Gemcitabine plus Vinorelbine in Nonsmall Cell Lung Carcinoma Patients Age 70 Years or Older or Patients Who Cannot Receive Cisplatin

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BACKGROUND. Although the prevalence of nonsmall cell lung carcinoma (NSCLC) is high among elderly patients, few data are available regarding the efficacy and toxicity of chemotherapy in this group of patients. Recent reports indicate that single agent therapy with vinorelbine (VNB) or gemcitabine (GEM) may obtain a response rate of 20–30% in elderly patients, with acceptable toxicity and improvement in symptoms and quality of life. In the current study the efficacy and toxicity of the combination of GEM and VNB in elderly patients with advanced NSCLC or those with some contraindication to receiving cisplatin were assessed.

METHODS. Forty-nine patients with advanced NSCLC were included, 38 of whom were age $\geq$ 70 years and 11 were age $<$ 70 years but who had some contraindication to receiving cisplatin. All patients were evaluable for response and toxicity. Treatment was comprised of VNB, 25 mg/m^2, plus GEM, 1000 mg/m^2, both on Days 1, 8, and 15 every 28 days. Patients received a minimum of three courses unless progressive disease was detected.

RESULTS. One hundred sixty-five courses were administered, with a median of 3.6 courses per patient. The overall response rate was 26% (95% confidence interval, 15–41%). Two patients attained a complete response (4%) and 11 patients (22%) achieved a partial response. Eastern Cooperative Oncology Group performance status improved in 35% of those patients with an initial value $>$ 0, whereas relief of at least 1 symptom without worsening of other symptoms was noted in 27 patients (55%). The median time to progression was 16 weeks and the 1-year survival rate was 33%. Toxicity was mild. Six patients (12%) had World Health Organization Grade 3-4 neutropenia, 2 patients (4%) had Grade 3-4 thrombocytopenia, and 2 patients (4%) had Grade 3 neurotoxicity. Three patients with severe neutropenia (6%) died of sepsis. The median age of those patients developing Grade 3-4 neutropenia was significantly higher than that of the remaining patients (75 years vs. 72 years; $P = 0.047$).

CONCLUSIONS. The combination of GEM and VNB is moderately active and well tolerated except in patients age $\geq$ 75 years. This age group had an increased risk of myelosuppression. Therefore the prophylactic use of granulocyte-colony stimulating factor should be considered with this treatment. New chemotherapy combinations with higher activity and lower toxicity are needed for elderly patients with advanced NSCLC. ***Cancer*** **1999;86:1463–9.** *© 1999 American Cancer Society.*

KEYWORDS: nonsmall cell lung carcinoma, elderly, gemcitabine, vinorelbine, comorbidity, toxicity.

Lung carcinoma is the most common malignant tumor in men and the third most common tumor common in women in developed countries. The peak incidence occurs between the ages of 60–65 years, but >60% of patients are age > 65 years[1,2] and approximately

30% are age > 70 years.[3] In Western Europe and North America, annual lung carcinoma rates for men ages 65–84 years are 400–600 cases per 100,000 habitants.[4]

Elderly patients with nonsmall cell lung carcinoma (NSCLC) pose a therapeutic challenge because the number of surgical procedures in each disease stage decreases with respect to younger patients.[5,6] Chemotherapy also has a number of complications: 1) to our knowledge there is a lack of studies assessing the efficacy and tolerance to chemotherapy among elderly people, particularly those with NSCLC; 2) chemotherapy is considered more toxic in these patients, mainly because of increased susceptibility to myelosuppression, neurotoxicity, and mucositis[7]; 3) chemotherapy offers a very limited survival benefit in patients with NSCLC, estimated at 1–2 months compared with supportive care alone, which translates into a 10% improvement in survival at 1 year[8]; and 4) comorbidity in the elderly adds to the difficulty in making a treatment decision. All these problems, along with concern that toxicity may decrease quality of life, have hampered the access to chemotherapy of elderly patients with advanced NSCLC.

