TABLE 1 Patient Characteristics and pTNM Staging in Each Group

Group	Treatment regimens	No. of patients	Male/ Female	Age (mean SD)	T4N0,1M01	T4N2M0	T4AnyNM1
1	Thermo-chemo-radiotherapy	30	9/21	63.4 8.8	16	6	8
2	R0-resection	19	6/13	65.3 8.6	19	0	0
3	R1,2-resection	39*	12/27	67.7 9.1	13	15	11
4	Chemo- and/or radiotherapy	57	21/36	66.2 9.9	18	12	27
5	Supportive therapy	125	45/80	72.2 10.1	28	30	67
	Total	270	93/177	68.5 9.5	94	63	113

39*: including 13 patients who also underwent intraoperative therapy.

According to treatments received, the 270 patients were divided into five groups as follows: group 1 consisting of 30 patients with nonresectable tumors treated with TCRT, group 2 consisting of 19 patients underwent R0-resection without post-residual tumor microscopically, group 3 consisting of 39 patients underwent R-1,2 resection with post-residual tumor microscopically or macroscopically, group 4 consisting of 57 patients treated with chemo- and/or radiotherapy, group 5 consisting of 125 patients with only supportive therapy. Patient characteristics and T, N, and M categories of each group are summarized in **Table 1**.

Thermo-Chemo-Radiotherapy (TCRT)

The heating equipment was RF-capacitive heating device, Thermotron RF-8 [Yamamoto Vinita company, Osaka, Japan (6)]. The patient lay in the prone position. The target was sandwiched with upper and lower electrodes, and an 8-MHz RF wave was applied. We administered heat to the patient for 40 minutes after the intratumor temperature had risen to 42°C. Intratumor temperature was measured using a needle thermosensor every time. The thermosensor was inserted beside or into the tumor from the skin surface through an 18-G angiocatheter under the aid of ultrasonography. The chemotherapeutic agents employed were cisplatinum (CDDP, 50mg/m^2) in combination with 5-fluorouracil (5-Fu, 800mg/m^2) or methotolexate (MTX, 30mg/m^2) in combination with 5-Fu (800mg/m^2). Hyperthermia and chemotherapeutic agents were administered simultaneously once weekly immediately following radiotherapy at 2 Gy. Usually it started within 15 min after the irradiation (**Figure 1**). Number of heat treatments ranged from 2 to 11 times (mean 4.5). Three cases were retreated.

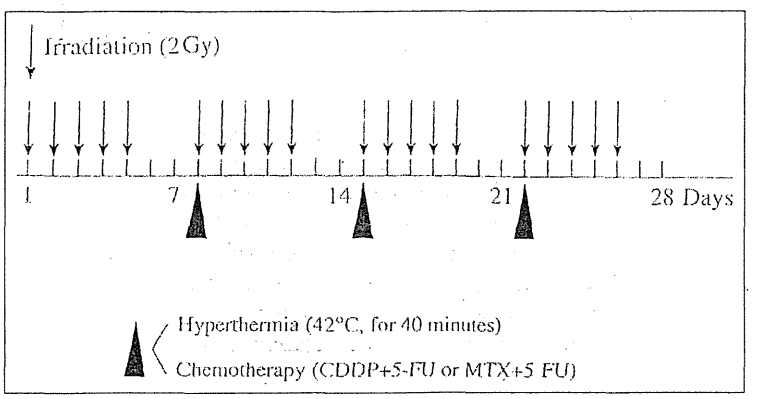

FIGURE 1 Schedule of thermo-chemo-radiotherapy.

Surgical Procedures, Intraoperative Radiation Therapy (IORT), External Beam Radiation Therapy (EBRT), and Chemotherapy

Combined resection of the involved organs such as liver, bile duct, pancreas, duodenum, or colon (31 cases), hepatic resection (39 cases), pancreatic duodenectomy (11 cases), partial resection of transverse colon (14 cases) was performed as far as anatomically possible.

Immediately after tumor removal, a high energy electron beam from a betatron was applied to the resected portions (intraoperative radiation therapy: IORT) was administered to 13 patients whose tumors had spread to the hepatoduodenal ligament or hepatic hilus in attempt to suppress the development of local recurrence (Group 3). The dose of IORT ranged from 18 to 20 Gy with energies of 8 to 12 million electron volts.

