Treatment of Elderly Patients With Non–Small-Cell Lung Cancer: Results of an International Expert Panel Meeting of the Italian Association of Thoracic Oncology

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Abstract

Most patients with non–small-cell lung cancer (NSCLC) are elderly, and age has important implications for their management and treatment. In May 2014, the Italian Association of Thoracic Oncology organized an International Experts Panel Meeting with the intent to review the available evidence regarding the treatment of elderly patients with NSCLC and to discuss the implications for clinical practice and future research in this field; this article summarizes the panelists' conclusions. All patients aged more than 70 years should receive an assessment of physiologic age, including mortality and toxicity prediction. Age itself does not contraindicate adjuvant chemotherapy after resection. Elderly patients with locally advanced NSCLC should be considered for combined chemo-radiotherapy. In the advanced setting, the combination of carboplatin/paclitaxel results in prolonged survival compared with single-agent gemcitabine or vinorelbine, albeit with increased toxicity. In fit selected patients, other carboplatin-based or cisplatin-based regimens are feasible, but randomized trials specifically showing survival prolongation in elderly patients are lacking. The survival benefit for bevacizumab added to chemotherapy seems limited to patients aged less than 75 years. In unfit elderly patients, single agents are recommended. Regardless of age, patients with advanced non-squamous NSCLC, and those who have never smoked independently of their histologic subtype, should be tested for epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement. In patients with NSCLC harboring EGFR mutation or ALK rearrangement, targeted drugs are feasible and well tolerated.

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Introduction

Lung cancer is the most common cancer worldwide and the leading cause of cancer-related deaths.[1,2] In an analysis by the Surveillance Epidemiology End Results database, approximately half of lung cancer cases are diagnosed in people aged more than 70 years, and approximately 15% of cases are diagnosed in patients aged more than 80 years.[3]

Aging may be associated with decreased physiologic reserve, polymorbidity and polypharmacy, functional dependence, and inadequate social support, which lead to limited life expectancy and reduced tolerance of stress, such as cancer chemotherapy.[4] The benefits of cancer treatment may be reduced and the risks increased in the older person. Undertreatment is an additional risk for older individuals. Practitioners may assume that age itself is a contraindication to treatment even when the physiologic reserve is adequate and there are no other serious medical conditions.[5] Furthermore, elderly patients are underrepresented in clinical trials,[6,7] and treatment decisions are based on results of trials conducted in younger individuals.

In May 2014, the Italian Association of Thoracic Oncology (Associazione Italiana di Oncologia Toracica) organized an International Experts Panel Meeting, with the intent to review the available evidence regarding the treatment of elderly patients with non–small-cell lung cancer (NSCLC) and to discuss the implications for clinical practice and future research in this field. The consensus results are presented in this article.

Materials and Methods

The International Experts Panel Meeting on the treatment of elderly patients with NSCLC was held in Sperlonga, Italy, on May 9, 2014. Nine medical oncologists (4 from Italy, 3 from the United States, and 1 each from Spain and The Netherlands) formed the scientific panel.

Published data useful for panel discussion were identified by a PubMed search, performed with combinations of the following search terms: "carcinoma, non-small-cell lung" [Majr] AND "elderly." Only articles written in English were considered. For the discussion, each panelist selected the references that were considered relevant to the assigned topic. Abstracts presented between 2009 and 2013 at the main international meetings also were searched. The search has been updated for this article with the proceedings of 2014 American Society of Clinical Oncology meeting. Relevant references from selected articles also were included, and other articles were selected from the personal collections of the panelists.

Clinical Assessment of Aging and Role of Geriatric Assessment in Clinical Practice

Elderly patients with NSCLC represent a diverse population; thus, accurate evaluation of prognosis, prediction of treatment tolerability, and selection of the most appropriate management for each patient are crucial issues in clinical practice. Comprehensive geriatric assessment (CGA) is a multidimensional, interdisciplinary patient evaluation that leads to the identification of patients' problems[8] (Table 1). CGA complements history and physical examinations. Although this can be time-consuming, it is considered the most appropriate clinical method to obtain a global view on the health status of elderly patients,[9] providing information on the risk of mortality[10] and treatment toxicity.[11,12] In particular, given the narrow therapeutic index of treatments for NSCLC, instruments allowing the estimate of individual risk of severe toxicity are particularly useful for elderly patients. The Chemotherapy Risk Assessment Scale for High-Age Patients score, developed through a prospective, multicenter study of patients aged more than 70 years who were starting chemotherapy, is an example of how both hematologic and nonhematologic toxicity may be predicted on the basis of the CGA (Table 2).[11]

