Weekly paclitaxel for advanced non-small cell lung cancer patients not suitable for platinum-based therapy

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Platinum-based combinations are efficacious in the treatment of advanced non-small cell lung cancer (NSCLC) but their toxicity makes them unsuitable for elderly and for patients with co-morbidities. We assessed the efficacy and toxicity of low-dose of paclitaxel in patients who were elderly or who had contraindications against cisplatin therapy.

Seventy-one patients (median age 68; range 42–82 years) with unresectable NSCLC were treated with weekly paclitaxel (80 mg/m^2) infusion (1 h) for several cycles without intervening rest periods. Thirty-seven patients had PS 1 and 34 had PS 2 status.

A total of 614 courses were administered (median 9, range 2–20). There were no episodes of grade 4 toxicities and only 1 patient had grade 3 thrombopenia. Grade 3 anemia or neutropenia were not observed and severe non-hematological toxicity was uncommon: grade 1–2 fatigue in 52%; grade 1–2 motor neuropathy in 42% and grade 3 in 5.5%; grade 1–2 sensory neuropathy in 46.3% of patients. Twenty-seven of the 67 evaluable patients (40.3%) had an objective response, whereas 26 patients (38.8%) had stable disease. The median overall survival for the entire group was 8.4 months (95% CI = 5.6 to 11.2) and the 1-year and 2-year survival was 37.4% and 12.1%, respectively. The median time-to-progression was 5.4 months (95% CI = 3.3 to 7.4).

Our data show that low-dose weekly paclitaxel is active and well tolerated in this group of patients with NSCLC and poor prognosis and, as such, is useful for patients in whom platinum-based combinations are not suitable.

Key words: Weekly paclitaxel, non-small cell lung cancer, co-morbidities, non-cisplatin therapy, second-line therapy.

Lung cancer is the leading cause of cancer deaths, worldwide. More than 50% of lung cancer patients are diagnosed over the age of 65 years, and 30% over the age of 70 years [8]. Histologically-demonstrable non-small-cell lung cancer (NSCLC) accounts for 75 to 80% of these lung cancer cases. Several recent meta-analyses indicate that median survival was improved in patients treated with combination chemotherapy that included a platinum agent as compared to patients treated with best supportive care alone [17, 18, 27]. However, elderly patients tolerate chemotherapy poorly because of co-morbidities and poor functional status, and, hence, these patients are excluded from clinical trials.

Very few clinical studies with platinum-based chemotherapy have been conducted in elderly NSCLC patients and toxicity has been the most relevant outcome in all reports to-date. Hence, the advent of new active agents such as paclitaxel, docetaxel, gemcitabine, vinorelbine and irinotecan has stimulated interest in the development of novel chemotherapy regimens for the treatment of NSCLC patients.

Paclitaxel was the first member of the new class of anticancer drugs identified and became known as the taxanes. It has a novel mechanism of action in that it promotes the polymerization of tubulin and induces the formation of hyper-stable, and thus dysfunctional microtubules, which interferes with the mitosis process [20]. Paclitaxel, as a single agent or in combination, has produced responses ranging from 10 to 38% and median survival ranging from 6 to 11 months in chemotherapy-naive NSCLC patients [24]. Several different administration schedules of paclitaxel have been used including 24h, 3h and 1h infusions in addition to weekly dosing alone or in combination. More frequent

dosing schedules of this phase-specific agent, such as weekly administration, may offer a theoretical advantage in terms of cytotoxicity due to prolonged cellular exposure to paclitaxel [16].

In a phase I trial, 175 mg/m^2 weekly paclitaxel was defined as the maximum tolerated dose [2]. Objective response was observed in 35% of patients with further dose escalation being limited by hematological and neurological toxicities. The preliminary data from a phase II trial [1] confirmed the efficacy (56% partial responses). Also, low-dose weekly paclitaxel (80–100 mg/m^2) is effective in other tumors, such as advanced breast cancer; with markedly decreased myelosuppression [15, 21, 26]. The good tolerance of low-dose weekly paclitaxel with minimal severe hematological toxicity and only occasional non-hematological grade 3 or 4 toxicities, makes this treatment regimen an attractive approach for patients with poor tolerance to platinum-based therapy.

