original contribution

Weekly Paclitaxel in Elderly Patients (Aged ≥ 70 Years) with Advanced Non–Small-Cell Lung Cancer: An Alternative Choice? Results of a Phase II Study

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Abstract

Purpose: Paclitaxel and platinum-based chemotherapy is considered to be a standard approach for locally advanced and metastatic non–small-cell lung cancer (NSCLC). In recent years, weekly paclitaxel has been widely used for its safety profile, especially in breast and ovarian cancer. Otherwise, only a few studies are available in NSCLC. The aim of our study was to investigate the activity and safety of weekly paclitaxel in elderly patients with locally advanced (stage IIIB) and metastatic (stage IV) NSCLC. **Patients and Methods:** Twenty-seven patients entered the study; 10 had stage IIIB disease (5 "wet" and 5 "dry"), and 17 had stage IV disease. Median age was 73 years (range, 70-83 years). Sixteen patients (59%) presented with comorbidities. The schedule was weekly paclitaxel 80 mg/m^2 for 6 weeks with 2 weeks of rest (1 cycle). **Results:** All patients were evaluable for response and toxicity; a median of 1 cycle was administered (range, 1-5 cycles). Partial responses were recorded in 9 patients (37.5%; 33.3%, according to intention-to-treat analysis; 95% CI, 15.5%-51.1%); 7 had stable disease (29%), and 8 had progressive disease (33.5%). Median time to progression was 5 months (range, 1-23 months), and median survival was 12 months (range, 1-36 months). Grade 2/3 asthenia was the main toxicity in 7 patients (29%); a hypersensitivity reaction presented in 1 patient. No other episode of grade 3/4 toxicity was recorded. **Conclusion:** Our study confirmed that paclitaxel 80 mg/m^2 weekly is active in patients with locally advanced and metastatic NSCLC with a good safety profile; this schedule might be considered an alternative choice to gemcitabine or vinorelbine as first-line treatment in elderly patients, particularly patients with comorbidities. Phase III studies that compare these third-generation drugs are warranted to draw definitive conclusion about the best approach in these patients.

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Introduction

Lung cancer is the most common cancer in the world and the leading cause of cancer-related deaths in Western countries.[1] More than 50% of advanced non–small-cell lung cancer (NSCLC) occurs in people aged > 65 years,[2] with a median age at diagnosis of 70 years.[3]

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For younger patients (< 65 years), a doublet with a cisplatin-containing regimen is considered the standard approach in inoperable or metastatic NSCLC, providing a slight advantage over supportive care (6 weeks' benefit in term of overall survival [OS]).[4] Unfortunately, these results are not suitable for elderly patients, who are often "frail," with a number of comorbidities and physiologic changes in functional status, organ function, and drug pharmacokinetics. American Society of Clinical Oncology (ASCO) guidelines[5] and an International Expert Panel on the Treatment of Advanced NSCLC in the Elderly[6] recommended a single-agent chemotherapy with a third-generation drug as standard approach in elderly patients with advanced NSCLC. These recommendations derived particularly from 2 phase III Italian trials: ELVIS (Elderly Lung Cancer Vinorelbine Italian Study) and MILES

Table 1 Patient Characteristics

Characteristic	Number of Patients
Patients Enrolled	27
Median Age, Years (Range)	73 (70-83)
Disease Stage	
IIIB	10 (5 "Wet" and 5 "dry")
IV	17
ECOG PS	
0	11
1	10
2	6
Histologic Types	
Squamous	11
Adenocarcinoma	9
Anaplastic	5
Mixed (adeno-squamous)	1
Bronchioloalveolar	1
Metastatic Sites (Median, 1; Range, 1-5)	
Lung	10
Brain	4
Bone	3
Adrenal gland	2
Spleen	1
Abdominal lymph nodes	1

