Cisplatin-Based Therapy for Elderly Patients With Advanced Non-Small-Cell Lung Cancer: Implications of Eastern Cooperative Oncology Group 5592, a Randomized Trial

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Background: **Older patients, even if fit, are often considered incapable of tolerating platinum-based systemic therapy. We performed a retrospective analysis of Eastern Cooperative Oncology Group (ECOG) 5592, a phase III randomized trial of platinum-based chemotherapy regimens for non-small-cell lung cancer (NSCLC), and compared outcomes in enrollees 70 years of age and older with those in younger patients.** ***Methods:*** **ECOG carried out a randomized phase III trial of cisplatin plus either etoposide or paclitaxel in chemotherapy-naïve NSCLC patients with stages III_B or IV disease. Toxic effects, response rates, and survival rates were compared between age groups. All *P* values were two-sided.** ***Results:*** **A total of 574 patients enrolled from August 1993 through December 1994 were evaluable. Eighty-six (15%) were 70 years old or older. Older patients had a higher incidence of cardiovascular (*P* = .009) and respiratory (*P* = .04) comorbidities and nonanalgesic medication use (*P* = .02). Leukopenia (*P*<.001) and neuropsychiatric toxicity (*P* = .002) were more common in elderly men than in younger men. Elderly women lost more weight than younger women (*P* = .006). Other toxic effects were similar in older and younger patients. The proportions with clinical partial or complete response (21.5% versus 23.3%; Fisher's exact test, *P* = .66), median time to progression (4.37 versus 4.30 months; log-rank test, *P* = .29), and survival distribution (log-rank test, *P* = .29; median survival, 9.05 versus 8.53 months; 1-year survival, 38% versus 29%; and 2-year survival, 14% versus 12%) were similar in patients younger than 70 years and 70 years old or older. Baseline quality-of-life and treatment-outcome indices were similar. Equivalent declines over time in functional well-being occurred in both groups.** ***Conclusion:*** **Response rate, toxicity, and survival in fit, elderly NSCLC patients receiving platinum-based treatment appear to be similar to those in younger patients, although patients 70 years old or older have more comorbidities and can expect more leukopenia and neuropsychiatric toxicity. Advanced age alone should not preclude appropriate NSCLC treatment. [J Natl Cancer Inst 2002;94:173–81]**

Forty-two percent of those patients who are newly diagnosed with non-small-cell lung cancer (NSCLC) are older than 65 years, and one third are older than 70 years *(1)*. However, the elderly are underrepresented in clinical research trials evaluating new treatments in advanced disease *(2)*. Several randomized trials and a major meta-analysis have clearly demonstrated improvements in survival for patients with advanced disease treated with chemotherapy [reviewed in *(3)*]. However, a nihilistic attitude exists in many clinicians. The elderly, even those with a good performance status (PS), are often considered to be unfit for aggressive therapy; the benefits, if they do occur, are thought to be limited in terms of prognosis or quality of life (QOL). Many studies *(4,5)*, particularly those outside North America, explicitly exclude the elderly from participating, and this mindset has been associated with impaired outcome in the elderly. Yet the elderly clearly benefit: A multicenter randomized trial of vinorelbine versus best supportive care in patients 70 years of age or older demonstrated a nearly threefold improvement in

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See "Notes" following "References."

1-year survival rate, with attendant improvement in QOL *(6)*. Despite the obvious benefit of single-agent therapy, a bias often exists, even among those inclined to treat the elderly, against combination therapy or cisplatin-based treatment.

Although cisplatin-based therapy has yielded improved survival in patients with advanced NSCLC *(3,7)*, the role of combination therapy, particularly cisplatin-based treatment, in the elderly has not been explored systematically. In retrospective multivariate and recursive partitioning analyses of the Eastern Cooperative Oncology Group (ECOG) database in which patients received multiple different regimens, most platinum-based, age did not prove to be an important factor in determining prognosis *(8,9)*. To systematically examine whether advanced age compromises outcome or exacerbates toxicity, we performed a retrospective analysis of patients enrolled on ECOG 5592, a phase III study employing a fixed dose of cisplatin and randomly assigning patients to receive either standard therapy (etoposide) or two different doses of paclitaxel. This study, previously reported by Bonomi et al. *(10)*, demonstrated an outcome benefit for patients randomly assigned to treatment with paclitaxel and cisplatin (Table 1). The effect of age on outcome or toxicity, however, was not explored explicity.

PATIENTS AND METHODS

Eligibility

Fig. 1 provides information about accrual, randomization, and availability of patients for analysis. Eligibility stipulated histologically or cytologically confirmed NSCLC; bidimensional measurable or evaluable stage III, stage IV, or recurrent disease; ECOG PS of 0 or 1; no history of malignant disease in the previous 5 years, with the exception of skin cancer or *in situ* carcinoma of the cervix; and no brain metastasis. In addition, enrollment mandated adequate organ function defined as follows: a leukocyte count of greater than or equal to 4000/mm^3, a platelet count of greater than or equal to 100 000/mm^3, a bilirubin level of less than or equal to 1.5 mg/dL, and a serum creatinine level of less than or equal to 1.5 mg/dL. A minimum age of 18 years was required. There were no upper age restrictions. Active infections rendered patients ineligible, as did prior chemotherapy or mixed small-cell and non-small-cell histology.

Patients were permitted prior radiation therapy, as long as it had been completed 2 weeks or more before trial entry. However, patients whose only measurable lesion was within a previous radiation portal were deemed to be ineligible. Additional exclusion criteria included uncontrolled diabetes mellitus (random blood sugar level >200 mg/dL), uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction within the previous year, or evidence of pre-existing peripheral neuropathy. Written informed consent, in accordance with the institutional review board of each participating institution, was required before study entry. Patients were accrued from the ECOG, a consortium of academic and community cancer centers and practices across North America and South Africa.

