

Bevacizumab in the treatment of nonsquamous non-small cell lung cancer: clinical trial evidence and experience

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Abstract: Angiogenesis is one of the hallmarks of cancer. Antivascular endothelial growth factor therapy, including bevacizumab, is therefore a major option in targeting angiogenesis, especially for the management of stage IV nonsquamous non-small cell lung cancer patients. This review focuses first on the data from clinical trials available to date regarding efficacy and safety of chemotherapy plus bevacizumab. This review then highlights the current remaining questions related to the use of this drug in daily practice and how the patients might be clinically and radiologically selected. Finally, this review explores the future directions for bevacizumab development in nonsquamous non-small cell lung cancer and for a biological selection of patients with research on predictive biomarkers.

Keywords: angiogenesis, bevacizumab, lung neoplasms, vascular endothelial growth factor

Introduction

Angiogenesis has been studied for a long time [Folkman, 1971] and is now considered as one of the 10 hallmarks of cancer [Hanahan and Weinberg, 2011]. Angiogenesis is the consequence of interactions between the tumor and its environment with many factors involved in the development of this vasculature such as the vascular endothelial growth factor (VEGF), the fibroblast growth factor (FGF) and the platelet-derived growth factor (PDGF). Consequently, treatment strategies have focused on inhibition of one or some of these factors or their receptors [Al-Husein *et al.* 2012]. To date, anti-VEGF therapy has been the most studied strategy to target angiogenesis in non-small cell lung cancer (NSCLC) patients.

This review is focusing on bevacizumab, a monoclonal antibody which blocks the binding of VEGF to its high-affinity receptors. Bevacizumab was the first angiogenesis inhibitor to complete clinical development in NSCLC. After summarizing the clinical trial evidence on this antibody, crucial questions concerning the use of bevacizumab in daily practice will be raised and future directions in anti-angiogenesis therapy will be discussed.

Clinical development of bevacizumab in NSCLC

Bevacizumab is the recombinant humanized version of the murine anti-human VEGF monoclonal antibody A4.6.1 [Presta *et al.* 1997]. A phase Ib clinical trial demonstrated that bevacizumab in combination with cytotoxic chemotherapy was well tolerated with no exacerbation of the expected toxicities of chemotherapy [Margolin *et al.* 2001]. A subsequent randomized phase II study exploring bevacizumab in NSCLC was conducted in the 1990s [Johnson *et al.* 2004]. Chemotherapy-naïve advanced NSCLC patients were randomized between three arms (carboplatin/paclitaxel alone *versus* the same chemotherapy plus bevacizumab 15 or 7.5 mg/kg). The efficacy of the combination was significantly superior to the chemotherapy alone regarding objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) (Table 1). The tolerance was characterized by new safety issues and especially development of hypertension, proteinuria, and bleeding events. Of concern was the occurrence of grade 5 pulmonary hemorrhages predominantly in squamous NSCLC patients who were therefore excluded from the next trials.

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Table 1. Main clinical trials of bevacizumab in previously-untreated patients with advanced NSCLC.

References	Treatment	Bevacizumab (mg/kg)	PFS (months)	OS (months)
Johnson <i>et al.</i> [2004]	CBDCA + TXL ± BEV (6 cycles)	0	4.2	14.9
		7.5	4.3	11.6
		15	7.4 ($p = 0.023$)	17.7 ($p = 0.63$)
Sandler <i>et al.</i> [2006]	CBDCA + TXL ± BEV (6 cycles) ± BEV until progression	0	4.5	10.3
		15	6.2 ($p < 0.001$)	12.3 ($p = 0.03$)
Reck <i>et al.</i> [2009, 2010]	CDDP + GEM ± BEV (6 cycles) ± BEV until progression	Placebo	6.1	13.1
		7.5	6.7 ($p = 0.003$)	13.6 ($p = 0.420$)
		15	6.5 ($p = 0.03$)	13.4 ($p = 0.761$)
Zhou <i>et al.</i> [2015]	CBDCA + TXL ± BEV (6 cycles) ± BEV until progression	Placebo	6.5	17.7
		15	9.2 ($p < 0.001$)	24.3 ($p = 0.0154$)
Zinner <i>et al.</i> [2015]	CBDCA + TXL + BEV (4 cycles) + BEV until progression CBDCA + PEM (4 cycles) + PEM until progression	15	5.49	11.7
		0	4.44 ($p = 0.610$)	10.5 ($p = 1.070$)

BEV, bevacizumab; CBDCA, carboplatin; CDDP, cisplatin; GMZ, gemcitabine; NSCLC, non-small cell lung cancer; OS, overall survival; PEM, pemetrexed; PFS, progression-free survival; TXL, paclitaxel.

