ORIGINAL ARTICLE

Safety and efficacy of single-agent docetaxel (Taxotere) administered weekly in non-small cell lung carcinoma patients in Korea: An observational study

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Keywords
Carcinoma; docetaxel; non-small cell lung cancer; safety.

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Abstract

Background: To investigate the efficacy, safety, and tolerability of weekly docetaxel treatment in advanced non-small cell lung cancer (NSCLC) patients in Korea.

Methods: This prospective observational study included Korean advanced NSCLC patients with Eastern Cooperative Oncology Group performance status <2 who received weekly monotherapy of docetaxel at a dose determined by the physician. Efficacy measurements included tumor response rate, overall survival (OS), progression-free survival, and one-year survival rate. Safety was analyzed through recorded incidences of adverse events (AEs), serious adverse events (SAEs), deaths, and other related safety parameters, along with their toxicity grades.

Results: Of 274 patients analyzed, one patient achieved a complete response and 42 partial responses; thus, the overall response rate was 15.7%. The OS rate at baseline and at one-year follow-up was 38.3% and 33.8%, respectively. AEs were reported in 229 (83.6%) patients. The most frequently reported hematologic AE of grade ≥3 was a decrease in neutrophils, with 6.6% of the patients developing neutropenia. In non-hematologic AEs of grade ≥3, the most common were infection with unknown absolute neutrophil count and death not associated with Common Terminology Criteria for Adverse Events (CTCAE) (4.7% each). The most common SAE reported was death, not associated with CTCAE (7.3%).

Conclusions: In Korean patients, the weekly regimen of docetaxel monotherapy was safe and efficacious against advanced NSCLC.

Introduction

Lung cancer is the leading cause of cancer-related mortality, responsible for about 1.4 million deaths per year worldwide.[1] With an estimated 1.6 million new cases per year constituting about 13% of all newly diagnosed cancers, lung cancer is the most prevalent of all cancers, with the majority of these cases now occurring in the developing world.[1,2] Approximately 85% of lung cancers are classified as non-small cell lung cancer (NSCLC), which histologically comprises adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, and not otherwise specified carcinomas.[3,4] Despite significant

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progress in imaging and diagnostic techniques, early detection of NSCLC has been unsuccessful, with as high as 70% of the cases presenting locally advanced or metastatic disease.[5] Historically, the standard therapy for treatment of advanced NSCLC has been platinum-based doublet therapy in combination with taxanes, antimetabolites, or vinca alkaloids, with response rates between 20–30% and median survival of eight to 10 months.[6,7] However, a substantial proportion of patients ultimately progress and should be offered second-line treatment.[7]

Docetaxel (Taxotere, Sanofi-Aventis Korea Co. Ltd) is a semi-synthetic taxane that is clinically used as a chemotherapeutic agent against many cancers, such as breast, head and neck, gastric, ovarian, and prostate cancers. Docetaxel is also indicated for use as a single agent in patients with locally advanced and metastatic NSCLC and in whom prior platinum-based therapy has failed to elicit a favorable response. The recent guidelines from the American Society of Clinical Oncology have recommended docetaxel as a second-line therapy for patients with unresectable NSCLC.[8]

