

# Weekly Paclitaxel as Second/Third-line Treatment in Advanced Non-small Cell Lung Cancer Patients: Efficacy and Tolerability

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**Abstract.** *Background: The aim of the present study was to evaluate the efficacy and toxicity of weekly paclitaxel as second- or third-line treatment in non-small cell lung cancer (NSCLC) patients. Materials and Methods: The outcome measured in 37 patients were: response rates, symptom relief (dyspnoea, asthenia and pain), toxicity, overall survival (OS) and time to progression (TTP). Results: Objective response was seen in 8%, stable disease in 27% and disease progression in 62%. Three paclitaxel courses reduced the frequency of WHO grade 2-3 dyspnoea and asthenia from 38% and 43% to 13.5% and 8.1%, respectively. Moderate to severe pain (VAS score 3-8) was reduced from 35.1% to 24.3%. Median OS was 38 weeks and TTP 12 weeks. Haematological toxicity included anaemia (30% grade 2-3) and neutropenia (8% grade 3). Non-haematological toxicity included peripheral neuropathy (41% grade 1-2). Conclusion: In the routine outpatient setting, weekly paclitaxel is feasible, active and well-tolerated as second/third-line chemotherapy in patients with advanced NSCLC.*

Non-small cell lung cancer (NSCLC) is the main cause of cancer death worldwide both in men and women, accounting for approximately 32% of cancer deaths in men and 24% in women (1). The poor survival in lung cancer is primarily due to late referrals, as the majority of tumours are diagnosed at a locally advanced or metastatic stage (stages III and IV) when there is no possibility of curative surgery.

Platinum-based combinations remain the standard first-line treatment for advanced NSCLC, yielding improved

survival, symptoms and quality-of-life. This has been confirmed in a large meta-analysis (2) comparing cisplatin-based chemotherapy with best supportive care. However, first-line responses are mainly partial, with a median survival of approximately 8.5 months and a 1-year survival rate of 35%.

Recently, novel platinum-based schedules for advanced NSCLC have demonstrated response rates of approximately 30-40%, median survival times of about 11 months and 1-year survival rates of 40-44%, thus clearly superior to best supportive care (3, 4). These data confirm that the first-line chemotherapy option in patients with NSCLC should be a platinum-based chemotherapy (4).

Until recently, the role of second-line treatment in advanced NSCLC was unresolved, despite a number of phase II studies evaluating novel drugs, such as vinorelbine, gemcitabine (5-7), paclitaxel and docetaxel (8, 9). With the exception of docetaxel, an overview (10) reported negligible response rates in the evaluated studies. The median survival ranged from 4 to 11 months.

Paclitaxel, another taxane, has been administered tri-weekly as first-line treatment for advanced NSCLC (11-13). Recent studies evaluating weekly paclitaxel administration to patients with NSCLC (14-16) have demonstrated improved tolerability with less haematological and neurological toxicity when compared to the tri-weekly schedule.

In the present study, the efficacy and feasibility of weekly second/third-line paclitaxel was examined in an unselected patient population with advanced NSCLC, treated in the outpatient clinic.

## Materials and Methods

*Patient characteristics.* Thirty-seven patients with locally-advanced NSCLC (stage III-IV) and previously treated with mainly first-line platinum-based chemotherapy were included in this study. The patients were >18 years, had ECOG performance status (PS) from 0 to 3 and measurable disease. A life expectancy >12 weeks and

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adequate haematological and renal function were required. Hepatic function was normal or near normal.

*Treatment and methods of assessment.* Pre-treatment assessments included medical history, physical examination, complete blood counts, blood chemistry and baseline tumour assessments. Diagnostic work-up and treatment effect evaluation included computed tomographic (CT) scans of at least the chest and upper abdomen. Before each cycle, complete blood counts and blood chemistry were performed in all patients.

A 3-h intravenous infusion of paclitaxel was administered once a week at a dose range of 60-80 mg/m<sup>2</sup> over a period of 3 weeks followed by a 1 week break in each 4-week cycle. At myelosuppression (granulocyte count <1x10<sup>9</sup>/L, platelets <50x10<sup>9</sup>/L), the weekly dose was not reduced, but treatment was delayed. Routine prophylactic medication prior to the paclitaxel infusions was 8 mg dexamethasone, 50 mg diphenhydramine and 50 mg ranitidine.