Table 1 Main Elements of a Comprehensive Geriatric Assessment

Parameter	Elements
Functional status	Performance status
	Activities of Daily Living
	Instrumental Activities of Daily Living
Comorbidity	No. of comorbidities
	Severity of comorbidities
	Comorbidity index or scale
Socioeconomic status	Living conditions
	Presence and adequacy of caregivers
	Income
	Access to transportation
Cognitive status	Folstein's Mini Mental Status
	Other tests
Emotional status	Geriatric Depression Scale
Poly-pharmacotherapy	No. of drugs assumed
	Appropriateness of medications
	Risk of drug interactions
Nutritional status	Mini-Nutritional Assessment
Presence of geriatric syndromes	Dementia, delirium, depression, falls, neglect and abuse, spontaneous bone fractures, failure to thrive

In patients with NSCLC, the role of CGA for therapeutic decision-making remains undefined. A randomized trial conducted in patients aged more than 70 years with stage IV NSCLC compared a "classic" strategy of treatment allocation based on age and performance status versus an experimental strategy based on geriatric assessment.[13] In the control arm, patients aged less than 75 years and with performance status 0 to 1 received a platinum-based doublet, whereas patients aged more than 75 years or with performance status 2 received single-agent docetaxel. In the experimental arm, patients were classified as fit, pre-frail, or frail according to a geriatric evaluation: Fit patients received platinum-based doublet regardless of age, pre-frail patients received single-agent docetaxel, and frail patients received best supportive care (BSC) only. The primary end point was treatment failure-free survival. In the control arm, 66% of patients received single-agent docetaxel, whereas in the experimental arm only 32% received single-agent, and 21% were considered frail and received BSC only. There was no difference observed between the 2 arms in treatment failure-free survival or overall survival. However, this study has not been published, thus limiting panelists' discussion of its full results. In a randomized trial dedicated to elderly patients, comparing carboplatin plus paclitaxel with single-agent gemcitabine or vinorelbine, Activities of Daily

Table 2 Chemotherapy Risk Assessment Scale for High-Age Patients Score

	Points		
	0	1	2
Score for hematologic toxicity[a]			
Diastolic blood pressure	≤72 mm Hg	>72 mm Hg	
Instrumental Activities of Daily Living	Score 26-29	Score 10-25	
LDH (if ULN 618 U/L; otherwise, 0.74 U/L x ULN)	0-459 U/L		>459 U/L
Chemotox value[b]	0-0.44	0.45-0.57	>0.57
Score for nonhematologic toxicity[a]			
ECOG performance status	0	1-2	3-4
Mini Mental Health Status	Score = 30		Score <30
Mini Nutritional Assessment	Score = 28-30		Score <28
Chemotox value[b]	0-0.44	0.45-0.57	>0.57

Abbreviations: ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; ULN = upper limit of normal.
[a]For the combined score, add the points from the hematologic and nonhematologic scores, counting Chemotox only once.
[b]For examples of Chemotox values associated with specific chemotherapy regimens, see Extermann et al.[11]
(Modified From Extermann et al[11])

Living and Mini-Mental State Examination showed no useful predictive role for the efficacy of the treatments compared.[14]

Although the formal role of CGA for therapeutic decision-making remains uncertain, panelists agreed that all patients with cancer who are aged more than 70 years should have some form of assessment of physiologic age, which should include estimate of mortality risk and prediction of toxicity. Although age should be ideally defined in functional rather than chronologic terms, it is reasonable to consider the cutoff of 70 years as the threshold of senescence: Subjects aged more than 70 years, on average, have an increased incidence of age-related changes, including functional decline, concomitant diseases, and geriatric syndromes.[15]

