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ORIGINAL ARTICLE

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Combination of low-dose cisplatin and gemcitabine for treatment of elderly patients with advanced non-small-cell lung cancer

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Abstract *Purpose*: To evaluate the feasibility, toxicity and efficacy of the combination of low-dose cisplatin (CDDP) and gemcitabine (GEM) in elderly patients with advanced non-small-cell lung cancer (NSCLC). *Patients and methods*: This phase II trial included 46 patients aged 70 years or older with previously untreated advanced NSCLC. All patients were evaluable for response and toxicity. Treatment consisted of CDDP 50 mg/m^2 on day 1 plus GEM 1000 mg/m^2 on days 1 and 8. The regimen was repeated every 21 days. Patients received a minimum of three courses unless progressive disease was detected. *Results*: A total of 190 GEM-CDDP courses were administered (median 4.1 courses per patient). The chemotherapy regimen was well tolerated. No patients developed grade 4 toxicity. Grade 3 toxicities were as follows: neutropenia in six patients (13%), and anemia, thrombopenia and nausea/vomiting in one (2%) each. Two patients (4%) had mild nephrotoxicity. Of the 46 patients, 16 had a partial response (35%, 95% confidence interval, CI, 28–52%), 17 (37%) remained stable and 13 (28%) had disease progression. Eastern Cooperative Oncology Group performance status improved in 17 patients (37%), whereas 25 (54%, 95% CI 44–74%) showed a clinical benefit. Median time to progression was 20 weeks. Overall median survival was 44 weeks, with a 1-year actuarial survival rate of 35%. *Conclusions*: The combination of low-dose CDDP and GEM for elderly patients with advanced NSCLC is an effective and well-tolerated chemotherapeutic approach.

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

This work is presented on behalf of the Oncopaz Cooperative Group.

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Introduction

Lung cancer is the most common malignancy in men, and ranks third in women in developed countries. More than 60% of patients are 65 years of age or older at diagnosis [42, 44], and approximately 30–40% of patients are older than 70 years [28].

Despite the burden of lung cancer, treatment in the elderly remains a challenge. Several studies have shown that the proportion of patients with lung cancer who are operated on decreases with age (85% of patients under 65 years vs 70% of patients older than 65 years) [9]. Furthermore, as far as chemotherapy is concerned, it has been reported that only 20% of elderly patients with advanced lung cancer ever receive cytotoxic therapy [10]. A number of factors may account for the reluctance to use chemotherapy in the elderly: (1) the limited number of studies addressing the efficacy and toxicity of chemotherapy in this age group [20]; (2) concern that elderly patients may be more susceptible to adverse effects from chemotherapy, which would have a negative impact on their quality of life [1, 20]; and (3) comorbidity that may complicate or even preclude chemotherapy [24].

However, it is currently accepted that chemotherapy in patients with non-small-cell lung cancer (NSCLC) results in a benefit in survival, extending survival by 1–3 months as compared with the best supportive care [39]. Thus, a meta-analysis of randomized trials has shown that patients treated with chemotherapy based on cisplatin (CDDP) have an increase in median survival of about 6 weeks and a 10% improvement in 1-year sur-

vival as compared to those managed with supportive care [34]. Although these studies have not specifically focused on elderly patients, the benefits might be extrapolated to this age group [11].

In the last few years, therapeutic approaches specifically developed for elderly patients with NSCLC have aroused clinicians' interest. Most of these regimens rely on a single drug approach [22, 38, 40] or combinations of new drugs such as gemcitabine (GEM) and vinorelbine (VNB) [13, 16]. Despite the results from the above meta-analysis and the evidence from numerous studies showing that CDDP toxicity does not increase with age [8, 25, 30, 41], many clinicians remain reluctant to manage elderly patients with NSCLC with CDDP-based approaches.

Classically, it was thought that there was a certain relationship between CDDP dose and the likelihood of response [18]; however, this assumption has been challenged in recent years. Thus, a randomized phase II trial comparing two CDDP-GEM approaches (70 mg/m^2 CDDP vs 100 mg/m^2 CDDP) failed to find differences in response rate, although toxicity was less severe in the arm treated with 70 mg/m^2 CDDP [36]. Also, others have undertaken a trial with the MIP combination (mitomycin-ifosfamide-CDDP) as a neoadjuvant therapy for patients with IIIA NSCLC. The authors randomly assigned patients to receive MIP with either 50 mg/m^2 CDDP or 100 mg/m^2 CDDP, and, while they did find a significantly greater response rate in patients treated with 100 mg/m^2 CDDP (59% vs 30%, $P = 0.01$), they found no significant differences in the resection rate or median survival [12].