The availability of new drugs such as gemcitabine (GEM), vinorelbine (VRB), or the taxanes has expanded the therapeutic options for patients with advanced NSCLC. Recent reports confirm that both GEM and VRB are active as single agent therapy in elderly patients with NSCLC,[9–11] with a response rate of 23–39%, symptomatic improvement in 40% of patients, and acceptable toxicity. GEM is particularly attractive for the treatment of cancer in the elderly due to its low toxicity.[7,12]

Given the activity of GEM and VRB in single agent therapy and their in vitro synergism,[13] we decided to assess their efficacy and toxicity in combination. Our objective was to determine the response rate and toxicity obtained with the combination of GEM and VRB in patients with advanced NSCLC who either were age ≥ 70 years or had some contraindication to receive a cisplatin-containing regimen.

MATERIALS AND METHODS

Forty-nine patients were enrolled in this Phase II trial from November 1996 until March 1998. All had histologically or cytologically proven NSCLC (squamous cell carcinoma, adenocarcinoma, or large cell carcinoma) and Stage IIIB or Stage IV disease according to the TNM staging system.[14] All patients had measurable disease. Pleural effusion, ascites, osteoblastic lesions, or previously irradiated lesions were not considered as measurable disease.

Eligible patients were age ≥ 70 years or, if younger, had some contraindication to receiving cisplatin (creatinine clearance < 60 mL/minute or heart failure that could be worsened by fluid overload). They had not previously been treated with chemotherapy and had an Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 2, according to Zubrod's scale. Other requirements were adequate bone marrow function (i.e., a granulocyte count ≥ 2×10^9/L and a platelet count > 100×10^9/L), adequate hepatic function (i.e., serum bilirubin level < 35 μmol/L), and serum glutamic oxalacetic transaminase and serum pyruvic transaminase levels < 3 times the upper limit of normal.

Patients who had undergone radiotherapy were eligible for the study provided that there was at least 1 measurable lesion outside the radiation field and radiation was completed at least 4 weeks before enrollment. Patients with brain metastases or who previously were treated with chemotherapy or those with a history of other tumors (with the exception of nonmelanomatous skin cancer or in situ cervical carcinoma that was radically resected) were excluded. Informed consent was obtained from all patients according to local ethical committee directives.

Basal evaluation was performed with clinical examination and hematologic and biochemical assessment. The Charlson comorbidity scale was used.[15] The staging procedure included two-view chest X-ray, contrast-enhanced computed tomography (CT) scans of the chest, abdomen, and pelvis and a radionuclide bone scan. A brain CT scan was performed in the presence of symptoms suspicious of brain metastases.

Treatment was comprised of VNB, 25 mg/m^2, diluted in 100 mL normal saline for 15 minutes weekly for 3 weeks followed by a 1-week rest period. GEM was given intravenously for > 30 minutes at a dose of 1000 mg/m^2 on the same days. The treatment was repeated every 28 days for a minimum of 3 times per patient unless disease progression was detected. Patients received up to six courses if no disease progression was noted at reevaluation, provided that tolerance was acceptable. Patients with Stage IIIB disease also received radiation therapy after three courses of chemotherapy.

Complete blood counts were obtained before each administration of chemotherapy. If the neutrophil count was < 1.5×10^9/L or the platelet count was < 100×10^9/L, treatment was delayed 1 week. Therapy was discontinued if toxicity persisted after a 2-week delay. Dose reduction was not allowed. Granulocyte-colony stimulating factor (G-CSF) was not administered prophylactically.

Response was evaluated after three courses of treatment and at the end of the last chemotherapy cycle by repeating staging procedures. World Health Organization (WHO) guidelines were followed for

evaluation.[16] Confirmation of response after 1 month was not performed. Death due to disease progression or toxicity occurring before those dates were considered as therapeutic failure. Response duration and survival were calculated from the first day of chemotherapy.

ECOG performance status and symptom assessment were performed prior to each cycle of chemotherapy by the same physician for each patient. The presence of cough, dyspnea, pain, hemoptysis, and anorexia was registered and graded from 0–4 according to the scale devised by Hollen et al.[17] and modified by Gridelli et al.[9] The best subjective outcome for each patient was recorded.

Toxicity for each course was recorded and graded according to the WHO scale before the beginning of the next course. For toxicity analysis, the worst data for each patient across all cycles of chemotherapy were used.

