conducted independently of the CT analysis. All patients with PML underwent treatment, which included chemotherapy and radiotherapy for HL, chemotherapy and/or radiotherapy for Med-DLBCL, and chemotherapy and radiotherapy for T-LBL. Follow-up documentation was reviewed for any evidence of misdiagnosis at any repeat imaging examinations, biopsies, laboratory tests, or on the basis of ongoing symptoms and signs. At the time of this review, there has been no case of initial misdiagnosis.

To determine whether or not CT findings can accurately differentiate PML from the other common nonlymphomatous diseases, a total of 70 patients including thymoma (n = 19), thymic cancer (n = 26), germ cell tumor (n = 13), and small cell lung cancer (n = 12) were also enrolled in this study (Table 1). Selective criteria of these cases were 1) main anterior mediastinal mass identified on CT at presentation, 2) definite diagnosis confirmed by the pathologic observation of main mass, and 3) CT examination performed prior to therapy. These cases were selected from the radiologic files of our institute, and clinical details and follow-up information were also reviewed retrospectively by a radiologist who was one of the authors.

Imaging Studies

CT was performed on a 4-row multidetector scanner (Aquilion V-detector, Toshiba Medical Systems, Tokyo, Japan). The images were obtained at 240–260 mAs, 120 kV, 7-mm collimation sections overlapped in 3.5-mm intervals from the level of the orbit to the proximal femur, and a pitch of 10.5. All patients received 150 mL of nonionic intravenously administered contrast material at 3.0 mL/s with a power injector (Autoenhance A-250; Nemoto-kyorindo, Tokyo, Japan) after a 60-second delay. All patients also received 200–300 mL of sterile water orally prior to CT examination.

Image Analysis

Two experienced radiologists who had knowledge of the diagnosis of primary mediastinal lymphoma but were blinded to histologic subtypes and any clinical information other than patient age and sex independently reviewed the CT images on hard copies. The 2 readers analyzed the images for tumor size, tumor margins (well defined or ill defined), and presence of surface lobulation. The presence of a single mass or confluent lymphadenopathy in the anterior mediastinum was analyzed as representing the primary tumor mass and the measurement based on the short axis diameter. The contrast enhancement of the primary lesions was compared with that of normal muscle. The tumor was considered homogeneous if it enhanced to the same degree throughout. The patterns of local invasion were recorded: encasement of vascular structures, chest wall invasion, cutaneous involvement, and lung invasion. Vascular encasement was considered present when there was circumferential narrowing or complete obstruction of the superior vena cava or brachiocephalic vein by tumor. The presence or absence of lymphadenopathy, pleural effusion, pericardial effusion, and other organ involvement were also evaluated. Nodes were considered enlarged when their short axis diameter was greater than 10 mm. Hepatomegaly and splenomegaly were considered present when the liver and spleen were greater than 13 cm and 12 cm in longitudinal diameter at the midclavicular line, respectively.[29]

Statistical Analysis

Kruskal-Wallis test was used to compare the clinical variables and all CT findings in the 3 histologic subtypes of PML and the other common nonlymphomatous disorders. Student t test was used to compare mean tumor size of the mediastinal mass. The interobserver variation in the interpretation of all CT findings was analyzed using Kappa statistics. The interobserver agreement was classified as follows: poor, k = 0–0.20; fair, k = 0.21–0.40; moderate, k = 0.41–0.60; good, k = 0.61–0.80; and excellent, k = 0.81–1.00. The relationship between CT findings and the likelihood of the histologic subtypes was tested for independent predictors using multiple logistic regression analysis, which determined the odds ratio after adjusting for the other variables examined. All P values less than 0.05 were considered to indicate a statistically significant difference.

RESULTS

Statistically significant CT findings which have possibility of discriminating PML from the other common nonlymphomatous diseases were tumor margins, the presence of lung invasion, involvement of various lymph nodes including cervical (superficial and deep), mediastinal, hilar, axillary, paraaortic, inguinal lymph nodes, the presence of pericardial effusion, splenomegaly, the presence of lung metastasis, and liver metastasis. Patient demographics are listed in Table 2. Patients with Med-DLBCL were slightly older (mean age ± SD: 46.4 ± 18.0) than those with HL (34.6 ± 10.7) or T-LBL (30.6 ± 12.4) ($P < 0.01$). No other significant difference was seen in patient demographics between the 3 subtypes of PML.

TABLE 2. Demographic and Clinical Data in Patients With PML

Disease	HL	Med-DLBCL	T-LBL
No. of patients	29 (44)	21 (32)	16 (24)
Age (mean ± SD) (y)	34.6 ± 10.7	46.4 ± 18.0	30.6 ± 12.4*
Age range (y)	19–57	23–84	13–64
Gender			
Male	17 (59)	15 (71)	13 (81)
Female	12 (41)	6 (29)	3 (19)
IPI score			
Low	23 (79)	12 (57)	6 (38)
Low–intermediate	5 (17)	2 (10)	8 (50)
Intermediate–high	0	5 (24)	1 (6)
High	1 (3)	2 (10)	1 (6)
Clinical stage			
I	7 (24)	11 (52)	2 (13)
II	15 (52)	3 (14)	2 (13)
III	4 (14)	1 (5)	3 (19)
IV	3 (10)	6 (29)	9 (56)

Data in parentheses are percentages. Significant difference is found in the mean age between Med-DLBCL and T-LBL (*$P < 0.01$).

HL, Hodgkin lymphoma; Med-DLBCL, mediastinal diffuse large B-cell lymphoma; T-LBL, T-cell lymphoblastic lymphoma; IPI, International Prognostic Index.

Enlargement of cervical lymph nodes was seen more commonly in T-LBL (10 of 16 patients, 63%) than in HL (9 of 29 patients, 31%) ($P < 0.05$) and was not present in any of the patients with Med-DLBCL (Fig. 1). Of the cervical nodes, deep cervical nodes were affected more frequently in HL (31% [9 of 29 patients]) or T-LBL (56% [9 of 16 patients]) than those in Med-DLBCL (no patients). Superficial nodes were also involved more often in T-LBL (44% [7 of 16 patients]) than in HL (10% [3 of 29 patients], $P < 0.05$). Involvement of supraclavicular lymph nodes was seen more frequently in T-LBL (50% [8 of 16 patients]) compared with that in HL (10% [3 of 29 patients], $P < 0.01$). Submandibular, submental, and parotid lymph nodes were involved only in T-LBL (19% [3 of 16 patients]).

No significant difference was found in the size and margin of the primary lesion between the three histologic subtypes (Table 3). Surface lobulation (Fig. 2) was more common in HL (69% [20 of 29 patients]) than in both Med-DLBCL (33% [7 of 21 patients]) and T-LBL (25% [4 of 16 patients]) ($P < 0.01$, Table 3). The prevalence of vascular involvement including encasement of superior vena cava and left brachiocephalic vein in Med-DLBCL (62% [13 of 21 patients], $P < 0.0001$) and T-LBL (38% [6 of 16 patients],