Based on the benefits from the approaches using CDDP for NSCLC treatment shown by the above meta-analysis and the lack of evidence of a clear-cut dose-response relationship for CDDP, we developed a strategy for elderly patients with advanced NSCLC. The regimen consisted of a combination of low-dose CDDP (50 mg/m^2) and GEM. This dose was established according to the findings of the above-mentioned studies [12, 36] aiming to ameliorate potential treatment toxicities. The purpose of the present phase II clinical trial was to assess feasibility, toxicity and efficacy of the combination of low-dose CDDP and GEM in elderly patients with advanced NSCLC.

Patients and methods

From January 1999 to May 2001, 46 patients with histologically or cytologically proven NSCLC and stage IIIB or IV disease according to the staging system proposed by Mountain [32] were included. All patients had measurable disease. Pleural effusion, ascites, osteoblastic lesions or previously irradiated lesions were not accepted as measurable disease.

Eligible patients were to meet the following inclusion criteria: (1) age 70 years or older; (2) performance status ≤ 2 according to the Eastern Cooperative Oncology Group (ECOG) scale; (3) life expectancy of at least 3 months; (4) adequate bone marrow function (i.e. granulocyte count 2×10^9/l and platelets $>100\times10^9$/l); (5) adequate liver function (i.e. serum bilirubin less than 1.25 times the upper normal limit, SGOT and SGPT less than three times the upper normal limits in the absence of hepatic metastases); and (6) adequate renal function (i.e. serum creatinine less than 150 μmol/l, or creatinine clearance of at least 60 ml/min). 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. Oral and written informed consents were obtained from all patients according to the local ethics committee guidelines.

Treatment consisted of 50 mg/m^2 CDDP on day 1. Hydration with 2 l normal saline over 4 h was given before CDDP administration. GEM was administered i.v. over 30 min at a dose of 1000 mg/m^2 on days 1 and 8. This regimen was repeated every 21 days for a minimum of three courses per patient unless disease progression was detected. Patients with objective response or disease stabilization with symptom improvement continued to be treated until the occurrence of disease progression or unacceptable toxicity with a maximum of six courses. Patients with stable disease and no symptom improvement received six courses. All patients received antiemetic prophylaxis with ondansetron or granisetron plus dexamethasone.

Patients with stage IIIb disease and with no pleural effusion were re-evaluated after the third course of chemotherapy and before they received chest radiotherapy at a dose of 60 Gy. Complete blood counts were obtained before each course of chemotherapy. Full doses of the drugs were given if neutrophil and platelet counts on the day of treatment were at least 1.5×10^9/l and 100×10^9/l, respectively. If WHO grade 2 or worse neutropenia or grade 1 or worse thrombopenia were found on the day of CDDP-GEM administration, chemotherapy was delayed for 1 week. If grade 2 neutropenia or grade 1 thrombopenia still persisted 1 week later, CDDP and GEM doses were reduced by 25%, but if a greater degree of toxicity persisted for 2 weeks after the scheduled time of recycling, chemotherapy was definitively discontinued. The GEM dose was reduced by 25% in the case of grade 2 neutropenia or grade 1 thrombopenia on day 8. The dose of each drug was reduced by 50% for the next cycles if grade 4 neutropenia/thrombopenia or grade 3/4 nonhematologic toxicity occurred.

The Cockcroft-Gault formula [5] was used to calculate creatinine clearance before each course. If creatinine clearance was <60 ml/min, cisplatin was discontinued.

