Lung Cancer: Targets and Therapy

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REVIEW

Bevacizumab in the treatment of NSCLC: patient selection and perspectives

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Abstract: Non-small-cell lung cancer (NSCLC) represents about 85% of all lung cancers, and more than half of NSCLCs are diagnosed at an advanced stage. Chemotherapy has reached a plateau in the overall survival curve of about 10 months. Therefore, in last decade novel targeted approaches have been developed to extend survival of these patients, including antiangiogenic treatment. Vascular endothelial growth factor (VEGF) signaling pathway plays a dominant role in stimulating angiogenesis, which is the main process promoting tumor growth and metastasis. Bevacizumab (bev; Avastin®) is a recombinant humanized monoclonal antibody that neutralizes VEGF's biologic activity through a steric blocking of its binding with VEGF receptor. Currently, bev is the only antiangiogenic agent approved for the first-line treatment of advanced or recurrent nonsquamous NSCLC in "bev-eligible" patients. The ineligibility to receive bev is related to its toxicity. In the pivotal trials of bev in NSCLC, fatal bleeding events including pulmonary hemorrhage were observed with rates higher in the chemotherapy-plus-bev group. Therefore, in order to reduce the incidence of severe pulmonary hemorrhage, numerous exclusion criteria have been characteristically applied for bev such as central tumor localization or tumor cavitation, use of anticoagulant therapy, presence of brain metastases, age of patients (elderly). Subsequent studies designed to evaluate the safety of bev have demonstrated that this agent is safe and well tolerated even in those patients subpopulations excluded from pivotal trials. This review outlines the current state-of-the-art on bev use in advanced NSCLC. It also describes patient selection and future perspectives on this antiangiogenic agent.

Keywords: bevacizumab, nonsquamous NSCLC, eligibility, safety, subpopulations

Introduction

Lung cancer is the most common cause of cancer-related mortality worldwide. Non-small-cell lung cancer (NSCLC) represents about 85% of all lung cancer cases;[1] the majority of NSCLC patients present with advanced-stage disease at diagnosis, and even if platinum-based doublet chemotherapy has improved the outcome of these patients, prognosis remains poor with a median survival time that does not exceed 10 months.[2] Therefore, in last decade novel targeted therapies have been developed. In 2015, two immune checkpoint inhibitors targeting programmed cell death-1 (PD-1), nivolumab and pembrolizumab, were approved for second-line therapy of NSCLC.[3–6] In 2016, another checkpoint inhibitor targeting program death-ligand 1 (PD-L1), atezolizumab, was approved for the same indication.[7] Moreover, pembrolizumab also received approval in 2016 for first-line NSCLC treatment in patients with high PD-L1-expressing tumors.[8]

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Angiogenesis inhibition is regarded another attractive therapeutic strategy for patients with NSCLC. In 1971, Folkman[9] first suggested that tumor growth was dependent on angiogenesis, a complex process in which new blood vessels form out of preexisting capillaries; the development of hypoxic regions in the tumor promotes the production of proangiogenic factors. The vascular endothelial growth factor (VEGF) signaling pathway plays a dominant role in stimulating tumor angiogenesis.[10] VEGF is overexpressed by most of solid tumors, and circulating levels of VEGF are elevated in many cancers, including lung cancer.[11] These findings have given rise to the development of agents that block the VEGF pathway to limit tumor angiogenesis. Bevacizumab (bev, Avastin) is a recombinant, humanized monoclonal antibody that blocks VEGF.[12] The Eastern Cooperative Oncology Group (ECOG) 4599 study compared the efficacy of carboplatin (carbo)/paclitaxel with or without bev in patients with advanced nonsquamous NSCLC.[13] The addition of bev to paclitaxel and carbo has significantly improved the median overall and progression-free survival (PFS), marking the beginning of a new paradigm for the first-line treatment of advanced or metastatic NSCLC with nonsquamous cell histology in appropriately selected patients.

This review summarizes current data and future perspectives on bev in NSCLC. It also describes evidences of its good safety profile in patient subpopulations previously considered ineligible for bev, underlining that the selection of patients able to receive bev is currently based only on two valid eligibility criteria (NSCLC with nonsquamous histology and no history of clinically significant hemoptysis), considering the lack of valid biomarkers predictive of response to treatment with antiangiogenic therapy.

