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ORIGINAL ARTICLE

Phase II study of nedaplatin and irinotecan followed by gefitinib for elderly patients with unresectable non-small cell lung cancer

Fumihiro Oshita · Kouzo Yamada · Haruhiro Saito · Kazumasa Noda

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Abstract
Purpose We conducted a phase II study of combination chemotherapy with nedaplatin (NP) and irinotecan (CPT) followed by gefitinib to determine the effects and toxicities in patients 70 years or older with unresectable non-small cell lung cancer (NSCLC).
Methods Eligible patients were entered to receive 3 courses of 50 mg/m^2 NP and 60 mg/m^2 CPT on days 1 and 8 every 4 weeks and sequential gefitinib 250 mg po once a day was followed until tumor progression.
Results Twenty-eight patients received NP and CPT combination chemotherapy. One patient achieved CR, 10 PR, 14 SD and 3 PD, and the response rate was 39.3%. Twenty-one patients received gefitinib 250 mg per day until tumor progression after completion of the NP and CPT chemotherapy. Two patients with SD after NP and CPT chemotherapy achieved PR. For the 3-drug combination, there were 13 responders and the overall response rate was 42.9%. Of the toxicities associated with NP and CPT chemotherapy, grade 4 neutropenia, and grade 3 febrile neutropenia were observed in 24 (33.8%) and 3 (4.2%) courses, respectively. Of the toxicities associated with gefitinib treatment, grade 3 anemia, and SGOT and SGPT elevation were observed in one patient (4.8%) each, respectively. The median survival time was 8.7 months, and the 1- and 2-year survival rates were 42.9 and 32.1%, respectively.
Conclusion NP and CPT followed by gefitinib is feasible for elderly patients with unresectable NSCLC.

F. Oshita (✉) · K. Yamada · H. Saito · K. Noda
Department of Thoracic Oncology, Kanagawa Cancer Center, Nakao 1-1-2, Asahi-ku, Yokohama 241-0815, Japan
e-mail: foshita@kcch.jp

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Introduction

Current chemotherapy regimens for metastatic non-small cell lung cancer (NSCLC) are not particularly effective. Regimens based on combinations of new anticancer agents such as vinorelbine, gemcitabine, docetaxel and paclitaxel with platinum compounds have emerged as a gold standard for such patients [1].

In a subset analysis of randomized trials, the response rate, toxicity and survival rates in fit, elderly patients with NSCLC receiving platinum-based treatment appeared to be similar to those in younger patients [2]. However, elderly patients with normal organ function had been selected as subjects for the analysis. A feasibility study of standard cisplatin-based chemotherapy in elderly lung cancer patients with normal organ function showed that only 29% satisfied the eligibility criteria, and that these patients experienced severe neutropenia after cisplatin-based chemotherapy [3]. It is generally believed that elderly patients are less able to tolerate aggressive chemotherapy than their younger counterparts. The randomized Elderly Lung Cancer Vinorelbine Study Group trial demonstrated that elderly patients treated with vinorelbine—in combination with best supportive care (BSC)—have a significantly improved chance of survival and quality of life in comparison with patients treated with BSC alone [4]. The Multicenter Italian Lung Cancer in the Elderly Study trial demonstrated that the use of a combination of gemcitabine plus vinorelbine in this patient population did not further improve the survival rate or quality of life in comparison with either vinorelbine or gemcitabine monotherapy [5]. Thus, standard combination chemotherapy

has not been established for elderly patients with advanced NSCLC.

Three-dimensional analysis models have demonstrated a remarkable synergistic interaction of concurrently administered nedaplatin (NP) and irinotecan (CPT) [6]. In our previous phase I/II study, a combination of NP and CPT showed high activity against NSCLC: the response rate was 31.0%, and the 1-year survival rate was 45.2% [7]. A phase II study of combination chemotherapy with NP and CPT in 38 patients aged 70 years or older with advanced NSCLC demonstrated a 65.8% response rate, a median survival time of 418 days, and a 1-year survival rate of 55.3% [8]. However, seven of the 38 patients could not receive a second cycle of the chemotherapy because of toxicities such as vomiting, diarrhea and febrile neutropenia. Dose or schedule modifications are therefore required to make the NP and CPT combination safe for elderly patients.