Toxicity for each course was recorded and graded according to WHO scales [25]. For toxicity analysis, the worst data for each patient across all courses were used. Response was evaluated using WHO guidelines [43]. A complete response required the total disappearance of all tumors initially observed on two occasions not less than 4 weeks apart, with no evidence of new areas of malignant disease. A partial response was defined as a reduction of at least 50% in the sum of the products of the longest perpendicular diameters of all clearly measurable tumor masses on two occasions not less than 4 weeks apart, with no increase in the size of any lesion and no evidence of new lesions. Stable disease was defined as a decrease in total tumor size of less than 50% or an increase of less than 25% in any measurable lesion. Disease progression was defined as a 25% increase in the size of any lesion, the appearance of new areas of malignant disease or performance status deterioration by more than one level. Time to tumor progression was estimated by the product limit estimation method from the date of the first course to the first evidence of disease progression. Survival was calculated by the same method from the date of the first course until the date of death or last follow-up visit.

ECOG performance status and symptom assessment was 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 on a 0–4 rating scale based on the scale described by Hollen et al. [23] as modified by Gridelli et al. [21]. This scale has been validated and has been previously proven by us [13] and others [16]. The best subjective outcome for each patient was recorded. Symptom improvement was considered when: (1) there was an improvement in the ECOG performance status by at least one score from baseline; and (2) there was an improvement by 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. Clinical benefit was defined as: (1) ECOG performance status improvement without worsening of symptoms; or (2) symptom improvement without worsening of ECOG performance status. An evaluation of comorbidities was made before starting chemotherapy, and a score was calculated for each patient using the scale of Charlson et al. [4]. This score was calculated excluding the malignant disease category.

The primary endpoint was the response rate. The sample size was designed to reject a response rate of less than 20%. According to the method of Fleming [15], 19 patients were first included. As the response rate was over 21%, up to 35 patients were included plus 10% to allow for inevaluable patients, giving 38 patients. The Wilcoxon rank-sum method was used to compare quantitative variables, Fisher's exact test for percentages, and the Kaplan-Meier method for survival and duration of response. Disease progression-free survival was measured from chemotherapy initiation to the date on which disease progression or death without progression occurred.

Results

A total of 46 patients with advanced NSCLC and aged 70 years or older were entered. The patient characteristics are shown in Table 1. The median age of the patient group was 74 years (range 70–81 years). There were 18 patients (39%) aged 75 years or older, and 42 patients were male (91%) and 4 were female (9%). Stage IV disease was present in 57% of patients. Stage IIIb disease was present in 20 patients (43%), of whom 8 had malignant pleural effusion, and 12 had T4 disease or contralateral mediastinal node involvement. Of the 46 patients, 30 (65%) had an ECOG performance status of 1, 22 (48%) had squamous cell carcinoma, 34 (74%) showed body weight loss at diagnosis (in 45% the loss was more than 5% of their usual body weight), and 38 (83%) had comorbid conditions, mainly obstructive lung disease (48%), diabetes (22%), hypertension (17%), peptic ulcer disease (11%), and coronary failure (11%). Comorbidity was present in 74% of patients as assessed by the scale of Charlson et al. [4]. On this scale, 21 patients (45%) scored one, 8 (17%) scored two, and 5 (11%) scored three or higher.

Table 1 Patient characteristics ($N = 46$)

	No. of patients (%)
Sex	
Male	42 (91%)
Female	4 (9%)
Age (years)	
≥75	18 (39%)
70–74	28 (61%)
Median	74
Range	70–81
Stage	
IIIB	20 (43%)
IV	26 (57%)
ECOG performance status	
1	30 (65%)
2	16 (35%)
Weight loss	
None	12 (26%)
0–10%	20 (43%)
>10%	14 (31%)
Histology	
Squamous cell	22 (48%)
Adenocarcinoma	11 (24%)
Large cell	13 (28%)
Symptoms present at entry	
Cough	26 (56%)
Dyspnea	25 (54%)
Pain	22 (48%)
Hemoptysis	6 (13%)
Anorexia	13 (28%)
Comorbidity (Charlson scale)	
0	12 (26%)
1	21 (45%)
2	8 (17%)
≥3	5 (11%)

A total of 190 courses of chemotherapy were given with a median of 4.1 per patient (range 1–6). Four patients received fewer than three courses (one patient refusal and three disease progression). All patients were considered analyzable for toxicity and response. Five patients required treatment delay due to neutropenia. The median dose intensities were 15.3 and 634 mg/m^2 per week for CDDP and GEM, respectively. Of the 46 patients, 40 (87%) received at least 90% of the scheduled doses.

