omitted if any of the following toxicities were noted on days 8 and 15: a white blood cell count $<2.0 \times 10^9$/l, a platelet count $<75 \times 10^9$/l, or grade 1–3 diarrhea. Each course was repeated every 3 or 4 weeks until the occurrence of unacceptable toxicity, disease progression, patient's refusal to continue treatment, or the investigator's medical decision to stop treatment. To control for cisplatin-induced emesis, a 5-HT3 receptor antagonist and dexamethasone were given prior to cisplatin administration.

Study Design

We retrospectively reviewed the patients' clinical records, including patient characteristics (age, sex, Eastern Cooperative Oncology Group performance status, histology of primary disease, clinical stage, prior treatment, evidence of liver metastasis), the dose and schedule of chemotherapy, and pre-treatment complete blood counts and serum chemistry profiles. We defined 'severe toxicity' as grade 4 neutropenia or grade 3–4 diarrhea during the first cycle of chemotherapy, in accordance with the NCI-CTC Version 2.0 criteria. All patients were treated as in-patients, and complete blood counts and serum chemistry profiles were assessed at least once a week. PTB was defined as the serum total bilirubin level at fasting just prior to the administration of cisplatin and irinotecan.

Table 1. Patient characteristics

		No. of patients
Sex	Male/female	93/34
Age	Median (range)	61 (24–74)
Performance status	0/1/2	34/91/2
Histology	Non-small cell lung cancer	57
	Small cell lung cancer	63
	Others	7
Liver metastasis	Yes/no	18/109
Prior chemotherapy	Yes/no	17/110
PTB (mg/m^2)	Median (range)	0.6 (0.2–2.4)
PNC ($\times 10^9$/l)	Median (range)	4.1 (1.8–8.5)
Chemotherapy Regimens (mg/dl)	CDDP (60) day 1 + CPT-11 (60) days 1.8 q3w	32
	CDDP (60) day 1 + CPT-11 (60) days 1.8.15 q4w	39
	CDDP (80) day 1 + CPT-11 (60) days 1.8 q3w	24
	CDDP(80) day1 + CPT-11 (60) days 1.8.15 q4w	32

PTB, pre-treatment total bilirubin; PNC, pre-treatment neutrophil count.

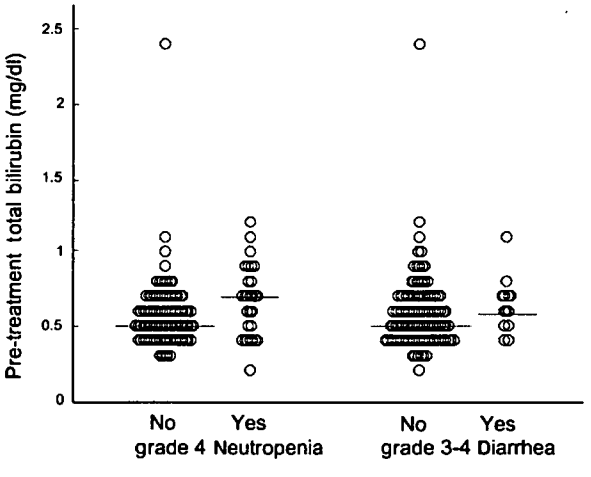

Figure 1. Association of PTB in patients who developed severe toxicity and in those who did not. The median PTB in patients who developed grade 4 neutropenia and those who did not was 0.7 (range, 0.2–1.2) mg/dl and 0.5 (range, 0.3–2.4) mg/dl, respectively ($P = 0.03$, Mann–Whitney U test). The median PTB in patients who developed grade 3–4 diarrhea and those who did not was 0.6 and 0.5 mg/dl, respectively ($P = 0.22$). The bars represent the median values.

Table 2. Univariate analysis of association between grade 4 neutropenia and pre-treatment clinical variables

	Neutropenia grade		Odds ratio (95% CI)
	Grade <4 (n = 98)	Grade 4 (n = 29)	
Sex			
Male	70	23	1
Female	28	6	0.65 (0.24–1.77)
Age			
Median (range)	61 (24–74)	65 (38–73)	1.04 (0.99–1.09)
Performance status			
0	29	5	1
1, 2	69	24	2.02 (0.70–5.80)
Liver metastasis			
No	82	27	1
Yes	16	2	0.38 (0.08–1.76)
Prior chemotherapy			
No	84	26	1
Yes	14	3	0.69 (0.19–2.60)
Treatment schedule			
Every 3 weeks	41	15	1
Every 4 weeks	57	14	0.67 (0.29–1.54)
Cisplatin dose (mg/m^2)			
60	56	15	1
80	42	14	1.24 (0.54–2.86)
AST (IU/l)			
Median (range)	22 (11–161)	22 (11–56)	0.98 (0.95–1.01)
ALT (IU/l)			
Median (range)	18 (6–266)	20 (5–67)	0.99 (0.97–1.02)
PNC ($\times 10^9$/l)			
Median (range)	4.4(2.0–8.5)	3.9 (1.8–8.3)	0.84 (0.61–1.14)
PTB (mg/dl)			
Median (range)	0.5 (0.3–2.4)	0.7 (0.2–1.2)	3.74 (0.70–19.9)
≤0.7	87	20	1
>0.7	11	9	3.56 (1.30–9.73)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; PNC, pre-treatment neutrophil count; PTB, pre-treatment total bilirubin.

