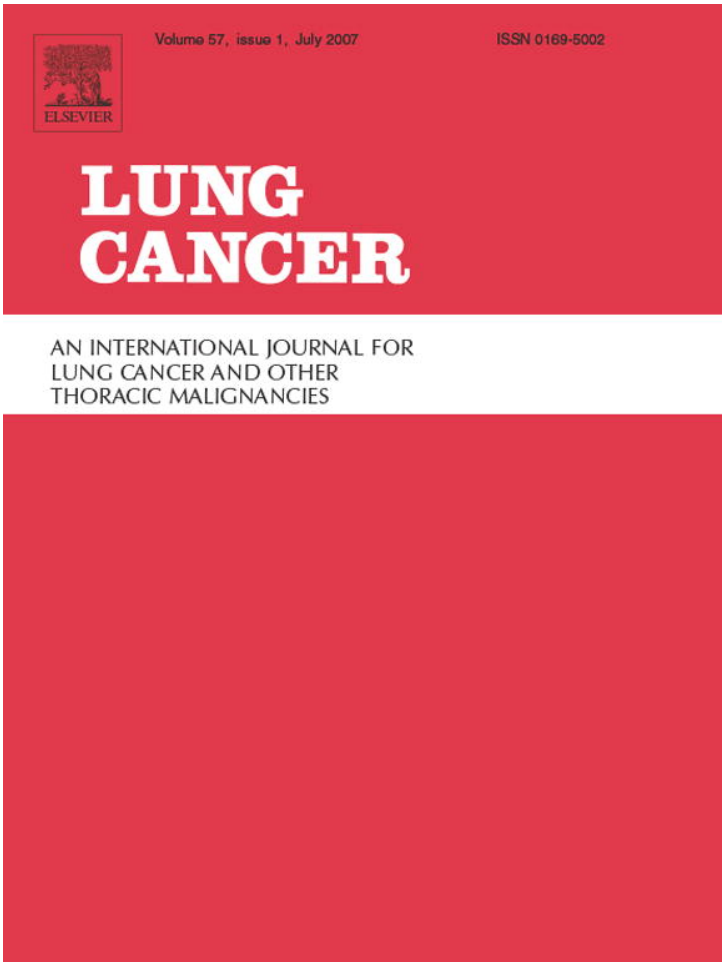

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An open multicenter phase II trial of weekly docetaxel for advanced-stage non-small-cell lung cancer in elderly patients with significant comorbidity and/or poor performance status: The GFPC 02-02b study

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Summary
Context: The objective of this study was to evaluate the feasibility and activity of weekly docetaxel monotherapy in frail elderly patients with advanced-stage non-small-cell lung cancer, selected on the basis of their precise age, general condition, and number of comorbid disorders (Charlson score).
Methods: Analysis of the response rate, toxicity, quality of life, median survival and 1-year survival rates after 1—3 six-week cycles of docetaxel 30 mg/m^2 weekly.
Results: Fifty patients were enrolled and 42 were assessable. Five patients (10%, [3.7—22.6]) had objective responses, 14 (28%, [16.9—41.6]) had stable disease, and 23 (46%, [32.6—52.8])

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progressed. The main grade 3—4 toxicity was fatigue (30%). Quality of life remained stable during treatment. The median survival time was 4.3 months, and the 1-year survival rate was 21.8%.
Conclusion: In frail elderly patients selected on the basis of their age, general condition and comorbidity, weekly docetaxel monotherapy has acceptable toxicity and does not negatively affect quality of life. In contrast, it has only moderate activity.

