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REVIEW ARTICLE

# Non–Small-Cell Lung Cancer in Elderly Patients: A Discussion of Treatment Options

*Ajeet Gajra and Aminah Jatoi*

Ajeet Gajra, Upstate Medical University, State University of New York, Syracuse, NY; and Aminah Jatoi, Mayo Clinic, Rochester, MN.

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Corresponding author: Aminah Jatoi, MD, 200 First St SW, Rochester, MN 55905; e-mail: jatoi.aminah@mayo.edu.



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## ABSTRACT

Lung cancer is a disease of the elderly. In older patients, the management of a malignancy as complex and potentially as lethal as lung cancer is challenging. Despite the fact that a large proportion of patients with non–small-cell lung cancer are elderly, information remains scant on how best to treat these patients. The goal of this review is to discuss the published literature and to provide guidance on how to treat elderly patients within three broad stages: (1) metastatic cancer, (2) early-stage cancer after surgery, and (3) locally advanced inoperable cancer. Because decisions on how and when to prescribe systemic treatment can be particularly difficult, this review focuses heavily on chemotherapy-related treatment decisions with some discussion of emerging data on the use of the comprehensive geriatric assessment.

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## INTRODUCTION

A discussion of how to manage non–small-cell lung cancer (NSCLC) in elderly patients is timely. This malignancy is the leading cause of cancer-related death in the United States, and 47% of patients with lung cancer are 70 years of age or older.[1,2] Demographics that are shifting toward an older population suggest that oncologists will be seeing more elderly patients with lung cancer in years to come.[3,4] Second, although the incidence and mortality of lung cancer has decreased in patients 50 years of age or younger, such is not the case for patients 70 years of age or older.[5,6] Many older patients with metastatic NSCLC do not receive chemotherapy.[5-7] Only 66% of older adults with locally advanced NSCLC receive any cancer treatment, and only 45% of those treated receive a standard approach of combined chemotherapy and radiation.[6] It is difficult to know whether these observations reflect appropriate management or age bias, but the fact remains that age-based differences in outcomes exist and merit further study. Finally, enrollment rates of elderly patients onto cancer clinical trials are grim. The Southwest Oncology Group (SWOG) reported that patients 65 years of age or older accounted for one quarter of trial participants but for 63% of the US cancer population within this same interval,[8] thus suggesting that trial conclusions might not be generalizable to elderly patients. Of note, trials designed for elderly patients with NSCLC capture patients with an older median age, confer lower rates of severe adverse events, and appear to provide no statistically significant differences in survival compared with elderly patients enrolled onto age-unspecified trials.[9] Yet a search of the ClinicalTrials.gov Web site reveals a dearth of practice-changing trials for the elderly: 11 of 484 are specific to the elderly, despite few previous trials (Table 1).[10] This article focuses on systemic therapy in older patients with NSCLC, a topic laden with controversy for some of the reasons cited.

### *Chemotherapy in Elderly Patients With Metastatic NSCLC*

When discussing chemotherapy in elderly patients with metastatic NSCLC, the question arises: Will it prolong life? The ELVIS trial was a 191-patient multicenter trial that helped answer this question by randomly assigning patients to vinorelbine versus best supportive care alone.[11] Patients had to have been 70 years of age or older with stage IV or IIIB NSCLC and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better. Chemotherapy improved median survival from 21 to 28 weeks ($P = .03$), with a relative hazard of death for vinorelbine-treated patients of 0.65 (95% CI, 0.45 to 0.93). Chemotherapy was also, to some extent, associated with improved quality of life. However, these survival data are not definitive. First, the ELVIS trial recruited only 191 of the 350-patient target, closing because of slow accrual and raising the question of whether this survival advantage would have been maintained with full accrual. Second, the primary end point was quality of life, not

 