Table 1. Eastern Cooperative Oncology Group 5592: overall outcome [as reported in *(10)*]*

	EC	PCG	PC
No.	200	201	198
Objective response rate, %	12.4	27.7	25.3
FFS, mo	2.8	5.0	4.4
MS, mo	7.6	10.0	9.5
1-y overall survival, %	31.8	40.3	37.4
2-y overall survival, %	11	15	13

*FFS = median failure-free survival; MS = median survival; EC = etoposide/cisplatin; PC = paclitaxel/cisplatin; G = granulocyte colony-stimulating factor.

Randomization

Patients were given a fixed dose of cisplatin at 75 mg/m^2 and were randomly assigned to one of three distinct chemotherapy regimens as follows: 1) etoposide–cisplatin regimen (EC)—cisplatin administered over a 1-hour period on day 1 and etoposide at a dose of 100 mg/m^2 administered intravenously over a 45-minute period on days 1, 2, and 3; 2) high-dose paclitaxel regimen (PCG)—paclitaxel at a dose of 250 mg/m^2 administered intravenously by 24-hour infusion on day 1, followed by cisplatin on day 2, plus granulocyte colony-stimulating factor, at 5 μg/kg subcutaneously beginning on day 3 and continuing until the granulocyte count rose above 10 000/mm^3; and 3) low-dose paclitaxel regimen (PC)—paclitaxel at a dose of 135 mg/m^2 given intravenously by 24-hour infusion on day 1, followed by cisplatin on day 2. In the absence of persistent toxicity or evidence of disease progression, treatment was cycled at 21-day intervals.

Stratification parameters included the following: ECOG PS of 0 versus 1 *(11)*, weight loss during the previous 6 months of less than 5% versus greater than or equal to 5%, stage $IIII_B$ versus stage IV disease *(12)*, and bidimensional measurable disease versus evaluable disease.

History and physical examination, complete blood cell count, and serum chemistries were performed before each treatment cycle. Tumor measurements were obtained after every two cycles. QOL, based on the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale *(13)*, was assessed at baseline and periodically over the course of treatment. Toxicity and tumor responses were defined according to ECOG criteria *(14)*.

Statistical Methods

The accrual goal of the study (585 patients) was estimated to yield a greater than 90% power to detect a 50% increase in median survival from 6 months on standard treatment to 9 months on either of the paclitaxel regimens, with an experimental type 1 significance level of 5%, by use of an O'Brien–Fleming type group sequential method *(15,16)*. Fisher's exact test *(17)* was used to compare response rates, and the Kruskall–Wallis test *(18)* was used to compare levels of toxicity. Survival estimates were calculated by the Kaplan–Meier method *(19)*, and the log-rank test *(20)* was used for survival comparisons. All *P* values were two-sided.

For this analysis, patient characteristics were broken down by age (<70 years versus ⩾70 years) and sex and included treatment assignment, race, PS, weight loss in previous 6 months, disease stage, prior therapy, primary disease symptoms, metastatic disease symptoms, presence of paraneoplastic syndrome, systemic symptoms, associated chronic diseases, chronic medications, initial laboratory values, histology, and sites of metastatic lesions. Fisher's exact test and the Kruskall–Wallis test were used to compare proportions and distributions of variables between the two groups. Fisher's exact test *(17)* was also used to compare response rates between the two groups, with confidence