1. Introduction

Two-thirds of patients with non-small-cell lung cancer (NSCLC) are over 65 years [1] and some are particularly fragile because of their old age, poor general condition, or comorbidity. Trials specifically involving elderly subjects, and especially fragile elderly subjects, are rare in thoracic oncology [2]. The notion of ''clinical benefit'' is now gradually supplanting classical quantitative outcome measures, i.e. the tumor response rate and the survival rate, in the geriatric setting [3]. For patients under 65 who are in good general health, the recommended first-line treatment for metastatic or locally advanced NSCLC consists of dual-agent platinum-based chemotherapy. There is no consensus on the management of patients over 65, and especially those over 70 [4], but ASCO recommends monotherapy for elderly patients and patients with PS 2 [5]. In this latter population, dual-agent chemotherapy with cisplatin [6] or carboplatin [7] can be particularly toxic. Platinum-free dual-agent therapy is feasible [8,9], but its toxicity in particularly fragile patients is poorly documented and it has not been shown to be more effective than monotherapy [4]. In elderly subjects, only monotherapies have proven to be advantageous, in terms of survival and quality of life, relative to best supportive care [10]. This is particularly the case of vinorelbin and docetaxel, with lower toxicity during weekly administration. Thus, in a population of elderly patients and/or patients with poor performance status, at a dose of 36 mg/m^2, 6 weeks every 8 weeks, docetaxel gave an objective response rate of 18% and disease stabilization in 34% of patients, but with a significant toxicity [11]. Lower doses of docetaxel have recently been studied [12] and the results confirm that the weekly schedule is a good alternative for patients at risk of severe neutropenia.

One limitation of previous studies in this setting is that patients over 65 were selected on the basis of their performance status alone, as for the general population of patients with NSCLC. Indeed, in addition to performance status, the patient's precise age and comorbidity [13] may also influence the tolerability of chemotherapy and, indirectly, its efficacy. Specific geriatric scoring systems include the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), in which a severity index (SI) above 2 is associated with poor vital outcome [14]. The Charlson score combines age and comorbidity [15], and a score above 2 is also predictive of survival [16], independently of performance status [17].

The objective of this study was to evaluate the feasibility and activity of weekly docetaxel monotherapy in fragile elderly patients selected on the basis of geriatric criteria taking into account the precise age, general condition and comorbidity, as assessed using the Charlson score. A dose regimen of 30 mg/m^2/week was chosen, owing to the fragility of the study population.

2. Patients and methods

2.1. Study design

This was a multicenter, open-label, phase II study (GFPC 02-02b) of weekly docetaxel in selected elderly patients with unresectable advanced or metastatic NSCLC. Primary endpoints were the objective response rate (complete + partial responses), as determined with the RECIST method [18], the safety and tolerability of docetaxel Secondary endpoints were the disease control rate (objective reponse + stable disease) at study completion, progression-free survival, overall survival and quality of life (QoL). QoL was measured with the Spitzer index (19) and the Lung Cancer Symptom Scale (LCSS) (20). The protocol was approved by an independent ethics committee in Marseille, on behalf of all participating centers, and the study was conducted in accordance with Good Clinical Practices and the Helsinki Declaration (World Medical Association, 1997).

2.2. Eligibility criteria

The following oncologic inclusion criteria applied: cytologically or histologically proven NSCLC of stage IV or NIB with T4 stage by neoplastic pleurisy, not previously treated with chemotherapy, and a measurable tumor (18); life expectancy more than three months, and biological results compatible with chemotherapy (bilirubin < 1.25 ULN, transaminase activity < 3 ULN, alkaline phosphatase < 2.5 ULN, polymorphonuclear neutrophil count > 1.5 G/l, and platelet count > 100 G/l).

We also applied specific geriatric inclusion criteria, combining age, the Charlson comorbidity score, and performance status (Table 1).

The following oncologic non-inclusion criteria applied: small-cell lung cancer, bronchioloalveolar carcinoma, previous chemotherapy; symptomatic brain metastases, unstable heart disease, uncontrolled infection, grade > 2 neuropathy; a concurrent metastatic malignancy; and permanent contraindications to the use of steroids.

The geriatric non-inclusion criteria were age >89 years and a combined comorbidity-PS score incompatible with the values shown in Table 1.