The role of tumor angiogenesis in NSCLC

Tumor growth and spread is dependent on the formation of new blood vessels out of preexisting capillaries;[9,14] this process, termed tumor angiogenesis, is largely mediated by the hypoxia-inducible factor (HIF)-1α which promotes transcription of proangiogenic genes encoding proteins such as VEGF, basic fibroblast growth factor, angiopoietins, interleukin-8, and placental growth factor, under hypoxic conditions.[15,16] The overexpression of these proangiogenic factors stimulates resident endothelial cells to proliferate and migrate to form new capillary tubes.[17,18] Bone-marrow-derived angiogenic cells are also recruited by tumor-associated stroma.[19]

The VEGF signaling pathway plays a dominant role in tumor angiogenesis. Its consists of five ligands (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor) and three VEGF tyrosine kinase receptors (VEGFR-1, VEGFR-2, and VEGFR-3). VEGFR-2 is the major mediator of VEGF-driven responses in endothelial cells.[20] VEGF is overexpressed by a majority of solid tumors, and circulating levels of VEGF are elevated in many cancer patients, including those with lung cancer.[11] It has been demonstrated that levels of VEGF correlate significantly with increased angiogenesis, poor prognosis, and lymph node metastasis in patients with NSCLC.[21–25] Furthermore, Chen et al[26] have found that microvessel density, an indirect measure of angiogenesis, was higher in NSCLC tumor specimens from patients with advanced-stage than those with early-stage NSCLC, and it was also higher in patients with lymph node metastases than in those with no metastases. In addition, in a recent paper analyzing the role VEGFR2 expression in NSCLC cells lines, it has been shown that VEGF-dependent VEGFR2 activation was relevant in a subset of NSCLC cells and was associated with increased tumor cell proliferation.[27]

Currently, the most established approach for limiting tumor angiogenesis is blockade of the VEGF pathway using monoclonal antibodies or tyrosine kinase inhibitors.

bev in the treatment of NSCLC

bev is a recombinant humanized monoclonal IgG1 antibody comprising amino acid sequences which are about 93% human and 7% murine. It has high affinity in binding with all VEGF-A isoforms circulating in blood and neutralizes VEGF's biologic activity through a steric blocking of its binding with VEGFR.

bev was approved for first-line treatment of bev-eligible patients with advanced nonsquamous NSCLC in combination with chemotherapy according to results of two Phase III trials (Table 1). In the randomized Phase III trial ECOG 4599, 878 patients with recurrent or advanced NSCLC (stage IIIB or IV) were randomized to receive carbo/paclitaxel with or without bev.[13] Chemotherapy was administered every 3 weeks for six cycles and bev was administered at 15 mg/kg every 3 weeks until evidence of disease progression or unacceptable toxicity. Patients with squamous-cell tumors, brain metastases, clinically significant hemoptysis, or inadequate organ function or performance status ECOG >1 were excluded. Improvement of overall survival (OS), PFS and objective response rate (ORR) were observed for the combination of bev and chemotherapy. Specifically, the median survival was 12.3 months in patients treated with chemotherapy plus bev, as compared with 10.3 months in the chemotherapy-alone group (hazard ratio (HR) for death,

Table 1 Pivotal Phase III studies of bev in NSCLC: ECOG4599 and AVAiL

	ECOG 4599[13]	AVAiL[28]
Eligibility criteria		
Diagnoses	Stage IIIB, IV, or recurrent	Stage IIIB, IV, or recurrent
Histology	No predominantly squamous-cell cancer	Only nonsquamous NSCLC
Age	≥18 years	≥18 years
Performance Status	ECOG 0–1	ECOG 0–1
Main exclusion criteria	– Significant hemoptysis – CNS metastases – Hemorrhagic diathesis – Coagulopathy – Therapeutic anticoagulation – Use of aspirin – Uncontrolled hypertension	– Significant hemoptysis – CNS metastases – History of thrombotic or hemorrhagic disorders – Therapeutic anticoagulation – Use of aspirin – Uncontrolled hypertension – Tumors invading or abutting major blood vessels
Treatment arms	Arm 1: bev + carbo + pac Arm 2: carbo + pac	Arm 1: cis + gem + bev 7.5 mg/kg Arm 2: cis + gem + bev 15 mg/kg Arm 3: cis + gem + placebo
Primary endpoint	OS	PFS
Results	Improvement in OS, PFS, ORR with bev	Improvement in PFS and ORR with both doses of bev No significant difference in OS

