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ORIGINAL ARTICLE

Combination therapy with docetaxel and low dose of cisplatin in elderly patients with advanced non-small cell lung cancer: multicenter phase II study

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Abstract
Purpose To determine the efficacy and safety of the combination therapy with docetaxel and cisplatin (CDDP) at low doses in elderly patients with advanced NSCLC.
Patients and methods A total of 42 patients aged ≥70 years with previously untreated advanced NSCLC received docetaxel 75 mg/m^2 plus CDDP 50 mg/m^2 on day 1. The regimen was repeated every 21 days. Patients received a minimum of three courses unless progressive disease was detected.
Results By intent-to-treat analysis, the overall response rate was 31% (95% CI, 17.8–47.2%). A total of 18 patients (43%) had stable disease and 11 (26%) progressed. Median time to progression was 5.2 months. Overall median survival was 8.9 months, with 1-year actuarial survival rate of 41%. Eastern Cooperative Oncology Group performance status was improved in 18 patients (43%). The chemotherapy regimen was well tolerated. A total of 11 patients (26%) had grade 3/4 adverse events: 7 (17%) neutropenia (one of them was diagnosed with febrile neutropenia), 3 (7%) asthenia, 3 (7%) nausea/vomiting, 1 (2%) diarrhea, 1 (2%) thrombocytopenia and 1 (2%) neurotoxicity. No death due to toxicity was seen.
Conclusion The combination of low-dose CDDP and docetaxel for elderly patients with advanced NSCLC is an efficient and well-tolerated chemotherapeutic approach.

Keywords Non-small cell lung cancer · Elderly · Docetaxel · Cisplatin · Chemotherapy

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Introduction

In Europe, lung cancer represents the leading cause of death due to cancer [1] because most patients are diagnosed at advanced stages, which lack curative therapies. In this setting, palliative chemotherapy is the mainstay of clinical management. Currently it is accepted that chemotherapy benefits NSCLC patients, extending survival by 1–3 months as compared with the best supportive care (BSC) [2], and platinum-based combination chemotherapy is now considered the standard of care [3, 4].

More than 50% of lung cancer are diagnosed in people aged 70 years or older, including 14% of cases that are diagnosed in patients older than 80 years [5]. However, treatment of elderly patients is still a challenge. Factors that influence the reluctancy to use chemotherapy in the elderly

include: the general lack of studies in this age group; the concern with the progressive reduction of functional reserve that occurs in several organs with aging, which might cause an increase in the susceptibility of elderly patients to adverse effects, particularly diarrhea, mucositis, and myelosuppression, and lead to a potential reduction in the quality of life [6]; and the comorbidity that hinders or prevents the use of chemotherapy [7]. In this regard, although some studies show that CDDP toxicity does not increase with age [8, 9], others have detected more toxicities in elderly patients when compared to treatment of their younger counterparts [10, 11]. As a result, many clinicians are still reluctant to manage elderly NSCLC patients with CDDP-based therapies.

Historically, it was thought that there was some kind of relationship between CDDP dose and the probabilities of response [12]; however, this assumption has been modified in the last decade when a randomized phase II trial failed to find differences between the two CDDP-GEM approaches (70 mg/m^2 CDDP vs. 100 mg/m^2 CDDP) though toxicity was less severe in the arm treated with low CDDP dose [13]. Furthermore, other investigators evidenced similar results for median overall survival in the neoadjuvant setting with the MIP combination (mitomycin–ifosfamide–CDDP) either with 50 or 100 mg/m^2 CDDP [14].

Based on the benefits observed in the approaches using CDDP for the treatment of NSCLC as shown by the meta-analysis above mentioned and on the efficacy in terms of overall survival evidenced by low CDDP doses, we have developed a strategy for elderly patients with advanced NSCLC. The regimen consisted of a combination of a low dose (50 mg/m^2) of CDDP and docetaxel. This dose was established according to the aforementioned studies [13, 14] with the aim of improving the potential treatment toxicities. The objective of the present phase II clinical trial was to assess feasibility, toxicity and efficacy of the combination of low-dose CDDP and docetaxel for elderly patients with advanced NSCLC.