2.3. Treatment

The treatment schedule comprised a maximum of three 8-week treatment cycles consisting of weekly docetaxel 30 mg/m^2 for 6 consecutive weeks followed by a 2-week treatment-free period. The patients were assessed after each cycle and a final assessment was done after three cycles. Erythropoietin (epoietin alpha, 4,00,000 units once

Table 1 Geriatric inclusion criteria

Age score	Charlson score	Age + Charlson score	PS	Regimen
65—69 = 2	0—2	[2—4]	0—1	Not eligible
	0—2	[2—4]	2	Not eligible
	3—4	[5—6]	0—1	Not eligible
	3—4	[5—6]	2	Docetaxel
	5—6	[7—8]	0—2	Docetaxel
70—79 = 3	0—1	[3—4]	0—1	Not eligible
	0—1	[3—4]	2	Docetaxel
	2—5	[5—8]	0-2	Docetaxel
80—89 = 4	0	[4]	0-1	Not eligible
	1—4	[5—8]	0-1	Docetaxel
	Any	Any	2	Not eligible

a week) was used systematically when the hemoglobin level fell below 12 g/l. The use of neutrophil growth factors was left to the investigators. Infusions could be postponed for up to 2 weeks if the patient had not fully recovered from the hematological toxicity of the previous cycle. Two 25% dose reductions were allowed, and dose re-escalation was prohibited. The trial chemotherapy was withdrawn if chemotherapy had to be delayed twice; if severe adverse effects occurred; if two dose reductions were necessary; in case of documented disease progression; treatment completion (3 cycles); or patient refusal to continue.

2.4. Assessments

2.4.1. Primary endpoints

2.4.1.1. Activity. Objective assessments of the tumor responses were done at the end of each treatment cycle. All responses were reviewed and confirmed by a panel of experts convened by Groupe Français de Pneumo-Cancérologie (GFPC).

2.4.1.2. Safety and tolerability. Patients were monitored for adverse events, biological abnormalities, vital signs and electrocardiographic changes, throughout the study and for 30 days following the last dose of study treatment. The nature, incidence and severity of adverse events were recorded and graded using the NCI-CTC Version 2.0 system (National Cancer Institute, 1999).

2.4.2. Secondary endpoints

Patients were considered to have controlled disease if they had an objective response lasting ≥4 weeks, or stable disease for ≥6 weeks during the study or at study closure. Progression-free survival (PFS) was calculated from the date of first treatment to the first date of disease progression or death of any cause, or the last on-trial tumor assessment. Overall survival (OS) was calculated from the date of first treatment to the date of death of any cause, or the last date the patient was known to be alive.

2.4.3. Statistical analysis

Quantitative data were expressed as the population, number, mean, standard deviation and range; qualitative data were expressed as the population, number and frequency. All tests were two-sided, and significance was assumed at $p > 0.05$. Quantitative variables were compared with Student's t test or with Wilcoxon's test when the groups were too small or the data were not normally distributed. Qualitative parameters were compared with the χ^2 test for theoretical group sizes above 5, and with Fisher's test in other cases.

Assuming that this chemotherapy designed for fragile patients should be rejected if the objective response rate was 10% or less, and would be validated by a response rate of 30% or more, with an alpha risk of 0.07 and a beta risk of 0.08, the number of subjects required was 39 [21]. PFS and OS were assessed by means of Kaplan—Meier analysis at study closure. A Cox model was used to identify explanatory variables for survival among the following: sex, age, the comorbidity score, performance status, the Spitzer score at enrollment, and the disease stage.

Quality of life was assessed during the initial work-up (intention-to-treat) and at the end of each cycle, using the Spitzer index [19] and the lung cancer symptom scale (LCSS) [20]. Each item of the Spitzer score is attributed a score of 0—2, with higher values reflecting better health. A mean global score is then calculated. Each item of the LCSS questionnaire is scored from 0 to 10: the higher the score, the more intense the symptom. The LCSS questionnaire yields two scores: a symptom score, and a global score.

Quantitative scores are expressed as the mean, the median and the confidence interval. The groups were compared with Fisher's exact test. Statistical analyses were done with SAS software Version 8.02 (Institute Inc., Carry, USA).

