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Adjuvant chemotherapy and targeted therapy in elderly non-small-cell lung cancer patients

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Abstract

Adjuvant chemotherapy and targeted therapies comprise two salient practice-changing improvements in the treatment of non-small-cell lung cancer. Despite the fact that these improvements have been largely data-driven, the following questions arise: what is the role of adjuvant chemotherapy in elderly patients with non-small-cell lung cancer? What is the role of targeted agents, such as erlotinib and bevacizumab, in older non-small-cell lung cancer patients? These questions are relevant because the current median age of lung cancer patients at diagnosis in the USA is 69 years, and the number of older patients developing this malignancy is increasing. This review provides guidance on how best to approach the use of adjuvant chemotherapy and targeted therapies in older patients with this disease.

Keywords

adjuvant; chemotherapy; elderly; non-small-cell lung cancer; targeted therapy

Non-small-cell lung cancer: newer developments & older patients

Over the past 10 years, two areas of focus have garnered increasing attention because of their practice-changing effects in patients with non-small-cell lung cancer: adjuvant chemotherapy and the use of targeted agents. The former has evolved into the standard of care after a series of randomized controlled trials clearly demonstrated that postoperative, cisplatin-based chemotherapy in patients with stage II and IIIA non-small-cell lung cancer provides a statistically significant survival advantage. Similarly, the use of targeted agents – such as epidermal growth factor receptor inhibitors and bevacizumab – have yielded notable results in terms of survival and/or tumor response in non-small-cell lung cancer patients. What remains to be further considered is the following question: what is the role of these interventions in elderly non-small-cell lung cancer patients?

This last question is becoming increasingly more relevant because of an increasing number of older patients who are being diagnosed with this malignancy. Today the median age of diagnosis of lung cancer in the USA is 69 years [101]. Considering current population statistics and projected trends, many anticipate that by the year 2030, 20% of the US

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population will be older than 65 years [1]. Moreover, in other countries, such as Italy and Europe, these US projections pallor compared with the anticipated trends that will tilt demographics even more so in favor of a growing proportion of geriatric patients [2,3]. Thus, at the present time and on an international scale, lung cancer is a disease of the elderly, and in the near future it will become even more so.

Adjuvant chemotherapy in the elderly

A lack of Phase III prospective data & alternative data sources

To date and to the author's knowledge, there has been no published, large Phase III trial that has been completed and reported in elderly patients with the goal of examining prospectively whether adjuvant chemotherapy in older patients yields the same benefits as it does in younger patients. The Adjuvant Navelbine International Trialist Association 02 study has examined a single drug, nonplatinum-containing regimen, specifically vinorelbine at 30 mg/m² weekly for 16 weeks, but slow accrual suggests that results from this trial may not provide definitive conclusions on how and whether to treat elderly non-small-cell lung cancer patients in an adjuvant setting, particularly with a noncisplatin regimen. Instead, investigators have taken advantage of earlier, prospectively conducted studies and have undertaken subgroup analyses to examine outcomes in older patients within those studies [4–8]. Of note, when taken together, these previous trials have demonstrated that in general populations of lung cancer patients chemotherapy regimens that demonstrate a survival advantage have invariably utilized cisplatin-based chemotherapy, with the latter posing particular issues in older patients because of compromised renal function (which sometimes drops with age alone) and the problematic side effect of neuropathy (which creates greater challenges for older patients, who sometimes have mobility issues). Similarly, investigators have looked at large population-based databases and have focused on outcomes among older patients, as relevant to the administration of adjuvant chemotherapy. Such databases provide an important real-world perspective to adjuvant chemotherapy administration in older patients.

Post hoc analyses of prospective clinical trials

Pepe *et al.* performed one of the first such *post hoc* analyses and did so with JBR.10, a study of cisplatin and vinorelbine in 482 patients with resected non-small-cell lung cancer [9]. Within this cohort, 155 patients were elderly, or ≥ 65 years of age. These investigators found that chemotherapy prolonged survival for elderly patients with a hazard ratio of 0.61 (95% CI: 0.38–0.98; *p* = 0.04) and commented upon how this survival advantage was similar to what nonelderly patients acquired. Moreover, age-based analyses revealed no major differences between groups with respect to adverse events, including hospitalization and treatment-related death. Importantly, however, older patients received less cisplatin: 49% received less than five doses, 19% received five to seven doses and 32% received eight doses. These findings suggest that older lung cancer patients could well acquire benefit from postoperative chemotherapy, but they also suggest a need for cautious administration of cisplatin among older cancer patients under such circumstances.