The most extensively studied dose of docetaxel is 75 mg/m^2 administered every three weeks. This regimen, while demonstrating efficacy and tolerability, is often accompanied by incidences of grade 3/4 neutropenia.[9,10] Docetaxel-induced myelosuppression and its related complications can be considerably serious in elderly patients.[11] Docetaxel is associated with increased hematologic toxicity, infection, and treatment-related mortality when given at a higher dose of 100 mg/m^2 in patients who have received prior chemotherapy. With the intent of reducing these toxic side effects, alternative regimens consisting of lower doses of docetaxel have been evaluated in patients with NSCLC. Randomized phase II and III trials of docetaxel administered weekly show a significantly improved toxicity profile in comparison with the standard tri-weekly regimen.[12–15] Apart from a favorable overall toxicity profile, these trials also report no incidences of alopecia, pulmonary toxicity, fever, diarrhea, infection, or fluid retention, and a lower incidence of grade 3/4 or febrile neutropenia.[13,15] A meta-analysis conducted by Bria *et al*., based on six randomized controlled trials comparing the two regimens of docetaxel, concluded that weekly docetaxel has an advantage in terms of reducing incidences of neutropenia.[16] Similarly, other clinical trials have demonstrated the efficacy and safety of a weekly regimen of docetaxel in advanced metastatic NSCLC and breast cancer.[17,18] A trial comparing a weekly versus a tri-weekly regimen demonstrated that while global quality of life (QOL) was the same for both groups, parameters such as cognitive function, pain, appetite, and hair loss showed improvement in the patients who received a weekly regimen of docetaxel.[19] Thus, the tolerability of docetaxel as a single agent administered weekly for NSCLC could be particularly helpful in elderly patients or in patients with a low performance status, as well as for use in long-term maintenance therapy.

This study aimed to investigate the efficacy, safety, and tolerability of weekly docetaxel treatment in NSCLC patients in Korea. This study was observational by nature and designed to record trends in NSCLC treatment in Korea. Therefore, the independent decisions made by the physicians in optimizing therapy reflect the real-life scenario of the treatment of advanced NSCLC in Korea.

Methods

Study population

This observational study was designed to evaluate the safety, efficacy, and tolerability of docetaxel in Korean advanced NSCLC patients. The purpose of this subanalysis was to evaluate these parameters in a weekly regimen of docetaxel monotherapy.

Between November 2005 and October 2007, patient recruitment was carried out at 14 centers in Korea. Patients with advanced NSCLC who had been administered weekly docetaxel at a dose determined by physicians and who had provided consent for the release of their data, were included for evaluation in this study. Patients who had received combination therapy, with an Eastern Cooperative Oncology Group performance status (ECOG PS) >2, or whose data collection forms could not be retrieved, were excluded from the analysis. Docetaxel dose and schedule was determined at the discretion of the treating physician.

The baseline characteristics, including demographic data, medical history, disease characteristics, status of prior chemotherapy, and dose of docetaxel monotherapy, were collected. Tumor response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) and classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The overall response rate (ORR) was calculated as the percentage of CR and PR reported in the total number of patients. Other parameters, such as number of treatment cycles, reasons for discontinuation of docetaxel, subsequent treatments after docetaxel, and patient status, were evaluated at the one-year follow-up visit. All adverse events (AEs) observed during the study were assessed by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Serious adverse events (SAEs) were defined as any AEs which caused death, were life-threatening, or which resulted in persistent or significant disability or incapacity.

All incidences of AEs and SAEs, along with their frequency and toxicity grades were analyzed and listed. Deaths and other related safety parameters were also reported.

The study protocol was in compliance with the recommendations of the 18th World Health Congress (Helsinki 1964)

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and approved by the applicable institutional review boards. The study was conducted in compliance with Good Clinical Practice (GCP) guidelines, and international and Korean laws and regulations. Study monitoring for accuracy, completeness, and GCP compliance was performed by the sponsor, Sanofi-Aventis Korea Co. Ltd.

Statistical analyses

This analysis included all eligible patients. Descriptive statistics were provided. Continuous variables were summarized using mean, median, standard deviation (SD), inter-quartile range, and the minimum and maximum value. Categorical variables were summarized by counts and percentages. Overall survival (OS) and progression-free survival (PFS) were reported as Kaplan–Meier plots, and 95% confidence intervals (CIs) were calculated. Safety analysis was descriptive with AEs classified by body organ system and toxicity grade, and summarized by counts and percentages. SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for the analysis.