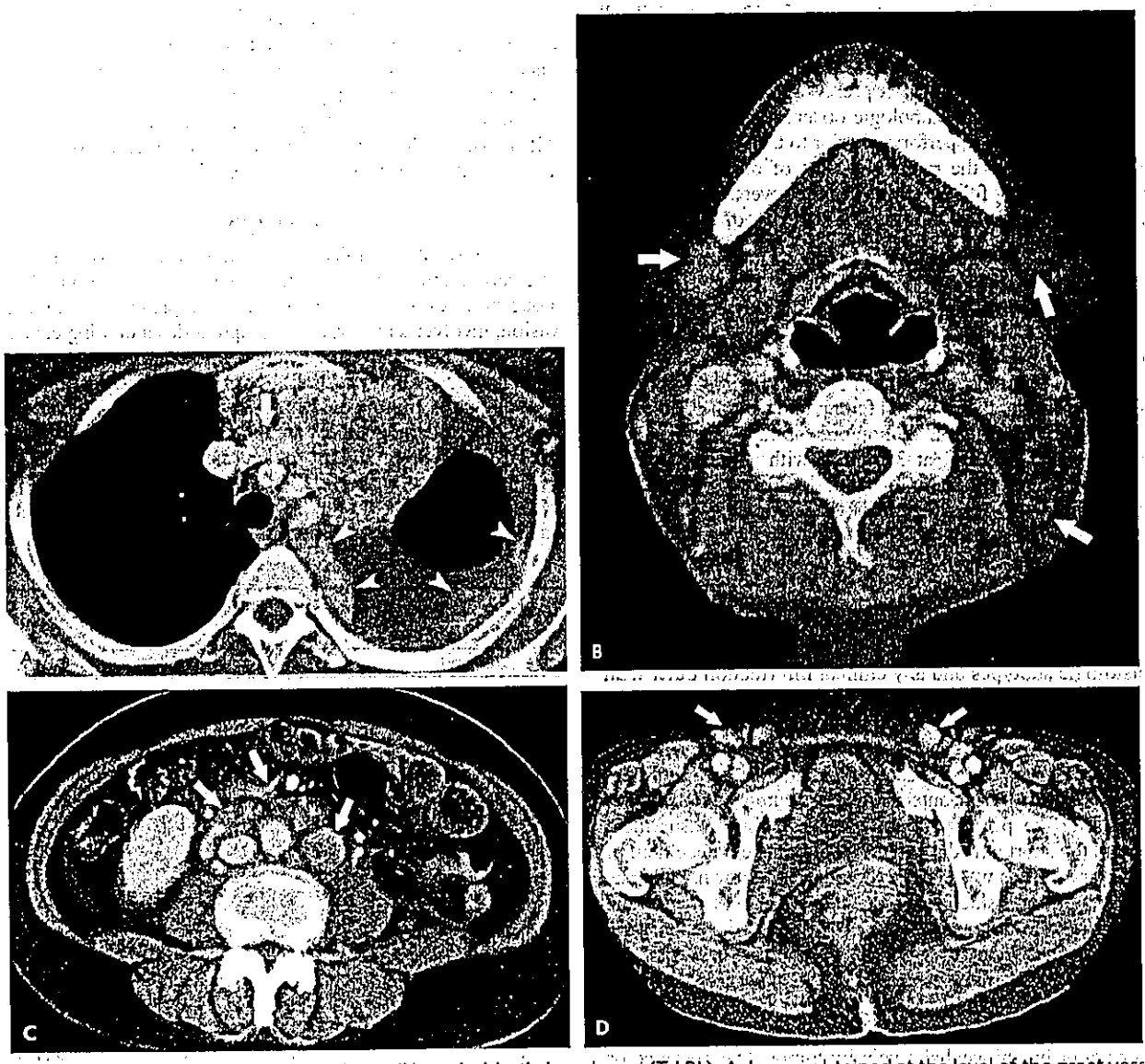

FIGURE 1. Thirty-two-year-old man with T-cell lymphoblastic lymphoma (T-LBL). A, Image obtained at the level of the great vessels shows a large anterior mediastinal mass with encasement and stenosis of the left brachiocephalic vein (arrow). Also noted are left pleural effusion and soft-tissue masses (arrowheads) in the left pleura suggestive of pleural dissemination. B, Image at the level of the upper neck demonstrates several enlarged of cervical nodes (arrows). C, Image at the level of the lower pole of the right kidney shows multiple enlarged paraaortic and mesenteric nodes. D, Image at the level of the inguinal region shows enlarged inguinal lymph nodes (arrows).

TABLE 3. CT Findings in Patients With PML

Disease	HL	Med-DLBCL	T-LBL
No. of patients	29 (44)	21 (32)	16 (24)
Tumor margins			
Well-defined margins	19 (66)	10 (48)	10 (62)
Ill-defined margins	10 (34)	11 (52)	6 (38)
Size of main mass (mean ± SD) (cm)	9.7 ± 2.8	9.7 ± 2.5	10.2 ± 3.3
Presence of surface lobulation*	20 (69)	7 (33)	4 (25)
Presence of vasular encasement†	2 (7)	13 (62)	6 (38)
Presence of chest wall invasion	4 (14)	4 (19)	2 (13)
Presence of cutaneous involvement	0	2 (10)	1 (6)
Presence of lung invasion	8 (28)	2 (10)	1 (6)
Presence of nodal involvement			
Cervical lymph node (superficial)*	3 (10)	0	7 (44)
Cervical lymph node (deep)†	9 (31)	0	9 (56)
Submandibular lymph node	0	0	1 (6)
Submental lymph node‡	0	0	2 (13)
Parotid lymph node‡	0	0	2 (13)
Supraclavicular lymph node§	3 (10)	0	8 (50)
Mediastinal lymph node†	28 (97)	14 (67)	8 (50)
Hilar lymph node‡	10 (34)	1 (5)	1 (6)
Axillary lymph node†	4 (14)	0	8 (50)
Celiac lymph node	3 (10)	0	1 (6)
Paraaortic lymph node*	6 (21)	0	6 (38)
Mesenteric lymph node‡	0	0	2 (13)
Iliac lymph node	0	0	1 (6)
Inguinal lymph node†	0	0	5 (31)
Presence of pleural effusion‡	6 (21)	12 (57)	8 (50)
Presence of pericardial effusion‡	5 (17)	10 (48)	9 (56)
Hepatomegaly‡	0	0	2 (13)
Splenomegaly†	1 (3)	1 (5)	11 (63)

Date in parentheses are percentages.
*$P < 0.01$, †$P < 0.001$, ‡$P < 0.05$, §$P < 0.0001$.
HL, Hodgkin lymphoma; Med-DLBCL, mediastinal diffuse large B-cell lymphoma; T-LBL, T-cell lymphoblastic lymphoma.

$P < 0.05$) was greater than that in HL (7% [2 of 29 patients], Figs. 1 and 2). Complete obstruction of the superior vena cava (SVC syndrome) was present in one of 29 patients with HL (3%), 4 of 21 with Med-DLBCL (19%), and 2 of 16 patients with T-LBL (13%). Forty-one of 66 tumors (62%) showed heterogeneous enhancement on CT, with no significant difference between 3 histologic subtypes.

Enlarged mediastinal nodes distinct from the primary lesion were present more commonly in HL (97% [28 of 29 patients]) than in Med-DLBCL (67% [14 of 21 patients], $P < 0.05$) and T-LBL (50% [8 of 16 patients], $P < 0.0001$, Table 3). Involvement of hilar nodes (Fig. 3) was significantly more common in HL (34% [10 of 29 patients]) compared with Med-DLBCL (5% [1 of 21 patients], $P < 0.05$) and T-LBL (6% [1 of 16 patients], $P < 0.05$). Involvement of bilateral axillary nodes was significantly more common in T-LBL (50% [8 of 16 patients]) than in Med-DLBCL (no patients, $P < 0.0001$) and HL (14% [4 of 29 patients], $P < 0.05$). Pleural effusion (Figs. 1 and 2) was significantly more common in Med-DLBCL (57% [12 of 21 patients], $P < 0.01$) or T-LBL (50% [8 of 16 patients], $P < 0.05$) than in HL (21% [6 of 29 patients]). Of the patients with pleural effusion, tumor cells were confirmed by cytology in 6 of 6 patients with HL (100%), in 5 of 12 with Med-DLBCL (42%), and in 2 of 8 patients (25%) with T-LBL. Pericardial effusion (Fig. 4) was significantly more common in T-LBL (56% [9 of 16 patients], $P < 0.01$) and Med-DLBCL (48% [10 of 21 patients], $P < 0.05$) than in HL (17% [5 of 29 patients]).

Statistically significant CT findings in the abdomen included splenomegaly, and involvement of paraaortic, mesenteric, and inguinal lymph nodes (Table 3). Splenomegaly was present more commonly in T-LBL (63% [11 of 16 patients]) than in HL (3% [1 of 29 patients], $P < 0.0001$) and Med-DLBCL (5% [1 of 21 patients], $P < 0.0001$). Involvement of abdominal paraaortic nodes (Fig. 1) was more common in T-LBL (38% [6 of 16 patients], $P < 0.01$) or HL (21% [6 of 29 patients], $P < 0.05$) than in Med-DLBCL (no patients). Involvement of inguinal (31% [5 of 16 patients]) or mesenteric lymph nodes (13% [2 of 16 patients]) was found only in T-LBL (Fig. 1). Extranodal lesions in the abdomen were proved pathologically in 3 patients. Two patients with Med-DLBCL had mass lesions in the stomach and kidney, and the

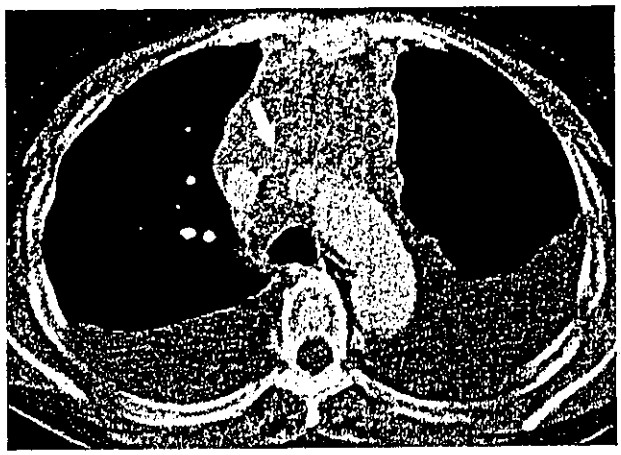

FIGURE 2. Thirty-two-year-old man with mediastinal diffuse large B-cell lymphoma (Med-DLBCL). CT image at the level of the aortic arch demonstrates a large, homogeneous enhancing anterior mediastinal mass without surface lobulation that compresses the left brachiocephalic vein (arrow). Also noted are bilateral pleural effusions.

other patient with HL had focal splenic mass. None of patients with T-LBL had evidence of extranodal involvement on the abdominal CT images.

There was excellent interobserver agreement for CT findings, including morphology and extent of main mass, enhancement pattern, lymph node enlargement, the presence of pleural effusion, pericardial effusion, hepatomegaly, and splenomegaly (Kappa = 0.82–1.00). Multiple logistic regression analysis demonstrated that the CT finding independently associated with increased likelihood of HL was surface lobulation ($P < 0.01$; Table 4), the absence of vascular involvement ($P < 0.01$), or pleural effusion ($P < 0.05$). The presence of vascular involvement was independently associated with increased likelihood of Med-DLBCL ($P < 0.001$, Table 4). In addition, CT findings including the presence of cervical lymph nodes or inguinal lymph nodes ($P < 0.001$; Table 4), the presence of pericardial effusion ($P < 0.05$), and the absence of surface lobulation ($P < 0.05$) were significantly associated with the likelihood of T-LBL.