Statistical Methods

The Mann–Whitney U test was used to compare the PTB levels of patients who developed severe toxicity and those who did not. Possible explanatory factors were compared using a logistic regression model. A PTB threshold of ≤0.7 mg/dl was selected to categorize this variable because a total bilirubin level higher than 0.7 mg/dl has been correlated with a mutated UGT1A1 genotype and the occurrence of grade 4 neutropenia (8). Furthermore, sex, performance status, liver metastasis, prior chemotherapy, treatment schedule and cisplatin dose were defined as categorized variables, and age, AST, ALT and pre-treatment neutrophil count (PNC) were examined as continuous variables. Variables that seemed to be associated with severe toxicity ($P < 0.1$) were considered for inclusion in a multivariate analysis using a backward stepwise regression model. We performed these analyses using the SPSS statistical package (SPSS version 11.0 for Windows; SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 127 consecutive patients with thoracic malignancy received cisplatin and irinotecan therapy. The patient characteristics are listed in Table 1. In all, two patients (1.5%) had

Table 3. Backward stepwise regression analysis of association between severe toxicity and pre-treatment clinical variables

Variable	Co-efficient	*P*	Odds ratio (95% CI)
Grade 4 neutropenia			
Cisplatin dose	1.04	0.04	2.84 (1.03–7.81)
PNC	0.42	0.04	1.53 (1.02–2.27)
PTB	1.59	0.02	4.93 (1.37–17.7)
Grade 3–4 diarrhea			
Liver metastasis	2.41	0.004	11.2 (2.18–57.4)
Cisplatin dose	1.61	0.03	5.00 (1.18–21.3)
PNC	0.67	0.03	1.96 (1.07–3.60)

Adjusted for age and PS.
PNC, pre-treatment neutrophil count; PTB, pre-treatment total bilirubin.

stage IIA disease, seven patients (5.5%) had stage IIIA disease, 26 patients (20%) had stage IIIB disease and 85 patients (67%) had stage IV disease. The median PTB level was 0.6 (range, 0.2–2.4) mg/dl and the median PNC was 4.1 (range 1.8–8.5) $\times$ 10^9/l. A total of 93 patients (73%) received the planned doses without skipping the irinotecan administrations on day 8 or 15. Among the remaining 34 patients, the irinotecan on day 8 or 15 was omitted in 27 of 164 (16.5%) planned doses in patients with PTB level $\leq$0.7 mg/dl, while in 11 of 34 (32.4%) planned doses in patients with PTB level >0.7 mg/dl ($P = 0.053$). Thus, the actual irinotecan dose delivered was lower with marginal significance in patients with PTB level >0.7 mg/dl. Grade 4 neutropenia occurred in 29 (23%) patients and grade 3–4 diarrhea occurred in 13 (10%) patients.

The median PTB level was higher in patients who developed grade 4 neutropenia than in those who did not (0.7 and 0.5 mg/dl, respectively; $P = 0.03$) (Fig. 1), but PTB was not correlated with the presence or absence of grade 3–4 diarrhea ($P = 0.22$).

In a univariate analysis, grade 4 neutropenia was associated with only the PTB level ($\leq$0.7 versus >0.7 mg/dl; $P = 0.01$, Table 2). When PTB level was analyzed as a continuous variable, the association was not significant (OR: 3.74; 95% CI: 0.70–19.9; $P = 0.12$). In a multivariate analysis, grade 4 neutropenia was associated with the PTB level ($\leq$0.7 versus >0.7 mg/dl; $P = 0.02$), the cisplatin dose ($P = 0.04$), and PNC ($P = 0.04$, Table 3). In a univariate analysis, grade 3–4 diarrhea was associated with only liver metastasis ($P = 0.01$, Table 4). We analyzed serum levels of PTB and pre-treatment AST and ALT between patients with ($n = 18$) or without ($n = 109$) liver metastasis. The median (range) PTB was 0.6 (0.4–2.4) mg/dl in patients with liver metastasis and 0.6 (0.2–1.2) mg/dl in patients without liver metastasis ($p = 0.19$). In contrast, the median (range) levels of pre-treatment AST and ALT were 30 (16–114) IU/l and 30 (11–84) IU/l, respectively, in patients with liver metastasis and 21 (11–161) IU/l and 17 (5–266) IU/l, respectively, in patients without liver metastasis ($P = 0.0054$). In a multivariate analysis, grade 3–4 diarrhea was associated with liver metastasis ($P = 0.004$), the cisplatin dose ($P = 0.03$) and PNC ($P = 0.03$, Table 4).

DISCUSSION

This study showed that the PTB level was significantly associated with severity of neutropenia in patients treated with cisplatin and weekly irinotecan. Although irinotecan-induced toxicity can be reduced by skipping irinotecan on day 8, 15, or both, this dose modification is not enough to eliminate severe toxicity completely. In this study irinotecan was more frequently omitted on days 8 and 15 in patients with PTB level >0.7 mg/dl, and therefore, the association between PTB and irinotecan-induced toxicity may be underestimated. Thus, the PTB level, a simple routine measure in clinical practice, can be a useful predictive marker for irinotecan-induced toxicity.