External beam radiation therapy (EBRT) was administered five times per week at a dose of 2 Gy per fraction. Total radiation dose ranged from 30 to 60 Gy. EBRT other than TCRT was performed for 13 patients with nonresected tumors.

Chemotherapy not combined with hyperthermia was performed by MTX, CDDP, 5-Fu, mitomycin C, or adriamycin for 49 patients with nonresected tumors.

Response and Toxicity Criteria

The effectiveness of TCRT on nonresectable tumors was evaluated about tumor regression by follow-up CT, and resolution of biliary obstruction by cholangiographies. Tumor regression was graded as complete regression (CR: more than 80% tumor volume reduction), partial regression (PR: more than 50% and less than 80% regression), and no change (NC). Response of stenotic or obstructed bile duct was graded as CR: complete resolution of the bile duct, PR: partial resolution of the bile duct, and NC.

We examined histologically the state of the gallbladder and bile duct, and hematogenous, lymphogenous metastases at autopsy in 11 patients with advanced gallbladder carcinoma treated with TCRT. Modes of hematogenous and lymphogenous metastases were evaluated by high and moderate degree according to the criteria reported before (7).

Side effects were evaluated and graded according

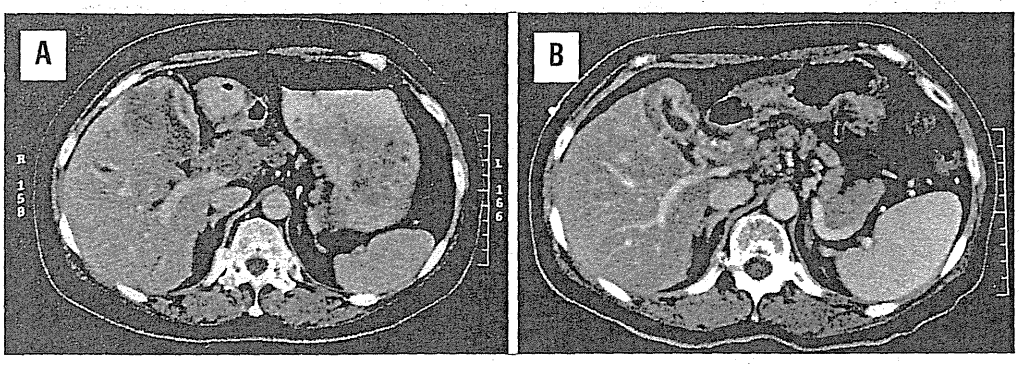

FIGURE 2
CT scan of Case 4. A large gallbladder carcinoma with thickening of the gallbladder wall **(A)** had almost completely disappeared after TCRT **(B)**.

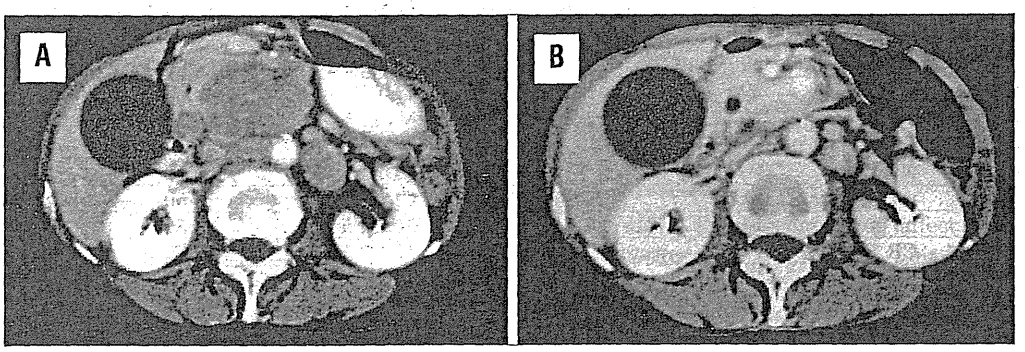

FIGURE 3
CT scan of Case 2. A large peripancreatic lymph node metastasis **(A)** had completely disappeared four months after TCRT **(B)**.

to National Cancer Institute Common Toxicity Criteria (NCI-CTC) (8).