All patients received treatment until progression of disease, severe toxicity, death, or patient refusal of further treatment. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 (17). Tumour response was assessed according to the WHO criteria (18). The symptom assessments were performed by the patient's doctor. Assessments of pain were performed on a visual analogue (VAS) scale, whereas asthenia and dyspnoea were categorised according to the WHO criteria. Time to progression (TTP) was calculated as the period from treatment start to disease progression, and overall survival (OS) from treatment start to death.

*Statistical considerations.* Study end-points were efficacy and toxicity of weekly paclitaxel treatment administered in the daily clinical outpatient setting. Due to the descriptive nature of the study, no formal rules of power calculation were applied to determine sample size requirements. Efficacy was evaluated according to objective response rates (ORR), doctor-assessed symptom relief, OS and TTP. OS and TTP were evaluated by the Kaplan-Meier method.

## Results

*Patients' characteristics and treatment.* Between January 2002 and November 2003, 37 patients were enrolled in the study. Ninety-seven per cent had previously received platinum-based chemotherapy. The patient and tumour characteristics are listed in Table I. Of the patient group, 25 (68%) received weekly paclitaxel 60 mg/m<sup>2</sup> and 12 (32%) weekly 80 mg/m<sup>2</sup>. Thirty-four (92%) patients received paclitaxel as second-line and 3 (8%) patients as third-line therapy. The median number of cycles administered was 3 (range 1-11).

*Response rate, symptoms relief and survival.* Thirty-six (97%) patients were evaluable for response, whereas 1 patient (3%) developed an anaphylactic reaction at initiation of the first paclitaxel course, discontinued the treatment and, hence, was not evaluable for response. The overall response rate was 8% (n=3), as 3% (n=1) had complete (CR) and 5% (n=2) partial response (PR). Twenty-seven percent (n=10) had stable disease (SD) and 62% (n=23) progressive disease (PD).

Table I. Characteristics of 37 patients with advanced NSCLC prior to second- or third-line chemotherapy with weekly paclitaxel.

Characteristic	No.	%
Age		
Median		69
Range		27-82
Gender		
Male	35	94.6
Female	2	5.4
Performance status		
0	5	13.5
1	23	62.2
2	5	13.5
3	4	10.8
Histology		
Adenocarcinoma	17	46.0
Squamous	12	32.4
large cell	6	16.2
Undifferentiated	2	5.4
Tumour stage		
IIIB	19	51.4
IV	18	48.6
Metastatic sites		
Liver	6	16.2
Adrenal	4	10.8
Lung	3	8.1
Bone	3	8.1
Other	2	5.4
Previous chemotherapy		
Platinum-based	36	97.3
Non-platinum-based	1	2.7

Prior to therapy, grade 2-3 dyspnoea and asthenia were observed in 43% and 38%, respectively, while a pain VAS score 3-8 was seen in 35% (Table II). There were no cases with grade 4 dyspnoea/asthenia or a pain VAS score 9-10. At assessments after 3 courses of weekly paclitaxel, the frequency of grade 2-3 symptoms or VAS 3-8 were notably reduced to 8%, 14% and 24% for dyspnoea, asthenia and pain, respectively.

The median and 1-year overall survival was 38 weeks (range 14-63) and 35%, respectively. The median TTP was 12 weeks (range 11-14).

*Treatment complications and toxicity.* The treatment regimen was well tolerated: 22 patients (60%) were without haematological toxicity throughout the treatment. Among the others, 11 (30%) patients had grade 2/3 anaemia, 3 (8%) grade 3 neutropenia, and 1 (3%) grade 4 thrombocytopenia. Dose reduction was not required due to toxicity, but discontinuation was necessary in 1 patient due to anaphylactic reaction (as noted above).

The most frequent non-haematological toxicities were grade 1-2 sensory neuropathy in 15 patients (41%) and

Table II. Doctor-assessed symptoms prior to and after 3 weekly paclitaxel courses in 37 advanced NSCLC patients receiving second- or third-line chemotherapy.

