Pergamon

European Journal of Cancer Vol. 33, No. 3, pp. 392–397, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(96)00471-6

Original Paper

Vinorelbine is Well Tolerated and Active in the Treatment of Elderly Patients with Advanced Non-small Cell Lung Cancer. A Two-stage Phase II Study

C. Gridelli,[1] F. Perrone,[2,3] C. Gallo,[3] F. De Marinis,[4] G. Ianniello,[5] S. Cigolari,[6] S. Cariello,[7] F. Di Costanzo,[8] M. D'Aprile,[9] A. Rossi,[1] R. Migliorino,[4] R. Bartolucci, A.R. Bianco,[10] M. Pergola[1] and S. Monfardini[2]

[1]Divisione di Oncologia Medica B, Istituto Nazionale Tumori "G. Pascale", Via M. Semmola 3, 80131 Napoli; [2]Direzione Scientifica, Istituto Nazionale Tumori, Napoli; [3]Centro Elaborazione Dati Clinici del Mezzogiorno, CNR-ACRO; [4]III Divisione di Pneumologia, Ospedale Forlanini, Roma; [5]Servizio di Oncologia, Ospedale Rummo, Benevento; [6]Cattedra di Medicina Interna, Università Federico II, Napoli; [7]Servizio di Oncologia, Ospedale S. Leonardo, Salerno; [8]Unità di Chemioterapia e T.L.R. dei Tumori, Ospedale S. Maria, Terni; [9]Divisione di Oncologia Medica, Ospedale S. Maria Goretti, Latina; and [10]Cattedra di Oncologia Medica, Università Federico II, Napoli, Italy

More than 30% of lung cancers arise in patients aged 70 years or more; however, because elderly patients are not considered to tolerate chemotherapy, they are generally excluded from clinical trials and are not considered eligible for aggressive cisplatin-based chemotherapy in clinical practice. The aims of the present study were to test tolerability and activity of weekly vinorelbine in advanced non-small cell lung cancer (NSCLC) patients aged 70 years or more, and to define whether minimum conditions existed for a randomised comparison with best supportive care. The study was designed as a multicentre two-stage phase II trial according to Simon's optimal design: 8 or more responses out of 43 treated patients were expected at the end of the trial. Patients aged 70 years or more were eligible if they had a cytological or histological diagnosis of NSCLC at stage IIIb–IV and a performance status less than or equal to two according to the ECOG scale. Vinorelbine was given intravenously (i.v.) at a dose of 30 mg/m^2 every week for 12 doses. As planned, 43 patients entered the study; median age was 73 years (range 70–80); 11 patients were older than 75 years. Median dose-intensity (mg/m^2/week) of vinorelbine was 21.2 (range 7.5–30) and was not affected by age of patients. Toxicity was generally mild, mainly haematological and never life-threatening. ECOG performance status improved in 26% of patients; cough and pain improved in more than 40% of patients symptomatic at entry, while dyspnoea improved in 28%; approximately half the patients had a stabilisation of their symptoms. 10 patients (23–95% exact confidence interval (CI): 12–39%) obtained a partial response. Median time to progression was 11 weeks (95% CI 8–30) and median survival 36 weeks (95% CI 28–53). One-year estimated progression-free and overall survival rates are 16% and 36%, respectively. In conclusion, vinorelbine was well tolerated and active in the treatment of elderly NSCLC patients. A phase III trial (ELVIS—Elderly Lung Cancer Vinorelbine Italian Study) comparing best supportive care versus best supportive care plus vinorelbine is now ongoing. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: vinorelbine, elderly, non-small cell lung cancer

Eur J Cancer, Vol. 33, No. 3, pp. 392–397, 1997

Correspondence to C. Gridelli.
Received 8 Jul. 1996; revised 20 Sep. 1996; accepted 13 Nov. 1996.

