Original contribution

Multicenter Phase II Trial of Carboplatin/Vinorelbine in Elderly Patients with Advanced Non–Small-Cell Lung Cancer—Efficacy and Impact on Quality of Life: Groupe Français de Pneumo-Cancérologie Study 9902

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Abstract

BACKGROUND: Approximately 30% of lung cancer cases are diagnosed in patients > 70 years of age. Standard chemotherapy regimens are generally considered too toxic for elderly patients. We conducted a multicenter phase II trial to determine the efficacy and safety of carboplatin combined with vinorelbine every 4 weeks as first-line treatment for advanced non–small-cell lung cancer (NSCLC) in elderly patients. PATIENTS AND METHODS: Patients were eligible if they were aged ≥ 70 years, had stage IIIB (with pleural effusion) or stage IV NSCLC, had a performance status of 0/1, had not previously received chemotherapy, and had normal organ function. Forty patients (31 men and 9 women) were enrolled and received 3-5 courses of treatment. Median age was 72 years (range, 70-82 years). Eighty percent of patients had stage IV NSCLC, with squamous cell (n = 21), adenocarcinoma (n = 12), and undifferentiated (n = 7) histologies. RESULTS: Forty patients were assessable for toxicity and 32 for treatment response. Among these 32 patients, 8 had a partial response (intent-to-treat response rate, 20%), and 10 (25%) had stable disease. The median survival was 7.8 months (range, 4-11.6 months). The 1- and 2-year survival rates were 25% and 7%, respectively; median time to progression was 4.3 months (range, 0.2-13.8 months). Grade 3/4 neutropenia was seen in 27 patients (68%), and grade 3/4 anemia was seen in 5 patients (13%). One patient died of febrile neutropenia during treatment. The main nonhematologic adverse effect was fatigue (grade 3/4 in 18% of patients). CONCLUSION: Carboplatin/vinorelbine is well tolerated by elderly patients with extensive-stage NSCLC. Efficacy is low but similar to that of other treatments used in this setting.

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Introduction

Combinations of several cytostatic agents have become the standard treatment for non–small-cell lung cancer (NSCLC) in patients < 70 years of age with a good performance status (PS) based on the results of a metaanalysis showing an advantage of cisplatin-based combinations.[1] Relative to palliative care alone, cisplatin-based chemotherapy plus palliative care for metastatic NSCLC is associated with a slight improvement in survival and a marked improvement in quality of life (QOL); it also reduces global treatment costs.[2,3] Adverse effects, especially nausea and vomiting, are frequent.

It is difficult to know whether chemotherapy offers a survival benefit for patients > 70 years of age, as these subjects are gener-

ally excluded from clinical trials in Europe.[4] Yet Western populations are aging rapidly: the proportion of people > 65 years of age increased from 8% to 13% between 1950 and 1990, reaching nearly 20% in 2000. The incidence of cancer increases with age, from 300 cases per 100,000 people aged 45-49 years to 1400 per 100,000 people aged > 65 years.[5] In 2003, two thirds of patients diagnosed with lung cancer were > 65 years of age.[6] However, the mean age of patients enrolled in clinical trials in this setting is 60-62 years, suggesting a selection bias. In a study of a monitoring, epidemiology, and survival program, Earle et al found that only 32% of elderly patients received chemotherapy, mainly because of fears of severe adverse effects in these often fragile individuals.[7]

The general review by Souquet et al underscored the need for prospective trials of chemotherapy in elderly subjects, provided they complete a QOL analysis.[8]

The Elderly Lung Cancer Vinorelbine Italian Study (ELVIS), the first randomized trial in elderly subjects with NSCLC, showed better QOL and a survival advantage in the vinorelbine arm compared with the best supportive care arm, justifying further trials in this population.[9]

Cisplatin is difficult to use in elderly patients because of its renal, gastrointestinal, and neurologic toxicity. In contrast, carboplatin, which is also active in NSCLC,[10,11] is easy to administer on an ambulatory basis because it does not necessitate hyperhydratation.[12] Several recent studies have shown that vinorelbine is active and well tolerated in the elderly.[13-15] To determine whether combination therapy not containing cisplatin, which would in principle be less toxic, is feasible in elderly patients with NSCLC, the Groupe Français de Pneumo-Cancérologie (GFPC) conducted a trial of the carboplatin/vinorelbine combination (GFPC 9902).