Patients and methods

Patient population

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 with malignant pleural effusion, Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$2, age $\geq$70 years, life expectancy of at least 3 months, adequate bone marrow function (i.e., granulocyte count $\geq 2 \times 10^9$/L and platelets $>100 \times 10^9$/L), adequate liver function (i.e., serum bilirubin <1.25 times the upper normal limit, glutamic oxaloacetic transaminase values [SGOT] and glutamic pyruvic transaminases [SGPT] <3 times the upper normal limit in the absence of hepatic metastases or up to 5 times in presence of liver metastases; and adequate renal function (i.e., serum creatinine less than 150 μmo/L, or creatinine clearance of at least 60 mL/min).

All patients had measurable disease. Pleural effusion, ascites, osteoblastic lesions or previously irradiated lesions were not accepted as measurable disease. Patients who had undergone radiotherapy were eligible provided that there was at least one measurable lesion outside the radiation field and radiation treatment was completed at least 4 weeks before enrollment. Verbal and written informed consents were obtained from all patients according to the local ethics committee guidelines.

Treatment plan

Treatment consisted of docetaxel 75 mg/m^2 immediately followed by CDDP 50 mg/m^2 on day 1, repeated every 3 weeks. The infusion of docetaxel was administered over 60 min. Anti-emetic premedication with 8 mg of dexamethasone was initiated 12 h prior to each docetaxel infusion and continued every 12 h with ondansetron or granisetron. Hydration with normal saline 2 L over 4 h was given before CDDP administration.

Patients received a minimum of three courses of chemotherapy unless disease progression was detected. Patients with objective response or disease stabilization with symptom improvement received six courses.

Patients were evaluated for adverse events before each course of treatment and graded according to NCI Common Toxicity Criteria (version 2.0). For toxicity analysis, the worst data for each patient across all courses were selected. Complete blood counts were obtained before each course of chemotherapy. On the day of treatment, the total dose of both drugs was given, if neutrophil and platelet counts were at least 1.5×10^9 and 100×10^9/L, respectively. If grade $\geq$2 neutropenia or grade $\geq$1 thrombopenia were found on the day of docetaxel–CDDP administration, chemotherapy was delayed for up 2 weeks. The dose of docetaxel was reduced by 25% if grade 4 myelosuppression or febrile neutropenia was present. If there was a second episode of grade 4 myelosuppression or febrile neutropenia, an additional reduction of docetaxel and cisplatin dose was required, but if toxicity persisted 2 weeks after the scheduled time of treatment administration, chemotherapy was definitively discontinued. The dose of each drug was reduced by 25% if grade 3–4 non-hematological toxicity had occurred in the previous therapy course. If neuropathy grade 2 was observed, a 25% dose reduction of both drugs was implemented during the subsequent treatment course. The Cockcroft-Gault formula [15] was used to calculate

creatinine clearance before each course. If creatinine clearance was <60 mL/min, CDDP was discontinued. The prophylactic administration of G–CSF was not permitted. Administration of G–CSF was permitted in patients with grade 4 neutropenia and/or leucopoenia or grade 3 febrile neutropenia.

Pretreatment and follow-up evaluation

A diagnostic work-up was performed within 3 weeks prior to the treatment initiation, consisting of a complete clinical history, physical examination, blood analysis (hematology and complete biochemistry), and imaging studies as needed (chest X-ray, thorax computed tomography, ECG and bone scan). The Charlson comorbidity scale [16], patients' ECOG performance status and weight were also recorded. An ECG was performed in all patients prior to receiving study treatment. Symptom assessment, physical examination, and blood biochemistry were repeated before each treatment course. Tumor measurements were taken every three treatment courses or sooner if clinically indicated.

Patients were evaluated clinically at least every 3 weeks and radiographically every 9 weeks. The same evaluation modality was used throughout the study. RECIST response guidelines were used [17], defining all responses after 9 weeks of therapy at least as follows: complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Confirmation of all responses was required after 4 weeks. Time to progression (TTP) was estimated from the dates of the first course of treatment to the first documentation of disease progression. Survival (OS) was calculated by the same method from the date of the first course of treatment until the date of death or last known follow-up.

