Molecular-targeted therapy for elderly patients with advanced non-small cell lung cancer (Review)

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Abstract. Lung cancer is the most common cause of cancer-related mortality in men and women. Non-small cell lung cancer (NSCLC) represents close to 90% of all lung cancers. When diagnosed, >50% of patients are >65 years old. Through an improved understanding of the molecular mechanisms involved in lung oncogenesis, molecular-targeted approaches have become an essential element for the treatment of patients with NSCLC. As the toxicity profiles of the techniques are definitely more favorable compared with chemotherapy, they are particularly attractive for use in elderly patients, who are potentially more susceptible to the toxicity of systemic oncological therapies. However, studies on the activity of molecular-targeted agents in this aged patient setting are much more limited compared with those in their younger counterparts. In the present review, the literature on molecular-targeted therapy for elderly patients with advanced NSCLC is discussed. It is concluded that bevacizumab should be reserved only for highly select elderly patients with advanced NSCLC when the clinician deems it useful in the face of acceptable toxicities. In elderly patients with advanced epidermal growth factor receptor mutation-positive NSCLC, erlotinib and gefitinib appear to repeat the same favorable performance as that documented on a larger scale in the overall population of patients with activating mutations. A good toxicity profile is also confirmed for active molecules on different pathways, such as crizotinib.

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1. Introduction

The 'elderly' patient with lung cancer treated with cytotoxic chemotherapy has been the subject of several studies that have assumed international importance due to sample size, methodological rigor and impact on clinical practice. Confirmed by evidence-based medicine, these important trials have led to the definition of therapeutic standards validated in this patient subset: The ELVIS study showed the superiority of vinorelbine over placebo (1); the MILES study showed a similar effectiveness between single-agent vinorelbine or gemcitabine, and single-agent efficacy over the combination of vinorelbine plus gemcitabine (2); the MILES 2P study showed better survival for cisplatin plus gemcitabine compared with cisplatin plus vinorelbine (3); the IFCT-0501 study showed survival benefits with carboplatin plus weekly paclitaxel compared with vinorelbine or gemcitabine monotherapy (4); another study showed improved survival with platinum-based adjuvant chemotherapy (5); and in a phase II trial involving elderly patients with advanced-stage small cell lung cancer, the weekly regimen of gemcitabine and docetaxel demonstrated no advantage over standard therapy (6).

The last decade of research in this field has witnessed the emergence of molecular-targeted therapies as an essential element for the treatment of patients with non-small cell lung cancer (NSCLC) (7). The studies on the activity of these novel therapies in the elderly patient with NSCLC are few (8,9), comprising a more fragmented and less numerous casuistry than the experience accumulated in the younger patient (10,11). The majority of significant retrospective data

are obtained by subgroup analysis of elderly patients from the large studies performed without age restriction (12-14). To date, a lower contribution has been provided from prospective studies specifically designed to evaluate the efficacy and safety of molecular-targeted drugs in elderly patients with NSCLC (15-21).

The aim of the present review is to summarize the current data on the efficacy and safety of molecular-targeted therapy in elderly patients with advanced NSCLC.

2. Activity of bevacizumab

Comparing bevacizumab plus carboplatin and paclitaxel with carboplatin plus paclitaxel alone, the elderly subset analysis of the Eastern Cooperative Oncology Group (ECOG) 4599 study showed no statistically significant improvement in objective response rate (ORR), progression free survival (PFS) or overall survival (OS) in 224 patients aged ≥70 years (26% of cases). Grade III-IV adverse events were significantly more frequent in the elderly subjects compared with the younger subjects (87 vs. 61%) (12). Another retrospective analysis was performed on 304 elderly patients aged ≥65 years, out of a total of 1,430 patients enrolled in the AVAiL study, comparing the cisplatin/gemcitabine regimen alone or in combination with two different bevacizumab doses. Adding an antiangiogenic agent extended the PFS time, with no impact on survival and no significant toxicities, as in the younger patients (13).

Similarly, no significant difference was shown in the incidence and severity (grade ≥3) of adverse events and in the outcome for elderly versus younger patients in a safety sub-analysis of bevacizumab in 623 patients aged >65 years who were included in the SAiL study, a phase IV international trial in a broad population of >2,000 patients with advanced NSCLC (22).