Based on these premises, we evaluated the efficacy and toxicity profile of low-dose weekly paclitaxel in the treatment of patients with advanced NSCLC who were not candidates for platinum-based therapy. Two simultaneous studies were conducted to test low-dose weekly paclitaxel in patients aged ≥65 years and/or co-morbidities (Elderly Study) or patients who had received prior cisplatin therapy (Second Line Study). Our objective was to determine the response rate and toxicity of weekly paclitaxel at a dose of 80 mg/m^2 in this group of patients with advanced NSCLC and poor prognosis.

Patients and methods

Eligibility. Patients with histologically- or cytologically-confirmed unresectable or metastatic NSCLC were eligible if they were considered poor candidates for platinum-based combination regimens because of advanced age (>65 years) and/or coexistent illnesses such as chronic obstructive lung disease, vascular disease, heart disease and renal impairment (Elderly Study) or had had prior platinum-based therapy (Second Line Study). The others eligibility criteria were the same for both studies: life expectancy of at least 3 months; Eastern Cooperative Oncology Group (ECOG) performance status of ≤2; absolute neutrophil count (ANC) ≥1500/μl and platelet count ≥75000/μl; creatinine level ≤2.5 mg/dl; adequate hepatic function (defined as serum AST and ALT ≤1.5 times the upper limit of normal, bilirubin ≤1.5 mg/dl, alkaline phosphatase values ≤5 times the upper limit of normal). Patients with brain metastases were not excluded from the study. Exclusion criteria included pre-existing motor or sensory neurologic symptoms ≥2 (NCI-CTC), active infections or serious social conditions that precluded weekly attendance at the hospital.

Both studies were conducted in compliance with institutional review board regulations and all patients were required to provide written informed consent prior to entry into the study.

Pretreatment evaluation included a complete clinical history and physical examination, complete blood cell count, serum chemistries, prothrombin time and partial thromboplastin time, chest x-ray and computed tomographic (CT) scans of the chest and upper abdomen. If symptoms suggestive of metastasis at other sites were present, additional tests were performed to confirm or refute this possibility. During the first four weeks, a complete blood cell count was performed before the administration of each dose of paclitaxel. Follow-up history and physical examination, complete blood cell count, serum chemistries, tumor measurements, and toxicity assessment according to NCI-CTC scale were performed before each 5-week of course of therapy. Besides toxicity assessment performed by the oncologist, a neurological examination of each patient was performed by the same neurologist (TV or RS) to determine the grade of sensory and motor neuropathy according to the NCI-CTC scale. For response evaluation, the pertinent CT scans were repeated after every 8 weeks of treatment.

Treatment schedule. Treatment consisted of paclitaxel at a dose of 80 mg/m^2 administered as a 1-hour intravenous infusion weekly, without a rest period, until disease progression, development of unacceptable drug toxicity, attainment of best response or until the attending physician/investigator considered that there was no benefit accruing from the chemotherapy. Dexamethasone (8 mg), dexchlorpheniramine (5 mg) and ranitidine (50 mg) were prescribed 30 minutes before paclitaxel infusion. Prophylactic antiemetics were not routinely provided.

A full dose of weekly paclitaxel was administered as long as ANC was ≥1500/μl and platelet count ≥75000/μl. If either count was less than this minimum level the dose was omitted and the patient re-evaluated weekly until recovery. Therapy was discontinued if toxicity persisted following a 2-week deferment. If grade 3 or 4 reversible non-hematological toxicity was observed, the dose was omitted until toxicity was resolved to ≤grade 2. Dose reduction was not allowed in the present protocol.