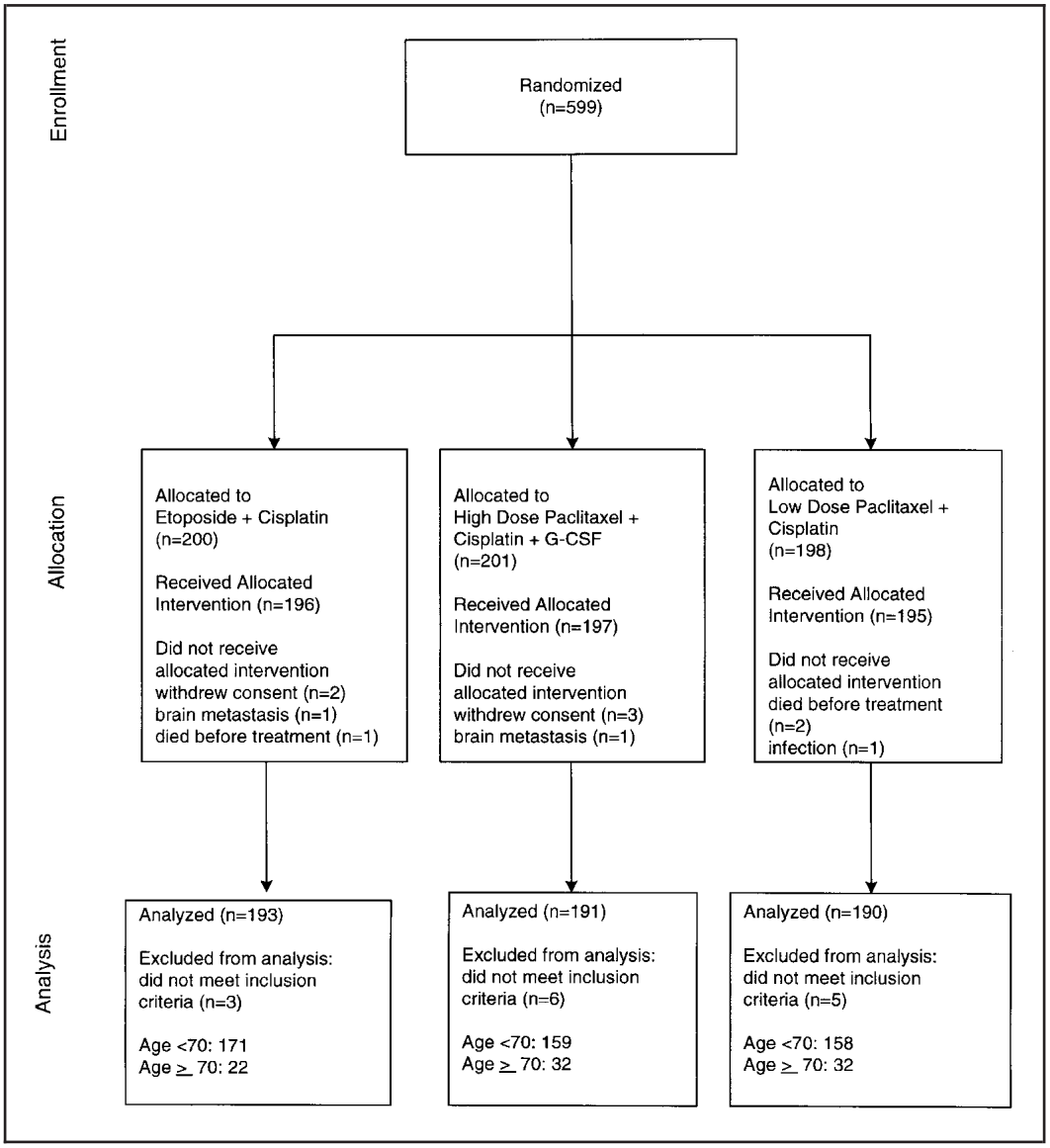

Fig. 1. CONSORT trial flow diagram for Eastern Cooperative Oncology Group (ECOG) 5592, a randomized phase III trial of fixed doses of cisplatin plus either etoposide or paclitaxel in chemotherapy-naive patients with stage III_B or IV non-small-cell lung cancer.

intervals (CIs) for response estimated by use of exact binomial CIs *(21)*. Survival curves were estimated by the method of Kaplan and Meier *(19)*. The method of Mehta et al. *(22)* was used to test for differences in patterns of toxicity between younger and older patients.

Quality of Life

QOL was assessed by version 2 of the FACT-L instrument *(18)*, consisting of 35 questions, each scored using a 5-point scale: 1) 0 = not at all, 2) 1 = a little bit, 3) 2 = somewhat, 4) 3 = quite a bit, and 5) 4 = very much. The questions addressed six areas: 1) physical well-being, 2) functional well-being, 3) lung cancer symptoms, 4) social well-being, 5) emotional well-being, and 6) relationship with doctor. A subgroup of 21 questions relating to physical well-being, functional well-being, and lung cancer symptoms was combined in a designated trial outcome index (TOI), which, based on prior studies, was considered to be the best summary indicator of the physical component of QOL *(13)*. Patients were asked to complete the FACT-L questionnaire before the first course of chemotherapy and again 6, 12, and 26 weeks later. Numeric values for each item were added to obtain the total score and scores for subsets of questions, such as the TOI. Each patient was classified according to his/her QOL response. The QOL response category for individual patients was determined by calculating the difference between a baseline TOI score and the TOI scores at 6, 12, and 26 weeks. In addition, we compared baseline QOL between patients aged 70 years and older and patients less than 70 years of age. For patients completing the 6-month assessment, we also computed a differential score between baseline and 6-month QOL. A Student's *t* test was used to compare each of these QOL measures, with appropriate *P* values assigned. Because missing data at later time points might have been related to both QOL and survival status, the method of analysis suggested by Schluchter *(23)* was employed to test for age-related differences in FACT-L scores. Schluchter's method jointly models the longitudinal QOL assessments and survival to better control for possible bias because of differential missing data in the two groups. With the use of this method, missing observations that occurred after the last observed measurements were assumed to be informatively missing (i.e., not missing at random). The longitudinal model is the random-effects model proposed by Laird and Ware *(24)*. The survival model is a log-normal model.

RESULTS

From August 1993 through December 1994, a total of 599 patients were enrolled in the trial; 574 were evaluable. The reasons for cancellation and ineligibility have been delineated previously *(10)*. Patient demographics are summarized in Table 2. A total of 488 patients were under 70 years of age; 86 (15%) were 70 years of age or older. There was equal distribution across sex, race, PS, pretreatment weight loss, disease stage (III_B versus IV), and prior radiation therapy. A significant increase in comorbid conditions, including cardiovascular disease ($P = .009$) and respiratory disease ($P = .04$), was observed in older patients. There was no difference with respect to prior analgesic usage or need for corticosteroids, although older patients exceeded younger patients in their use of other medications ($P = .015$).

Pretreatment symptoms and sites of disease are also summarized in Table 2. A slightly higher proportion of younger patients experienced cough ($P = .10$) and hoarseness ($P = .09$). There were no statistically significant differences with respect to symptoms of respiratory infection, as well as other primary symptoms, hemoptysis, dyspnea, chest pain, Pancoast symptoms, bone pain, or appetite loss.

Older patients had a slightly higher percentage of squamous histology and a slightly lower percentage of adenocarcinoma, but this trend was statistically nonsignificant (two-sided Fisher's exact test, $P = .15$). The elderly had a significantly lower incidence of mediastinal involvement ($P = .009$) and a trend toward more hepatic involvement ($P = .07$) but no other differences in sites of metastases. There was no difference in baseline levels of albumin, lactate dehydrogenase, or alkaline phosphatase using Kruskal–Wallis tests.