DISCUSSION

Several studies have described the CT manifestations of PML. The typical presentation consists of an anterior mediastinal mass often associated with enlarged nodes in the middle and posterior mediastinum, and hila.[13–24] The mediastinal mass may involve vascular structures, pericardium, heart, pleura, lung, and chest wall on CT.[13–27] PML often affects extrathoracic sites at the time of diagnosis, particularly abdomen, head, and neck.[28,29]

The current study demonstrates that the different subtypes of PML often have characteristic manifestations that allow their distinction on CT. HL is characterized by the presence of a discrete anterior superior mediastinal mass with surface lobulation. Surface lobulation was present in 69% of patients with HL compared with 33% of patients with

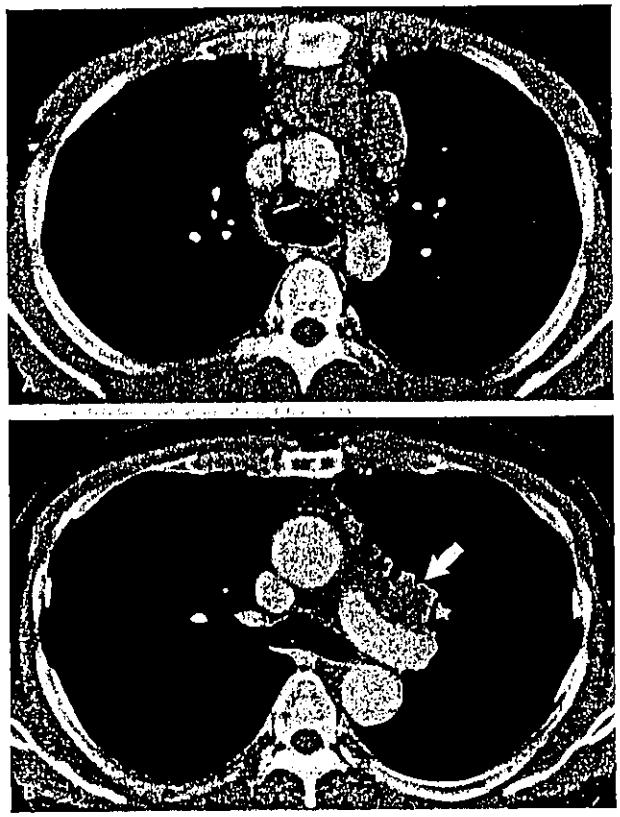

FIGURE 3. Twenty-nine-year-old man with Hodgkin's lymphoma (HL). A, Image at the level of the aortopulmonary window shows anterior mediastinal mass with surface lobulation and heterogeneous enhancement. B, Section obtained at the level of the carina demonstrates enlarged left hilar nodes (arrow).

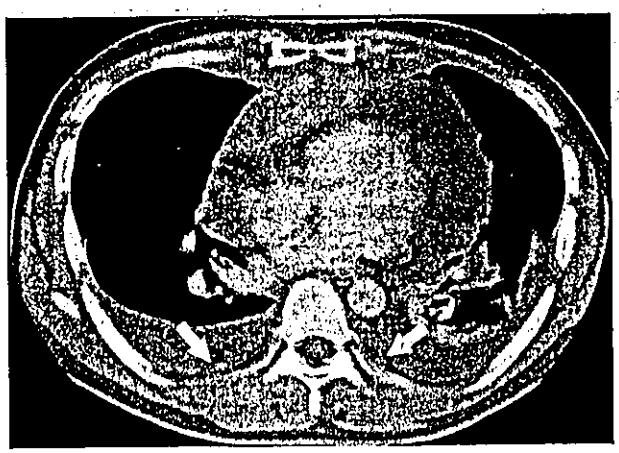

FIGURE 4. Thirty-two-year-old man with T-LBL. Image obtained at the level of the right ventricle shows a large anterior mediastinal mass (asterisk) with marked pericardial effusion. Also noted are pleural effusion bilaterally and soft-tissue nodular dissemination (arrows) in the pleura.

TABLE 4. Relationship Between CT Findings and the Likelihood of the PML Hisologic Subtypes

	CT findings	OR	95% CI	P
HL	Presence of surface lobulation	11.9	2.5–56.0	<0.01
	Absence of vascular involvement	11.8	1.9–71.9	<0.01
	Absence of pleural effusion	6.6	1.3–33.2	<0.05
Med-DLBCL	Presence of vascular involvement	7.5	2.3–24.1	<0.001
T-LBL	Presence of cervical or inguinal lymph node	33.9	4.7–244.6	<0.001
	Presence of pericardial effusion	11.4	1.7–77.6	<0.05
	Absence of surface lobulation	7.0	1.2–43.1	<0.05

HL, Hodgkin lymphoma; Med-DLBCL, mediastinal diffuse large B-cell lymphoma; T-LBL, T-cell lymphoblastic lymphoma; OR, odds ratio; CI, confidence interval.

Med-DLBCL and 25% with T-LBL. The surface lobulation of the main mass is due to involvement of multiple nodes and coalescence, a finding previously noted in HL at CT.[13,14] Enlarged nodes elsewhere in the mediastinum were seen in 97% of patients with HL in the current study and less commonly in the other subtypes.

Masses typically exhibit homogeneous soft-tissue attenuation, while large tumors may demonstrate heterogeneity with complex low attenuation representing necrosis, hemorrhage, and cystic degeneration.[20] Sixty-two percent of our cases showed heterogeneous enhancement on CT, with no significant difference between 3 histologic subtypes.

Med-DLBCL typically is initially confined to the mediastinum and contiguous nodal areas without showing extrathoracic disease at presentation.[3,5] Med-DLBCL may present with hematogenous spread to parenchymal organs such as kidney, liver, ovary, adrenal gland, gastrointestinal tract, and central nervous system during disease progression or at recurrence.[3] Extranodal involvement was found on the initial CT assessment and was confirmed by biopsy in 2 of our Med-DLBCL cases, whereas extrathoracic nodal involvement was not found in any of our patients with Med-DLBCL. Some observers consider that Med-DLBCL is a pathologic and clinical entity of non-Hodgkin lymphoma derived from mature thymic B-cells recognized by previous immunophenotypic studies.[30,31] However, the histogenesis is controversial, because Med-DLBCL can result in diffuse nodal involvement in advanced stages.[3,5]

Extrathoracic lymphadenopathy including superficial cervical, supraclavicular, submandibular, submental, parotid, mesenteric, and inguinal nodes, was seen in the majority of patients with T-cell lymphoblastic lymphoma in the present study. Another common finding in T-cell lymphoblastic lymphoma in the current study was the presence of splenomegaly, which was seen in 63% of cases. HL often involved axial lymph nodes including cervical, mediastinal, axillary, and paraaortic regions. However, none of the patients with HL in the current study had submandibular, submental, parotid, mesenteric, and inguinal lymphadenopathy. The low prevalence of nonaxial lymphadenopathy in HL had been recognized in previous studies.[29,32]

Diagnosis of subtypes in all patients was established by core or excisional biopsy in all cases. The ability to classify PML in small samples has improved considerably in the last few years because of progress of pathologic criteria and immunocytochemistry.[33,34] HL is characterized by a large inflammatory cell reaction within a fibrotic stroma, and the diagnosis is established by the identification of Hodgkin and Reed-Sternberg (HRS) cells.[2] Med-DLBCL is composed mainly of large clear cells within a characteristic background of compartmentalized fibrosis.[5] T-LBL is composed of a homogeneous population of immature lymphoblastic cells cytologically similar to acute lymphoblastic leukemia.[8–10] Biopsy provides sufficient information for the diagnosis of and subsequent therapeutic decision to treat patients with PML, because the definitive selection of therapeutic regimen is needed.

Our study has several limitations. It is retrospective and includes a relatively small number of patients. In clinical practice, the differential diagnosis would need to include a variety of other conditions that can present with an anterior mediastinal mass. However, we believe that the study demonstrates that the various histologic subtypes of PML have features on CT that allow distinction in the majority of cases. The anatomic distribution of the disease varies among the histologic subtypes of HL. Mediastinal involvement is most frequently seen in the nodular sclerosis HL subtype, while splenic involvement is more common in the mixed cellularity HL subtype.[29]

In conclusion, we found that CT findings often allowed differentiation of the various subtypes of PML. HL commonly presents as a mediastinal mass with surface lobulation and involves cervical, mediastinal, hilar, and paraortic nodes. Med-DLBCL demonstrates mediastinal mass without surface lobulation, often associated with vascular involvement, and pleural or pericardial effusion. T-LBL is characterized by mass without surface lobulation involving vascular structures often associated with pleural or pericardial effusion, by systemic nodal involvement including cervical, axillary, paraaortic, mesenteric, and inguinal, and by hepatomegaly and splenomegaly.

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Original article

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A phase II study of cisplatin and docetaxel administered as three consecutive weekly infusions for advanced non-small-cell lung cancer in elderly patients

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Background: To evaluate the efficacy and safety of treatments for advanced non-small-cell lung cancer in elderly patients aged 75 years or older, we conducted a phase II study of cisplatin and docetaxel administered in three consecutive weekly infusions.

Patients and methods: The eligibility criteria for the study included the presence of chemotherapy-naive advanced non-small-cell lung cancer, age ≥75 years, Eastern Cooperative Oncology Group performance status of 0 or 1, a measurable lesion, adequate organ functions and signed informed consent. The chemotherapy regimen consisted of cisplatin (25 mg/m^2) and docetaxel (20 mg/m^2) on days 1, 8 and 15 every 4 weeks.

Results: Between February 2000 and March 2002, 34 elderly patients with non-small-cell lung cancer were enrolled in the study and 33 patients were treated. Two complete responses and 15 partial responses were obtained for an objective response rate of 52% in 33 treated patients. The median survival period was 15.8 months, and the 1-year survival rate was 64%. Toxicities were mild with no grade 4 toxicities. Only grade 3 leukopenia (6%), neutropenia (12%), anemia (3%), hyponatremia (3%) and nausea/vomiting (3%) were observed.

Conclusion: Cisplatin and docetaxel administered in three consecutive weekly infusions was safe and effective for the treatment of elderly patients with chemotherapy-naive non-small-cell lung cancer.