Results

Demographics and baseline characteristics

A total of 274 patients who had received docetaxel monotherapy at 14 centers in Korea were enrolled in the study. Table 1 demonstrates the characteristics of the study population at baseline. The majority of the patients (73.7%) were men and the average age of the patients (±SD) was 61.9 ± 10.6 years. The 60–69 year age group comprised 44.9% of the patients. More than 90% of the patients had received previous anticancer therapy. Of those patients who had received prior chemotherapy, a combination of gemcitabine and cisplatin was the most commonly prescribed first-line chemotherapy (30.2%). The most commonly prescribed second-line chemotherapeutic agent was gefitinib, used in 28.4% of patients. Past operative history and concomitant disease was reported in 134 (48.9%) patients, and hypertension was the most frequent concomitant disease, reported in 44% of these patients. Active smoking was reported in 60.6% of the patients, and the average number (±SD) of smoking years was 34.4 ± 12.4. Eighty-five percent of the NSCLCs were diagnosed as stage IV, and adenocarcinoma was the most common histology, reported in 149 (54.4%) patients, followed by squamous cell carcinoma, reported in 101 (36.9%) patients.

Docetaxel prescription

Physicians prescribed according to their preference based on clinical evidence. The most commonly prescribed regimen was 30 mg/m^2 on days one, eight, and 15, (30.7%), followed

Table 1 Basesline patient characteristics

Total number of patients	N = 274
Demographics	
Males: n (%)	202 (73.7)
Age (years): mean ± SD	61.9 ± 10.6
BMI (kg/m^2): mean ± SD	22.5 ± 3.0
BSA (m^2): mean ± SD	1.6 ± 0.2
ECOG performance status: n (%)	
0	9 (3.3)
1	211 (77.0)
2	54 (19.7)
Medical history	
Active smoking: n (%)	166 (60.6)
Duration (years): mean ± SD	34.4 ± 12.4
Previous anticancer therapy: n (%)	248 (90.5)
Chemotherapy	96 (35.0)
Chemotherapy + Radiotherapy	54 (19.7)
Chemotherapy + Radiotherapy + OP	42 (15.3)
N/A	56 (22.6)
Previous chemotherapy: n (%)	
No	46 (16.8)
1	40 (14.6)
2	72 (26.3)
2	109 (39.8)
>3	7 (2.6)
Previous first-line chemotherapy: n (%)	228 (83.2)
Gemcitabine + Cisplatin	67 (24.5)
Paclitaxel + Carboplatin	45 (16.4)
Paclitaxel + Cisplatin	29 (10.6)
N/A	87 (31.8)
Previous second-line chemotherapy: n (%)	234 (85.4)
Gefitinib	23 (8.4)
Pemetrexed	13 (4.7)
Paclitaxel + Carboplatin	7 (2.6)
N/A	191 (69.7)
Disease characteristics	
NSCLC Location: n (%)	
Right	146 (53.3)
Left	104 (38.0)
Both	24 (8.8)
Stage: n (%)	
III a	2 (0.7)
III b	40 (14.6)
IV	232 (84.7)
Histological type (overlap count): n (%)	
Adenocarcinoma	149 (54.4)
Squamous cell carcinoma	101 (36.9)
Large cell	7 (2.6)
Other	18 (6.6)
Docetaxel (Taxotere) weekly regimen: n (%)	
35 mg/m^2 (Day 1, 8, 15)	69 (25.3)
30 mg/m^2 (Day 1, 8, 15)	96 (35.2)
25 mg/m^2 (Day 1, 8, 15)	51 (18.7)
Other†	57 (20.9)
N/A	1 (0.3)

Other† – see Supplementary Table S1. BMI, body mass index; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; OP, operative procedure; SD, standard deviation.

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by 35 mg/m^2 on days one, eight, and 15 (16.1%). The other regimens are listed supplementary Table S1.