Table 2. Eastern Cooperative Oncology Group (ECOG) 5592: age distribution at baseline

	Age, y		Total	
	<70, %	⩾70, %	(%)	Two-sided *P**
Sex				
Male	63	67	365 (64)	.47
Female	37	33	209 (36)	
Performance status *(11)*				
ECOG 0	33	26	182 (32)	.21
ECOG 1	67	74	392 (68)	
Baseline weight loss				
<5% body weight	71	66	403 (70)	.44
⩾5% body weight	29	34	171 (30)	
Stage *(12)*				
III_B	20	15	112 (20)	.30
IV/recurrent	80	85	462 (80)	
Histology				
Squamous cell	21	28	128 (22)	.09
Nonsquamous cell	70	58	390 (68)	
Not specified	9	14	56 (10)	
Baseline comorbidities				
Cardiac	22	35	135 (24)	.009
Respiratory	16	26	100 (17)	.04
Other comorbidities	25	35	153 (27)	.08
Analgesics	42	31	232 (40)	.14
Other medications	51	66	306 (53)	.02
Baseline symptoms				
Respiratory infection	15	14	86 (15)	1.00
Cough	48	37	267 (46)	.10
Hemoptysis	13	15	78 (14)	.61
Dyspnea	45	41	253 (44)	.55
Hoarseness	9.2	3.5	48 (8.4)	.09
Chest pain	31	26	172 (30)	.44
Osseous pain	26	22	144 (25)	.59
Respiratory symptoms	26	21	145 (25)	.42
Decreased appetite	28	30	165 (29)	.70
Sites of involvement				
Lung	63	60	358 (62)	.90
Pleura	30	26	168 (29)	.52
Mediastinum	50	34	274 (48)	.009
Supraclavicular lymph node	14	9.3	76 (13)	.30
Liver	17	26	105 (18)	.07
Bone	34	26	189 (33)	.20
Other	24	23	136 (24)	.67

*P value from Fisher's exact test.

Treatment Distribution

Among subjects under 70 years, 35% received EC, 33% received PCG, and 32% received PC, while, among subjects 70 years old or older, 26%, 37%, and 37% received EC, PCG, and PC, respectively. No statistically significant difference in the distributions of treatment received was observed between the two groups (two-sided Fisher's exact test, $P = .22$).

Clinical Response Rates

Table 3 shows the clinical response rates. Of 488 patients under 70 years of age, 105 had either a complete or a partial response (22%; 95% CI = 18% to 25%). Of 86 subjects 70 years old or older, 20 achieved a complete or a partial response (23%; 95% CI = 15% to 34%). No statistically significant difference in response rates between the two groups was observed ($P = .67$). Of note, a slightly higher proportion of younger patients (50.6%) had progressive disease as their best overall response compared with older patients (40.7%). When we grouped patients with stable disease with responders and compared the elderly with younger patients, there was no statistically significant difference in outcome ($P = .15$). There were no sex-related differences in response rate. Among the elderly, 16 (25%) of 64 subjects receiving taxane-containing regimens had either a complete or a partial response (95% CI = 15% to 37%), whereas four (18%) of 22 receiving EC responded (95% CI = 5.2% to 40%); among subjects less than 70 years old, 85 (27%) of 317 randomly selected to receive taxane-containing regimens responded (95% CI = 22% to 32%), whereas 20 (12%) of 171 patients receiving EC responded (95% CI = 7.3% to 17%).

Survival and Time to Disease Progression

There was no statistically significant difference in the distribution of survival times between the two groups ($P = .29$). Overall median survival time in patients younger than 70 years

Table 3. Eastern Cooperative Oncology Group 5592: clinical response data

	No. (%)	
Objective response	<70 y old	⩾70 y old
Responders*,†	105 (22)	20 (23)
Nonresponders‡	362 (74)	60 (70)
Unevaluable	21 (4.3)	6 (6.7)

*Patients who had either a complete or a partial response.

†$P = .67$. Statistical comparison of response rates for those <70 versus ⩾70 years of age.

‡Patients whose best response was either progressive disease or no change.

was 9.05 months compared with 8.53 months in patients 70 years old or older. At 1 year, the relative survival rates were 37.7% and 29.1%, respectively; at 2 years, they were 13.5% and 11.6%, respectively. The relative survival curves are depicted in Fig. 2, A. Among the elderly, there was no statistically significant difference in survival times between patients receiving the taxane-containing regimen and those receiving EC ($P = .62$). For the elderly receiving either PC or PCG, the median survival time and the 2-year survival proportion were 9.2 months and 12%, respectively, compared with 6.34 months and 9%, respectively, for those receiving EC.

There was no statistically significant difference with respect to time to progression ($P = .29$). At 1 year, 11.3% of subjects under 70 years of age were free from progression compared with

