

# Non-Small Cell Lung Cancer Therapy in the Elderly

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**Abstract:** To date, lung cancer is still the leading cause of cancer-related mortality worldwide, with the majority of lung cancers arising in the elderly. As a consequence, we can expect an increase in the number of older lung cancer patients considered suitable for chemotherapy in the near future. Elderly patients often have comorbid conditions and progressive physiologic reduction of organ function, which can make the selection of proper treatment daunting. Some patients will be able to tolerate chemotherapy as well as their younger counterparts, whereas others will experience severe toxicity and require treatment modifications. Thus, a major issue is effectively selecting patients suitable for standard or attenuated therapy. A comprehensive geriatric assessment performed at baseline is a useful tool that can help select the best treatment regimen to be administered to elderly patients. Until now, few trials have specifically focused on elderly patients affected by non-small cell lung cancer (NSCLC), particularly those with advanced disease; prospective elderly-specific studies in early stages are still lacking. High priority should be given to evaluating the role of new targeted therapies. Unfortunately, to date, clinical trials that include functional status and comorbidity as part of the geriatric assessment are rare. Future trials, specifically in the elderly population, should include these kinds of evaluations. The most recent therapies for the treatment of elderly patients with NSCLC will be discussed here.

## Increasing Interest in the Elderly Population

In the United States, between 2004 and 2008, 68% of diagnosed lung cancer cases were in patients over 65 years of age, and approximately 37% were in patients over 75 years.<sup>1</sup> Age-adjusted incidence rates for 2004–2008 reported by the National Cancer Institute Surveillance Epidemiology End Results (SEER) program are 19.4 per 100,000 inhabitants under the age of 65, and 356 among people aged 65 years or older. These data suggest that the median age of

diagnosis is 70 years. More than two-thirds of patients in the United States who die from lung cancer are over 65 years of age.<sup>2</sup> Moreover, in the last decade, the incidence and mortality rates from lung cancer have decreased in patients aged 50 years or younger, but have increased among those aged 70 or older.<sup>3</sup>

Unfortunately, despite the high incidence of non-small cell lung cancer (NSCLC) in older patients, they are frequently underrepresented in clinical trials evaluating new anticancer agents.<sup>4,5</sup> Furthermore, the likelihood of receiving any kind of treatment for NSCLC, particularly chemotherapy, decreases significantly with age.<sup>6,7</sup> This is likely due to a general misconception that older patients are incapable of tolerating the treatment-related toxicities. Indeed, old age is frequently associated with comorbid conditions and the progressive physiologic reduction of organ function, which could negatively impact the degree of toxicity. It has been reported that among individuals aged 65–74 years, the mean number of chronic diseases is 6. The most important coexisting pathologies in lung cancer patients are cardiovascular and pulmonary diseases, which are common in heavy smokers.<sup>8</sup>

Moreover, the expectations for long-term benefits are limited, not only from the perspective of physicians but also from that of patients and their families. Overall, lung cancer in elderly patients is an increasingly common problem that practitioners of oncology must face.

### Cut-Off Age to Define an Elderly Patient

There is no cut-off point at which an adult is considered old. Aging is a highly individualized process, and each change involved in this process cannot be predicted based on chronologic age alone. In clinical practice, biologic age should be considered instead. Unfortunately, to date, laboratory tests and geriatric evaluations are inadequate at defining age. Thus, it is clear that there is an emerging need for developing tools to better evaluate patients' "functional age" rather than their chronologic age. This is especially necessary in the oncology field, where chemotherapy and radiotherapy have substantial side effects. Older patients often have a decrease in bone marrow reserves, renal function, and drug clearance, which increases the risk of treatment-related toxicity. At present, chronologic age should be used as a frame of reference for clinical trials. A cut-off age of 70 years appears to be the most appropriate, since it is considered the lower boundary of senescence, after which the incidence of age-related changes increases.<sup>9</sup>