Statistical Analysis

Life table survival probabilities were calculated using the Kaplan-Meier method. The generalized Wilcoxon test was used to assess the difference in survival rates. A p-value of less than 0.01 was considered statistically significant.

RESULTS

Effectiveness of TCRT

In respect to tumor regression by TCRT, there were 5 CR, 14 PR, and 11 NC. CR rate and CR+PR rate was 17% and 63%. Marked reduction of the gallbladder tumor or lymph node metastasis was observed in some cases after TCRT **(Figures 2 and 3)**.

As for resolution of the bile duct, there were 6 CR, 9 PR, and 5 NC in 20 patients with obstructed or markedly stenotic bile duct. CR rate and response rate was 30% and 75%. In four patients with resolution of the obstructed bile duct, percutaneous transhepatic cholangiodrain (PTCD) could be removed **(Figure 4)**. However, as the four patients developed obstructive jaundice again due to disease progression, we placed self-expandable metallic stent after TCRT into the patency-restored bile duct for prevention of restenosis and the partially resolved bile duct for improvement of patients' quality of life **(Table 2)**.

Long-term Survival Results

Three patients of group 2 survived for more than three years. No patient of group 3, 4 and 5 survived for more than two years, but one patient of group 1 survived for 33 months. Mean survival months (mean±SD) and the 1-year survival rates for patients of groups 1-5 were 9.5±6.3 - 33%, 24.7±26.8 - 79%, 8.4±4.9 - 21%, 5.7±4.2 - 11%, and 3.4±3.5 - 3%, respectively. The survival rate was best in group 2 ($p<0.01$). A significant improvement of long-term survival was exhibited in group 1 and 3 compared to group 4 and 5 ($p<0.01$). The difference of survival rate between group 1 and 3 was not significant **(Figure 5)**.

Histological Findings at Autopsy in Patients Treated with TCRT

In almost all cases, marked hyalinization or fibrosis with necrosis replaced extensively gallbladder tumor and wall, in which suppressed cohesiveness of

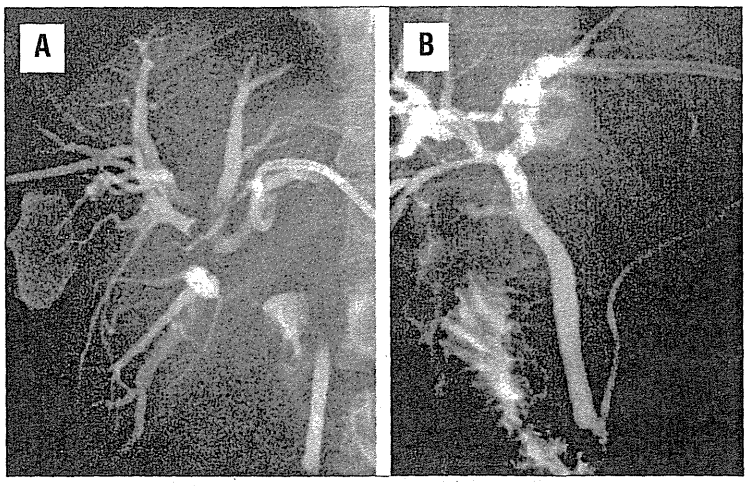

FIGURE 4 Percutaneous transhepatic cholangiography of Case 3. Complete obstruction of the upper bile duct **(A)** had completely resolved after TCRT **(B)**.

