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Non-small cell lung cancer in the elderly: Defining treatment options

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Abstract

Lung cancer is the leading cause of cancer deaths in the Western countries. Recent advancements in the treatment of non-small cell lung cancer (NSCLC) have led to an improvement in outcomes, although 5-year survival rates remain about 15%. Moreover, the number of patients diagnosed and treated with lung cancer over the age of 65 is a growing population. Despite this fact, elderly patients are infrequently included into clinical trials, which results in a limited amount of evidence-based options regarding therapy for the elderly. The limited data correlates directly with the lack of established treatment guidelines for elderly patients with NSCLC. In this article, we review both retrospective and prospective studies that help to define treatment of the elderly with early stage, locally advanced and metastatic NSCLC. Ultimately, increasing participation of the elderly within clinical trials is essential to firmly establish treatment regimens to increase survival while minimizing toxicity.

INTRODUCTION

The elderly population, those over the age of 65, represents the fastest-growing segment in the United States. By 2030, it is postulated that this subgroup will double from 35 million to 70 million people.[1] Similar trends are projected for other industrialized nations and for developing countries, solidifying this pattern as a universal occurrence. With a median incidence age of 70 years, non-small cell lung cancer (NSCLC) is a disease that is closely linked with the elderly.[2] Since lung cancer is the leading cause of cancer deaths in both men and women in the United States, improving therapy for patients is essential.[3] Despite the increasing prevalence, treatment options for the elderly population with lung cancer remains poorly studied.[4] This review explores the under representation of the elderly in clinical trials and the resulting consequences. We also investigate the completed studies that attempt to standardize NSCLC treatment for the elderly population. Finally, we conclude that future prospective studies are needed as we attempt to ascertain the most effective, and nontoxic manners to treat the elderly patients with lung cancer.

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IMPORTANCE OF STUDYING ELDERLY PATIENTS IN CLINICAL TRIALS

The data garnered from clinical trials has invaluably guided medical oncologists in the treatment of all cancers, including lung cancer. However, many studies have shown the limited representation of the elderly population in most clinical trials for cancer.[5–8] Hutchins et al. performed a retrospective analysis of all patients enrolled onto Southwest Oncology Group trials between 1993 and 1996.[5] The findings demonstrated only 25% of these patients were aged 65 years and older, while patients aged 70 years and older represented only 13% of patients who participated in these clinical trials. Multiple explanations have been provided to clarify the under representation of the elderly in clinical trials. The patients are often deemed "too old" to be offered participation in clinical trials or physicians may carry the perception that they are too frail to withstand treatment.[9] However, multiple studies have demonstrated that the benefit of active therapy in the elderly is comparable to the benefit seen in younger patients.[10–12] These analyses conclude that biases against the elderly cannot be defended, and that patients must be assessed by aspects other than age to assure that all patients are given the option of receiving appropriate therapy. Other studies have determined that the lack of accrual of elderly patients into clinical trials leads directly to a paucity of data for treatment options in a geriatric population, and that increasing participation in trials is essential to improving therapy for this group.[1, 13]

Enrollment into clinical trials can lead to an improved understanding of the physiological and pharmacodynamic changes related to aging, which may have a substantial effect on treatment outcomes and toxicities. As an example, decreased hepatic reserves and differences in renal function in the elderly increase the likelihood of treatment-related toxicities in this population.[1] Additionally, susceptibility to toxicity from treatment regimens in the elderly population endangers the hematopoietic system, the cardiovascular system, the central and peripheral nervous systems and the mucous membranes.[11] An analysis which evaluated outcomes for elderly patients with NSCLC treated on elderly-specific trials when compared to age-unspecified trials, demonstrated that those who were treated on elderly-specific trials experienced fewer severe adverse events with similar survival outcomes.[6] These trials may improve our understanding of true toxicities and outcomes in older patients.