In addition to the investigation from Pepe *et al.*, a subgroup analysis of all the five adjuvant trials alluded to earlier in this paper, as conducted by the Lung Adjuvant Cisplatin Evaluation group, found that age did not influence survival [10]. This analysis examined individual data from 4584 patients but did not specifically focus on age. Rather these investigators looked at numerous clinical variables, including – but not limited to – type of chemotherapy administered, performance score, tumor histology, tumor stage and type of previous surgery. Age, too, was embedded within this analysis, but it was not the primary focus of this report. Moreover, age was defined in broad terms that do not perhaps appear as

relevant to capturing data specific to older lung cancer patients. Nonetheless, using age cutoffs of less than 50 years, 50–59 years, 60–69 years and greater than or equal to 70 years, these investigators did not find that age, as defined in this manner, had a statistically significant impact on survival. Importantly, with a median follow-up of 5.2 years, this study found a 5-year absolute benefit from chemotherapy of 5.4%, thus providing some context of the modest degree of benefit sought when prescribing chemotherapy in this setting.

Focusing more on the age issue, Fruh *et al.* followed-up the above with a more specific, age-based analysis and also utilized the Lung Adjuvant Cisplatin Evaluation collaborative project [11]. In this analysis, patients were stratified into three groups: <65 years of age, 65–70 years of age and greater than 70 years old. Of relevance, despite the large number of patients included in this analysis, the distribution of age per trial shows that the number of patients older than 70 years at the time of study entry represented a minority. With respect to the individual trials, rates of participation within this age group were 10, 15, 17, 41 and 17% in the ALPI, ANITA, BLT, ALT and JBR.10 trials, respectively, thus suggesting that any conclusions among the oldest of the old might not be as robust as desired [4–8]. Nonetheless, this analysis provided some interesting conclusions. First, the hazard ratios of death were not statistically significant between age groups ($p = 0.29$ for the trend). This observation is particularly notable, in view of the third observation below, which describes that lower doses of chemotherapy were given to older patients. Second, no statistically significant differences in severe toxicity were observed based on age groups. Third, older patients received less chemotherapy, and, specifically, they received lower first-dose and total doses of cisplatin. This third observation may explain why the adverse event profiles were similar between groups. Fourth, not surprisingly, elderly patients died more often from noncancer-related events with 12% of younger patients, 19% of mid-range patients and 22% of much older patients ($p < 0.001$) dying from such events. Thus, it appears that there is no evidence of lack of benefit or increased toxicity in giving cisplatin-based adjuvant chemotherapy to older lung cancer patients, but lower patient numbers in the elderly group and higher rates of competing mortality might make one pause and think before prescribing it. Also of note, the fact that older patients received less chemotherapy suggests that patients might receive some benefit even if they receive only part of the planned course.

Population-based data sources

Wisnevesky *et al.* recently published relevant findings from an observational cohort study [12]. These investigators utilized the Surveillance Epidemiology and End Results registry, which was linked to Medicare Files between 1992 and 2005. They included follow-up data through to 2007. A total of 3324 patients, who were older than 65 years of age, were the subject of this study, which focused on patients with stage II and IIIA non-small-cell lung cancer. Using such a resource, these investigators observed the following. First, 21% of patients received adjuvant chemotherapy. This percentage may not be reflective of current practice patterns, as this study spanned an interval that preceded the publication of much of the true practice-changing data that showed benefits of adjuvant chemotherapy. Hence, this percentage should perhaps not be quoted to describe current practice patterns in the USA. In effect, however, this lower percentage derived from this long time span allows for less biased assessments between chemotherapy-treated and nontreated groups, as many of the nontreated groups probably did not receive chemotherapy only because it had not yet been defined as the standard of care, not because of a high degree of comorbidity that precluded its administration. Second, chemotherapy administration, for the most part, was associated with an improved survival (hazard ratio: 0.78–0.81), but this observation was not observed in patients who were older than 80 years of age (hazard ratio: 1.33; 95% CI: 0.86–2.06). This last conclusion underscores the fact that few prospectively conducted studies include the oldest of the old, thus otherwise limiting conclusions that we might be able to draw in

patients of this very old age group. Third, adjuvant chemotherapy was associated with increased adverse events. This last observation is perhaps too obvious to even state, as few would argue that chemotherapy has side effects.