Therefore, conflicting retrospective data have been generated; it is possible that the following factors have led to this heterogeneity: A higher median age for the ECOG 4599 cases than the other two studies; difficulty in distinguishing between side-effects caused by bevacizumab (such as hypertension and proteinuria) and complications associated with the disease and/or age; and increased attention by clinicians on the side-effects of bevacizumab, with better management in the most recent studies (23).

The role of maintenance bevacizumab in elderly patients has also been investigated. A multicenter United States study extrapolated data on the elderly from a clinic trial that compared the efficacy and safety of pemetrexed plus carboplatin plus bevacizumab, followed by pemetrexed plus bevacizumab maintenance with paclitaxel plus carboplatin plus bevacizumab, followed by bevacizumab maintenance in patients with advanced NSCLC. There was no OS advantage in any of the age subgroups (≤70, 71-75 and >75 years). The pemetrexed plus bevacizumab maintenance arm exhibited significantly better PFS, but this advantage was lost in patients >70 years, who also suffered from increased toxicity (24).

At the 2013 American Society of Clinical Oncology Annual Meeting, Schuette *et al* presented a German multicenter phase III trial of pemetrexed and bevacizumab versus pemetrexed, bevacizumab and carboplatin as first-line treatment for elderly patients ≥65 years with advanced non-squamous NSCLC. A total of 271 patients were enrolled and the primary endpoint was PFS. The triplet combination was superior to the doublet regimen in terms of median PFS time (6.8 vs. 4.8 months), objective response (44.4 vs. 31.4%) and median OS time (15.2 vs. 11.6 months); in only the small group of patients with an ECOG performance status (PS) of 2, the median OS time was longer for the pemetrexed plus bevacizumab arm (11.5 vs. 3.8 months). Serious adverse events occurred with a similar incidence in the two treatment groups (48.1 vs. 49.2%). Based on those results, the study conclusion placed emphasis on the significant impact of the triplet regimen on survival in elderly patients, with the median OS time of 15.2 months being in accordance with the most favorable results observed in this subset in the general population. The addition of carboplatin is recommended for eligible patients. However, in patients with an ECOG PS of 2, the administration of carboplatin must be carefully reviewed (25).

Despite its known toxicity, bevacizumab has been frequently used in clinical settings where the risk/benefit ratio has not been thoroughly evaluated prior to market entry and the subsequent large-scale use. This methodological problem is more clearly highlighted by the use of bevacizumab in colorectal cancer, which is the most dated indication for this drug. In subjects with lung cancer who were >65 years old, bevacizumab-related toxicities were observed in 28% of cases, with cardiovascular and hemorrhagic events being the most common. The elderly subset with lung cancer was more likely to have one or more contraindication to receiving bevacizumab than patients affected by other types of cancer (odds ratio, 1.7) (26). Therefore, it is necessary to extend inclusion criteria of pivotal clinical trials in order to include specific subgroups, such as elderly patients; similarly, it is important to maintain an active monitoring system in the context of pharmacovigilance programs for the detection of safety problems in the 'real world' (26).

Therefore, bevacizumab should be administered only to highly select elderly patients with advanced NSCLC when the clinician deems it useful in the face of acceptable toxicities.

3. Activity of gefitinib and erlotinib

Gefitinib and erlotinib are small molecule tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR), extensively studied in patients with NSCLC (27,28). Although the inhibitors are also used in pretreated and non-selected patients on the basis of EGFR mutational status (11,29-31), these molecules have elective indication for EGFR mutation-positive patients as front-line treatment (32,33).

In a prospective phase II study, erlotinib was evaluated as first-line treatment in 80 patients >70 years of age with previously untreated advanced NSCLC and no selection by EGFR mutation. Erlotinib was associated with a lower incidence of toxicity compared with that observed in elderly patients treated with different chemotherapy regimens; the disease control rate of 51% was encouraging, with an ORR of 10% and disease stabilization in 41% of cases (15).

Another study with anti-EGFR therapy was performed in chemotherapy-naïve, molecularly non-selected elderly patients aged ≥70 years with advanced NSCLC. This randomized phase II study (The INVITE trial) compared gefitinib with

Table I. Randomized trials of molecular-targeted agents for elderly patients with advanced non-small cell lung cancer.