The epidermal growth factor receptor (EGFR) superfamily was identified early on as a potential target for therapy of solid tumors. Given the biological importance of the EGFR molecular network in carcinomas, several molecules that can inhibit the EGFR tyrosine kinase domain have been synthesized. The inhibitor gefitinib at 250 mg per day demonstrated an 18.4% objective response in 103 patients with previously treated advanced NSCLC [9]. Adverse events associated with use of the drug were mainly skin reactions and diarrhea. As no hematological adverse events or infections related to chemotherapy safety in elderly patients with NSCLC were observed in a trial of gefitinib at 250 mg per day, gefitinib treatment is considered to be feasible for such patients.

Here we report a phase II study of combination chemotherapy with NP and CPT followed by sequential gefitinib treatment for elderly patients with advanced NSCLC. We modified the NP arm so that it was divided on days 1 and 8, in order to ensure safety and to allow continuous use of gefitinib after completion of the NP and CPT chemotherapy until tumor progression.

Patients and methods

The Institutional Review Board of Kanagawa Cancer Center reviewed and approved this study prior to commencement.

Patients

Patients with histologically or cytologically proven unresectable NSCLC were registered for the NP and CPT combination followed by gefitinib chemotherapy. Eligibility criteria for the chemotherapy were: no prior chemotherapy, expected survival of at least 6 weeks, age $\geq$ 70 years, Eastern Cooperative Oncology Group PS score $\leq$ 2, leukocyte count $\geq$ 4,000/μl, hemoglobin count $\geq$ 9 g/dl, platelet count $\geq$ 100,000/μl, total serum bilirubin $\leq$ 1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase $\leq$ 90 IU/l, serum creatinine $\leq$ 1.5 mg/dl, and creatinine clearance more than 40 ml/min. We did not attempt their geriatric assessment in the present study. Patients experiencing postoperative recurrence and patients who had received radiotherapy for metastatic lesions were eligible for the present study, and at least 4 weeks' rest was required after prior surgery or radiation therapy. Patients with massive pleural effusion, pericardial effusion, symptomatic brain metastasis, paralytic ileus, severe infection or pneumonitis were excluded. Patients with uncontrolled ischemic heart disease, severe cardiac insufficiency, hypertention or diabetes mellitus were also excluded. Written informed consent was obtained in every case.

Chemotherapy

Patients exhibiting no progression of the disease were treated every 4 weeks with 60 mg/m^2 CPT and 50 mg/m^2 NP on days 1 and 8. Patients received 5-HT$_3$ antagonist IV and 8 mg dexamethasone IV before administration of the anticancer drugs. Both drugs were administered on day 8 when the following criteria were satisfied: leukocyte count $\geq$ 3000/μl, neutrophil count $\geq$ 1,500/μl, platelet count $\geq$ 75,000/μl, non-hematologic toxicity of less than grade 2 except for alopecia, and leukocyte or neutrophil count greater than 1,000/μl or 500/μl respectively during the period between day 2 and 8. Recombinant human granulocyte colony-stimulating factor (G-CSF), 50 mg/m^2 per day or 2 μg/kg per day, was administered subcutaneously once a day when the patient's leukocyte or neutrophil counts were below 1,000 and 500/μl, respectively. Subsequent cycles of chemotherapy were started when patients were able to satisfy the organ function eligibility criteria, with the exceptions of hemoglobin count and creatinine clearance, for entry to the study. The doses of CPT and NP were reduced by 10 mg/m^2 for the subsequent cycle if dose-limiting toxicities (DLT) were observed, such as grade 4 neutropenia lasting $\geqq$4 days or grade 4 neutropenia with fever $\geqq$38°C, grade 4 thrombocytopenia, other grade 4 blood/bone marrow toxicities, except for leukocyte and hemoglobin toxicities, grade 4 vomiting, grade 4 anorexia, grade 4 constipation, grade 4 stomatitis/pharyngitis, grade 4 metabolic/laboratory toxicities, grade 4 coagulation toxicities, or grade 3 or 4 other non-blood/bone marrow toxicities, except for nausea and vomiting. The NP and CPT chemotherapy was repeated for a maximum of three cycles unless the disease progressed, or if severe toxicities developed, such as septic shock, irreversible renal failure, grade 4 hepatic toxicity, grade 4 cardiovascular toxicity, grade 4 pulmonary toxicity, grade 4 diarrhea, grade 4 CNS cerebrovascular