Efficacy

Tumor response at baseline was assessed in 237 patients; 37 patients were non-evaluable. Table 2 summarizes the best response to weekly docetaxel, as judged by the physicians. Assessment was determined by RECIST criteria in most of the patients (215, 90.7%) while World Health Organization criteria were used in the remaining 22 (9.3%) patients. One (0.4%) patient achieved a CR and 42 (15.3%) patients showed PRs. The ORR was 15.7%. SD was reported in 73 (26.6%) patients, while 121 (44.2%) patients showed PD. Figure 1 depicts the Kaplan–Meier survival curves for OS and PFS at baseline and OS at one-year follow-up. The median OS time at baseline was seven months (95% CI 0.54–0.82) and the one-year survival rate was 38.3%. At one-year follow-up, median OS was 5.8 months (95% CI 0.43–0.71) and the one-year survival rate was 33.8%. The median PFS was 2.4 months (95% CI 0.20–0.27) and one-year PFS rate was 12.5%.

Table 3 shows the efficacy parameters, evaluated at the one-year follow-up visit. The average number (±SD) of treatment cycles of docetaxel that had been prescribed to the patients was 2.7 ± 1.6. Docetaxel monotherapy had been discontinued in 214 (78.1%) patients as a result of disease progression. At the time of the one-year follow-up visit, 195 (71.2%) of the patients had died and 49 (17.9%) had been lost to follow-up. After completion of docetaxel therapy, 129 (47.1%) patients received subsequent therapies; of these gefitinib (39.5%) and vinorelbine (4.7%) were the most common.

Safety

Overall, 229 (83.6%) patients experienced 828 AEs. All AEs are listed in Table 4. A total of 101 episodes of AEs of grade 3 or higher occurred in 75 patients, based on CTCAE version 3.0. A total of 75 SAEs were reported in 65 (23.7%) patients and 91 (33.2%) patients experienced 133 events, which were either an AE of grade 3 and above or a SAE.

Hematologic AEs were reported in 92 (33.6%) patients and the most commonly observed AE of grade 3 or higher was neutropenia, reported in 6.6% of the patients. No other hematologic AE had more than a 2% incidence rate. Hematologic SAEs were reported in three patients; of these, two had developed neutropenia and one developed leukocytopenia.

A total of 693 episodes of non-hematologic AEs were experienced by 216 (78.8%) patients, with grade 3 or higher in 59 (21.5%) patients. While the most frequent non-hematologic AEs were pain (21.9% patients), fatigue (19.0%), and anorexia (17.5%), grade 3 or higher infection with unknown absolute neutrophil count and death not associated with CTCAE, was observed in 4.7% of the patients. Non-hematologic SAEs were experienced in 62 (22.6%) patients, with the most common SAE being death not associated with CTCAE (7.3% patients), followed by infection with unknown absolute neutrophil count (5.8%).

During the study period, 20 (7.3%) patients discontinued docetaxel treatment as a result of toxicities. At the time of the one-year follow-up, 195 (71.2%) patients had died.

Table 2 Efficacy of docetaxel monotherapy (N = 274)

	N (%)
Best response	
Complete response	1 (0.4)
Partial response	42 (15.3)
Stable disease	73 (26.6)
Progressive disease	121 (44.2)
Non-evaluable	37 (13.5)
Lost to follow-up	13 (35.1)
Patient refusal	8 (21.6)
Not available	2 (5.4)
Others	14 (37.8)
Criteria for tumor response evaluation	
RECIST criteria	215 (90.7)

RECIST, Response Evaluation Criteria in Solid Tumors.