Out of the 46 patients, a partial response was achieved in 16 (35%, 95% CI 28–52%), 17 (37%) remained with stable disease, and 13 (28%) had disease progression. Median time to progression was 20 weeks. Median survival was 44 weeks, and actuarial 1-year survival was 35%. No relationships between response rate or median survival and ECOG performance status, disease stage (IIIB with or without pleural effusion, or stage IV), Charlson scale or age (70–75 years vs >75 years) were noted.

All patients met the criteria for assessment of palliative benefit. All the included patients had an ECOG performance status of ≥1, and 36 (78%) had symptoms at entry (Table 2). Dyspnea was improved in 17 patients (37%), cough in 12 (26%), hemoptysis in 6 (13%), anorexia in 13 (28%), and pain in 13 (28%). A body weight gain of >5% occurred in 11 patients (23%). Concerning ECOG performance status, 17 patients (37%) improved, whereas 23 (50%) remained stable, and 6 (13%) worsened. Overall, 25 patients (54%, 95% CI 44–74%) had clinical benefit.

All 46 patients were evaluable for toxicity (Table 3). The chemotherapy regimen was well tolerated, and its chief side effects were hematologic in nature. No toxic deaths were seen. No patient developed grade 4 toxicity. Grade 3 toxicities were neutropenia in six (13%), and anemia, thrombopenia and nausea/vomiting in one (2%) each. Grade 1/2 toxicities were nausea/vomiting in 39% of patients, neutropenia in 24%, anemia in 9%, neurotoxicity in 13%, asthenia in 7%, and transitorily increased transaminases in 7%. Three patients (7%) had mild a 'flu-like syndrome consisting of myalgia,

Table 2 Effect of treatment on performance status and symptoms

Variable	Improvement		No change		Worsening	
	No.	%	No.	%	No.	%
ECOG performance status[a]	17	37	23	50	6	13
Dyspnea[a]	17	37	21	46	8	17
Pain[a]	13	28	31	68	2	4
Cough[a]	12	26	28	60	6	13
Hemoptysis[a]	6	13	32	70	1	2
Anorexia[a]	13	28	23	50	10	22
Weight loss[b]	11	23	23	50	12	27

[a]Improvement in by one score or more scores
[b]Weight increase change > 5%

Table 3 Treatment toxicities per patient (WHO grade)

Toxicity	Grade 1/2		Grade 3/4	
	No.	%	No.	%
Nausea/vomiting	18	39	1	2
Anemia	4	9	1	2
Leukocytes	12	26	6	13
Platelets	2	4	1	2
Peripheral neurotoxicity	6	13		
Asthenia	3	7		
Elevated transaminases	3	7		
Nephrotoxicity	2	4		
Alopecia	4	9		

arthralgia and fever. Two patients (4%) had mild nephrotoxicity. Baseline creatinine levels at chemotherapy initiation were not significantly different from those at chemotherapy completion in any patient (0.92 ± 0.18 vs 0.98 ± 0.28 μmol/l). There were no differences between pretreatment and posttreatment creatinine clearance either (78 ± 14.7 vs 73 ± 15.1 ml/min). Toxicity was found to be unrelated to age, performance status or comorbidity. Five patients (11%) required administration of erythropoietin, one patient required blood transfusions (2%), and six patients G-CSF (13%). No patients required antibiotics or platelet transfusion.

Discussion

Over recent years, the need to include elderly patients in clinical trials has been stressed. However, there is still very little clinical experience in this area, and, as a consequence, little data on the efficacy and toxicity of cytotoxic agents in this population are available. Therefore, the clinician often has to make decisions as to treatment for elderly patients on an empiric basis or in accordance with results from retrospective studies with selected samples of elderly patients. However, results from these studies are difficult to generalize to other populations of elderly people with cancer.