Abbreviations: bev, bevacizumab; carbo, carboplatin; cis, cisplatin; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; gem, gemcitabine; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; pac, paclitaxel; PFS, progression-free survival.

0.79; p=0.003). The median PFS in the two groups was 6.2 and 4.5 months, respectively (HR for disease progression, 0.66; p<0.001), with corresponding response rates of 35% and 15% (p<0.001). Rates of clinically significant bleeding were 4.4% and 0.7%, respectively (p<0.001). There were 15 treatment-related deaths in the chemotherapy-plus-bev group, including 5 from pulmonary hemorrhage.

In the randomized, placebo-controlled, Phase III trial Avastin in Lung Cancer (AVAiL), 1,043 patients with advanced (stage IIIB, with supraclavicular lymph node metastasis or malignant pleural or pericardial effusion, or stage IV) or recurrent nonsquamous NSCLC were randomized to receive cisplatin (cis) and gemcitabine (gem) for up to six cycles plus low-dose bev (7.5 mg/kg), high-dose bev (15 mg/kg), or placebo every 3 weeks until disease progression.[28] PFS was significantly prolonged with both doses of bev; the HRs for PFS were 0.75 (median PFS, 6.7 vs 6.1 months for placebo; p=0.003) in the low-dose group and 0.82 (median PFS, 6.5 vs 6.1 months for placebo; p=0.03) in the high-dose group compared with placebo. ORRs were 20.1%, 34.1%, and 30.4% for placebo, low-dose bev, and high-dose bev plus cis and gem, respectively. No significant difference in OS was observed, possibly because of high use of efficacious second-line therapies.[29] The rates of ≥ grade 3 hypertension, vomiting, neutropenia, bleeding, and proteinuria were modestly higher in the bev arms than in the placebo arm.

Analyzing the results of five randomized clinical trials (2,252 patients) comparing platinum-based chemotherapy doublets with or without bev in the first-line setting, Lima et al[2] showed that the addition of bev to chemotherapy resulted in a significant improvement in both PFS (absolute benefit of 1.4 months in median) and response rate (RR) (absolute difference of 16%). Moreover, it has been also observed that there is a small homogeneous but significant OS improvement with an 11% reduction in risk of death, but with an estimated absolute benefit of less than 1 month in median survival.

The randomized, open-label, Phase III PRONOUNCE trial compared the efficacy and safety of pemetrexed + carbo followed by pemetrexed (Pem + Cb) with paclitaxel + carbo + bev followed by bev (Pac + Cb + Bev) in patients with advanced nonsquamous NSCLC. The primary endpoint was PFS without grade 4 adverse events (G4PFS). Secondary endpoints included OS, PFS, RR, safety, and tolerability. Pem + Cb did not produce significantly better G4PFS compared with Pac + Cb + Bev. Pem + Cb was not superior in PFS, OS, or ORR compared with Pac + Cb + Bev. Both regimens were well tolerated, although toxicity profiles differed.[30]

The emerging role of pemetrexed in treatment of nonsquamous NSCLC has aroused great interest in evaluating this agent in combination with bev. In the Phase III POINTBREAK trial, 939 patients were randomized to receive pemetrexed– carbo –bev, followed by pemetrexed plus bev in maintenance therapy or paclitaxel– carbo –bev followed by maintenance therapy with bev alone.[31] PFS was statistically significantly longer for pemetrexed– carbo –bev than for paclitaxel– carbo –bev group (6.0 vs 5.6 months; HR,

0.83; 95% confidence interval [CI], 0.71–0.96; p=0.012). Median PFS for the maintenance population was 8.6 months for pemetrexed– carbo –bev and 6.9 months for paclitaxel– carbo –bev groups. However, improvements in PFS did not translate into an OS advantage.

