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Original Article

Triplet Chemotherapy with Cisplatin, Docetaxel, and Irinotecan for Patients with Recurrent or Refractory Non-small Cell Lung Cancer

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We examined the feasibility of triplet chemotherapy using cisplatin, docetaxel, and irinotecan for patients with recurrent or refractory non-small cell lung cancer (NSCLC), retrospectively. Twenty-five patients (21 men and 4 women) with NSCLC and good performance status who were ≤70 years old were analyzed. The median age was 58 years. Most patients had performance status 1 (16/25), stage IV disease (18/25) and adenocarcinoma-histology (16/25). Cisplatin and docetaxel were given on day 1 and irinotecan on day 2; the cycle was repeated every 3 weeks. The objective response rate was 39.1% (95% confidence interval: 18.7–59.5%). The median survival time and actual 2-, 3-, and 5-year survival rates were 14.3 months, 32%, 20%, and 8%, respectively. Of note, only 6 patients were treated with gefitinib at the recurrence after triplet chemotherapy; of these, 4 (67%) achieved a partial response, which might result in favorable survival. Grade 3/4 toxicities consisted of neutropenia (100%), neutropenic fever (56%), nausea/vomiting (40%), and diarrhea (16%); no cases of treatment-related death occurred. Triplet chemotherapy showed impressive survival data in our clinical trial, but proved too toxic for use in treating patients with NSCLC in the clinical practice.

Key words: cisplatin, docetaxel, irinotecan, triplet chemotherapy, gefitinib

Lung cancer is a leading cause of cancer death worldwide including Japan. Platinum-based combination chemotherapy is the standard care for patients with advanced non-small cell lung cancer (NSCLC) [1]. At present, docetaxel, pemetrexed, erlotinib, and gefitinib are used as second-line treatments for recurrent or refractory advanced NSCLC [2–5].

A phase I/II clinical trial of combination chemotherapy with cisplatin, docetaxel, and irinotecan for untreated patients with advanced NSCLC demonstrated promising results in objective response rate and in survival [6]. Three drugs were selected to obtain the best response based on the interactions between 2 drugs [7], two-drug schedule dependency [8] and the sensitivity spectrum of each drug to lung cancer cell lines [9] in *ex vivo* experiments [6]. Although a phase III trial (OLCSG 0403) is ongoing to confirm the superiority of triplet over doublet chemotherapy, the results of the phase I/II trial encour-

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aged us to expand triplet chemotherapy to patients with recurrent or refractory NSCLC who were excluded from the original phase I/II trial [6].

We describe here the results of a particular triplet chemotherapy for relatively young NSCLC patients with good performance status (PS) and adequate organ function who were treated previously.

Patients and Methods

Patients. Twenty-five patients aged ≤70 years with Eastern Clinical Oncology Group (ECOG) PS of 0 to 1 and who had histologically or cytologically confirmed NSCLC were treated with triplet chemotherapy. All patients had received prior therapy, such as surgery and/or thoracic curative and palliative radiotherapy, or systemic chemotherapy, and did not require measurable lesions. Prior treatments had to have been completed at least 4 weeks prior to triplet chemotherapy. Other inclusion and exclusion criteria were the same as those for the phase II trial previously reported [6]. Briefly, patients had to have adequate functioning of the bone marrow [white blood cell (WBC) count of 4,000 to 12,000/μl, and platelets ≥100,000/μl], kidneys [serum creatinine level <1.5 mg/dl, 24-h creatinine clearance (Ccr) ≥60 ml/min], and liver (total bilirubin level ≤1.5 mg/dl, alanine transaminase and asparagine transaminase levels no more than twice the upper limit of normal values). Patients were excluded if they had a second primary tumor other than basal cell carcinoma of the skin or carcinoma *in situ* of the cervix, severe cardiopulmonary insufficiency, severe angina pectoris or myocardial infarction, active infection, uncontrolled diabetes mellitus, or a life expectancy of less than 3 months. Written informed consent was obtained prior to treatment.

Baseline evaluation. Tumors were staged on the basis of a physical examination, routine chest radiograph, bone scintigraphy, computed tomography of the chest and abdomen, enhanced magnetic resonance imaging of the brain, and fiber optic bronchoscopy. Stages were assessed according to the Union International Contra le Cancer TNM classification for lung cancer staging [10].