Symptom		WHO criteria			
		Grade 0	Grade 1	Grade 2	Grade 3
Dyspnoea	Before chemo	45.9	10.8	32.4	10.8
	After 3 courses	62.2	29.7	2.7	5.4
Asthenia	Before chemo	40.5	21.6	27.0	10.8
	After 3 courses	67.6	18.9	10.8	2.7

  

Symptom		Visual analogue scale (VAS)			
		0	1-2	3-5	6-8
Pain	Before chemo	59.5	5.4	24.3	10.8
	After 3 courses	73.0	2.7	13.5	10.8

alopecia in 13 patients (35%). Other less frequent toxicities were mucositis (grade 1-2) in 4 patients, diarrhoea or nausea/vomiting (grade 1-2) in 3 patients and fever (grade 2) in 2 patients. Two patients experienced an initial anaphylactic reaction to paclitaxel, but discontinuation was necessary in only 1 of these patients. There were no toxic deaths due to the cytotoxic treatment.

## Discussion

Until recently, the role of second-line chemotherapy in patients with advanced NSCLC (regionally or metastatic) was unclear. In 2000, Shepherd *et al.* (19) reported that second-line single agent treatment with the taxane docetaxel, at a 75 mg/m<sup>2</sup> dose every 3 weeks, gave a limited but significant survival benefit and outweighed the treatment risks when compared with best supportive care. In 2003, the ASCO Guidelines established docetaxel as the gold standard for second-line therapy in patients with locally-advanced or metastatic NSCLC at reasonable performance status, previously treated with platinum-based therapy (4). Docetaxel has also demonstrated superiority in second-line when compared to other single agent treatments such as vinorelbine or ifosfamide (10), but recently single agent pemetrexed in second-line has demonstrated response rates and survival similar to that of single agent docetaxel (20).

Previous second-line chemotherapy trials in other solid tumours (21, 22) have indicated that different schedules of another taxane, paclitaxel, achieve responses by various mechanisms of action. The main antitumour effect of paclitaxel is due to the tubule polymerisation-stabilisation which inhibits mitosis. In addition, this agent also acts as a

specific G2-M-phase inhibitor without affecting the cells in inter-phase. In other experimental studies, paclitaxel has been demonstrated to promote apoptosis with a dose lower than that required to inhibit mitosis (23).

In palliative chemotherapy, and especially with respect to second-line treatment of advanced NSCLC, it is essential that the treatment benefits outweigh toxicity and other chemotherapy discomforts for the patients. The main problem with the tri-weekly chemotherapy schedules has been the high haematological grade 3-4 toxicity rate. As lower dose weekly paclitaxel appears to be more tolerable, but with a similar response rate to the tri-weekly paclitaxel schedule (24, 25), we chose to use the former schedule for this observational study of second-line treatment in the routine outpatient clinic.

The 37 relapsing or progressing NSCLC patients presented herein were unselected and representative of the overall candidate for second-line cytotoxic therapy in the clinic. Regardless of the significantly higher median age and poorer performance status in our series in contrast to that of most phase II and III chemotherapy trials carried out in this patient category, our patient group achieved an overall response rate of 35%, a median survival of 9 months and a 1-year survival of 35%. The high response rate corroborates the substantial reduction in grade 2-3 dyspnoea and asthenia to 19% and 36% of pre-treatment prevalences and pain to 35.12%. In previously published studies of second-line therapy in advanced NSCLC patients, reported response rates have been between 3% and 36%, median survival 5 to 10 months, and 1-year survival at 20% (15, 25, 26-29). In contrast, patients progressing after first-line chemotherapy, administered best supportive care only, will have an estimated median survival of 4-5 months.

In our series, the weekly paclitaxel regimen was quite well tolerated with only 1 (3%) grade 4 thrombocytopenia and 3 (8%) grade 3 neutropenia. The majority (60%) of the patients had no haematological toxicity. Previous studies, reported no (15, 29) or <10% grade 3-4 haematological toxicity (25, 28). The non-haematological toxicity profile in our patients was similar to other studies (15, 25, 28, 29), as peripheral neuropathy grade 1-2 was the most frequently reported toxicity.

In conclusion, this observational study demonstrates that low-dose weekly paclitaxel is active and well tolerated as second-line chemotherapy in a non-selected patient population with advanced NSCLC. Weekly paclitaxel may be an appropriate treatment for good performance status patients failing first-line platinum-based regimens.

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