World Health Organization criteria were used for efficacy analysis. Patients who were withdrawn from trial prior to response evaluation because of rapidly progressing lung carcinoma were considered as non-responders. All patients who received at least one week of chemotherapy were considered evaluable for toxicity.

Survival-time and time-to-progression were both calculated on an intent-to-treat basis. Overall survival-time and time-to-progression were measured from the date of entry into the trial up to time-of-death or up to the date of the last follow-up clinical assessment. Survival curves were constructed using the method of Kaplan and Meier. The overall survival curves estimated by this method were compared

between subgroups by a log-rank test. Multivariate analyses of the effect of the different parameters on survival were performed using a Cox model that included performance status (ECOG 0 or 1 vs 2), previous treatment (no vs yes), age (<65 years vs 65-75 years vs >75 years) and response (complete response (CR) or partial response (PR) vs stable disease (SD) or progressive disease (PD)) as variables.

Results

The first seventy-one patients included in the studies were analyzed. The clinical characteristics are presented in Table 1. The median follow-up was 6.4 months (range: 0.5 to 36 months). Forty patients (56%) had received prior platinum-based therapy. The whole study population showed a high prevalence of co-morbid diseases (Tab. 2) which included altered bone marrow reserve (Hb ≤12.5 g/dl, platelets ≤100,000/μl, or neutrophils ≤2,000/μl), diabetes, impaired renal or hepatic function, malnutrition, alcohol abuse, hypertension and antecedents of other tumors. Ten percent of the patients were female. The majority of the patients (n=46) presented with stage IV disease (65%), 20 patients had stage IIIB (28%) and 5 patients presented unresectable stage IIIA and stage II disease with associated co-morbidity (severe chronic obstructive lung disease).

Compliance and response. A total of 614 courses of weekly paclitaxel were delivered (median: 9; range 2 to 20). Three patients had a grade 3 hypersensitivity reaction during the second week of treatment despite premedication and chose to withdraw from the study. Another patient had poor compliance due to social problems and was withdrawn from the study after the second cycle of treatment. These patients were considered non-evaluable for response. Only 5% of doses were deferred or omitted because of toxicity (4.5%) or social reasons. No dose reductions were necessary.

Of the 67 patients evaluable for response, two (3%) achieved CR and 25 (37.3%) had PR. The overall response rate of evaluable patients for response to weekly paclitaxel was 40.3% (27/67; 95% CI: 29.3 to 52.4). SD was achieved in 26 patients (38.8%) and 14 (20.9%) patients experienced PD. Four patients were considered non-evaluable. The rate of responses observed in the group of elderly patients (age ≥65 years) was similar to that observed in the younger patient group (<65 years). The median overall survival for the entire patient population (intent-to-treat) was 8.4 months (95% CI: 5.6 to 11) and the 1-year and 2-year survival was 37.4% and 12.1%, respectively (Fig. 1). Surprisingly, patients without previous chemotherapy had shorter median survival than pretreated patients (7.7 vs 9.7 months), but this difference was not statistically significant (p=0.37). Patients with performance status 0 or 1 showed better survival than patients with performance status 2 (10.3 vs 6.1 months, p=0.03), but in the multivariate Cox model analysis for survival following adjustment for performance status, previous treatment, age and response, only the variable relating to response to weekly paclitaxel achieved a statistically significant difference (p=0.016). Median time to progression was 5.4 months (95% CI: 3.3 to 7.4; Fig. 2).

Toxicity. Treatment-related toxicity data was available for all patients and all cycles and are summarized in Table 3. In general, weekly paclitaxel was well tolerated by this group of patients with poor prognosis. No patients devel-

Table 1. Patients' characteristics (N=71)

Characteristic		N(%)
Age:	Median	68 years
	Range	42–82
Gender:	Male	64 (90)
	Female	7 (10)
PS:	1	37 (52)
	2	34 (48)
Stage:	II	2 (2.8)
	IIIA	3 (4.2)
	IIIB	20 (28)
	IV	46 (65)
Carcinoma type:	Squamous cell	44 (62)
	Adeno	13 (18.3)
	Large cell	3 (4.2)
	Undifferentiated	11 (15.5)
Prior to chemotherapy:	Yes	40 (56)
	No	31 (44)

PS – ECOG performance status.