TABLE 2 Results of Thermo-Chemo-Radiotherapy for Advanced Gallbladder Carcinoma

Case	Age	Sex	Stage factors	Tumor regression	Resolution of bile duct	Biliary drainage	Heat sessions	Chemotherapy regimen	Dose of RT (Gy)	Survival months
1	66	f	T4N2	CR	NC	PTCD	x6, x1	MTX, 5-Fu	54	15.5
2	60	f	T4N2	CR	no stenosis	None	x5, x6	MTX, CDDP, 5-Fu	50, 24	33
3	52	f	T4	CR	CR	Withdrawal of PTCD	x6	CDDP, 5-Fu	56	10
4	57	f	T4	CR	CR	PTCD → metallic stent	x5	MTX, 5-Fu	40	5.5
5	62	m	T4M1	CR	no stenosis	None	x5	MTX, 5-Fu	54	10
6	57	m	T4	PR	CR	PTCD	x5, x3	CDDP, 5-Fu	46	21
7	48	f	T4M1	PR	PR	PTCD → metallic stent	x2	CDDP, VP16	40	16
8	64	f	T4	PR	no stenosis	None	x4	MTX, 5-Fu	40	14
9	41	f	T4M1	PR	PR	Withdrawal of PTCD	x3	MTX, 5-Fu	50	13
10	69	f	T4M1	PR	CR	Withdrawal of PTCD	x5	MTX, 5-Fu	50	13
11	83	f	T4	PR	CR	Withdrawal of PTCD	x4	MTX, 5-Fu	50	12.5
12	69	m	T4N2	PR	no stenosis	None	x5	MTX, 5-Fu	50	10.5
13	62	f	T4N2	PR	no stenosis	None	x6	MTX, 5-Fu	54	7
14	65	f	T4	PR	no stenosis	None	x3	CDDP, 5-Fu	50	8 alive
15	70	m	T4	PR	PR	PTCD→ metallic stent	x4	MTX, 5-Fu	56	6.5
16	72	m	T4M1	PR	PR	None	x5	CDDP, 5-Fu	60	5.5
17	72	m	T4	PR	NC	PTCD	x4	CDDP, 5-Fu	46	5
18	73	m	T4N2	PR	no stenosis	None	x6	CDDP, 5-Fu	50	4.5
19	72	f	T4M1	PR	no stenosis	None	x6	MTX, 5-Fu	50	3
20	68	f	T4	NC	CR	PTCD → metallic stent	x4	MTX, 5-Fu	52	5
21	59	f	T4	NC	PR	PTCD → metallic stent	x3	CDDP, 5-Fu	50	13.5
22	72	f	T4N2	NC	PR	PTCD → metallic stent	x2	MTX, 5-Fu	42	12
23	65	m	T4	NC	PR	PTCD	x2	MTX, 5-Fu	50	8.5
24	53	f	T4	NC	PR	PTCD	x4	CDDP, 5-Fu	38	6.5
25	55	f	T4	NC	PR	PTCD → metallic stent	x3	CDDP, 5-Fu	38	6
26	69	f	T4	NC	no stenosis	None	x3	CDDP, 5-Fu	32	4
27	64	m	T4M1	NC	no stenosis	None	x3	MTX, 5-Fu	30	2.5
28	57	f	T4M1	NC	NC	PTCD	x4	MTX, 5-Fu	50	8.5
29	72	f	T4	NC	NC	PTCD	x4	MTX, 5-Fu	32	8
30	57	f	T4M1	NC	NC	PTCD	x4	MTX, 5-Fu	50	3

RT: radiotherapy; CR: complete response; PR: partial response; NC: no change; PTCD: percutaneous transhepatic cholangiodrainage.

carcinoma cells and degenerative cells were sparsely observed. Carcinoma cells were also detected peripherally. Common bile duct of six cases was not completely obstructed, though it was partly obstructed with debris or necrotic mass. Frequency and degree of hematogenous or lymphogenous metastases were not different from other cases **(Table 3)**.

Complication of TCRT

Treatment complications by TCRT were nausea and vomiting (Grade 1-2, 16 cases), gastritis (Grade 2, 7 cases), leukocytopenia (Grade 2, 4 cases; Grade 3, 2 cases; Grade 4, 1 case), thrombocytopenia (Grade 2, 1 case; Grade 3, 1 case), gastric or duodenal ulcer (Grade 2, 2 cases), fistula due to tumor necrosis (2 cases), and hemobilia from ruptured pseudoaneurysm of the hepatic artery (1 case). These complications were successfully treated conservatively.

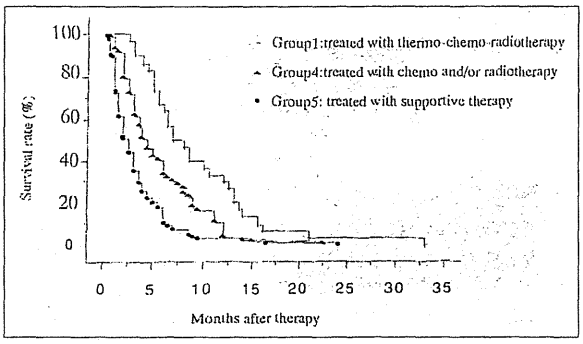

FIGURE 5 Comparison of survival (Kaplan-Meier) according to treatment regimen. There was a significant difference in the survival rate between group 1 and group 4,5 ($p<0.01$).