Differences in proportions were investigated using the chi-square test and the Fisher exact test. The Mann–Whitney nonparametric μ test was used for comparison of quantitative variables. Overall survival was calculated as the interval between Day 1 of the first cycle and the date of death or the date of the last follow-up visit. Both progression free and overall survival curves were estimated by the Kaplan–Meier product limit method.[18]

RESULTS

Forty-nine patients were included, 38 of whom were age $\geq$ 70 years (median age, 74 years; range, 70–80 years) and 11 of whom were age $<$ 70 years. Of the latter group of patients, seven had inadequate renal function and four had heart failure. Table 1 shows their clinical characteristics. Ninety percent of the patients were male and 96% had comorbid conditions, mainly obstructive lung disease (45%), diabetes (10%), hypertension (16%), and coronary insufficiency (8%). Comorbidity was present in 76% of patients when using Charlon's scale.[15] The majority of patients presented with Stage IV disease (61%) and a poor performance status (ECOG score of 2 in 65%); 35 patients (59%) also reported weight loss in the previous 6 months ($>$ 10% weight loss in 31% of patients). The predominant symptoms at diagnosis were anorexia (76%), dyspnea (69%), cough (49%), and pain (43%).

A total of 165 courses were given with a median of 3–6 courses per patient (range, 1–6 courses). Nine patients received fewer than three courses, three due to toxic death and six due to progressive disease. Nine patients required treatment delay on one occasion and patients required a treatment delay in two instances. The median dose intensity of VNB was 15.3 mg/m^2/week and that of GEM was 654 mg/m^2/week. No differences in the median dose intensity were apparent with regard to age $<$ or $>$ 75 years. Twenty-eight patients (58%) received $\geq$ 90% and 41 patients (84%) received $\geq$ 75% of the planned dose.

TABLE 1
Patient Characteristics (N = 49)

	No. of patients
Gender	
Male	44 (90%)
Female	5 (10%)
Median age (yrs) (range)	74 (60–80)
$\geq$ 75	16 (33%)
70–74	22 (45%)
$<$ 70	11 (22%)
TNM stage	
IIIB	19 (39%)
IV	30 (61%)
ECOG performance status	
0	4 (8%)
1	13 (27%)
2	32 (65%)
Weight loss	
None	14 (29%)
0–10%	20 (41%)
$>$ 10%	15 (30%)
Histology	
Squamous cell	28 (57%)
Adenocarcinoma	10 (20%)
Large cell	11 (23%)
Symptoms present at study entry	
Cough	24 (49%)
Dyspnea	34 (69%)
Pain	21 (43%)
Hemoptysis	9 (18%)
Anorexia	37 (76%)
Comorbidity Charlson scale	
0	12 (24%)
1	19 (39%)
2	16 (33%)
3	2 (4%)

ECOG: Eastern Cooperative Oncology Group.

The overall response rate was 26% (95% confidence interval; 15–41%). Two patients (4%) obtained a complete response, 11 (22%) achieved a partial response, 16 (32%) had stable disease, and 20 (41%) had progressive disease. The response rate was 47% (8 of 17) for those patients with ECOG scores of 0–1 compared with 12% (4 of 32) for those with an ECOG score of 2. No difference in the response rate was observed according to disease stage or age. The median time to progression was 16 weeks and the 1-year survival rate was 33%. Survival was not influenced by patient age. Sixteen patients (35%) experienced an improvement in their ECOG performance status and 17 (38%) remained with stable disease whereas 15 (31%) devel-

TABLE 2
Effect of Treatment on ECOG Performance Status and Symptoms

Variable	Improvement	No change	Worsening
Performance status[a]			
All patients	16 (33%)	18 (36%)	15 (31%)
ECOG score > 0 at study entry	16 (35%)	17 (38%)	12 (27%)
Dyspnea[a]			
All patients	12 (25%)	29 (59%)	8 (16%)
Symptomatic at entry	12 (35%)	16 (47%)	6 (18%)
Pain[a]			
All patients	8 (16%)	35 (71%)	6 (12%)
Symptomatic at entry	8 (38%)	12 (57%)	1 (5%)
Cough[a]			
All patients	11 (23%)	33 (67%)	5 (10%)
Symptomatic at entry	11 (46%)	10 (42%)	3 (12%)
Hemoptysis[a]			
All patients	4 (8%)	43 (88%)	2 (4%)
Symptomatic at entry	4 (44%)	5 (56%)	
Anorexia[a]			
All patients	15 (31%)	26 (53%)	8 (16%)
Symptomatic at entry	15 (40%)	17 (46%)	5 (14%)
Weight loss[b]			
All patients	11 (22%)	24 (49%)	14 (29%)
Symptomatic at entry	11 (31%)	16 (46%)	8 (23%)

ECOG: Eastern Cooperative Oncology Group.
[a] Improvement of ≥ points.
[b] Weight increment > 5%.