Study name (ref.)	n	Age, years	EGFR status	Treatment arms	Efficacy	Safety
Subset analysis of ECOG 4599 trial (12)	224	≥70	Unknown	Arm 1: Bev+carbo+pac Arm 2: Carbo+pac	Similar ORR, PFS and OS	Higher degree of toxicity with arm 1 compared with younger patients
Subset analysis of AVAiL trial (13)	304	≥65	Unknown	Arm 1: Cis+gem+bev 7.5 mg/kg Arm 2: Cis+gem+bev 15 mg/kg Arm 3: Cis+gem+placebo	Improvement in PFS with bev Similar OS	No significant toxicities with bev
Subset analysis of SAiL trial (22)	623	>65	Unknown	Arm 1: Bev 7.5 mg/kg+chemo followed by bev Arm 2: Bev 15 mg/kg+chemo followed by bev	Similar level of clinical benefit irrespective of age	Similar toxicity compared with younger patients
Socinski *et al*, 2013 (24)	692	≤70	Unknown	Arm 1: Pem+carbo+bev followed by pem+bev	No overall survival advantage in any of the age subgroups	
	247	≥70	Unknown	Arm 2: Pac+carbo+bev followed by bev	Longer PFS in arm 1 only for patients ≤70 years old	Higher degree of toxicity compared with younger patients
Schuette *et al*, 2013 (25)	271	≥65	Unknown	Arm 1: Bev+pem followed by bev±pem Arm 2: Bev+pem+carbo followed by bev±pem	Improvement in ORR, PFS and OS with arm 2	Acceptable toxicity with arm 2
Jackman *et al*, 2007 (15)	80	≥70	Unknown	Single-arm: Erlotinib	Encouraging disease control rate	Good tolerance
INVITE trial (16)	196	≥70	Unknown	Arm 1: Gefitinib Arm 2: Vinorelbine	Similar ORR, PFS and OS	Better tolerability with arm 1
NEJ 003 trial (17)	31	≥75	Positive	Single-arm: Gefitinib	Strong antitumor activity	Mild toxicity
Takahashi *et al*, 2013 (18)	20	≥70	Positive	Single-arm: Gefitinib	Strong antitumor activity	Mild toxicity
Tateishi *et al*, 2013 (34)	55	≥75	Positive	Single-arm: Gefitinib	Strong antitumor activity	Good tolerance
Fujita *et al*, 2012 (19)	22	≥70	Positive	Arm 1 with EGFR mutations: Gefitinib Arm 2 without EGFR mutations: Gem or vinorelbine	Improvement in ORR and OS with arm 1	Better tolerability with arm 1
	32	≥70	Negative			
GFPC 0505 trial (20)	94	≥70	Unknown	Arm 1: Gem followed by erlotinib Arm 2: Erlotinib followed by gem	Modest antitumor activity for both strategies	No major unexpected toxicity for either strategy
BR.21 trial (14)	163	≥70	Unknown	Arm 1: Erlotinib	Similar ORR, PFS and OS between age groups	Higher degree of toxicity with arm 1 in elderly patients
	568	<70	Unknown	Arm 2: Placebo		
Blackhall *et al*, 2013 (35)	199	≥65	Unknown[a]	Single-arm: Crizotinib or Arm 1: Crizotinib Arm 2: Standard chemo	-	Mild and similar toxicity between age groups
	1056	<65	Unknown[a]			
			Unknown[a]			
ZELIG trial (21)	124	≥70	Unknown	Arm 1: Vand+gem Arm 2: Gem+placebo	Improvement in PFS with arm 1 Similar ORR and OS	Acceptable toxicity with arm 1

[a]ALK+. Bev, bevacizumab; carbo, carboplatin; pac, paclitaxel; cis, cisplatin; gem, gemcitabine; pem, pemetrexed; vand, vandetanib; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; chemo, chemotherapy.

Table II. Ongoing clinical trials of molecular-targeted agents for elderly patients with advanced non-small cell lung cancer.