The observations from this investigation are particularly important because they side step the biases inherent in *post hoc* analyses of prospectively conducted studies. Prospectively conducted clinical trials often include in their eligibility criteria strict qualifications that often preclude patients of a lesser performance score to enroll, thus making results less able to be generalized to a broad population of patients. Furthermore, these previous, prospectively conducted clinical trials were typically designed for younger patients, and, hence, the older patients who did enroll were perhaps more fit than older patients in the general population. Thus, the study from Wisnevesky is important because it provides real-world guidance on prescribing adjuvant chemotherapy to older non-small-cell lung cancer patients from a real-world source.

Discussing adjuvant chemotherapy in older non-small-cell lung cancer patients

This author can recall at least a few conversations when everyone in the room – the patient, family members and the healthcare provider – grappled with the decision of whether to recommend adjuvant chemotherapy and grappled with whether to receive it/prescribe it. These conversations have yielded a few instructive lessons. First, although it might be daunting to consider prescribing chemotherapy to an older, otherwise extremely healthy patient, it is important to keep in mind that the primary goal of adjuvant chemotherapy is to increase the chance of cure. In this context, it is also important to forecast and anticipate conversations that might occur in the event the patient were to develop recurrent disease. Would this patient be a candidate for chemotherapy upon recurrence when the goal of chemotherapy would shift from cure to modest prolongation of life? If the answer is a possible ‘yes’, then there may be more reason to attempt to prescribe adjuvant chemotherapy. Admittedly, cisplatin-based chemotherapy can be more challenging to prescribe than other regimens, particularly in an older patient, but, nonetheless, this exercise can provide all stakeholders – the patient, his/her family members and his/her team of healthcare providers – a clearer perspective on decision-making as the conversation on adjuvant chemotherapy unfolds.

Second, competing morbidity and mortality is a sobering reality in older patients. However, many patients who are in their 70s or 80s anticipate living into their next decade, largely because their parents or grandparents did the same. Understanding and acknowledging a family’s health history and patients’ expectations for longevity can contribute much to the conversation on adjuvant chemotherapy. Additionally, Walter and Covinsky have provided gender-specific graphs that help us better understand how to estimate patients’ remaining survival independently of their underlying recent lung cancer diagnosis [13]. For example, these graphs tell us that an 80-year-old woman is likely to live for another 9 years if her health is good, an extra 13 years if her health is exceptional or another 5 years if her overall health is more tenuous. Similarly, an 80-year-old man is likely to live 7 years in the setting of average health, 11 years if his health is exceptional and an extra 3 years with marginal health. These projections represent only rough estimates, but they can provide data that might enter into the conversation on whether or not to prescribe adjuvant chemotherapy to an older cancer patient.

Third, one should acknowledge that the assessment of the older lung cancer patient for adjuvant chemotherapy entails more than a simple assessment of performance score and laboratory results. Previous studies in other, nongeriatric noncancer settings make the point that performance score does not appear to be highly sensitive in terms of identifying patients at a high risk for adverse events from chemotherapy. A host of other clinical factors, such as