ischemia, or grade 4 CNS hemorrhage/bleeding. Tumor responses were evaluated according to the RECIST criteria [10]. Toxicities were evaluated according to the NCI-CTC ver.2 criteria [11].

Sequential chemotherapy with gefitinib 250 mg po once a day was started after completion of the NP and CPT combination chemotherapy when the following criteria were satisfied: PS score ≤ 2, leukocyte count $\geq 4{,}000/\mu l$, hemoglobin count ≥ 9 g/dl, platelet count $\geq 100{,}000/\mu l$, total serum bilirubin ≤ 1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase ≤ 90 IU/l, serum creatinine ≤ 1.5 mg/dl. Sequential gefitinib treatment was interrupted for a maximum 14 days until the toxicities became less than grade 2, if grade 4 hematological toxicities, grade 3 skin toxicity, grade 3 diarrhea, or grade 3 other non-hematological toxicities appeared. The sequential chemotherapy was stopped if the disease progressed, toxicities did not recover to grade 0 or 1 within 14 days, 2 breaks of treatment were required due to toxicities, or patients refused the treatment.

Study design

We chose a 60% response rate as a desirable target level for the NP and CPT regimen, and considered a 40% response rate as not significant. The study design had the power to detect responses greater than 90%, with less than 10% error. Therefore, we required 28 assessable patients in the first stage and 13 in the second stage, according to the Minimax design of Simon [12]. We decided to stop the study if less than 11 patients responded to NP and CPT in the first stage. This regimen was defined as active if the number of responders out of 41 patients was $\geqq 21$, and inactive if the number of responders was $\leqq 20$ [12, 13]. Overall survival was estimated using the method of Kaplan and Meier.

We also defined toxic regimen when one-third patients experienced grade 4 thrombocytopenia, grade 3 neutropenic fever or other grade 3 non-hematological toxicities in this study.

Results

Between November 2002 and July 2005, 28 patients were registered in the study. Patient characteristics are summarized in Table 1. Twenty patients were male and 8 were female, with a median age of 74 years (range 70–81 years). Six patients had a performance status (PS) of 0 and the other 22 patients had a PS of 1. Twenty-three patients had adenocarcinoma, 4 had squamous cell carcinoma, and 1 had non-small cell carcinoma. Seven and 21 patients were stage IIIB and stage IV, respectively. All 28 patients were assessed for response, toxicities and survival. Twenty-five patients received 2 or 3 cycles of NP and CPT combination chemotherapy. Three patients dropped out the study after the first cycle of NP and CPT chemotherapy: 1 with disease progression, 1 with febrile neutropena requiring 15 days for improvement, and 1 with grade 2 diarrhea and grade 3 CNS cerebrovascular ischemia. Treatment-related toxicities during the total 71 courses of NP and CPT chemotherapy are listed in Table 2. Of the hematological toxicities, grade 4 anemia and neutropenia were observed during 2 (2.8%) and 24 (33.8%) courses, respectively. There was no grade 4 thrombocytopenia, and none of the patients required transfusion. Of the non-hematological toxicities, grade 3 febrile neutropenia was observed in three courses (4.2%). Grade 3 diarrhea and grade 3 CNS cerebrovascular ischemia was observed in 1 course (1.4%) each, respectively. Other non-hematological toxicities were mild. The outcome of the NP and CPT regimen in 28 patients were 1 CR, 10 PR, 14 SD and three PD, and the response rate was 39.3%. Thus, the study was stopped in the first stage.