Without substantial data with regards to the treatment options for the elderly population, age alone has often led to the denial of therapy, the premature discontinuation of therapy, and exclusion of patients from clinical trials.[9] However, elderly patients with good performance scores have shown similar toxicity profiles and benefits as non-elderly patients.[12] A study analyzed the prognostic role of 77 variables in 5000 patients with inoperable lung cancer.[14] The most important prognostic factors for survival were performance status (PS), extent of disease, and weight loss in the last 6 months, but age was not an important independent prognostic factor. In another study, Asmis et al. analyzed patients enrolled in two prospectively randomized trials of systemic chemotherapy for NSCLC to determine the roles of age and comorbid conditions in predicting survival.[15] Of the 1255 patients, 34% were over the age of 65 years of age. Using the Charlson comorbidity index (CCI), a validated measure of patient comorbidity, a CCI score was established for these patients. In multivariate analysis, a CCI score ≥ 1 was associated with a shorter survival ($P = .03$), yet, importantly, age itself, was not prognostic. Those with comorbidities were more likely to have statistically significant side effects including gastrointestinal (GI) toxicity, infection, rash or nausea. This data supports the notion that recommendations for the elderly should consider chronological age less, and focus more on individual comorbidities when individualizing treatment plans.

ADJUVANT TREATMENT

In early stage NSCLC, limited data exists, and prospective trials have not been completed for the elderly population. In the adjuvant setting, it is not possible to extrapolate data on toxicity and efficacy obtained from the younger population and apply it in the elderly population.[16] Older patients may not tolerate treatment following lung surgery due to comorbid diseases or decreased organ function. Therefore, the adjuvant trials which demonstrate efficacy of platinum-based chemotherapy in a younger population may result in unacceptable toxicities and increased mortality in an elderly population.[17–19]

The most informative data for adjuvant chemotherapy in the elderly comes from a retrospective analysis of the National Cancer Institute of Canada BR10 trial comparing pretreatment characteristics and survival benefit for patients older and younger than 65 years of age.[20] 327 patients in the younger group were compared to 155 patients in the older group, and elderly patients maintained the benefit in overall survival that was seen in the whole population (68% 5-year survival for patients who received adjuvant chemotherapy versus 48% in those on the control arm). The advantage was seen even though the elderly patients received less total chemotherapy than did the younger patients. Although this retrospective analysis suffers from selection bias since 41% of the elderly population in this study had a performance score of 0, it does demonstrate that fit elderly patients derive a similar survival benefit from chemotherapy. Patients who were older than 75 had a decreased survival compared to those aged 66–74, although the numbers in this group were small. Furthermore, the elderly did not experience an increased rate of adverse events when compared with the patients under the age of 65. Age alone, therefore, should not prohibit elderly patients from standardized treatment in the adjuvant setting.

TREATMENT OF LOCALLY ADVANCED NSCLC

For the treatment of locally advanced NSCLC, the superiority of chemotherapy combined with radiation over radiation alone has been demonstrated in randomized controlled trials.[21,22] Furuse et al. enrolled 320 patients in a phase III study and randomized them to receive concurrent radiation with chemotherapy versus sequential combined therapy.[22] The concurrent approach led to an improvement in median survival of 3 months and led to its standardization as a treatment modality in advanced NSCLC. Yet, this study excluded patients over 75 years of age. In fact, minimal elderly-specific, prospective data are available regarding the role of combined-modality approaches in locally advanced NSCLC.

Langer et al. performed a retrospective analysis of 104 patients aged 70 or older with good PS and little weight loss, enrolled onto phase III RTOG protocol 94–110, in which patients received either sequential chemotherapy followed by daily radiotherapy, concurrent chemotherapy with daily radiotherapy, or concurrent chemotherapy with twice daily radiation.[23] Concurrent therapy proved to be more favorable in the elderly, although acute toxicity was more pronounced, including grade ≥ 3 neutropenia and grade ≥ 3 esophagitis. Median survival was 22.4 months for concurrent therapy with daily radiation, 16.4 months for concurrent therapy with twice daily radiation, and 10.8 months for those receiving sequential therapy ($p = .069$). It is important to note the inherent selection bias that may have been present with these patients, since only fit elderly patients were included. Yet, this study concluded that elderly patients with NSCLC are candidates for combined-modality therapy.