In the Phase III AVAPERL trial, 376 patients received four cycles of chemotherapy with cis, pemetrexed, and bev; those achieving response or stable disease were randomly assigned to maintenance therapy with bev or bev plus pemetrexed. A significant PFS benefit was associated with bev plus pemetrexed maintenance compared with bev alone, and the combination was well tolerated.[32] However, this study had some limitations that should be considered. First, survival data were based on selected patients who were eligible for bev and maintenance therapy. Second, there was no arm with pemetrexed alone as maintenance therapy.

Recently, treatment with dose-dense pemetrexed, gem, and bev demonstrated promising efficacy and manageable safety profile in patients with untreated advanced NSCLC.[33]

Several trials have been designed to define bev's role in maintenance beyond progression and in an adjuvant setting. Nadler et al[34] have retrospectively analyzed US Oncology network's electronic medical records, dividing patients with advanced nonsquamous NSCLC treated from July 2006 through June 2008, in two cohorts based on whether or not they received bev monotherapy to progression (BTP) after completion of first-line chemotherapy plus bev. From the total 498 patients, 403 received first-line chemotherapy plus bev: 154 received BTP, 249 did not. Longer PFS and OS times were observed in patients who received BTP than in those who received no BTP (median OS, 20.9 months vs 10.2 months; median PFS, 10.3 months vs 6.5 months). Therefore, continued VEGF suppression led to more favorable clinical outcomes. According to promising results of this retrospective analysis, the multicenter, open-label, randomized, Phase IIIb AvaALL trial has randomized patients with advanced nonsquamous NSCLC whose disease has progressed after four to six cycles of first-line treatment with bev plus a platinum-based doublet and a minimum of two cycles of bev (monotherapy) maintenance treatment to standard second-line therapy (pemetrexed, docetaxel, or erlotinib) with or without bev. The primary endpoint was OS. Secondary endpoints included the 6-month, 12-month, and 18-month OS rates, PFS, and time to progression at second and third progressive disease, response rate, disease control rates, and duration of response at second and third progressive disease. The study has been completed, but results are not yet available.[35]

The ECOG E1505 study is currently assessing if adjuvant chemotherapy is more effective with or without bev in treating patients with completely resected stage IB–IIIA NSCLC.[36]

About 20% of advanced NSCLC cases harbors somatic mutations in the tyrosine kinase domain of *EGFR* gene. In these patients, the standard first-line treatments are the EGFR-tyrosine kinase inhibitors, such as gefitinib, erlotinib, or afatinib. Most of these patients develop resistance and relapse within about 1 year of initiation of an EGFR-tyrosine kinase inhibitor. Consequently, it is important to develop new combination strategies to delay this resistance. Preclinical data have showed that EGFR and VEGF share a common downstream pathway, suggesting the important role of VEGF in the resistance to EGFR blockade. The combination of erlotinib and bev showed very interesting clinical results. The JO25567 study is an open-label, randomized, multicenter, Phase II study that was conducted in Japan in order to assess the efficacy and safety of the combination of erlotinib and bev compared with erlotinib alone as first-line regimen in patients with nonsquamous NSCLC with activating EGFR mutation-positive disease. Median PFS (primary endpoint) was 16 months with erlotinib plus bev and 9.7 months with erlotinib alone (HR 0.54, 95% CI, 0.36–0.79; log-rank test p=0.0015);[37] the BELIEF study (bev and ErLotinib In EGFR Mut + NSCLC) is the European ongoing equivalent clinical trial.[38]