Table 3 Docetaxel monotherapy efficacy and patient outcomes at one-year follow-up

Total number of patients	N = 274
Treatment cycles	
Mean ± SD	2.7 ± 1.6
Median	2
Min–max	1–7
No. of cycles	n (%)
1	68 (24.8)
2	95 (34.7)
3	34 (12.4)
>3	77 (28.1)
Reason for discontinuation	n (%)
Progressive disease	214 (78.1)
Toxicity	20 (7.3)
Other	40 (14.6)
Patient status	n (%)
Dead	195 (71.2)
Alive	30 (11.0)
Lost to follow-up	49 (17.9)
Treatment after docetaxel monotherapy	n (%)
Yes	129 (47.1)
No	145 (52.9)
Subsequent therapy after docetaxel	n (%)
Gefitinib	51 (39.5)
Erlotinib	35 (27.1)
Pemetrexed	10 (7.8)
Other	33 (25.6)

SD, standard deviation.

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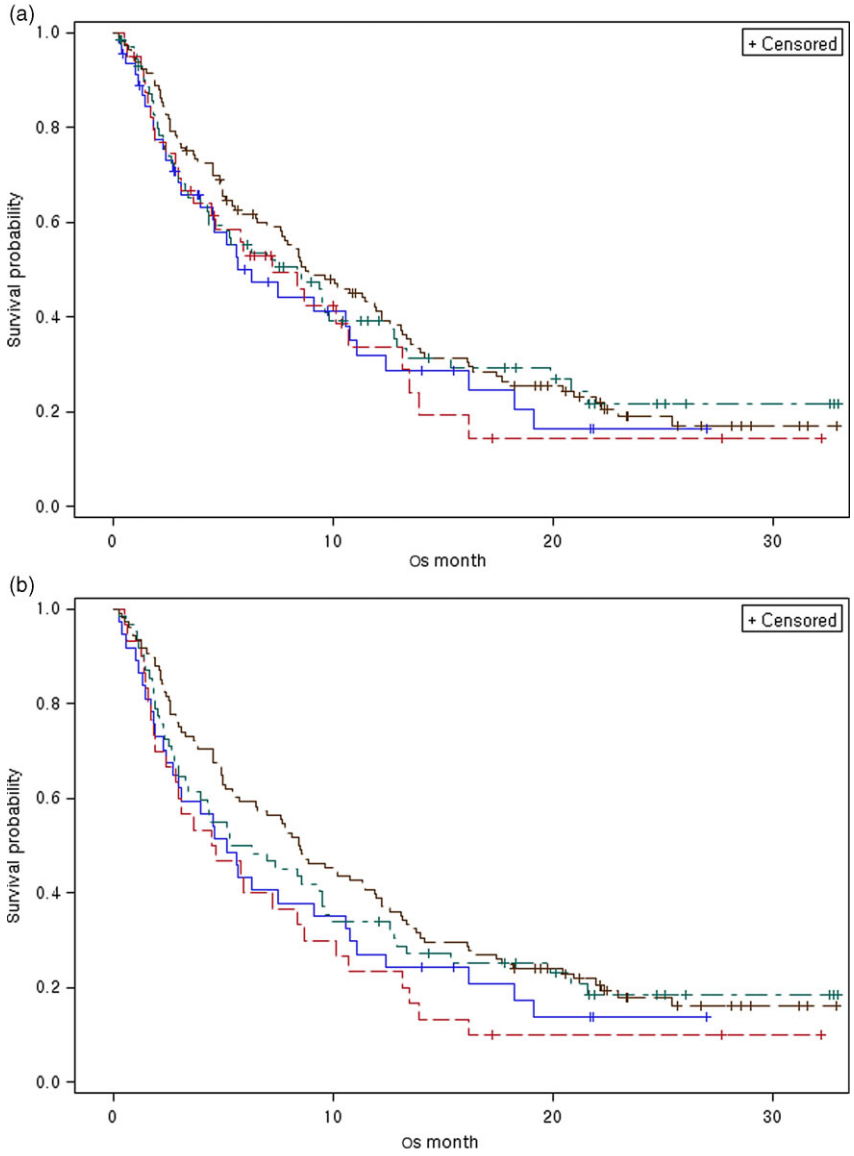

Figure 1 Kaplan–Meier survival curve for (**a**) overall survival (OS) at baseline, (**b**) OS at one-year follow-up, and (**c**) progression-free survival (PFS) at baseline.