Role of Adjuvant Chemotherapy in Elderly Patients With Early-Stage NSCLC

On the basis of the demonstration of a significant overall survival benefit in a number of randomized trials, platinum-based chemotherapy has become standard treatment after surgery for patients with completely resected stage II to III NSCLC.[16] However, patients aged more than 70 years have comprised only a small proportion of those enrolled in the randomized trials that have demonstrated the efficacy of adjuvant chemotherapy.[15] Of note, in the Lung Adjuvant Cisplatin Evaluation (LACE) pooled analysis, the median age was 59 to 60 years.[17] No significant interaction for treatment efficacy with patients' age was shown for disease-free survival or overall survival, but patients aged more than 70 years comprised less than 10% of the whole population.

Unfortunately, there are no elderly-specific randomized trials in the adjuvant NSCLC setting. To date, data in the elderly largely have been based on extrapolation. In this regard, a retrospective analysis of the JBR10 trial is informative.[18] This trial randomized 482 patients with completely resected stage IB or stage II NSCLC to adjuvant cisplatin/vinorelbine or observation. Chemotherapy significantly improved survival with a hazard ratio (HR) of 0.69, and later retrospective subgroup analysis of the 155 patients aged more than 65 years confirmed this finding, with an HR of 0.61.[18] Although chemotherapy delivery was lower in the elderly, toxicity, hospitalizations, and treatment-related deaths did not differ by age. The LACE meta-analysis combined individual patient data from JBR.10 with 4 other adjuvant trials.[19] In this analysis, age subgroup analysis was performed for 3 subgroups: young (< 65 years: 3269 patients), mid-category (65-69 years: 901 patients), and elderly (≥ 70 years: 414 patients). The HR for death with the addition of chemotherapy to surgical resection was 0.86 (95% confidence interval [CI], 0.78-0.94) for the youngest category, 1.01 for the midcategory (95% CI, 0.85-1.21), and 0.90 for the elderly category (95% CI, 0.70-1.16); there was no age-by-treatment effect interaction. The lack of effect in the mid-category was attributed to an excess of male patients, patients with poor performance status, and patients treated with older regimens, but not to age itself. Elderly patients again received less total therapy, but there was no difference in major toxicity.

One concern about extrapolating the results of JBR.10 and LACE to clinical practice is that these patients are not necessarily representative. They likely constitute the fittest of the elderly, and therefore these results might not necessarily apply to a general population. Despite this concern, the use of adjuvant chemotherapy in patients aged more than 70 years has consistently increased after the publication of pivotal adjuvant chemotherapy trials, although it remains lower than its use in younger patients.[20] A retrospective analysis of the Ontario Cancer Registry suggested that the use of adjuvant chemotherapy was associated with a significant survival benefit in patients aged more than 70 years, with tolerability similar to that of younger patients.[20] Likewise, in a population-based analysis of elderly patients with resected early-stage NSCLC,[21,22] the minority of patients who received platinum-based adjuvant chemotherapy fared better with respect to overall survival than patients who did not receive treatment. Carboplatin was more commonly given than cisplatin (5:1 ratio), and the 2 drugs produced a comparable survival advantage. However, this was not a randomized study, and it is assumed that most patients receiving adjuvant chemotherapy in this community practice retrospective analysis were in better general condition that those who did not receive adjuvant chemotherapy. However, because both groups of patients were able to tolerate surgical resection, one might assume that their functional reserve was adequate, at least a priori. This study provides a strong suggestion, although speculative and hypothesis-generating at best, that adjuvant chemotherapy might be beneficial to older patients with lung cancer.

Despite concerns regarding the reproducibility of the results from pivotal randomized trials to elderly patients, panelists agreed that age itself should not be a contraindication for adjuvant chemotherapy in fit patients treated in clinical practice. As with younger patients, adjuvant chemotherapy should be considered in resected stage II and III NSCLC, and might be considered in resected stage IB tumors > 4 cm. However, evidence about the efficacy of adjuvant chemotherapy in patients aged more than 75 years is limited, and virtually no information is available on patients aged more than 80 years. The optimal regimen to be used as adjuvant treatment in

elderly patients is not well defined. As a general rule, the adjuvant treatment of choice should be platinum plus a third-generation agent: cisplatin is preferable if the patient is suitable.[16] Carboplatin could represent an alternative to cisplatin.[22] As for the third-generation agent, vinorelbine is the drug best studied in the randomized trials of adjuvant treatment; other agents (pemetrexed, gemcitabine, taxanes), although with less evidence in the adjuvant setting, are commonly used in patients with advanced disease. In elderly patients, often exposed to higher risk of toxicity, predictive factors for efficacy and toxicity would be particularly useful. As in younger patients, at the moment, there are no established molecular analyses useful for predicting chemotherapy benefit or determining the chemotherapy regimen.