A randomized, double-blind, placebo-controlled Phase III study (ATLAS) enrolled 1,157 patients with NSCLC (stage IIIB with malignant pleural effusion, stage IV, or recurrent) to receive maintenance bev every 3 weeks with or without erlotinib after four cycles of platinum-based chemotherapy plus bev.[39] The addition of erlotinib to bev significantly improved PFS but not OS. Moreover, during the postchemotherapy phase, there were more adverse events (AEs) overall, more grade 3 and 4 AEs (mainly rash and diarrhea), more serious AEs, and more AEs leading to erlotinib/placebo discontinuation in the bev/erlotinib arm than the bev/placebo arm. A second randomized Phase III trial (the Bevacizumab/Tarceva (BeTa) lung trial) evaluated the addition of erlotinib to bev as second-line therapy in patients with recurrent or refractory NSCLC.[40] The combination therapy significantly improved PFS (3.4 vs 1.7 months; HR, 0.62, 95% CI, 0.52–0.75) and elevated the disease control rate (45% vs 34%) compared with erlotinib alone. However, there was no significant difference in OS between the two groups (9.3 vs 9.2 months; HR, 0.97, 95% CI, 0.80–1.18; p=0.758). In the BeTa trial, 355 (56%) patients were screened for EGFR mutations, and only 30 were positive (12 in the combination group and 18 in

the Erl group). Although the subgroup analysis data indicated a benefit in favor of patients with mutant EGFR compared with those with wild-type EGFR, the difference did not reach significance (p=0.1826). The ongoing randomized Phase III BEVERLY trial is evaluating if the first-line combination of erlotinib plus bev is better in terms of PFS than erlotinib alone in 200 Caucasian patients with NSCLC harboring activating EGFR mutations.[41] The abovementioned randomized trials are summarized in Table 2.

Patient selection and future perspectives

The use of bevis indicated in selected patients only, because of its toxicity. Generally in subjects with NSCLC, it is safe and well tolerated.[42–46] The most common AEs are hypertension, proteinuria, and epistaxis. Infrequent serious AEs include neutropenia complications, thromboembolic events, and pulmonary hemorrhage.

Hypertension appears to be dose dependent and related to increased peripheral vascular resistance induced by microcapillary rarefaction due to the inhibition of proangiogenic factors stimulating resident endothelial cells to proliferate and migrate to form new capillary tubes.[47] Another potential pathogenetic mechanism may be decreased production of nitric oxide induced by bev. Decreased serum levels of nitric oxide cause constriction of the vasculature and a reduction in sodium ion renal excretion, leading to increased blood pressure.[48]

Bleeding in bev-treated patients may be related to inhibition of the endothelial repair processes mediated by VEGF and tumor erosion of vessels.

In order to reduce the incidence of severe hemorrhage, the first randomized clinical trials of bev in NSCLC excluded: 1) subjects with squamous histology; 2) subjects with significant hemoptysis; 3) subjects with tumors invading or abutting major blood vessels or with central tumor localization or with tumor cavitation, based on a radiological assessment; 4) subjects with hemorrhagic disorders or in treatment with anticoagulant therapy; 5) subjects with brain metastases; 6) subjects with ECOG>1; and 7) elderly patients (age ≥75 years). In these last couple of years, the scientific community is speculating if some of these exclusion criteria for bev could be too precautionary or scientifically not so much valid, leading clinicians to inappropriately avoiding the use of bev in patients who might benefit from it.[49,50]

No statistically significant association was found between baseline or on-treatment cavitation tumor and severe pulmonary hemorrhage incidence in bev-treated patients.[50] Similarly, central tumor location has not been shown to be a consistent predictive factor for severe pulmonary hemorrhage in these patients.[51,52]

Major blood vessel infiltration and bronchial vessel infiltration, encasement, and abutting may predict pulmonary hemorrhage. However, their valuation is an individual assessment, and divergence between trained observers may occur even when radiological criteria are standardized. In