INTRODUCTION

MORE THAN 30% of lung cancer arises in patients aged 70 years or more [1]. However, impairment of hepatic, renal, and particularly bone marrow function in these patients, combined with frequently observed comorbidity, usually has a negative impact on tolerability of antineoplastic chemotherapy. Thus, because elderly patients are not considered able to tolerate chemotherapy, they are generally excluded from clinical trials and are not considered eligible for aggressive cisplatin-based chemotherapy in clinical practice. Nevertheless, they frequently suffer tumour-related symptoms and need some kind of treatment to obtain palliation.

Non-small cell lung cancer (NSCLC) includes a group of tumours that respond poorly to drugs. Indeed, out of several studies comparing chemotherapy to best supportive care in advanced NSCLC, only three trials have shown a statistically significant, albeit small, survival advantage for chemotherapy [2–4]. Recently, a meta-analysis showed that the overall benefit of chemotherapy is small compared with best supportive care, being of the order of approximately, a 1.5 month increase in median survival [5]. The meta-analysis provided no definitive data on the relative efficacy of drugs used in combination regimens, although it suggested that cisplatin-based chemotherapy could be more effective; however, based on the overall low activity of chemotherapy, more attention should be paid to quality of life as the primary endpoint rather than survival.

Vinorelbine is a new vinca-alkaloid, active in the treatment of advanced NSCLC with a 15–30% objective response rate reported [6–8]. Published studies, although including patients up to 75 years, do not report details on toxicity and activity of vinorelbine in the older subgroup of patients [6–8]. A small phase II study on vinorelbine in NSCLC patients aged 65 years or more was published [9] after the start of the present trial. In this study, Colleoni and associates reported a 16% (95% CI 5–36) response rate, a 5-month median survival and mild toxicity; however, only 12 patients aged 70 or more years were entered into this trial.

In 1994, we started a phase II trial to determine tolerability and activity of weekly vinorelbine in advanced NSCLC patients aged 70 or more years, and to define whether minimum conditions existed for a randomised comparison versus best supportive care.

MATERIALS AND METHODS

Design of the study

It was a multicentre two-stage phase II trial with response rate as the main outcome. The study would be stopped early if the response rate was lower or equal to 10% (null hypothesis) and that the probability of refusing erroneously the null hypothesis (type I error inducing a false-positive result) should be less than 5%. If the true response rate would be 25% or more, the probability of rejecting the drug as non-active (type II error inducing a false-negative result) should be less than 20%. According to the optimal design of Simon [10], if less than three responses were recorded within 18 patients, the trial would be stopped because of low activity of the treatment; otherwise, the enrolment would continue for up to 43 patients; eight or more responses were expected at the end of the trial to meet the requirements for further testing the treatment in a phase III trial. The trial was approved by ethical committees of participating institutions.

Eligibility criteria

Patients aged 70 years or more were eligible for the trial if they had a cytological or histological diagnosis of NSCLC at stage IIIb–IV and a performance status less than or equal to two according to the ECOG scale. Patients with brain metastases or previously treated with chemotherapy or with a history of other cancers (with the exception of non-melanomatous skin cancer and *in situ* cervical cancer radically resected) were excluded. Previous radiotherapy was accepted if completed at least 4 weeks before the enrolment. Also, a normal bone marrow, kidney, liver and heart function was required for patients to enter the trial. Patients gave verbal consent.

Basal evaluation was performed with clinical examination, haematological and biochemical assessment and cardiological evaluation with EKG. Staging procedure included: two-view chest X-ray; brain, chest, abdomen and pelvis contrast enhanced CT scans; ultrasound liver scan; radionuclide bone scan with X-ray details of hot spots.

Drug schedule

Vinorelbine was given i.v. at a dose of 30 mg/m^2, diluted in 100 ml normal saline in 15 min, every week for 12 doses. Following response evaluation at the end of the sixth cycle, only patients with responding or stable disease remained on treatment. No dose reduction was allowed, but a cycle could be delayed for up to 2 weeks if there was a leucocyte count < 4000/mm^3 or platelets < 100 000/mm^3 on the day of planned treatment. Following a 2-week delay and persisting toxicity, treatment was stopped due to prolonged toxicity.

