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Cisplatin plus docetaxel combination in the first-line treatment of metastatic non-small cell lung cancer

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ABSTRACT

Aims. To evaluate activity and toxicity of cisplatin plus docetaxel combination in the first-line treatment of chemotherapy-naive patients with metastatic non-small cell lung cancer.

Patients and methods. Between October 2004 and July 2008, 186 patients with metastatic non-small cell lung cancer treated with first-line cisplatin plus docetaxel were retrospectively evaluated in 7 centers. The chemotherapy schedule consisted of cisplatin, 75 mg/m² iv infusion, and docetaxel, 75 mg/m² iv infusion on day 1, every 3 weeks.

Results. Median age was 56 years (range, 28-75). Eighteen patients (9.7%) were females and 168 (90.3%) were males, with a median ECOG performance status of 1 (range, 0-2). A total of 833 cycles of chemotherapy was administered (median, 4 cycles; range, 1-6). Two patients (1.1%) achieved clinical complete response, 77 patients (41.4%) partial response, and 66 patients (35.5%) stable disease. Median time to disease progression was 6 months (95% CI, 5.54-6.46). Median overall survival was 14.6 months (95% CI, 11.47-17.73). One- and 2-year overall survival was 55.2% and 19.7%, respectively. The most common grade 3-4 hematological toxicities were neutropenia (n = 32, 17.2%) and anemia (n = 4, 2.2%).

Conclusions. The cisplatin plus docetaxel combination was effective and safe in the first-line treatment of patients with metastatic non-small cell lung cancer. Free full text available at www.tumorionline.it

Key words: cisplatin, docetaxel, metastatic non-small cell lung cancer.

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Introduction

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, comprising approximately 80% of cases[1,2]. Most patients present with metastatic disease, resulting in a median survival of 5-6 months, if untreated[1].

Randomized trials have reported improved survival with better quality of life using platinum-based doublets compared with best supportive care alone[3,4]. Current American Society of Clinical Oncology guidelines recommend platinum-based doublets as the standard treatment for patients with advanced NSCLC with good performance status (PS)[5]. The guidelines also recommend single-agent chemotherapy for elderly patients and those with a poor PS. However, there is no consensus on the cytotoxic

agent to combine with platinum compounds in terms of efficacy and toxicity[5].

Randomized trials using platinum in combination with new agents such as vinorelbine, gemcitabine or taxanes have shown 1-year survival rates ranging from 35-40%[6-8]. However, most of the studies failed to show a significant survival advantage with new agents compared with older combinations[9,10].

Docetaxel is a semisynthetic taxane with high activity against NSCLC[11]. Docetaxel might have greater efficacy relative to other third-generation compounds, as compared recently with vinorelbine in combination with cisplatin in the first-line therapy of advanced NSCLC[12]. We investigated the efficacy and safety profile of the combination of cisplatin plus docetaxel in the first-line treatment of metastatic NSCLC.

Patients and methods

Patients

Medical records of patients treated with cisplatin plus docetaxel combination for metastatic NSCLC between October 2004 and July 2008 were retrospectively evaluated in 7 institutions. All patients were required to have untreated metastatic histologically or cytologically proven NSCLC with measurable lesions. Disease staging was performed with clinical examination, chest radiographs, bone scan and computed tomography scans of the chest and abdomen, and cranial magnetic resonance imaging. Most of the patients had also undergone positron emission tomography scanning.

All patients had adequate bone morrow function (white blood cell count >3 × 10^9/l, platelets >100 × 10^9/l, hemoglobin >10 g/dl), liver function (total bilirubin <2 mg/dl, aspartate or alanine aminotransferase <3 × the upper limit of normal) and renal function (blood urea nitrogen <30 mg/dl, creatinine <1.5 × the upper limit of normal). Cardiac evaluations were done with electrocardiography, telecardiography and echocardiography.

Treatment

The chemotherapy schedule consisted of cisplatin (75 mg/m² as a 2-hr infusion) and docetaxel (75 mg/m² as a 1-hr intravenous infusion) every 3 weeks. Docetaxel was given before cisplatin. All patients were premedicated with methlyprednisolone, 32 mg daily for 3 days starting on day -1. Anti-emetic prophylaxis was done with 5-HT-3 antagonists and dexamethasone. Patients received at least two cycles of treatment unless disease progression or unacceptable toxicity was documented.

