Artigo Original
Weekly docetaxel as first-line therapy for NSCLC
Artigo submetido em 11/05/04; aceito para publicação em 13/09/04

Weekly Docetaxel as first-line chemotherapy in stage IV non-small cell lung cancer: effective treatment with low toxicity

Docetaxel em administração semanal como quimioterapia de primeira linha para câncer de pulmão de não-pequenas células em estádio IV: tratamento eficaz com toxicidade baixa

Renato G. Martins[1], G. Advincula[1], R. Costa[2], B. Aragão[3], Waldelice Santos[1], Edson Toscano[1], Walter Roriz[1], Mauro Zamboni[1], Aureliano Sousa[1], Paulo de Biasi[1], Mauro Zukin[1].

Resumo

O estudo avaliou a segurança e eficácia do docetaxel como terapia de primeira linha em pacientes com câncer de pulmão de não-pequenas células avançado (CPNPC). Trinta e seis pacientes com CPNPC de estádio IV receberam docetaxel 36 mg/m²/ semana X 6 com 2 semanas de descanso em um total de seis ciclos programados. Os ciclos foram repetidos a cada 8 semanas. O *status* tumoral foi avaliado por exame clínico e radiológico. Neutropenia foi a toxicidade hematológica mais comum (14% dos pacientes). A taxa de resposta global foi de 14% (5 respostas parciais), 9 (25%) pacientes apresentaram respostas menores ou doença estável por ≥17 semanas. Tempo mediano para progressão e sobrevida mediana foram de 3,4 meses e 7,0 meses, respectivamente. Sobrevida em 1 ano foi de 32%. Esses dados sugerem que o docetaxel em administração semanal é bem-tolerado, com uma taxa de resposta compatível com agentes únicos usados em CPNPC avançado, representando uma opção adicional para pacientes com dificuldade de tolerar o esquema padrão a cada 3 semanas, com uma toxicidade bastante aceitável.
Palavras-chave: Docetaxel; Administração semanal; Toxicidade; Tolerância a drogas; Neoplasias pulmonares de célula não pequena; Quimioterapia.

Abstract

This study proposes to evaluate the safety and efficacy of weekly docetaxel for first-line therapy in patients with advanced non-small cell lung cancer (NSCLC). Thirty-six patients with stage IV NSCLC were enrolled and treated with docetaxel 36 mg/m² weekly for 6 weeks, followed by two resting weeks, in a total of 6 cycles. The cycles were repeated every 8 weeks. The tumor status was assessed by clinical and radiological examination. Neutropenia was the most common hematological toxicity observed (14% of patients). Overall response rate was 14% (5 partial responses), 9 (25%) patients had minor responses or stable disease lasting ≥17 weeks. Median time to progression and survival was 3.4 months and 7.0 months, respectively, and the 1-year survival was 32%. These data suggest that weekly docetaxel is a well-tolerated schedule with a compatible response rate when single agents were used in patients with advanced NSCLC, providing an additional option for patients who may have difficulty tolerating the standard every 3 weeks regimen, with acceptable toxicity.
Key words: Docetaxel; Weekly; Toxicity; Drug tolerance; Non-small cell lung cancer; Chemotherapy.

INTRODUCTION

Lung cancer is now the leading cause of cancer-related death between both sexes worldwide[1]. Approximately three-quarters of lung cancers are of the non-small cell histology, and the majority of these are locally advanced stage III or metastatic stage IV at diagnosis[2]. The prognosis for such patients is poor, median survival being approximately 4-5 months if left untreated once the disease has become metastatic [3]. A meta-analysis of clinical studies conducted between 1965 and 1991 reported that the use of systemic chemotherapy (primarily cisplatin-based regimens) in addition to supportive care also conferred a 10% improvement in 1-year survival and an additional 1.5 months' median survival gain in patients with non-small cell lung cancer (NSCLC) compared with supportive care alone [4]. However, it is important to remember that chemotherapy is beneficial because it also palliates disease-related symptoms. Given that the improvement in survival is relatively modest, the toxicity of the agents and their effect on patient's quality of life are major considerations when selecting therapy for NSCLC.