Schild et al. retrospectively analyzed a North Central Cancer Treatment Group (NCCTG) study in which 246 patients over the age of 70 with locally advanced NSCLC were randomized to receive etoposide and cisplatin with concurrent radiation therapy daily or twice daily.[24] The original study did not show a difference in survival or tumor progression rates between the two radiotherapy fractionation patterns. The retrospective analysis showed that grade ≥ 4 toxicity

occurred more frequently in patients over 70 compared with those less than 70 years of age (81% vs. 62%). These toxicities included myelosuppression, similar to the RTOG 94-10 study, as well as pneumonitis. Despite the increase in toxicity, the combined modality treatment had disease control rates and survival rates similar to those of younger patients.

A retrospective review by Rocha Lima et al. evaluated outcomes for patients over the age of 70 in two randomized, prospective studies performed by the Cancer and Leukemia Group B (CALGB).[25] One of studies included, CALGB 9130, investigated vinblastine and cisplatin followed by radiation alone or radiation with carboplatin. The trial did not include an upper age limit entry criterion, and accrued over 250 patients. Despite the absence of a specified upper age limit entry criterion, no patients over 80 years of age were accrued to either trial. Over 60% of patients enrolled were aged 60 or older, and 22% of patients were between 70 years and 79 years old. Elderly patients had significantly greater grade ≥ 3 or greater neutropenia (P =.04) and renal toxicity (P = .0025). However, age was not a factor in survival or response rate. As in the previous retrospective studies examined, this analysis suffers from selection bias since all of the patients in these studies were required to have performance scores of 0 or 1. These studies provide encouraging data for fit elderly patients with locally advanced NSCLC.

TREATMENT FOR METASTATIC NSCLC

Current practices for the treatment of advanced NSCLC in elderly patients is largely based on retrospective analyses of clinical trials.[16] Cisplatin-based doublet chemotherapy with or without bevacizumab, is the established recommendation for patients with advanced NSCLC.[26, 27]

Randomized Trials of Single Agent Chemotherapy in Elderly Patients

Few phase III randomized controlled studies have been completed with a specific focus on an elderly population, explaining the lack of standardized treatment recommendations for elderly patients with advanced lung cancer.[16] In 1999, the Elderly Lung Cancer Vinorelbine Italian study demonstrated evidence of the clinical utility of chemotherapy in elderly patients with advanced NSCLC.[28] In this randomized phase III trial with 161 patients older than 70 years of age, single agent vinorelbine improved quality of life and survival compared with supportive care alone (median survival 27 vs. 21 weeks, p = .04). Toxicity of therapy in this study was acceptable. Five of 71 elderly patients discontinued treatment due to severe toxic events (grade 3 constipation in 3 patients, grade 4 constipation in 1 patient, and grade 2 heart toxicity in 1 patient), and grade 4 leukopenia occurred in 4 patients which did not require discontinuation of therapy. This landmark study for elderly patients with NSCLC became the first randomized trial specifically designed for this subgroup of patients, and provided justification for further chemotherapeutic trials.

Another randomized, phase III trial demonstrated that docetaxel had similar efficacy to vinorelbine in terms of median survival time in the elderly.[29] 182 patients aged 70 years or older were randomized to receive docetaxel 60 mg/m2 (day 1) vs. vinorelbine 25 mg/m2 (days 1 and 8) every 21 days for four cycles. In comparison to vinorelbine, docetaxel showed a statistically significant improvement in progression free survival (5.5 months vs. 3.1 months), response rate (22.7% vs. 9.9%) and better disease-related symptom important. However, overall survival which favored docetaxel (10.3 months v. 6.4 months) did not reached statistical significance (hazard ratio, 0.78; 95% CI, 0.56 to 1.09; P = 0.65). Toxicity profiles for both treatments were mild and tolerable; grade 3 to 4 neutropenia occurred in more patients on the docetaxel arm than on the vinorelbine arm (P = 0.031), although there was no difference in the incidence of grade 3 to 4 febrile neutropenia and infection. This study represents the first phase

III trial for taxane monotherapy in the elderly population with advanced NSCLC, and makes docetaxel an option in the standard treatment for these patients.