Response and toxicity evaluation

Responses were evaluated every two cycles during treatment according to the Response Evaluation Criteria in Solid Tumors[13]. Hematological and non-hematological toxicities were assessed every cycle and graded using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0[14].

Statistical analysis

Median time to progression (TTP) was defined as the time from start of treatment to disease progression. Overall survival was calculated as the period from the diagnosis until death from any cause or until the date of the last follow-up. Based on the intention to treat principle, data on all enrolled patients were used in statistical analysis. TTP and overall survival were calculated using the Kaplan-Meier method, and survival curves were compared with the logrank test. Differences between response rates of the subgroups were tested using Person's χ^2- test. The SPSS 12 computer program was used for analysis. *P* values of less than 0.05 were accepted as significant.

Results

Patient characteristics

One hundred and eighty-six patients treated with the cisplatin plus docetaxel regimen in the first-line therapy of metastatic NSCLC between October 2004 and July 2008 were identified. Patient characteristics are shown in Table 1. The median age was 56 years (range, 28-75). Most of the patients were males (168 males [90.3%] and 18 [9.7%] females). Median ECOG performance status was 1 (range, 0-2). Histologic tumor type was adenocarcinoma (n = 70), squamous cell carcinoma (n = 60), large cell carcinoma (n = 5) and not specified (n = 51).

Table 1 - Patient characteristics

Characteristics	Patients (n = 186)	%
Median age, yr (range)	56 (28-75)	
Sex		
Males	168	90.3
Females	18	9.7
Performance status*		
0	32	17.2
1	130	69.9
2	24	12.9
Histologic subtypes		
Adenocarcinoma	70	37.6
Squamous cell	60	32.3
Large cell	5	2.7
NSCLC, not specified	51	27.4
Metastatic sites°		
Pulmonary parenchyma	97	52.2
Bone	60	32.3
Liver	32	17.2
Brain	30	16.1
Adrenal gland	28	15
Other	3	1.6

*Eastern Cooperative Oncology Group.
°Some patients had more than 1 metastatic site.

A total of 833 cycles of chemotherapy was administered for all patients (median, 4 cycles; range, 1-6). Six patients (3.2%) received one cycle, 18 (9.7%) two cycles, 36 (19.4%) three cycles, and 126 patients (67.7%) four or more cycles of chemotherapy. Patients with brain metastases also received whole-brain radiotherapy.

Response to treatment

Two patients (1.1%) achieved clinical complete response and 77 patients (41.4%) partial response. Overall response rate (ORR) was 42.5%. Stable disease was observed in 66 patients (35.5%), whereas 41 patients (22 %) progressed. There was no significant difference in response rates when adenocarcinomas were compared with other tumor types ($P = 0.655$).

Survival characteristics

Median follow-up duration of all patients was 16 months (range, 5-42). Median TTP was 6 months (95% CI, 5.54-6.46) (Figure 1). Median overall survival was 14.6 months (95% CI, 11.47-17.73) for all patients (Figure 2). One- and 2-year survival rates were 55.2% and 19.7%, respectively. Responding patients had a longer overall survival than non-responders: 18.5 (95% CI, 17.46-19.54) *vs* 10 months (95% CI, 8.89-13.11), $P = 0.001$ (Figure 3). Moreover, patients with a good PS achieved a longer median overall survival (17, 15, and 8.6 months for PS 0, 1 and 2, respectively [$P = 0.0046$]) (Figure 4).

Toxicity

There were no treatment-related deaths. Adverse events are shown in Table 2. The most common hematologic toxicity during therapy was neutropenia. Grade 3-4 neutropenia was observed in 32 patients (17.2%). Febrile neutropenia was observed in 9 patients (4.8%). Grade 3-4 anemia was observed in 4 patients (2.2%). Other grade 3-4 non-hematologic toxicities were nausea and vomiting (n = 5, 2.7%), mucositis (n = 9, 4.8%), peripheral neuropathy (n = 4, 2.2%), and asthenia (n = 8, 4.3%). Dose reduction was performed in 10 patients with grade 4 neutropenia without fever and in 9 patients with febrile neutropenia. Chemotherapy was discontinued in 4 patients (2.2%) because of grade 3-4 neuropathy.