Treatment: triplet regimen. We administered cisplatin (60 mg/m^2) and docetaxel (60 mg/m^2) on day 1, and irinotecan (50 mg/m^2) on day 2. Because patients analyzed had undergone prior therapies, the dose of irinotecan was held at 50 mg/m^2. The schedule used was the same as previously described [6] except for the irinotecan dose. Briefly, on day 1, docetaxel was given as a 1-h infusion, and cisplatin was administered subsequently as a 1-h infusion. On day 2, irinotecan was given as a 1-h infusion. If patients experienced grade 4 neutropenia or febrile neutropenia in the first cycle, they received lenograstim or filgrastim prophylactically in the subsequent cycles. The triplet regimen was repeated every 3 weeks when patients had recovered from any drug-related toxicities associated with the previous cycle other than grade 1 neutropenia. The cisplatin dose was reduced to 30 mg/m^2 if a patient's Ccr level was 30–60 ml/min. Cisplatin was discontinued if the Ccr level fell below 30 ml/min. If patients experienced any grade 3 toxicities other than renal impairment, chemotherapy was repeated with a 10 mg/m^2 reduction of irinotecan. Chemotherapy was continued until the disease progressed or until unacceptable toxicity developed. Each physician decided the treatments following triplet chemotherapy. All patients who survived have received gefitinib since September, 2002.

Follow-up evaluation. Tumor response was assessed at every chemotherapy cycle using the WHO criteria [7]. Toxicity was assessed and graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0, revised in 1998). A complete blood count (CBC) including a differential WBC count and blood chemistry was repeated at least once a week; if the absolute neutrophil count decreased to ≤500/μl or if the leukocyte count was ≤1,000/μl, the CBC was repeated every day until recovery.

Statistical considerations. The overall survival time was defined as the period from the beginning of treatment until death or the last follow-up evaluation, and the time to progression (TTP) was defined as the period from the beginning of treatment until progressive disease (PD) or until death from causes other than NSCLC. Survival curves were calculated using the Kaplan-Meier method.

Results

Patient characteristics. Between October, 1998 and July, 2001, 25 patients with NSCLC who

met our criteria were consecutively treated at Okayama University Hospital with triplet chemotherapy. The characteristics of the patients are listed in Table 1. The group consisted of 21 men and 4 women, with a median age of 58 years (range, 40–67 years). Sixteen patients (64%) had adenocarcinoma, 7 (28%) had squamous cell carcinoma, and 1 patient each had large cell and signet ring cell carcinoma (4%). All patients had an ECOG PS of 0 to 1 and had undergone prior therapy: 13 patients had palliative radiotherapy for metastatic lesions of the brain or the bone, 6 patients had recurrent disease after surgery, and 6 patients were refractory to first-line platinum-based systemic chemotherapies consisting of cisplatin, mitomycin-C, and vindesine, or of cisplatin and 5-fluorouracil. Following triplet chemotherapy, 12 patients received no additional treatments, 6 received palliative radiotherapy, 6 gefitinib, 2 vinorelbine, 2 gemcitabine + vinorelbine, 1 gemcitabine, 1 carboplatin + gemcitabine, and 1 carboplatin + paclitaxel.

Response. Among the 25 patients, 2 who had no measurable lesions had been treated with systemic chemotherapy. One had malignant pleural effusion, and another could not be evaluated for tumors because of in-field recurrence after radiotherapy. Responses of the 23 remaining patients were as follows: 1 (4.3%) CR, 8 (34.8%) partial response (PR), 10 no change (NC) (43.5%), and 4 (17.4%) PD. The overall response rate was 39.1% (95% CI: 18.7–59.5%). Responses of the 19 chemotherapy-naïve patients were as follows: 1 (5.3%) CR, 6 (31.6%) PR, 8 (42.1%) NC, and 4 (21.1%) PD, for an overall response rate of 36.8% (95% CI: 14.6–59.1%). Two (50%) of 4 evaluable patients previously treated with platinum-based systemic chemotherapy achieved a PR.

Only 6 patients (24%) had been treated after disease progression with gefitinib, which was not approved in Japan until August, 2002. Of the 6 patients, 4 (66%) achieved a PR, including 1 patient whose tumor genome contained a 752–759 deletion mutation in exon 19 of the EGFR tyrosine kinase domain, as detected in a surgical specimen.