In the RAndomized, Double-blind trial In Adjuvant NSCLC with Tarceva (RADIANT) study, a randomized phase 3 trial comparing adjuvant erlotinib versus placebo after complete tumor resection (with or without adjuvant chemotherapy) in patients with stage IB-IIIA NSCLC, erlotinib did not produce a benefit in the whole study population, but was associated with a significant disease-free survival prolongation in the subgroup of patients with epidermal growth factor receptor (EGFR) mutation.[23] While we await the definitive results of that trial, panelists agreed that currently, regardless of age, there is no established role for adjuvant treatment with EGFR tyrosine kinase inhibitors (TKIs) in clinical practice. This question will be addressed prospectively by the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST) study and other studies.[24]

Management of Elderly Patients With Locally Advanced Disease

Current guidelines state that patients with locally advanced NSCLC who are ineligible for surgery with curative intent should receive combined chemo-radiotherapy.[25] An individual patient data meta-analysis has demonstrated the superiority of concurrent chemo-radiotherapy compared with sequential treatment, but panelists noted that elderly patients were clearly underrepresented: The median age in clinical trials was 62 years, and less than 20% were aged more than 70 years.[26] Similar to the adjuvant setting, prospective data obtained in studies dedicated to elderly patients would substantially improve the quality of evidence for clinical decisions.

As in other stages of disease, elderly patients with locally advanced disease are at risk of undertreatment compared with their younger counterparts, even in the absence of relevant comorbidities.[5] One of the reasons is the increased risk of toxicity associated with the administration of combined chemo-radiotherapy in elderly patients.[27-29] In a retrospective subgroup analysis of a randomized trial comparing once-daily with twice-daily radiotherapy added to chemotherapy, survival of patients aged more than 70 years was not significantly different than of younger patients, but toxicity was more frequent and more severe in the elderly cohort.[28] Likewise, in an updated analysis of a randomized phase III trial testing the addition of consolidation docetaxel to concurrent chemo-radiotherapy for patients with unresectable stage III NSCLC, elderly patients had similar survival compared with younger patients, but higher rates of grade 3/4 toxicity and hospitalization during induction.[29]

In a Japanese randomized phase III trial, patients aged more than 70 years with unresectable stage III NSCLC were randomized to radiotherapy alone (60 Gy) or radiotherapy plus concurrent low-dose carboplatin (30 mg/m^2/d, 5 dd/wk for 20 days).[30] The trial enrolled 200 patients, and the second planned interim analysis showed a benefit in overall survival for the chemo-radiotherapy arm. Toxicity was higher with the concurrent treatment, with more severe leucopenia, neutropenia, thrombocytopenia, and infection. This was the first prospective trial comparing concurrent chemo-radiotherapy with radiotherapy alone in elderly patients with NSCLC. However, the low number of enrolled patients and the severe toxicity of the combination represent a limitation for the reliability and the applicability of those results in clinical practice.[31]

Given the available evidence, panelists agreed that elderly patients with locally advanced NSCLC should not be excluded from combined modality chemo-radiotherapy treatment because of age alone. Fit elderly patients might benefit from concurrent treatment, if the real risk of significant toxicity is acceptable to the patient. Elderly patients who are judged ineligible for concurrent chemo-radiotherapy might be considered for sequential treatment and the prospect of lower toxicity compared with concurrent therapy.[26] Population-based data suggest that, even if patients are considered unfit for chemotherapy, they may benefit from radical radiotherapy alone.[32] As expected, patients treated with radiotherapy were also at higher risk of toxicity, particularly pneumonitis and esophagitis.