The 1990s gave hope of a significant improvement in this scenario with the introduction of a number of new chemotherapeutic agents for use in NSCLC, including vinorelbine, gemcitabine, irinotecan, and the taxanes - paclitaxel and docetaxel. Docetaxel has proved particularly active in this setting. In clinical trials, docetaxel 100 mg/m^{2} administered as a 1-hour intravenous infusion every 3 weeks achieved response rates of 13-38% and resulted in a median survival of 6-11 months in previously untreated NSCLC patients [5, 6]. In NSCLC patients who had relapsed after previous platinum-based chemotherapy, the same docetaxel regimen was associated with an overall response rate of 6-25% and a median survival of 6-10 months[5, 7, 8]. The major toxicity associated with this docetaxel regimen is myelosuppression, which is predictable and can be managed with granulocyte colony-stimulating factor (G-CSF)[9]. The toxicity profiles of docetaxel and platinum compounds, such as cisplatin and carboplatin, are relatively non-overlapping, making combinations of these agents an attractive option. Of particular note, neuropathy, one of the most important dose-limiting toxicities of cisplatin, is generally minimal with docetaxel[5]. Phase III studies in chemotherapy-naïve patients with advanced NSCLC have shown docetaxel-platinum doublets to be safe and at least as effective in prolonging survival as paclitaxel-platinum and gemcitabine-platinum doublets[10], and to provide a significant survival and quality-of-life advantage over vinorelbine-cisplatin therapy[11].

Recently, attention has turned to the evaluation of new administration schedules for these agents in an attempt to improve on their tolerability/toxicity profiles when given either as monotherapy or in combination with other agents. One such approach has been to administer taxanes weekly at low doses rather than giving a much higher dose every 3 weeks[12, 13]. The potential advantages of this approach include more frequent drug exposure, antiangiogenic effects, and the use of doses well below the maximum tolerated dose, thus improving tolerability[14]. In patients with advanced NSCLC previously treated with platinum agents, a low-dose (35-40 mg/m2) weekly regimen of docetaxel has demonstrated activity comparable with that of the standard 3-weekly schedule, but with minimal myelosuppression and reduced levels of nonhematological toxicity[12, 15, 16]. The present phase II study was conducted to evaluate the safety and efficacy of a low-dose weekly schedule of docetaxel for first-line therapy in patients with advanced NSCLC.

PATIENTS AND METHODS

This single-arm, multicenter study was conducted in accordance with the Declaration of Helsinki and with the approval of an independent ethics committee. All patients provided written informed consent before enrolment.

Adults (aged ≥18 years) with histologically or cytologically proven stage IV NSCLC, a Karnofsky performance status of ≥60% (ECOG 0-2), and at least one measurable lesion were eligible for enrollment. Patients were not to have received prior therapy with a biological response modifier or a chemotherapeutic agent. Prior NSCLC-related surgery or radiotherapy was permitted providing that a minimum of 4 weeks had elapsed between the procedure and enrollment, and that the measurable lesion was outside the irradiated area. Patients were required to have adequate organ function, defined as neutrophils $\geq 2 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, hemoglobin ≥10 g/dL, total bilirubin ≤ the upper limit of the institutional normal range [ULN], alanine and aspartate aminotransferases ≤ 2.5 × ULN, alkaline phosphatase ≤ 5 × ULN, creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 60 mL/min. Patients with leptomeningeal or brain metastases were included as long as they had received radiotherapy and were neurologically stable. No patients with stage III, or even stage IIIB NSCLC due to malignant pleural effusion were included.

Patients were excluded for the following reasons: current or prior malignancy at other sites (excluding *in situ* cancer of the cervix or adequately treated non-melanoma skin cancer); peripheral neuropathy >grade 1;

other serious illness or medical conditions; prior taxane therapy; pregnancy; lactation; inadequate contraceptive measures (if patient was of reproductive potential); conditions (psychological, family, social, or geographic) preventing weekly medical follow-up or adherence to study procedures.

