CORRESPONDENCE

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

A recent report by Langer et al. (1) in the Journal suggests that cisplatin-based therapy for treatment of advanced non-small-cell lung cancer (NSCLC) should not be denied to fit elderly patients. Their conclusion is based on a retrospective analysis of the Eastern Cooperative Oncology Group (ECOG) 5592 phase III randomized trial of three cisplatin-based regimens, which showed that outcomes did not differ between adult patients younger than 70 years of age and elderly patients 70 years of age or older, i.e., 84 septuagenarians and two octogenarians (15% of the study population).

However, we believe that the generalizability of these results is poor because of possible selection bias and because nowadays there is no evidence that “elderly do as well (or as poorly) as younger patients” as stated by Langer et al. (1). With regard to selection bias, Langer et al. acknowledge that the percentage of elderly patients among patients diagnosed with lung cancer in clinical practice is much higher than the percentage of elderly patients among patients enrolled in clinical trials for lung cancer treatment (2). It is predictable that eligibility criteria for participation in clinical trials become more stringent when increasingly toxic treatments are involved. In addition, further selection bias can occur when physicians attempt to recruit particularly well performing patients. Without such biases, elderly patients would not be underrepresented in U.S. clinical trials.

We suspect that selection biases are more of a problem in retrospective studies, in which age–treatment interactions are derived from a substantially younger population, than in prospective studies focused specifically on the elderly; we agree, therefore, with Langer et al. that there is a “need for elderly-specific trials” (1). In the ECOG 5592 study, the proportion of elderly patients was less than half of what would have been expected on the basis of population data (2). In two recent trials of chemotherapy for NSCLC (ELVIS and MILES) (3,4), we enrolled elderly patients by using selection criteria similar to those used in the ECOG 5592 trial but with a lower age limit (70 years). In the same time period, we also ran two trials (GemVin phase 1–2 and GemVin phase 3) with adult patients (Fig. 1), again with similar selection criteria (5,6). Forty-five of the 115 Italian centers participating in these trials enrolled subjects in both the elderly and adult studies, with 960 patients randomly assigned overall—455 (47%) adult and 505 (53%) elderly—from February 1997 through October 2000. Clearly, representation of elderly patients is much higher in these trials than in the ECOG 5592 trial and, we suspect, than in all clinical trials ever conducted on chemotherapy for advanced NSCLC. An important finding of our trials of chemotherapy dedicated to elderly NSCLC patients (3,4) is that single-agent chemotherapy with vinorelbine or gemcitabine, without cisplatin, is an appropriate NSCLC treatment for elderly patients. Similar evidence is still lacking for cisplatin-based chemotherapy.

The selection biases affecting the retrospective study by Langer et al. mean that great caution is needed in the interpretation of their data. On one hand, their conclusion might be of value only for a small proportion of elderly patients, but there is no reliable method available to select these patients from the elderly population as a whole. On the other hand, and more important, if the data reported by Langer et al. (1) were to stimulate the use of cisplatin-based chemotherapy in elderly patients, many elderly patients could potentially be put at risk because no prospective trial has yet shown that cisplatin is safe in the elderly.

We agree that cisplatin combinations should be tested in elderly patients, with the goal of improving results obtained with single-agent treatments. However, safety issues should be addressed, and the use of lower, tailored doses of treatment regimens that are thought to be effective (7) should be tested in prospective studies before evaluation in large randomized clinical trials.

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Fig. 1. Time course of clinical trials conducted for the evaluation of chemotherapy in advanced NSCLC by the Clinical Trials Promoting Group–Lung Cancer Section (CTPG–LCS). Two trials, ELVIS and MILES, specifically investigated the elderly by enrolling 898 patients that were 70 years of age or older. In the same time period, two trials—GemVin phase 1–2 and GemVin phase 3—were conducted on 644 adult patients with an age exclusion criteria of 70 years or older.