3. Results

3.1. Study population

Between June 2003 and December 2004, 17 centers enrolled 50 patients in this study. The median age was 76.6 years (70—84 years) and 88% of the patients were men; 88% had stage IV disease, 48% epidermoid carcinoma, 40% adenocarcinoma and 12% undifferentiated carcinoma (Table 2). Fifty-two percent of patients were between 70 and 79 years old and had two or more comorbid disorders and a performance status of 0—2; 24% of patients had 0 or 1 comorbid

Table 2 Characteristics of the patients

Age (years) [mean (range)]	76.6 [70—84]
Sex (%)	
Male	88
Female	12
ECOG PS (%)	
0	22
1	46
2	32
Clinical stage (%)	
IV	88
IIIB	12
Histology (%)	
Squamous cell	48
Adenocarcinoma	40
Undifferentiated	12
Charlson score [mean (range)]	1.9 [0—5]
Comorbidity (age + Charlson) [mean (range)]	5.1 [3—8]
Weight loss (>10%)	22

disorder but a PS of 2; and 24% of patients were over 80 years old and had at least one comorbid disorder (Table 3). Forty-two patients (84%) had at least one comorbid disorder, consisting of chronic obstructive pulmonary disease (22.4%), a history of heart failure (18.4%), peripheral arterial disease (17.1%) or diabetes (17.1%).

The patients received a mean of 1.5 ± 0.8 docetaxel cycles. The reasons for premature treatment cessation were progression ($n = 27$), toxicity ($n = 12$), intercurent disease ($n = 6$), or the patient's decision ($n = 1$). The relative dose intensity was 91.7% overall, 96.8% in cycle 1, 92.6% in cycle 2 and 83.3% in cycle 3.

Among the 42 assessable patients, objective responses occurred in 5 patients (10%, [3.7—22.6]), stabilization was achieved in 14 cases (28%, [16.9—41.6]), and progression occurred in 23 cases (46%, [32.6—52.8]). The disease was thus controlled in 19 cases (38%, [24.6—52.8]).

The ITT population of all 50 patients was assessable for safety. The most common non-haematological adverse events were diarrhea and fatigue (Table 4). Haematological adverse events were rare, with no cases of grade 3—4 neutropenia. Only 4% of patients developed grade 3—4 anemia, probably because of the routine use of erythropoietin alfa as soon as the hemoglobin level fell below 12 g/l. Indeed, 60% of patients received epoietin alpha, while only 2% received red cell transfusions and none received platelet transfusions.

Table 4 Most common adverse events

Adverse event	Patients $N = 50$ (%)	
	Grade 1/2	Grade 3/4
Anemia	17 (34%)	2 (4%)
Neutropenia	2 (4%)	0 (0%)
Thrombocytopenia	2 (4%)	0 (0%)
Nausea/vomiting	10 (20%)	1 (2%)
Fatigue	21 (42%)	15 (30%)
Peripheral neuropathy	4 (8%)	0 (0%)
Diarrhea	11 (22%)	1 (2%)
Infection	7 (14%)	3 (6%)

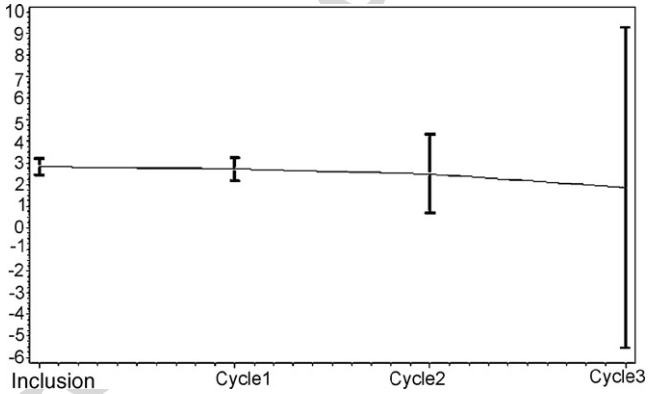

Fig. 1 Global LCSS score. Changes over time ($n = 44$) LCSS: lung cancer symptom scale.

Forty-four patients completed the initial QOL assessment before treatment: the median global LCSS score was 3.31 (95% CI, 2.73—3.81), the mean symptom score was 2.84 (2.46—3.22) and the mean Spitzer score was 7.0 (6.4—7.6). These scores did not change significantly during the study (Fig. 1), even when the response to treatment was taken into account. Multivariate analysis included the following baseline variables that were significant in univariate analysis: age, sex, the comorbidity score, performance status, the initial Spitzer score with two of its components (activity and daily life), the stage, and the histological type. Only the Spitzer index ($p < 0.0024$, HR = 1.73) was independently linked to survival.