It should be of interest to individualize treatment choice within a group of elderly lung cancer patients of the same chronologic age by subdividing them into 3 main categories: fit, pre-frail, and frail. To perform such

a categorization, it is important to utilize a comprehensive geriatric assessment. This is a diagnostic procedure that evaluates a patient's global and functional status in order to improve treatment decisions and outcomes. The comprehensive geriatric assessment estimates a patient's functional and mental status, presence of comorbidities, emotional conditions, social support, nutritional status, polypharmacy, and presence or absence of geriatric syndromes.<sup>10</sup> When compared to their younger counterparts, fit older patients have similar prognoses, treatment tolerances, and outcomes.<sup>11–13</sup> Pre-frail patients experience significant treatment-related toxicity and are usually offered a single-agent palliative chemotherapy with adequate best supportive care and specific clinical trials. For frail patients, the third and largest category of patients, only best supportive care or an individualized approach is recommended.<sup>14</sup>

Overall, to optimize treatment of older NSCLC patients, prospective phase III trials should incorporate the use of some form of comprehensive geriatric assessment to evaluate functional status. This approach would allow for the selection of patients suitable for chemotherapy and for more individualized treatment of less fit patients.

### Adjuvant Chemotherapy

There is no standard adjuvant therapy for elderly patients undergoing surgery. Unfortunately, only retrospective data are available in this setting. The influence of age on survival, chemotherapy delivery, and toxicity were evaluated retrospectively in the JBR.10 trial, in which stage IB–II NSCLC patients who were radically resected were randomized to 4 cycles of adjuvant cisplatin plus vinorelbine or control.<sup>15</sup> An analysis of median overall survival (OS) by age revealed a trend favoring the young in both univariate (hazard ratio [HR] for death, 0.77;  $P=.084$ ) and multivariate analyses (HR for death, 0.75;  $P=.059$ ). Patients older than 75 years had significantly shorter OS than those 66–74 years (HR for death, 1.95;  $P=.02$ ). However, OS for patients over 65 years was significantly better with chemotherapy versus observation, with a 5-year survival rate of 68% versus 48%, respectively (HR for death 0.61;  $P=.04$ ). The elderly received significantly fewer doses of chemotherapy. Fewer elderly patients completed treatment and more refused treatment than those who were younger ( $P=.03$ ). There were no significant differences in granulocyte-colony stimulating factor (G-CSF) use, hospitalization by age group, or toxicities, except for myalgias and mood alteration, which were more frequent among the younger patients.

A pooled analysis of the effect of age on adjuvant cisplatin-based chemotherapy was reported.<sup>16</sup> Efficacy and toxicity were compared among 3 age groups: young

(<65 years; n=3,269, 71%), mid-category (65–69 years; n=901, 20%), and elderly ( $\geq$ 70 years; n=414, 9%). No differences in severe toxicity rates were observed among the age groups. Elderly patients received significantly lower first and total cisplatin doses and fewer chemotherapy cycles ( $P<.0001$ ). The hazard ratio for death was 0.86 in the young group (95% confidence interval [CI], 0.78–0.94), 1.01 in the mid-category group (95% CI, 0.85–1.21), and 0.90 in the elderly group (95% CI, 0.70–1.16;  $P=.29$ ). The hazard ratio for event-free survival was 0.82 (95% CI, 0.75–0.90) in the young group, 0.90 (95% CI, 0.76–1.06) in the mid-category group, and 0.87 (95% CI, 0.68–1.11) in the elderly group ( $P=.42$ ). More elderly patients died from non-lung cancer-related causes (12% young, 19% mid-category, 22% elderly;  $P<.0001$ ). The survival benefit from cisplatin-based adjuvant therapy for NSCLC patients was not significantly different according to age.

Overall, despite the lack of prospective data and based on the few retrospective studies, adjuvant cisplatin-based chemotherapy should not be withheld from elderly patients with NSCLC purely on the basis of age. Rather, it should be administered to elderly patients who are in very good clinical condition with no main comorbidities, who have a very good post-surgery time, and who have received only a lung lobectomy.