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance status

Figure 1 Time to Progression of All Patients

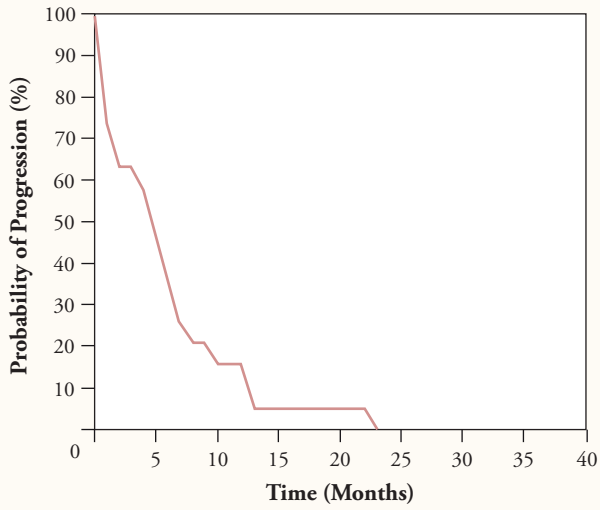
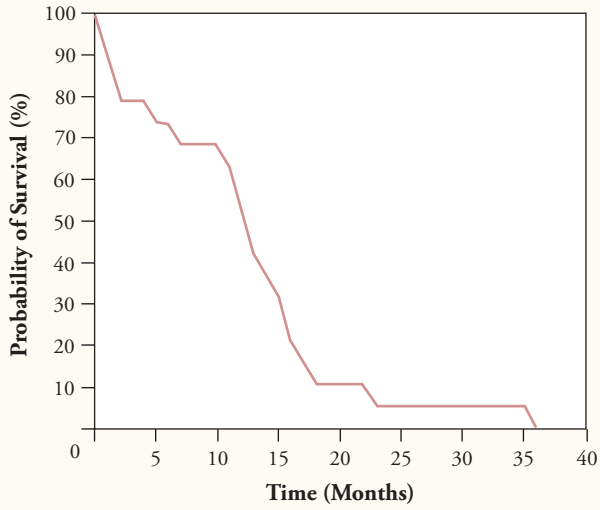


Figure 2 Survival of All Patients



(Multicenter Italian Lung Cancer in the Elderly Study). The ELVIS trial documented that vinorelbine improved quality of life and survival compared with best supportive care (median survival, 28 weeks vs. 21 weeks, respectively; P = .04).[7] The MILES study showed that the combination of vinorelbine plus gemcitabine did not improve survival compared with single-agent vinorelbine or gemcitabine with higher toxicity.[8]

A few phase II studies showed that the taxanes docetaxel and paclitaxel also yielded activity and safety in the treatment of advanced NSCLC. Recently, a phase III study by Kudoh et al showed that docetaxel 60 mg/m^2 every 3 weeks achieved the same results in terms of median survival compared with vinorelbine (14.3 months vs. 9.9 months, respectively),[9] although these data should be considered cautiously because the study was not planned to assess this endpoint. Grade 3/4 neutropenia was higher with docetaxel (82.9% vs. 69.2%). However, in this trial, docetaxel improved progression-free survival (5.5 months vs. 3.1 months) and response rate (22.7% vs. 9.9%) compared with vinorelbine.

Paclitaxel every 3 weeks has been demonstrated to achieve significant activity as first line in advanced NSCLC, with responses ranging from 10%-38% and median survival from 6 months to 11 months.[10] The common dose was 200-225 mg/m^2 every 3 weeks (often in combination with carboplatin), with moderate or severe neutropenia and neurologic toxicity. To reduce these toxicities and improve quality of life, paclitaxel has been administered in a weekly fashion; this schedule offers a theoretical advantage in terms of cytotoxicity as a result of prolonged cellular exposure to paclitaxel with lower toxicity.[11] Moreover, the continuous low-dose administration of paclitaxel allows exploration of its antiangiogenic effect.[12] Until 2001, only 1 study with weekly paclitaxel (90 mg/m^2 for 6 weeks) has been published as an original article, reporting a response rate of 23% and median survival of 10.3 months.[13] However, in the same year, other phase II studies presented at the ASCO annual meeting with paclitaxel 80 mg/m^2 for 3 weeks showed conflicting results in terms of response rates (3.7% vs. 19%).[14,15] On this basis, in 2003, we decided to investigate this latter dose of weekly paclitaxel, prolonging the administration from 3 weeks to 6 weeks with 2 weeks of rest. The aim of our study was activity and toxicity of this weekly schedule in elderly patients (aged ≥ 70 years) with locally advanced (stage IIIB) and metastatic (stage IV) NSCLC.