Table 3 Age and comorbidity

Age score	Charlson score	Age + Charlson score	PS	Patients, $N = 50$
65—69 = 2	3—4	[5—6]	2	0
	5—6	[7—8]	0—2	0
70—79 = 3	0—1	[3—4]	2	12
	2—5	[5—8]	0—2	26
80—89 = 4	1—4	[5—8]	0—1	12

Forty-three of the 50 patients died before the closure date (14 February 2006) and the seven surviving patients were censored at the date of the last news for the survival analysis; for the analysis of time to progression, three patients were censored at the date of the last news. The median time to progression was 2.16 months (1.63—3.56 months), the median survival time was 4.33 months (1.73—11.1 months), and the one-year survival rate was 21.8%.

4. Discussion

Weekly docetaxel monotherapy was well tolerated in this phase 2 trial involving elderly patients with NSCLC selected on the basis of their age, comorbidity and performance status. Very few haematological adverse events occurred. The main non-haematological event was fatigue, which is probably explained in part by the fragility of these elderly patients. This single-drug chemotherapy regimen yielded objective responses in 10% of patients and disease stability in 28%. The median survival time was 4.33 months. The treatment did not appear to have a negative impact on quality of life. One possible explanation for this good tolerability is the low dose used (30 mg/m^2 rather than 36 mg/m^2 normally), but the decision to administer doxetaxel 6 out of every 8 weeks seems to increase the intensity of fatigue compared to administration 3 out of every 4 weeks [22]. This low dose was chosen on the basis of its better tolerability [23]. Several recent studies have compared weekly docetaxel to the standard 3-weekly schedule [23,12]. In a Spanish randomized phase III trial [23], 259 patients from 33 centers were randomized to receive either docetaxel 75 mg/m^2 every 3 weeks or docetaxel 36 mg/m^2 weekly for 6 weeks followed by 2 weeks of rest. Febrile neutropenia was significantly more frequent in the standard treatment arm but more patients in the weekly arm experienced mucositis. Another randomized phase III study (12) compared a weekly schedule (33.3 mg/m^2 for 6 weeks) to the standard dose (75 mg/m^2) in patients $\leq$75 years of age with an ECOG PS $\leq$2. No difference in the global QoL scores was found at 3 weeks. Pain, cough and hair loss were significantly milder with the weekly schedule, while diarrhoea was worse. Loss of appetite and overall health were significantly worse in the 3-week arm during the first week, while nausea and loss of appetite were more severe in the weekly arm during the third week. Grade 3—4 haematologic toxicity was significantly more frequent in the standard arm. At higher doses (40 mg/m^2) weekly administration remains significantly less toxic with respect to grade 3/4 leukopenia and neutropenia, but drug-induced pneumonitis is more frequent [24,25]. A recent literature-based meta-analysis [26] selected six randomized clinical trials (three phase III, two phase II, 1018 patients) and confirmed these results, with a significant advantage of weekly docetaxel with respect to grade 3—4 neutropenia (absolute benefit of 15—19%, without a survival improvement). In the 3-week schedule, even with a lower dose (60 mg/m^2), grade 3—4 neutropenia remained frequent (86.7% in the study by Takagawi et al.) [27].

Although modest, the activity observed in our study was similar to that reported with monotherapies in the recent literature: the ORR was 18% in the trial by Hainsworth (docetaxel 36 mg/m^2 weekly) and the median survival time was 5 months [11]; with oral vinorelbine the ORR was 11% and the median survival time 8.2 months [25]; and the ORR was 14.3% with gemcitabine at a dose of 1000 mg/m^2 3 out of every 4 weeks, and 28.2% at a dose of 1125 mg/m^2 given 2 out of every 3 weeks [28].

Patients over 65 fall into at least four categories with respect to NSCLC management: (1) patients under 70, or perhaps under 75, who are in excellent general health and can probably be treated in the same way as younger patients, with platinum-based dual-agent chemotherapy; (2) patients under 70 who are in mediocre general health and patients over 70 years who have comorbidity but are in good general health, who can receive dual-agent chemotherapy without platinum; (3) patients under 70 with severe comorbidity and those over 70 who are in poor general health (fragile elderly subjects), who can probably only tolerate monotherapy; and finally (4) as at younger ages, some elderly patients who are in very poor general health or who have severe comorbidity and should only receive symptomatic cares. The main originality of this study is that the patients were selected on the basis of geriatric criteria combining their precise age, performance status and comorbidity, as expressed using the Charlson score. These three items stratify the elderly population more precisely and make studies of patients over 65 more comparable. It is noteworthy that a recent study clearly showed that performance status does not correlate with the Charlson score [29,30]. However, PS remains one of the principal (and unfortunately one of the only) prognostic factors for survival in NSCLC.