### Therapeutic Approaches in Locally-Advanced Disease

Currently there is no standard therapeutic approach employed in elderly patients affected by locally advanced NSCLC. Only several prospective studies have investigated the role of combined chemoradiotherapy in this setting. A phase III trial randomly assigned stage III NSCLC patients over 70 years of age to either radiotherapy or radiotherapy plus concurrent daily carboplatin. This trial was terminated early because of 4 deaths due to treatment toxicity (1 in the radiotherapy alone arm and 3 in the radiotherapy plus carboplatin arm). Only 46 patients were treated, reporting an OS of 14.3 months with radiotherapy alone versus 18.5 months with chemotherapy plus radiotherapy.<sup>17</sup>

A retrospective analysis examined the relationship between patient age and outcome in a phase III trial that evaluated 2 different schedules of radiation therapy (twice-daily versus once-daily) with concurrent chemotherapy in patients with stage III NSCLC. The 2- and 5-year survival rates were 39% and 18% in patients younger than 70 years, compared with 36% and 13% in elderly patients ( $P=.4$ ). Grade 4 or higher toxicity occurred in 62% of patients younger than 70 years, compared with 81% of elderly patients ( $P=.007$ ). Despite increased

toxicity, elderly patients treated with concurrent chemoradiotherapy had survival rates equivalent to younger individuals.<sup>18</sup> Another retrospective analysis evaluated the outcomes of 166 patients aged 65 years or older who were enrolled in 2 phase III trials for stage III NSCLC. The first trial included 3 arms: once-daily versus twice-daily radiotherapy alone versus concurrent chemotherapy plus twice-daily radiotherapy. The second trial included 2 arms comparing concurrent chemotherapy with either once-daily or twice-daily radiotherapy. The chemotherapy arms in both trials included etoposide and cisplatin. A total of 37 patients received radiotherapy alone, and 129 patients received concurrent chemoradiotherapy. The OS and the 5-year survival rate were 10.5 months and 5.4% compared with 13.7 months and 14.7%, respectively ( $P=.05$ ). As expected, patients who received combined therapy experienced significantly greater grade 3 or higher toxicity than those receiving radiotherapy alone (89.9% vs 32.4%;  $P<.01$ ).<sup>19</sup>

Overall, the lack of consistent data specifically addressed to elderly patients reserved the aggressive concurrent chemoradiotherapy approach for only selected fit patients with unresectable disease, good performance status, and minimal weight loss.

### Chemotherapy in the General Elderly Population With Advanced Disease

A third-generation, single-agent, chemotherapeutic approach is the best choice in unselected elderly patients with advanced NSCLC. This standard of care originates from 4 phase III randomized trials specifically evaluating elderly patients (Table 1).<sup>20–24</sup> ELVIS (Elderly Lung Cancer Vinorelbine Italian Study) was the first randomized phase III trial ever performed in elderly patients with advanced NSCLC. A total of 191 elderly patients were randomized, and single-agent vinorelbine improved quality of life and OS compared to best supportive care alone (OS, 27 vs 21 weeks;  $P=.04$ ).<sup>20</sup> A randomized, phase III trial compared 2 single agents (vinorelbine vs docetaxel), demonstrating a trend towards higher OS in favor of docetaxel (14.3 vs 9.9 months;  $P=.138$ ). All other outcome measures, specifically progression-free survival (PFS; 5.5 vs 3.1 months;  $P<.001$ ), overall response rate (ORR; 22.7% vs 9.9%;  $P=.019$ ), and disease-related symptoms, were significantly improved with docetaxel compared to vinorelbine. Adverse events were similar between the 2 agents, with the exception of neutropenia, which was more common with docetaxel compared to vinorelbine (83% vs 69%;  $P=.03$ ).<sup>21</sup>

Two randomized phase III trials compared single-agent vinorelbine versus a nonplatinum-based doublet, gemcitabine (Gemzar, Eli Lilly) plus vinorelbine. The first

**Table 1.** Results From Phase III Trials Employing Non-Platinum-Based Therapy in the Treatment of Advanced Non-Small Cell Lung Cancer in Elderly Patients

Author	Age (years)	Regimen	No. pts	OR (%)	Median OS (months)
ELVIS, <sup>20</sup> 1999	≥70	Vinorelbine	76	20	6.5
		vs Best Supportive Care	78	NA	4.8
Fraci, <sup>22</sup> 2000	≥70	Vinorelbine	60	15	4.2
		vs Vinorelbine + Gemcitabine	60	22	6.7
Gridelli, <sup>24</sup> 2003	≥70	Vinorelbine	233	18	8.3
		or Gemcitabine	233	16	6.5
		vs Vinorelbine + Gemcitabine	232	21	6.9
Kudoh, <sup>21</sup> 2006	≥70	Vinorelbine	91	9.9	9.9
		vs Docetaxel	88	22.7	14.3