Key words: cisplatin, docetaxel, elderly patients, non-small-cell lung cancer, weekly administration

Introduction

Lung cancer is one of the most common carcinomas not only in Japan, but also in the United States and Europe. More than 55 000 patients die from lung cancer each year, and the mortality rate is still increasing in Japan [1, 2]. In particular, the number of elderly lung cancer patients is increasing in Japan [1, 2]. Surgery is the most effective curative treatment for early stage non-small-cell lung cancer (NSCLC); however, only 30% of patients with NSCLC receive a curative resection [3]. Cisplatin-based chemotherapy offers a survival benefit and symptom relief for patients with inoperable NSCLC [4]. However, we have demonstrated that classic standard cisplatin-based chemotherapy regimens such as cisplatin (80 mg/m^2) on day 1 with etoposide (100 mg/m^2) on days 1–3 or cisplatin (80 mg/m^2) on day 1 with vindesine (3 mg/m^2) on days 1 and 8 cause severe myelotoxicity in elderly NSCLC patients aged ≥75 years [5]. We used a very restricted eligibility criteria to select patients who could tolerate the cisplatin-based standard chemotherapy. Among 34 elderly patients, only 10 fitted the eligibility criteria. In spite of granulocyte colony-stimulating factor (G-CSF) support, nine of the 10 eligible patients experienced grade 4 neutropenia and six had infectious episodes [5]. Thus, we hypothesized that the recommended dose for elderly patients aged ≥75 years should be determined in a specific phase I study only for elderly patients.

Docetaxel has demonstrated antitumor activity in NSCLC patients with chemotherapy-naive lesions and tumor progression after receiving cisplatin-based regimens [6–10]. Docetaxel with cisplatin is one of the most promising chemotherapy regimens for NSCLC [11]. The commonly used dose and schedule of docetaxel is 60–100 mg/m^2 every 3 weeks; however, moderate to severe neutropenia is frequently observed [6–11]. Recent studies have shown that weekly administration of docetaxel produces a higher dose intensity and less myelotoxicity [12–14]. Thus, we conducted two independent phase I studies for elderly and non-elderly patients with NSCLC to determine the recommended dose for phase II studies and to evaluate the safety and efficacy of cisplatin and docetaxel administered as three consecutive weekly infusions in both non-elderly (≤74 years) and elderly (≥75 years) patients

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[15]. Different recommended doses of docetaxel were obtained for non-elderly and elderly patients [15]. The recommended doses were 25 mg/m^2 cisplatin and 35 mg/m^2 docetaxel on days 1, 8 and 15 for non-elderly patients, and 25 mg/m^2 cisplatin and 20 mg/m^2 docetaxel on days 1, 8 and 15 for elderly patients.

Two phase II studies of cisplatin and docetaxel administered as three consecutive weekly infusions for non-elderly and elderly patients were conducted. The results of the phase II study for non-elderly patients with NSCLC have been reported elsewhere; the objective tumor response was 30% [95% confidence interval (CI) 15% to 46%] and the median survival time was 12.8 months [16]. Here, we report the promising results of a phase II study for elderly patients with NSCLC.

Patients and methods

Patient selection

Patients with histologically and/or cytologically documented NSCLC were eligible for the study. Each patient was required to meet the following criteria: clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy), an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, age ≥75 years, no prior chemotherapy, measurable lesions, adequate hematological function [white blood cell count (WBC) 4000–12 000/mm^3; neutrophils ≥2000/mm^3; platelets ≥100 000/mm^3; hemaglobin ≥9.0 g/dl], adequate hepatic function (total bilirubin <1.1 mg/dl, aspartate aminotransferase and alanine aminotransferase <60 IU/l), and adequate renal function (creatinine ≤1.2 mg/dl, creatinine clearance ≥60 ml/min). Patients with active infection, severe heart disease, uncontrollable hypertension or diabetes mellitus, active concomitant malignancy and pleural and/or pericardial effusion requiring drainage were excluded. The study was approved by the Institutional Review Board at the National Cancer Center, Yokohama Municipal Citizen's Hospital and Niigata Cancer Center. Written informed consent was obtained from each patient.

Patient evaluation

The pretreatment evaluation consisted of complete blood cell count, differential count, routine chemistry measurements, a chest radiograph, a chest computed tomography (CT) scan, abdominal ultrasound or CT scan, whole-brain magnetic resonance imaging or CT scan, and an isotope bone scan. Complete blood cell count, differential, count and routine chemistry measurements were carried out at least twice a week during the first course of chemotherapy.

Treatment schedule

All patients were admitted to hospital during the first course of chemotherapy. Chemotherapy consisted of cisplatin (25 mg/m^2) on days 1, 8 and 15 and docetaxel (20 mg/m^2) on days 1, 8 and 15 every 4 weeks. Docetaxel was infused over 30 min with 16 mg dexamethasone and 3 mg granisetron administered just before the docetaxel infusion. Ninety minutes after the completion of the docetaxel infusion, 25 mg/m^2 cisplatin were administered over 15 min with 1500 ml normal saline over 3.5 h. The prophylactic administration of G-CSF was not permitted. Administration of G-CSF was permitted in patients with grade 4 neutropenia and/or leukopenia or grade 3 febrile neutropenia. The administration of both cisplatin and docetaxel were skipped on day 8 and/or day 15 if the patients met the following criteria: WBC <2000/mm^3 and/or platelets <50 000/mm^3. No dose modifications were carried out on days 8 and/or day 15 of the cisplatin and docetaxel administrations. Treatment was carried out for at least two courses, unless unacceptable toxicity or disease progression occurred.

Response and toxicity evaluation

The patients' responses were evaluated according to the World Health Organization criteria [17]. A complete response (CR) was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks. A partial response (PR) was defined as a reduction of ≥50% in the product of the largest perpendicular diameters of one or more clearly measurable lesions or as a >50% reduction in evaluable malignant disease lasting for >4 weeks with no new areas of malignant disease. No change included: the regression of indicator lesions that were insufficient to meet the criteria for PR, <25% increase in any measurable lesion and no new lesions of malignant disease. Progressive disease was defined as an increase in any measurable lesion by >25% or a new lesion of malignant disease. Survival times from the start of treatment were calculated using the Kaplan–Meier method. The toxicity grading criteria of the Japan Clinical Oncology Group (JCOG) were used to evaluate toxicity [18]. Most detailed gradings for individual organ toxicity in the JCOG Toxicity Criteria are identical to those of the National Cancer Institute Common Toxicity Criteria proposed in 1988. The only differences in the definitions used in the present study were that neutrophils were used instead of granulocytes and the definitions for nausea and vomiting were combined.

Statistical analysis

According to the minimax two-stage phase II study design by Simon [19], the treatment program was designed to refuse response rates of 20% and to provide a significance level of 0.05 with a statistical power of 80% in assessing the activity of the regimen as a 40% response rate. The upper limit for first-stage drug rejection was four responses among 18 evaluable patients; the upper limit of second-stage rejection was 10 responses among 33 evaluable patients. Overall survival was defined as the interval between enrolment in this study and death or the last follow-up visit. Median overall survival was estimated using the Kaplan–Meier analysis method [20].

Results

Patient characteristics

Between February 2000 and March 2002, 34 elderly patients with NSCLC were enrolled and 33 were treated in this study (Table 1). One patient did not receive the protocol treatment because the PS of the patient decreased before the start of the treatment and the patient no longer met the eligibility criteria. All treated patients were assessed for response, survival and toxicity. The median age of the patients was 77 years (range 75–86). The gender, PS and histology of the patients were as follows: 26 males, seven females; seven patients with PS 0, 26 patients with PS 1; 20 patients with adenocarcinoma, nine patients with squamous cell carcinoma, three patients with large cell carcinoma and one patient with NSCLC. Twenty-four patients had no prior treatment, five patients had undergone surgery, three patients had received radiotherapy for brain and/or bone metastases, and one patient had undergone both surgery and radiotherapy as prior treatments.

Treatment received and dose intensity

The total number of treatment cycles was 101 and the median was 3 (range 1–15). Two patients received only one course because of a decrease in their PS. Of the 33 treated patients, 12 patients received two courses, 13 received three and six received four or more. One patient received 15 courses; however, he received

Table 1. Characteristics of treated patients

No. of entered patients	34
No. of treated patients	33
Sex	
Male	26
Female	7
Age (years)	
Median	77
Range	75–86
PS (ECOG)	
0	7
1	26
Histology	
Adenocarcinoma	20
Squamous-cell carcinoma	9
Large-cell carcinoma	3
Non-small-cell	1
Stage	
IIIA	1
IIIB	9
IIIB with effusion	3
IV	17
Relapse	6
Prior treatment	
None	24
Radiotherapy	4
Surgery	6

PS (ECOG): performance status (Eastern Cooperative Oncology Group).

treatments on only days 1 and 15 of the fifth to fifteenth courses. Between the first and fourth cycles, 77–100% of the patients received treatments on days 8 and 15 treatment (Table 2). Of the 303 planned administrations, 272 (90%) were carried out.

The median actual dose intensities of docetaxel and cisplatin were 13.4 mg/m^2 (range 8.9–16.4) and 16.7 mg/m^2 (range 11.1–20.4) per week, whereas the projected dose intensities were 15.0 and 18.8 mg/m^2 per week for docetaxel and cisplatin, respectively.

Objective tumor response and overall survival

The objective tumor response is shown in Table 3. Two CRs and 15 PRs occurred for an objective response rate of 52% (95% CI 31% to 67%) in 33 treated patients. The overall survival periods of all treated patients are shown in Figure 1. The median survival time of the 33 treated patients was 15.8 months with a median follow-up time for 11 censored patients of 18.1 (15.2–35.5) months. The 1-year and 2-year survival rates were 64% and 26%, respectively.