Table 2 Randomized Phase III trials of bev in NSCLC

Study name	Treatment arms	Total pts (n) Pts (n) arm 1 Pts (n) arm 2	Outcomes	Safety
ECOG 4599[13]	Arm 1: bev + carbo + pac Arm 2: carbo + pac	878 444 434	Improvement in OS, PFS, ORR with bev HR (95% CI) for OS =0.79 (0.67 to 0.92); p=0.003 HR (95% CI) for PFS =0.66 (0.57 to 0.77); p<0.001 ORR: 15 % (arm 1) vs 35% (arm 2) (p<0.001)	Rates of significant bleeding: 4.4% (arm 1) vs 0.7% (arm 2) 15 treatment-related deaths with bev (5 from pulmonary hemorrhage)
AVAiL[28]	Arm 1: cis + gem + bev 7.5 mg/kg Arm 2: cis + gem + bev 15 mg/kg Arm 3: cis + gem + placebo	1,043 345 351 347	Improvement in PFS and ORR with both doses of bev. Limited follow-up for OS analysis HR (95% CI) for PFS arm 1=0.75 (0.62 to 0.91); p=0.003 HR (95% CI) for PFS arm 2=0.82 (0.68 to 0.98); p=0.03 ORR: 20.1% (arm 3) vs 34.1% (arm 1, p<0.0001) vs 30.4% (arm 2, p=0.0023)	Similar incidence of grade 3 or greater AEs

(*Continued*)

Table 2 (*Continued*)

Study name	Treatment arms	Total pts (n) Pts (n) arm 1 Pts (n) arm 2	Outcomes	Safety
PRONOUNCE[30]	Arm 1: pem + carbo followed by pem maintenance Arm 2: pac + carbo + bev followed by bev maintenance	361 182 179	Similar PFS, OS, and ORR HR (95% CI) for PFS =1.06 (0.84 to 1.35); p=0.610 HR (95% CI) for OS =1.07 (0.83 to 1.36); p=0.615 ORR: 23.6% arm 1 vs 27.4% arm 2 (p=0.414)	Tolerated but differed in their toxicity profiles
POINTBREAK[31]	Arm 1: pem +carbo + bev followed by pem + bev maintenance Arm 2: pac + carbo + bev followed by bev maintenance	939 472 467	Improvement in PFS with arm 1 No significant difference in OS HR (95% CI) for PFS =0.83 (0.71 to 0.96); p=0.012 HR (95% CI) for OS =1.00 (0.86 to 1.16); p=0.949	Tolerated but differed in their toxicity profiles
AVAPERL[32]	bev + cis + pem (induction) if response or stable disease arm 1: bev maintenance arm 2: bev + pem maintenance	376 125 128	Improvement in PFS with arm 2 HR (95% CI) for PFS from random assignment =0.48 (0.35 to 0.66); p<0.001 OS from random assignment: 12.8 months (arm 1), it was not yet reached in arm 2.	No new safety signals were observed
AvaALL[35]	Progressive disease on first-line treatment with 4–6 cycles of bev + platinum-doublet and at least 2 cycles of bev maintenance: Arm 1: bev + standard-of-care (erlo or doce or pem) as second-line treatment Arm 2: Standard of care (erlo or doce or pem) as second-line treatment	487	Results are not yet available	Results are not yet available
ECOG E1505[36]	Arm 1: adjuvant chemotherapy + bev Arm 2: adjuvant chemotherapy	_	This study is ongoing, but not recruiting participants	_
ATLAS[39]	Bev + platinum-doublet (induction) Arm 1: bev maintenance Arm 2: bev + erlo maintenance	1145 373 370	Improvement in PFS but not in OS HR (95% CI) for PFS from random assignment =0.708 (0.580 to 0.864); p<0.001 HR (95% CI) for OS from random assignment =0.917 (0.698 to 1.205); p=0.5341	Higher degree of toxicity with arm 2
BeTa[40]	As second-line therapy: Arm 1: erlo + bev Arm 2: erlo + placebo	636 319 317	PFS and DCR seem to be better in arm 1 but they cannot be defined as significant No significant difference in OS HR (95% CI) for OS =0.97 (0.80 to 1.18); p=0.7583 HR (95% CI) for PFS =0.62 (0.52 to 0.75) DCR: 45% (arm 1) vs 34% (arm 2)	Mild toxicity with arm 1
BEVERLY[41]	As first-line therapy: Arm 1: erlo + bev Arm 2: erlo + placebo	_	This study is currently recruiting participants.	_

Abbreviations: AE, adverse event; bev, bevacizumab; carbo, carboplatin; CI, confidence interval; cis, cisplatin; DCR, disease control rate; gem, gemcitabine; HR, hazard ratio; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; pac, paclitaxel; PFS, progression-free survival; pts, patients.

particular, in the retrospective multicenter study of Barlesi et al,[53] discordance in bev's eligibility decisions among radiologists and oncologists based on 150 chest computed tomography scans from patients with central NSCLC tumors has been demonstrated.