Symptoms assessment

ECOG performance status and symptom assessment were performed prior to each course of chemotherapy by the same physician for each patient. The targeted symptoms were cough, dyspnea, hemoptysis, anorexia, and pain. They were rated with a 0–4 rating scale based on Hollen scale [18] modified by Gridelli [19]. This scale has been validated and previously evaluated by ourselves [20] and other authors [21]. The best subjective outcome for each patient was recorded.

Symptom improvement was considered when: (1) there was an improvement in the ECOG performance status in at least one score from baseline; and (2) there was an improvement in at least one score from baseline in disease-related symptoms (i.e., dyspnea, cough, hemoptysis, anorexia, and pain). Improvement had to be sustained for at least 4 weeks.

Statistical methods

The primary endpoint of the trial was to determine the activity of the docetaxel–CDDP regimen in the intent-to-treat population. Secondary objectives were the safety profile, symptom improvement, TTP, and overall survival. Dose intensity was calculated for each patient from the total dose of docetaxel and CDDP administered during the entire course of treatment and expressed as the mean drug dose in mg/m^2/week.

The sample size was designed to reject a response rate of less than 20%. According to the Fleming method [22], 19 patients were first included. As the response rate was greater than 21%, up to 35 patients were included plus a 10% to allow for those who could not be evaluated, which gives 38 patients. Wilcoxon's signed-rank test (to compare quantitative variables) and Fisher's exact test (to compare percentages) were used. Overall survival and TTP were calculated using the Kaplan–Meier method. Survival differences between subgroups were compared by a two-sided log rank test.

Results

Between January 2004 and October 2005, 42 consecutive patients with NSCLC and aged ≥70 years were enrolled in this study. Patients' characteristics are shown in Table 1. The median age of the series was 75 years (range 70–80). There were 20 patients (48%) aged ≥75 years. Of all the patients, 37 were male (88%) and five were female (12%). Stage IV disease was present in 84% of patients; seven patients (16%) presented with stage IIIb disease; 69% of patients had an ECOG performance status of 1; 50% had squamous cell carcinoma; 23 patients (79%) had comorbid conditions, mainly obstructive lung disease (69%), diabetes (17%), hypertension (17%), peptic ulcer disease (14%), and coronary failure (12%). Comorbidity was present in 74% of patients as assessed by Charlson′s scale [16]. According to this scale, 17 patients (41%) scored 1, 11 (26%) scored 2 and 3 (7%) patients equal or higher than 3.

A total of 166 courses of chemotherapy were given with a median of 4 per patient (range 1–6). Nine patients received less than three courses (one due to patient's refusal, six due to disease progression, one due to a decrease in their PS, and one due to death caused by massive hemoptysis). All patients were eligible for toxicity and response analyses; 12 patients required treatment delay due to neutropenia. The median dose intensity of docetaxel was 23.8 mg/m^2/week, which corresponded to 85% of the predicted dose intensity. The median dose intensity of CDDP was 15.8 mg/m^2/week, which corresponded to 90% of the

Table 1 Patient characteristics ($N = 42$)

	No. of patients (%)
Sex	
Male	37 (88%)
Female	5 (12%)
Median age (range)	75 (70–80)
≥75 años	20 (48%)
70–74 años	22 (52%)
Stage	
IIIB	7 (16%)
IV	37 (84%)
ECOG performance status	
0	6 (14%)
1	29 (69%)
2	7 (17%)
Weight loss	
None	11 (26%)
0–10%	24 (57%)
>10%	7 (17%)
Histology	
Squamous cell	21 (50%)
Adenocarcinoma	14 (33%)
Large cell	7 (17%)
Symptoms at baseline	
Cough	22 (52%)
Dyspnea	21 (50%)
Pain	14 (33%)
Hemoptysis	5 (12%)
Anorexia	14 (33%)
Comorbidity Charlson scale	
0	11 (26%)
1	17 (41%)
2	11 (26%)
≥3	3 (7%)

predicted dose intensity; 36 patients (86%) received at least 90% of the scheduled doses.