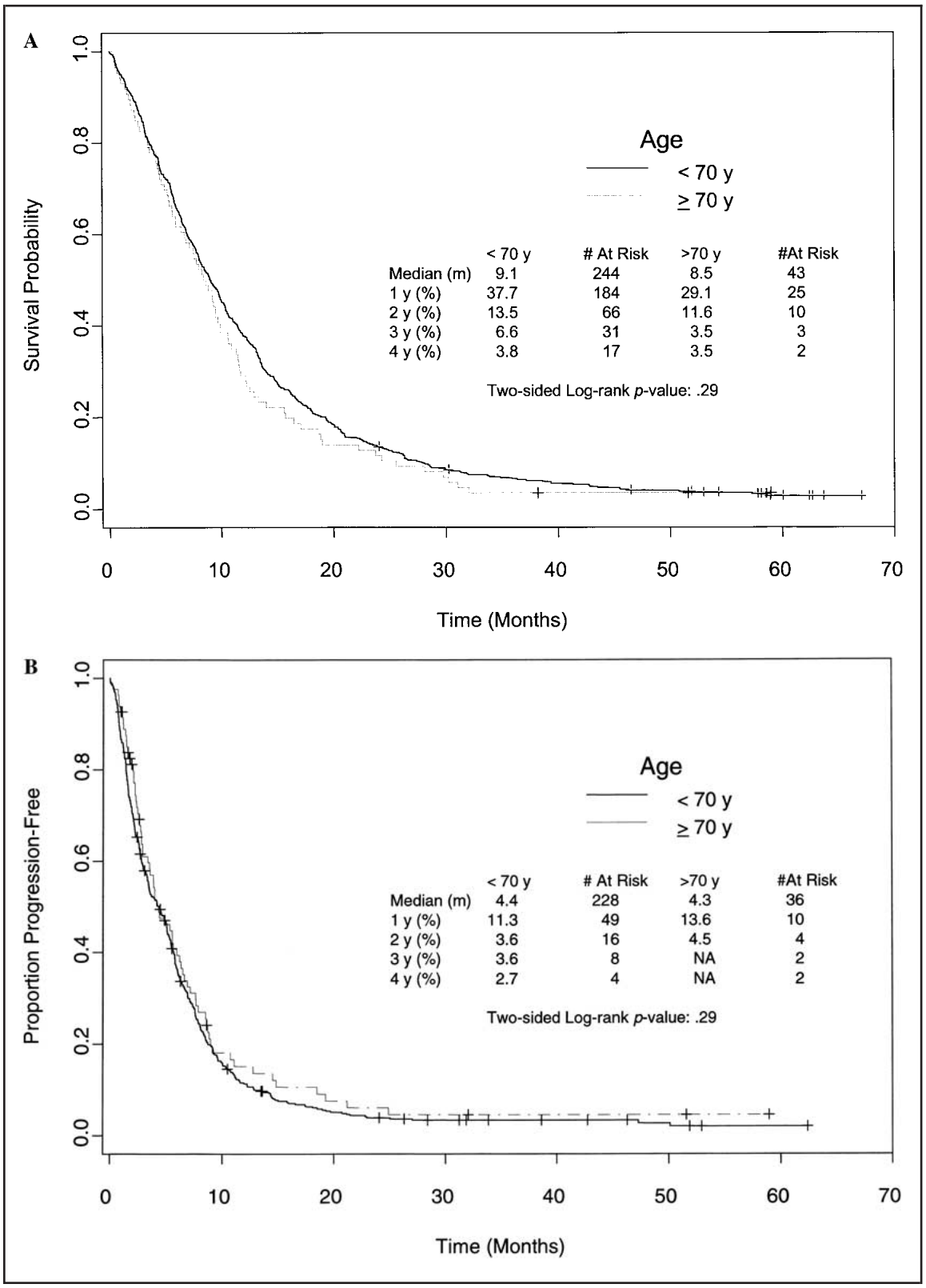

Fig. 2. Kaplan–Meier estimate of the survivor functions (**A**) and the time to progression distributions (**B**) for patients younger than 70 years and patients 70 years old or older. **Tick marks** represent censored observations.

15.1% of those 70 years of age or older. The median time to progression in each group was 4.37 and 4.30 months, respectively. Median time to progression for the elderly receiving EC was 2.76 versus 5.29 months for those receiving PC or PCG (log-rank test, $P = .36$). Time to progression curves are shown in Fig. 2, B.

Sex had no influence on survival or time to progression in either age cohort. The median overall survival time in the group of male subjects less than 70 years old was 8.64 months; it was 7.72 months in the group 70 years of age or older. The median time to progression was 4.14 and 3.84 months for male subjects in the less than 70-year group and greater than or equal to 70-year group, respectively. There were no statistically significant differences with respect to overall survival and time to progression between the two groups (overall survival, $P = .0863$; time to progression, $P = .3864$). The median overall survival time in the group of female subjects less than 70 years old was 9.79 months; it was 10.25 months in the group 70 years old or older. The median time to progression was 4.83 and 5.52 months for the female subjects in the less than 70-year group and greater than or equal to 70-year group, respectively. There were no statistically significant differences with respect to overall survival and time to progression between the two groups (overall survival, $P = .6540$; time to progression, $P = .5527$).

Toxicity

All patients (n = 588), regardless of eligibility, were included in the toxicity analyses. Toxic effects by maximum grade are detailed separately for males and for females in Table 4. Overall, older males were more likely to experience high-grade leukopenia ($P<.001$) then their younger counterparts (42% versus 17%), and they had a higher incidence of neuropsychiatric toxicity ($P = .002$) (17% grade ⩾2 versus 7%), although the precise nature of this toxicity was not delineated. In addition, the severity of toxicity or worst degree of toxicity manifest was significantly higher in elderly males ($P = .007$). There was a 7% incidence of grade 5 toxicity in males 70 years old or older versus 3% in males under 70 years. Of seven grade 5 events occurring in the elderly, five occurred in the high-dose paclitaxel group (three in the setting of neutropenic fever). Four of the grade 5 events among the elderly occurred in males and three occurred in females. Elderly women were likely to experience more severe weight loss than younger women; 33% of elderly women had weight loss of 10% or more compared with 17% of younger women. No other differences in toxicity were observed between younger and older patients.

Quality of Life

QOL was assessed at baseline, at 6 weeks, at 3 months, and at 6 months (Table 5). The mean scores for the entire FACT-L, the TOI, and the physical and functional well-being subscales, along with the number of assessments completed at each time point, are shown in Table 6 and Fig. 3. We found no statistically significant differences in either baseline QOL ($P = .20$) or changes in QOL over time ($P = .12$) between younger and older males. Among female patients, older patients had higher scores at baseline on the FACT-L instrument than younger women (114.5 versus 104.1; $P = .003$). Older women also had less change in QOL over time ($P = .003$). A model that assumed no association between differential missing data and survival produced similar but not identical results and resulted in the same conclusions. It should be noted that substantially fewer patients were assessed at 3 and 6 months than at baseline. Those who did not undergo 6-month evaluation were presumably sicker, had progressive disease, or had died.