Discussion

This report presents the findings of an observational study conducted at various centers in Korea to evaluate the efficacy, safety, and tolerability of single-agent docetaxel given as a weekly regimen in advanced NSCLC patients. The goal of this study is to reflect the real-life scenario in the management of advanced NSCLC in general clinical practice in Korea.

Despite having shown favorable results in terms of efficacy and survival, the standard tri-weekly regimen is associated with significant toxicity issues, mainly high-grade myelosuppression. With the goal of improving the tolerability of docetaxel, various regimens have been analyzed. Phase II trials that evaluated the weekly regimen of docetaxel and compared it to the standard regimen have demonstrated an improved outcome with regard to hematological toxicity. Moreover, a larger phase III trial comparing the two schedules did not show any difference in survival.[16] The efficacy of weekly docetaxel in previous studies was comparable with that of the tri-weekly schedule, with ORRs of 10.5–24%[12,14,15,20,21] and one-year survival rates of 6–58%.[12–14,21] In our study, the ORR of weekly docetaxel was 15.7% and the one-year survival rate was 33.8%. These results from real-life practice are comparable to the findings of the

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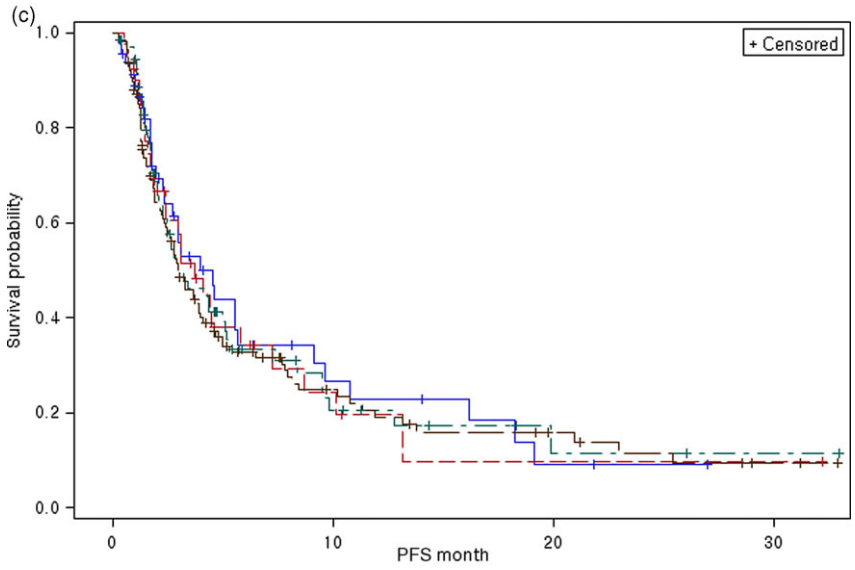

Figure 1 *Continued*

Table 4 Summary of adverse events (N = 274)

	Total AE		AE of 3 ≥ grade	
	N[1)] (%)	N[2)]	N[1)] (%)	N[2)]
Leucopenia (total WBC)	15 (5.47)	24	3 (1.09)	3
Neutropenia	40 (14.60)	69	18 (6.57)	26
Anemia	27 (9.85)	32	2 (0.73)	2
Thrombocytopenia	9 (3.28)	9	2 (0.73)	2
Lymphopenia	1 (0.36)	1	0 (0.00)	0
Total (A)		135		33
Pain	60 (21.90)	79	0 (0.00)	0
Fatigue/asthenia	52 (18.98)	63	7 (2.55)	7
Anorexia	48 (17.52)	58	2 (0.73)	2
Alopecia	36 (13.14)	41	3 (1.09)	3
Cough	32 (11.68)	35	0 (0.00)	0
Dyspnea	31 (11.31)	33	6 (2.19)	6
Mucositis	29 (10.58)	36	1 (0.36)	1
Neuropathy	27 (9.85)	27	1 (0.36)	1
Diarrhea	26 (9.49)	27	1 (0.36)	1
Infection with unknown ANC	23 (8.39)	23	13 (4.74)	13
Death not associated with CTCAE term	22 (8.03)	22	13 (4.74)	13
Nausea	22 (8.03)	26	0 (0.00)	0
Pulmonary/Upper Respiratory	20 (7.30)	21	3 (1.09)	3
Nail changes	19 (6.93)	22	1 (0.36)	1
Vomiting	19 (6.93)	23	2 (0.73)	2
Edema	14 (5.11)	16	1 (0.36)	1
Constipation	14 (5.11)	18	0 (0.00)	0