TABLE 3
Treatment Toxicities per Patient

WHO toxicity	Grade 1–2 No. (%)	Grade 3–4 No. (%)
Nausea/emesis	3 (6%)	
Anemia	6 (12%)	1 (2%)
Neutropenia	7 (14%)	6 (12%)
Thrombocytopenia	7 (14%)	2 (4%)
Peripheral neurotoxicity	5 (10%)	1 (2%)
Stomatitis	2 (4%)	1 (2%)
Phlebitis	5 (10%)	
Alopecia	4 (8%)	

WHO: World Health Organization.

oped a clinical deterioration (Table 2). Cough was improved in 11 of the patients who initially reported it (46%), dyspnea was improved in 12 patients (35%), hemoptysis was improved in 4 patients (44%), and anorexia was improved in 15 patients (40%). As a whole, 27 patients (55%) obtained an improvement in at least 1 symptom without worsening in other symptoms, 6 remained stable (12%), and 16 (33%) experienced some worsening. A weight gain > 5% was reported in 11 of 35 patients (31%) with previous weight loss.

Treatment was well tolerated. Neutropenia and neurotoxicity were the main side effects, as shown in Table 3. Six patients (12%) had Grade 3-4 neutropenia and 2 patients (4%) had Grade 3-4 thrombocytopenia. Three of the patients who experienced severe neutropenia died of sepsis (6%). This fatal complication appeared during the first course, after the first dose in two patients and after the second dose in the other patients. Two of these patients were age 75 years and the other was age 77 years. The median age of the patients who developed Grade 3-4 neutropenia was 75 years, which was significantly higher than that of patients who had Grade 1-2 neutropenia (72 years; $P = 0.047$). Four of 16 patients age ≥ 75 years had severe neutropenia. Grade 3 neurotoxicity was present in two patients and Grade 1-2 neurotoxicity was noted in six patients. Age did not appear to be related to the presence of neurotoxicity. One patient had a cutaneous rash attributable to GEM. No relation was found between comorbidity (as measured with Charlson's scale[15] and toxicity.

DISCUSSION

In recent years, a longer life span in Western countries has increased the number of elderly patients with cancer. Hence the search continues for treatments that do not diminish quality of life while improving survival or, at least, symptoms. A few studies in this area have been published with regard to NSCLC, but the majority are retrospective or include a small number of patients.

Some authors have studied the impact of patient age on survival and the likelihood of attaining a response in patients with NSCLC. One study found that age > 70 years was a favorable prognostic factor[19] whereas others did not find a relation between patient age and survival.[8,20,21] To our knowledge in none of these studies was old age found to be associated with poor survival. Patients age > 70 years may have the same response rates to chemotherapy found in the general population[21,22] or even better.[23,24]

Single agent therapy has been used widely in elderly patients, but with poor results until recently. The overall response rate for doxifluridine has been reported to be 13%[25] and has been reported to be 10–20% for vindesine.[26,27] A randomized trial of best supportive care versus lonidamine versus vindesine versus lonidamine plus vindesine found even a lower level of response for the cytotoxic drug (0%, 1%, and 2% in the cytotoxic arms, respectively).[28] Combination chemotherapy has not improved these results significantly (lonidamine plus cyclophosphamide, 15%; carboplatin plus oral etoposide, 0%; and vindesine plus ifosfamide, 15%).[29–31]