**Table 1.** First-Line Randomized Trials in Elderly Patients With NSCLC

| Trial Name | Reference | No. of Patients | Chemotherapy | RR (%) | OS | | | Median PFS (months) | Toxicity |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Median (months) | HR | 95% CI | | |
| ELVIS* | [No authors listed][11] | 161 | Vinorelbine 30 mg/m$^2$ on days 1 and 8 every 3 weeks | 19.7 | 6.9† | 0.65 | 0.45 to 0.93 | NR | Early discontinuation of vinorelbine in 7%; total grade 3 to 4 toxicity, 14% |
| | | | Best supportive care | 0 | 4.9 | | | NR | |
| MILES‡ | Gridelli et al[13] | 698 | Vinorelbine 30 mg/m$^2$ on days 1 and 8 every 3 weeks | 18 | 8.4 | 1.17 for doublet *v* vinorelbine | 0.95 to 1.44 | 4.2 | Gemcitabine + vinorelbine resulted in higher rates of toxicity |
| | | | | | | 1.06 for doublet *v* gemcitabine | 0.86 to 1.29 | | |
| | | | Gemcitabine 1,200 mg/m$^2$ on days 1 and 8 every 3 weeks | 16 | 6.9 | | | 4.4 | |
| | | | Gemcitabine 1,000 mg/m$^2$ + vinorelbine 25 mg/m$^2$ on days 1 and 8 every 3 weeks | 21 | 7.0 | | | 4.4 | |
| | Frasci et al[12] | 120 | Vinorelbine 30 mg/m$^2$ on days 1 and 8 every 3 weeks | 15 | 4.2 | 0.45 | 0.29 to 0.79 | NR | Higher rates of hematologic and nonhematologic toxicity occurred in the doublet; three deaths related to toxicity occurred with the doublet *v* one with vinorelbine |
| | | | Gemcitabine 1,200 mg/m$^2$ + vinorelbine 30 mg/m$^2$ on days 1 and 8 every 3 weeks | 22 | 6.8 | | | NR | |
| | Kudoh et al[15] | 182 | Docetaxel 60 mg/m$^2$ once every 21 days | 22.7† | 14.3 | 0.78 | 0.56 to 1.09 | 5.5† | Grade 3 to 4 adverse event rates were higher with docetaxel *v* vinorelbine (83% *v* 69%; $P = .03$) |
| | | | Vinorelbine 25 mg/m$^2$ on days 1 and 8 every 3 weeks | 9.9 | 9.9 | | | 3.1 | |
| | Quoix et al[14] | 451 | Gemcitabine 1,150 mg/m$^2$ on days 1 and 8 every 21 days or vinorelbine 25 mg/m$^2$ on days 1 and 8 every 21 days | 10.2 | 6.2 | 0.64 | 0.52 to 0.78 | 2.8 | More hematologic grade 3 to 4 toxicity, asthenia, and neuropathy and deaths as a result of toxicity occurred in the combination arm (4.4% *v* 1.3%); early deaths within 3 months occurred in the single-agent arm (25.6% *v* 16.7%) |
| | | | Carboplatin (AUC 6) on day 1 + paclitaxel 90 mg/m$^2$ on days 1, 8, and 15 every 28 days | 27.1† | 10.3‡ | | | 6.0† | |

Abbreviations: AUC, area under the curve; ELVIS, The Elderly Lung Cancer Vinorelbine Study; HR, hazard ratio; MILES, Multicenter Italian Lung Cancer in the Elderly Study; NR, not reached; NSCLC, non–small-cell lung cancer; OS, overall survival; PFS, progression-free survival; RR, response rate.

*Trials that reported survival in weeks are reported here in months.

†Denotes statistical significance.

‡This trial reported time-to-progression, not PFS.

survival. Hence, the strength of this survival advantage is diminished because of the lesser rank of this end point. To the best of our knowledge, the ELVIS (The Elderly Lung Cancer Vinorelbine Italian Study) trial is the only prospective study to examine and suggest a survival advantage of chemotherapy in elderly patients with NSCLC. In view of data that demonstrate chemotherapy's life-prolonging effects in age-unspecified NSCLC populations, another prospective attempt to answer this question is unlikely.