ELVIS=Elderly Lung cancer Vinorelbine Italian Study; NA=not applicable; OR=overall response; OS=overall survival.

trial reported a survival benefit in favor of the vinorelbine/gemcitabine doublet (OS, 29 vs 18 weeks; 1-year survival, 30% vs 13%;  $P < .01$ ) with no significant differences in toxicity.<sup>22,23</sup> The largest phase III trial, MILES (Multi-center Italian Lung Cancer in the Elderly), failed to yield any benefit for vinorelbine, gemcitabine, or the vinorelbine/gemcitabine doublet in terms of OS (36, 28, and 30 weeks; probability of being alive at 1 year, 38%, 28%, and 30%, respectively) or time to tumor progression (TTP; 18, 17, and 19 weeks, respectively).<sup>24</sup> Toxicity was acceptable in all arms, although it was more pronounced in the combination arm. The discrepancy between these 2 trials could be due to differences in patient sampling.<sup>22,24</sup>

Overall, based on these observations, third-generation, single-agent chemotherapy should be considered a reasonable treatment choice and the standard for comparison in unselected elderly patients with advanced NSCLC. In clinical practice, the decision of what drug to administer to advanced elderly patients with NSCLC should take into account the expected toxicity profile of the agent, pharmacokinetics, organ function, and comorbidities.

### Platinum-Based Chemotherapy in Advanced Disease

The issue of cisplatin- and carboplatin-based therapy for elderly patients with advanced NSCLC has been

addressed in retrospective analyses of large randomized trials, in which treatment outcomes of platinum-based chemotherapy were compared between patients younger and older than 70 years. The small increase in toxicity in the elderly suggested that advanced age alone should not preclude platinum-based chemotherapy. However, elderly patients enrolled in these kinds of trials are not representative of the elderly population as a whole, but rather a small subgroup considered by investigators to be eligible for aggressive treatments.<sup>25</sup>

Prospective clinical trials explored innovative schedules and attenuated doses of the combination of third-generation cytotoxic agents with cisplatin that would be more suitable in the elderly.<sup>25</sup> Among these, the phase I/II trials such as MILES-2P evaluated the efficacy of cisplatin at attenuated doses combined with gemcitabine or vinorelbine in elderly patients with advanced NSCLC.<sup>26</sup> Cisplatin was feasible and active at 60 mg/m<sup>2</sup> with gemcitabine and at 40 mg/m<sup>2</sup> with vinorelbine. With the former combination, 50 of 60 patients (83.3%) were treated without unacceptable toxicity; the ORR was 43.5% (95% CI, 30.6–56.8); median PFS and OS were 25.3 and 43.6 weeks, respectively. With the latter combination, 50 of 61 patients (82.0%) were treated without unacceptable toxicity; the ORR was 36.1% (95% CI, 24.2–49.4); median PFS and OS were 21.1 and 33.1 weeks, respectively. Therefore, the former com-

**Table 2.** Results From Phase III Trials Employing Platinum-Based Therapy in the Treatment of Advanced Non-Small Cell Lung Cancer in Elderly Patients

Author	Age (years)	Regimen	No. pts	OR (%)	Median OS (months)
Biesma, <sup>27</sup> 2011	≥70	Carboplatin + Gemcitabine	90	27	8.6
		vs Carboplatin + Paclitaxel	91	19	6.9
Quoix, <sup>28</sup> 2010	≥70	Gemcitabine or Vinorelbine	226	10.9	6.2
		vs Carboplatin + Paclitaxel	225	29.5	10.3

OR=overall response; OS=overall survival.

bination (cisplatin plus gemcitabine), which provides a higher dose of cisplatin, deserves comparison versus single-agent chemotherapy in this setting of patients within a phase III randomized trial named MILES-3, which has yet to be initiated.