a timed get-up-and-go assessment, an assessment of falls in the previous 6 months, a history of weight loss, an assessment of activities of daily living and other such variables all provide further predictive capability. Recently, Hurria *et al.* further validated this approach [14]. These investigators focused on 500 patients with a mean age of 73 years (range: 65–91 years). This group included patients with a broad range of cancer types, including stage I–IV lung cancer (29%), gastrointestinal malignancies (27%), gynecologic cancers (17%), breast cancer (11%) and genitourinary malignancies (10%), as well as some miscellaneous other cancer types (6%). Adverse events were assessed prospectively in this study of chemotherapy-treated patients, and grade 3–5 events occurred in 53% of the patients. Specifically, 39% suffered a grade 3 event, 12% a grade 4 event and 2% died. Utilizing a variety of geriatric assessment variables – including several of those alluded to above – as well as other clinical parameters, such as laboratory values and treatment and tumor characteristics, these investigators constructed a scoring system. These investigators assigned a seven as a median risk score and then stratified patients based on risk of adverse events. In effect, older adult cancer patients who had a variety of cancer types and who were treated with a variety of chemotherapy regimens were categorized into the following groups: low risk with a score of 0–5 with a 30% risk of suffering a grade 3–5 event; intermediate risk with a score of 6–9 with a 52% risk of developing a grade 3–5 adverse event; and high risk with a score of 10–19 with an 83% risk of developing one or more of these higher grade adverse events ($p = 0.001$). Such methodology appears to provide a data-driven approach to predicting risk among older cancer patients and will likely be further tested and refined in the near future. For now, such an approach would probably make conversations between patients and healthcare providers somewhat more informative as decisions are made about adjuvant chemotherapy and as discussion of risk of adverse events become a part of such conversations.

The use of targeted agents in the elderly

Targeted therapy in older versus younger patients

The dramatic difference in adverse event rates between lung cancer patients who receive conventional chemotherapy and those who receive newer, more targeted agents has prompted some clinicians to lower their threshold for prescribing cancer treatment to older cancer patients. The relatively more favorable adverse event profiles of these newer agents allows them to be prescribed more readily to older patients or to those with a less favorable performance score. However, now that these agents have been available for a few years, most clinicians have come to realize that these agents can be more challenging to prescribe to older patients than we had once thought. Of note, this article does not focus on gefitinib given its limited availability in the USA.

Erlotinib

The above conclusion was quickly reached when an age-based re-analysis of the National Cancer Institute of Canada's Clinical Trials Group Study BR.21 was undertaken in a previously conducted study in a general population of metastatic lung cancer patients. This placebo-controlled study had shown that erlotinib, when prescribed in a second- or third-line treatment setting at 150 mg per day, yielded a survival advantage [15]. The original 731 patients in this trial were then re-analyzed based on whether they were 70 years of age or younger at the time of enrollment into the trial.

This re-analysis was designed around 163 elderly patients, of whom 112 had been assigned to erlotinib and 51 to placebo, as well as around 568 younger patients, of whom 376 had been assigned to erlotinib and 192 to placebo [16]. Importantly, clinical outcomes were not statistically different between groups based on erlotinib efficacy with older and younger

patients performing similarly with respect to cancer progression-free survival, overall survival and tumor response rates. However, compared with younger patients, older erlotinib-treated patients manifested more overall and more severe (grade 3 and 4) adverse events (35 vs 18%; $p < 0.001$). Specifically, older patients suffered more from rash, fatigue and dehydration. As a result, older patients were more likely to stop treatment earlier. These conclusions should not deter a healthcare provider from prescribing erlotinib, but the discussion with the patient should include a candid discussion of the side effects associated with this agent and should also point out that the severity of such side effects were such that older patients, at times, appeared more likely to stop the erlotinib early.

One other point that is often ignored but merits further attention in older lung cancer patients deals with polypharmacy – a common issue in older patients – and resulting drug interactions. For example, a recent case report describes a 78-year-old woman with a history of depression, dyslipidemia and metastatic adenocarcinoma of the lung adenocarcinoma [17]. The patient was a good candidate for erlotinib 150 mg per day because her tumor had an activating mutation of the epidermal growth factor receptor (exon 19 deletion). Erlotinib was thus started at the recommended dose of 150 mg per day in conjunction with other ongoing medications that included escitalopram, alprazolam and fenofibrate. The unusual combination of tumor progression coupled with no erlotinib-related side effects (no rash and no diarrhea) prompted the authors to probe further into erlotinib pharmacokinetics, an endeavor that revealed that the plasma trough concentration of erlotinib was unexpectedly low at 657 ng/ml (expected value of 1200 ng/ml). Erlotinib dose escalation resulted in a trough concentration of 1360 ng/ml and evidence of tumor response. In searching for explanations for the above observations, the authors pointed out that erlotinib is extensively metabolized by CYP3A4 and that fenofibrate could potentially induce a higher rate of metabolism of erlotinib. This unexpected observation – which could potentially occur more frequently in older patients because they often take many more drugs than younger patients – underscores the importance of maintaining a high degree of vigilance for such interactions in older non-small-cell lung cancer patients.