Docetaxel 36 mg/m^2 was administered as a 30-minute intravenous infusion each week for 6 consecutive weeks, followed by a 2-week therapy-free interval (i.e. 21 days was to elapse between the last and first infusions of consecutive cycles). This 8-week treatment cycle was continued until disease progression, unacceptable toxicity, or death. The recommended duration of treatment was three to six cycles. All patients received pre-medication with oral dexamethasone 8 mg on the night before docetaxel infusion, 1 hour before infusion, and 12 hours after infusion. Prophylactic G-CSF could be administered after completion of cycle 1 for neutropenia. A delay in therapy of up to 2 weeks was permitted for toxicity reasons, and was mandated for the following toxicities: absolute neutrophil count $<1.5 \times 10^9$/L and/or platelet count $<100 \times 10^9$/L before administration of the subsequent cycle of treatment; grade 4 neutropenia lasting more than 7 days; grade 3 or 4 infection; febrile neutropenia; grade 4 nausea/vomiting; grade 3 or 4 diarrhea; grade 2 neurotoxicity; grade 2 asthenia; alanine and aspartate aminotransferases $>2.5 \times$ ULN; alkaline phosphatase $>5.0 \times$ ULN; total bilirubin $>1.0 \times$ ULN; alanine and aspartate aminotransferases $>1.5 \times$ ULN plus alkaline phosphatase $>2.5 \times$ ULN. Patients who had not recovered from the toxicity after that period were removed from the study. Dose adjustments were not allowed.

In the 4 weeks before study entry, all patients underwent a complete physical examination, had their medical history taken, and underwent radiology assessments of measurable lesions (if this could be established with a chest X-ray and the patient had no symptoms suggesting a metastatic site that needed evaluation; no other radiological evaluation was performed, reflecting what occurs in clinical practice). No radiological evaluation was done beyond the diagnosis of stage IV. Other baseline assessments included a complete blood count (white blood cells, neutrophils, platelets and hemoglobin), blood chemistry (to include assessment of liver and renal function), assessment of creatinine clearance, and an electrocardiogram.

All sites of measurable disease were re-evaluated by clinical and radiological examination (X-ray, bone scans, or other indicated imaging techniques) every two-treatment cycles (16 weeks), or earlier in cases of suspected disease progression, and at the end of the last treatment cycle. The primary endpoint of the study was overall response rate (ORR). Secondary endpoints included time to progression, duration or response, and 1- and 2-year survival. Responses were classified according to the new revised WHO response criteria. A complete response (CR) was defined as disappearance of all known disease (measurable and evaluable) and absence of any new malignant lesions, whereas a partial response (PR) was a $\geq 50\%$ decrease in the size of all lesions. Complete and partial responses had to be confirmed at two evaluations not less than 4 weeks apart. Progressive disease (PD) was defined as a $\geq 50\%$ or 10 cm increase (whichever is the smaller) in the sum of the products of all measurable lesions, evident worsening of evaluable disease, or the appearance of a new lesion, whereas stable disease (SD) was defined as any modification that did not meet the criteria for complete response, partial response, or progressive disease. A second radiologist verified measurements from patients classified as responders. Patients were regularly assessed for potential adverse events and disease-related signs and symptoms. Differential blood counts were performed each week, and blood chemistry parameters were monitored before the second and fourth infusion of each cycle. Toxicity was graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC).

All analysis were done on an intention-to-treat basis. ORR was defined as the percentage of patients achieving a complete or partial response, and 95% confidence intervals (95% CI) were calculated for this parameter. Disease progression was defined as clinical progression or death due to any cause, and progression and survival times were dated from the time the consent form was signed until the event occurred. Progression-free survival and overall survival were estimated using the Kaplan-Meier method. Demographic variables of continuous nature were described by medians and ranges, and discrete variables were summarized in frequency tables. Data were censored on 12 March 2002. Investigators were not asked to categorize adverse events according to the likelihood of them being related to study medication. Therefore, adverse events data are reported in the result sections on an 'all-cause' basis rather than as possibly or probably related to study medication. As pain and pulmonary adverse events are most likely to reflect the underlying lung cancer, these events have not been included in the nonhematological adverse events tables.

RESULTS

Between January and October 2000, 36 patients from three different academic medical centers in Brazil were enrolled in the study. All patients received at least one

dose of treatment and were included in the efficacy and safety analysis. Characteristics and baseline demographics for these patients are described in Table 1. The study population was predominantly male (72%) and have median age 59 years (33% were aged >65 years). The primary histological diagnosis was adenocarcinoma (69%) followed by squamous cell carcinoma (19%). Eighty-three per cent of patients had an ECOG performance status of 0 or 1.