Table 4. Relative toxic effects, by age

	Age cohort										
	Males, <70 y, %, by CTC* toxicity grade (n = 314)					Males, ⩾70 y, %, by CTC toxicity grade (n = 60)					Two-sided
Toxic effect	1	2	3	4	5	1	2	3	4	5	P†
Leukopenia	11	20	39	17	0	3	12	38	42	0	<.001
Granulocytopenia	5	4	11	64	0	3	3	5	80	0	.08
Thrombocytopenia	34	12	8	2	0	43	12	13	3	0	.74
Anemia	31	46	17	1	0	18	50	24	2	0	.06
Hemorrhage	8	1	<1	<1	0	5	0	0	0	2	.64
Infection	5	16	5	1	2	3	15	12	5	2	.09
Genitourinary	27	14	<1	0	0	33	13	2	0	0	.74
Nausea	31	26	22	0	0	25	35	25	0	0	.31
Vomiting	22	26	7	6	0	33	13	7	12	0	.48
Diarrhea	16	11	3	2	0	22	7	3	2	0	.37
Pulmonary	5	5	2	1	<1	7	3	0	0	0	.15
Cardiac	5	3	2	2	<1	12	3	3	0	3	.58
Allergy	1	1	1	<1	0	0	0	0	0	0	
Weight loss	25	18	1	0	0	42	20	2	0	0	.41
Neurosensory	15	11	15	0	0	10	20	17	0	0	.46
Neuromotor	20	11	8	<1	0	25	15	10	2	0	.73
Neuropsychiatric	11	5	2	<1	0	2	10	7	0	0	.002
Neuroclinical	21	18	10	0	0	27	22	12	0	0	.89
Worst degree‡	0	9	20	68	3	9	2	13	78	7§	.007

	Age cohort										
	Females, <70 y, %, by CTC toxicity grade (n = 186)					Females, ⩾70 y, %, by CTC toxicity grade (n = 28)					Two-sided
Toxic effect	1	2	3	4	5	1	2	3	4	5	P†
Leukopenia	10	25	36	13	0	7	18	32	32	0	.05
Granulocytopenia	3	2	19	60	0	0	7	11	71	0	.47
Thrombocytopenia	38	11	7	4	0	43	7	7	11	0	.75
Anemia	19	46	26	3	0	11	54	25	0	0	.83
Hemorrhage	3	1	0	1	0	0	4	4	4	0	.14
Infection	6	14	8	1	1	0	14	4	0	7	.17
Genitourinary	26	9	1	1	0	39	18	4	4	0	.46
Nausea	26	33	28	0	0	32	25	43	0	0	.59
Vomiting	23	30	10	11	0	25	25	14	11	0	.97
Diarrhea	17	12	3	3	0	14	18	4	11	0	.19
Pulmonary	8	5	1	0	0	4	4	0	4	4	.10
Cardiac	7	2	2	1	2	11	7	7	0	0	.87
Allergy	2	2	1	1	0	0	0	0	0	0	
Weight loss	28	15	2	0	0	7	29	4	0	0	.006
Neurosensory	13	18	17	1	0	11	18	18	0	0	.82
Neuromotor	18	14	4	1	0	25	14	4	0	0	.52
Neuropsychiatric	15	8	1	0	0	7	7	0	0	0	.96
Neuroclinical	22	22	8	0	0	21	14	18	4	0	.24
Worst degree	1	9	22	66	3	0	4	21	64	11§	.18

*CTC = common toxicity criteria.

†*P* value from Fisher's exact test.

‡Worst degree or grade of toxicity observed per patient.

§Five or seven patients received high-dose paclitaxel, cisplatin, and granulocyte colony-stimulating factor; linked to neutropenia fever/sepsis.

Patients Greater Than or Equal to 75 Years of Age

Because concerns exist that those patients over age 75 years may be different with respect to treatment tolerance and outcome from those between the ages of 70 and 75 years, we also analyzed the older group (>75 years; n = 24) and compared

Table 5. Summary of quality-of-life measurements by age group and assessment time point*

	Baseline	6 wk	3 mo	6 mo
Male, age <70 y				
No. assessed (FACT-L)	293	202	160	107
Mean FACT-L	107.3	106.8	106.7	107.5
Mean TOI	56.5	54.8	54.5	55.0
Mean physical well-being†	21.4	19.8	19.7	19.3
Mean functional well-being†	16.8	16.2	16.5	16.7
Male, age ⩾70 y				
No. assessed (FACT-L)	54	34	24	12
Mean FACT-L	102.9	102.6	101.9	100.6
Mean TOI	53.5	52.2	51.8	52.2
Mean physical well-being†	20.2	18.4	18.9	19.2
Mean functional well-being†	16.3	15.3	15.1	15.9
Female, age <70 y				
No. assessed (FACT-L)	164	122	91	67
Mean FACT-L	104.1	103.9	103.4	100.2
Mean TOI	54.7	53.4	52.9	51.6
Mean physical well-being†	20.4	19.0	18.4	18.2
Mean functional well-being†	16.4	16.3	16.6	15.9
Female, age ⩾70 y				
No. assessed (FACT-L)	25	18	13	7
Mean FACT-L	114.5	108.5	114.9	117.6
Mean TOI	60.6	55.9	58.1	63.7
Mean physical well-being†	22.4	20.4	20.3	23.3
Mean functional well-being†	18.9	16.2	18.0	20.6

*FACT-L = Functional Assessment of Cancer Therapy-Lung; TOI = Treatment Outcome Index.

†Defined as in *(13)*.