Combined Chemotherapy in the Elderly

In an effort to build upon the increased survival seen with single-agent chemotherapy in the elderly population, combination chemotherapy has also been evaluated. Frasci et al. compared gemcitabine and vinorelbine to vinorelbine alone.[30] An interim analysis was presented after 120 patients were enrolled, and showed a significant advantage for the combination arm, leading to an interruption of the study. Median survival was 7 months for the combination arm and only 4.5 months with the vinorelbine. Important to note in this study, is that the overall survival for single agent vinorelbine was not consistent with other trials testing this drug, and was comparable to data described with best supportive care alone. Toxicity for the combination arm resulted in grade 3–4 neutropenia and thrombocytopenia in 38% and 13% respectively and was more prevalent than the vinorelbine arm (28% and 8%, respectively).

Data from this study was contradicted in a large, randomized phase III trial, the Multicenter Italian Lung Cancer in the Elderly Study (MILES).[11] 698 patients with a median age of 74 years were accrued. They found that the combination of vinorelbine and gemcitabine was no more effective than single agent vinorelbine or gemcitabine in elderly patients with NSCLC (median survival was 36 weeks for vinorelbine, 28 weeks for gemcitabine, and 30 weeks for the combination). In fact, the combination arm was slightly more toxic, although quality of life was similar across the three treatment arms. A retrospective analysis from the MILES study was performed to explore the prognostic value of baseline assessment of functional status, comorbidity and quality of life for overall survival in patients treated with chemotherapy.[31] Using the European Organization for Research and treatment of Cancer (EORTC) core questionnaire QLQ-C30 to assess quality of life as well as assessments of activities of daily living (ADL) and instrumental ADL (IADL), Maione et al. demonstrated that for elderly patients with advanced NSCLC, baseline IADL and quality of life (QOL) predicted overall survival while ADL and comorbidity did not show the same prognostic value. These discoveries, when used in clinical practice, may allow for the ability to identify prognostic factors for better selections of treatment options in the elderly with advanced NSCLC. The conclusions reached from the MILES study were that until new studies show a clear benefit for polychemotherapy for the elderly with advanced NSCLC, recommended treatment should be single agent chemotherapy.

A recent phase III study by Hainsworth et al. compared the efficacy of single-agent versus combined chemotherapy to further investigate the optimal treatment for the elderly (>65 years of age) or poor performance status patients.[32] 345 patients were randomized, and 80% of patients were over 65 years of age. By comparing weekly docetaxel with combined deocetaxel and gemcitabine, the trial showed that combination chemotherapy resulted in a modest improvement in time to progression (4.8 vs. 2.9 months; $p = 0.004$) without an impact on overall survival (5.5 vs. 5.1 months; $p = 0.65$). Incidence of grade 3 or 4 myelosuppression was significantly higher in the combination group. In essence, the results of this study reinforce the previous claim from the MILES study by providing further evidence that treatment with a single agent produces similar results and less toxicity than does a combination regimen with regards to advanced NSCLC in the elderly.