Table 2. Treatment received

No. of treatment cycles	No. of patients	Treatment received on	
		Day 8	Day 15
1	33	31 (94%)	32 (97%)
2	31	28 (90%)	24 (77%)
3	19	19 (100%)	17 (89%)
4	6	5 (83%)	5 (83%)
5	2	1 (50%)	1 (50%)

Toxicity

The worst grades of hematological and non-hematological toxicities experienced by each patient are listed in Table 4. Both hematological and non-hematological toxicities were relatively mild. No grade 4 hematological or non-hematological toxicities were observed. Only grade 3 leukopenia (6%), neutropenia (12%), anemia (3%), hyponatremia (3%) and nausea/vomiting (3%) were observed. None of the patients received G-CSF. Renal toxicity was also relatively mild: grade 2 renal toxicity was observed in only one of 33 patients.

Discussion

We previously reported that classic standard cisplatin-based chemotherapy regimens cause severe myelotoxicity in elderly patients aged ≥75 years [5]. Based on that previous study of elderly patients with NSCLC, we conducted phase I studies in which cisplatin and docetaxel were administered as three consecutive weekly infusions in both non-elderly and elderly patients with NSCLC using the same eligibility criteria, except for age, and the same definitions of dose-limiting toxicity and maximum-tolerated dose [15]. Our hypothesis was that the recommended dose for elderly patients aged ≥75 years would differ from that for non-elderly patients. In the previous phase I studies, we demonstrated a difference in the recommended dose of docetaxel combined with cisplatin between non-elderly and elderly patients [15]. The recommended doses of docetaxel with 25 mg/m^2 cisplatin were 35 and 20 mg/m^2 on days 1, 8 and 15 for non-elderly and elderly patients, respectively. We also conducted phase II studies for non-elderly and elderly patients with NSCLC using each recommended dose and the same eligibility criteria, except for age. The

Table 3. Response rate

No. of patients	CR	PR	NC	PD	NE	Response rate (95% CI)
33	2	15	13	2	1	52% (31% to 67%)

CI, confidence interval; CR, complete response; NC, no change; NE, not evaluable; PD, progressive disease; PR, partial response.

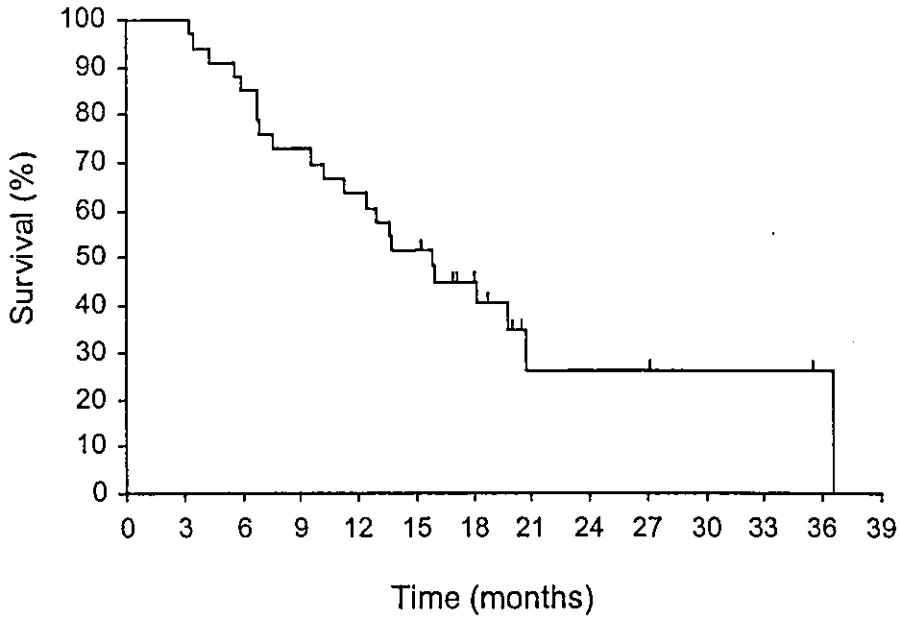

Figure 1. Overall survival time. The median survival time of the 33 treated patients was 15.8 months, and the median follow-up time for 11 censored patients was 18.1 (15.2–35.5) months. The 1-year and 2-year survival rates were 64% and 26%, respectively.

Table 4. Maximum toxicity grades associated with weekly docetaxel and cisplatin in 33 treated patients

	Grade (Japan Clinical Oncology Group)					Grade ≥3
	0	1	2	3	4	
Leukopenia	13	6	12	2	0	6%
Neutropenia	16	5	8	4	0	12%
Anemia	9	8	15	1	–	3%
Thrombocytopenia	30	2	1	0	0	0
Nausea/vomiting	12	10	10	1	–	3%
Hyponatremia	22	8	2	1	0	3%
Diarrhea	23	6	4	0	0	0
Infection	32	1	0	0	0	0
Fever	27	4	2	0	0	0
Bilirubin	25	–	8	0	0	0
Transaminase	25	8	0	0	0	0
Creatinine	28	4	1	0	0	0
Fatigue	26	6	1	0	0	0

results of the phase II study for non-elderly patients with NSCLC have been reported elsewhere [16]. Among the 33 evaluable patients, an objective tumor response of 30% (95% CI 15% to 46%) and a median survival time of 12.8 months were observed [16]. In the current study, we observed an objective tumor response of 52% (95% CI 31% to 67%) and a median survival time of 15.8 months for elderly patients with NSCLC. In spite of the lower dose of docetaxel, the efficacy of the treatment did not seem to be diminished.

Italian oncology groups have conducted randomized trials for elderly patients aged ≥70 years [21–23]. In these studies, non-platinum-based single or double chemotherapy regimens, such as vinorelbine alone or vinorelbine plus gemcitabine were used for elderly patients with NSCLC [21–23]. These chemotherapy regimens might not be adequate for non-elderly patients with a good PS because the cisplatin plus vinorelbine regimen was significantly superior to vinorelbine alone with regard to both the response rate and the survival [24, 25]. Kubota et al. [26] reported that the frequency of grade 4 leukocytopenia in the elderly (≥70 years of age) group was significantly greater than in the non-elderly group and that no difference in overall survival was observed between the two groups. Langer et al. [27] reported that advanced age alone

Table 5. Chemotherapy for elderly patients with non-small-cell lung cancer

Study	Chemotherapy	Age (years)	No. of patients	PS 2 (%)	Stage III (%)	RR (%)	MST
ELVIS [21]	None	≥70	78	24	28	–	21 weeks
	VNR 30 mg/m^2 days 1, 8 q3 weeks		76	24	26	20	28 weeks
	VNR 30 mg/m^2 days 1, 8 q3 weeks		233	19	29	18	36 weeks
MILES [22]	GEM 1200 mg/m^2 days 1, 8 q3 weeks	≥70	233	18	30	16	28 weeks
	GEM 1000 mg/m^2 + VNR 25 mg/m^2 days 1, 8 q3 weeks		232	19	31	21	30 weeks
SICOG [23]	VNR 30 mg/m^2 days 1, 8 q3 weeks	≥70	60	22	42	15	18 weeks
	GEM 1200 mg/m^2 + VNR 30 mg/m^2 days 1, 8 q3 weeks		60	27	40	22	29 weeks
MPCRN [29]	DTX 36 mg/m^2 weekly × 6 q8 weeks	≥65[a]	39	41	31	18	5 months
Current study	CDDP 25 mg/m^2 + DTX 20 mg/m^2 days 1, 8, 15 q4 weeks	≥75	33	0	29	52	15.8 months (69 weeks)

[a]Or poor candidates for combination chemotherapy due to coexistent medical illness.
ELVIS, The Elderly Lung Cancer Vinorelbine Italian Study; MILES, Multicenter Italian Lung Cancer in the Elderly Study; SICOG; Southern Italy Cooperative Oncology Group; MPCRN, Minnie Pearl Cancer Research Network.
CDDP, cisplatin; DTX, docetaxel; GEM, gemcitabine; VNR, vinorelbine.
MST, median survival time; PS, performance status; RR, response rate.

should not preclude appropriate NSCLC treatment, although elderly patients aged ≥70 years have more co-morbidities and can expect a higher incidence of leukopenia and neuropsychiatric toxicity. In the United States, upper age limits are not included in eligibility criteria to avoid age discrimination. In contrast, most Japanese studies have upper age limits because Japanese government guidelines recommend that elderly patients, >75 years, should not be accrued in common clinical trials [28]. This recommendation was made in concern for the safety of elderly patients. In Japan, most clinical trials include patients aged ≤74 years, and the full-dose chemotherapy is administered. Clinical trials for elderly patients have generally been conducted as specific trials focusing on the treatment of elderly patients in Japan. However, the definition of 'elderly' is still unclear. Thus, the use of platinum-based chemotherapy in elderly patients with NSCLC remains controversial because no randomized phase III studies have been conducted to resolve this question.

Several chemotherapy trials for elderly patients with NSCLC have been reported [21–23, 29] (Table 5). Of the subjects in these trials, 18–41% were PS 2 patients. Eligible patients were 70 or 65 years or older. The response rates of the non-platinum-based single or double chemotherapy regimens ranged from 15% to 22%, and the median survival times ranged from 18 to 36 weeks [21–23, 29]. In the current study, however, PS 2 patients were excluded and only patients aged ≥75 years were included. The objective response rate of 52% (95% CI 31% to 67%) and the median survival time of 15.8 months (69 weeks) in our trial were extremely better than those of previous trials. We considered that the main reason for the better results was the exclusion of PS 2 patients. However, cisplatin chemotherapy might be important not only for non-elderly, but also for elderly patients with NSCLC.