Nonetheless, age-based subanalyses of prospective trials support our conclusion based on the ELVIS trial. For example, Ansari et al[16] reported on a large phase III trial that examined chemotherapy-naïve patients with good performance status (PS; 0 to 1) who were randomly assigned to gemcitabine 1,000 mg/m$^2$ on days 1 and 8 plus carboplatin at area under the curve (AUC) 5.5 on day 1 versus the same schedule of gemcitabine plus paclitaxel 200 mg/m$^2$ on day 1 versus paclitaxel 225 mg/m$^2$ on day 1 plus carboplatin at AUC 6.0 on day 1. By analyzing data for 1,135 patients, these investigators observed that 797 were younger than 70 years of age (70.2%), and 338 were 70 years of age or older. They also reported that overall survival was comparable between age groups: 8.6 months (95% CI, 7.9 to 9.5 months) and 7.9 months (95% CI, 7.1 to 9.5 months), respectively, and that, for the most part, doublet chemotherapy was tolerable. This study is important for two reasons. First, the comparable survival across age groups suggests that chemotherapy prolongs survival in elderly patients. Second, this study also suggests that in select patients with good PS, doublet NSCLC chemotherapy can be administered with minimal toxicity. Age-based subanalyses of other trials have found similar survival benefits (Table 2).

To answer the question of whether or not to prescribe doublet chemotherapy in the elderly, the MILES (Multicenter Italian Lung Cancer in the Elderly Study) trial compared vinorelbine plus gemcitabine versus vinorelbine versus gemcitabine in a 698-patient cohort of patients 70 years of age or older.[13] Of note, the doublet did not contain a platinum compound. The primary end point was survival.

**Table 2.** Examples of Age-Based Subanalyses of Prospective Randomized Trials

| Reference | Patients | | Chemotherapy | Median OS (months) | |
|---|---|---|---|---|---|
| | No. | Age 70 Years or Older | | Elderly Patients | Younger Patients |
| Langer et al[17] | 574 | 15 | Cisplatin with etoposide or paclitaxel | 8.53 | 9.05 |
| Lilenbaum et al[18] | 561 | 28 | Paclitaxel *v* paclitaxel + carboplatin | 5.8 *v* 8.0 | 6.8 v 9.0 |
| Ramalingam et al[20] | 878 | 26 | Paclitaxel + bevacizumab + carboplatin *v* paclitaxel + carboplatin | 11.3 *v* 12.1 | 12.3* *v* 10.3 |
| Socinski et al[19] | 1,052 | 15 | Nab-paclitaxel + carboplatin *v* paclitaxel + carboplatin | 19.9† *v* 10.4 | 11.4 *v* 11.3 |

Abbreviation: OS, overall survival.
*Denotes median OS for the entire trial population.
†Survival difference is statistically significant.

Compared with each single drug, combination treatment did not improve survival. The hazard ratio (HR) of death for patients who received two drugs was 1.17 (95% CI, 0.95 to 1.44) compared with vinorelbine and 1.06 (95% CI, 0.86 to 1.29) compared with gemcitabine. Administering two drugs also led to worse toxicity. The authors concluded that one drug is appropriate for treating elderly patients with metastatic NSCLC.

In contrast, Quoix et al[14] conducted a 451-patient multicenter randomized trial that tested either a doublet or monotherapy in patients with cancer who were 70 years of age or older with a PS of 2 or better. Doublet chemotherapy consisted of carboplatin at AUC 6 on day 1 and paclitaxel 90 mg/m$^2$ on days 1, 8, and 15; monotherapy consisted of vinorelbine 25 mg/m$^2$ on days 1 and 8 or gemcitabine 1,150 mg/m$^2$ on days 1 and 8. The doublet yielded a median overall survival of 10.3 months in contrast to 6.2 months with monotherapy (HR, 0.64; 95% CI, 0.52 to 0.78; $P < .001$). Doublet therapy caused more severe myelosuppression and myasthenia, but the treatment was tolerable. In the context of the MILES trial, the authors stated, "We feel that the current treatment paradigm for these patients should be reconsidered."