National clinical trial ID numbers (ref.)	Country	Study design	Phase	Treatment arms
NCT00678964 (36)	Germany	Randomized	II	Arm 1: Erlotinib Arm 2: Vinor+carbo
NCT01642017 (37)	France	Non-randomized	I	Single-arm: Pazop
NCT01684111 (38)	Germany	Non-randomized	I	Single-arm: Ninted+vinor
NCT01683682 (39)	Germany	Non-randomized	I	Single-arm: Ninted+vinor+carbo
NCT01077713 (40)	Italy	Randomized	II	Arm 1: Bev+gem Arm 2: Bev+gem+cis

Vinor, vinorelbine; carbo, carboplatin; pazop, pazopanib; ninted, nintedanib; bev, bevacizumab; cis, cisplatin.

vinorelbine as first-line treatment; activity (ORR, 3.1% with gefitinib vs. 5.1% with vinorelbine) and efficacy parameters (PFS time of 2.7 months and OS time of 6 months for gefitinib vs. 2.9 and 8 months for vinorelbine, respectively) showed no significant differences between treatments. Grade 3 to 5 adverse events were more frequently observed in the vinorelbine arm (42%) compared with the gefitinib arm (13%). The merits of this trial are the perspective design specifically aimed at elderly patients and sample sizes; however it does not add relevant elements to clinical practice, such as not taking into account the EGFR mutational status (16).

The initial experiences in elderly patients with advanced EGFR mutation-positive NSCLC are beginning to be reported in the literature. A small study was performed with gefitinib as first-line treatment in 31 patients aged ≥75 years with NSCLC harboring EGFR mutations. The results were quite similar to those most widely reported for the younger population, with an objective response of 74% and an overall disease control rate of 90% (17).

Limited experience was gained in a Japanese study conducted with gefitinib as first-line treatment in 20 patients aged ≥70 years with non-squamous NSCLC harboring EGFR mutations. The ORR was 70%, the disease control rate (complete response, partial response and stable disease) was 90% and the median PFS time was 10 months; the functional assessment of a cancer therapy-lung cancer subscale questionnaire recorded a significant improvement in the first four weeks of treatment, particularly for dyspnea and cough (18).

Another Japanese study reported a retrospective analysis of the efficacy and tolerability of first-line gefitinib in 55 NSCLC patients aged ≥75 years with EGFR activating mutations. Activity (ORR, 72.7%) and efficacy parameters (PFS, 13.8 months; OS, 29.1 months) associated with the safety profile and easy management of toxic effects confirmed the role of gefitinib as the first choice treatment for elderly patients with advanced EGFR mutation-positive NSCLC (34).

A further Japanese study confirmed the activity of gefitinib in this subset of patients, tailoring treatment according to EGFR mutation status. A total of 57 chemotherapy-naïve patients aged ≥70 years with advanced NSCLC were enrolled. Of these, 3 patients were deemed ineligible. Of the remaining 54 patients, the 22 patients with EGFR mutations were treated with gefitinib, and the 32 patients without mutations received vinorelbine or gemcitabine. In this series, gefitinib showed superiority in terms of objective responses (45.5 vs. 18.8%) and OS time (27.9 vs. 14.9 months) compared with chemotherapy; tolerability was predictably better for anti-EGFR therapy (19).

An innovative scheme for the use of erlotinib was proposed by French researchers. In one series of 97 vulnerable elderly patients with advanced NSCLC who were not selected for by EGFR expression, the activity of weekly gemcitabine followed by erlotinib at disease progression versus the reverse sequence was evaluated. Each strategy proved feasible, but with modest efficacy, producing similar results in terms of OS, and time to first and second progression (20).

The efficacy of erlotinib in second- or third-line treatment was evaluated in a retrospective analysis of 163 elderly patients with advanced NSCLC, selected from a total of 731 patients screened for the BR.21 study. Although at the expense of more severe toxicity (35 vs. 18%), the results in terms of OS survival and quality of life were similar to those of younger patients (14).