Two phase III randomized trials addressed the question of platinum-based chemotherapy in elderly patients affected by advanced NSCLC (Table 2). In the first study, a total of 182 patients were randomized to receive carboplatin plus gemcitabine or paclitaxel. The doses administered were similar to those given to younger patients. Grade 3/4 toxicity occurred in 75% and 60% of patients treated with carboplatin plus gemcitabine or paclitaxel, respectively. The ORRs were 27% and 19%; PFS was 4.7 and 4.5 months; and median OS was 8.6 and 6.9 months, respectively. The mean global quality of life score at baseline did not differ between the 2 arms, and showed no statistical difference at the 18-week analysis.<sup>27</sup>

Recently, a multicenter, randomized phase III study enrolled patients aged 70–89 years, with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, to receive a 3-weekly single-agent therapy (gemcitabine or vinorelbine) regimen or a 4-weekly combination of carboplatin on day 1 plus paclitaxel on days 1, 8, and 15. In the 313 patients analyzed, median OS, which was the primary endpoint, was significantly longer for patients treated with combination chemotherapy (10.4 vs 6.2 months;  $P < .0001$ ). However, as expected, grade 3/4 hematologic toxicities and treatment-related deaths were significantly more frequent in patients treated with carboplatin and paclitaxel than those treated with single-agent gemcitabine or vinorelbine.<sup>28</sup>

Overall, a platinum-based doublet chemotherapy can be suggested for fit elderly patients (PS 0–1, adequate organ function, no main comorbidities). Moreover, the

schedules investigated in the trials addressed specifically to the elderly are the ones we should look to for use in treatment regimens.

### Targeted Therapies in Advanced Disease

There appears to be a role for targeted therapies, if we consider gefitinib (Iressa, AstraZeneca), an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that can be administered orally and daily in patients with advanced NSCLC who are harboring EGFR mutations.<sup>29</sup> Gefitinib has been investigated specifically in elderly patients unselected for any clinical or molecular factors. The combination of gefitinib with either vinorelbine or gemcitabine was studied in 60 untreated patients aged 70 years or older. Gefitinib combined with gemcitabine showed low activity, but was generally well tolerated. In contrast, toxicity was unacceptable in the vinorelbine arm, in which there were 3 treatment-related deaths, with no ORR reported.<sup>30</sup> The large, phase II, randomized INVITE (IRESSA in NSCLC versus Vinorelbine Investigation in The Elderly) trial compared gefitinib to vinorelbine as first-line treatment in elderly advanced NSCLC patients.<sup>31</sup> Both drugs showed similar efficacy, with a lower toxicity profile and a better quality of life favoring gefitinib.

Erlotinib (Tarceva, Genentech/OSI Oncology), another EGFR-TKI administered orally every day, was investigated in a phase II study in which 80 unselected elderly patients with previously untreated advanced NSCLC reported an ORR of 10%, with stable disease (SD) seen in 41%. There was a significant improvement of key symptoms (dyspnea, cough, fatigue, pain) and median OS, which was 10.9 months. Rash and diarrhea were the most common toxicities, occurring respectively

in 81% and 69% of the patients.<sup>32</sup> A randomized, phase II trial compared vinorelbine to erlotinib as first-line therapy of unselected elderly patients. Preliminary results reported an ORR of 21.6% with erlotinib and 12.8% with vinorelbine, and no differences in terms of TTP between the 2 arms (4.4 vs 3.9 months, respectively).<sup>33</sup>

There really is no role in advanced disease for bevacizumab (Avastin, Genentech), a vascular endothelial growth factor (VEGF) monoclonal antibody inhibitor, due to the lack of prospective data on its use in the elderly population. In fact, the only data available are retrospective and contrasting. Bevacizumab is approved worldwide for first-line treatment in combination with chemotherapy in advanced nonsquamous NSCLC due to a higher incidence of pulmonary hemorrhage reported in squamous histology. A subgroup analysis of older patients ( $\geq 70$  years;  $n=224$ ) in the ECOG 4599 study (Carboplatin Plus Paclitaxel With or Without Bevacizumab) showed a trend towards higher ORR (29% vs 17%;  $P=.067$ ) and higher PFS (5.9 vs 4.9 months;  $P=.063$ ) in favor of the bevacizumab arm, and no difference in median OS (11.3 vs 12.1 months;  $P=.4$ ). On the other hand, a Cox model analysis showed that treatment effects were not different between young and elderly patients ( $P=.34$ ), and that age was not a negative prognostic factor for survival. A noteworthy observation was that older patients experienced significant grade 3 or higher toxicities with the addition of bevacizumab, compared to the paclitaxel/carboplatin doublet. Seven treatment-related deaths were observed among elderly patients treated with the 3-drug combination compared with only 2 deaths in the chemotherapy-alone arm. Furthermore, older patients who received bevacizumab suffered more grade 3 or higher toxicities compared to their younger counterparts.<sup>34</sup>