Following the end of the treatment (maximum 12 cycles), neither second-line chemotherapy nor maintenance vinorelbine were planned, independently of the obtained response.

Calculation of dose intensity

As dose reductions were not allowed, the total dose of vinorelbine was calculated as the product of the single dose (30 mg/m^2) for the number of delivered cycles. Total time on treatment was calculated as the interval between day 1 of the first cycle up to day 8 of the twelth cycle or to the date of progression, whichever occurred first. Dose intensity was calculated as the ratio between total dose and total time and it was expressed as mg/m^2/week. Cycles not delivered because of early termination of treatment due to toxicity were counted as given at dose 0 and being one week long; the last cycle was always assumed as one week long; by this approach, the dose intensity was corrected for patients stopping treatment because of toxicity and results in a lower dose intensity than that calculated on delivered cycles only. Cumulative dose intensity at each cycle was calculated with the same assumptions made for dose intensity, but using cumulative total dose and cumulative total time at each cycle.

Scales for toxicity, symptoms and response assessment

The WHO graded scale [11] was used to record toxicity. Assessment of toxicity was made prior to each cycle of

chemotherapy. For toxicity analysis, the worst data for each patient across all cycles of chemotherapy were used.

ECOG performance status [11] and symptom assessment was performed prior to each cycle of chemotherapy by the same physician for each patient. Symptoms were categorised according to a modification of the Hollen's scale [12]. In detail, the following categories were used: (a) cough: 0 = absent; 1 = mild, no medications needed; 2 = moderate, medications needed; 3 = marked, disturbs sleep and other normal functioning; 4 = severe, nearly constant, disrupts any normal activities; (b) dyspnoea: 0 = absent, 1 = mild, noticed only with major activity; 2 = moderate, present when walking at normal pace and interferes with ability to carry out some usual activities; 3 = marked, present with minimal activities, with supplemental oxygen used only occasionally; 4 = severe, supplemental oxygen required most or all of the time; (c) pain: 0 = absent; 1 = mild, but either no medications required or only non-narcotic, non-codeine type oral agents for satisfactory pain control; 2 = moderate, codeine or codeine containing oral medications needed for satisfactory pain control; 3 = marked, narcotic oral agents required for satisfactory pain control; 4 = severe, narcotic oral medications required but pain control not satisfactory, or parental narcotics required; (d) haemophtysis: 0 = absent; 1 = mild, less frequently than daily; 2 = moderate, daily but generally just flecks as part of the sputum; 3 = marked, sputum often purely blood (not just flecks) on daily basis; 4 = severe, some as marked, but blood loss by haemophtysis measurably lowering haemoglobin. The best subjective outcome for each patient was recorded.

Objective responses were also evaluated according to WHO [11] at the end of the sixth and the last chemotherapy cycle by repeating staging procedures. The best response was recorded for each patient. In case of clinically evident or suspected progression of the disease, response evaluation was anticipated. Confirmation of response after one month was not performed, the objective response rate was defined as the proportion of complete and partial responses for all randomised patients.

Statistical analysis

For response rate, 95% exact confidence intervals (CI) were calculated [13]. Progression-free survival was calculated as the interval between day 1 of the first cycle up to progression of disease or death, whichever occurred first. Overall survival was calculated as the interval between day 1 of the first cycle and date of death or date of the last follow-up visit. Both progression-free and overall survival curves were estimated by the Kaplan–Meier [14] product limit method; 95% CI of median values were calculated according to Brookmeier and Crowley [15].

RESULTS

As planned, 43 patients entered the study between October 1994 and October 1995 (the study was not terminated early since 5 of the first 18 patients entered responded to therapy). Patients' characteristics are shown in Table 1.