Most recently, a retrospective analysis of the Eastern Cooperative Oncology Group ECOG 4599 trial was performed with respect to the elderly.[33] The study randomized patients to receive carboplatin, paclitaxel and bevacizumab (PCB) versus carboplatin and paclitaxel alone (PC), and demonstrated a survival advantage for patients the bevacizumab arm. Patients older than 70 years of age made up only 26% ($n = 224$) of this study population, of which 113 were randomized to the PC arm with 111 assigned to PCB arm. When compared with the younger

patients, the elderly experienced more toxicity with PCB (87% of the elderly had grade 3 toxicity compared to 70% of the younger population, P < .001). Significant toxicities included grade 4 neutropenia, GI bleed, proteinuria, muscle weakness, neuropathy, and dizziness with a nonsignificant difference in relation to treatment related deaths (P = .08). Although there was a superior response rate and a nonsignificant trend towards improved progression free survival in the elderly, the analysis showed that there was no difference in overall survival (PCB = 11.3 months; PC = 12.1 months; P = .4) with the addition of bevacizumab to PC for the elderly.

Targeted Therapy in Elderly Patients

Concern for treatment-related toxicities seen in chemotherapeutic clinical trials in the elderly population has led the search of an effective, less toxic therapy in advanced NSCLC. The emergence of targeted therapies for lung cancer has provided the potential for more tolerable therapy. Erlotinib, an orally available tyrosine kinase inhibitor of the epidermal growth factor receptor, has shown a survival advantage when compared with best supportive care in a randomized, phase III trial for patients as second- or third-line treatment of advanced NSCLC.[34] In this 731 patient study, 57% of patients who received erlotinib and 49% of patients who received placebo were aged 60 or older. Erlotinib has also been evaluated in an elderly-specific study. In a phase II study, 80 chemotherapy-naïve, elderly patients (≥ 70 years of age) were treated with erlotinib 150 mg daily.[35] The median survival time of 10.9 months compares favorably with the survival seen in elderly patients receiving single agent chemotherapy.[11, 28,29] Toxicity was more favorable with erlotinib than in other elderly population-based studies, as less than 20% developed ≥ grade 3 toxicity. Four patients had suspected interstitial lung disease, and one patient experienced a treatment-related death. Most frequently, rash (79%) and diarrhea (69%) were seen, but these were mild and easily managed without further complications. The efficacy in this study, with a low toxicity profile provides reinforcement for ongoing clinical trials with erlotinib in the elderly. Improved understanding of patient selection and the mechanism of action for erlotinib and other targeted therapies will lead to increased benefits for all patients.

TREATMENT FOR PATIENTS OVER EIGHTY

Limited data exists for treating patients with lung cancer who are older than 65 years, and even less evidence is available to guide treatment recommendations for octogenarians. Owonikoko et al. specifically targeted the this subgroup of patients with lung cancer to study their outcomes.[1] By analyzing the national Surveillance, Epidemiology and End Results, they attempted to better characterize the undertreatment of the very elderly with lung cancer. Observations showed that patients who were 80 or older had worse survival outcomes than those 70 or older, after controlling for histological subtype or stage at diagnosis. Trends demonstrated that these patients had lower rates of surgery and radiation therapy in comparison to the younger population. In fact, the very elderly population was twice as likely to receive no therapy as younger patients, and less likely to undergo cancer-site directed surgical intervention. Fears of toxicity in elderly patients and increased operative morbidity and mortality were postulated to be concerns that withheld therapy from elderly patients; even in the fit, elderly patient. Unfortunately, as Owonikoko shows, this population also has an increase in mortality, and barriers to optimal care should be investigated further.

In an attempt to characterize current practices in the elderly, a recent study by Oxnard et al. performed a retrospective review of 111 patients with NSCLC who were aged 80 years or older.[36] Using a standard, stage-specific guideline-recommended therapy, reviews were performed to compare treatments actually received with those therapies that were recommended according to current practice guidelines. The study demonstrated encouraging results in that 84% received some form of antineoplastic treatment. This is a substantial improvement from historical trends that offered no more then best supportive care to this cohort

of patients.[37] However, only 32% were determined to receive stage-specific, guideline-recommended therapy. Although both age and performance status were important predictors for failing to receive guideline-recommended therapy, a low performance status was a much greater deterrent for guideline-recommended therapy than chronological age (OR 17.1 and 4.8 for PS and age, respectively).[36] Moreover, 14% of patients refused curative surgery and 24% with advanced disease refused chemotherapy, suggesting that the lack of data for treatment in the elderly population not only limits physicians from offering therapy, but may also pose an obstacle for patients who are faced with the troubling decision of accepting guideline-recommended therapy and its potential toxicities.