We divided the cisplatin and docetaxel dosages on days 1, 8 and 15 because full-dose cisplatin is too toxic for elderly patients. The weekly administration of docetaxel produces a higher dose intensity and less myelotoxicity [12–14]. Moreover, a weekly schedule may be safer than a 3-weekly schedule because treatment on day 8 and/or day 15 can be omitted if severe toxicity is observed. In the current study, the toxicity, including nausea/vomiting and renal toxicity, was relatively mild, and 90% of the planned administrations were carried out. The dose-limiting toxicities of docetaxel administered in six consecutive weekly infusions were reported to be fatigue and asthenia [12–14]. In the previous phase I study, two out of six patients refused chemotherapy on day 15 because of fatigue and asthenia at level 2: 25 mg/m^2 cisplatin and 25 mg/m^2 docetaxel [15]. However, fatigue and asthenia were relatively mild in the current study because of the relatively low-dose of docetaxel (20 mg/m^2).

We conclude that cisplatin and docetaxel administered as three consecutive weekly infusions is very effective and safe for elderly patients with chemotherapy-naive NSCLC. The JCOG is conducting a phase III study of cisplatin and docetaxel versus docetaxel alone, administered as three consecutive weekly infusions, for elderly patients with NSCLC to examine the role of cisplatin in the treatment of elderly patients with NSCLC.

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Short Communication

Phase I study of cisplatin analogue nedaplatin (254-S) and paclitaxel in patients with unresectable squamous cell carcinoma

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The recommended phase II dose of paclitaxel 180 mg m^{-2} given as a 3-h infusion followed by nedaplatin 100 mg m^{-2} in a 1-h infusion every 3–4 weeks was determined in 52 chemo-naive patients with unresectable squamous cell carcinoma (SCC), with a promising response rate for lung SCC of 55%.
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Keywords: squamous cell carcinoma; paclitaxel; nedaplatin; lung cancer

Clinical

Squamous cell carcinoma (SCC) arises from the epithelial tissue of many different organs. Although localised diseases can be treated using surgical resection or curative radiotherapy, advanced SCC continues to have a poor prognosis and the standard treatment has not been established (DeVita *et al*, 2001). Cisplatin-based chemotherapy has been used for the treatment of advanced SCC, regardless of the site of tumour origin (DeVita *et al*, 2001).

Nedaplatin (cis-diammine-glycolate-*O,O'*-platinum II, 254-S) is a second-generation platinum derivative that has an antitumour activity comparable to that of cisplatin (Kobayashi *et al*, 1991) but is less toxic to the kidney (Kameyama *et al*, 1990), as seen in preclinical experiments. Nedaplatin produced promising response rates in phase II trials for the treatment of SCC arising from the head and neck (Inuyama *et al*, 1992), lung (Yamamoto *et al*, 2000), oesophagus (Taguchi *et al*, 1992), and uterine cervix (Noda *et al*, 1992). Paclitaxel is another promising drug for the treatment of advanced SCC, as shown by the favourable response rates obtained in phase II trials for head and neck (Forastiere *et al*, 1998), non-small-cell lung (Sekine *et al*, 1996), oesophageal (Ajani *et al*, 1994), and cervical (McGuire *et al*, 1996) cancers.

A combination of nedaplatin and paclitaxel is a promising chemotherapeutic regimen because a significant synergistic effect was obtained for this combination in a preclinical mice tumour model (Yamada *et al*, 2001), and the combination of platinum compounds and paclitaxel is one of many standard regimens (Schiller *et al*, 2002). The objectives of this phase I trial were (1) to evaluate the toxicity of the regimen and to determine the maximum tolerated dose (MTD) and recommended phase II dose (RPTD) of nedaplatin and paclitaxel, and (2) to observe the antitumour effects of this regimen on SCC arising in various organs.

PATIENTS AND METHODS

Patient selection

The eligibility criteria for enrolment in the trial were as follows: histologically or cytologically proven SCC; unresectable disease; measurable disease; no previous chemotherapy; age between 20 and 75 years; performance status of 0 or 1 (Oken *et al*, 1982); adequate bone marrow function (white blood cell (WBC) count $\geqslant 4.0 \times 10^9 l^{-1}$, neutrophil count $\geqslant 2.0 \times 10^9 l^{-1}$, haemoglobin $\geqslant 10.0$ g dl^{-1} and platelet count $\geqslant 100 \times 10^9 l^{-1}$), liver function (total bilirubin $\leqslant 1.5$ mg dl^{-1} and transaminase $\leqslant 100$ IU l^{-1}), and renal function (serum creatinine $\leqslant 1.5$ mg dl^{-1} and creatinine clearance $\geqslant 60$ ml min^{-1}); and a PaO_2 $\geqslant 60$ Torr. Patients were excluded from the trial for any of the following reasons: uncontrolled malignant pleural or pericardial effusion; a concomitant serious illness contraindicating chemotherapy; pregnancy; or breast-feeding. All patients gave their written informed consent.

Treatment schedule

The levels and respective doses of paclitaxel (mg m^{-2}) and nedaplatin (mg m^{-2}) are shown in Table 1. Paclitaxel diluted in 500 ml of 5% glucose was administered as a 3-h intravenous infusion with premedication as previously described (Sekine *et al*, 1996). Normal saline (500 ml) and granisetron (40 μg kg^{-1}) in 100 ml of normal saline were given intravenously, followed by nedaplatin diluted in 250 ml of normal saline administered in a 1-h intravenous infusion. This treatment was repeated every 3–4 weeks.

Toxicity assessment and treatment modification

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest X-ray were performed at least once a week throughout the course of treatment. If grade 4 neutropenia was noted, the neutrophil count was repeated 4 days later to determine whether the grade 4 neutropenia had lasted for 5 days or longer. Acute toxicity was graded according to the NCI Common Toxicity Criteria, version 2.0, issued in 1998 (JCOG, 1998). Subsequent cycles of chemotherapy were delayed if any of the following toxicities were noted on day 1: WBC count $\leqslant 3.0 \times 10^9 l^{-1}$, neutrophil count $\leqslant 1.5 \times 10^9 l^{-1}$, platelet count $\leqslant 100 \times 10^9 l^{-1}$, serum creatinine level $\geqslant 1.6$ mg dl^{-1}, grade 2 elevated hepatic transaminase level or total serum bilirubin, fever $\geqslant 38$°C, or a performance status $\geqslant 2$.

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Table 1 Dose level and number of patients accrued

Level	Paclitaxel ($mg\,m^{-2}$)	Nedaplatin ($mg\,m^{-2}$)	No. of patients: Accrued	Evaluable for DLT[a]	Developing DLT[a]
1	135	60	6	6	2
2	150	60	3	3	0
3	150	80	3	3	0
4	180	80	7	6	1
5	180	100	12	12	4
6	210	100	21	19	8

[a]Dose-limiting toxicity.

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The treatment was terminated if the above-mentioned toxicity did not disappear in 3 weeks. If grade 4 leukopenia, grade 4 neutropenia for 5 days or longer, grade 3–4 febrile neutropenia, or grade 3–4 neutropenia with infection was noted, $50\,mg\,m^{-2}$ of granulocyte colony-stimulating factor (G-CSF) was given subcutaneously, and the doses of paclitaxel and nedaplatin were reduced by 25% in subsequent chemotherapy cycles.

Dose-limiting toxicity, MTD, and RPTD

The dose-limiting toxicity (DLT) was defined as grade 4 neutropenia lasting 5 days or longer, grade 3–4 febrile neutropenia, grade 3–4 neutropenia with infection, grade 4 leukopenia, a platelet count $<20\times10^{9}\,l^{-1}$, and grade 3 or greater nonhaematological toxicity other than nausea and vomiting. Doses were escalated according to the frequency of DLT evaluated during the first cycle of chemotherapy. Three patients were initially enrolled at each dose level. If none of the patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If one of the three patients experienced DLT, then three additional patients were enrolled at the same dose level, bringing the total to six patients for that dose level. If two or fewer patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If three or more of the six patients experienced DLT, that level was considered to be the MTD. If two or all the initial three patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD. Six to 15 additional patients were enrolled at the RPTD to confirm that the frequency of DLT was less than one-third.

Response evaluation

The objective tumour response was evaluated according to the WHO criteria issued in 1979 (WHO, 1979).

Study design, data management, and statistical considerations

The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center, Tokyo Japan. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 24 months and a follow-up period of 12 months were planned. The overall survival time was estimated using the Kaplan–Meier method (Armitage and Berry, 1994). Survival time was measured from the date of study registration until the date of death from any cause.

RESULTS

Patient characteristics

Between August 1999 and December 2002, 53 patients were registered in the study. One patient at level 5 developed a bone fracture prior to treatment and did not receive chemotherapy. This patient was excluded from all the analyses. Of the remaining 52 patients (42 males and 10 females) with a median age of 62 years (range 49–75), 42 (81%) patients had lung SCC, followed by thymic SCC in five patients and head and neck SCC in four patients. Of the 52 patients, 24 and 24 had metastatic and locally advanced diseases, respectively.