Twenty-one patients received sequential gefitinib treatment, and 7 patients were unable to do so, 3 because of decreased PS, 3 due to refusal, and 1 because of the need for whole brain irradiation for progressive brain metastasis. The median duration of sequential gefitinib treatment was 68 days (range 21–932 days). Two patients, whose

Table 1 Patient characteristics

	No. of patients
Total	28
Age (years)	
Median	74
Range	70–81
Gender	
Male	20
Female	8
Performance status (ECOG)	
0	6
1	22
Smoker	22
Clinical stage	
IIIB	7
IV	18
Postoperative recurrence	3
Histology	
Adenocarcinoma	23
Others	5
No. of metastatic organs	
1	16
$\geqq 2$	5
Brain metastasis	1

Table 2 Toxicities in NP and CPT combination chemotherapy

	Grade (NC I-CTC ver.2)					
	0	1	2	3	4	Grade 3, 4 (%)
Hemogbbin	7	21	27	14	2	22.5
Leukocytes	10	9	24	23	5	39.4
Neutrophils	10	5	10	22	24	64.8
Platelets	19	27	9	16	0	22.5
Bilirubin	68	1	2	0	0	–
SGOT	56	15	0	0	0	–
SGPT	63	7	1	0	0	–
Creatinine	62	7	2	0	0	–
Fatigue	2	48	16	5	0	7.0
Fever	65	6	0	0	0	–
Alopecia	48	22	1	0	0	–
Rash/desquation	68	3	0	0	0	–
Diarrhea	37	27	6	1	0	1.4
Nausea-vomiting	40	25	6	0	0	–
Febrile neutrophenia	62	6	0	3	0	4.2
CNS cerebrovascular ischemia	70	0	0	1	0	1.4
Neuropathy	71	0	0	0	0	–
Pneumonitis	71	0	0	0	0	–

response to NP and CPT was SD, responded to gefitinib treatment, and the overall response rate for NP and CPT followed by gefitinib was 42.9%. Treatment-related toxicities for the total of 21 patients who received gefitinib treatment are listed in Table 3. Of the hematological toxicities, grade 3 anemia was observed in one patient (4.8%). Of the non-hematological toxicities, infection with grade 3 SGOT and SGPT elevation was observed in one patient (4.8%). Other hematological and non-hematological toxicities were mild.

The overall survival curve is shown in Fig. 1. Five patients survived and the other 23 patients died during the follow-up period. The median survival time was 8.7 months. The 1- and 2-year survival rates were 42.9 and 32.1%, respectively.

Discussion

The combination of NP with CPT followed by gefitinib treatment showed activity against NSCLC in the present study. We chosen 60% response rate as a desirable target level in NP and CPT regimen. The responders in 28 entered patients of first stage were required 12 patients, the responders were 11 and this regimen was concluded inactive. However, two patients, whose response to NP and CPT was SD, responded to gefitinib treatment. Thus, overall response rate 42.9% for NP and CPT followed by gefitinib was considered to be active. A previous study of NP and CPT combination chemotherapy showed that it was effective for elderly patients with advanced NSCLC, although 29% of patients experienced febrile neutropenia [8]. In the present study design, we defined toxic when one third patients experienced grade 4 thrombocytopenia, grade

Table 3 Toxicities in gefitinib treatment

	Grade (NC I-CTC ver.2)					
	0	1	2	3	4	Grade 3, 4 (%)
Hemogbbin	1	12	7	1	0	4.8
Leukocytes	16	4	1	0	0	–
Neutrophils	18	2	1	0	0	–
Platelets	15	4	2	0	0	–
Bilirubin	19	2	0	0	0	–
SGOT	13	7	0	1	0	4.8
SGPT	16	4	0	1	0	4.8
Creatinine	17	3	1	0	0	–
Fatigue	1	18	2	0	0	–
Fever	21	0	0	0	0	–
Alopecia	19	2	0	0	0	–
Dry skin	12	9	0	0	0	–
Nail change	20	1	0	0	0	–
Pruritis	13	8	0	0	0	–
Rash/desquation	7	12	2	0	0	–
Anorexia	20	1	0	0	0	–
Diarrhea	15	6	0	0	0	–
Gastritis	20	1	0	0	0	–
Nausea-Vomiting	19	2	0	0	0	–
Epistaxix	20	1	0	0	0	–
Infection	20	0	1	0	0	–
Neuropathy	21	0	0	0	0	–
Pneumonitis	21	0	0	0	0	–