Bevacizumab

Bevacizumab is an anti-cancer agent that works to block vascular endothelial growth factor. It is currently used to treat patients with a variety of cancers, including those with non-small-cell lung cancer. In the latter situation, it improves survival [18]. The addition of this drug to the armamentarium of agents used to treat lung cancer patients raises the question of whether this drug is as efficacious and well tolerated in older patients as it is in younger ones.

To gain further insight, Ramalingam and others re-analyzed a Phase III trial, from the Eastern Cooperative Oncology Group, that tested bevacizumab in combination with carboplatin and paclitaxel versus the last two agents alone in first-line patients with metastatic disease [19]. These investigators defined elderly in terms of patients' being 70 years of age or older at study entry. Moreover, the elderly cohort consisted of 224 patients (26% of the entire cohort). In analyses that focused exclusively on the elderly with comparisons between patients treated with chemotherapy plus bevacizumab versus chemotherapy alone, there were only trends to suggest higher tumor response rates (29 vs 17%; $p = 0.067$) and cancer progression-free survival (5.9 vs 4.9 months; $p = 0.63$) with the addition of bevacizumab. Overall survival was not statistically significant between groups. Of note, grade 3 or worse adverse events, which included a greater number of deaths, were observed in 87% of elderly patients treated with bevacizumab versus 61% who were not ($p < 0.001$). These investigators concluded that the addition of bevacizumab resulted in greater toxicity with no evident survival advantage. These findings were such that further analyses with comparisons to the larger, younger cohort seemed superfluous, and the bottom line

from the standpoint of these investigators was that more study on the role of bevacizumab in older lung cancer patients is indicated.

Since the publication of these Eastern Cooperative Oncology Group data, more investigation of bevacizumab in older patients has been forthcoming. The Safety of Avastin in Lung study was an international, single-arm trial that comprised 2212 first-line lung cancer patients and was intended to examine the efficacy and safety of conventional chemotherapy when given in conjunction with bevacizumab, with the option of prolonged bevacizumab maintenance in patients with stable disease after roughly 4 months of cancer treatment [20]. These investigators performed a subgroup analysis that focused on patients who were 65 years of age or older, with their primary goal being an assessment of safety. Six hundred and twenty three patients were eligible for this subgroup analysis. Adverse events such as bleeding, hypertension and proteinuria, occurred at a comparable rate and grade based on age-groups, but, overall, major adverse events occurred more often in older than younger patients with rates of 45.3 and 34.7%, respectively. Other clinical outcomes, such as median survival, time-to-cancer progression and tumor response rates were comparable between groups in age-based comparisons. These investigators concluded that older patients derived “similar clinical benefit from first-line bevacizumab-based therapy as their younger counterparts” with no “increased toxicity”.

Similarly, Leighl *et al.* also found that bevacizumab seemed relatively safe in older non-small-cell lung cancer patients [21]. In a placebo-controlled Phase III trial, called AVAiL, the combination of bevacizumab with cisplatin and gemcitabine was compared with these two chemotherapy agents with placebo; and it was the goal of this subanalysis to evaluate the efficacy and toxicity of a bevacizumab-based regimen in non-small-cell lung cancer patients who were 65 years of age or older. This 304-patient analysis focused specifically on patients aged 65 years or older. Elderly patients treated with bevacizumab only manifested a suggestion of improvement in cancer progression-free survival compared with placebo-exposed patients who also received conventional chemotherapy with a hazard ratio of 0.71 ($p = 0.023$) with the lower bevacizumab dose and a hazard ratio of 0.84 ($p = 0.26$) with a slightly higher bevacizumab dose. Moreover, overall survival was similar for each bevacizumab arm versus placebo arm. From a safety standpoint, the addition of bevacizumab was not associated with a worse adverse event profile. The improvement in cancer progression-free survival in one bevacizumab-treated arm led these investigators to conclude, “This analysis of the randomized, Phase III AVAiL trial shows that bevacizumab-based therapy improves outcomes for elderly patients with non-small-cell lung cancer. Furthermore, bevacizumab-based therapy is well tolerated in elderly patients”. Of note, however, overall survival did not seem to have been improved with the addition of bevacizumab in older patients.