First-Line Treatment for Elderly Patients With Advanced NSCLC in the Absence of "Actionable" Molecular Markers

For many years, the evidence of efficacy of platinum-based combinations in elderly patients with advanced NSCLC, compared with single-agent chemotherapy, was limited to retrospective analyses of selected subgroups of elderly patients enrolled in clinical trials without an upper age limit.[33-39] As a general rule, however, only a select group of elderly patients will be considered for enrollment in clinical trials designed for the general, fit population.[6] Panelists agree that those observations should not automatically be applied to the general, unselected elderly population.

Historically, the first randomized trial dedicated to elderly patients with advanced NSCLC did not test the efficacy of platinum-based chemotherapy, which was considered too toxic for these patients, but focused instead on the role of single-agent chemotherapy.[40] In detail, the Elderly Lung cancer Vinorelbine Italian Study (ELVIS), conducted in Italy at the end of the 1990s, was the first randomized phase III trial published in this setting, and it demonstrated a clear benefit for single-agent vinorelbine compared with BSC alone in elderly patients with advanced NSCLC[40] (Table 3). Patients aged more than 70 years were randomized to receive BSC alone or BSC plus vinorelbine. Of note, the accrual in the ELVIS study became progressively slower because of the reluctance to randomize patients to accept a BSC arm, and the study was terminated early. Although the main end point of the study was health-related quality of life, a benefit in overall survival was demonstrated: patients assigned to vinorelbine had significantly longer survival. Patients receiving chemotherapy reported worse scores for several side effects associated with treatment (nausea and vomiting, constipation, peripheral neuropathy, and hair loss), but scored better on many subscales, including global health status/quality of life, several functioning scales (role, cognitive, social, and physical functioning), fatigue, pain, dyspnea, and cough.

Table 3 Main Randomized Trials Dedicated to Patients Aged > 70 Years With Advanced NSCLC

Trial	Study Arm	No. of Patients	Median Overall Survival	1-Year Overall Survival (%)	HR	Other Relevant End Points
ELVIS[40]	BSC	78	21 wk	14	Vinorelbine versus BSC: 0.65 (95% CI, 0.45-0.93)	Quality of life functional scales and several cancer-related symptoms better for vinorelbine
	Vinorelbine	76	28 wk	32		
MILES[41]	Vinorelbine	233	36 wk	38	Combination versus vinorelbine: 1.17 (95% CI, 0.95-1.44) Combination versus gemcitabine: 1.06 (95% CI, 0.86-1.29)	Quality of life was similar among the 3 treatment arms
	Gemcitabine	233	28 wk	28		
	Vinorelbine + gemcitabine	232	30 wk	30		
IFCT-0501[14]	Single-agent vinorelbine or gemcitabine	226	6.2 mo	25.4	Combination versus single-agent: 0.64 (95% CI, 0.52-0.78)	Increased toxic effects with combination, particularly neutropenia and fatigue
	Carboplatin plus weekly paclitaxel	225	10.3 mo	44.5		
JCOG0803/ WJOG4307L[45]	Docetaxel every 3 wk	134	14.8 mo	58.2	Combination versus single-agent: 1.18 (95% CI, 0.83-1.69)	Increased neutropenia and febrile neutropenia with single-agent docetaxel; higher proportion of patients with symptom improvement with single-agent docetaxel
	Cisplatin plus weekly docetaxel	138	13.3 mo	54.5		

Abbreviations: BSC = best supportive care; CI = confidence interval; ELVIS = Elderly Lung cancer Vinorelbine Italian Study; HR = hazard ratio; MILES = Multicenter Italian Lung cancer in the Elderly Study.

A few years later, the Multicenter Italian Lung cancer in the Elderly Study (MILES) trial, designed to test the superiority of a non-platinum doublet (vinorelbine + gemcitabine) compared with single-agent gemcitabine or single-agent vinorelbine, failed to show any benefit for the combination compared with either single agent, with similar overall survival in the 3 arms[41] (Table 3).