So should it be one drug or two? Doublets are commonly prescribed to younger patients, prolong survival, and represent the standard of care.[21] The CAPPA-2 (Cisplatin Added to Gemcitabine in Poor Performance Advanced NSCLC Patients) study, which was undertaken in patients with PS 2 (not limited to the elderly), randomly assigned patients to gemcitabine 1,200 mg/m$^2$ on days 1 and 8 versus the two-drug combination cisplatin 60 mg/m$^2$ on day 1 plus gemcitabine 1,000 mg/m$^2$ on days 1 and 8.[22] It showed a median overall survival of 3 months with single-agent gemcitabine in contrast to 5.9 months with cisplatin plus gemcitabine (HR, 0.52; 95% CI, 0.28 to 0.98; $P = .039$). Although the authors noted that "the addition of cisplatin to single-agent gemcitabine improves survival as first-line treatment of patients with PS 2 who have advanced NSCLC," that study illustrates two other points. First, the fact that it closed early at 57 patients because of poor accrual suggests that oncologists selected trial patients. An oncologist might be reluctant to enroll an elderly patient with a poor PS onto a trial with a platinum-based doublet and equally reluctant to enroll a relatively healthy, chemotherapy-naive patient to a trial without one. It is impossible to generalize a treatment approach because of this well-intentioned, appropriate, and inevitable selection bias. Second, prescribing practices among the elderly cannot entail a blanket recommendation. The elderly are heterogeneous: some are functional, some are not; some have excellent organ function, others do not. Assessing the individual patient is optimal and might be accomplished with a geriatric assessment (GA) in conjunction with PS.

Of relevance, Weiss et al[23] have reanalyzed prospective data that compared pemetrexed and docetaxel; they concluded that pemetrexed provides a more favorable toxicity profile in older patients. Parenthetically, the decision on maintenance therapy with agents such as pemetrexed depends on how a patient tolerates initial chemotherapy, occurs with sparse data in elderly patients, and is not discussed further here.[24]

### *Targeted Therapy for Elderly Patients With Metastatic NSCLC*

Bevacizumab improves overall survival from 10.3 to 12.3 months (HR for death, 0.79; $P = .003$) in patients with metastatic nonsquamous NSCLC when combined with paclitaxel and carboplatin.[25] However, four subanalyses in the elderly have been unable to conclusively attest to its benefits. First, in a post hoc subset analysis of patients 70 years of age or older (n = 224; 26%), Ramalingam et al[20] reported a trend in favor of higher response rates (29% *v* 17%; $P = .067$) and improved progression-free survival (5.9 *v* 4.9 months; $P = .063$) with bevacizumab. Overall survival in elderly patients appeared to be comparable (11.3 months and 12.1 months, respectively; $P = .4$). However, grade 3 or worse adverse events, which included death, were observed in 87% of elderly patients treated with bevacizumab versus 61% of patients not receiving bevacizumab ($P < .001$). Second, the AVAIL (Avastin in Lung Cancer) trial provided a similar subgroup analysis of patients 65 years of age or older (n = 304). AVAIL was a phase III trial that evaluated bevacizumab with cisplatin and gemcitabine versus this conventional chemotherapy with placebo.[26] The lower dose of bevacizumab (7.5 mg/kg once every 3 weeks) yielded an improvement in progression-free survival (HR, 0.71; $P = .023$), but such was not the case with the higher dose (15 mg/kg once every 3 weeks; HR, 0.84; $P = .26$). Adverse event rates with bevacizumab were comparable between elderly and younger patients. However, this subanalysis did not show an improvement in survival with bevacizumab in elderly patients.[26] Third, the Safety of Avastin in Lung study included 2,212 patients and administered bevacizumab in a first-line setting to examine the safety of bevacizumab. In a subgroup analysis, 623 patients, all of whom were 65 years of age or older, experienced adverse events at a rate comparable to that in younger patients, but severe adverse events occurred more frequently in the older patients (45.3% *v* 34.7%).[27] Finally, Socinski et al[28] reported an age-based

  

subgroup analysis from a phase III study that tested various drug combinations with bevacizumab. Although bevacizumab was associated with longer progression-free survival in younger patients, such was not the case in older patients. Taken together, these analyses show no definitive survival advantage with bevacizumab in elderly patients. Although adverse events were not consistently worse for older patients, the dubious efficacy of this agent in the elderly should prompt health care providers to use greater caution when prescribing this agent to older patients with NSCLC.