N[1)] – No. of patients, N[2)] – No. of AEs. AE, adverse events; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal; GU, genitourinary; SGOT, serum glutamic oxaloacetic transaminase; WBC, white blood cells.

aforementioned interventional trials, suggesting that the efficacy and safety of weekly docetaxel treatment observed in previous clinical trials can be replicated in the routine clinical management of advanced NSCLC.

Myelosuppression, as previously mentioned, is a major shortcoming of the standard docetaxel therapy, with high-grade neutropenia the most often reported hematological toxicity. The incidence of neutropenia in previously conducted clinical trials was in the range of 15.9–28%.[12–15] In comparison, in our study, neutropenia of grade 3 or higher was reported in only 6.6% of the patients, followed by leucopenia in 1.1%. Thus, weekly docetaxel demonstrated an acceptable safety profile, somewhat better than seen in previously reported trials.

While the utility of standard platinum-based therapies is limited, novel molecular targeted agents and long-term maintenance therapy are currently being investigated for improving the survival outcome for NSCLC patients.[22] Maintenance therapy refers to a long-term treatment paradigm following a favorable response (CR, PR, or SD) to front-line therapy. Thus, tolerability and manageable toxicity are major requirements for an agent to be used in maintenance therapy. Third-generation chemotherapeutic agents, including docetaxel, are being evaluated for their suitability in maintenance therapy or as single agents.[22–24] In a phase III study, docetaxel (given as per standard regimen and limited to 6 cycles), administered immediately following gemcitabine and carboplatin as front-line therapy in advanced NSCLC, demonstrated a marked improvement in PFS and OS without any toxicity issues or deterioration of QOL.[25]

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As more than half of the newly reported NSCLC cases occur in patients over the age of 65, NSCLC indeed poses a serious health concern to the elderly.[26] Given the increased threat of toxicity resulting from age-related physiologic processes in elderly patients, the development of well-tolerated chemotherapeutic regimens is imperative for successful treatment.[27] A phase III study carried out in elderly patients in Japan reported a slight advantage of docetaxel over vinorelbine as a single agent in terms of OS, PFS, and response rate.[28] However, the results of this study were not significant enough to make them statistically relevant.

This study has certain inherent limitations. The safety and efficacy profile of weekly docetaxel was observational by nature and, hence, needs to be verified in large scale randomized phase III trials. Survival analysis in this study was carried out at baseline and at one-year follow-up. While these data allow some degree of comparison with previous trials, it is inadequate to judge the utility in assessing long-term survival in patients. This study exclusively analyzed a particular regimen of docetaxel, namely, monotherapy, administered weekly. Inclusion of other regimens of docetaxel or other agents, either individually or in combination, would have allowed comparison and also provided an overview of the various treatment modalities for advanced NSCLC.

This study indicates a favorable safety, efficacy, and tolerability profile of single-agent weekly docetaxel in patients with advanced NSCLC. These results do offer promise for the utilization of a particular regimen of docetaxel in long-term maintenance therapy and in patients in whom tolerability of chemotherapy is a primary concern. Further extensive phase III studies are warranted.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Different dosing regimens of docetaxel.

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