The most compelling evidence for a genetic marker of toxicity caused by irinotecan therapy is seen with the *UGT* gene. In some retrospective pharmacogenetic studies, patients with at least one *UGT*1A1*28 allele encountered severe irinotecan-induced toxicity, compared with those with the wild-type genotype who were homozygous for the 6 TA repeat allele (6,9,10). In a prospective study, the *UGT*1A1 genotype was strongly associated with severe neutropenia in patients treated with irinotecan (8). More than 30 polymorphic variations have been reported to date for the *UGT*1A1 gene (17). Novel polymorphisms (*1, *6, *28,*60 and so on) in *UGT*1A1 and the functional characterization of known variants are helpful in elucidating the role of *UGT*1A1 genetic variation in irinotecan toxicity (18). The FDA has approved a *UGT*1A1 molecular assay test to detect polymorphisms in the *UGT*1A1 gene in clinical practice, so that patients with particular *UGT*1A1 gene variations that raise the risk of certain adverse effects can receive safer doses of irinotecan. This assay is intended to aid physicians to make decisions for individualized patient. Nevertheless, other important factors that affect dosing should also be considered, because severe toxicity sometimes occurs even in patients without particular *UGT*1A1 gene variations that place them at risk.

The *UGT*1A1 enzyme is responsible for hepatic bilirubin glucuronidation. A polymorphism in the *UGT*1A1 promoter has been linked with reduced *UGT*1A1 expression and is consequently associated with familiar hyperbilirubinemia. Accordingly, bilirubin levels may be associated with *UGT*1A1 function. The PTB level may reflect the total function of some polymorphisms in the *UGT*1A1 region and may be used as a simple and available surrogate marker for *UGT*1A1 function.

Recent studies have revealed that two major hepatic UGT, *UGT*1A1 and *UGT*1A9, and extra-hepatic *UGT*1A7 are involved in SN-38 glucuronidation (SN-38G) (7,19). The

Table 4. Univariate analysis of association between grade 3–4 diarrhea and pre-treatment clinical variables

	Diarrhea grade		Odds ratio (95% CI)
	Grade 0–2 (n = 114)	Grade 3–4 (n = 13)	
Sex			
Male	84	9	1
Female	30	4	1.24 (0.36–4.34)
Age			
Median (range)	65 (24–74)	65 (53–73)	1.07 (0.99–1.16)
Performance status			
0	29	5	1
1, 2	85	8	0.55 (0.17–1.80)
Liver metastasis			
No	101	8	1
Yes	13	5	4.86 (1.38–17.1)
Prior chemotherapy			
No	99	11	1
Yes	15	2	1.20 (0.20–7.04)
Treatment schedule			
Every 3 weeks	50	6	1
Every 4 weeks	64	7	0.91 (0.29–2.88)
Cisplatin dose (mg/m^2)			
60	66	5	1
80	48	8	2.20 (0.68–7.14)
AST (IU/l)			
Median (range)	21 (11–161)	23 (15–65)	1.00 (0.98–1.03)
ALT (IU/l)			
Median (range)	17 (5–266)	21 (14–84)	1.01 (0.99–1.02)
PNC ($\times 10^9$/l)			
Median (range)	4.2 (1.8–8.5)	3.5 (2.2–5.2)	0.77 (0.49–1.20)
PTB (mg/dl)			
Median (range)	0.55 (0.2–2.4)	0.6 (0.4–1.1)	1.95 (0.29–13.2)
≤0.7	96	11	1
>0.7	18	2	0.97 (0.20–4.75)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; PNC, pre-treatment neutrophil count; PTB, pre-treatment total bilirubin.

efficacy of irinotecan is possibly affected by the activity of these genes. Thus, the product of some genetic polymorphisms in several genes may be a better pharmacogenetic marker for selecting patients who may not respond favorably to irinotecan-containing chemotherapy.

Cisplatin and irinotecan therapy is a standard regimen for both advanced non-small cell and small cell lung cancer (4). A randomized trial of irinotecan with or without cisplatin in patients with non-small cell lung cancer showed that grade 4 neutropenia was observed more frequently in the cisplatin–irinotecan arm (37%) than in the irinotecan-alone arm (8%), whereas grade 3 and 4 diarrhea was observed at the same frequency in both arms. In the present study, a higher cisplatin dose was associated with both grade 4 neutropenia and grade 3 and 4 diarrhea. The addition of cisplatin to another anti-cancer agent aggravated diarrhea in phase III studies (20), although diarrhea was moderate in cisplatin monotherapy observed in clinical trials (21). Thus, a higher dose of cisplatin seems to be associated with diarrhea, but the mechanism for this association remains unclear.

In this study PTB level was associated with the severity of neutropenia, but not with severity of diarrhea. When SN-38G is excreted in the bile and intestines, the bacteria-derived enzyme beta-glucuronidase converts SN-38G back

into SN-38 (22,23). Presence of SN-38 in the stool is associated with the occurrence of severe diarrhea as a result of the direct enteric injury caused by SN-38 (24). This phenomenon probably occurs because UGT1A1 is not involved in this step.

Liver metastasis was associated with the development of grade 3–4 diarrhea in both univariate and multivariate analyses in this study. This may be explained by small, but statistically significant differences in the pre-treatment transaminase levels between patients with or without liver metastasis. However, in contradiction to this explanation are that: (1) neither the pre-treatment AST nor ALT level was associated with grade 3–4 diarrhea in this study, and (2) in dose-finding studies of irinotecan monotherapy in patients with liver dysfunction, patients were categorized into subgroups by the PTB and serum AST and ALT levels, criteria of which were three times or five times the upper limit of normal (25,26). Thus, the small difference in the AST and ALT levels in this study is unlikely to be significant from the medical point of view.