Several studies involving elderly subjects have tested this combination. A phase I study by Jacoulet et al, after carboplatin dose escalation, showed that the optimal dose of the combination was carboplatin 325 mg/m^2 every 21 days and vinorelbine 30 mg/m^2 on days 1 and 8.[16]

Santomaggio et al, using carboplatin 350 mg/m^2 on day 1 and vinorelbine 25 mg/m^2 on days 1 and 8, every 28 days, obtained a response rate of 36% among 55 patients with advanced-stage NSCLC, with acceptable toxicity.[17]

Parente et al treated 75 patients with advanced-stage NSCLC with carboplatin 300 mg/m^2 on day 1 and vinorelbine 30 mg/m^2 on days 1 and 8, every 21 days, and obtained an overall response rate (ORR) of 45%.[18] Hematologic toxicity was significant but controllable. More recently, von Bültzingslöwen et al used carboplatin 300 mg/m^3 then at an area under the curve (AUC) of 5/6 and vinorelbine 30 mg/m^2 to treat 37 patients, with good tolerance.[19] The use of AUC dosing of carboplatin is expected to result in more acceptable toxicity in elderly patients relative to the body surface area (BSA)–based dosing strategy. Crawford and O'Rourke used carboplatin at an AUC of 7 on days 1 and 29 with vinorelbine weekly in a phase I study and found that the patients were able to tolerate the highest dose of vinorelbine (30 mg/m^2) but required granulocyte colony-stimulating factor.[20]

In this article, we report the results of an open multicenter phase II trial of carboplatin (day 1) combined with vinorelbine (days 1 and 8) in patients with NSCLC aged > 70 years. Treatment responses were confirmed by panel review. The principal endpoint was ORR. Secondary endpoints were overall survival, event-free survival, tolerability, and QOL.

Patients and Methods

Patients

Patients were enrolled by GFPC members. Eligibility criteria were as follows: age > 70 years; cytologically or histologically proven stage IV NSCLC; metastatic relapse (cytologic or histologic confirmation) of primary lung cancer in a nonirradiated area after surgical excision or local external radiation therapy; stage IIIB disease with T4 stage by neoplastic pleurisy (cytologic or histologic confirmation); Eastern Cooperative Oncology Group PS of 0/1; ≥ 1 measurable lesion (2 dimensions) in a nonirradiated region; written informed consent; normal hepatic function with bilirubin level < 1.25 times the upper limit of normal (ULN) and aminotransferase activity < 3 times the ULN; and normal hematologic and renal function. Patients were ineligible if they had previously received chemotherapy or had cerebral metastases, another severe concurrent disease (cardiac, neurologic, or psychiatric disease or uncontrolled infection), peripheral neuropathy of grade > 2, or steroid contraindications. The protocol was approved by the ethics committee of Marseille University Hospital.

Evaluations

The preenrollment assessment included a full physical examination, biologic tests (including differential blood cell count, platelet count, serum biochemistry with creatinine measurement, and liver function tests), chest radiography, computed tomography (CT) of the thorax and brain, abdominal ultrasound or CT, and bone scintigraphy with radiographs centered on pathologic zones.

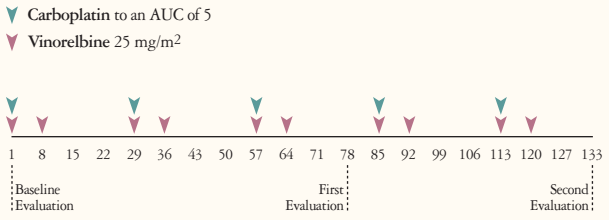
Quality of Life

Quality of life was assessed at enrollment and after the first, third, and fifth cycles with use of the QLQ-C30 questionnaire from the European Organization for Research and Treatment of Cancer (EORTC),[21] its specific lung cancer module QLQ-LC13, and the Spitzer index QLQ-C30 and QLQ-LC13 questionnaires.[22] The QLQ-C30 questionnaire was self-administered. It includes 30 items, 24 of which are grouped into 9 dimensions: 5 functional (physical, role, cognitive, social, and emotional) and 3 symptomatic (nausea, pain, and fatigue); the other 6 items are dyspnea, insomnia, loss of appetite, constipation, diarrhea, and subjective financial difficulties. The Spitzer questionnaire was administered by the investigators, and symptoms were assessed with use of visual analog rating scales.