In contrast, the epidermal growth factor receptor (EGFR) inhibitor erlotinib improves survival but yields a worse adverse event profile in older patients. To the best of our knowledge, no prospective trials have been conducted in older patients, but some trials such as the EURTAC (European Randomised Trial of Tarceva vs. Chemotherapy) trial accrued an older cohort (median age, 65 years). This trial was undertaken in patients with EGFR-mutated tumors, and it showed that erlotinib yielded a longer progression-free survival than chemotherapy.[29] An age-unspecified trial in patients not selected for mutation status, the BR.21 study, showed that in a second- or third-line setting, erlotinib improves survival but at a cost to older patients.[30] Within this older cohort, 112 had received erlotinib and 51 had received placebo.[31] Although older and younger patients manifested comparable progression-free survival, overall survival, and tumor response rates, older patients suffered worse toxicity with worse rash, fatigue, and dehydration—indeed, more adverse events and more severe (grade 3 and 4) adverse events (35% *v* 18%; $P < .001$) occurred. Such toxicity resulted in early erlotinib discontinuation. Thus, erlotinib plays an important role in treating elderly patients with NSCLC, particularly those with EGFR-mutated tumors. A prescription for erlotinib should be preceded by a realistic discussion of adverse effects.

### *Adjuvant Chemotherapy*

The standard for age-unspecified groups of patients with stages IB to IIIA (high-risk) NSCLC is postoperative cisplatin-based combination chemotherapy for four cycles.[32-39] A series of large randomized phase III trials demonstrated improved overall survival.

To the best of our knowledge, no prospective trial has specifically examined adjuvant chemotherapy in elderly patients (Table 3). Cisplatin is cleared by the kidney and is sometimes less well-tolerated in elderly patients, but it serves as the key agent. Pepe et al[40] reanalyzed JBR.10, which investigated adjuvant cisplatin and vinorelbine in 482 patients with resected NSCLC. Of the 155 patients who were 65 years of age or older, chemotherapy prolonged overall survival (HR, 0.61; 95% CI, 0.38 to 0.98; $P = .04$). Adverse events, including hospitalization and chemotherapy-related death, were comparable between groups. Older patients received less cisplatin than their younger counterparts: 49% were prescribed fewer than five doses, 19% five to seven doses, and 32% eight doses. These findings suggest that cisplatin-based adjuvant chemotherapy can benefit older patients, although doses may need to be omitted or adjusted.

The LACE (Lung Adjuvant Cisplatin Evaluation) meta-analysis reviewed all five cisplatin-containing trials with 4,584 patients; that study reported an overall survival benefit of 5.4% at 5 years.[39] In that consolidated analysis, 20% of patients were older than age 65 years and 9% were older than age 70 years.[39] Despite the limited number of elderly patients, Früh et al[41] reported an age-based analysis of the LACE data. Patients were categorized into three age groups: younger than 65 years, 65 to 70 years, and older than 70 years. No major age-based differences in the HRs of death were noted ($P_{trend} = .29$). Rates of severe toxicity were comparable between groups. Older patients received lower doses of cisplatin. Finally, elderly patients died more frequently as a result of noncancer-related causes. These data suggest that select elderly patients can benefit from adjuvant cisplatin-based chemotherapy, even if they receive a lower total dose.