Treatment delivery, toxicity, MTD, and RPTD

Treatment delivery was summarised in Table 2. Severe toxicity was mainly manifested as leucopenia, neutropenia, and associated infection, but the frequency of these symptoms did not differ between dose levels (Table 3). Grade 3 anaemia and thrombocytopenia were only noted in one patient (5%) each; both these patients had been treated at dose level 6. No grade 3–4 nausea, neuropathy, or myalgia was noted. A grade 3–4 elevation in creatinine, grade 3–4 hyponatremia, appetite loss, and diarrhoea were only observed at level 6. One patient treated at level 6

Table 2 Treatment delivery

	No. of patients (%): Levels 1–4 ($n=19$)	Level 5 ($n=12$)	Level 6 ($n=21$)
Chemotherapy cycles			
5	1 (5)	0 (0)	0 (0)
4	7 (37)	4 (33)	5 (24)
3	2 (11)	2 (17)	3 (14)
2	5 (26)	4 (33)	8 (38)
1	4 (21)	2 (17)	5 (24)
Median	3	3	2
Dose reduction in subsequent cycles			
None	12 (63)	9 (75)	12 (50)
Required	3 (16)	1 (8)	4 (19)
Not administered	4 (21)	2 (17)	5 (24)

Table 3 Toxicity in all courses

	Levels 1–4 ($n=19$)			Level 5 ($n=12$)			Level 6 ($n=21$)		
	3	4	3–4 (%)	3	4	3–4 (%)	3	4	3–4 (%)
Leukopenia	6	0	(32)	5	0	(42)	6	1	(33)
Neutropenia	3	10	(68)	2	9	(92)	3	12	(71)
Anaemia	0	0	(0)	0	0	(0)	1	0	(5)
Thrombocytopenia	0	0	(0)	0	0	(0)	1	0	(5)
AST	0	0	(0)	0	0	(0)	1	0	(5)
ALT	0	0	(0)	1	0	(8)	0	1	(5)
Creatinine	0	0	(0)	0	0	(0)	0	1	(5)
Hyponatremia	0	0	(0)	0	0	(0)	2	1	(14)
Infection	4	0	(21)	4	0	(33)	6	0	(29)
Appetite loss	0	0	(0)	0	0	(0)	1	0	(5)
Diarrhoea	0	0	(0)	0	0	(0)	2	0	(10)
Constipation	0	0	(0)	0	0	(0)	0	1	(5)
Arrhythmia	2	0	(11)	0	0	(0)	0	0	(0)
Lung toxicity	0	0	(0)	0	0	(0)	2	0	(10)

developed grade 2 leukopenia, fever, watery diarrhoea, and grade 4 ileus, but recovered in 5 days. Two patients at level 6 developed grade 3 interstitial pneumonitis, but quickly recovered with oxygen therapy alone in one patient and with oxygen and steroid therapy in the other patient. No treatment-related deaths occurred in the study.

In all, 19 DLTs were noted in 15 patients. Of the 1nine DLTs, 13 were neutropenic fever or documented infection and six were nonhaematological. At level 6, only two of the first six patients developed DLT; therefore, 15 additional patients were entered at this level to confirm the frequency of DLT. Two patients were excluded from the DLT analysis because G-CSF was administered before the duration of grade 4 neutropenia had been determined (protocol violation). Of the remaining 13 patients, six developed DLT. Thus, eight (42%) of the 19 patients evaluated for DLT developed DLT at level 6; this dose level was therefore determined to be the MTD. An additional six patients were registered at level 5, and four (33%) of the 12 patients at level 5 developed DLT; this level was determined to be the RPTD.

Objective responses and survival

Of the 42 patients with lung SCC, two CRs and 21 PRs were noted, and the overall response rate (95% confidence interval) was 55% (39–70%). No difference in the response rates for levels 1–4 and levels 5–6 were observed. One PR was noted in a patient with thymic SCC, and one PR was noted in a patient with head and neck SCC. The overall survival time (95% confidence interval) in all patients ($n = 52$) was 11.1 (6.4–15.8) months.

DISCUSSION

This study showed that the combination of nedaplatin and paclitaxel was feasible with acceptable toxicity, and that the RPTD of nedaplatin was 100 mg m^{-2} over 1 hour, which is the full dose of this agent, while that of paclitaxel was 180 mg m^{-2} over 3 h. These doses are comparable to doses for practical use and those determined by previous phase I trials of cisplatin or carboplatin in combination with paclitaxel, where 180–225 mg m^{-2} of paclitaxel was given with the full dose of platinum-agent (Akiyama *et al*, 2001; Kurata *et al*, 2001). The toxicity profile in the present study was similar to that of the carboplatin and paclitaxel combination (Akiyama *et al*, 2001).

The primary objectives of phase I trials are to evaluate toxicity and to establish a recommended drug dose for a given administration schedule; an additional goal of these trials is to look for evidence of the drug's antitumour activity. Objective tumour responses to newly investigated drugs are a promising clue for determining specific tumour types for subsequent phase II trials; therefore, patients with various tumours are usually registered in phase I trials (Sekine *et al*, 2002). In cases where some information on the antitumour activity of a drug is available, patients can be selected so that the chance of a response is maximised. This study was a histology-oriented phase I trial, and objective tumour responses were observed in about half of the patients.

The combination of nedaplatin and paclitaxel is particularly promising for the treatment of patients with lung SCC, as shown by the high response rate of 55%. Adenocarcinoma, large-cell carcinoma, adenosquamous carcinoma, and SCC of the lung have been grouped together as non-small-cell lung cancer because treatment response and prognosis are similar for these histologies. A recent cDNA microarray analysis of non-small-cell lung cancer tissue, however, showed that the gene expression profiles of SCC and adenocarcinoma are different (Kikuchi *et al*, 2003), and these differences may lead to different responses to anticancer agents, including nedaplatin. Thus, optimal chemotherapy regimens for the treatment of non-small-cell lung cancer should be established according to each tumour's histology. The numbers of patients with head and neck SCC and patients with thymic SCC were too small to comment on the antitumour effects of this regimen.

In conclusion, the combination of nedaplatin and paclitaxel is a feasible treatment, and the RPTD is paclitaxel 180 mg m^{-2} given as a 3-h infusion followed by nedaplatin 100 mg m^{-2} in a 1-h infusion every 3–4 weeks. This regimen was highly effective for the treatment of untreated lung SCC.

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Randomized Trial of Oral Versus Intravenous Antibiotics in Low-risk Febrile Neutropenic Patients with Lung Cancer

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Background: Neutropenic fever is one of the most serious adverse effects of cancer chemotherapy. Neutropenia may cause a life-threatening bacterial infection. Therefore, febrile neutropenic inpatients are empirically treated with intravenous broad-spectrum antibiotics. Recently, several studies have suggested the presence of low-risk groups among febrile neutropenic patients.

Methods: A prospective randomized trial was conducted to compare treatment with oral ciprofloxacin (200 mg) and amoxicillin-clavulanate (375 mg) administered every 8 h against that with intravenous ceftazidime (1 g) administered every 12 h in low-risk febrile neutropenic patients with lung cancer. All patients received chemotherapy and antibiotic therapy while being hospitalized.

Results: A total of 177 patients with lung cancer agreed to participate in this study prior to undergoing chemotherapy. Among them, a total of 36 neutropenic patients with 42 febrile episodes were enrolled in the study. Treatment was successful without the need for modification in 91% of the episodes in patients receiving the oral regimen and 79% of the episodes in patients receiving the intravenous regimen. No treatment-related deaths occurred. One patient developed nausea while receiving the oral regimen, so the oral regimen was changed to the intravenous regimen in this patient.

Conclusions: This prospective study suggested that treatment with oral antibiotics ciplofloxacin plus amoxicillin-clavulanate was effective for low-risk febrile neutropenic patients after chemotherapy.

Key words: oral antibiotics – low-risk – febrile neutropenia

INTRODUCTION

Neutropenic fever is one of the most serious adverse effects in cancer chemotherapy. Neutropenia may cause a life-threatening bacterial infection. The risk of infection increases in patients with a neutrophil count of <1000/mm^3 (1). As a result, most cancer patients remain in hospital after undergoing chemotherapy in Japan, and empirical broad-spectrum intravenous antibiotics are administered to febrile neutropenic patients. This approach is effective in reducing morbidity and mortality but is associated with toxicity related to intravenous antibiotics, as well as physical and psychological discomfort for the patient. In addition, parenteral antibiotic administration requires insertion of an intravenous catheter, which carries a risk of infection. Prolonged hospitalization may cause infection to drug-resistant organisms, is expensive, and has a detrimental effect on quality of life.

Recently, several studies have suggested the presence of low-risk groups among febrile neutropenic patients (2–4). Medical complications were less frequent overall for patients whose neutropenia (<500/mm^3) resolved in 7 days or less, compared to other patients (4). A study demonstrated that neutropenia lasted for 1 week or less in 85% of the patients selected using the following exclusion criteria: hepatic insufficiency (alanine aminotransferase activity > four times normal), a history of recurrent pyrexia of undetermined origin (PUO), shock (systolic blood pressure <80 mmHg or peripheral circulatory failure), any other comorbid conditions requiring hospitalization (except for anemia or thrombocytopenia) and the expectation of prolonged neutropenia (>7 days) based on the presence of aplastic anemia, myelodysplasia, leukemia or other causes (5). Patients who did not meet any of these exclusion criteria were considered to belong to a low-risk group. A randomized trial comparing oral ciplofloxacin and amoxicillin-clavulanate with

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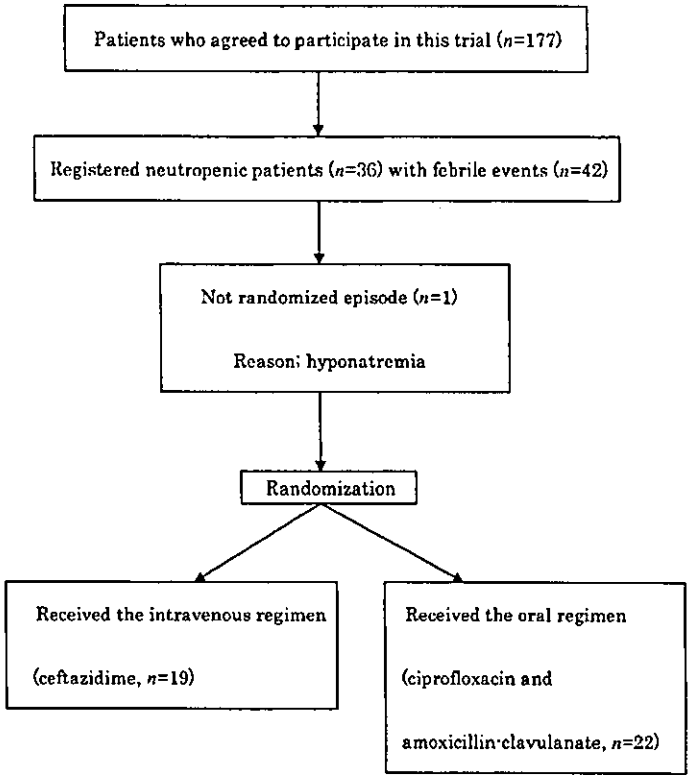

Figure 1. Study flow diagram.

intravenous aztreonam and clindamycin was conducted in these low-risk febrile neutropenic patients (6). This trial demonstrated that oral antibiotics were as effective as intravenous ones.