More recently, in a French randomized trial, the combination of carboplatin and weekly paclitaxel produced better overall survival compared with single-agent gemcitabine or vinorelbine, at the cost of increased toxicity (particularly neutropenia), in a population of elderly patients (aged 70-89 years, performance status 0-2) with advanced NSCLC[14] (Table 3). Patients in both arms received erlotinib at progression. Median overall survival was 10.3 months for doublet chemotherapy versus 6.2 months in the control arm (HR, 0.64; 95% CI, 0.52-0.78; $P < .0001$). Other carboplatin-based combinations have been suggested as feasible and reasonable options,[42,43] but without elderly-specific phase III prospective comparative trials versus single agent. In a subgroup analysis of elderly patients enrolled in a randomized phase III trial comparing carboplatin plus nab-paclitaxel with carboplatin plus weekly solvent-based paclitaxel, treatment with carboplatin plus nab-paclitaxel was well tolerated.[44] Although median overall survival was similar between arms in the whole study population, overall survival was significantly better with nab-paclitaxel in the elderly subgroup. However, elderly patients constituted only 15% of the whole study population, and the trial was designed with overall response rate as the primary end point. In fit selected elderly patients with adequate organ function, cisplatin-based chemotherapy is feasible, but there are no definitive randomized trials dedicated to elderly patients showing a survival benefit. In a phase III randomized trial conducted in Japan in 276 elderly patients with advanced NSCLC, the combination of weekly docetaxel and cisplatin did not improve survival compared with single-agent docetaxel, administered at full dose every 3 weeks[45] (Table 3). Other randomized trials comparing cisplatin-based combination with the constituent nonplatinum single agent are still ongoing.[46]

Panelists agreed that in unfit elderly patients, single-agent third-generation therapy could be considered standard treatment on the basis of the results of the ELVIS and MILES trials.[40,41] As discussed earlier, platinum-based chemotherapy is feasible in fit selected patients.

On the basis of existing NSCLC guidelines, the addition of bevacizumab to platinum-based chemotherapy is one of the standard options for the first-line treatment of advanced nonsquamous NSCLC,[47] based on the Eastern Cooperative Oncology Group (ECOG) 4599 phase III trial comparing paclitaxel/carboplatin with the same regimen in combination with bevacizumab, in which a 2-month prolongation of median overall survival was observed.[48] However, independently of age, only a minority of patients are eligible for the administration of bevacizumab because of histology, risk of bleeding, untreated central nervous system metastases, or other contraindications.[49] In the subgroup analysis of the 224 elderly patients enrolled in the ECOG 4599,[50] the addition of bevacizumab did not produce a statistically significant survival prolongation, but it was associated with a significant increase in toxicity (more grade 4 neutropenia, melena and gastrointestinal bleeding, muscle weakness, motor neuropathy) compared with younger counterparts. Treatment-related deaths occurred in 6% of patients aged more than

70 years and 3% of younger patients ($P = .08$). A recent exploratory subgroup analysis of patients enrolled in 2 randomized trials suggests that survival benefit for bevacizumab added to chemotherapy likely would be limited to patients aged less than 75 years,[51] although the small number of subjects in this subgroup precludes firm conclusions. Considering the weight of evidence, panelists agreed that, outside of a clinical trial, clinicians should exercise judgment when administering bevacizumab to patients aged more than 75 years with advanced NSCLC.

On the basis of the results of randomized phase III trials, pemetrexed and erlotinib have been approved as maintenance treatment for patients without progression after first-line treatment.[47] As a general rule, panelists agreed that elderly patients without progression after first-line platinum-based chemotherapy should not be excluded from maintenance treatment with pemetrexed, erlotinib, or bevacizumab (the latter for patients who received it as part of first-line treatment) on the basis of age alone. Detailed subgroup analysis of elderly patients enrolled in the randomized trials exists for pemetrexed alone.[52] In the PARAMOUNT trial, pemetrexed as continuation maintenance after achieving stability or response on frontline cisplatin/pemetrexed produced comparable survival and toxicity profiles in the elderly and nonelderly subgroups. Elderly patients experienced similar levels of mild and moderate toxicities, but a higher incidence of grade 3/4 anemia and neutropenia than nonelderly patients, although this did not result in increased rates of febrile neutropenia.