The PNC in patients who developed grade 3–4 diarrhea was slightly lower than that in the other patients and the PNC was associated with grade 3–4 diarrhea in the multivariate analysis. Neutrophils play an important role in maintaining the mucosal barrier of the intestine and inflammatory responses against mucosal damage (27). Thus, reduced number, dysfunction, or both, of neutrophils may lead to impairment of the mucosal integrity, rendering these patients prone to develop diarrhea. In addition, the decreased number of neutrophils in the blood is closely related to malnutrition associated with cancer (28), which may in turn be associated with enhanced toxicity during chemotherapy with irinotecan and cisplatin.

In conclusion, the PTB level was significantly associated with severity of neutropenia in patients treated with cisplatin and weekly irinotecan. This will provide a simple and useful marker required for individualized therapy to reduce the risk of harmful chemotherapy.

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Conflict of interest statement

None declared.

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Concurrent Chemoradiotherapy for Limited-disease Small Cell Lung Cancer in Elderly Patients Aged 75 Years or Older

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Background: The optimal treatment for limited-disease small cell lung cancer (LD-SCLC) in patients aged 75 years or older remains unknown.
Methods: Elderly patients with LD-SCLC who were treated with chemoradiotherapy were retrospectively reviewed to evaluate their demographic characteristics and the treatment delivery, drug toxicities and antitumor efficacy.
Results: Of the 94 LD-SCLC patients treated with chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1998 and 2003, seven (7.4%) were 75 years of age or older. All of the seven patients were in good general condition, with a performance status of 0 or 1. Five and two patients were treated with early and late concurrent chemoradiotherapy, respectively. While the four cycles of chemotherapy could be completed in only four patients, the full dose of radiotherapy was completed in all of the patients. Grade 4 neutropenia and thrombocytopenia were noted in seven and three patients, respectively. Granulocyte-colony stimulating factor support was used in five patients, red blood cell transfusion was administered in two patients and platelet transfusion was administered in one patient. Grade 3 or more severe esophagitis, pneumonitis and neutropenic fever developed in one, two and three patients, respectively, and one patient died of radiation pneumonitis. Complete response was achieved in six patients and partial response in one patient. The median survival time was 24.7 months, with three disease-free survivors for more than 5 years.
Conclusion: Concurrent chemoradiotherapy promises to provide long-term benefit with acceptable toxicity for selected patients of LD-SCLC aged 75 years or older.

Key words: elderly – small cell lung cancer – chemotherapy – radiotherapy

INTRODUCTION

Small cell lung cancer (SCLC) accounts for approximately 20% of all pulmonary neoplasms and 25–40% of patients with this disease are 70 years of age or older. The number of elderly patients with such disease are expected to increase with the growing geriatric population (1).

Because SCLC is highly sensitive to chemotherapy and radiotherapy, the standard treatment for limited-disease SCLC (LD-SCLC) has been a combination of platinum and etoposide with concurrently administered thoracic radiotherapy, as long as the patients are in good general condition (2, 3). Such elderly patients, however, may show decreased clearance of the anticancer agents commonly used for the treatment of SCLC, including cisplatin and etoposide, because of the decrease of the lean body mass, hepatic blood flow and renal function that are associated with aging. In addition, myelotoxicity is sometimes more severe in this population than in younger populations, because the absolute area of hematopoietic marrow decreases with age (4). Retrospective subset analyses of patients with LD-SCLC treated with concurrent chemotherapy and radiotherapy in phase III trials have shown that the percentage of patients in whom the planned number of chemotherapy cycles can be completed is usually 10% lower in patients

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70 years of age or older as compared with that in younger patients (5). One study reported that myelotoxicity was more severe in elderly patients than in younger patients (5), while another reported no such difference between the patients of the two age groups (6). The delivery of thoracic radiotherapy was not influenced by age in these patients (7). However, 78–85% of patients in these analyses were aged between 70 and 75 years old and a few were over 80 years old. Thus, the most suitable treatment options for elderly patients with LD-SCLC aged 75 years or older still remain unknown.

The objective of this retrospective analysis was to evaluate the patient characteristics and the treatment delivery, toxicity and antitumor efficacy of the administered treatments in LD-SCLC patients 75 years of age or older who were treated with chemotherapy and thoracic radiotherapy.

PATIENTS AND METHODS

We retrospectively reviewed the medical charts, chest X-rays and computed tomography (CT) scans of LD-SCLC patients aged 75 years or older. To evaluate the thoracic irradiation field, the standard initial field was defined as follows: the field including the primary tumor and involved nodes with a short axis length of 1 cm or more on CT scans with a 1.0–1.5 cm margin, and the subclinical ipsilateral hilum and bilateral mediastinal lymph node regions with a 1.0 cm margin. The supraclavicular lymph node regions were included only if there was tumor involvement of these nodes. Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 3.0, Japanese edition (8). The objective tumor response was evaluated according to the WHO criteria issued in 1979 (9). The overall survival time was measured from day 1 of chemotherapy to the date of death as a result of any cause or the date of the last follow-up.