Several studies evaluated safety of bev in patients with NSCLC and brain metastases. In the Phase II PASSPORT trial, addition of bev to various chemotherapy agents or erlotinib in patients with NSCLC and treated brain metastases was found to be safe and related to a low incidence of central nervous system (CNS) hemorrhage.[45] The ATLAS and BeTa trials also included patients with treated brain metastases and recorded a low rate of CNS hemorrhage, similarly.[39,40]

Besse et al[54] conducted a retrospective exploratory analysis using datasets from 17 clinical trials to assess the risk of cerebral hemorrhage in patients with brain metastases treated with bev for various solid tumors. The results of this study suggested that patients with brain metastases from advanced/metastatic breast cancer, NSCLC, renal, and colorectal cancer should not be generally excluded from bev therapy because they present similar risk of developing cerebral hemorrhage, independent of bev therapy.

Recruiting subpopulations either excluded or underrepresented in clinical trials of bev in NSCLC (elderly aged ≥75, patients with ECOG ≥2, and/or patients receiving full-dose anticoagulation therapy), the Phase IV SAiL trial and observational ARIES registry have shown that severe hemorrhage incidence is low and similar to that in Phase III trials patients.[42,55] The observational cohort study ARIES also showed that none of the 67 patients with brain metastasis at baseline developed CNS hemorrhage.[55]

Recently, analyzing the efficacy and safety of bev, pemetrexed, and carbo as induction therapy, followed by maintenance therapy with bev plus pemetrexed in nonsquamous NSCLC patients with or without brain metastases, Stefanou et al[56] concluded that this regimen was effective and well tolerated in advanced NSCLC, whether brain metastases were present or not.

A cost analysis of pemetrexed–platinum with maintenance vs paclitaxel– carbo –bev with maintenance in patients with lung cancer has been performed. Mean total costs per patient per month were significantly lower for pemetrexed–platinum patients compared to paclitaxel– carbo –bev patients in the setting of first-line treatment to progression in lung cancer patients with commercial or Medicare supplemental health insurance.[57]

Conflicting retrospective data have been generated about efficacy and safety of bev in elderly patients with NSCLC. The elderly subset analysis of the ECOG 4599 study showed no statistically significant improvement in ORR, PFS, or OS in 224 patients aged ≥70 years (26% of cases). Grade III–IV AEs were significantly more frequent in the elderly subjects compared with the younger subjects (87% vs 61%).[58] In contrast, in the retrospective analysis performed on 304 elderly patients aged ≥65 years, out of a total of 1,430 patients enrolled in the AVAiL study, improved PFS, with no impact on survival and no significant toxicities, has been documented, as in the younger patients.[59]

Similarly, no significant difference was shown in rates of OS, PFS, and overall AEs among older and younger patient subsets in the SAiL and ARIES studies, with the exception of lower survival rates in patients aged 80 years or above vs those below 80 years of age.[31,60] Moreover, a recent Phase II study has documented the good safety and efficacy of carbo plus weekly paclitaxel with bev as first-line regimen for elderly NSCLC patients.[61] It is possible that the following factors have led to this heterogeneity of results: a higher median age for the ECOG 4599 cases than the other abovementioned studies; difficulty in distinguishing between side effects caused by bev (such as hypertension and proteinuria) and complications associated with the disease and/or age; and increased attention by clinicians to the side effects of bev, with better management in the most recent studies.[62]

Currently, there are no validated predictive biomarkers of response to treatment with bev according to which it could be possible to select patients with nonsquamous NSCLC without targetable molecular abnormality.[63] Potential biomarkers could be circulating levels of short VEGF-A isoforms, expression of neuropilin-1 and VEGFR-1 in tumors and plasma, genetic variants in VEGF-A and VEGFR, and TP53 mutations (which are associated with increased VEGF-A transcript levels).[64] Several recent studies suggest that these biomarkers could correlate with better clinical outcomes in NSCLC patients treated with antiangiogenesis agents.[65–68] These preliminary interesting results merit an additional investigation. Therefore, currently the eligibility for bev in NSCLC is based solely on clinical and histopathological features.