Therefore, a first phase III randomized trial (ECOG4599) was conducted, randomizing previously untreated stage IV NSCLC patients between carboplatin/paclitaxel for 6 cycles *versus* the same chemotherapy regimen plus bevacizumab 15 mg/kg until progression [Sandler *et al.* 2006]. The efficacy of the combination was again significantly superior to the chemotherapy alone for ORR, PFS, and OS (Table 1). The safety profile was comparable, with the exception of a decrease in the rate of severe pulmonary hemorrhages, in keeping with the exclusion of squamous NSCLC patients.

Another phase III randomized trial (AVAIL) was also conducted with three specificities [Reck *et al.* 2009]. Firstly, this trial was blinded regarding the use of the bevacizumab; secondly, this trial was based on a 'European' chemotherapy regimen (i.e. cisplatin/ gemcitabine); and thirdly, two different dosages were explored as in the first phase II trial (7.5 and 15 mg/kg). The efficacy of the combination was significantly superior to the chemotherapy alone regarding ORR and PFS (Table 1), but not OS [Reck *et al.* 2010]. The safety profile was as expected.

Altogether, these two phase III studies led to the approval of bevacizumab in combination with first-line platinum-based chemotherapy for stage IV NSCLC patients.

Recently, adding bevacizumab to carboplatin/paclitaxel chemotherapy significantly improved the ORR, PFS and OS in 276 Chinese patients with nonsquamous NSCLC (Table 1) [Zhou *et al.* 2015].

A meta-analysis published in 2013 demonstrated the PFS (HR = 0.72, 95% CI: 0.66–0.79, $p < 0.001$) and the OS (HR = 0.90, 95% CI: 0.81–0.99, $p = 0.03$) benefits of the combination of chemotherapy plus bevacizumab *versus* chemotherapy alone [Soria *et al.* 2013].

Following these phase III trials, two phase IV studies were conducted (SAIL and ARIES) in order to assess the safety profile of the combination of bevacizumab plus chemotherapy in daily practice [Crinò *et al.* 2010; Lynch *et al.* 2014]. These studies confirmed the safety profile of the combination of chemotherapy plus bevacizumab. In addition, a meta-analysis confirmed an increase in neutropenia, febrile neutropenia, proteinuria, hypertension, and hemorrhages [Soria *et al.* 2013].

Recently, a phase III randomized trial (PRONOUNCE) investigated whether first-line chemotherapy with carboplatin/pemetrexed was superior to carboplatin/paclitaxel/bevacizumab in patients with stage IV nonsquamous NSCLC, in terms of progression-free survival without grade 4 toxicity (G4PFS) [Zinner *et al.* 2015]. The study

did not meet its primary endpoint. Median G4PFS was 3.91 months for carboplatin/pemetrexed and 2.86 months for carboplatin/paclitaxel/bevacizumab (HR = 0.85, 90% CI, 0.7–1.04; $p = 0.176$). Moreover, PFS, OS, or ORR did not differ significantly between the arms (Table 1).

Bevacizumab in daily practice

The patients' clinical selection

The patients' selection is based on the characteristics of patients who participated in the proof of concept clinical trials and also the known safety profile of the drug. The European Medicines Agency (EMA) summary of product characteristics highlights the hypersensitivity to the drug and recent pulmonary hemorrhage/hemoptysis (>2.5 ml of red blood) as contraindications to the use of bevacizumab [EMA, 2009]. However, caution is needed and the treatment should be stopped in case of development of: a gastrointestinal perforation, need for a major surgery (interval of 28 days needed), medically significant hypertension that cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy, posterior reversible encephalopathy syndrome, grade 4 proteinuria (nephrotic syndrome), arterial or grade 4 venous thromboembolic reactions, and grade 3 or 4 bleeding (of note, anticoagulation by itself is not a contraindication as patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of grade 3 or above bleeding when treated with a full dose of warfarin and bevacizumab concomitantly).

Obviously, the risk of bleeding into the brain forced clinicians to initially exclude patients with brain metastases from bevacizumab-based strategies. However, a retrospective review from all available data suggested that patients with central nervous system (CNS) metastases are at similar risk of developing cerebral hemorrhage, independent of bevacizumab therapy [Besse *et al.* 2010]. Consequently, patients with CNS metastases from advanced/metastatic breast cancer, NSCLC, and renal and colorectal cancer were not excluded anymore from bevacizumab therapy or clinical trials with anti-VEGF drugs. More recently, two prospective parallel phase II trials assessing carboplatin/paclitaxel/bevacizumab first-line and erlotinib/bevacizumab second-line in stage IV

NSCLC patients with untreated brain metastases were reported (BRAIN trial) [Besse *et al.* 2015]. In this study, only one patient presented with nonfatal intracranial bleeding out of 91 treated patients. In addition, the efficacy of combining anti-VEGF therapy in this patient population led to very encouraging results, notably in the first-line carboplatin/paclitaxel/bevacizumab cohort (median PFS of 6.7 months; median OS of 16.0 months; investigator-assessed overall response rate of 62.7%: 61.2% in intracranial lesions and 64.2% in extracranial lesions). In summary, stage IV NSCLC patients with multiple asymptomatic brain metastases should be considered for bevacizumab therapy.