Table 2 Results and Toxicity

Result	Number of Patients (%)
Evaluable for Response	24
Evaluable for Toxicity	24
Objective Response	
PR	9 (37.5; 33 According to intent-to-treat analysis)
SD	7 (29)
PD	8 (33.5)
Toxicity	
Grade 2/3 asthenia	7 (29%)
Grade 2 neutropenia	2 (8%)
Grade 2 neurotoxicity (paresthesia)	1 (4%)
Skin rash	1 (4%)

Abbreviations: PD = progressive disease; PR = partial response; SD = stable disease; TTP = time to progression

Patients and Methods

Eligibility Criteria

Patients with cytologically or histologically measurable stage IIIB/IV NSCLC entered the study. All patients had to be chemotherapy naive and elderly (aged ≥ 70 years). Other selection criteria included (1) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2; (2) adequate liver, renal, and bone marrow function; and (3) life expectancy of ≥ 3 months. Previous radiation therapy was accepted if measurable lesions were present in nonirradiated area. Comorbidities were recorded at the time of enrollment in the study. Patients with symptomatic brain metastases were excluded from the study. Staging procedures included physical examination, complete blood cell count and chemistry, chest/upper abdomen computed tomography (CT) scan, and bone-scan. A brain CT scan was performed if clinically indicated. Written informed consent was obtained from all patients.

Study Design and Statistical Methods

Paclitaxel was administered at the dose of 80 mg/m^2 once a week for 6 administrations with 2 weeks of rest (1 cycle); this treatment was continued to a maximum of 5 cycles. The aims of the study were activity and toxicity of weekly paclitaxel in elderly patients with locally advanced (stage IIIB) and metastatic (stage IV) NSCLC. Response to therapy was assessed according to World Health Organization standard criteria after the first cycle and then every other cycle; only patients with objective response continued treatment. Toxicity was evaluated at any administration according to National Cancer Institute Common Toxicity Criteria, version 2.0. Time to progression (TTP) was calculated from day 1 of the first cycle to the first documentation of progression;. Overall survival was calculated from day 1 of the first cycle to the date of death or, in absence of its assessment, last follow-up. Median TTP and median survival were calculated according to the Kaplan-Meier method. According to the optimal 2-stage design for a target activity level of ≥ 20% response rate, if no objective response was documented after the first 12 evaluable patients, the drug was considered inactive (α and β error probabilities 0.10 and 0.10, respectively). Stable disease (SD) was not included in response analysis.

Table 3 Results According to ECOG Performance Status

Efficacy Measure	ECOG PS 0 (11 Patients)	ECOG PS 1 (10 Patients)	ECOG PS 2 (6 Patients)
PR (%)	36.4	40	16.7
SD (%)	36.4	30	33.3
PD (%)	27.2	30	5
Median TTP (Months)	6	6	2
Median OS (Months)	15	13	3

Abbreviations: ECOG = Eastern Cooperative Oncology Group; OS = overall survival; PD = progressive disease; PR = partial response; PS = performance status; SD = stable disease; TTP = time to progression