We conducted a randomized trial to compare oral ciplofloxacin and amoxicillin-clavulanate with intravenous ceftazidime, which was empirically used, in low-risk febrile neutropenic patients with lung cancer. The combination of ciplofloxacin and amoxicillin-clavulanate provides sufficient coverage against gram-negative enteric bacilli and gram-positive cocci. The aim of our trial was to determine whether an oral regimen was an acceptable alternative to an intravenous regimen in low-risk patients.

PATIENTS AND METHODS

Criteria for Eligibility

Eligible patients included those with lung cancer and neutropenia after having undergone platinum-based chemotherapy. Patients were required to have a single axillary temperature of 37.5°C or higher after platinum-based chemotherapy, an absolute leukocyte count ≤1000/mm^3 or a neutrophil count ≤500/mm^3. Other criteria included an age of 20 years or more and an ECOG performance status (PS) of between 0 and 2 (inclusive). The exclusion criteria included the following conditions: previous anaphylactic reactions or hypersensitivity to any of the antibiotics used or related products; antibiotic treatment within the preceding 96 h; prior administration of non-steroidal anti-inflammatory drugs (NSAIDs); recurrent PUO; renal insufficiency (serum creatinine ≥2.5 mg/dl or need for dialysis); hepatic insufficiency (aspartate aminotransferase/alanine aminotransferase levels > four times the normal value); systolic blood pressure ≤90 mmHg or peripheral circulatory failure; uncontrolled hypercalcemia; altered sensorium; respiratory rate ≥30 breaths/min; serum sodium ≤128 mg/dl; and the inability to take oral medications because of painful mouth ulcers, intestinal malabsorption or severe nausea and vomiting. All patients were required to provide their written informed consent prior to undergoing chemotherapy, and the institutional review board at the National Cancer Center approved the study's protocol.

Treatment Plan

All patients received chemotherapy and antibiotic therapy on an inpatient basis. The baseline evaluation included a physical examination (blood pressure, pulse and respiratory rate, temperature). Cultures were obtained of blood, sputum, throat, urine and feces (anal swabs). Patients were randomly assigned to one of two regimens using consecutive sealed envelopes. The oral regimen consisted of ciprofloxacin (200 mg) plus amoxicillin-clavulanate (375 mg) administered every 8 h, while the intravenous regimen consisted of ceftazidime (1 g) administered every 12 h. Granulocyte colony-stimulating

Table 1. Patient characteristics

Characteristic	Oral ciprofloxacin and amoxicillin-clavulanate	Intravenous ceftazidime
Eligible episodes	22	19
Age (year)		
Median (range)	68 (54–76)	67 (51–75)
Gender		
Male/female	15/7	15/4
ECOG PS		
0/1	6/16	2/17
Smoking status		
Never	5	4
Past	4	5
Current	13	10
Smoking index		
Median (range)	910 (0–3480)	880 (0–2400)
Histologic type		
Adenocarcinoma	5	7
Squamous cell carcinoma	4	4
Large cell carcinoma	1	2
Small cell carcinoma	12	6
Absolute neutrophil count (at randomization)		
≤100/mm^3	3	0
101–500/mm^3	14	12
501–1000/mm^3	5	7
Duration of neutropenia after randomization (days)		
Median (range)	4 (2–7)	4 (2–12)
Treatment with G-CSF [no. (%)]	19 (86)	14 (74)

factor (G-CSF) support was allowed. The administration of NSAIDs was not allowed. The administration of aluminum- and magnesium-containing antacids and oral iron preparations was allowed if they were administered more than 3 h after the administration of ciplofloxacin. The use of other antibiotics was prohibited during the trial.

Diagnostic Criteria and Evaluation

Each febrile episode was classified as either a clinically or microbiologically documented infection or PUO. Microbiologically documented infection necessitated the isolation of a bacterial pathogen from blood, urine, pus or exudates, along with clinical, laboratory or radiographic evidence of infection at the same site. Clinical infection was diagnosed when clear evidence of an infection was present but an organism could not be isolated. PUO was defined as the requisite temperature elevation with no clinical or microbiologic evidence of infection within 72 h of enrolment in the study.

Clinical outcomes were evaluated at 48 h and 7 days after the start of antibiotic treatment. Each patient was physically examined every day. Patients who remained febrile (without a downward trend) after 48 h or who had a body temperature ≥37°C on day 7 were removed from the study and treated with appropriate therapy; antibiotic treatment in these patients was considered to have failed. Treatment outcome was classified into three categories (7). 'Success without modification' referred to episodes in which the patient successfully recovered from fever and neutropenia without the need of additional antimicrobial agents or the modification of the initial randomly assigned regimen. 'Success with modification' referred to episodes in which the patient successfully recovered from the fever and neutropenia but required a modification of the assigned regimen. 'Failure' referred to all other cases. The response rate was defined as the percentage of 'success without modification' cases among all eligible patients.

Statistical Analysis

Assuming a response rate to the intravenous regimen of 80%, the study was designed to enroll 63 patients per treatment arm to ensure that the oral regimen would not be 20% worse (i.e. 60%) at a level of significance alpha = 0.05 and 80% power using a two-sided chi-square test. An interim analysis was

Table 2. Response rate

	Oral regimen ($n = 22$)		Intravenous regimen ($n = 19$)	
	PUO	Documented infection	PUO	Documented infection
Success without modification	16	4	10	5
Success with modification	0	2	0	4
Response rate	91%		79% $P = 0.39$	

Response rate was defined as the percentage of success without modification cases among all eligible patients.

planned at an accrual level of 40 patients. If a significant difference in response rates ($P < 0.01$) was observed, or if septic shock appeared in more than 10% of the patients undergoing the oral regimen, the study was to be terminated. Comparisons between proportions were done using a Pearson chi-square test or a Fisher exact test, when appropriate.

RESULTS

Patient Population and Treatment

A total of 177 patients with lung cancer agreed to participate in this study prior to undergoing chemotherapy between May 1995 and February 2001. Among them, a total of 36 neutropenic patients with 42 febrile episodes were enrolled in the study. One episode was ineligible because of hyponatremia. Of the 41 episodes (in 35 patients) included in the analysis, four patients were enrolled more than once: three patients had two episodes each, and one patient had four episodes. The patient characteristics are listed in Table 1. Twenty-two episodes were assigned to the oral regimen and 19 episodes were assigned to the intravenous regimen (Fig. 1). No statistically significant difference was seen between the two groups with regard to age, gender, PS, smoking status, histologic subtype and absolute neutrophil count. During 33 episodes, G-CSF was administered in addition to the assigned treatment. The median duration of neutropenia was 4 days in both groups.

Evaluation before Antibiotic Therapy

PUO was observed in approximately two-thirds of all febrile episodes. Infection was documented in 15 episodes. Most documented infections consisted of bronchus or lung infections (10 episodes) or urinary tract infections (three episodes). Other infections included colitis and alveolar pyorrhea. Microbiological pathogens were detected in five episodes. *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* were isolated from sputum and *Pseudominas aeruginosa* and *Enterococcus faecalis* were isolated from urine.

Efficacy

The response rates were similar in the two groups (91% versus 79%, $P = 0.39$) (Table 2). PUO was successfully treated in all 26 episodes. On the other hand, documented infection was successfully treated in 60% of the patients (four out of six episodes in patients receiving the oral regimen and five out of nine episodes in patients receiving the intravenous regimen). A total of six patients received changes to their treatment regimen. Two patients in the oral regimen group were switched to piperacillin sodium or ceftazidime. Four patients in the intravenous regimen group were switched to carbapenem with or without the addition of clindamycin or amikacin.

In approximately half of the episodes in both groups, the fever disappeared by day 4 of the treatment. By day 8, the fever had resolved in 90% of all episodes.

Adverse Effects

Few adverse effects were encountered. One patient developed nausea while receiving the oral regimen. The oral regimen was therefore changed to an intravenous regimen (piperacillin sodium) in this patient.

DISCUSSION

Febrile neutropenia can be a life-threatening complication of cancer chemotherapy. Therefore, febrile neutropenic patients are usually hospitalized for the administration of empiric, broad-spectrum, intravenous antibiotic therapy. Several analyses have demonstrated that febrile neutropenic patients comprise heterogeneous subgroups among which are low-risk patients with a high response rate to antibiotic therapy and a low risk of serious complications (2–4). We conducted a randomized trial to compare the oral administration of ciplofloxacin and amoxicillin-clavulanate with the intravenous administration of ceftazidime in low-risk febrile neutropenic patients with lung cancer. However, this study was terminated in February 2001 because of slow enrolment and the publication of two large randomized trials comparing oral with intravenous antibiotic therapy for low-risk febrile patients who developed neutropenia during cancer chemotherapy (8,9). In one trial, oral ciplofloxacin plus amoxicillin-clavulanate was compared with intravenous ceftazidime (8). These regimens were almost identical to those in our trial. In the other trial, oral ciplofloxacin plus amoxicillin-clavulanate was compared with intravenous ceftriaxone plus amikacin (9). Both trials demonstrated that oral therapy with ciplofloxacin plus amoxicillin-clavulanate was as safe and effective as intravenous therapy. Our trial confirmed these results, in spite of the smaller sample size.