Single-drug approaches are frequently advocated for elderly patients with NSCLC [17], with vindesine, VNB, paclitaxel, docetaxel and GEM being some of the drugs tested for monotherapy strategies in this age group. Response rates reportedly range from 10% to 23% [14, 22, 31, 38, 40]. Single-drug approaches are supported by the results of a phase III trial showing that VNB yields a modest, though significant, prolongation of survival in elderly patients with NSCLC as compared to supportive therapy [40]. However, the role of combination chemotherapy in the elderly for advanced NSCLC remains controversial. Thus far, the results of two phase III randomized trials have been reported [16, 19]. In one of them, the combination GEM-VNB was compared to VNB alone. After the enrollment of 60 patients in each arm it was noted that GEM-VNB was more effective than VNB in prolonging survival of elderly patients with NSCLC (mean survival 29 vs 18 weeks, $P < 0.01$). These findings led to early termination of the study [16]. In the other trial, the administration of GEM-VNB was compared to VNB alone and GEM alone. Over 200 patients were included in each arm, and no differences were found in the overall response rates (18.5%, 17.5% and 20%, respectively) or in median survival (8.8, 6.6 and 7.6 months, respectively) [19].

Although CDDP-based combinations have been traditionally considered as being the most active approach for NSCLC, in our review of the medical literature in this field we have found only one prospective trial of CDDP in the elderly [29]. It was a pilot study testing weekly GEM and CDDP in 15 elderly patients with NSCLC. The response rate was 40%, but at the expense of significant toxicity, with grade 3/4 thrombopenia seen in 40% of patients. Nonetheless, nephrotoxicity was not seen [29]. The scarcity of studies on CDDP in the treatment of the elderly no doubt results form clinicians' concern over the nephrotoxic potential of CDDP. While it is known that there is a 30% loss of nephrons and decreased kidney clearance with age, one cannot conclude, based on the few clinical data published, that CDDP-induced renal toxicity is higher in elderly patients [8, 30, 41]. The clinical outcome and toxicity of different CDDP-based multiple drug approaches in elderly patients with NSCLC have been addressed in some retrospective studies. Response rates ranged from 20% to 40%, with no evidence of increased renal toxicity [2, 7, 26, 27, 33, 35]. However, in one of these studies patients ≥70 years of age treated with combinations including CDDP and mitomycin showed significantly higher myelosuppression as compared to younger patients [26]. Similar results have been shown in a recent study in which higher rates of leukopenia and neuropsychiatric toxicity were seen in patients aged ≥70 years [27]. In another study, a trend toward more

grade 3–5 toxicity in patients aged ≥70 years was found (94% vs 88%, $P = 0.06$) [25]. Moreover, in another study the rate of early death (before 30 days of chemotherapy initiation) in patients >70 years of age was 12.5%, this rate being significantly higher than that in patients <54 years (0.5%). These deaths were attributed to chemotherapy-induced toxicity, particularly to myelosuppression [35].

The most remarkable findings in our study were the 35% response rate, 54% clinical benefit, median survival of 44 weeks and 1-year survival rate of 35%, suggesting that the combination of low-dose CDDP and GEM is an effective approach for advanced NSCLC. Although comparing these results with those from previous trials using a combination of GEM and CDDP at the usual dose (75–100 mg/m^2) is difficult, they do not suggest a reduction in efficacy when CDDP is administered at a dose of 50 mg/m^2 [3, 6, 37]. On the other hand, our chemotherapy regimen was well tolerated: there was no grade 4 toxicity and only 13% of patients had grade 3 neutropenia, 2% grade 3 thrombopenia and 2% grade 3 nausea and vomiting. In addition, we did not note any worsening in renal function. This is in sharp contrast to other studies with CDDP-based approaches at higher doses that resulted in greater hematologic toxicity and a higher rate of grade 3/4 nausea and vomiting [6, 26, 27, 33]. The retrospective study by Nguyen et al. [33] deserves special consideration. In this study of the combination CDDP-GEM (100 mg/m^2), in patients aged ≥70 years the rate of grade 3/4 neutropenia was 66%, grade 3/4 thrombopenia was 55%, and grade 3/4 vomiting was 26%.

On the basis of our results we conclude that chemotherapy is beneficial in elderly patients with advanced NSCLC in terms of survival prolongation and symptom relief. Therefore, we believe this option should be offered to these individuals. In addition, in making a choice of the most adequate chemotherapy combination, CDDP-based combinations should not be rejected based only on age-related concerns. The approach we used consisting of low-dose CDDP and GEM was both effective and well tolerated and it was able to relieve symptoms and prolong survival. This approach therefore represents an attractive option for the treatment of elderly patients with adequate renal function. We think that this regimen could be compared with GEM alone.

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