Results

From January 2003 to December 2005, 27 consecutive elderly patients with locally advanced (10 with stage IIIB disease, 5 "wet" and 5 "dry") and metastatic (17 with stage IV disease) NSCLC entered the study. Median age was 73 years (range, 70-83 years); there were 24 men and 4 women. The ECOG PS was 0 in 11 patients, 1 in 10 patients, and 2 in 6 patients. Histologic types were as follows: squamous, 11 patients; adenocarcinoma, 9 patients; anaplastic, 5 patients; mixed cells (adeno-squamous), 1 patient; and bronchioloalveolar, 1 patient (Table 1). Sixteen patients (59%) presented with comorbidities, and 8 of them presented with ≥ 2 concomitant illnesses (heart disease, 5 patients, diabetes, 5 patients; chronic bronchitis, 3 patients; chronic kidney failure, 2 patients; vascular disease, 4 patients). All patients were evaluable for response and toxicity. A median of 1 cycle was administered (range, 1-5 cycles). Partial responses (PRs) were recorded in 9 patients (37.5%; 33.3% according to intention-to-treat analysis; 95% CI, 15.5%-51.1%), SD in 7 patients (29%), and progressive disease (PD) in 8 patients (33.5%). Median TTP was 5 months (range, 1-23 months), and median survival was 12 months (range, 1-36 months; Figures 1 and 2). Patients with stage IIIB "wet" and "dry" had the same response rates (3 PRs in each group, with 1 SD and 1 PD). Seven of the 9 objective responses were reported in patients with comorbidities (5 patients had SD).

Grade 2/3 asthenia was the main toxicity in 7 patients (29%; 6 of them had concomitant illnesses). Hypersensitivity reaction was reported in 1 patient. No other episode of grade 3/4 toxicity was recorded (Table 2).

Results in ECOG PS 0 patients were consistent with those in ECOG PS 1. Results in patients with ECOG PS 2 were disappointing (Table 3). Only 1 patient stopped treatment after the first cycle for toxicity because of grade 3 asthenia. Fifteen other "nonresponding" patients (8 with PD and 7 with SD) did not carry on treatment as planned by the protocol. Three patients stopped paclitaxel after the first administration and have been considered "nonresponders." The reasons were as follows: 2 patients died after the first administration of paclitaxel because of cardiovascular complications (the patients had ECOG PS 2, and the deaths were not related to drug infusion; 1 of them had a slight chronic kidney failure with creatinine ≤ 2 mg/dL and a previous ischemic attack); a third patient refused to carry on treatment after the first administration.

Table 4 Phase II Studies with Weekly Paclitaxel in Elderly Patients

Study	No. of Patients	Median Age (Years)	Schedule	Response Rate (%)	Toxicity (%)	Median Survival (Months)
Fidias et al (2001)[13]	35	76	90 mg/m^2 for 6 weeks (2 weeks off)	23	Neuropathy, 5.8; neutropenia, 5.8; hyperglycemia, 17.6; infection, 8.8; 2 treatment-related deaths, 5.7	10.3
Garbo et al (2001)[14]	60	72.4 (83% Aged ≥ 70 years and PS 2)	80 mg/m^2 for 3 weeks (1 week off)	3.7	Neuropathy, 3; leukopenia, 3; asthenia, 7; diarrhea, 3	8.2
West et al (2001)[15]	21	76 (Elderly or PS ≥ 2)	80 mg/m^2 for 3 weeks (1 week off)	19	Anemia, 4.7; neuropathy, 4.7; hypersensitivity, 4.7	6.8
Massutì et al (2004)[17]	74	73 (Elderly or frail; age and comorbidities: 29% of patients)	80 mg/m^2 for 3 weeks (1 week off)	23	Neutropenia: 1.5; anemia: 1.5; thrombocytopenia, 1.5; asthenia, 4.7; hypersensitivity, 3.1; neurotoxicity: 4.7; arrhythmia, 1.5	9
Juan et al (2007)[18]	57	74 (Elderly and frail patients)	80 mg/m^2 weekly (without rest)	44	Neutropenia, 1.8; thrombocytopenia, 1.8; neuropathy, 7; hypersensitivity, 1.8; cardiac ischemia, 1.8; pneumonia, 1.8	7.8
Rossi et al (2008) Present Trial	27	73 (Elderly; comorbidities: 62%)	80 mg/m^2 for 6 weeks (2 weeks off)	37.5	Asthenia, 4.1; hypersensitivity, 4.1	12