Survival. Fig. 1 shows the overall survival curve for the 25 patients. At a median follow-up time of 96.1 months (95% CI: 86.2–106.1 months), 1 patient (4%) was alive with lung cancer. The overall survival rates at 1, 2, 3, and 5 years were 48, 32, 20, and 8%, respectively. The median survival time (MST) and the median TTP were 14.3 months (95% CI: 8.8–19.8 months) and 5.4 months (95% CI: 4.6–6.2 months), respectively. Six patients (24%) were treated with gefitinib after triplet chemotherapy. Surprisingly, the response rate and disease control rate [CR + PR + NC] for gefitinib treatment were 67 and 100%, respectively. The response duration of gefitinib treatment ranged from 8 to 28 months.

Table 1 Patient characteristics

No. of patients analyzed		25
No. of patients with measurable lesions		23
Median age, years (range)		58 (40–67)
Gender, male/female		21/4
Performance status	0	9
	1	16
Histology		
Adenocarcinoma		16
Squamous cell carcinoma		7
Large cell carcinoma		1
Signet ring cell carcinoma		1
Stage when treated with triplet chemotherapy		
IIIB		4
IV		18
First relapse after surgical resection with a single recurrence site		3

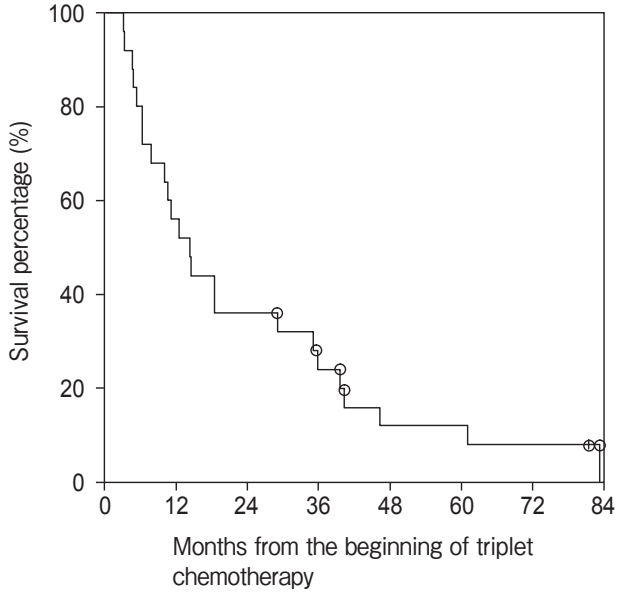

Fig. 1 Overall survival from the beginning of triplet chemotherapy for 25 previously treated patients with NSCLC. Open circles represent 6 patients treated with gefitinib following triplet chemotherapy. The tic indicates a censored case.

Furthermore, the survival times of the 6 patients treated with triplet chemotherapy followed by gefitinib were 83.3, 81.4 (survival), 40.4, 39.0, 35.9 and 29.0 months, as indicated by open circles in Fig. 1.

Toxicity. The hematological and non-hematological toxicities observed in all 25 patients during treatment are listed in Tables 2 and 3, respectively. The most common toxicities were leukopenia and neutropenia. Both grade 3/4 leukopenia and neutropenia were observed in the 25 patients (100%). The median neutrophil count nadir was 125/μl (range 11–486/μl). The median days to nadir, the median duration of grade 4 neutropenia, and the median length of recombinant human granulocyte-colony stimulating factor (rhG-CSF) administration were 9 days (range 7–13 days), 3 days (range 5–7 days), and 6 days (range 4–12 days), respectively. rhG-CSF was administered in 70 (98.6%) of 71 cycles. Grade 3/4 thrombocytopenia and anemia occurred in 1 (4%) and 4 (16%) patients, respectively. Grade 3/4 nausea/vomiting and diarrhea occurred in 10 (40%) and 4 (16%) patients, respectively. Fourteen patients (56%) developed febrile neutropenia and recovered uneventfully following treatment with intravenous broad-spectrum antibiotics and rhG-CSF support. No treatment-related deaths occurred.

Table 4 summarizes the actual dose rate in the regimens, individual drugs used, and the number of cycles. Those patients receiving a third or fourth cycle of triplet chemotherapy received over 90% of the full dose of each drug.