A currently ongoing French trial (Maintenance vs. Observation After inDuction Chemotherapy in Non-progressing Elderly Patients With Advanced Non-small-Cell Lung Cancer, ClinicalTrials.gov Identifier NCT01850303) is testing the efficacy of maintenance with pemetrexed or gemcitabine versus observation in elderly patients without progression after 4 cycles of carboplatin plus paclitaxel.

Molecular Testing and Use of Targeted Agents in Elderly Patients With Advanced NSCLC

Regardless of age, patients with advanced nonsquamous NSCLC (and never smokers independently of their histologic subtype) should be tested for EGFR mutation.[53] According to current guidelines, an EGFR TKI should be the first-line treatment for patients with EGFR mutation-positive tumors.[47] To date, no direct comparison between the available EGFR TKIs (gefitinib, erlotinib, afatinib) has been reported. Subgroup analysis of randomized trials comparing 1 TKI with platinum-based combination chemotherapy showed no relevant interaction between treatment efficacy and age.[54-57] Furthermore, all available evidence shows that TKIs are characterized by better tolerability compared with platinum-based chemotherapy, and panelists agreed that these drugs should be considered the standard option for elderly patients with EGFR mutation-positive advanced NSCLC.

Regardless of age, patients with advanced nonsquamous NSCLC also should be tested for ALK rearrangement.[53] This rearrangement is relatively more common in younger patients than in elderly patients: the median age in the pivotal phase I trial was 51 years.[58] Likewise, patients aged more than 65 years represented only 14% of the patients enrolled in the randomized phase III trial comparing crizotinib with pemetrexed or docetaxel as second-line treatment for ALK-positive cases.[59] However, the activity of crizotinib is well documented in elderly patients: in the updated analysis of the phase I trial, the objective response rate was 60.2% in 123 subjects aged less than 65 years and 65.0% in 20 patients aged more than 65 years.[60] On the basis of the available evidence and its acceptable tolerability, crizotinib should be offered to all patients with ALK+ tumors regardless of age, preferably as first-line treatment.[61] Furthermore, crizotinib-resistant patients should be considered for ceritinib, when available, because the latter agent has shown considerable activity, even in patients whose disease has responded to, and then progressed, on frontline crizotinib.[62]

Second-Line Treatment in Elderly Patients With Advanced NSCLC

According to current guidelines, after the failure of first-line treatment, patients with advanced NSCLC should be considered for second-line therapy with chemotherapy (pemetrexed or docetaxel) or erlotinib.[47] There are no trials specifically dedicated to elderly patients in this setting, but subgroup analyses of several trials suggest similar efficacy in this population compared with younger patients.[63,64] Likewise, the analysis of second-line treatment with erlotinib in the French trial comparing first-line carboplatin plus paclitaxel versus single-agents in elderly patients suggested similar efficacy and tolerability compared with data previously obtained in trials not dedicated to elderly patients.[65]

Panelists agreed that the safety profile of drugs registered for second-line treatment can be crucial in therapeutic decision-making in the elderly with advanced NSCLC. Regardless of age, despite differences in progression-free survival, the majority of trials comparing chemotherapy with erlotinib as second-line treatment of advanced NSCLC have not shown a consistent difference in overall survival between the 2 strategies.[66-69]

Conclusions: Issues for Future Clinical Research in Elderly Patients With NSCLC

With the aim of prioritization for clinical research in the treatment of elderly patients with NSCLC, panel members identified a

Table 4 Research in the Field of Elderly Patients With Advanced NSCLC: Priorities

Issue	Priority
Validation of laboratory markers (eg, inflammatory index, P16-INK4a) for assessment of physiologic age	Medium
Better prediction of noncancer-related mortality	Medium
Better prediction of treatment-related toxicity	High
Better shared decision-making modules for patients and their caregivers	Medium
Research about barriers to access potentially curative treatments	High
Definitive validation of adjuvant chemotherapy, >75 years	Medium
Definitive validation of combined CT-RT for locally advanced disease	Medium
Definitive validation of combination chemotherapy for wild-type advanced NSCLC tailored to different risk categories	High
Strategies to enrich elderly patients enrolment in clinical trials	High
Treatment of octogenarians	High

Abbreviations: CT-RT = chemoradiotherapy; NSCLC = non–small-cell lung cancer.

number of issues (Table 4). As a general rule, in all treatment settings, prospective data produced by clinical research focused on elderly patients would substantially improve the opportunity for evidence-based decisions.