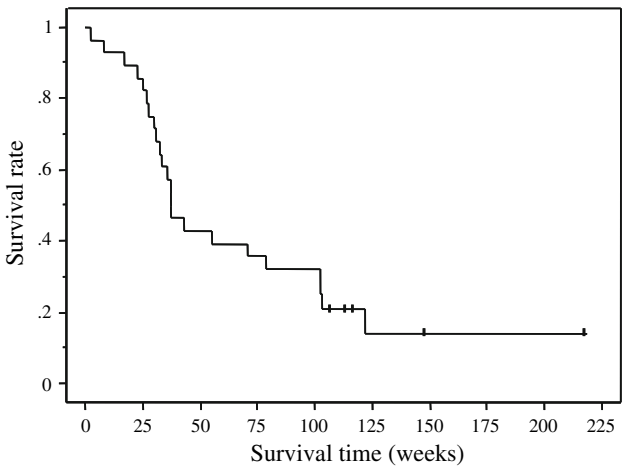

Fig. 1 Survival curves constructed by the Kaplan–Meier method. Five of the 28 patients were alive, the MST was 8.7 months, and the 1- and 2-year survival rates were 42.9 and 32.1%, respectively

3 neutropenic fever or other grade 3 non-hematological toxicities. Only five patients (17.9%) experienced these toxicities and the treatment was concluded to be safe. We also considered the incidence of 33% for grade 4 neutropenia and 4.2% for grade 3 neutropenic fever to be acceptable in this study. Although the response rate of 39.3% for NP and CPT chemotherapy was not high, 25 of 28 patients (89.3%) were able to receive 2–3 cycles of the combination chemotherapy. Division of the NP arm on days 1 and 8 with CPT was confirmed to be safe for elderly patients with NSCLC.

Sequential gefitinib treatment resulted in tumor regression in only 2 of 21 patients (9.5%) achieving SD or PD with NP and CPT treatment. We considered that this small adjuvant effect of gefitinib after NP and CPT treatment may have been due to gefitinib resistance in most of the elderly patients who entered the trial. However, the response rate in the present study was higher than that in a study of gefitinib monotherapy for 40 elderly patients with pretreated NSCLC, which demonstrated a 5% objective response [14]. Responsiveness to gefitinib has been demonstrated in distinct subgroups of patients, such as women, patients who have never smoked, patients with adenocarcinoma, and Asians [15–17]. Twenty-two and 21 of the 28 patients registered in this study were smokers and males, respectively. Only four patients in this study were women who had never smoked, and were sensitive to gefitinib. This may have accounted for the small impact of gefitinib treatment in this study. Median survival time was 8.7 months, but nine patients (32.1%) survived more than 2 years. The presence of such long survivors suggested that gefitinib treatment could be effective for some elderly patients who are gefitinib-sensitive. Although the level of EGFR protein expression is not associated with the response to gefitinib, specific missense and deletion mutations in the tyrosine kinase domain of the EGFR gene have been reported to be associated with gefitinib sensitivity [18, 19]. A retrospective study demonstrated that NSCLC patients with EGFR mutations had a better outcome with gefitinib treatment than patients with the wild-type EGFR gene [20]. Our recent study has also demonstrated a significantly higher gefitinib response in patients with EGFR mutation than in those with wild-type EGFR (90.9 vs. 14.3%), and significantly longer overall and progression-free survivals in patients with EGFR mutation [21]. Unfortunately, the patients in the present study were not analyzed their EGFR genetic status, gefitinib treatment seems to be of some benefit to patients with EGFR mutation.

In conclusion, sequential gefitinib treatment added to NP and CPT combination chemotherapy does not improve the response rate but can have a longer survival benefit for at least some elderly patients with advanced NSCLC. Gefitinib treatment can be considered when candidate patients have EGFR mutation in NSCLC.

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