Future clinical developments of bev in NSCLC treatment could include its combination with immunotherapy. This novel approach could have a synergistic effect and enhance the efficacy of both treatments, according to preclinical growing evidence that proangiogenic factors modulate the immune response (both by reducing T-cell infiltration into the tumor microenvironment and through systemic effects on immune-regulatory cell function).[69,70]

Moreover, recent studies have documented that continued VEGF suppression with bev beyond progression on the first-line therapy in patients with nonsquamous NSCLC led to more favorable clinical outcomes when this agent is combined with second-line chemotherapy; positive results have been demonstrated also for bev plus pemetrexed maintenance after first-line chemotherapy with bev, carbo, and pemetrexed. Further well-conducted, large-scale trials are needed to validate these findings. Last, results of trials on efficacy of the addition of bev to adjuvant chemotherapy in patients with completely resected stage IB–IIIA NSCLC and results concerning benefit of first-line combination of erlotinib plus bev instead of erlotinib alone, in patients with NSCL, harboring activating EGFR mutations are still ongoing.

Cellular microRNAs (miRNAs) regulate gene expression through modulation of messenger RNA transcription and are involved in epigenetic regulation, metastasis, and cancer immunity. Recently, Huang et al[71] have evaluated the changes in microRNA profile in lung cancer cell treated with cis and pemetrexed or pemetrexed–ciaplatin with bev. There is a difference of the miRNA profile in these 2 treatment groups suggesting that they may influence the regulation of miRNA, which could be involved in the activity of chemotherapy and development of resistance.

Combretastatin A4-phosphate, fosbretabulin tromethamine, is a vascular disrupting agent that targets tumor vasculature. Combretastatin A4-phosphate plus carbo, paclitaxel, and bev appears to be a tolerable regimen with an acceptable toxicity profile in subjects with advanced NSCLC.[72]

In nonsquamous NSCLC, the efficacy of combination of first-line chemotherapy with onartuzumab, a monovalent monoclonal antibody that binds with the extracellular domain of the MET receptor, has been investigated. Patients with untreated stage IIIB/IV nonsquamous NSCLC, stratified by MET diagnostic status, were randomized to receive onartuzumab (15 mg/kg intravenously every 3 weeks) or placebo in combination with either paclitaxel/platinum/bev (bev cohort), or in combination with platinum/pemetrexed (pemetrexed cohort) with maintenance bev or pemetrexed and onartuzumab/placebo as appropriate. The results of this Phase II study were negative: onartuzumab does not appear to provide any additional clinical benefit when given in combination with current first-line standard-of-care chemotherapy for nonsquamous NSCLC.[73]

Patents for bev will soon expire in Europe and the US, and several bev biosimilars are in development.[74] A physician survey examined barriers to the access of bev in patients with advanced solid tumors and the potential impact of biosimilars. Lack of reimbursement and high out-of-pocket costs were cited as predominant barriers to prescribing and as common reasons for reducing the number of planned cycles. Overall, ~50% of physicians reported they "definitely" or "probably" would prescribe a bev biosimilar, if available. Efficacy and safety data in specific tumor types and lower cost were factors cited that would increase likelihood to prescribe a bev biosimilar.[75]

Conclusion

bev has led to improved clinical outcomes when added to standard first-line chemotherapy in patients with advanced or recurrent nonsquamous NSCLC without targetable molecular abnormality. Innovative combinations of bev and its maintenance beyond disease progression in NSCLC are currently under study.

Eligibility for bev is not affected by patient age, performance status, anticoagulation therapy, and brain metastases. The only absolute contraindications to its use are squamous histology and a history of clinically significant hemoptysis. There are as yet no validated predictive biomarkers of response to treatment with antiangiogenic therapy. Therefore, there is the need for additional translational research to identify those patients who can really benefit from the use of bev, through the identification of specific response markers.

Disclosure

The authors report no conflicts of interest in this work.

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