Table 2. Prevalence of co-morbidities in the population under study (N=7)

Variable	N(%)
Decrease of bone marrow reserve[1]	34 (48)
Chronic pulmonary obstructive disease	20 (28)
Oxygen supplementation at home	2 (2.8)
Diabetes	9 (12.6)
Malnutrition	11 (15.5)
Alcohol abuse	11 (15.5)
Impairment of renal function	12 (17)
History of other tumors	5 (7)
Hypertension	5 (7)
Chronic hepatic disease	7 (10)
Ischemic heart disease or heart rhythm disturbance	5 (7)
Dementia	2 (2.8)
Parkinson	2 (2.8)
Peripheral vasculopathy	3 (4.2)

[1]Defined as Hb ≤12.5 g/dl, platelets ≤100,000/μl, or neutrophils ≤2,000/μl.

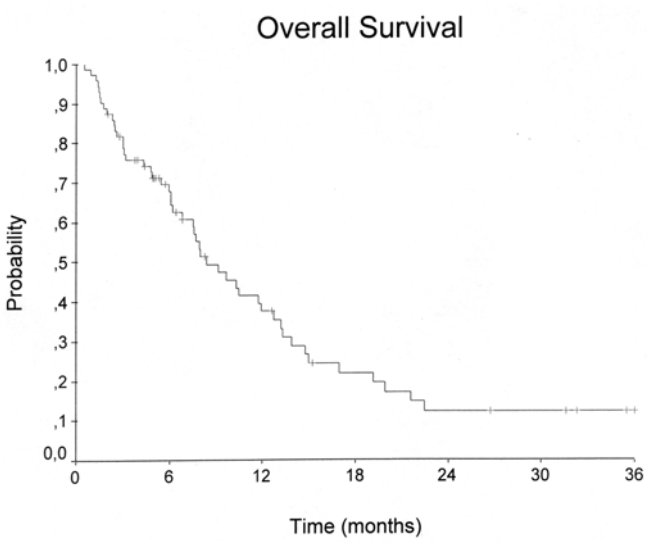

Figure 1. Overall survival (n=71 patients).

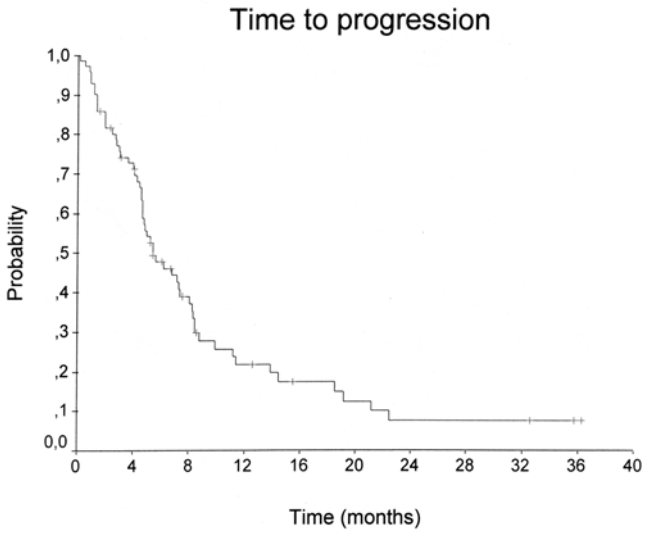

Figure 2. Time to progression (n=71).

oped grade 4 hematological or non-hematological toxicities. Grade 3 thrombocytopenia was reported in only 1 patient and no grade 3 neutropenia nor anemia was observed. Fatigue and alopecia were the most common non-hematological treatment-related toxicity. However, both were mild: 37 patients had grade 1–2 fatigue and 45 patients had alopecia grade 1–2. Three patients developed severe fatigue (grade 3) and 1 patient severe alopecia. Other grade 3 non-hematological toxicities were uncommon and included nausea (2 patients), motor neuropathy (4 patients), sensory neuropathy (3 patients) and hypersensitivity reaction (3 patients). One patient with PR died after 9 weeks of treatment due to pneumonia without neutropenia, and was considered a toxic death.