DISCUSSION

Gallbladder carcinoma carries a poor prognosis, with the only chance for cure lying in early detection and complete surgical resection. The 5-year survival rate following surgery for gallbladder carcinoma has been reported to be between 5 and 13% in the literature (9,10). Such distressing results are due partly to a low resectability rate and late diagnosis but also to certain limitations in the radical removal of the tumors. Therefore, the postoperative recurrence rate is high. Clinical benefit of radical resection for advanced gallbladder carcinoma is still controversial. For advanced gallbladder carcinoma, we have performed TCRT. We have also performed combined resection of the alimentary tract with or without the liver, with adjuvant IORT in some cases, chemotherapy and/or radiotherapy, and supportive therapy for

TABLE 3 Pathological Findings at Autopsy in Patients Treated with Thermo-Chemo-Radiotherapy

		Change of gallbladder wall and tumor				Metastases		
Case	Histology	Necrosis	Hyalinization or fibrosis	Scattered degenerative tumor cells	Bile duct	Liver	Lung	Lymph node
2	well diff. adenoca.	+	++	++	stenosis	++	+	++
6	poorly diff. adenoca.	+	++	++	obstructed	+	-	+
7	poorly diff. adenoca.	+	++	+	stenosis	++	-	++
8	adenosquamous ca.	+	++	+	obstructed	-	-	-
11	well diff. adenoca.	+	+	+	obstructed	+	+	-
15	well diff. adenoca.	+	++	+	stenosis	+	+	+
18	pleomorphic ca.	++	+	+	open	+	+	-
20	well diff. adenoca.	+	++	+	stenosis	+	+	+
21	well diff. adenoca.	++	++	++	stenosis	+	-	-
22	well diff. adenoca.	+	+	+	obstructed	+	+	+
28	well diff. adenoca.	++	++	+	obstructed	+	+	++

well diff. adenoca.: well differentiated adenocarcinoma; poorly diff. adenoca.: poorly differentiated adenocarcinoma; adenosquamous ca.: adenosquamous carcinoma; pleomorphic ca.: pleomorphic carcinoma.

these tumors (4). We analyzed the effectiveness of TCRT for Stage IV gallbladder carcinoma compared with other treatment regimens.

R0-resection was the most beneficial for prolonging survival. However, despite aggressive tumor removal with adjuvant IORT, there was no significant difference in the survival rate between patients treated with R1,2-resection and TCRT.

Most reasons for unresectability for cure in cases without distant metastases are due to the involvement of the hepatoduodenal ligament. Deeply invaded tumors, especially those located in the neck or body of the gallbladder, are apt to spread to the bile duct or the connective tissues in the hepatoduodenal ligament, with encasement of major vessels, or both. Moreover, tumor cells that spread to the ligament often cannot be cleared away completely, even when dissection of the tissue is performed. In nonresected cases, tumor spread to the hepatoduodenal ligament also frequently induces the development of obstructive jaundice which cannot be controlled, resulting in early death from cholangitis. One of the desired strategies for advanced gallbladder carcinoma appears to be control of this involvement of the hepatoduodenal ligament.

Effectiveness of TCRT on nonresctable tumors was surprising. In respect to tumor regression, there were 5 CR cases and 14 PR cases. At autopsy, marked hyalinization or fibrosis with necrosis replaced the gallbladder wall or tumor in almost all cases. Additionally, we observed that biliary obstruction resolved completely in 6, and partially in 9 of 20 patients with obstructive jaundice. TCRT was effective for management of involved hepatoduodenal ligament. In 11 patients, PTCD was able to be removed. Moreover, placement of self-expandable metallic stent into the patency-restored bile duct after TCRT was useful for keeping the longer patent period of the duct.

First of all, we consider why it is effective to combine radiation therapy on chemotherapy with hyperthermia. When the target lesion is heated up to around 42°C, the cancer killing effect of radiation or anticancer drug is enhanced. This fact is well documented by many reports on biological research (11-14). Furthermore, research in the fields of molecular biology and genetics is being conducted actively to clarify the mode of action of hyperthermia (15,16).