Treatment

Induction Chemotherapy. The first phase of treatment comprised 3 cycles of carboplatin at an AUC of 5 (according to the Cockroft formula)[23] on day 1 and vinorelbine 25 mg/m^2 on days 1 and 8, every 28 days (Figure 1). Elderly patients differ from younger subjects in fundamental pharmacokinetic characteristics such as drug metabolism and excretion, volume of distribution,

Figure 1 Study Design



and drug absorption. For these reasons, the 28-day schedule was adopted in an attempt to reduce the number of patients needing a delay in dose administration or a reduction in the dose administered. The doses were adjusted according to hematologic toxicity: on day 8, the vinorelbine dose was halved if the polymorphonuclear neutrophil (PNN) count was between 1000/µL and 1500/µL and the platelet count was between 75,000/µL and 100,000/µL; the vinorelbine injection was canceled if the PNN was < 1500/µL and the platelet count was < 100,000/µL; the cycle was postponed for 7 days if the PNN was < 1500/µL and the platelet count was < 100,000/µL. The blood counts were obtained on day 15 but not on day 21.

Subsequent Treatments. After 3 cycles, patients with an overall repsonse (OR) or disease stabilization received 2 further cycles, but individual patients could continue beyond 5 cycles.

Assessment of Response

The principal endpoint was ORR. Tumor response was measured at the end of induction chemotherapy (day 78). Complete responses, partial responses (PRs), stable disease (SD), and progressive disease were defined as recommended by the World Health Organization.[24] Patients with disease progression were discontinued from the study. All patients were assessed for toxicity and survival.

The patients were seen every 2 months after the end of treatment for a minimum of a physical examination and a chest radiograph. Other examinations were prescribed as necessary. All PRs had to be confirmed 1 month later by the same examination. The inclusion criteria and responses were validated by a panel of investigators.

Analysis of Toxicity. As a secondary endpoint, tolerability was analyzed according to the National Cancer Institute (NCI) Common Toxicity Criteria.[25]

Statistical Analysis. This phase II study was designed to determine the activity of the carboplatin/vinorelbine combination in terms of tumor response rate and patient survival before conducting a phase III study of survival. The study was thus a pilot trial, and the number of subjects was arbitrarily set at 50.

In order to be able to halt the trial rapidly if the study combination was ineffective, we adopted a multistep procedure described by Fleming.[26] Assuming that the study regimen should be rejected if the ORR was ≤ 15% and accepted if the response rate was ≥ 30%, with an α risk of 0.012 and a β risk of 0.08, the trial would be terminated if there were < 3 responses among the first 20 patients or < 7 responses among the first 35 patients (20 + 15). The treatment would be considered ineffective at the end of the study if the response rate was < 15% in the overall population of 50 patients (ie, 20 + 15 + 15). An ORR of ≥ 22% was required to authorize a phase III trial.

Toxicity was analyzed per cycle and per patient. The duration of ORs, time to progression, and survival were estimated with the Kaplan-Meier method and the log-rank test. Data collected with the EORTC QLQ-C30 and QLQ-LC13 and Spitzer questionnaires were analyzed according to current recommendations. For each population, the response rates at the different time points were taken into account; normality tests were applied if the group was too small to guarantee normal distribution. The results of the 2 scales were compared. Statistical significance was assumed if $P < 0.05$.

Table 1 Patient Characteristics (N = 40)

Characteristic	Number (%)
Median Age, Years (Range)	72 (70-82)
Sex	
Male	31 (77.5)
Female	9 (22.5)
ECOG Performance Status	
0	15 (37.5)
1	25 (62.5)
Clinical Stage	
IIIB	2 (5)
IV	38 (95)
Histology	
Squamous cell	21 (52.5)
Adenocarcinoma	12 (30)
Undifferentiated	7 (17.5)

Abbreviation: ECOG = Eastern Cooperative Oncology Group

Results

Patient Characteristics

Forty patients were enrolled from July 2000 to June 2002. The target of 50 patients was not reached because the analysis of the first 35 patients showed only 6 objective responses based on the adopted multistep procedure; however, 40 patients had been enrolled by this time and were thus included in the final analysis. Median age was 72 years (range, 70-82 years), and 77.5% of the patients were men. Ninety-five percent of the patients had stage IV NSCLC, and the histologic type was squamous carcinoma in 52.5% of cases (Table 1).