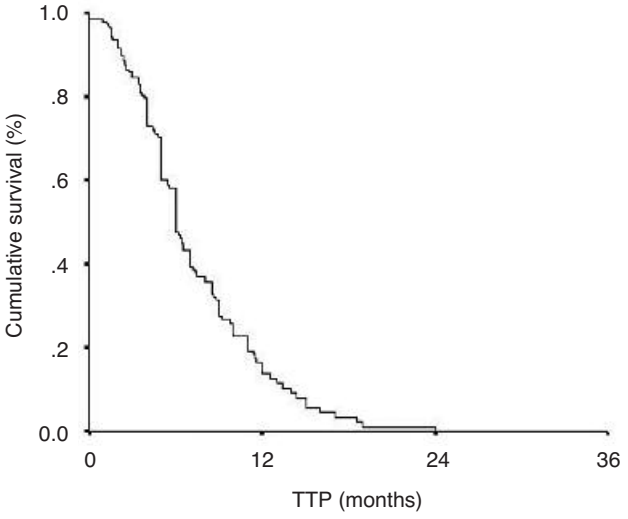

Figure 1 - Median time to disease progression for all patients.

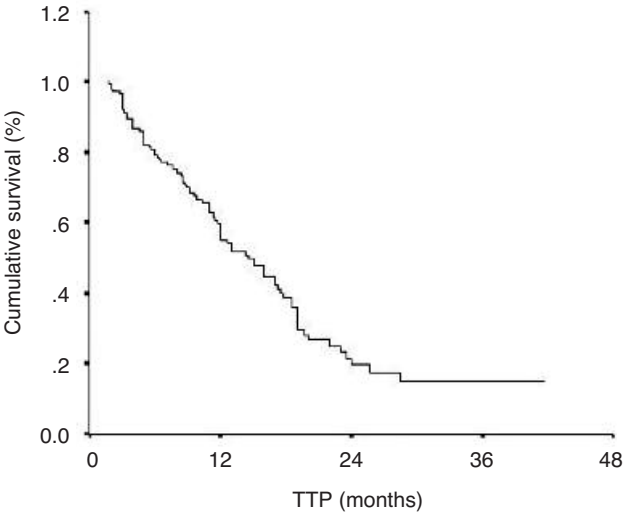

Figure 2 - Median overall survival for all patients. TTP, time to progression.

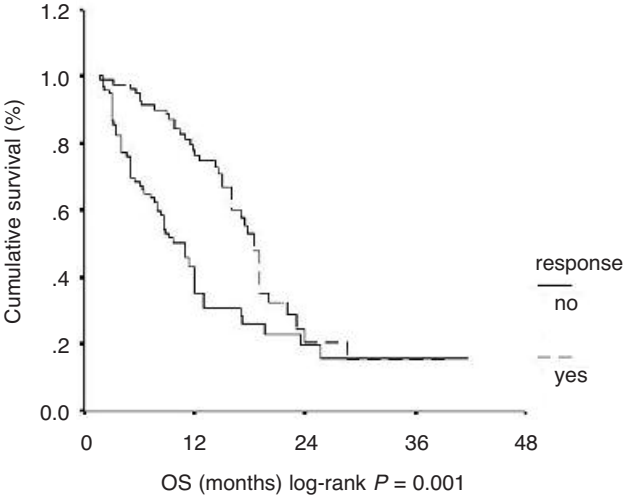

Figure 3 - Median overall survival (broken line) for responders (complete + partial response) and non-responders (solid line).

Discussion

We evaluated efficacy and tolerability of first-line treatment with a cisplatin plus docetaxel regimen in

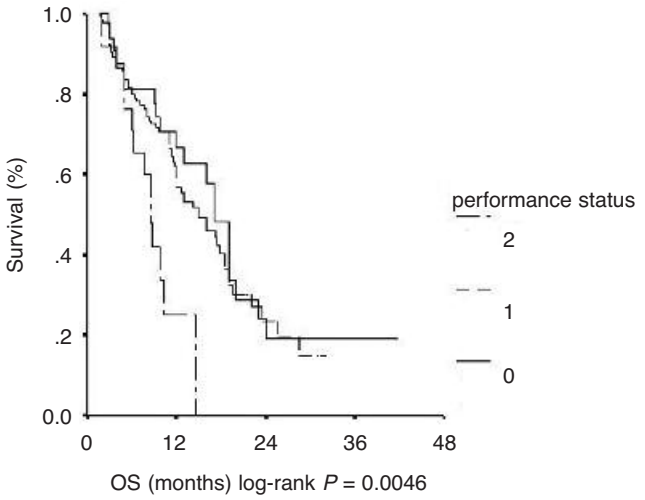

Figure 4 - Median overall survival in patients according to performance status: solid line, PS 0; broken line, PS 1; solid-hyphenated line, PS 2.