In addition, several investigators have used databases to understand the role of cisplatin-based adjuvant chemotherapy in the elderly. By using the Surveillance, Epidemiology, and End Results (SEER) database, Wisnivesky et al[42] reported on 3,324 patients who were 65 years of age or older. All patients had undergone surgery for stage II or IIIA NSCLC. Only 21% had received platinum-based chemotherapy. Of parenthetical note, this percentage does not reflect current rates, because this study spanned an interval when adjuvant chemotherapy

**Table 3.** Age-Based Summary of Prospective Adjuvant Chemotherapy Trials

| Variable | Adjuvant Lung Cancer Project Italy (ALPI)[36] | | Big Lung Trial (BLT)[35] | | International Adjuvant Lung Trial (IALT)[32] | | National Cancer Institute of Canada (NCIC) JBR.10[34] | | Adjuvant Navelbine International Trialist Association (ANITA)[33] | | Cancer and Leukemia Group B (CALGB) 9633[37] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Total No. of patients | 1,088 | | 307 | | 1,867 | | 482 | | 840 | | 344 | |
| Age (years) | | | | | | | | | | | | |
| 65-69 | 276 | 25 | 43 | 14 | 328 | 18 | 84 | 17 | 170 | 20 | NA | |
| Older than 70 | 42 | 4 | 69 | 23 | 168 | 9 | 71 | 15 | 64 | 8 | 72 | 21 |
| Upper limit | None | | None | | 75 | | None | | 75 | | None | |
| Stage | I-IIIA | | I-III | | I-III | | IB-II | | IB-IIIA | | IB | |
| PS | NA | | 0-2 | | 0-2 | | 0-1 | | 0-2 | | 0-1 | |
| Planned cumulative dose of cisplatin, mg/m$^2$ | 300 | | 240 or 150 | | 300-400 | | 400 | | 400 | | None (carboplatin) | |
| Nonplatinum agents | Mitomycin + vindesine | | Multiple | | Multiple | | Vinorelbine | | Vinorelbine | | Paclitaxel | |
| % 5-year overall survival increase | 0 | | 0 | | 4.1 | | 15 | | 8.6 | | 0 | |

Abbreviations: NA, not applicable; PS, performance status.

was not the standard of care. An overall survival benefit for stage II or IIIA patients treated with chemotherapy emerged (HR, 0.78). Improved survival was seen in patients younger than age 70 years (HR, 0.74; 95% CI, 0.62 to 0.88) and in patients age 70 to 79 years (HR, 0.82; 95% CI, 0.71 to 0.94). No survival advantage was observed in patients older than age 80 years (HR, 1.33; 95% CI, 0.86 to 2.06). As expected, adjuvant chemotherapy was associated with an increased likelihood of serious adverse events (odds ratio, 2.0; 95% CI, 1.5 to 2.6). This study suggests that, in patients with lung cancer who are older (but not necessarily in their 80s), adjuvant chemotherapy should be considered.

Similarly, Cuffe et al[43] reported on 6,304 surgically treated patients with NSCLC and compared use of chemotherapy across age groups: younger than 70, 70 to 74, 75 to 79, and 80 years or older. Hospitalization rates within 6 to 24 weeks of surgery were assumed to be reflective of chemotherapy-related toxicity. In all, 2,763 (44%) of 6,304 surgical patients were at least 70 years of age. Adjuvant chemotherapy in this age group increased from 3.3% (2001 to 2003) to 16.2% (2004 to 2006). Among assessable older patients, 70% received cisplatin and 28% received carboplatin-based regimens. Rates of dose adjustments or drug substitutions were similar across age groups. Hospitalization rates within 6 to 24 weeks of surgery were also similar (28% for patients younger than age 70 years; 27.8% for patients age 70 years and older; $P = .54$). Importantly, 4-year survival of older patients increased over time (47.1% for patients from 2001 to 2003; 49.9% for patients from 2004 to 2006; $P = .01$). Survival was improved, except in patients 80 years of age or older. This study also supports adjuvant chemotherapy in elderly patients younger than 80 years of age.

Finally, the Veterans Administration Cancer Registry reported on 10,036 surgically resected patients, 3,958 (39.4%) of whom were 70 years of age or older, describing 11.2% of older and 22.3% of younger patients who received adjuvant chemotherapy.[44] Of the chemotherapy-treated patients, a smaller proportion of older patients received cisplatin-based treatment (86.4% *v* 91.8%; $P < .001$). Older stage II and III patients who received cisplatin-based adjuvant chemotherapy had a better 3-year overall survival compared with those who received carboplatin-based adjuvant chemotherapy or no adjuvant chemotherapy (55% *v* 42% *v* 35%, respectively; $P = .01$). Again, adjuvant cisplatin-based chemotherapy appears to provide benefit to older patients with NSCLC.