Conduct of the Study

The trial flowchart is shown in Figure 2. Among the 40 enrollees, 8 patients (20%) were not assessable at the end of chemotherapy because of toxicity in 2 cases, intercurrent events in

Figure 2 Study Flowchart

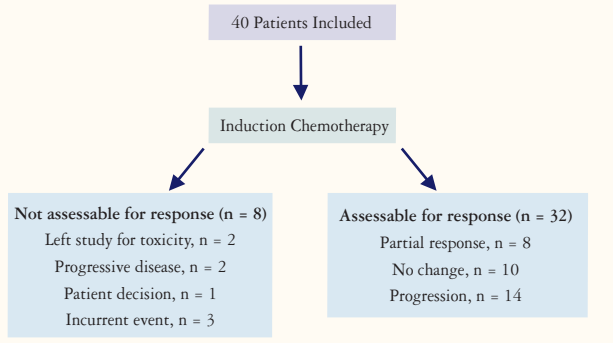
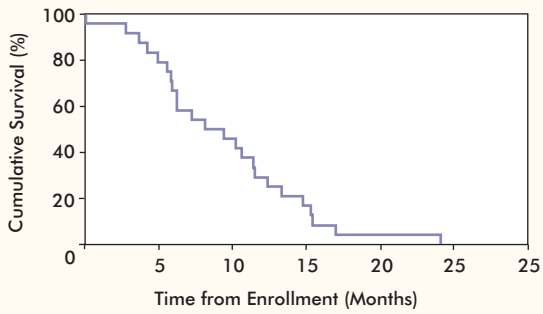


Figure 3 Survival in Intent-to-Treat Analysis



3 cases, disease progression in 2 cases, and patient refusal in 1 case. Among the 32 available patients on an intent-to-treat basis, 14 (35%) had progressive disease and were therefore discontinued from the study, 10 (25%) had SD, and 8 (20%) had an OR.

Treatments Delivered

Twenty-nine patients (72.5%) received 3 cycles of chemotherapy, and 16 patients (40%) received 5 cycles. Only 2 patients received 6 cycles. The relative dose intensities were 91.1% for vinorelbine and 100% for carboplatin, and the mean number of cycles administered per patient was 3.4.

Toxicity

A total of 136 cycles of chemotherapy were administered to 40 patients (Table 2). Sixty-nine cases of grade 3/4 toxicity occurred (50.7% of cycles). Grade 3/4 neutropenia was the most frequent severe adverse event (36.1%). Anemia was the most frequent event regardless of grade (n = 63; 46.3%). Fatigue was the second most frequent grade 3/4 adverse effect (n = 5; 3.6%). Toxicity was assessed at every cycle in all patients. Grade 3/4 neutropenia occured in 27 patients (68%), grade 3/4 anemia in 5 patients (13%), and fatigue in 7 patients (18%). One patient with febrile neutropenia died of septic shock.

Response

Treatment response was assessable in 80% of patients (Figure 2). The PR rate was 20% (95% CI, 9.05%-56.5%), and the rate of disease stabilization was 25% (95% CI, 12.69%-41.2%); thus, tumor progression was controlled in 45% of patients (95% CI, 29.26%-61.5%). The overall median time to progression was 4.3 months (range, 0.2-13.8 months).

Survival

The median survival time was 7.8 months (range, 4.0-11.6 months; Figure 3). The 1- and 2-year survival rates were 25% and 7%, respectively.

Quality of Life

The QOL questionnaires were completed by 39 patients (97.5%) at enrollment, 31 patients (77.5%) after the first cycle, 22 patients (55%) after the third cycle, and 11 patients (27.5%) after the fifth cycle. The questionnaires were completed by 11 patients (27.5%) at all 4 time points, by 11 patients (27.5%) at 3 time points, 9 patients (22.5%) at 2 time points, 8 patients (20%) at 1 time point, and never by only 1 patient. A significant improvement in QOL between baseline and cycles 1, 3, and 5 was noted in all 40 patients with regard to emotional function (P = 0.006) and insomnia (P = 0.008) on the QLQ-C30 questionnaire, and a trend toward an improvement was noted in general health (P = 0.09), dyspnea (P = 0.05), cough (P = 0.07), and pain (P = 0.09).

After normalizing the QOL scores at cycles 1, 3, and 5 according to baseline values, the comparison of changes in QOL between patients with disease control (OR + SD) and those with disease progression showed a significant improvement in the general health of the patients with disease control (QLQ-C30, P = 0.009; Figure 4) and a trend toward an improvement in pain (P = 0.09) and emotional function (P = 0.08). This significant improvement was also found with the Spitzer health index (P = 0.03) and, to a lesser extent, with the total Spitzer QOL score (P = 0.052; Figure 5).