Enrolled patients were predominantly male (88%); median age was 73 years (range 70–80); 11 patients were older than 75 years. The majority (65%) had at least one concomitant illness: most frequently chronic obstructive lung disease (23%), diabetes (16%), hypertension (14%) and previous episodes of heart ischaemic disease (14%). Stage IV disease was present in 56% of patients; the most frequent histological type was epidermoid (72%). ECOG performance status was predominantly poor (91% with a score greater than 0); many patients reported cough (65%) and dyspnoea (67%) at entry; pain was also frequently reported at entry (44%).

Table 1. Characteristics of 43 enrolled patients

	No. of patients (%)
Sex	
Male	38 (88)
Female	5 (12)
Comorbidity	
No comorbid condition	15 (35)
At least one concurrent illness	28 (65)
Stage	
IIIB	19 (44)
IV	24 (56)
Histology	
Epidermoid	31 (72)
Adenocarcinoma	11 (26)
Large cell	1 (2)
ECOG performance status	
0	4 (9)
1	17 (40)
2	22 (51)
Symptoms present at entry	
Cough	28 (65)
Dyspnoea	29 (67)
Pain	19 (44)
Haemophtysis	7 (16)

Overall, 314 cycles of vinorelbine were administered with a median number of six cycles (range 1–12). 12 patients received all planned cycles; 23 patients stopped treatment because of disease progression and 8 because of toxicity. Median dose intensity of vinorelbine was 21.2 mg/m^2/week (range 7.5–30). Analysis of cumulative dose intensity across cycles (Figure 1) showed that it progressively decreased up to the sixth cycle; thereafter, it slightly increased possibly because of the selection of patients with better prognosis after the first restaging procedure. Median dose intensity of treatment was not affected by the age of the patients (Figure 2).

No death related to treatment toxicity was recorded; toxicity was overall mild, prevalently haematological and never life-threatening (Table 2).

Observed effects of vinorelbine on performance status and symptoms are summarised in Table 3; data are reported both for all patients and for symptomatic patients at entry. ECOG performance status improved in 26% of patients with a PS greater than 0 at entry, but worsened in 28% of the whole group. Cough and pain improved in more than 40% of patients symptomatic at entry, while dyspnoea improved in 28%; overall, approximately half the patients had stabilisation of their symptoms, but around 11–21% suffered worsening of symptoms while on treatment. No patient received palliative irradiation therapy while on chemotherapy.