Three key points summarize the previous discussion. First, cisplatin-based adjuvant chemotherapy is appropriate for relatively healthy older patients with NSCLC. Second, the benefit of adjuvant chemotherapy has not been established in patients 80 years of age or older and should be undertaken with extra caution. Finally, although presumably inferior to cisplatin-based adjuvant chemotherapy, carboplatin-based chemotherapy may confer modest benefit.[45] However, a lack of prospective data to confirm this last point should prompt clinicians to prescribe it with extra caution.

### *Locally Advanced NSCLC*

Cisplatin and etoposide with concomitant radiation provide a standard nonsurgical approach to patients with locally advanced NSCLC.[46-49] However, in the intergroup trial from Albain et al, the median age of patients was 60 years, and age was not predictive of outcomes.[46] The better-tolerated regimen of low-dose once-per-week carboplatin and paclitaxel with concomitant radiation subsequently emerged but can nonetheless be challenging to administer in older patients.[50]

The Japanese Cancer Oncology Group undertook one of the few phase III trials in patients 70 years of age or older (n = 200).[51] All eligible patients had unresectable stage III NSCLC. Patients were randomly assigned to concomitant chemotherapy and radiation (60 Gray with concurrent low-dose carboplatin at 30 mg/m$^2$ per day, 5 days a week for 20 days) or radiotherapy alone. The primary end point was overall survival. Overall median survival for the combined modality arm was 22.4 months and for the radiotherapy alone arm, it was 16.9 months (HR, 0.68; 95% CI, 0.47 to 0.98; $P = .0179$). As expected, patients in the combined modality arm suffered more grade 3 to 4 hematologic toxicity and grade 3 infections. No significant differences occurred in grade 3 to 4 pneumonitis and late lung toxicity. These data provide clear justification for combined-modality therapy in elderly patients. However, in view of the worse adverse event profile of combined-modality therapy, treatment decisions in elderly patients must still be undertaken on a case-by-case basis.

In pooled analyses of previous trials, conclusions have been mixed. In trials conducted before 2000, two studies reported no improvement in survival or quality of life with the addition of chemotherapy to radiation.[52,53] In contrast, however, at least three other analyses report improved outcomes among elderly patients with concurrent chemotherapy and radiation but in exchange for greater toxicity. First, the North Central Cancer Treatment Group examined cisplatin and etoposide in conjunction with radiation[54] and reported median survival and 5-year survival rates of 10.5 months and 5.4%, respectively, for the radiotherapy alone group compared with 13.7 months and 14.7%, respectively, for combined-modality therapy (log-rank $P = .05$). Patients treated with chemotherapy and radiation suffered higher rates of grade 3 or worse toxicity when compared with those who received radiation alone (89.9% *v* 32.4%; $P < .01$). Second, in a combined analysis of two trials for stage III NSCLC conducted within the Cancer and Leukemia Group B, cisplatin and vinblastine chemotherapy followed by radiation or concurrently with radiation were assessed among elderly patients.[55] Elderly patients manifested significantly worse grade 3 or worse neutropenia ($P = .04$) and renal toxicity ($P = .0025$). However, age was not a factor in survival ($P = .8$) or tumor response rate ($P = .3$).

Third, a robust meta-analysis that includes seven randomized, controlled trials that in total comprised 1,205 patients served to compare concurrent to sequential chemotherapy and radiotherapy in patients with locally advanced NSCLC.[56] This analysis included 459 patients (38%) who were 65 years of age or older; 16% of the cohort was 70 years of age or older. This study reported improved overall survival with concomitant chemotherapy and radiation (HR, 0.84; 95% CI, 0.74 to 0.95; $P = .004$), with an absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years compared with sequential therapy. Concomitant chemotherapy and radiation resulted in increased esophagitis (grade 3 to 4) from 4% to 18% with a relative risk of 4.9 (95% CI, 3.1 to 7.8; $P < .001$) but there were no significant differences in pulmonary toxicity. Germane to this discussion of the elderly, no age-based differences in efficacy outcomes were observed.