Abbreviation: PS = performance status

Discussion

Single-agent chemotherapy with a third-generation regimen was the best approach for "fit" elderly patients with advanced NSCLC. Three phase III studies showed that vinorelbine, gemcitabine, and docetaxel achieve similar results in terms of median survival.[7-9] In contrast, no phase III study has been performed to compare paclitaxel with one of these drugs, and the available data were derived only from phase II studies: a review of 2 phase II trials at the dose of 210 mg/m^2 every 3 weeks revealed that tumor response and median survival time did not differ between the elderly (aged ≥ 70 years) and younger (aged ≤ 70 years) patients. However, the most common toxicity, neutropenia, was higher in the older than in the younger group (89.3% vs. 73.9%).[16]

To assess a better safety profile, a weekly paclitaxel schedule was used in 3 phase II studies until 2001. The Fidias et al study reported a response rate of 23% and a median survival of 10.3 months in 35 elderly patients.[13] In this trial, paclitaxel has been administered at the dose of 90 mg/m^2 for 6 weeks (2 weeks off) with mild toxicity, particularly hematologic and neurologic, although 2 treatment-related deaths were recorded. In the Garbo et al[14] and West et al[15] trials, a slightly different schedule was administered with paclitaxel at 80 mg/m^2 for 3 weeks (1 week off) achieving conflicting response rates (3.7% vs. 19%, respectively), although the median survival was similar (8.2 vs. 6.8 months). Toxicity was mild in both trials.

To improve response rates maintaining the same improved safety profile, we decided in 2003 to start a phase II study with weekly paclitaxel 80 mg/m^2 for 6 weeks with 2 weeks of rest. To the best of our knowledge, this is the only trial with this particular schedule in elderly patients with advanced NSCLC. In 2004, Massutì et al reported data on 74 patients with a response rate of 23% and a median survival of 9 months; the schedule was weekly paclitaxel 80 mg/m^2 for 3 weeks (1 week off). Main grade 3/4 toxicities were neutropenia, anemia, thrombocytopenia, neuropathy, and asthenia.[17] In 2007, Juan et al reported the results on 57 patients with comorbidities. The response rate was 44% with paclitaxel 80 mg/m^2 weekly, without rest (median survival, 7.8 months).[18] Grade 3/4 toxicity was consistent with the aforementioned trial. Moreover, the authors demonstrated that comorbidity indexes (Charlson comorbidity index, Kaplan-Feinstein index, and Cumulative Illness Rating Scale) were useful to better characterize the population of elderly patients, although they did not define a subgroup with poorer prognosis. In our study, we obtained a response rate of 33.3% according to intent-to-treat analysis, with a median survival of 12 months, which is consistent with results achieved in the previous trials (Table 4).[13-15,17,18] In addition, 7 patients were aged > 80 years (26%), and 16 patients (59%) presented comorbidities that complicate the medical approach to lung cancer, particularly for multiple drug interactions associated with decrease in marrow reserve, drug clearance, and lean body mass. Toxicity was particularly low; only 1 patient presented with grade 3 asthenia, and no other episode of grade 3 (particularly, hematologic and neurologic) toxicity was recorded. Response rates, median TTP, and median survival overlapped in patients with ECOG 0 and 1

(Table 3), while they were disappointing in ECOG 2, suggesting again that the choice of chemotherapy should be a very cautious one in this group of patients. Seven of 9 objective responses were obtained in patients with comorbidities with a median of 2 cycles, confirming the low toxicity profile of the schedule. However, these patients seem to tolerate less chemotherapy in terms of asthenia. Six of the 7 grade 2/3 episodes were recorded in this group. Regarding the Fidias et al trial,[13] the paclitaxel reduction from 90 to 80 mg/m^2 seems to offer a slightly better safety profile, although definitive conclusion could not be drawn between a comparison of 2 phase II studies. However, the dose of 80 mg/m^2 (for 3 weeks with 1 week off or for 6 weeks with 2 weeks off) is probably the best choice when we decide to use paclitaxel in a weekly fashion.