RESULTS

Of the 94 LD-SCLC patients treated with chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1998 and 2003, seven (7.4%) were 75 years of age or older (Table 1). During this period, we had three other patients with LD-SCLC who were aged 75 years or older. They were treated with chemotherapy alone because of complications in two patients and refusal of intensive therapy in one patient. There were five males and two females, and four patients were between 75 and 79 years of age and three patients were 80 years old or older. Three patients presented with persistent cough, while the remaining four patients complained of no symptoms and were diagnosed based on the detection of an abnormal shadow on a plain chest X-ray obtained during a mass screening or routine health examination program. All the patients were in good general condition. One patient had a history of inferior wall myocardial infarction suffered 9 years prior to this admission. However, echocardiography at this admission revealed normal heart function with an ejection fraction of 73%. One patient had stage I pulmonary emphysema with % FEV_1 predicted of 58%, but no abnormal findings on blood gas analysis. The % FEV_1 predicted in other four patients was within 98% and 116%, and was not measured in the other two patients. A median (range) PaO_2 level at the room air before treatment in the seven patients was 77.4 (66.9–87.2) Torr. A decreased creatinine clearance, 48.8 ml/min at a urine volume of 600 ml/day, was noted in one patient, while the other patients had a creatinine clearance of 78 ml/min or higher. Four and three patients had a performance status of 0 and 1, respectively, and five patients gave no history of loss of body weight. The diagnosis of small cell carcinoma was confirmed cytologically or histologically in all the patients.

The chemotherapy regimens used were cisplatin at 80 mg/m^2 on day 1 combined with etoposide at 100 mg/m^2 on days 1–3 in four patients aged between 75 and 19 years. For patients aged 80 years of older, carboplatin was dosed to a

Table 1. Patient characteristics

n	Age (yr)/ gender	Smoking history	Symptom	Weight loss (%)	Complications	Performance status	TNM stage
1	81/male	6/day × 62 yr	None	0	Type 2 DM	0	T1N2M0
2	81/female	20/day × 62 yr	None	0	OMI (inferior wall), thoracic aortic aneurysm	0	T1N1M0
3	80/female	20/day × 50 yr	Cough	11	Hypertension	1	T4N3M0
4	78/male	20/day × 46 yr	None	0	None	0	T2N2M0
5	77/male	30/day × 50 yr	Cough	7	COPD, Hypertension	1	T4N3M0
6	75/male	10/day × 55 yr	None	0	None	0	T1N2M0
7	75/male	10/day × 55 yr	Cough, Hoarseness	0	None	1	T4N2M0

COPD, Chronic obstructive pulmonary disease; OMI, old myocardial infarction; DM, diabetes mellitus.

target AUC of 5 by Calvert's formula on day 1 combined with etoposide at 80 mg/m^2 on days 1–3 in two patients and cisplatin at 25 mg/m^2 on days 1–3 combined with etoposide at 80 mg/m^2 on days 1–3 in one patient (Table 2). These regimens have been reported to be used in a JCOG phase III trial for elderly patients with extensive SCLC (10). Four cycles of chemotherapy could be completed in four patients, whereas only three cycles could be completed in two patients and only one cycle could be completed in one patient. The reason for discontinuation of the chemotherapy in these patients was prolonged myelosuppression in two patients and patient refusal for continuation of treatment in one patient. The chemotherapy dose was reduced in the subsequent cycles in four patients. The reasons for the dose reduction were grade 4 thrombocytopenia in two patients, grade 4 leukopenia in one patient and both grade 4 thrombocytopenia and leukopenia in one patient. Thoracic radiotherapy was started concurrently with the chemotherapy in five patients (early concurrent chemoradiotherapy). Treatment began with chemotherapy alone in the remaining two patients, because of a mild cytology-negative pleural effusion in one patient and too large an irradiation volume in the other patient. Two cycles of chemotherapy reduced the tumor volume successfully in both the patients and thoracic radiotherapy was then added concurrently with the third and fourth cycles of chemotherapy (late concurrent chemoradiotherapy). Thoracic radiotherapy was delivered using photon beams from a liniac or microtron accelerator with energy between 6 and 20 MV at a single dose of 2 Gy once daily up to a total dose of 50 Gy in four patients aged between 78 years or older and at a single dose of 1.5 Gy twice daily up to a total dose of 45 Gy in three patients aged between 75 and 77 years. This selection of conventional or hyperfractionated radiotherapy was determined arbitrarily. The initial irradiation field was judged as the standard in six patients and reduced in one patient. A multi-leaf collimator and conventional lead blocks were used for shaping of the irradiation field. The median irradiation area was 169 cm^2 (range, 95–278 cm^2). The projected total radiation dose was administered in all the patients, but a treatment delay of 5 days or longer was observed in three patients. The criteria of radiotherapy suspension were white blood cell count $< 1.0 \times 10^9$/L, platelet count $< 20 \times 10^9$/L, esophagitis $\geq$ grade 3, fever ≥ 38°C and performance status ≥ 3. The reason for the delay in the three patients was esophagitis, decreased platelet count and poor performance status.