Why did these three studies with bevacizumab in elderly patients with metastatic non-small-cell lung cancer yield conflicting results with respect to the safety and efficacy of this agent? We can only speculate. However, it could well be that the elderly patient groups differed in some fundamental, biological manner between these studies and that the Eastern Cooperative Group Trial enrolled older patients who were less likely to acquire benefit and more likely to acquire adverse events. Similarly, with respect to the adverse event profile of bevacizumab in the elderly, it could be that the complexity of distinguishing adverse events related to the lung cancer itself versus any other intervention is such that a clinician can never truly tell the difference. It could also be that Ramalingam *et al.* reported their findings first, and, subsequently, a heightened awareness of the potential for toxicity prompted other investigators to exercise more caution as they enrolled elderly patients on subsequent non-small-cell lung cancer trials with bevacizumab [19]. Finally, it should be noted that AVAiL appeared to include a ‘younger’ group of elderly patients, and this focus on a younger group

may perhaps account for the more favorable findings within the elderly subanalysis. Regardless of our ability or inability to reconcile these findings, it seems reasonable to exercise greater caution when prescribing bevacizumab to older non-small-cell lung cancer patients.

Conclusion

The foregoing summary has attempted to make the point that a clinician cannot draw solid, sweeping recommendations on adjuvant chemotherapy or the use of targeted agents in older patients with non-small-cell lung cancer. Based on subgroup analyses and often including only a very small subset of the oldest of the old, the current data, at best, provide clinicians with only general guidance on how to approach such conversations and make recommendations to patients. If an older patient's general health suggests to the clinician that adjuvant chemotherapy or targeted therapies would not be well tolerated, it appears acceptable to recommend to the patient that such therapies should not be pursued. Moreover, the fact that many published reports showed some degree of benefit, even when a short course of treatment is prescribed, suggests that trying and stopping early in the event of toxicity is another approach that could be tried in select circumstances.

Future perspective

A growing interest in geriatric oncology – coupled with a growing interest in developing and validating tools to assess risk of the administration of chemotherapy in older patients – suggest that the current dilemmas faced by clinicians when deciding whether or not to prescribe chemotherapy or targeted therapies will soon be partially mitigated. Such prediction tools are unlikely to ever make such decision-making starkly black and white, but they will provide a greater degree of guidance to make conversations between healthcare providers and patients far more informative and data-driven.

Furthermore, although only a sparse number of trials currently focus specifically on older cancer patients, it appears that in years to come, the growing number of elderly cancer patients will ensure that ongoing trials include a larger number of elderly patients. Currently, the percentage of elderly patients participating in clinical trials is quite low. Even among elderly-specific trials, the percentage of the oldest of the old patients who are enrolled is lower than anticipated. Over time, with a larger population of elderly patients from which to draw, our ability to capture older patients in trials will probably improve. This anticipated accrual success will probably improve our ability to generalize clinical trial findings to older patients who receive cancer treatment off-study. Such changes will promote our understanding of how best to treat older cancer patients.

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Executive summary

- The median age of patients with non-small-cell lung cancer is currently 69 years of age, and the number of elderly patients with this disease is expected to rise based on USA and international demographics.
- Adjuvant cisplatin-based chemotherapy is currently the standard of care for patients with stage II and IIIA non-small-cell lung cancer, but the inherent challenges of prescribing cisplatin to elderly patients and a lack of prospective data that specifically focused on the elderly should make one pause before recommending this approach to elderly patients.
- The latter point can also be made with respect to prescribing erlotinib and bevacizumab to older non-small-cell lung cancer patients with metastatic disease.
- The use of geriatric assessment tools appears to provide extra information to aid cancer treatment decision-making in older, non-small-cell lung cancer patients. As these tools become more refined and as they continue to be validated, their utility will likely only increase.