Partial response (PR) was achieved in 13/42 (31%) patients, (95% CI: 17.8–47.2%). Out of 42 (43%) patients, 18 remained with stable disease and 11/42 patients (26%) had disease progression. Median time to progression was 5.2 months. Median survival was 8.9 months, whereas actuarial 1-year survival was 41% (95% CI: 25.9–56.8%). No relationship between response rate or median survival and baseline performance status (measured by ECOG scale), stage (IIIB or IV), Charlson scale or age (70–75 years vs. >75 years) was observed.

All patients were evaluable for symptoms or ECOG score response. A total of 36 patients had ECOG performance status ≥1, and 24 (57%) had symptoms at entry (Table 1). Dyspnea was improved in 16 patients (38%), cough in 20 (48%), hemoptysis in 3 (7%), anorexia in 8 (19%), and pain in 8 (19%). A body weight gain >5% was reported in 5 (12%) patients (Table 2). Concerning ECOG performance status, an improvement was observed in 18 (43%) patients, whereas 16 (38%) patients remained stable and 8 (19%) worsened. An improvement in ECOG score was presented by 22 patients (52%; 95% CI: 36.4–70.3) and/or at least one symptom without worsening in other symptoms or ECOG score. The median duration of this improvement was 3.2 months (95% CI: 1–9 months).

Treatment was generally well tolerated. Twenty-six patients (62%) had an adverse event, usually of grade 1/2. The main adverse events were gastrointestinal and hematological (Table 3). No death due to drug toxicity was seen. Eleven patients (26%) had grade 3/4 adverse events: 7 (17%) neutropenia (one of them was diagnosed with febrile neutropenia), 3 (7%) asthenia, 3 (7%) nausea/vomiting, 1 (2%) diarrhea, 1 (2%) thrombocytopenia and 1 (2%) neurotoxicity. Nine patients (21%) received G–CSF. Renal toxicity was relatively mild: grade 2 renal toxicity was observed in three (7%) patients. Toxicity was found to be unrelated to age, status performance or comorbidity.

Discussion

The aim of this phase II study was to analyze the efficacy and safety of the combination therapy with docetaxel and low dose of cisplatin in elderly patients with advanced NSCLC. Our results, with a 31% of response rate, a median TTP of 5.2 months and a median survival of 8.9 months, are similar to those obtained by other authors with a docetaxel–cisplatin combination regimen in a non-geriatric population [23–25], showing in addition an acceptable toxicity profile.

Table 2 Effect of treatment on performance status and symptoms

Variable	Improvement no. (%)	No change no. (%)	Worsering no. (%)
ECOG performance status	18 (43)	16 (38)	8 (19)
Dyspnea[a]	16 (38)	21 (50)	5 (12)
Pain[a]	8 (19)	33 (79)	1 (2)
Cough[a]	20 (48)	20 (48)	2 (5)
Hemoptysis[a]	3 (7)	37 (88)	2 (5)
Anorexia[a]	8 (19)	29 (69)	5 (12)
Weight loss[b]	5 (12)	33 (79)	4 (9)

[a] Improvement in ≥1 items (rated by a 0–4 scale)

[b] Weight gain >5%

Table 3 Treatment toxicities per patient

WHO toxicity	1–2 No. (%)	3–4 No. (%)
Anemia	21 (50)	
Neutropenia	5 (12)	7 (17)
Thrombopenia	3 (7)	
Nausea/vomiting	15 (36)	2 (6)
Peripheral neurotoxicity	5 (12)	
Asthenia	9 (21)	3 (7)
Nephrotoxicity	3 (7)	1 (2)
Alopecia	11 (26)	
Fever	5 (12)	
Diarrhea	5 (12)	1 (2)

However, absence of phase III trials demand caution when comparing data from several trials because differences among populations may explain disparate results. So, a control group in our trial would be of interest to correctly explain both ECOG and symptoms improvement during treatment.