The hematological toxicities observed in the patients are summarized in Table 3. Grade 4 leukopenia, neutropenia and thrombocytopenia were noted in four, seven and three patients, respectively. Granulocyte-colony stimulating factor support was used in five patients, red blood cell transfusion was administered in two patients and platelet transfusion was administered in one patient. The non-hematological toxicities included grade 3 or more severe esophagitis, pneumonitis and neutropenic fever in one, two and three patients, respectively. One patient died of radiation pneumonitis that developed 4 months after the end of radiotherapy (Case No. 6).

Of the seven patients, complete response was achieved in six patients and partial response in one patient (Table 3). However, prophylactic cranial irradiation was given in only one patient (Case No. 6). Three patients remained alive for

Table 2. Treatment and its delivery

n	Chemotherapy				Thoracic radiotherapy			
	Regimen (mg/m^2 if not specified)	Number of cycles	Dose reduction	Duration of one cycle (days)*	Timing	Total dose (Gy)/fractions	Field size	Delay (days)
1	C (AUC = 5) d1 + E (80) ds1–3	3	Yes	30	Early Co	50/25	S	4
2	P (25) ds1–3 + E (80) ds1–3	1	NA	NA	Early Co	50/25	S	7
3	C (AUC = 5) d1 + E (80) ds1–3	4	Yes	23	Late Co	50/25	S	14
4	P (80) d1 + E (100) ds1–3	4	Yes	26	Late Co	50/25	R	1
5	P (80) d1 + E (100) ds1–3	4	No	28	Early Co	45/30	S	3
6	P (80) d1 + E (100) ds1–3	4	No	27	Early Co	45/30	S	0
7	P (80) d1 + E (100) ds1–3	3	Yes	35	Early Co	45/30	S	7

*Calculated as follows: Duration of one cycle (days) = (Day 1 of the 1st cycle – Day 1 of the last cycle)/(Number of cycles – 1).
C, carboplatin; E, etoposide; NA, not applicable; P, cisplatin; Co, concurrent; S, standard; R, reduced.

Table 3. Toxicity, tumor response and survival

n	Hematological toxicity (grade by CTC-AE v3.0)				Blood transfusion	G-CSF support	Non-hematological toxicity ≥ grade 2 (grade by CTC-AE v3.0)	Tumor response	Survival time (mo)/outcome
	WBC	Neu	Hb	Plt					
1	3	4	1	4	Platelet	None	None	CR	80.3/Alive
2	3	4	1	2	None	Used	Pneumoniti (3), esophagitis (2), anorexia (2)	CR	21.3/Dead
3	4	4	3	4	RBC	Used	Neutropenic fever (3), esophagitis (3)	CR	65.6/Alive
4	4	4	2	1	None	Used	None	CR	97.4/Alive
5	3	4	2	3	None	Used	Neutropenic fever (3), esophagitis (2), anorexia (2)	CR	13.1/Dead
6	4	4	2	1	None	None	Pneumoniti (5), neutropenic fever (3)	CR	6.4/Dead
7	4	4	4	4	RBC	Used	None	PR	24.7/Dead

WBC, white blood cell count; Neu, neutrophil count; Hb, hemoglobin; Plt, platelet count; G-CSF, granulocyte- colony stimulating factor; CTC-AE, Common Terminology Criteria for Adverse Events; CR, complete response; RBC, red blood cell; PR, partial response.

more than 5 years without recurrence. The median survival of the seven patients was 24.7 months.

DISCUSSION

The antitumor effects of the treatment regimens were reasonably good, with six complete responses and one partial response and three long-term disease-free survivors in spite of discontinuation/dose reduction of chemotherapy. This is perhaps mainly attributable to the strict selection of patients in good general condition. Thus, we believe that the standard chemoradiotherapy can be applied to LD-SCLC patients aged 75 years or older as long as they are in good general condition.

The general condition of elderly patients, however, varies widely from patient to patient. Thus, in many elderly patients 75 years of age or older, it may be better to reduce the treatment intensity, although it may be difficult to establish the standard schedule applicable to all elderly patients. There are four possible ways to modify the intensity of therapy: (1) administer chemotherapy alone; (2) change the relative timing of chemotherapy and radiotherapy; (3) decrease the drug doses and number of cycles of chemotherapy, and (4) decrease the dose and intensity of thoracic radiotherapy.

Chemotherapy alone versus chemotherapy and thoracic radiotherapy for LD-SCLC were compared in many randomized trials between the 1970s and 1980s. A meta-analysis of these trials demonstrated survival benefit of radiotherapy added to chemotherapy in younger populations of patients less than 65 years of age, but the benefit is still unclear in older patients (11). Although the findings of this meta-analysis indicated that the standard treatment in elderly patients with LD-SCLC might be chemotherapy alone, the result based on the old trials using cyclophosphamide and doxorubicin-based chemotherapy cannot be applied in the current medical setting, because chemotherapy regimens, irradiation delivery equipment and staging procedures have all evolved greatly over time.