Table 1 - Patient and disease characteristics at baseline

Baseline characteristics	No. of patients (%)
Total	36
Gender	
Male	26 (72)
Female	10 (28)
Age (years)	
Median [range]	59 [38–76]
Time from diagnosis to enrollment (months)	
Median [range]	1 [0.3–11.0]
Histologic tumor subtype	
Adenocarcinoma	25 (69)
Large cell carcinoma	1 (3)
Squamous cell carcinoma	7 (19)
Carcinoma broncoalveolar	1 (3)
NSCLC NOS	2 (6)
ECOG performance status	
0	15 (42)
1	15 (42)
2	6 (17)

ECOG = Eastern Cooperative Oncology Group.

A total of 81 treatment cycles and 424 treatment infusions were administered during the study. Overall, 39% of patients received just one treatment cycle, 30.5% received two cycles, and 30.5% received the planned three to six cycles of treatment. The median number of infusions received was 9 (range: 1-36), of which 91% were administered without delay. Of the 40 infusions that had to be delayed, 18 were due to hematological toxicity, 4 were due to nonhematological toxicity, 7 were for adverse events unrelated to study medication, and 11 were for other reasons. At the cut-off date of 12 March 2002, 2 (6%) patients had received the maximum number of cycles permitted in the protocol (6 cycles). Among the other patients, study medication was stopped because of disease progression or adverse events

in 18 (50%) and 9 (25%) patients, respectively. There were six deaths, all of which were considered to be a consequence of the cancer, and one patient was lost to follow-up.

Therapy was extremely well tolerated. Hematological and grade 3-4 nonhematological toxicities are reported in tables 2 and 3 by NCI-CTC grade. Neutropenia was the most common hematological toxicity, being reported by 5 (14%) patients. Four patients experienced anemia, although with the exception of one case, this was of grade 2 or below, and one patient had grade 3 thrombocytopenia. There was one case of febrile neutropenia (grade 4), which developed after 3 infusions of chemotherapy. The patient was hospitalized, received antibiotics, parenteral fluids and supportive care, and was withdrawn from the study. Patients who developed neutropenia without fever did not received G-CSF or prophylactic antibiotics. Fatigue was the most frequent grade 3-4 nonhematological toxicity, reported by 19% of patients. However, no patient discontinued therapy because of this adverse event. Other grade 3-4 nonhematological toxicities included diarrhea (14% of patients) and infection (8% of patients). Eight (22%) patients experienced fluid retention, although in all cases this was of grade 2 or below. No grade 3-4 nausea, vomiting, neurosensory or neuromotor disorders, fever or weight loss. No patients experienced a hypersensitivity reaction necessitating additional treatment.

Table 2 - Hematological toxicities reported by patients receiving weekly docetaxel monotherapy first line

	No. of patients with worst NCI grade (%) [n=36]				
	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Neutropenia	1 (3)	0 (0)	1 (3)	3 (8)	5 (14)
Anemia	1 (3)	2 (6)	1 (3)	0 (0)	4 (11)
Thrombocytopenia	0 (0)	0 (0)	1 (3)	0 (0)	1 (3)

Table 3 - Grade 3-4 nonhematological toxicities in patients receiving weekly docetaxel monotherapy first line (irrespective of likely relationship to study medication)

	No. of patients with worst NCI grade (%) [n=36]		
	Grade 3	Grade 4	Total
Fatigue	6 (17)	1 (3)	7 (19)
Diarrhea	1 (3)	4 (11)	5 (14)
Anorexia	2 (6)	0 (0)	2 (6)
Infection	2 (6)	1 (3)	3 (8)
Epigastralgia	1 (3)	0 (0)	1 (3)
Stomatitis	1 (3)	0 (0)	1 (3)