Conclusion

Our trial confirmed activity and safety of this weekly paclitaxel schedule that might be considered a reasonable choice in elderly patients with advanced NSCLC also in the presence of comorbidities; however, a phase III study that compares paclitaxel with another third-generation drug (gemcitabine or vinorelbine) might indicate the best approach in these patients.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2008. *CA Cancer J Clin* 2008; 58:71-96.
2. Gridelli C, Perrone F, Monfardini S. Lung cancer in the elderly. *Eur J Cancer* 1997; 33:2313-4.
3. Havlik RJ, Yancik R, Longo S, et al. The National Cancer Institute on Aging and the National Cancer Institute SEER collaborative study on comorbidity and early diagnosis in the elderly. *Cancer* 1994; 74(suppl 7):2101-6.
4. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a metaanalysis using updated data on individual patients from 52 randomised trials. *BMJ* 1995; 311:899-909.
5. Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small cell lung cancer: update 2003. *J Clin Oncol* 2004; 22:330-53.
6. Gridelli C, Aapro M, Ardizzoni A, et al. Treatment of advanced non-small cell lung cancer in the elderly: results of an international expert panel. *J Clin Oncol* 2005; 23:3125-37.
7. Elderly Lung Cancer Vinorelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small cell lung cancer. *J Natl Cancer Inst* 1999; 91:66-72.
8. Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst* 2003; 95:362-72.
9. Kudoh S, Takeda K, Nakagawa K, et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). *J Clin Oncol* 2006; 24:3657-63.
10. Socinsky MA. Single-agent paclitaxel in the treatment of advanced non-small cell lung cancer. *The Oncologist* 1999; 4:408-16.
11. Lopes NM, Adams EF, Pitts TW, et al. Cell kill kinetics and cell cycles effects of Taxol on human and hamster ovarian cancer cell lines. *Cancer Chemother Pharmacol* 1993; 32:235-42.
12. Bocci G, Nicolaou KC, Kerbel RS. Protracted low-dose effects on human endothelial cell proliferation and survival in vitro reveal a selective antiangiogenic window for various chemotherapeutic drugs. *Cancer Res* 2002; 62:6938-43.
13. Fidias P, Supko JG, Martins R, et al. A phase II study of weekly paclitaxel in elderly patients with advanced non-small cell lung cancer. *Clin Cancer Res* 2001; 7:3942-9.
14. Garbo L, Marsland T, Garfield D, et al. A phase II study of weekly paclitaxel (Taxol) in stage IIIB, IV or relapsed after local therapy, non-small cell lung cancer (NSCLC) patients with a performance status of 2 and/or ≥ 70 years of age, with Paraplatin administered at disease progression. *Proc Am Soc Clin Oncol* 2001; 20:267b (Abstract 2821).
15. West W, Birch R, Sysel I, et al. A phase II trial of weekly paclitaxel in elderly patients or those with decreased performance status with advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 2001; 20:258b (Abstract 2782).
16. Nakamura Y, Sekine I, Furuse K, et al. Retrospective comparison of toxicity and efficacy in phase II trials of 3-h infusion of paclitaxel for patients aged 70 years of age or older and patients under 70 years of age. *Cancer Chemother Pharmacol* 2000; 46:114-8.
17. Massutì B, Camps C, Barcelò JR, et al. Weekly paclitaxel in non-small cell lung cancer (NSCLC): Results in older or frail patients. A Spanish Lung Cancer Group Trial (GECP 00-02). *Proc Am Soc Clin Oncol* 2004; 23:734 (Abstract 8044).
18. Juan O, Albert A, Campos JM, et al. Measurement and impact of co-morbidity in elderly patients with advanced non-small cell lung cancer treated with chemotherapy. A phase II study of weekly paclitaxel. *Acta Oncol* 2007; 46:367-73.