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Editor’s note: F. Perrone and C. Gallo have obtained honoraria from GlaxoSmithKline (Verona, Italy) for editorial activities. F. Perrone is a member of a study steering committee for AstraZeneca (Milan, Italy). C. Gridelli is a member of the speaker’s bureau for Eli Lilly (Firenze, Italy), Pierre-Fabre (Geneva, France), GlaxoSmithKline (Research Triangle Park, NC), Aventis Pharmaceuticals (Milan), AstraZeneca, and Roche (Basel, Switzerland). C. Gridelli is currently conducting a clinical trial sponsored by AstraZeneca.

RESPONSE

We appreciate the comments of Perrone et al., who raise the specter of selection bias and, as evidence, cite the disproportionate underrepresentation of elderly patients in the Eastern Cooperative Oncology Group (ECOG) 5592 trial (1) and in other efforts (2). They contend that oncologists preferentially recruit particularly well performing patients and that such individuals are not representative of the elderly population at large. Unfortunately, in the context of a North American cooperative group trial, it is virtually impossible to track all potential enrollees and to delineate the reasons that patients who are screened for a particular study are ultimately not enrolled. There are two possible reasons for underrepresentation of the elderly in the ECOG 5592 trial: 1) A higher incidence of comorbidities and compromised performance status was observed in elderly patients, which would have rendered these patients ineligible or marginally eligible. 2) There was selection bias against including elderly patients in platinum-based chemotherapy trials because of the perceived unsuitability of these patients for platinum-based therapy and the potential increased risk of life-threatening toxicity.

Gridelli and colleagues have blazed the path for the elderly-specific research in non-small-cell lung cancer (NSCLC). Their studies have shown that single-agent therapy with vinorelbine has a positive impact on survival and quality of life (QOL) compared with supportive care (3), and non-platinum combination therapy with gemcitabine and vinorelbine appears to be no better than the constituent single-agent therapies (4). To date, however, no elderly-specific study in NSCLC has compared a single-agent therapy to a combination of that agent with platinum, either carboplatin or cisplatin. The randomized phase III Cancer and Leukemia Group B (CALGB) trial comparing paclitaxel alone with paclitaxel in combination with carboplatin, reported at this year’s (2002) annual meeting of the American Society of Clinical Oncology (ASCO) (5), demonstrated that both older (>70 years) and younger patients receiving combination carboplatin and paclitaxel fared better than those patients who received single-agent paclitaxel alone; they had statistically significantly higher response rates, better time to progression, and statistically significantly increased median survival. However, it should be noted that the CALGB trial was not designed specifically for the elderly.

Three other points must also be made with regard to the treatment of elderly patients diagnosed with NSCLC: 1) We need to assess the comorbidities of elderly patients prospectively, and we need to determine the influence of comorbidity on drug toxicity, survival, and QOL, particularly because other medical illnesses, within a specific performance status category, may have substantial influence on each of these study end points. 2) We need to design clinical trials that include fit octogenarians; they are virtually invisible in current trials. 3) We need to take great care in both the choice of platinum-containing chemotherapy regimens in the elderly and in the choice of dosages.

To this end, a retrospective secondary analysis by Kelly et al. (6) of the Southwest Oncology Group trials 9308 and 9509, which compared a combination of cisplatin and vinorelbine, first to cisplatin alone and then to a combination of paclitaxel and carboplatin, indicated that a substantially higher percentage of elderly patients who were receiving cisplatin plus vinorelbine were taken off the trial because of drug toxicity compared with younger patients (P = .003) (6). No such difference was seen for paclitaxel and carboplatin. In addition, at this year’s ASCO annual meeting, Shiller et al. (7), on behalf of ECOG, reviewed the ECOG NSCLC 5592 trial experience from 1980 through 2000. In that time, 3398 patients with no explicit age restrictions were accrued to chemotherapy trials for treatment of NSCLC; a Cox proportional hazards model showed that the decade of diagnosis (i.e., 1980–1990 versus 1990–2000), performance status, and treatment (i.e., platinum-based therapy versus non-platinum-based therapy) all had a statistically significant impact on survival, whereas age did not (7).

Even as our understanding of NSCLC matures, cancer in the elderly remains a challenging frontier of therapeutic oncology. We should not fear its exploration.

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