Of the 36 patients enrolled, 5 patients had a partial response, giving an overall response rate of 14% (95% CI: 3-25%). An additional group of 9 patients (25%)

had minor responses (including one patient with a 47% reduction of tumor mass) or stable disease lasting more than 17 weeks (median 27 weeks, range: 17.6-52.9 weeks). Twelve patients had progressive disease, and 10 patients were considered as nonresponders. Nonresponders consisted of patients who died before tumor evaluation, or those who were withdrawn from the study because of symptomatic progression or toxicity. The median duration of response was 3.4 months (range: 2.1-8.4 months). Of the 14 responding or stable disease patients, 3 had not progressed after 12 months, and a further 7 remained free from progression at 6 months. The median time to progression and the median survival for all patients enrolled was 3.4 months (95% CI: 2.2-4.9 months) and 7.0 months (95% CI: 5.6-9.1 months), respectively (Fig. 1 and Fig. 2). Patients who were still alive were followed up for a median of 19.5 months (95% CI: 19.0-26.5 months). The 1-year survival was 32%. Among the 6 patients with an ECOG performance status of 2 at baseline, there were no responders, and the median survival was only 5 weeks. When only those patients with ECOG performance status 0-1 were considered, the median time to progression and the median survival for all patients enrolled was 3.8 months (95% CI: 2.9-6.2 months) and 7.9 months (95% CI: 5.9-12.3 months), respectively.

Figure 1 - Time to disease progression among 36 NSCLC patients receiving weekly docetaxel monotherapy first-line.
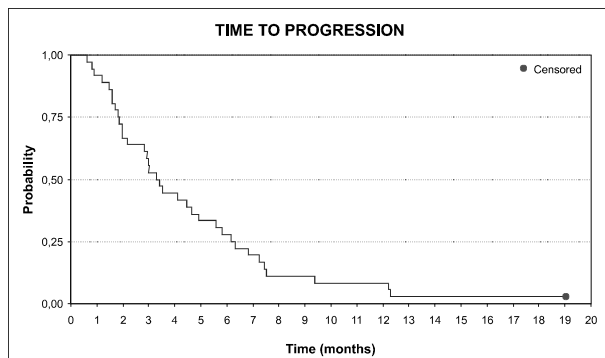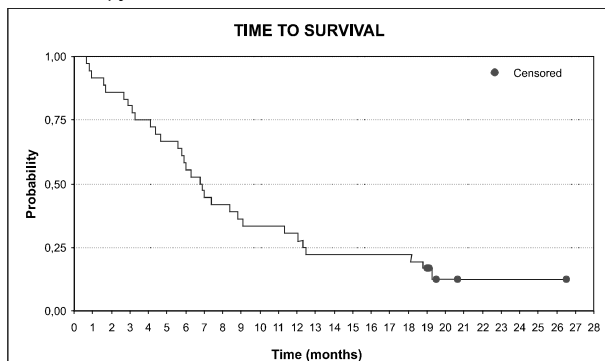

Figure 2 - Survival of 36 NSCLC patients receiving weekly docetaxel monotherapy first-line.

Eleven (31%) patients received platinum-based chemotherapy after disease progression on study medication; one of these patients had a documented partial response to the second-line regimen.

DISCUSSION

The use of alternative dosing schedules to improve the tolerability of systemic chemotherapeutic agents is an area that warrants further investigation. This is particularly true for cancers, such as advanced NSCLC, where the survival advantage of chemotherapy is relatively small, and it is therefore important that the potential benefits of therapy are not counter-balanced by treatment-related side effects[17]. In the present study the feasibility of using a weekly docetaxel dose of 36 mg/m^2 instead of the standard 75-100 mg/m^2 every 3 weeks in patients with advanced NSCLC was investigated, with the objective of minimizing drug-related toxicity whilst maintaining activity. Although other groups have evaluated a weekly low-dose docetaxel monotherapy regimen in platinum-pretreated NSCLC patients[15, 16], and as first-line therapy in elderly patients with NSCLC[12], to our knowledge this is the first study to evaluate weekly docetaxel monotherapy as first-line chemotherapy for all patients considered candidates for palliative treatment.