Several laboratory markers (eg, inflammatory index, leukocyte telomere length, P16-INK4a) have been proposed to better assess physiologic age.[70-72] Although there is no established role for these laboratory markers in clinical practice at the present time, validation of the independent prognostic role for any of these markers would probably enhance the pretreatment assessment of elderly patients.

A better prediction of noncancer-related mortality (particularly in the early stages of NSCLC, which is characterized by a potentially longer life expectancy compared with the advanced stage) and a better prediction of treatment-related toxicity (in all stages) would greatly facilitate therapeutic selection for elderly patients.[73] Some instruments have been developed (eg, the Chemotherapy Risk Assessment Scale for High-Age Patients score to predict hematologic and nonhematologic toxicity), but these instruments are not widely used in clinical practice. Further research in this field is clearly important.

Moreover, in all stages of disease, some elderly patients receive suboptimal treatment, often due to perception alone, independent of comorbidities.[5] More research focused on barriers to access potentially curative treatments, along with the development of strategies to enrich elderly enrollment in clinical trials, will improve our capacity to inform clinical decisions and potentially reduce the risk of suboptimal treatment. A systematic collection of data from clinical practice, although associated with a lower level of evidence than clinical trials, could help improving the evidence about "gray zones" of research. With the aim of allowing aggregation and analysis of a massive web of real-world cancer care data, the American Society of Clinical Oncology is developing the CancerLinQ initiative. In this program, all patients' data, including CGA for elderly patients, will be fed to a neuron processor, ultimately generating a critical source of unique data correlating patients' characteristics and treatment outcomes obtained from the everyday practice.

Panelists considered the definitive validation of adjuvant chemotherapy in early-stage NSCLC as a medium research priority, especially in those aged more than 75 years. Modified schedules or attenuated doses of platinum-based chemotherapy could be investigated in the adjuvant setting in prospective trials specifically designed for elderly patients.[74] The definitive validation of combined chemo-radiotherapy for elderly patients with locally advanced disease would be useful for clinical practice. A relevant issue for clinical research dedicated to elderly patients with advanced NSCLC is the definitive validation of combination chemotherapy, eventually tailored to different risk categories. The MILES-3 and MILES-4 phase III randomized trials both test the addition of cisplatin to gemcitabine or pemetrexed as first-line treatment of patients aged more than 70 years; these trials are currently ongoing.[46] Finally, evidence-based data for tailored strategies for patients aged more than 80 years, who are frequently excluded from most trials, would be useful in all stages of disease.

Clinical Practice Points

- Although the formal role of comprehensive geriatric assessment for therapeutic decision-making remains uncertain, all cancer patients older than 70 years should have some form of assessment of physiologic age, including estimate of mortality risk and prediction of toxicity.
- Despite concerns regarding the reproducibility of the results of pivotal randomized trials to elderly NSCLC patients, age itself should not be a contraindication for adjuvant chemotherapy in fit patients treated in clinical practice.
- Elderly patients with locally advanced NSCLC should be considered for combined chemo-radiotherapy. Fit elderly patients might benefit from concurrent treatment, if the risk of significant toxicity is acceptable to the patient. Elderly patients who are judged ineligible for concurrent chemo-radiotherapy might be considered for sequential treatment.
- Regardless of age, patients with advanced non-squamous NSCLC, and those who have never smoked independently of their histologic subtype, should be tested for Epidermal Growth Factor Receptor mutation and Anaplastic Lymphoma Kinase rearrangement.
- In elderly patients with advanced NSCLC, carboplatin plus paclitaxel prolonged overall survival compared with single-agent gemcitabine or vinorelbine, albeit with increased toxicity. In fit selected patients, other carboplatin-based or cisplatin-based regimens are feasible, but randomized trials specifically showing survival prolongation in elderly patients are lacking. In unfit elderly patients, single-agent third-generation drugs are recommended.
- Clinicians should exercise judgment when administering bevacizumab to advanced NSCLC patients older than 75 years.
- Elderly patients without progression after first-line platinum-based chemotherapy should not be excluded from maintenance treatment on the basis of age alone.

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