The relative timing of chemotherapy and radiotherapy greatly influences the severity of toxicity. In late concurrent chemoradiotherapy that follows induction chemotherapy, the chemotherapy dose can be adjusted to suit each patient by evaluating the toxicity of the previous chemotherapy. In addition, the irradiation volume can be reduced by modifying the radiation treatment planning in accordance with the extent of tumor shrinkage during the induction phase. In the two patients treated by this approach in this study, the dose of the platinum drug during the concurrent chemoradiotherapy phase was reduced to 66–75% of the initial dose and that of etoposide was reduced to 50–75% of the initial dose. Sequential chemoradiotherapy consists of induction chemotherapy and subsequent radiotherapy. Because the two treatment modalities are administered separately, the treatment dose in each can be optimized for the elderly in this approach. A phase III study of concurrent versus sequential chemoradiotherapy in LD-SCLC patients younger than 75 years old revealed a 5-year survival rate of 24% in the concurrent arm and a 5-year survival rate of 18% with a lower incidence of toxicity in the sequential arm (2). The sequential schedule has not yet been evaluated in LD-SCLC patients 75 years of age or older.

A recent phase III trial showed that etoposide at 80 mg/m^2 on days 1–3 combined with either carboplatin at AUC = 5 by Carvert's formula or cisplatin at 25 mg/m^2 on days 1–3 was feasible and effective in elderly patients with extensive-disease SCLC (10). These regimens may, therefore, be applied for the treatment of LD-SCLC as well. The standard number of chemotherapy cycles administered is four. In many elderly patients, however, all four cycles cannot be completed. In two phase II studies of two cycles

of chemotherapy and concurrent thoracic radiotherapy in elderly patients with LD-SCLC, 13–25% long-term survivors were noted (12,13). Thus, the optimal number of chemotherapy cycles in the elderly should be investigated in future trials.

Thoracic radiotherapy with accelerated hyperfractionation at a total dose of 45 Gy in 30 fractions, the standard schedule for LD-SCLC, was associated with grade 3–4 esophagitis in as high as 32% of the patients and grade 4 leukopenia in 44% of the patients (2,3,5). Thus, the conventional schedule at a total dose of 45–50 Gy in 25 fractions might be preferable in the elderly (3). The severity of esophagitis is also influenced by concomitant chemotherapy, the treatment schedule and the timing of thoracic radiotherapy.

In conclusion, concurrent chemoradiotherapy promises to offer long-term benefit with acceptable toxicity in selected patients of LD-SCLC aged 75 years or older. The optimal schedule and dose of chemotherapy and thoracic radiotherapy still remains to be established in this patient population.

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Conflict of interest statement

None declared.

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Multidisciplinary Treatment for Advanced Invasive Thymoma with Cisplatin, Doxorubicin, and Methylprednisolone

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Background and Objectives: Advanced invasive thymomas are not usually manageable by surgical resection and radiotherapy. We reviewed our experience with a multidisciplinary approach and evaluated chemotherapy in the treatment of invasive thymoma.

Patients and Methods: Seventeen consecutive patients with invasive thymoma were treated with multimodality therapy consisting of chemotherapy, surgery, and/or radiotherapy. Four patients had stage III disease with superior vena cava invasion, nine had stage IVa disease, and four had stage IVb disease. The chemotherapy regimen consisted of cisplatin, doxorubicin, and methylprednisolone (CAMP). Chemotherapy was administered in a neoadjuvant setting to the 14 patients and in an adjuvant setting to the remaining three patients. Surgical resection was intended in all patients. After those treatments, chemotherapy and/or radiation therapy were performed.

Results: All but one of the 14 patients with induction chemotherapy responded to the CAMP therapy, and the response rate was 92.9%. Seven of these patients underwent complete remission after surgical resection and chemoradiotherapy, and the others underwent partial remission. All three patients treated with surgical resection and then chemotherapy with or without radiotherapy also achieved complete remission. Tumor progression after multimodality therapy occurred in 10 patients. After retreatment, eight of these patients were alive at the time of analysis, with a median survival time after recurrence of 30 months. The 5- and 10-year overall survival rates for all patients were both 80.7%. The major side effect of CAMP therapy was acceptable neutropenia.

Conclusions: CAMP therapy was highly effective for invasive thymomas, and the multimodality therapy containing this chemotherapy brought about good disease control in the majority of patients. We believe that this multidisciplinary treatment with CAMP therapy, surgery, and radiotherapy is a justifiable initial treatment for patients with advanced invasive thymoma. Furthermore, appropriate treatments are essential for the long-term survival of patients with recurrences after multimodality therapy.

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In patients with thymoma, surgical resection with or without radiation therapy has been advocated as the treatment of choice for early-stage diseases.[1–3] Nevertheless, advanced-stage diseases such as tumors with great vessel invasion, pleural and/or pericardial dissemination, lymph node involvements, or distant metastases are difficult to manage by surgery and radiotherapy, and the treatment strategy for those diseases remains controversial.[4,5]

Chemotherapy has been shown to have significant antitumor activity against unresectable, recurrent, or metastatic thymomas.[6–9] Recently, multimodality therapy using chemotherapy has been examined in the treatment of advanced thymomas.[10–12] Investigators have demonstrated that combined-modality therapy can improve outcomes for advanced thymoma patients. Nevertheless, the chemotherapy regimens and treatment schedules in these studies were varied, and an optimal treatment strategy has not yet been determined. Furthermore, although it is well known that thymoma has a slow-growing nature and a late recurrent tendency, few reports contained longer follow-up data or results of retreatment of recurrences.[13–15]

To improve the outcome of patients with advanced invasive thymomas, we have conducted a study of multimodality therapy including chemotherapy. Here, we report the results with a longer follow-up.