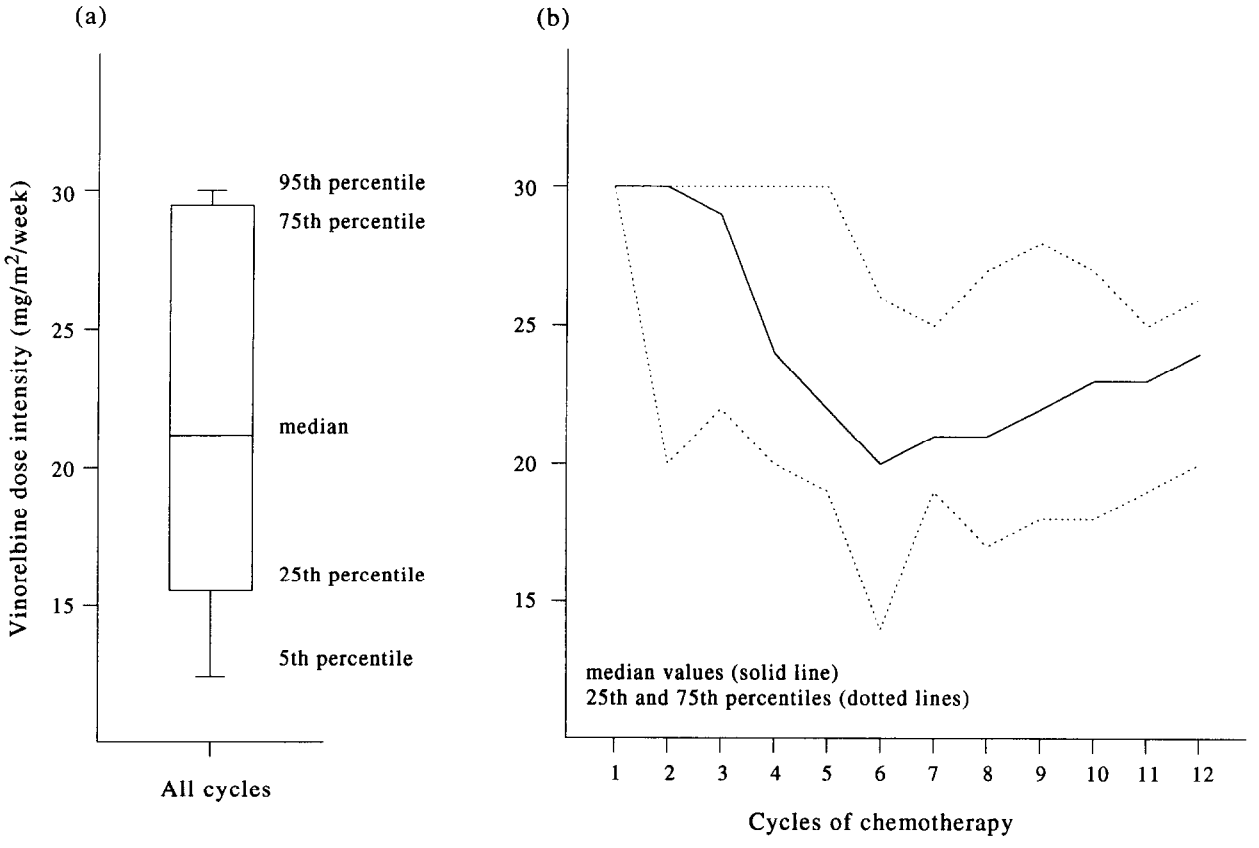

Figure 1. Distribution of vinorelbine delivered dose intensity across all cycles (a) and cumulative delivered dose intensity at each cycle (b).