There are also many clinical studies that reveal effectiveness of combination treatment of radiation therapy and hyperthermia. In the meantime, European and American researchers are applying microwave therapy to superficial tumors (17) and conducting phase III study to clarify the combined use of hyperthermia (18,19). The effectiveness of thermoradiotherapy for deep-seated tumors has been revealed by prospective randomized studies (16,20). In Japan, the clinical research on hyperthermia is more active than in other countries (21). Especially, stream is RF-capacitive heating for deep-seated tumors. Effective deep heating of chest and upper abdomen with less side effects can be achieved only by RF-capacitive heating equipment (21).

The treatment protocol of TCRT was established and its effectiveness was evidenced by a series of research reports published by Sugimachi and his colleagues. They treated esophageal carcinoma with combination of radiotherapy and chemotherapy and additionally with 6 sessions of intracelial heating. They demonstrated significant improvement in the clinical effectiveness and 5-year survival ratio (22). Furthermore, they applied chemoradiotherapy and TCRT in a randomized control study before operation of esophageal carcinoma. Their phase III study revealed that clinical and histopathological effects were superior in TCRT to chemoradiotherapy (23).

This study established the treatment protocol of TCRT for advanced gallbladder carcinoma, comparing it with four other treatment modalities, and clarifying its effectiveness. We prefer TCRT for patients whose tumors have invaded the hepatoduodenal ligament in place of an aggressive surgical approach.

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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.

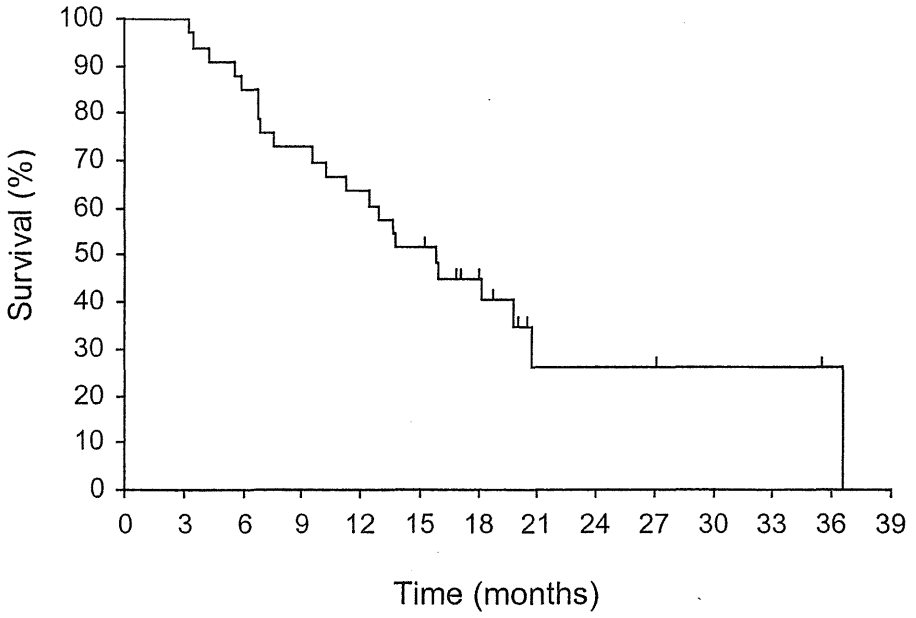

Figure 1. Overall survival time. The median survival time of the 33 treated patients was 15.8 months, and the median follow-up time for 11 censored patients was 18.1 (15.2–35.5) months. The 1-year and 2-year survival rates were 64% and 26%, respectively.

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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Clinical

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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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.