Weekly docetaxel was very well tolerated in the present trial, and toxicity was minimal compared with that usually observed with standard platinum-based chemotherapy regimens. As reported in other studies of weekly low-dose docetaxel[12, 15, 16], the incidence of grade 3-4 myelosuppression was found to be substantially lower than that reported with the standard once-every-3-weeks docetaxel regimen: grade 3-4 neutropenia occurred in approximately one-quarter of all patients in the present study compared with 89% in phase II studies with the standard docetaxel regimen[18], and only one patient in the present study was hospitalized with febrile neutropenia. Furthermore, there was only one case of grade 3-4 thrombocytopenia in the present study, and only one patient developed grade 3-4 anemia. Many of the nonhematological toxicities also appeared to be reduced by administering docetaxel every week as opposed to every 3 weeks. In particular, there were no cases of grade 3-4 nausea, vomiting, neurosensory or neuromotor disturbances, cutaneous reaction, edema, or fever in the present study. Fatigue was the most commonly reported grade 3-4 nonhematological toxicity, occurring in 19% of all patients treated. However, a large proportion of these episodes of fatigue are likely to be related to the disease itself rather than to the medication. Indeed, in a recent large randomized trial of docetaxel

versus best supportive care in platinum-naïve patients with advanced NSCLC, grade 3-4 fatigue/asthenia was reported for 22% of patients treated with docetaxel 100 mg/m² and in 28% of patients receiving best supportive care alone[8]. In the present study, however, a relatively high level of grade 3-4 diarrhea (14%) was found.

The 14% response rate achieved in our study is in line with the 19% response rate reported by Hainsworth et al.[12] in a similar study, but it is disappointing when compared with those reported (13-38%) in other phase II studies of once-every-3-week docetaxel schedules in chemotherapy-naïve patients with advanced NSCLC. However, it is important to remember that our analysis was conducted on an intention-to-treat basis, rather than on the frequently used per-protocol or 'evaluable' basis. Furthermore, an additional group of 9 patients (25%) in our study had minor responses and stable disease lasting more than 17 weeks, and therefore clearly derived benefit from the treatment (one of these patients had a 47% reduction of his tumor mass). The majority of patients with responses and stable disease had prolonged (>6 months) control of their lung cancer.

In our study population, weekly treatment with docetaxel was associated with a median survival of 7 months and a 1-year survival rate of 32%. These values are comparable with those reported in phase II trials of docetaxel 100 mg/m² monotherapy every 3 weeks in untreated patients with advanced NSCLC (median survival 6-11 months; 1-year survival rate, 25-45%) and somewhat higher than the 5-months survival and 27% 1-year survival rate reported by Hainsworth et al.[12] in a study using the same weekly dosing schedule for docetaxel in previously untreated elderly patients with advanced NSCLC. The lower survival in the study by Hainsworth et al.[12] may, however, be related to the fact that their patient population was substantially older than those in the present study (median age 71 vs 59 years), and included a high proportion of patients with an ECOG performance status of 2 (41% vs 17%). Indeed, in our study, patients with an ECOG performance status of 2 had a median survival of only 5 weeks, suggesting no benefit in chemotherapy in this group. Weekly docetaxel has also demonstrated good survival outcomes when used as second-line treatment in advanced NSCLC. In patients with recurrent or refractory NSCLC, previously treated with no more than one chemotherapy regimen, Lilenbaum et al.[15] reported that weekly docetaxel 36 mg/m² was associated with a median survival and a 1-year survival rate of 8 months and 31%, respectively, when all patients were considered, increasing to 12 months and 42%, respectively, in the subgroup of patients with an ECOG performance status of 0-1. Lastly, given the lack of

direct correlation between response rate and survival in NSCLC[19-21], it can be argued that the median and 1?year survival are more important determinants of a successful outcome than response rate.

Weekly paclitaxel monotherapy has also been evaluated in advanced NSCLC. In a recent phase II study, Fidias et al.[13] administered paclitaxel 90 mg/m² weekly for 6 consecutive weeks of an 8-week cycle to 35 elderly patients (aged ³70 years) with stage IIIB-IV NSCLC, to achieve a response rate of 23%, a median survival of 10 months, and a 1-year survival rate of 45%. The most commonly reported grade 3-4 toxicities associated with this regimen were hyperglycemia (18%), infection (9%), neutropenia (6%), and neuropathy (6%). In a phase II study reported by Akerley[22], 56% of patients with stage IIIB-IV NSCLC responded to weekly paclitaxel therapy; the 1-year survival rate being 53%. The response and survival rates reported by Akerley[22] are extremely impressive, even when compared with those achieved with combination chemotherapy. However, the Akerley study[22] used very high doses of paclitaxel - 175 mg/m² - and this was associated with significant neurotoxicity (32% of patients developed grade 2-3 neuropathy).