Another retrospective analysis of the AVAIL (Cisplatin Plus Gemcitabine With or Without Two Different Doses of Bevacizumab) study reported similar survival in all treatment arms, regardless of age, and higher incidence of bleeding-related problems in patients 65 years or older, when compared to younger patients in the placebo and bevacizumab 7.5 mg/kg arms.<sup>35</sup> Finally, a safety analysis in older patients ( $\geq 65$  years;  $n=361$ ) in the open-label SAiL (Safety and Efficacy of First-line Bevacizumab-based Therapy in Advanced Non-squamous Non-small-cell Lung Cancer) study showed no difference in the incidence of serious adverse events between older and younger patients, reporting the same results.<sup>36</sup> Based on the reported results, bevacizumab should be administered in strictly selected elderly patients waiting for ongoing prospective trials such as the EAGLES (Randomised Phase II Trial of Bevacizumab in Combination

With Gemcitabine or Attenuated Doses of Cisplatin and Gemcitabine as First-line Treatment of Elderly Patients With Advanced Non-squamous Non-Small Cell Lung Cancer) study, in which patients aged 70 years or older are randomized to receive cisplatin/gemcitabine with or without bevacizumab.

Further targeted agents were investigated in elderly patients, and among these, cetuximab—an EGFR monoclonal antibody—was studied in a phase II trial called the CALC1-E (Cetuximab in Advanced Lung Cancer study). In this study, cetuximab was given as first-line treatment to define the optimal combination of cetuximab with gemcitabine—either a concomitant (gemcitabine for a maximum of 6 cycles, plus cetuximab until disease progression) or a sequential (gemcitabine for a maximum of 6 cycles, followed by cetuximab) treatment strategy. The primary endpoint, 1-year survival rate, for the concomitant and sequential arms was 41.4% and 31.0%, respectively.<sup>37</sup> Table 3 summarizes the studies of targeted agents in elderly patients with advanced NSCLC.

Overall, to date, the EGFR-TKIs are the only drugs utilized in clinical practice for the treatment of elderly patients affected by advanced NSCLC.

## Second-Line Treatments

Unfortunately, to date, very few data are available for second-line treatment of advanced NSCLC elderly patients. A retrospective analysis was performed in 86 elderly patients ( $\geq 70$  years) from a total of 571 patients enrolled in a randomized phase III trial comparing second-line pemetrexed to docetaxel. Elderly patients receiving pemetrexed ( $n=47$ ) or docetaxel ( $n=39$ ) had a median OS of 9.5 and 7.7 months, respectively. Elderly patients treated with pemetrexed had a longer TTP (4.6 vs 2.9 months) and a longer median OS (9.5 vs 7.7 months) compared to patients treated with docetaxel (not statistically significant). Pemetrexed produced a more favorable toxicity profile with less febrile neutropenia (2.5% vs 19%;  $P=.025$ ) than seen with docetaxel, and no treatment-related deaths occurred.<sup>38</sup>

A prospective phase II trial investigated docetaxel (days 1–8, every 3 weeks) in 33 elderly patients who had progressed after 1 line of chemotherapy.<sup>39</sup> The ORR was 21.2%, and 12 patients (36.3%) reported SD. The treatment was well tolerated.