In contrast, at least one database study advises caution when using combined-modality therapy in elderly patients.[6] In a study from the SEER registry, Davidoff et al[6] examined patients with locally advanced NSCLC diagnosed between 1997 and 2000; only 66% of older

  

adults received any treatment at all. Of those treated, only 45% received combined chemotherapy and radiation therapy. Chemotherapy and radiotherapy conferred a survival advantage compared with radiation alone (HR, 0.78; 95% CI, 0.75 to 0.82). However, when concurrent chemotherapy and radiation was compared with sequential chemotherapy and radiation, increased mortality was noted with the former (HR, 0.73; 95% CI, 0.60 to 0.89). This study reflects treatment standards from more than a decade ago. Although many elderly patients might benefit from concomitant therapy, this study suggests using caution when considering this type of therapy in elderly patients.

Finally, a series of single-institution retrospective analyses suggest that PS and other factors—as opposed to chronologic age—are biologic determinants of clinical outcomes. Aridgides et al[57] examined 189 patients and observed that those who were 70 years of age or older (n = 86) were more likely to have an ECOG PS of 2 or worse and hence were more likely to receive therapy with palliative intent. In multivariable analysis, although older age was not associated ($P = .43$) with an increased risk of death, a PS of 2 or worse was ($P < .05$). In another study, Paripati et al[58] examined 389 patients with a favorable PS and observed that those who were 75 years of age or older manifested a median survival of 19.9 months with combined-modality therapy versus 7.8 months with less aggressive treatment ($P = .0048$). Although these data are retrospective and hence fraught with patient selection bias, they nonetheless suggest that select elderly patients derive benefit from combined-modality therapy. They also suggest that, in an effort to best serve the patient, some health care providers are no longer relying exclusively on age to make treatment decisions.

In summary, the fact that only one prospective trial has been conducted in elderly patients with locally advanced disease illustrates the challenge of defining a standard of care for older patients.[51] Importantly, that one trial demonstrated benefit with concomitant therapy with daily carboplatin. That study in conjunction with post hoc analyses of other trials suggests that elderly patients can derive benefit from combined-modality therapy. However, because toxicity is clearly worse, this approach should be used with caution and only in select elderly patients who appear to be assessable and to have good organ function.

### *PS, GA, and Other Tools*

As alluded to, the prognostic value of PS in patients with lung cancer, especially in patients with metastatic and locally advanced NSCLC, is well established. However, the ability to successfully treat an elderly patient also depends on his/her physical function, cognition, mobility, nutritional state, organ function, social support, concomitant health conditions, and concurrent medications. For this reason, geriatricians have long used the GA to predict morbidity and mortality in older patients.

Growing support favors using the GA to supplement PS.[59] In 566 elderly patients with metastatic NSCLC, Maione et al[60] reported on the prognostic value of a baseline assessment of functional status, comorbidity, and quality of life. Better baseline quality of life ($P < .001$) and greater facility with activities of daily living ($P = .04$) were associated with improved survival. Newer, patient self-administered versions of the GA are feasible, even in multi-institution settings.[61] By using the largely self-administered version of the GA with other clinical factors, Hurria et al[61] developed the Cancer and Aging Research Group (CARG) score that predicted chemotherapy-induced toxicity across tumor types and stages. In a subsequent study, Nie et al[62] examined 120 patients with NSCLC who were 65 years of age or older and were assigned a CARG score; Nie et al reported that the CARG score predicted severity of adverse events. The CARG itself also studied factors associated with early chemotherapy discontinuation in 100 elderly patients with metastatic NSCLC and found that subsequent-line chemotherapy and poor physical function predict poor outcomes.[63] The GA and similar tools promise to aid decision making.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Manuscript writing:** All authors
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