The present study indicates that a low-dose weekly docetaxel schedule is likely to have an improved therapeutic index in patients with advanced NSCLC as compared with the conventional once-every-3-weeks schedule. Randomized phase II and III trials comparing these two schedules are ongoing, and preliminary results from these verify this finding[20,23,24]. Other avenues for investigation include the use of low-dose weekly docetaxel as part of a combination regimen in advanced NSCLC. In view of the relatively low level of myelosuppression produced with weekly docetaxel, this schedule is a particularly attractive option when considering combining docetaxel with other myelosuppressive agents, and may negate the need for further dose reductions. When the present study was originally concluded there was a lack of evidence that single-agent chemotherapy with new agents was inferior to platinum-based combinations. However, recent results from Lilenbaum et al.[25] have concluded the contrary. Despite this, some patients in our trial clearly benefited from the low toxicity elicited by docetaxel monotherapy. Single-agent docetaxel could still be investigated in the future as first-line therapy in a study of 'window of opportunity'.

Niho et al.[26] have recently reported the successful use of docetaxel 35 mg/m² plus cisplatin 25 mg/m² for 3 consecutive weeks followed by a 1-week rest in chemotherapy-naïve patients with stage IIIB-IV NSCLC. This combination achieved an objective response rate of 30%, a median survival of 13 months, and a 1-year

survival rate of 54%, whilst causing minimal myelosuppression. The combination of docetaxel 30 mg/m² plus either gemcitabine 800 mg/m² or vinorelbine 20 mg/m² for 3 consecutive weeks in a 4-week cycle has also been evaluated as second-line treatment in patients with advanced NSCLC27, but neither regimen demonstrated a level of activity suggesting any advantage over weekly docetaxel monotherapy in this setting. Furthermore, the vinorelbine-docetaxel regimen was poorly tolerated[27]. Triplet combinations incorporating weekly docetaxel schedules are also being investigated. Indeed, a small phase II study of docetaxel (33 mg/m²), gemcitabine (700 mg/m2) plus carboplatin (AUC 1.8) in previously untreated patients with stage IIIB-IV NSCLC has generated a median survival of 18 months and a 1-year survival rate of 76%, which is exceptionally high for this setting[28].

In conclusion, the results from the present study indicate that a low-dose weekly schedule of docetaxel is a well tolerated schedule with a compatible response rate, when single agents were used in first-line therapy patients with advanced NSCLC, and provided an additional option for patients who may have difficulty tolerating the standard once-every-3-weeks regimen, with an acceptable toxicity. This low-dose weekly schedule warrants further investigation both as monotherapy and in combination with other agents.

REFERENCES

1. Jamison DT, Creese A, Prentice T. The world health report 1999: making a difference. Geneva: World Health Organization; 1999.

2. Livingston R. Current management of unresectable non-small cell lung cancer. Oncology. 1997;11 Suppl 12:11-5.

3. Rapp E, Pater JL, Willan A, Cormier Y, Murray N, Evans WK, et al. Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer: report of a Canadian multicenter randomized trial. J Clin Oncol. 1998;6:633-41.

4. Chemoterapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. Br Med J.1995;311:899-909.

5. Comer AM, Goa KL. Docetaxel: a review of its use in non-small cell lung cancer. Drugs Aging. 2000;17:54-80.

6. Roszkowski K, Pluzanska A, Krzakowski M, Smith AP, Saigi E, Aasebo U, et al. A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naive patients with metastatic or non-resectable localized non-small cell lung cancer

(NSCLC). Lung Cancer. 2000;27:145-57.

7. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The Tax 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol. 2000;18:2345-62. Erratum in: J Clin Oncol. 2004;22(1):209.

8. Shepherd FA, Dance J, Ramlau R, Mattson K, Gralla R, O`Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol. 2000;18:2095-103.

9. Gridelli C, Frontini L, Barletta E, Rossi A, Barzelloni ML, Scognamiglio F, et al. Single agent docetaxel plus granulocyte-colony stimulating factor (G-CSF) in previously treated patients with advanced non-small cell lung cancer. A phase II study and review of the literature. Anticancer Res. 2000;20:1077-84.

10. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med. 2002;346:92-8.