Table 2 Acute Toxicity (N = 40)

Toxicity	Number of Patients (%)	
	Grade 1/2	Grade 3/4
Hematologic		
Anemia	18 (45)	5 (13)
Neutropenia	7 (18)	27 (68)
Thrombocytopenia	6 (15)	2 (5)
Nonhematologic		
Nausea/vomiting	10 (25)	0
Dysphagia	1 (3)	0
Diarrhea	0	1 (3)
Constipation	10 (25)	1 (3)
Sensory neuropathy	2 (5)	0
Fever	3 (8)	1 (3)
Infection	4 (10)	2 (5)
Cardiac dysfunction	2 (5)	0
Alopecia	4 (10)	0
Fatigue	8 (20)	7 (18)

Figure 4 QLQ-C30 Global Health Status

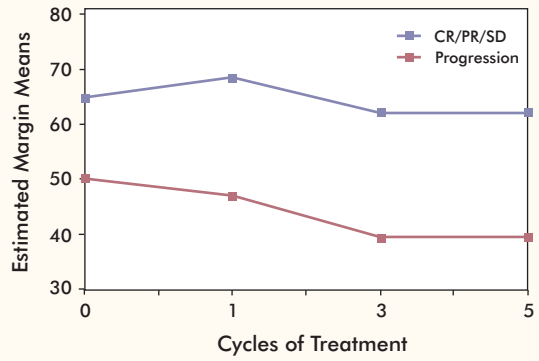
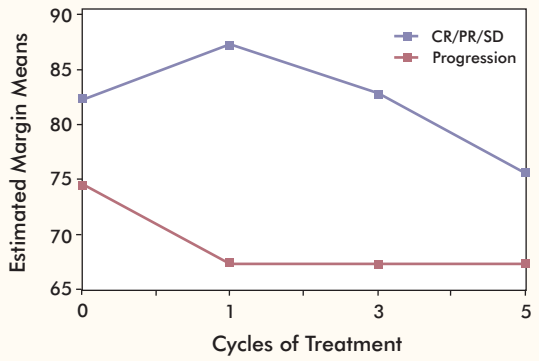


Figure 5 Spitzer Global Index



Patients whose disease was controlled and patients who had disease progression did not differ significantly at baseline in terms of QOL measured with the EORTC questionnaires, with the exception of physical function ($P < 0.05$) and trends toward a difference in cognitive function and insomnia (Table 3).

At baseline, the Spitzer and QLQ-C30 scores correlated on the following dimensions: physical function ($P = 0.001$), role function ($P = 0.001$), emotional function ($P = 0.009$), cognitive function ($P = 0.008$), fatigue ($P = 0.002$), nausea/vomiting ($P = 0.007$), pain ($P = 0.006$), and loss of appetite ($P = 0.001$); these correlations were lost at subsequent evaluations because of the smaller number of assessable patients. Overall, QOL improved among the 45% of patients whose NSCLC was controlled by this 2-drug combination.

Discussion

The choice of the carboplatin/vinorelbine combination was based on the results of several trials involving heterogeneous populations that included subjects > 70 years of age.[16-19] The median age of patients was 72 years. The combination of carboplatin at an AUC of 5 on day 1 plus vinorelbine 25 mg/m^2 on days 1 and 8, every 28 days yielded a 20% ORR and controlled the disease in 45% of patients. The median survival was 7.8 months, the time to progression was 4.3 months, and the 1-year survival rate was 25%. In the ELVIS trial, 19.7% of patients had ORs, and 30.3% had disease stabilization, with a median survival of 7 months in the vinorelbine arm.[27]

Table 3 Comparative Quality of Life of Patients with Disease Control and Those with Disease Progression (Initial Evaluation)

Dimensions (Mean ± SD)	Disease Control	Progression	*P* Value
Physical Function	80.5 ± 20.6	73.8 ± 16.5	0.03
Role Function	73.5 ± 33.9	65.0 ± 29.9	NS
Emotional Function	69 ± 24.6	64.6 ± 24.3	0.08
Cognitive Function	80.6 ± 25.7	80.6 ± 24.4	0.06
Fatigue	37.7 ± 33	40.4 ± 15.9	NS
Nausea/Vomiting	8.8 ± 20.3	5.6 ± 10.9	NS
Pain	27.2 ± 35.2	30.6 ± 27.4	NS
Insomnia	42.1 ± 38.2	24.2 ± 21.6	0.06