CONCLUSION

In summary, it becomes clear from the emerging retrospective reviews and prospective data that much is missing with regards to the elderly population and treatments for lung cancer. It is well known that the elderly population is under represented in clinical trials; further research uncovers the fact that their absence leaves physicians with difficult decisions. Oncologists are left to extrapolate data from clinical trials which have used exclusively younger patients, to make treatment recommendations for elderly patients. It is also understandably challenging for the elderly patients themselves, to accept the potentially life threatening toxicities of chemotherapy in this largely unstudied area of medical oncology. Several randomized trials including fit elderly patients in treating locally advanced NSCLC have shown statistically significant benefit in the elderly population. Randomized trials specific to elderly patients demonstrate improved efficacy with single agent chemotherapy, but have failed to show a clear benefit for combination chemotherapy. Targeted therapy also has a role in treatment of elderly populations with NSCLC. Unfortunately, the subgroup of patients older than 80, which constitutes the fastest growing subpopulation remains largely unstudied. Therefore, it is critical that studies targeted specifically at the elderly with lung cancer be performed to guide our recommendations for treatment choices and regimens. Increasing the number of elderly patients enrolled in clinical trials and offering specific treatment studies for this population will allow oncologists to more effectively treat this growing population that only stands to increase in number.

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REFERENCES

1. Owonikoko TK, Ragin CC, Belani CP, et al. Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database. J Clin Oncol 2007;25:5570–5577. [PubMed: 18065729]
2. Edwards BK, Howe HL, Ries LA, et al. Annual report to the nation on the status of cancer, 1973–1999, featuring implications of age and aging on U.S. cancer burden. Cancer 2002;94:2766–2792. [PubMed: 12173348]
3. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43–66. [PubMed: 17237035]
4. Fentiman IS, Tirelli U, Monfardini S, et al. Cancer in the elderly: why so badly treated? Lancet 1990;335:1020–1022. [PubMed: 1970072]
5. Hutchins LF, Unger JM, Crowley JJ, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341:2061–2067. [PubMed: 10615079]
6. Jatoi A, Hillman S, Stella P, et al. Should elderly non-small-cell lung cancer patients be offered elderly-specific trials? Results of a pooled analysis from the North Central Cancer Treatment Group. J Clin Oncol 2005;23:9113–9119. [PubMed: 16361618]