Table 3. Toxicities observed during treatment (National Cancer Institute-Common Toxicity Criteria)

Toxicity	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)
Hemoglobin	17 (24)	7 (10)	0
Neutrophils	3 (4)	4 (5.5)	0
Platelets	4 (5.5)	1 (1.4)	1 (1.4)
Nausea	13 (18)	2 (2.8)	2 (2.8)
Vomiting	10 (14)	6 (8.5)	0
Fatigue	23 (32.3)	14 (19.7)	3 (4)
Alopecia	36 (50.7)	9 (12.6)	1 (1.4)
Anorexia	25 (35.2)	13 (18)	0
Stomatitis	6 (8.5)	3 (4)	0
Diarrhea	5 (7)	1 (1.4)	0
Neuropathy-motor	27 (38)	3 (4)	4 (5.5)
Neuropathy-sensory	23 (32.3)	10 (14)	3 (4)
Hypersensitivity	2 (2.8)	0	3 (4)
Dyspnea	1 (1.4)	1 (1.4)	0
Rash	2 (2.8)	0	0

Discussion

Platinum-based chemotherapy has become the standard in the treatment of advanced NSCLC because of the survival benefit showed in comparison to best supportive care alone [17, 18, 27]. However, there are several subgroups of patients who were not candidates to platinum combination due to age, co-morbidities or previous therapy with platinum analogues. The advent of several new anti-neoplastic agents with favorable efficacy and toxicity profiles opens-up the possibility of new approaches in the treatment of advanced NSCLC. The results of the present trial confirm the efficacy of low-dose weekly paclitaxel in the treatment of non-resectable or metastatic NSCLC in elderly patients (age ≥65 years) and patients who cannot receive cisplatin.

Data on the application of chemotherapy in elderly NSCLC patients are limited. This subset of patients tolerates chemotherapy poorly and is not considered eligible for aggressive cisplatin-based regimens. Cisplatin-containing therapies generally induce severe myelotoxicity, neurotoxicity and nephrotoxicity despite copious hydration to mitigate these occurrences. Carboplatin is a cisplatin analogue that has less renal and neurological toxicity, but carboplatin-based chemotherapy has considerably marked myelotoxicity. Conversely, new chemotherapeutic agents such as vinorelbine, gemcitabine, docetaxel and paclitaxel have shown encouraging results. Overall response rates of between 12% and 40% have been reported with single agent vinorelbine or gemcitabine [10]. Docetaxel, as a weekly schedule, has also been evaluated in elderly patients with advanced NSCLC [11]. Thirty-nine patients aged ≥65 years, or younger patients who were considered to be poor candidates for combination chemotherapy due to co-existent illnesses, were included. Weekly docetaxel was well tolerated.

Seven of 38 evaluable patients (18%) had objective response. The median survival was 5 months and the survival at 1-year was 27%. Recently, a study using weekly paclitaxel in elderly patients (35 patients) was published. The overall response was 23% and the median survival 10.3 months [6].

In the other setting, second-line chemotherapy studies have increased in the last years. Docetaxel is the unique drug evaluated as second line therapy in phase III trials [7, 22]. These studies demonstrated that chemotherapy have an impact on survival and palliation in this population. Paclitaxel has been evaluated in phase II trial with responses between 0% and 38% [5, 13]. So far, Socinsky et al [25] has published the largest trial of paclitaxel as second-line therapy. Sixty-two patients were treated, the objective response rate was 8% and the median survival was 5.2 months.