Table 6. Eastern Cooperative Oncology Group 5592: subgroup analysis of elderly patients by age*

	70–75 y of age (n = 62)		>75 y of age (n = 24)	
	% ⩾Grade 3*	95% CI†	% ⩾Grade 3	95% CI
Toxic effect				
Leukopenia	71 (32)	59 to 82	84 (56)	64 to 95
Anemia	29 (3)	18 to 41	20 (0)	7 to 41
Thrombocytopenia	19 (6)	10 to 31	12 (4)	3 to 31
Nausea	30 (0)	19 to 43	32 (0)	15 to 53
Vomiting	22 (11)	13 to 34	16 (12)	5 to 36
Neurosensory	14 (0)	7 to 25	24 (0)	9 to 45
Lethal toxic effects, %	8	3 to 18	8	0.1 to 26
Outcome				
Mean No. of treatment cycles	4.65		4.25	
Median No. of treatment cycles	4		4	
Overall response, %	26	15 to 39	17	5 to 37
Median time to progression, mo	4.3	2.8 to 6.2	4.1	2.5 to 8.3
Median survival, mo	8.4	5.9 to 9.7	9.9	4.9 to 12.5
1-y survival, %	25.8	15 to 37	37.5	18 to 57

*As defined in ref. 4.

†CI = confidence interval.

their outcome with the outcome in a slightly younger cohort (70–75 years; n = 62) (Table 6). Except for a borderline increased incidence of leukopenia ($P = .06$), no discernible difference was noted, although sample size in the older group was rather small. Unfortunately, broad conclusions regarding patients 80 years of age or older could not be drawn. There were only two patients 80 years old or older: One received three cycles of therapy, and one received six cycles.

DISCUSSION

Response rates and survival rates in fit elderly NSCLC patients receiving platinum-based treatment are similar to those in younger patients. With the exception of leukopenia and neuropsychiatric toxicity, there were no obvious differences in the incidence of toxicity. This observation should pose no surprise. The relative safety of cisplatin in the elderly has been reported in several studies *(25–28)*. There was, however, a higher incidence of life-threatening grade 4 and fatal grade 5 events, particularly in the high-dose paclitaxel arm. This finding reinforces the need to carefully screen elderly patients who are put on such trials. It also raises the potential need for elderly-specific trials that address their unique physiologic needs and take into account the increased incidence and severity of their comorbidities. It should be noted that only two patients over the age of 80 years were enrolled in ECOG 5592; hence, any conclusions derived from this analysis do not apply to the oldest age group.

Some additional caveats must be applied to this secondary analysis. First, although equivalent declines in QOL over time occurred in the elderly and in younger patients, only 21.5% of those 70 years old or older completed the 6-month assessment compared with 37.2% of those less than 70 years. This difference is substantial and may indicate that the elderly were actually doing worse than the data would suggest. In retrospect, a 6-month endpoint may have been overly ambitious. Second, the higher incidence of neutropenia in the elderly underscores the observation that hematopoietic reserve declines with age and reinforces the need to consider growth factor support, particularly in diseases like breast cancer or lymphoma, where therapeutic dose intensity is crucial *(29)*. Moreover, given our knowledge of neurotoxicity in the elderly and the putative increased susceptibility of peripheral nerves with age to neurotoxic agents, the absence of any difference in neurotoxicity between the elderly and younger patents is curious, if not surprising. It should be noted that the case report forms used to track toxic effects were uniformly employed during the entire course of the study; hence, no unintended biases between those 70 years old or older and those less than 70 years of age existed in recording neurotoxicity. It is conceivable, however, that those with mild baseline neurotoxicity may have overlooked or failed to report subtle exacerbations of their symptoms. Finally, neuropsychiatric toxicity, which appeared worse in the elderly, was nonspecific; chart review strongly suggests that more global symptoms, including fatigue and lassitude, were included under this rubric along with more specific symptoms of depression or cognitive compromise. Consequently, the conclusion that psychologic and/or neurocognitive distress was more pronounced in the elderly may represent an overinterpretation of the data.

To date, the optimal regimen for fit, elderly patients is not certain. No elderly-specific study has yet compared platinum-based therapy with non-platinum-based combinations or single agents. The Elderly Lung Vinorelbine Italian Study (ELVIS) Trial *(6)* clearly established the role of systemic therapy, specifically vinorelbine, in the elderly, including patients with an ECOG PS of 2; however, a similar elderly-specific trial comparing vinorelbine–cisplatin with vinorelbine alone has not been conducted, nor has any other comparison between cisplatin–new agent combinations and new-agent monotherapy been mounted in this age group.

Gemcitabine, like vinorelbine, appears to be a reasonable choice in the treatment of elderly NSCLC patients. The impact