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 $<20 \times 10^9\,l^{-1}$, 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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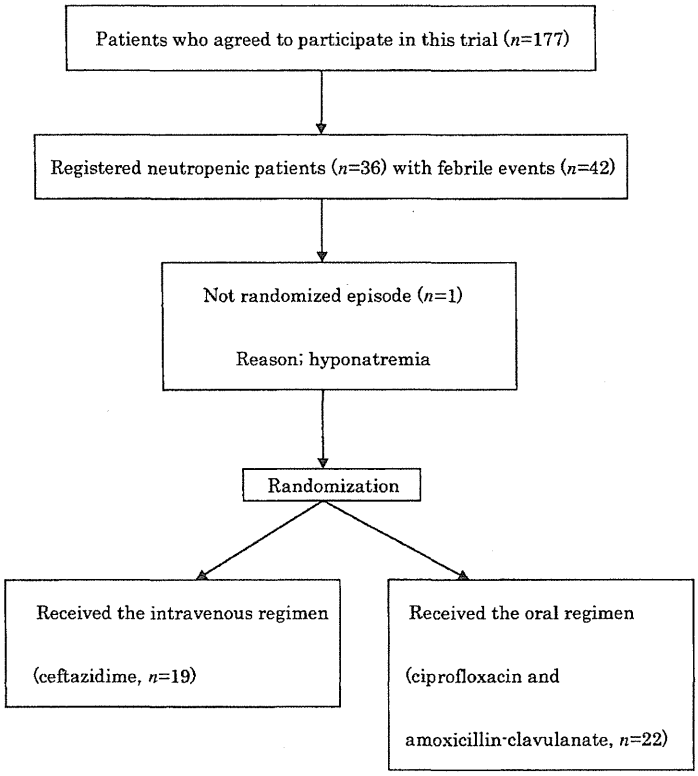

Figure 1. Study flow diagram.

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)		
$\leq 100/mm^3$	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 $\geq 37°C$ 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.

The selection of low-risk patients with febrile neutropenia is very important. A multinational trial demonstrated that predictive factors for low risk complications included a burden of illness indicating the absence of symptoms or the presence of mild symptoms [weight, 5; odds ratio (OR), 8.21] or moderate symptoms (weight 3; OR, 3.70); the absence of hypotension (weight, 5; OR, 7.62); the absence of chromic obstructive pulmonary disease (COPD) (weight, 4; OR, 5.35); the presence of a solid tumor or the absence of previous fungal infection in patients with hematologic malignancies (weight, 4; OR, 5.07); an outpatient status (weight, 3; OR, 3.51); the absence of dehydration (weight, 3; OR, 3.81); and an age <60 years (weight, 2; OR, 2.45). A risk-index score ≥21 was considered to indicate a low-risk (10). In our trial, all of the enrolled patients had solid tumors (lung cancer) without hypotension or dehydration and no or mild symptoms. All but one patient had no COPD, producing a risk score of 21 or greater.

PUO was observed in 63% of the low-risk febrile neutropenic patients. The PUO percentage was identical to that reported in previous trials. All patients with PUO were successfully treated with oral or intravenous antibiotic therapy in our trial. Oral ciplofloxacin plus amoxicillin-clavulanate was effective for the treatment of PUO. Documented infections were successfully treated with an oral regimen in four out of six episodes and with an intravenous regimen in five out of nine episodes. Six patients needed to modify their regimen to an intravenous regimen containing cephalosporin or carbapenem. Oral ciplofloxacin plus amoxicillin-clavulanate was also effective in selected low-risk patients with documented infections.

Oral antibiotics produced a successful outcome in 91% of the patients, although 86% of the patients also received G-CSF support. Whether G-CSF support is needed in low-risk patients remains uncertain. The clinical practice guidelines of the American Society of Clinical Oncology recommend that G-CSF should not be routinely used as adjunct therapy for the treatment of uncomplicated fever and neutropenia (11). Uncomplicated fever and neutropenia are defined as follows: fever of ≤10 days in duration; no evidence of pneumonia, cellulites, abscess, sinusitis or hypotension; and no uncontrolled malignancies. Oral antibiotics with ciplofloxacin plus amoxicillin-clavulanate are probably effective even if G-CSF support is not performed and can be easily administered to febrile neutropenic outpatients. In a randomized trial, oral antibiotics (ciplofloxacin plus amoxicillin-clavulanate) with early hospital discharge was compared with inpatient intravenous antibiotics (gentamicin plus tazocin) for the treatment of low-risk febrile neutropenic patients with cancer (12). This study suggested that oral antibiotics with early discharge was feasible and an alternative to conventional intravenous antibiotic regimens.

In conclusion, our trial suggested that oral antibiotic therapy with ciplofloxacin plus amoxicillin-clavulanate is effective for the treatment of low-risk febrile neutropenic patients, although the trial was prematurely terminated because of slow enrolment.

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