7. Jennens RR, Giles GG. Fox RM: Increasing underrepresentation of elderly patients with advanced colorectal or non-small-cell lung cancer in chemotherapy trials. Intern Med J 2006;36:216–220. [PubMed: 16640737]
8. Murthy VH, Krumholz HM. Gross CP: Participation in cancer clinical trials: race-, sex-, and age-based disparities. Jama 2004;291:2720–2726. [PubMed: 15187053]
9. Alam N, Shepherd FA, Winton T, et al. Compliance with post-operative adjuvant chemotherapy in non-small cell lung cancer. An analysis of National Cancer Institute of Canada and intergroup trial JBR.10 and a review of the literature. Lung Cancer 2005;47:385–394. [PubMed: 15713522]
10. Earle CC, Tsai JS, Gelber RD, et al. Effectiveness of chemotherapy for advanced lung cancer in the elderly: instrumental variable and propensity analysis. J Clin Oncol 2001;19:1064–1070. [PubMed: 11181670]
11. Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 2003;95:362–372. [PubMed: 12618501]
12. Langer CJ, Manola J, Bernardo P, et al. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. J Natl Cancer Inst 2002;94:173–181. [PubMed: 11830607](abstr)
13. Gridelli C, Aapro M, Ardizzoni A, et al. Treatment of advanced non-small-cell lung cancer in the elderly: results of an international expert panel. J Clin Oncol 2005;23:3125–3137. [PubMed: 15860872]
14. Stanley KE. Prognostic factors for survival in patients with inoperable lung cancer. J Natl Cancer Inst 1980;65:25–32. [PubMed: 6930515]
15. Asmis TR, Ding K, Seymour L, et al. Age and comorbidity as independent prognostic factors in the treatment of non small-cell lung cancer: a review of National Cancer Institute of Canada Clinical Trials Group trials. J Clin Oncol 2008;26:54–59. [PubMed: 18165640]
16. Gridelli C, Langer C, Maione P, et al. Lung cancer in the elderly. J Clin Oncol 2007;25:1898–1907. [PubMed: 17488989]
17. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351–360. [PubMed: 14736927]
18. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719–727. [PubMed: 16945766]
19. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589–2597. [PubMed: 15972865]
20. Pepe C, Hasan B, Winton TL, et al. Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. J Clin Oncol 2007;25:1553–1561. [PubMed: 17442999]
21. Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. N Engl J Med 1990;323:940–945. [PubMed: 2169587]
22. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 1999;17:2692–2699. [PubMed: 10561343]
23. Langer C, Hsu C, Curran WJ, et al. Elderly patients with locally advanced non-small cell lung cancer benefit from combined modality therapy: Secondary analysis of Radiation Therapy Oncology Group (RTOG) 94-10. Proc Am Soc Clin Oncol 2002;21
24. Schild SE, Stella PJ, Geyer SM, et al. The outcome of combined-modality therapy for stage III non-small-cell lung cancer in the elderly. J Clin Oncol 2003;21:3201–3206. [PubMed: 12874270]
25. Rocha Lima CM, Herndon JE 2nd, Kosty M, et al. Therapy choices among older patients with lung carcinoma: an evaluation of two trials of the Cancer and Leukemia Group B. Cancer 2002;94:181–187. [PubMed: 11815975]

26. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92–98. [PubMed: 11784875]
27. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–2550. [PubMed: 17167137]
28. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. J Natl Cancer Inst 1999;91:66–72. [PubMed: 9890172]
29. Kudoh S, Takeda K, Nakagawa K, et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 2006;24:3657–3663. [PubMed: 16877734]
30. Frasci G, Lorusso V, Panza N, et al. Gemcitabine plus vinorelbine yields better survival outcome than vinorelbine alone in elderly patients with advanced non-small cell lung cancer. A Southern Italy Cooperative Oncology Group (SICOG) phase III trial. Lung Cancer 2001;34:S65–S69. [PubMed: 11742706]
31. Maione P, Perrone F, Gallo C, et al. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol 2005;23:6865–6872. [PubMed: 16192578]
32. Hainsworth JD, Spigel DR, Farley C, et al. Weekly docetaxel versus docetaxel/gemcitabine in the treatment of elderly or poor performance status patients with advanced nonsmall cell lung cancer: a randomized phase 3 trial of the Minnie Pearl Cancer Research Network. Cancer 2007;110:2027–2034. [PubMed: 17823908]
33. Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. J Clin Oncol 2008;26:60–65. [PubMed: 18165641]
34. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123–132. [PubMed: 16014882]
35. Jackman DM, Yeap BY, Lindeman NI, et al. Phase II clinical trial of chemotherapy-naive patients > or = 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. J Clin Oncol 2007;25:760–766. [PubMed: 17228019]
36. Oxnard GR, Fidias P, Muzikansky A, et al. Non-small cell lung cancer in octogenarians: treatment practices and preferences. J Thorac Oncol 2007;2:1029–1035. [PubMed: 17975495]
37. Kurishima K, Satoh H, Ishikawa H, et al. Lung cancer in the octogenarian. Gerontology 2001;47:158–160. [PubMed: 11340322]