Cisplatin is considered the most active drug in NSCLC, but to our knowledge no prospective studies with this agent have been performed in the elderly, most likely due to fear of renal toxicity. Nephron loss of up to 30% and decreased creatinine clearance are associated with aging, but clinical experience does not support the concept that renal toxicity increases with age.[7,32] Three retrospective studies with combination chemotherapy including cisplatin in elderly patients with NSCLC assessed both response and toxicity. The response rate varied between 20–44%[21,22,24] and renal toxicity was not increased. However, in one study patients age $\geq$ 70 years who were treated with cisplatin plus mitomycin experienced myelosuppression more often than expected.[24] Another trial found an increased incidence of early death ($<$ 30 days from the start of therapy) among patients age $>$ 70 years compared with those age $<$ 54 years (12.5% vs. 0.5%). This excessive death rate was due to toxicity, particularly myelosuppression.[22] In a recent report of preliminary results, the combination of cisplatin and GEM showed a response rate of 33%, but with a 40% rate of Grade 3-4 thrombocytopenia.[33] These authors previously had found a lower rate of toxicity in younger patients. No patients were reported to have Grade 3-4 renal toxicity.

New anticancer drugs have expanded the therapeutic options for elderly patients. Single agent weekly VNB has yielded a response rate of 12–39%,[9,11,26,34] with an improvement in ECOG scores observed in 26% and symptom relief in observed 29–40% of patients.[9] A 24% response rate has been achieved with weekly GEM in patients age $>$ 65 years.[10] An ongoing Phase III trial compares single agent VNB and best supportive care in patients age $\geq$ 70 years with advanced NSCLC; the interim analysis of 191 patients showed a 6-month survival rate of 54% for VNB and 39% for best supportive care and 1-year survival rates of 27% and 5%, respectively ($P = 0.04$). The response rate for VNB has been reported to be 20%.[35] If these preliminary results are confirmed, the benefit of VNB in elderly patients with NSCLC would be similar to that obtained with combination chemotherapy including cisplatin in younger patients.[36]

We attempted to improve the results of single agent VNB by combining two drugs with proven efficacy and low toxicity in the treatment of patients with advanced NSCLC. Our results suggest that this regimen of GEM and VNB is moderately active with a 26% response rate and 32% of patients achieving stable disease. The response rate does not appear to be superior to that obtained with VNB alone or it could have been overestimated (because confirmatory evaluation 4 weeks later was not performed). However, this response rate is comparable to that of some combinations including cisplatin and the same can be said for the 1-year survival rate.[36] In general, therapy was well tolerated, although patients age $\geq$ 75 years were found to have an elevated risk of neutropenia. Neutropenia in people age $\geq$ 75 years, especially those with comorbid conditions, may increase the risk of sepsis and death (as happened to 3 patients in the current series). The prophylactic use of G-CSF should be considered when a regimen that produces myelosuppression is planned in this age group.

In the current trial the coexistence of other diseases did not increase toxicity or decrease survival. Clinical experience in patients with tumors other than NSCLC suggests that the presence of comorbid conditions enhances the risk of treatment-related toxicity,[37] but this did not appear to occur in the current series.

We administered VNB and GEM on Days 1, 8 and 15, following the recommended schedule for GEM alone.[11] Single agent VNB usually is given at a higher weekly dose (30 mg/m^2 vs. 25 mg/m^2)[9,11] without the 2-week rest included in our scheme. The recommended dose intensity for VNB alone is 20 mg/m^2/week, although the majority of combination regimens do not reach such intensity. In our study, the planned dose intensity was 18.7 mg/m^2/week and the actual dose intensity was 15.3 mg/m^2/week. This is lower than recommended, but it allows the administration of full doses of GEM and reduces the rate of neurotoxicity. Two ongoing trials use higher doses of GEM and VNB given on Days 1 and 8 every 21 days,[38,39] which may increase dose intensity and improve patient compliance. Although preliminary results show a 36% response rate in 1 of these studies, with a 37% rate of Grade 3-4 neutropenia,[38] elderly patients were not included in these trials.

The current study and other reports have shown that chemotherapy may improve symptoms and survival in elderly patients with advanced NSCLC; therefore we believe this option should be offered to these individuals. However, the potential toxicity of such treatment should not be underestimated in the elderly population, and special caution should be used in those patients age $\geq$ 75 years for whom new active treatments with lower toxicity are needed.