This fact draws attention to the accuracy in the evaluation of elderly patients, even in the course of seemingly more manageable therapies such as targeted drugs. In this sense, it is instructive to report the case of an EGFR mutation-positive advanced NSCLC patient treated with first-line erlotinib, who exhibited early progression in the absence of drug-related toxicities; the medical history and pharmacokinetic study revealed co-administration of potential inducers of cytochrome P450 3A4 (in this case, fenofibrate) and a blood level of erlotinib lower than expected. Upon increasing the erlotinib dose, the tumor regression was obtained, demonstrating both how the alleged resistance was indeed drug-related interference, and the importance monitoring the use of polypharmacy, which is more frequently used in elderly patients rather than young patients (41).

In summary, these data confirm the role of gefitinib as a first choice treatment for EGFR mutation-positive advanced non-squamous NSCLC elderly patients, with a favorable toxicity profile.

4. Other molecular-targeted therapies

Crizotinib is an orally administered molecule that is highly active on NSCLC with EML4-ALK translocations, in the first and second line of therapy. The toxicity profile of the drug in

elderly patients in comparison with the rest of the population (<65 vs. ≥65 years) was evaluated by an international multicenter study, presented at the 2013 European Society for Medical Oncology (ESMO) Annual Meeting, retrospectively analyzing data from three studies: Profile 1001 (Phase I, naive or pretreated patients), Profile 1005 (Phase II, pretreated patients) and Profile 1007 (second-line randomized vs. chemotherapy). The total sample consisted of 1,255 patients, of whom 199 (16%) were ≥65 years old. The frequency of grade III-IV adverse events associated with treatment with crizotinib was limited in absolute terms (visual disturbances, diarrhea, peripheral edema and vomiting); although the percentage was higher in patients aged ≥65 years compared with those aged <65 years (15 vs. 7%), this difference was not statistically significant (35).

Vandetanib is a novel orally administered molecule manifesting multikinasic inhibitory activity on EGFR, vascular endothelial growth factor (VEGF) and RET receptors, and showing activity in NSCLC when used alone or in combination with chemotherapy. The drug was recently used in an Italian study to treat 124 patients aged >70 years with advanced NSCLC, in combination with gemcitabine compared with gemcitabine alone (The ZELIG trial) (21). The combination of vandetanib and gemcitabine was significantly superior in terms of PFS compared with gemcitabine alone, whereas there was no difference in objective response and OS; the toxicity profile was similar between the two arms.

The aforementioned randomized trials are summarized in Table I.

5. Ongoing clinical trials

Several research groups are engaged in a series of clinical trials designed specifically to evaluate the role of novel molecules in this subset of patients. Examples of this, taken from browsing the CancerTrials.gov site (accessed October 2, 2013), are as follows: The role of first-line erlotinib is being compared to chemotherapy with carboplatin and vinorelbine in a randomized German study (36); a French pharmacokinetic study is evaluating the role of pazopanib in 'frail' patients (37); nintedanib dose escalation [active multikinase inhibitor of VEGF receptors (VEGFRs), platelet-derived growth factor receptor and fibroblast growth factor receptor) is being evaluated in combination with intravenous vinorelbine (38), or in combination with carboplatin and vinorelbine (39); and in an Italian study, the combination of bevacizumab and gemcitabine, with and without cisplatin is being evaluated (40). Table II summarizes the data of these ongoing clinical trials.

These trials represent just a few examples of studies specifically designed for elderly patients affected by NSCLC and treated with molecular-targeted therapy. However, further studies are required, as in the recent past, the data on elderly patients were extrapolated from numerous studies evaluating novel targeted drugs in the population with no age limit.

6. Conclusion

Clear expansion has been noted in the sector of molecular-targeted therapy for elderly patients with advanced NSCLC, from which a steady stream of novel data from the experience gained in clinical practice and the conclusions of ongoing studies is expected.

Based on these preliminary reports, it can be concluded that bevacizumab in elderly patients with advanced NSCLC should be reserved only for highly select patients for whom the clinician should assess the presence of a favorable risk/benefit ratio. Instead, small molecules inhibiting the EGFR pathway appear to repeat the same favorable performance in the elderly patient as that documented on a larger scale in the overall population of patients with activating mutations. The toxicity profile, definitely more favorable compared with chemotherapy, is also confirmed for active molecules on different pathways, such as crizotinib. This makes them particularly attractive for use in this group of patients who are potentially more susceptible to the toxicity of systemic oncological therapies.

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