Although prospective studies designed to assess the response to chemotherapy in elderly patient endorse the hypothesis that all patients regardless of age can benefit from treatment, to establish the most suitable regimen in this population is still a controversial issue. Single-agent chemotherapy is one of the most common therapeutic approaches for elderly patients with advanced NSCLC [26], and vindesine, vinorelbine, paclitaxel, docetaxel, gemcitabine and erlotinib are some of the drugs that have been tested for monotherapy strategies in this age group. The reported response rates range from 10 to 38% [19, 27–30]. Vinorelbine demonstrated to be superior to BSC in a randomized phase III trial (median survival 28 vs. 21 weeks) [31]. Recently, single-agent docetaxel produced superior survival when compared with single-agent vinorelbine in both a randomized trial (14.3 vs. 9.9 months; $P = 0.06$) [27] and a randomized phase II trial [32]. While this therapeutic strategy has the advantage of a low toxicity profile, a recently published meta-analysis has shown the superiority of the double combination chemotherapy over a single-agent regimen not only in terms of tumor response ($P < 0.0001$) but also in terms of 1-year survival ($P < 0.001$) in patients of any age with advanced NSCLC [33]. However, the benefits of the combination therapy in elderly patients with advanced NSCLC are still a controversial issue. At the moment, the results of two large phase III randomized trials have been reported [19, 27]. In one of them, the combination of gemcitabine–vinorelbine was no more effective than either agent used alone [19]. In the second clinical trial, the combination of docetaxel–gemcitabine had no impact on survival when compared with docetaxel alone [34]. Therefore, the benefit of non-platinum doublets in this population has not been substantiated.

The CDDP-based combinations have been traditionally considered the most active approaches for NSCLC [35]. Nevertheless, it is necessary to take into account that no prospective phase III study has explored the reproducibility of this benefit in elderly patients. Several retrospective studies have evaluated the clinical outcome and the toxicity of different CDDP-based multiple drug approaches for elderly patients with NSCLC. Response rates ranged from 20 to 40%, with no evidence of increased renal toxicity [8, 10, 11, 36–38]. However, an increase in other toxicities, such as myelosuppression [10, 36], neuropsychiatric toxicity [10], asthenia, infection, pain, and neurologic and pulmonary toxicities [11], was observed in elderly patients treated with CDDP containing regimens. Additionally, several authors have shown that the early death rate (within 30 days after the beginning of chemotherapy) in patients >70 years of age was 12.5%, in comparison with 0.5% in patients <54 years. These deaths were attributed to chemotherapy-induced toxicity, particularly to myelosuppression [39]. Based on these data and on the lack of evidence of a clear-cut dose–response relationship for CDDP, we considered that the dose of 50 mg/m^2 of cisplatin could improve the tolerability of this drug without decreasing its efficacy. The toxicity observed with our therapeutic regimen, including hematologic toxicity, was limited. Globally, 26% of patients experienced grade 3/4 adverse events. It is important to emphasize that only one (2.4%) case of febrile neutropenia was reported. On the other side, the results reported by other investigators who evaluated a group of 148 patients aged ≥65 years old that received cisplatin 75 mg/m^2 in combination with docetaxel 75 mg/m^2 evidenced a 53% of grade 3/4 toxicities and 8% of febrile neutropenia [11]. The low rate of neurotoxicity in our series can probably be attributed to the lower dose of CDDP and the reduced number of treatment courses received by our patients compared to other series (median of four courses per patient).

In our study, a 3-weekly CDDP–docetaxel regimen was administered to reduce the incidence of treatment-associated neutropenia and fever. However, other investigators have evaluated the use of weekly regimens with low doses of docetaxel in combination with CDDP [40]. However, a recent randomized phase II study comparing the administration of a 3-weekly CDDP–docetaxel regimen versus a weekly CDDP–docetaxel regimen showed that the treatment administered on a weekly schedule had no clear advantage over the standard 3-weekly regimen [41]. In addition, in a weekly regimen patients expend more time at the hospital, which may be a relevant issue for elderly patients who require the assistance of a family member or a social care giver to get to hospital.

In summary, the results of our study suggest that the combination therapy with docetaxel and low dose of CDDP is a good therapeutic option for elderly patients with low severe comorbidity. Thereby, this approach represents an attractive option for the treatment of elderly patients with adequate renal function. We consider that these results should be evaluated in a phase III trial.

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