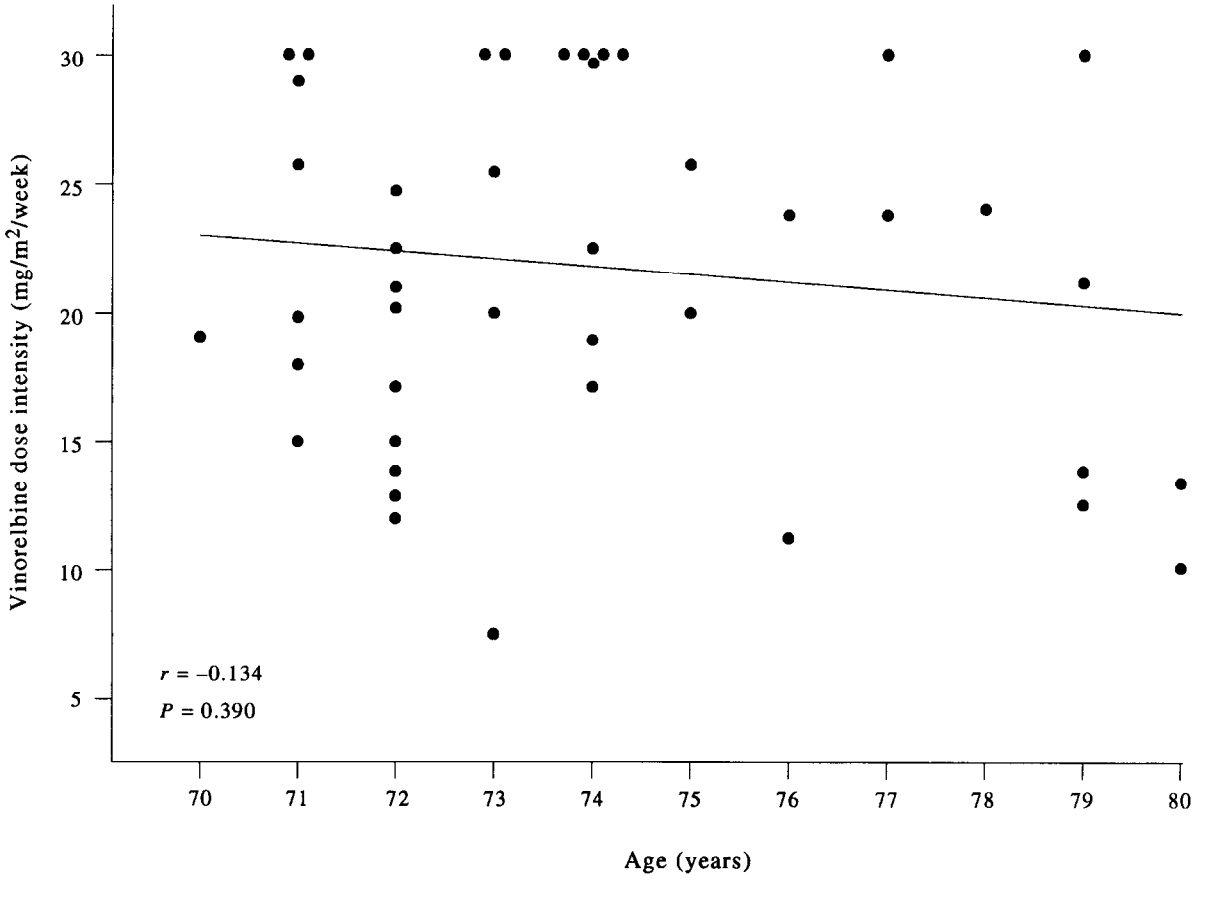

Figure 2. Scatter plot of vinorelbine dose intensity by age of patients.

Table 2. Toxicity according to WHO

	No. of patients (%)
Leucopenia (grade 3–4)	14 (33)
Thrombocytopenia (grade 2–3)	2 (5)
Anaemia (grade 2–3)	8 (19)
Infections (grade 2)	1 (2)
Nausea	4 (9)
Peripheral neurotoxicity (grade 1–2)	8 (19)
Oral mucositis (grade 1–2)	3 (7)
Oesophagitis (grade 1–2)	3 (7)
Fatigue (grade 1–3)	8 (19)
Phlebitis (grade (1–3)	5 (12)
Hair loss (grade 1)	10 (23)

No complete response was achieved; 10 patients (23–95% exact CI 12–39%) obtained a partial response, with 13 stable disease and 19 progressive disease (1 patient refused assessment before restaging). As of 31 August 1996, 39 patients have progressed and 32 have died. Median time to progression was 11 weeks (95% CI 8–30) and median survival 36 weeks (95% CI 28–53). At 1-year follow-up, Kaplan–Meier estimates of progression-free and overall survival are 16% and 36%, respectively. Follow-up of alive patients ranges from 47 to 85 weeks, with 7 patients surviving more than 1 year.

Neither toxicity nor activity of vinorelbine were affected by age of patients (data not shown).

DISCUSSION

A few papers have been published on chemotherapy for elderly NSCLC patients; most studies have been reported as an abstract and not yet confirmed. These are usually phase II trials, testing toxicity and activity of new drugs or new drug combinations. Salvati and associates [16], in the only study reported as a paper, reported a 15% response rate with cyclophosphamide and lonidamine; however, in this trial, 13 out of 41 entered patients had stage IIIA disease with more favourable prognosis. Among studies published in abstract form, the combination of carboplatin and oral VP-16 has produced disappointing results both in the experience of Rosti and associates [17], with 6.5% of objective responses and remarkable haematological toxicity in a group of 46 patients, and in a trial by Thomas and associates [18], with 5.5% responses out of 18 patients. Malarme and associates [19] used ifosfamide and vindesine, reporting a 15% response rate. Gallotti and associates [20], in a phase II trial on vindesine, including 22 elderly patients, reported a 20% response rate. Portalone and associates [21], in a phase III randomised trial, comparing best supportive care versus lonidamine versus vindesine versus lonidamine plus vindesine, reported similar negative results in all the arms (no response in the first two arms and 1% and 2% in the third and fourth, respectively); however, data in this study could be biased by the high rate (35%) of patients who were lost during the follow-up. Conte and associates, in a phase II study on 30 patients, using doxofluoridine, reported a 13% response rate [22]. There are no data in the literature on the activity of taxanes and gemcitabine in NSCLC elderly patients, and only retrospective data have been reported on their tolerability in the elderly [23, 24].