REFERENCES

1. Vercelli M, Quaglia A, Casella C, Parodi S, Micheli A, Capocaccia R. Cancer in elderly: the population-based indexes in Europe (incidence, mortality, survival and prevalence). *Ann Oncol* 1998;9(Suppl 3):55–6.
2. Yancik R. Cancer burden in the aged. An epidemiologic and demographic overview. *Cancer* 1997;80:1273–83.

3. Lee-Chiong TL Jr., Matthay RA. Lung cancer in the elderly patient. *Clin Chest Med* 1993;14:453–78.
4. Levi F, LaVecchia C, Lucchini F, Negri E. Worldwide trends in cancer mortality in the elderly, 1955–1992. *Eur J Cancer* 1996;32A:652–72.
5. de Rijke JM, Schouten LJ, Schouten HC, Jager JJ, Koppejan AG, van den Brandt PA. Age specific differences in the diagnostics and treatment of cancer patients aged 50 years and older in the province of Limburg, The Netherlands. *Ann Oncol* 1996;7:677–85.
6. Smith TJ, Penberthy L, Desch CE, Whittemore M, Newschaffer C, Hillner BE, et al. Differences in initial treatment patterns and outcomes of lung cancer in the elderly. *Lung Cancer* 1995;13:235–52.
7. Balducci L, Extermann M. Cancer chemotherapy in the older patient. What the Medical Oncologist needs to know. *Cancer* 1997;80:1317–22.
8. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer. A meta-analysis using updated data on individual patients from 52 randomized clinical trials. *BMJ* 1995;311:899–909.
9. Gridelli C, Perrone F, Gallo C, De Marinis F, Ianniello G, Cigolari S, et al. Vinorelbine is well tolerated and active in the treatment of elderly patients with advanced non-small cell lung cancer. A two-stage phase 11 study. *Eur J Cancer* 1997;33:392–7.
10. Shepherd FA, Abratt RP, Anderson H, Gatzemeier U, Anglin G, Iglesias J. Gemcitabine in the treatment of elderly patients with advanced non-small cell lung cancer. *Semin Oncol* 1997;24(Suppl 7):50–5.
11. Veronesi A, Crivellari D, Magri MD, Cartei G, Mansutti M, Foladore S, et al. Vinorelbine treatment of advanced non-small cell lung cancer with special emphasis on elderly patients. *Eur J Cancer* 1996;32:1809–11.
12. Martin C, Ardizzoni A, Rosso R. Gemcitabine: safety profile and efficacy in non-small cell lung cancer unaffected by age. *Aging Clin Exp Res* 1997;9:297–303.
13. Kanzawa F, Saijo N. In vitro between Gemcitabine and other anticancer drugs using novel three-dimensional model. *Semin Oncol* 1997;24 (Suppl 7):8–16.
14. International Union Against Cancer. TNM atlas. Illustrated guide to the TNM/pTNM classification of malignant tumors. Berlin: Springer-Verlag, 1997.
15. Charlson ME, Pompei P, Ales KL, MacKenzie R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987; 40:373–83.
16. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;42:207–14.
17. Hollen PJ, Gralla RJ, Kris M, Potanovich LM. Quality of life assessment in individuals with lung cancer: testing the lung cancer symptom scale (LCSS). *Eur J Cancer* 1993;29A (Suppl 1):51–8.
18. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
19. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Survival determinants in extensive-stage non-small cell lung cancer: the Southwest Oncology Group experience. *J Clin Oncol* 1991;9:1618–26.
20. Paesmans M, Sculier JP, Libert P, Bureau G, Dabouis G, Thiriaux J, et al. Prognostic factors for survival in advanced non-small lung cancer: univariate and multivariate analyses including recursive partitioning and amalgamation algorithms in 1052 patients. *J Clin Oncol* 1995; 13:1221–30.
21. Bizette GA, Gralla RJ, Rittenberg CN. Does older age or ethnic group influence survival or response in patients in clinical trials for non-small cell lung cancer (NSCLC)? *Proc Am Soc Clin Oncol* 1995;14:A333.