To the best of our knowledge, the present analysis constitutes the largest one where activity and toxicity of paclitaxel have been assessed. Weekly therapy with 1-hour infusions of paclitaxel has a substantial degree of activity in NSCLC [1, 2]. Myelotoxicity and neurotoxicity precluded dose escalation beyond 175 mg/m^2. However, the optimal dose of weekly paclitaxel has hot been well established although lower doses have shown activity both in other tumors [15, 21, 26] and lung cancer [12, 14]. Weekly dosing of paclitaxel produces extended cumulative exposure and is an important factor in cytotoxic activity of this drug [16]. Depending on the duration of exposure, cytotoxicity activities can be achieved at relatively low concentrations of paclitaxel and these are easily achievable with low doses of the drug. Moreover, weekly administration of paclitaxel is dose-intense and with a favorable toxicity profile; the schedule of the present trial, for example, being equivalent to 240 mg/m^2 per 3-week interval. Indeed, low-dose weekly paclitaxel appears to have high activity with mild toxicity. Of the 71 patients, 47 (66%) were ≥65 years and the median age for the entire group was 68 years. ECOG performance status was 2 in 34 patients (48%). Overall response rates of 40.3% and a median survival rate of 8.4 months are highly encouraging. Comparison of our results with previous trials using other recently-available drugs is difficult because of variations in the patient populations studied.

We found weekly paclitaxel therapy to be well tolerated, subjectively, by the majority of patients. This is supported by the findings that there were no grade 4 hematological or non-hematological toxicities, the median duration of therapy was 9 weeks and with less of 5% of doses omitted due to toxicities, and there were no dose reductions required. Grade 3 toxicities are also uncommon with low-dose of weekly paclitaxel. The most common toxicity was treatment-related fatigue (grade 1–3 = 56%), which was accumulative and, generally, present after 8 weeks of paclitaxel. Peripheral neuropathy was also frequent in this group of patients albeit, mild in most cases. Paclitaxel toxicity appears to be dependent on dosage as well as the schedule of administration. Infusion over 3 hours and 24 hours produces leukopenia as the dose-limiting toxicity [23] and shorter infusions have been associated with an increase in peripheral neuropathy [3]. With weekly paclitaxel schedules, increases in dose-intensities and cumulative doses have been attained with resulting increases in neurotoxicity. Apart from the dose of paclitaxel, several other risk factors for neuropathy have been described and include prior exposure to other neuro-toxic chemotherapies (e.g. cisplatin or vinca alkaloids), prior radiation therapy, diabetes mellitus, history of alcohol abuse, malnutrition and advanced age [4, 9, 19]. The population of our study had an increased risk of neuropathy due to the high prevalence of co-morbidities predisposing to neural damage and included age and prior platinum-based therapy. However, the peripheral neurotoxicity observed was moderate.

Most chemotherapy trials in lung cancer have been focused on patients who are in a relatively good clinical condition while data on patients who do not fulfil such inclusion criteria are limited. However, cancer is predominantly a disease of the elderly with more than 60% of all cases occurring in people greater than 65 years of age. Among elderly people, higher prevalences of concomitant diseases and treatment-related side effects have been observed. Since palliation is the most important goal in advanced NSCLC, the challenge is to devise an active and well-tolerated regimen. The low-dose weekly paclitaxel regimen is effective in the treatment of NSCLC patients and can be safely administered in this subset of patients who have a poor prognosis. Unlike high-dose and other conventional schedules, no severe toxicity was observed.

In conclusion, the favorable response rate, median time to progression and overall survival observed with low-dose weekly paclitaxel justifies its usage in patients with advanced NSCLC. The low toxicity profile suggests that this schedule would be promising following failed first-line chemotherapy or in patients with co-existent clinical conditions that precludes further aggressive combination therapy. Further randomized trials comparing weekly paclitaxel to combination chemotherapy as first-line chemotherapy in advanced non-small cell lung cancer are warranted.

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