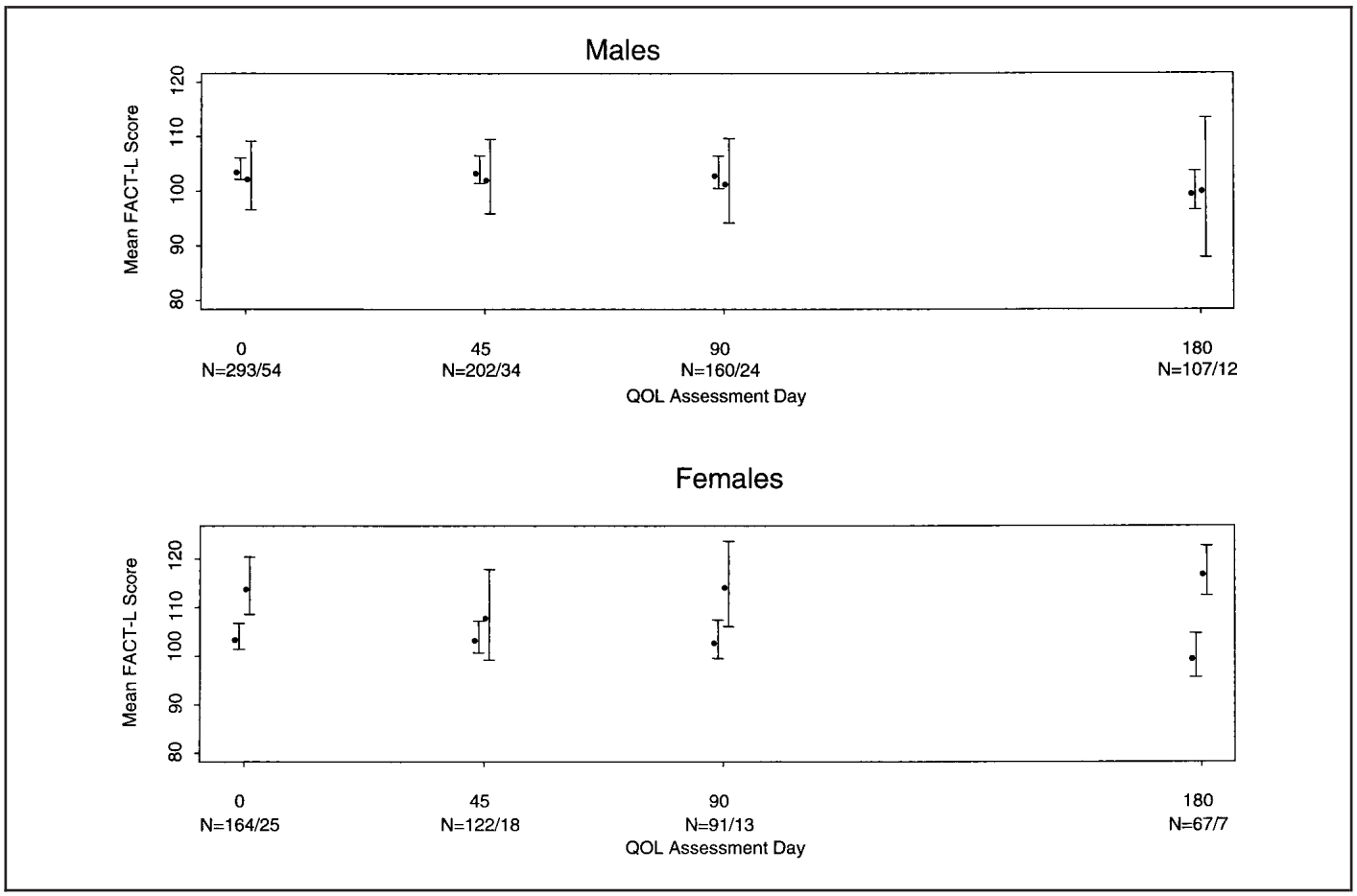

Fig. 3. Summary of number of patients assessed, mean Functional Assessment of Cancer Therapy-Lung (FACT-L) score *(13),* and standard deviations by age group at each time point. The **left-side line** in each group represents the patients under 70 years, and the **right-side line** represents patients 70 years old or older. **Points** represent means, and **lines** represent 95% confidence intervals. QOL = quality of life. **Ratios** show number of patients aged less than 70 years/greater than or equal to 70 years included in analysis at each time point.

of age on the efficacy and tolerance of gemcitabine as a single agent in the treatment of NSCLC was evaluated by Shepherd et al. *(30)* in a retrospective analysis of four separate phase II trials. Those patients under 65 years of age (255 patients) were compared with those 65 years of age or older (105 patients). Response rates were 16% and 24%, respectively; median and 1-year survival rates were 8.1 months and 27% and 9.1 months and 46%, respectively. There was no overt difference in hematologic and nonhematologic toxicity, nor was there any difference in weight reduction or dose omission. Similar findings were found by Russo and Martin *(31).*

Only two trials to date have compared combination chemotherapy with monotherapy in this age group. Frasci et al. *(32)* tested gemcitabine and vinorelbine in combination (GV) versus single-agent vinorelbine in patients 70 years old or older. The response rate for GV was 22% compared with 15% for vinorelbine. The respective median and 1-year survival rates were 29 weeks and 30% for GV versus 18 weeks and 13% for vinorelbine. The relative risk of death at multivariate analysis for GV was 0.48 (95% CI = 0.29 to 0.79; $P<.01$). The magnitude of the survival difference and the unexpectedly poor survival results observed in the single-agent vinorelbine arm led to early termination of the study. A much larger and potentially more credible trial by the same group that mounted the ELVIS study *(33)* demonstrated no benefit for GV versus the single-agent constituents. The relative response rates for vinorelbine, gemcitabine, and GV were 18.5%, 17.5%, and 20%, respectively; the relative median survivals were 8.8, 6.6, and 7.6 months, respectively.

A review by investigators from Fox Chase Cancer Center (Philadelphia, PA) evaluating combination paclitaxel (by 24- or 1-hour infusion) and carboplatin demonstrated no difference in toxicity, response, or survival for older patients compared with younger patients, although a trend toward more fatigue was noted in the elderly *(34).*

Our concern regarding elderly patients with NSCLC is not trivial. The incidence of lung cancer rises with advancing age; it is highest in the 70- to 80-year-old group and does not start to trail off until age 80 years or older *(35).* Unfortunately, elderly patients are underrepresented in clinical trials, making it difficult to evaluate properly the efficacy and safety of current treatment options in this patient population. Data from ECOG 5592 demonstrate clearly that the elderly do as well (or as poorly) as younger patients and that any decision to deny fit elderly patients access to protocol therapy is economic, not medical. Ultimately, functional status trumps age *(36).*

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NOTES

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