22. Rinaldi M, de Marinis F, Ardizzoni A, Pernucci MC, Bruzzi P, Salvati F, et al. Correlation between age and prognosis in patients with advanced non small cell lung cancer prognosis with cisplatin containing chemotherapy: a retrospective multicenter study. *Ann Oncol* 1994;5 (Suppl 8): 58.
23. Hickish TF, Smith IE, Ashley S, Middleton G. Chemotherapy for elderly patients with lung cancer. *Lancet* 1995;346: 580.
24. Kubota K, Furuse K, Kawahara M, Kodama N, Ogawara M, Takada M, et al. Cisplatin-based combination chemotherapy for elderly patients with non-small cell lung cancer. *Cancer Chemother Pharmacol* 1997;40:469–74.
25. Baldini E, Tibaldi E, Pfanner E, Ricci E, Falcone A, Ceribelli A, et al. Phase II of oral doxifluridine in elderly patients with advanced non small cell lung cancer. *Am J Clin Oncol* 1996; 19:592–4.
26. Furuse K, Fukuoka M, Hara N, Kurita Y, Kinuwaki E, Kawahara M, et al. Vinorelbine in the treatment of elderly patients with advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 1998;17:A1862.
27. Gallotti P, Chiesa E, Olgiati A, Bottaro G, Natale G, Freddi E. Vindesine as monochemotherapy in non small cell lung cancer in elderly patients. *Ann Oncol* 1992;3 (Suppl 5):36.
28. Portalone L, D'Aprile M, De Marinis F, et al. Management of chemotherapy in elderly patients with advanced non small lung cancer (NSCLC)- a phase III randomized trial. *Lung Cancer* 1994;11 (Suppl 1):110.
29. Salvati F, Antilli A, Cruciani AR, Lombardi A, Muguaini L, Nunziati F, et al. Lonidamine plus cyclophosphamide in the treatment of advanced non small cell lung cancer in the elderly: a phase II study. *Tumor* 1995;81:48–51.
30. Gridelli C, Rossi A, Scognamiglio F, Guida C, Fiore F, Gatani T, et al. Carboplatin plus oral etoposide in elderly patients with advanced non small cell lung cancer. A phase II study. *Anticancer Res* 1997;17:4755–8.
31. Malarme M, Marcelis L, Kaius JP, Brenez D, Feremans W, Bracops CHJ. Ifosfamide and vindesine therapy for non small lung cancer in the elderly. *Ann Oncol* 1992;3(Suppl 5):36.
32. Thyss A, Saudes L, Otto J, Creison A, Gaspard MH, Dassonville O, et al. Renal tolerance to cisplatin in patients more than 80 years old. *J Clin Oncol* 1994;12:2121–5.
33. Lippe P, Silva RR, Giuliodori L, Santo A, Cancellieri MA, Monterubbianesi MC, et al. Advanced non-small cell lung cancer in the elderly: effective and well tolerated weekly gemcitabine and cisplatin regimen. *Ann Oncol* 1998;9(Suppl 3):64.
34. Tononi A, Panzini I, Olivero G, Pasquini E, Gianni L, Nicolini M, et al. Vinorelbine chemotherapy in non small cell lung cancer: experience in elderly patients. *J Chemother* 1997;9: 304–8.
35. Perrone F, Rossi A, Iannello GP, Maiorino L, Piantedosi FV, Cigolari S, et al. Vinorelbine plus best supportive care vs best supportive care in the treatment of advanced non-small cell lung cancer elderly patients. Results of a phase III randomized trial. *Proc Am Soc Clin Oncol* 1998;17:A1752.

36. Lilenbaum RC, Langenberg P, Dickersin K. Single agent versus combination chemotherapy in patients with advanced nonsmall cell lung carcinoma. A meta-analysis of response, toxicity, and survival. *Cancer* 1998;82:116–26.
37. Yancik R, Wesley MN, Ries LAG, Havlik RJ, Long S, Edwards BK, et al. Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients. A population-based study. *Cancer* 1998;82:2123–34.
38. Lorusso V, Mancarella S, Carpagno F, Di Rienzo G, Cisterino L, Napoli G, et al. Gemcitabine plus vinorelbine in patients with stage IIIB-IV non small cell lung cancer. A phase II study. *Proc Am Soc Clin Oncol* 1998;17:A1808.
39. Esteban E, Llano JLG, Vieitez JM, Fra J, Puertas J, Estrada E, et al. Phase I/II study of gemcitabine plus vinorelbine in non-small cell lung cancer. *Proc Am Soc Clin Oncol* 1998;17: A1855.