Although this classification improves patient selection and allows treatment to be individually tailored, it probably remains suboptimal. Indeed, the Charlson score fails to give sufficient weight to certain comorbidities, such as moderate to severe renal failure, which is frequent in this population [31]. In addition, different comorbid disorders (elderly subjects have an average of five underlying health disorders) do not all have the same influence on treatment toxicity [32]. Finally, this approach does not take into account neuropsychological disorders, such as depression and cognitive deficits [33,34]. Indeed, Balducci et al. [1] have shown the importance of specific geriatric assessment taking into account functional, mental, social and nutritional status and daily activities.

If one were to follow SIOG recommendations [35], it would be necessary to use a minimum of a geriatric depression scale, the Folstein Mini Mental Status score, and a test of performance status, such as the Get Up and Go test, ADL, and especially IADL. Thus, a recent study [36] showed that quality of life and an instrumental activity index of daily life could be a good prognostic factor when combined with the Charlson score and performance status.

The main advantage of these evaluations is to improve the stratification of elderly patients and thereby to allow valid comparisons to be made among different studies. The use of a standardized geriatric evaluation that takes comorbidity into account therefore appears to be crucial for future trials in this population, as underlined by an expert meeting held in Italy in 2004 [4]. However, such tests must be sufficiently simple for use in clinical practice, as an excessively heavy battery of tests is unlikely to be adopted for routine use [4].

In conclusion, weekly docetaxel monotherapy for NSCLC in fragile elderly subjects with poor performance status and moderate to severe comorbidity is an alternative treatment with acceptable toxicity that does not negatively affect quality of life. The use of standardized specific geriatric evaluations appears to be crucial for future trials in this setting.