Abbreviations: NS = not significant; SD = standard deviation

Frasci et al noted a significant improvement in survival in the gemcitabine/vinorelbine arm relative to the vinorelbine monotherapy arm, with a median survival of 7.5 months, an ORR of 22%, and a 1-year survival rate of 30%.[28] In the Multicenter Italian Lung Cancer in the Elderly Study, Gridelli et al found no significant differences among the gemcitabine, vinorelbine, and gemcitabine/vinorelbine arms with regard to ORRs (16%, 18%, and 21%, respectively) and median survival (7.9 and 7.5 months).[29]

Kimura et al administered vinorelbine 25 mg/m^2 and gemcitabine 1000 mg/m^2 to 45 patients > 70 years of age on days 1 and 14 and obtained ORs in 27% of cases and SD in 47.7% (disease control rate, 74%); however, only 45% of patients had stage IV disease at enrollment.[30]

Overall, the carboplatin/vinorelbine combination gave results similar to those previously published in elderly subjects. The ORR of 22% required to authorize a phase III trial was not achieved. Nevertheless, the issue of the superiority of carboplatin-based doublets over single-agent therapy seems important in elderly patients[31] and could deserve a phase III trial comparing carboplatin/vinorelbine to vinorelbine as a single agent.

The carboplatin/vinorelbine combination had acceptable toxicity. Grade 3/4 neutropenia (a classical treatment-limiting effect of carboplatin)[32] was observed after 36.1% of the 136 cycles administered, with 1 toxic death caused by febrile neutropenia. In contrast, Gridelli et al, using the same therapeutic protocol to treat 37 elderly patients with small-cell lung cancer, observed 3 toxic deaths despite routine use of lenograstim.[33] Fatigue, regardless of severity, occurred in 17% of cycles (4% grade 3/4), and anemia occurred in 46% of cycles (4.5% grade 3/4). These 2 adverse effects are more frequent in elderly subjects, underscoring the need to correct anemia in future trials, as pointed out by Aapro et al.[34]

The tolerability of our treatment protocol was therefore acceptable and was in keeping with that of other regimens. This moderate toxicity underscores the value of AUC carboplatin dosing rather than BSA-based dosing. Masters treated 21 patients with stage IIIB/IV NSCLC in a phase I/II study using carboplatin at

an AUC of 2.5 on days 1 and 8, and vinorelbine 20-25 mg/m^2 on days 1 and 8, every 21 days. The regimen was very well tolerated, and the authors suggested that elderly patients may benefit from its minimal toxicity.[35] Five cycles seemed a reasonable option for elderly patients because the use of a brief duration of first-line treatment would reduce the risk of any cumulative toxicities according to the phase III trial published by Socinski et al.[36] This study showed no overall benefit in survival, response rates, or QOL with continuing treatment with carboplatin/paclitaxel beyond 4 cycles in advanced NSCLC.

Quality of life improved in the overall population, but some items improved significantly more in patients whose disease was controlled. These latter patients also had better QOL at enrollment, confirming that general health and global QOL are factors of good prognosis.[37,38]

Our study population consisted solely of patients > 70 years of age and was therefore more representative than populations mixing older and younger subjects. However, it must be stressed that only patients with a PS of 0/1 were eligible for our study and that patients' mean age was only 72 years, reflecting the difficulty of recruiting patients aged > 75 or 80 years. This raises the problem of the definition of chronologic age: the NCI has subdivided elderly patients into "young elderly" (65-74 years), "older elderly" (75-84 years), and "oldest elderly" subjects (≥ 85 years), but this is based on a postulate and does not therefore take physiologic age into account.[39] This suggests that the assessment of comorbidity may be used in the screening.

As underscored by Deppermann,[40] it is also important to take into account functional changes in aging organs, age-specific disorders such as depression, changes in mental status, nutritional status, the social environment, and comorbidity.[41] Our results suggest that it is reasonable to offer carboplatin combination chemotherapy to elderly subjects with good PS and little comorbidity, as previously suggested by Lilenbaum.[31]

Conclusion

This phase II trial shows that the carboplatin/vinorelbine combination using AUC-based carboplatin dosing has acceptable toxicity in elderly patients with NSCLC, yielding a response rate and a time to disease progression similar to those observed with other combinations in this setting. Quality of life was improved among patients whose disease was at least stabilized. Although monotherapy is generally used to treat this population, the carboplatin/vinorelbine combination appears to be suitable for elderly subjects who are in good general health and have little comorbidity. In future trials, physiologic age should be assessed with standardized geriatric rating methods. The importance of comorbidity in the treatment choice for this population remains to be addressed.

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