Table 2 - Treatment-related toxicity

Toxicity	All grades No. (%)	Grade 3-4 No. (%)
Hematologic		
Neutropenia	77 (41.7)	32 (17.2)*
Anemia	22 (11.8)	4 (2.2)
Thrombocytopenia	5 (2.7)	0
Non-hematologic		
Nausea-vomiting	70 (37.6)	5 (2.7)
Alopecia	34 (18.2)	5 (2.7)
Asthenia	32 (17.2)	8 (4.3)
Neuropathy	28 (15)	4 (2.2)
Mucositis	24 (12.9)	9 (4.8)
Diarrhea	14 (7.5)	3 (1.6)

*Nine patients (4.8%) had febrile neutropenia.

metastatic NSCLC patients. In our study, we achieved an ORR of 42.8% for all patients. Furthermore, there was no significant difference in response rates among NSCLC subtypes. We achieved a median TTP of 6 months and a median overall survival of 14.6 months, with a 1-year survival rate of 55.2%. Our results are in accord with similar studies published in the literature[6,12,15]. In addition, in our study, the most common hematologic toxicities were neutropenia (41.7% of all patients) and anemia (11.8% of all patients). Grade 3-4 neutropenia and anemia were observed in 32 patients (17.2%) and 4 patients (2.2%), respectively. The most common non-hematological toxicities were nausea/vomiting (37.6%), alopecia (18.2%), mucositis (12.9%), asthenia (17.2%) and peripheral neuropathy (15%). Chemotherapy was discontinued in 4 patients (2.2%) because of grade 3-4 peripheral neuropathy. The rate of grade 3-4 neutropenia was less than reported in similar studies in the literature. However, other non-hematological toxicities were similar[6,12].

Cisplatin-based chemotherapy has become the treatment of choice for metastatic NSCLC patients with a good PS, because platinum-based chemotherapy was shown to provide a survival benefit[5]. However, most of the trials used older drugs combined with platinum. New third-generation agents such as vinorelbine, gemcitabine or taxanes are currently being combined with platinum compounds.

In the ECOG trial that involved 1207 patients, four chemotherapy regimens – cisplatin plus paclitaxel, cisplatin plus gemcitabine, cisplatin plus docetaxel, and carboplatin plus paclitaxel – were compared in advanced NSCLC[6]. The ORR and median overall survival for the cisplatin plus docetaxel regimen were 17% and 7.4 months, respectively. One-year and 2-year survival rates were 31% and 11%, respectively. However, none of the combinations showed a clinical advantage over the others[6].

In contrast, in the TAX-326 trial including 1218 chemotherapy-naive patients, ORR and median overall survival were significantly superior in the cisplatin plus docetaxel arm compared to cisplatin plus vinorelbine (31.6% and 11.3 months *vs* 24.5% and 10.1 months, respectively)[12]. In another phase III study by The Japanese Taxotere Lung Cancer Study Group, the cisplatin plus docetaxel arm demonstrated improvements compared to cisplatin plus vindesine in ORR (37% *vs* 21%, $P<0.01$) and median overall survival (11.3 *vs* 9.6 months, $P = 0.014$)[15]. Two-year survival rates were also higher with cisplatin plus docetaxel (24% *vs* 12%). Grade 3 and 4 side effects were similar in all three studies[6,12,15].

In conclusion, the cisplatin plus docetaxel combination was very effective in the first-line treatment of patients with metastatic NSCLC. The treatment regimen demonstrated a tolerable side effect profile. The response rates and the outcome data are consistent with existing clinical experience in this setting. Novel agents, either alone or in combination with platinum compounds, are urgently needed for the treatment of these unfavorable prognostic patients.

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