11. Fossella F. Docetaxel + cisplatin (DC) and docetaxel + carboplatin (DCb) vs vinorelbine + cisplatin (VC) in chemotherapy-naïve patients with advanced and metastatic non-small cell lung cancer (NSCLC): results of a multicenter, randomized phase III study. Eur J Cancer. 2001;37 Suppl 6:562.

12. Hainsworth JD, Burris HA 3rd, Litchy S, Morrissey LH, Barton JH, Greco FA. Weekly docetaxel in the treatment of elderly patients with advanced non-small cell lung carcinoma. A Minnie Pear Cancer Research Network Phase II Trial. Cancer. 2000;89:328-33.

13. Fidias P, Supko JG, Martins R, Boral A, Carey R, Grossbard M, 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. Kamen BA, Rubin E, Ainsner J, Glatstein E. High-time chemotherapy or high time for low dose. J Clin Oncol. 2000;18:2935-7.

15. Lilenbaum R, Schwartz M, Siegel L, Belette F, Blaustein A, Wittlin FN, et al. Phase II trial of weekly docetaxel in second-line therapy for nonsmall cell lung carcinoma. Cancer. 2001;92:2158-63.

16. Valerio MR, Russo A, Latteri MA, Modica G, Gulotta G, Armata MG, et al. Weekly docetaxel as II line therapy in non-small cell lung cancer: an interim analysis of a phase II study. Lung Cancer. 2001;34 Suppl 4:S31-5.

17. Ramalingram S, Belani C. Meaningful survival in lung cancer patients. Semin Oncol. 2002;29 Suppl 4:125-31.

18. Fossella FV, Lee JS, Berille J. Summary of phase II data of docetaxel (Taxotere), an active agent in the first-and second-line treatment of advanced non-small cell lung cancer. Semin Oncol. 1995;22 Suppl 4:22-9.

19. Belani C, Natale RB, Lee JS. Randomized phase III trial comparing cisplatin/etoposide versus carboplatin/paclitaxel in advanced and metastatic non-small cell lung cancer. Proc Am Soc Clin Oncol. 1998;17:1752.

20. Crinó L, Conte P, Marinis F. A randomized trial of gemcitabine cisplatin (GP) versus mitomycin, ifosfamide and cisplatin (MIC) in advanced non-small-cell lung cancer (NSCLC): a multicenter phase III study. Proc Am Soc Clin Oncol. 1998;18:1750.

21. Cardenal F, López-Cabrerizo MP, Antón A, Alberola V, Massuti B, Carrato A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol. 1999;17:12-8.

22. Akerley W. III. Paclitaxel in advanced non-small cell lung cancer: an alternative high-dose weekly schedule. Chest. 2000;117(4 Suppl 1):152S-5S.

23. Schütte W, Nagal S, Lautenschläger C. Randomized phase III study of weekly versus three-weekly docetaxel as second-line chemotherapy for advanced non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol. 2002:1228.

24. Gervais R, Ducoloné AM, Breton JL. Multicenter, randomised, phase II trial of docetaxel (Taxotere) 75 mg/m2 q3w versus 40 mg/m2 weekly in patients with pretreated non small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol. 2002:1238.

25. Lilenbaum RC, Herdon J, List M. Single-agent (SA) versus combination chemotherapy (CC) in advanced non-small cell lung cancer (NSCLC): a CALGB randomized trial of efficacy, quality of life (QOL), and cost-effectiveness. Proc Am Soc Clin Oncol. 2002:2

26. Niho S, Ohe Y, Kakinuma R, Kubota K, Matsumoto T, Ohmatsu H, et al. Phase II study of docetaxel and cisplatin administered as three consecutive weekly infusions for advanced non-small cell lung cancer. Lung Cancer. 2002;35:209-14.

27. Hainsworth JD, Burris HA 3rd, Billings FT 3rd, Bradof JE, Bake M, Greco FA. Weekly docetaxel with either gemcitabine or vinorelbine as second-line treatment in patients with advanced nonsmall cell lung carcinoma: Phase II trials of the Minnie Pearl Cancer Research Network. Cancer. 2001;92:2391-8.

28. Tezcan H, Grosset AB, Tezcan AZ. Weekly chemotherapy with docetaxel, carboplatin and gemcitabine in stage IIIB and IV non-small cell lung cancer: a phase II study. Proc Am Soc Clin Oncol. 2002:2759.