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References

[1] Balducci L. Lung cancer and aging. American Society of Clinical Oncology 2005 Educational Book; 587—591.
[2] Jatoi A, Hillman S, Stella PG, et al. Should elderly non-small-cell lung cancer patients be offered elderly-specific trials? Results of a pooled analysis from the North Central Cancer Treatment Group. J Clin Oncol 2005;23:9113—9.
[3] Balducci L, Extermann M. Management of cancer in older person: a practical approach. Oncologist 2000;5:224—7.
[4] 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.
[5] Pfister DG, Johnson DH, Azzoli CG, et al. Treatment of unresectable non-small-cell lung cancer guideline update 2003. J Clin Oncol 2004;22:330—53.
[6] Rossi A, Gridelli C. Chemotherapy of advanced non-small-cell lung cancer in elderly patients. Ann Oncol 2006;17:58—60.
[7] LeCaer H, Delhoume JY, Thomas PA, et al. Multicenter Phase II trial of carboplatin/vinorelbine in elderly patients with advanced NSCLC -efficacy and impact on quality of life: Groupe Français de PneumoCancérologie Study 9902. Clin Lung Cancer 2005;7:114—20.
[8] Frasci G, Lorusso V, Panza N, et al. Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small cell lung cancer. J Clin Oncol 2000;18:2529—36.
[9] 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 randomised trial. J Natl Cancer Inst 2003;95:362—72.
[10] 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.
[11] Hainsworth JD, Burris HA, Litchy S, et al. Weekly docetaxel in the treatment of elderly patients with advanced non-small cell lung carcinoma. A Minnie Pearl Cancer Research Network Phase II Trial. Cancer 2000;89:328—33.
[12] Gridelli C, Gallo C, Di Maio M, et al. A randomized clinical trial of two docetaxel regimens (weekly vs. 3 weeks) in the second-line treatment of non-small cell lung cancer. The DISTAL 01 Study Br J Cancer 2004;91:1996—2004.
[13] Lebitasy MP, Monnet I, Depierre A, et al. Management of elderly lung cancer patients in France: a national prospective survey by the French Intergroup of Thoracic Oncology. Proc Am Soc Clin Oncol 2004;765:8163.
[14] Firat S, Byhardt RW, Gore E, et al. Comorbidity and Karnofsky performance score in stage III non-small-cell lung cancer: an institutional analysis of patients treated on four RTOG studies. Int J Radiat Oncol Biol Phys 2002;54(2):357—64.
[15] Charlson ME, Pompei P, Ales K-L, et al. A new method of classifying prognostic comorbidity in longitudinal studies development and validation. J Chron Dis 1987;40:373—83.
[16] Frasci G. Chemotherapy of lung cancer in the elderly. Crit Rev Oncol Hematol 2002;41:349—61.
[17] Extermann M, Overcash J, Lyman GH, et al. Comorbidity and functional status are independent in older cancer patients. J Clin Oncol 1998;16:1582—7.
[18] Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205—16.
[19] Spitzer WO, Dobson AJ, Hall J, et al. Measuring the quality of life of cancer patients: a concise QL-index for use by physicians. J Chron Dis 1981;34:585—7.
[20] Hollen PJ, Gralla RJ, Kris MG, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies.Psychometric assessment of the Lung Cancer Symptom Scale. Cancer 1994;73:2089—98.
[21] Gehan EA. The determinatio of the number of patients required in a preliminary and follow-up trial of new chemotherapeutic agent. J Chron Dis 1961;13:346—53.
[22] Hainsworth JD. Practical aspects of weekly docetaxel administration schedules. Oncologist 2004;9:538—45.
[23] Camps C, Massuti B, Jimenez A, et al. Randomized phase III study of 3-weekly versus weekly docetaxel in pretreated advanced non-small-cell lung cancer: a Spanish Lung Cancer Group trial. Ann Oncol 2006;17:467—72.
[24] Chen YM, Shih JF, Perng RP, et al. A randomized trial of different docetaxel schedules in non- small cell lung cancer patients who failed previous platinum-based chemotherapy. Chest 2006;129:1031—8.
[25] Rossi D, Graziano F, Ugolini M, et al. Weekly docetaxel as second-line therapy in non-small cell lung cancer: a phase II study. Tumori 2004;90:50—3.
[26] Bria E, Cuppone F, Ciccarese M, et al. Weekly docetaxel as second line chemotherapy for advanced non-small-cell lung cancer: meta-analysis of randomized trials. Cancer Treat Rev 2006;32:583—7.
[27] Takagawi N, Segawa Y, Kishino D, et al. Clinical and pharmacokinetic study of docetaxel in elderly non small-cell lung cancer. Cancer Chemother Pharmacol 2004;54:230—6.
[28] Gridelli C, Manegold C, Mali P, et al. Oral vinorelbine given as monotherapy to advanced, elderly non-small-cell lung cancer: a multicenter phase II trial. Eur J Cancer 2004;40:2424—31.
[29] Lilenbaum R. Treatment of elderly patients with advanced non-small cell lung cancer American Society of Clinical Oncology. Educational Book 2006:468—70.
[30] Dujon C, Azarian R, Azarian V, et al. Lung cancer in the elderly: performance status and/or geriatric indice? Rev Mal Respir 2006;23:307—18.
[31] Read WL, Tierney RM, Page NC, et al. Differential prognostic impact of comorbidity. J Clin Oncol 2004;22:3099—103.
[32] Aapro M, Kohne CH, Cohen HJ, et al. Never too old? Age should be a barrier to enrollment in cancer clinical trials. Oncologist 2005;10:198—204.
[33] Extermann M, Meyer J, Me Ginnis M, et al. A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. Crit Rev Oncol Hematol 2004;49:69—75.

[34] Chodosh J, Petitti DB, Elliot M, et al. Physician recognition of cognitive impairment: evaluating the need for improvement. J Am Geriatr Soc 2004;52:1051—9.
[35] Extermann M, Aapro MS, Bernabei R, et al. Use of comprehensive assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol 2005;55:241—52.
[36] Maione P, Perrone F, Gallo C, et al. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol 2005;23:6865—72.