Table 2 Hematologic toxicity

	Grade					
	0	1	2	3	4	3 and 4 (%)
Leukocytopenia	0	0	0	11	14	25 (100)
Neutropenia	0	0	0	1	24	25 (100)
Anemia	7	8	6	4	0	4 (16)
Thrombocytopenia	21	2	1	0	1	1 (4)

Table 3 Non-hematologic toxicity

	Grade					
	0	1	2	3	4	3 and 4 (%)
Nausea/vomiting	0	7	10	8	0	8 (32)
Diarrhea	13	6	4	2	0	2 (8)
Neutropenic fever	11	—	—	14	0	14 (56)
Liver	16	4	5	0	0	0
Renal	22	3	0	0	0	0
Peripheral neuropathy	25	0	0	0	0	0
Alopecia	12	11	2	—	—	0
Other	25	0	2	0	0	0

Table 4 Compliance of chemotherapy and actual doses delivered of cisplatin, docetaxel, and irinotecan

No. of cycles	No. of patients	No. of patients treated without dose reduction (%)	Actual dose (mg/m^2) delivered		
			Cisplatin	Docetaxel	Irinotecan
1	25	25 (100)	60	60	50
2	22	17 (77)	59	60	48
3	13	9 (69.2)	58	60	47
4	9	6 (67)	57	60	47
5	2	1 (50)	60	60	45

Discussion

The triplet chemotherapy of cisplatin, docetaxel, and irinotecan demonstrated an MST of 14.3 months with severe, but manageable toxicities and a favorable response rate of 39.1% among refractory or previously treated patients with NSCLC. Survival was markedly higher than expected, because the MST in this analysis corresponded to that of 11 to 14 months in untreated advanced NSCLC patients [11].

Treatments following the triplet regimen may have had an impact on long-term survival, although 48% of patients did not receive any follow-up treatments, 24% received palliative radiotherapy, and only 24% received further single-drug or doublet chemotherapy. Note that the response rate and response duration of the 6 patients treated with gefitinib at the recurrence after triplet chemotherapy are very high. Moreover, the survival times of these six patients ranged from 29 to 83 months. Although the phenomena might be by chance because of a small sample size, docetaxel was reported to be effective for patients with NSCLC harboring epidermal growth factor receptor (*EGFR*) mutations [5]. In addition, the 5-year survival rate of patients with advanced/recurrent NSCLC harboring activating *EGFR* mutations was 50% or more [12]. Patients responding to triplet chemotherapy between 1998 and 2001 could live long enough to have a chance to receive gefitinib, as gefitinib was approved in August, 2002 in Japan. We presume that long survivors selected by triplet chemotherapy including docetaxel might possess activating *EGFR* mutations, although EGFR status was checked in only 1 patient

retrospectively. We are currently conducting a prospective trial of this triplet chemotherapy followed by gefitinib on patients who have advanced/metastatic NSCLC with activating *EGFR* mutations (OLCSG 0704) according to our clinical experiences based on this and previous trials [6, 12].

Nineteen of 25 patients analyzed were chemotherapy-naïve patients who relapsed after surgical resection, or who underwent palliative radiotherapy for metastatic lesions to the brain or bone. Patients who underwent surgery and had a single brain metastasis or a single bone metastasis formed a subgroup of patients with advanced NSCLC. These patients were excluded from the common clinical trials against advanced /metastatic NSCLC only because they had a pretreatment other than chemotherapy. This analysis shows the possibility of intensive chemotherapy in a specific population in a strict clinical trial setting.

Toxicities were a main concern in this triplet chemotherapy, and were similar to those seen in the previous phase II trial [6]. Since more than 50% of patients experienced neutropenic fever, this triplet chemotherapy is unlikely to be used in clinical practice. Triplet chemotherapy, however, might be justified with the support of prophylactic G-CSF in the setting of an aggressive clinical trial to pursue a CR, such as an OLCSG 0704 trial.

In conclusion, toxicities were too great for clinical practice, but response and survival with triplet chemotherapy were favorable for previously treated patients with NSCLC. The survival of responders to triplet chemotherapy who also received gefitinib was notable. These findings should be confirmed by our ongoing prospective trial.

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