PATIENTS AND METHODS

From February 1988 to September 2003, 38 patients with thymoma were referred to our hospital. Their clinical characteristics are shown in Table 1. Of these patients, 17 consecutive patients with advanced invasive thymoma, (four patients with stage III disease, nine with stage IVa disease, and four with stage IVb disease) including four patients with recurrent tumor, were enrolled in the study of multimodality therapy including chemotherapy, surgery, and/or radiotherapy. In all but three patients, pathologic diagnosis of thymoma was obtained by thoracotomy, transthoracic needle biopsy, or fiberoptic bronchoscopic biopsy before initiation of treatment. Among the patients without pretreatment histologic diagnosis, one patient had multiple recur-

TABLE 1. Profile of Patients with Thymoma

Sex	
Male	17
Female	21
Age (yr)	
Median (range)	57 (25–75)
World Health Organization tumor type	
A	2
AB	6
B1	3
B2	22
B3	5
Masaoka stage	
I	15
II	4
III	6
IVa	9
IVb	4

rent pleural tumors after surgical treatment and chemotherapy for thymoma, and the remaining two had anterior mediastinal mass suspected invasive thymoma on computed tomography (CT) that were located at unsuitable places for needle biopsy. Clinical staging was determined by the medical history and physical examination, chest radiography, and chest CT. Other imaging modalities such as magnetic resonance imaging, echocardiography, or venography were performed when indicated. The staging was based on the Masaoka staging system.[16] All patients gave written informed consent for the study.

The treatment strategy of the multimodality therapy was as follows: (a) If a tumor of stage III with invasion to the great vessels or stage IV disease was distinctly demonstrated on diagnostic imaging at the initial staging, induction chemotherapy was conducted. After three or four cycles of the chemotherapy, surgical resection was attempted when the residual tumor was found, and consolidation chemotherapy and/or radiotherapy were given. (b) When stage IV disease was found on operation despite a clinically earlier stage, surgery for debulking the tumor was attempted. After that, chemotherapy was administered as a postsurgical adjuvant treatment, and then radiation therapy was applied if indicated.

The chemotherapy regimen consisted of cisplatin (20 mg/m^2 per day, continuous infusion on days 1 through 4), doxorubicin (40 mg/m^2 intravenously on day 1), and methylprednisolone (1000 mg/day intravenously on days 1 through 4 and 500 mg/day intravenously on days 5 and 6) (CAMP). Treatment cycles were repeated every 21 to 28 days. Prophylactic granulocyte colony stimulating factor was not routinely used. Surgery was intended through a median sternotomy in all patients. Resection was defined as complete (R0) if all gross disease was removed and if all surgical margins were free of the tumor. An incomplete resection meant that the surgical margins were microscopically positive (R1) or that gross residual tumors (R2) were left at the end of the operation. Radiation therapy was administered to the mediastinal or residual tumor areas using opposite anterior and posterior parallel fields and doses of more than 50 Gy. When malignant pericardial effusion was noted during the operation, whole mediastinal irradiation was carried out.

The patients were evaluated with CT for response after induction chemotherapy and completion of the multimodality treatment. A complete remission (CR) was defined as the complete disappearance of all objective evidence of disease on CT for at least 4 weeks. A partial remission (PR) was defined as a decrease of at least 50% in the sum of the product of the perpendicular diameter of measurable lesions for at least 4 weeks. Disease progression was defined as an increase of at least 25% in tumor size or new lesions. All other circumstances were classified as no change (NC).

Survival was measured from the first day of treatment until death or the last date of the follow-up (March 31, 2004). The survival curves were calculated according to the Kaplan–Meier method, and comparisons among the curves were made by means of the log-rank test. The median follow-up time of all patients (n = 17) was 54 months (range, 2–193 mo), and median follow-up time of surviving patients (n = 14) was 62 months (range, 6–193 mo).

RESULTS

Of the 17 patients, eight were women and nine were men, ranging in age from 25 to 72 years (median, 51 yr) (Table 2). Pretreatment pathologic diagnoses were obtained in 14 patients, and the tumor histology of the remaining three patients (patients 15–17) was revealed after chemotherapy and surgical treatment. Histologic types of the thymoma were B2 tumor in 14 patients and B3 tumor in three patients, according to the World Health Organization classification.[17] All four patients who were diagnosed as having stage III disease were found to have a tumor with superior vena cava invasion on diagnostic imaging. Nine patients with stage IVa disease had pleural tumor dissemination and/or pericardial effusion, and four with stage IVb disease had pulmonary metastasis or lymph node involvement.

A summary of treatments and outcomes is listed in Table 3. CAMP therapy was administered in a neoadjuvant setting to 14 patients (Figures 1 and 2). One complete response and 13 partial responses were obtained, with an overall response rate of 92.9% (95% confidence interval [CI], 66.1–99.8%). After chemotherapy, nine patients underwent surgical resection of the residual tumor with curative intent. However, R0 resection was performed in only two patients, R1 resection in one patient, and R2 resection in six patients. Postsurgical radiotherapy was performed in eight patients. Among the remaining four patients, one complete responder for CAMP therapy had no additional treatment. Two partial responders received radiotherapy because of the unresectable tumor, and the other one refused further treatment.

Three patients (patients 1, 2, and 11) who were categorized at the initial staging as having stage I to III disease were found on operation to have stage IVa disease with pleural dissemination or malignant pericardial effusion. The patients underwent resection of the main tumor and extended