Table 3. Effect of vinorelbine on performance status and symptoms

Variable	Better	No change	Worse
Performance status			
All patients	10 (23%)	21 (49%)	12 (28%)
PS > 0 at entry	10 (26%)	20 (51%)	9 (23%)
Cough			
All patients	12 (28%)	25 (58%)	6 (14%)
Symptomatic at entry	12 (43%)	10 (36%)	6 (21%)
Dyspnoea			
All patients	8 (19%)	28 (65%)	7 (16%)
Symptomatic at entry	8 (28%)	15 (52%)	6 (21%)
Pain			
All patients	8 (19%)	31 (72%)	4 (9%)
Symptomatic at entry	8 (42%)	9 (47%)	2 (11%)
Haemophtysis			
All patients	2 (5%)	40 (93%)	1 (2%)
Symptomatic at entry	2 (29%)	4 (57%)	1 (14%)

In our study, the outcome was better than those reported by others, both for activity (23% response rate) and for toxicity, which was mild and never life-threatening. Surprisingly, survival was relatively long (both as median and as estimated 1-year survival), and if such a result were confirmed in larger series, it would represent a significant progress in the treatment of elderly NSCLC patients. The apparent inconsistency between relatively long survival but a short median time to progression (11 weeks)—shorter in this than in other studies—can be explained by the weekly clinical assessments of patients, induced by the treatment schedule, that increased the probability of early detection of progressive disease. Positive results with the use of vinorelbine have also been reported by Crivellari and associates, with a 44% response rate in 18 elderly patients (including 5 with stage IIIA disease) taken from a broader non age-based phase II trial [25]. Colleoni and associates [9] attempted to improve results by adding weekly carboplatin to vinorelbine. In 22 patients treated, they reported a 14% response rate with notable myelotoxicity; thus, no apparent clinical advantage was evident compared to their previous experience with vinorelbine alone [26].

In our study, a positive effect of treatment on symptoms was noted, rates of symptom relief largely exceeding objective responses, and being consistent with results of a previous randomised trial comparing two three-drug polichemotherapy regimens, with or without cisplatin, in a patient population under 70 years [27].

Weekly administration has been primarily proposed for vinorelbine based on its mechanism of action. Median delivered dose intensity in the present trial was 21.2 mg/m^2/week. Thus, it seems that weekly administration could be safely planned at a dose exceeding 20 mg/m^2. However, an alternative schedule, that could increase the patients compliance without reducing expected dose intensity, could be 30 mg/m^2 days 1 and 8 recycling every 3 weeks; with this schedule, planned dose intensity would be 20 mg/m^2/week and compliance could be easier with the 14-day interval following administration on day 8.

Following these results, a phase III trial (named ELVIS—Elderly Lung Cancer Vinorelbine Italian Study), comparing best supportive care versus best supportive care plus vinorelbine in advanced NSCLC patients aged 70 years or more,

has been launched and is now ongoing with quality of life as primary endpoint of the analysis.