Data from studies of new biologic agents in second-line treatment have also been reported. A retrospective analysis of elderly patients ( $\geq 70$  years) from the BR.21 trial was performed. A total of 163 elderly patients (112 on erlotinib, 51 on placebo) of 731 randomized patients

**Table 3.** Studies Employing Targeted Agents in First-Line Treatment of Elderly Patients With Advanced Non-Small Cell Lung Cancer

Author	Type of study	Regimen	Age (years)	No. pts	OR (%)	Median OS (months)
<b>Gefitinib</b>						
Scagliotti, <sup>30</sup> 2004	Phase II, randomized	GEM + Gefitinib	≥70	35	5.7	9.2
		vs VIN + Gefitinib		25	0	12.3
Crinò, <sup>31</sup> 2008	Phase II, randomized	VIN	≥70	99	5.1	HR, 0.98
		vs Gefitinib		97	3.1	
<b>Erlotinib</b>						
Jackman, <sup>32</sup> 2007	Phase II	Erlotinib	≥70	80	10	10.9
Chen, <sup>33</sup> 2009	Phase II, randomized	VIN	≥70	40	12.8	NR
		vs Erlotinib		37	21.6	
<b>Cetuximab</b>						
Gridelli, <sup>37</sup> 2010	Phase II, randomized	GEM + Cetuximab	≥70	29	10.3	6
		vs GEM → Cetuximab		29	10.3	9
<b>Bevacizumab</b>						
Ramalingam, <sup>34</sup> 2008	Retrospective	CBDCA + PAC + BEVA	≥70	111	29	11.3
		vs CBDCA + PAC		113	27	12.1
Leighl, <sup>35</sup> 2010	Retrospective	CDDP + GEM + BEVA 7.5 mg/kg	≥65	89	40	HR, 0.84
		or		103	29	HR, 0.88
		CDDP + GEM + BEVA 15 mg/kg vs CDDP + GEM		112	30	-

BEVA=bevacizumab; CBDCA=carboplatin; CDDP=cisplatin; GEM=gemcitabine; HR=hazard ratio; NR=not reported; OR=overall response; OS=overall survival; PAC=paclitaxel; VIN=vinorelbine.

were evaluated. PFS was 3 and 2.1 months ( $P=.009$ ) and median OS was 7.6 and 5 months ( $P=.67$ ) for erlotinib and best supportive care, respectively. The ORRs were similar between age groups. Elderly patients, compared with younger patients, had significantly more overall and severe (grade 3/4) toxicity (35% vs 18%;  $P<.001$ ), and were more likely to discontinue treatment as a result of treatment-related toxicity (12% vs 3%;  $P<.0001$ ). They also had lower relative dose-intensity (64% vs 82% received >90% planned dose;  $P<.001$ ). Elderly patients treated with erlotinib gained survival and quality of life benefits similar to younger patients, but experienced greater toxicity.<sup>40</sup>

Overall, in clinical practice, the choice of a second-line therapy in elderly patients should be evaluated on a case-by-case basis.

## Conclusion

Research, both molecular and clinical, should continue, and any new advancements are welcome. All of the reported studies clearly demonstrate that chemotherapy treatment is feasible and safe for older NSCLC patients. Age is not a negative predictive factor, and treatment should not be omitted based only on chronologic age, since treatment tolerance and effectiveness are affected by comorbidities. To date, lung cancer is still the leading cause of cancer-related mortality worldwide, and the majority of lung cancers arise in the elderly. Consequently, we can expect an increase in the number of older lung cancer patients considered suitable for chemotherapy in the near future. The therapy in the adjuvant and locally-

advanced settings should be evaluated on an individual basis, and, when possible, the standard approach used for adult patients should be applied. Regarding first-line treatment, prospective data support the use of a third-generation agent as treatment in unselected patients. However, in selected patients, a platinum-based therapy with weekly schedules or attenuated platinum doses should be the main choice. The administration of EGFR-TKIs is mandatory in patients harboring an EGFR mutation in any line of treatment. The selection of second-line therapy should be driven by the characteristics of each patient.

In daily clinical practice, the main characteristic of older NSCLC patients is heterogeneity. Some patients will be able to tolerate chemotherapy as well as their younger counterparts, whereas others will experience severe toxicity and require treatment modifications. Thus, it is important to effectively select patients suitable for standard or attenuated therapy. A useful tool for this selection is to perform a comprehensive geriatric assessment at baseline in order to select the best treatment to administer to each elderly patient. However, to date, clinical trials that include functional status and comorbidity as part of geriatric assessment are still rare. Future trials, specifically those addressed to the elderly, should include these kinds of evaluations.

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