1. Silverberg E. Cancer statistics. *CA J* 1988, **38**, 5–22.
2. Cormier Y, Bergeron D, La Farge J, *et al.* Benefits of polichemotherapy in advanced non small cell bronchogenic carcinoma. *Cancer* 1992, **50**, 845–849.
3. Rapp E, Peter J, Villan A, *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* 1988, **6**, 633–641.
4. Cartei G, Cartei F, Cantone A, *et al.* Cisplatin, cyclophosphamide, mitomycin combination chemotherapy with supportive care versus supportive care alone for treatment of metastatic non small cell lung cancer. *J Natl Cancer Inst* 1993, **85**, 794–800.
5. 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 randomised clinical trials. *Br Med J* 1995, **311**, 899–909.
6. Furuse K, Kubota K, Korwahara M, *et al.* A phase II study of vinorelbine, a new derivative of vinca alkaloid, for previously untreated advanced non small cell lung cancer. *Lung Cancer* 1994, **11**, 385–391.
7. Le Chevalier T, Brisgand D, Dovillard J, *et al.* Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non small cell lung cancer: a result of a European Multicenter Trial including 612 patients. *J Clin Oncol* 1994, **12**, 360–367.
8. Depierre A, Chastang C, Quoix E, *et al.* Vinorelbine versus vinorelbine plus cisplatin in advanced non-small cell lung cancer: a randomized trial. *Ann Oncol* 1994, **5**, 37–42.
9. Colleoni M, Geion F, Nelli P, *et al.* Weekly vinorelbine in elderly patients with non small cell lung cancer. *Tumori* 1994, **80**, 448–452.
10. Simon R. Optimal two-stage designs for phase II clinical trials. *Contr Clin Trials* 1989, **10**, 1–10.
11. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
12. 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), S51–S58.
13. *Geigy Scientific Tables,* 8th edn. Lentner C, ed. 1982.
14. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
15. Dixon WJ. *BMDP Statistical Software,* Los Angeles, CA, University of California Press, 1992.
16. Salvati F, Antilli A, Cruciani AR, *et al.* Lonidamine plus cyclophosphamide in the treatment of advanced non small cell lung cancer in the elderly: a phase II study. *Tumori* 1995, **81**, 48–51.
17. Rosti G, Zumaglini F, Gridelli C, *et al.* Carboplatin and oral VP-16 in advanced lung cancer patients aged ≥70 years. A phase II trial. *Cancer in the Elderly. Genova,* 19–21 September, 1994.
18. Thomas, P, Castelnau O, Kleisbauer JP. Carboplatin plus oral etoposide in elderly patients with bronchogenic carcinoma. Preliminary results of a phase II trial. *Cancer in the Elderly.* Genova, 19–21 September, 1994.
19. Malarme M, Marcelis L, Kalas JP, *et al.* Ifosfamide (IFO) and vindesine (VDS) therapy for non small cell lung cancer (NSCLC) in the elderly. *Ann Oncol* 1992, **3** (Suppl. 5), 36.
20. Gallotti P, Chiesa E, Olgiati A, *et al.* Vindesine as monochemotherapy in non small cell lung cancer (NSCLC) in elderly patients. *Ann Oncol* 1992, **3** (Suppl. 5), 36.
21. 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.
22. Baldini E, Tibaldi E, Pfanner E, *et al.* Phase II study of oral doxifluridine in elderly patients with advanced non small cell lung cancer. *Am J Clin Oncol* 1996, **19**, 592–594.
23. Rosso R, Martin C. Effect of patient age on gemcitabine toxicity profile and efficacy in advanced non small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 1994, **13**, 366 (abstract).
24. Zaheer W, Lichtman SM, De Marco L, *et al.* The use of taxol in elderly patients. *Proc Am Soc Clin Oncol* 1994, **13**, 441 (abstract).
25. Crivellari D, Veronesi A, Sacco C, *et al.* Phase II study of vinorelbine (v) in 50 patients (pts) with non small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 1994, **13**, 355 (abstract).
26. Colleoni M, Vicario G, Pancheri F, *et al.* Weekly carboplatin and vinorelbine in elderly patients with non small cell lung cancer (NSCLC). *VI International Congress on Anti-Cancer Treatment,* 6–9 February, 1996.
27. Gridelli C, Perrone F, Palmeri S, *et al.* Mitomycin C plus vindesine plus etoposide (MEV) versus mitomycin C plus vindesine plus cisplatin (MVP) in stage IV non small cell lung cancer: a phase III multicentre randomised trial. *Ann Oncol* 1996, 7, 821–826.