The patients' radiological selection

In fact, the risk of severe pulmonary hemorrhage was initially possibly related to the presence of a centrally-located or a caveated tumor. However, the definition of a centrally-located tumor (<2 cm of the carina or the main bronchus) was subject to controversy, and the assessment's reproducibility of this criterion was also the subject of concern [Barlesi *et al.* 2010]. Therefore, a large proportion of patients with centrally-located tumors were in fact included in bevacizumab-based studies. Conversely, the definition of a caveated tumor is easy and this criterion is still recognized as an exclusion criterion in ongoing trials.

In summary, no clinical or radiological features (including cavitation and central tumor location) have been shown to be reliable predictive factors for severe pulmonary hemorrhage in bevacizumab-treated patients. Major blood vessel infiltration and bronchial vessel infiltration, encasement and abutting, may predict pulmonary hemorrhage. However, standardized radiological criteria for defining infiltration have not been established [Reck *et al.* 2012].

The role of the maintenance with bevacizumab

No clinical trial assessed the place of bevacizumab maintenance in nonprogressing NSCLC patients after bevacizumab-based induction regimens. Although the biological mode of action of the anti-VEGF therapy, the preclinical data, and the results of clinical trials in other solid tumors [Burger *et al.* 2011] favor the continuation of bevacizumab, there are only retrospective or indirect data in stage IV NSCLC. The retrospective

Table 2. Main clinical trials of maintenance therapy with bevacizumab in patients with advanced NSCLC.

References	Drugs	Median PFS (months)	HR (95% CI)	Median OS (months)	HR (95% CI)
Continuation maintenance					
Lopez-Chavez <i>et al.</i> [2012]	OBS <i>versus</i> BEV (exploratory)	2.8 <i>versus</i> 4.4	0.64 (NR)	11.4 <i>versus</i> 12.8	0.75 (NR)
Barlesi <i>et al.</i> [2013, 2014]	BEV <i>versus</i> BEV/PEM	3.7 <i>versus</i> 7.4	0.48 (0.35–0.66)	13.2 <i>versus</i> 17.1	0.87 (0.63–1.21)
Patel <i>et al.</i> [2013]	BEV <i>versus</i> BEV/PEM	5.6 <i>versus</i> 6.0	0.83 (0.71–0.96)	12.6 <i>versus</i> 13.4	1.00 (0.86–1.16)
Switch maintenance (TKI)					
Johnson <i>et al.</i> [2013]	BEV <i>versus</i> BEV/ERL	3.7 <i>versus</i> 4.6	0.71 (0.58–0.86)	13.3 <i>versus</i> 14.4	0.92 (0.70–1.21)

BEV, bevacizumab; CI, confidence interval; ERL, erlotinib; HR, hazard ratio; NSCLC, non-small cell lung cancer; OBS, observation; OS, overall survival; PEM, pemetrexed; PFS, progression-free survival; TKI, tyrosine-kinase inhibitor.

analysis of the nonprogressing patients included in the ECOG4599 trial showed a significantly better post-induction PFS and OS for patients continuing bevacizumab *versus* patients on observation only (Table 2) [Lopez-Chavez *et al.* 2012]. Furthermore, the retrospective analyses of a USA community-based analysis [Nadler *et al.* 2011] and the SAIL study [Crinò *et al.* 2010] also showed a significantly longer PFS and OS for the patients continuing bevacizumab *versus* patients who did not.

In addition, three prospective studies assessed the role of bevacizumab-based combinations in the maintenance setting. The first one was the ATLAS study that looked at the combination of bevacizumab plus erlotinib [Johnson *et al.* 2013]. The ATLAS study demonstrated a significant improvement in median PFS but not in median OS (Table 2). The second one is the AVAPERL study which assessed the continuation maintenance by bevacizumab plus pemetrexed [Barlesi *et al.* 2013]. The AVAPERL study showed a PFS benefit of an unprecedented magnitude (7.4 *versus* 3.7 months, HR = 0.48, 95% CI: 0.35–0.66) for the nonprogressing patients receiving a continuation maintenance based on bevacizumab plus pemetrexed. The updated analysis of survival outcomes confirmed the significant PFS benefit and showed a survival improvement without reaching statistical significance (Table 2) [Barlesi *et al.* 2014]. The third one is the PointBreak trial randomizing stage IV nonsquamous NSCLC between first-line carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab *versus* carboplatin/paclitaxel/bevacizumab followed

by bevacizumab, with OS as the primary endpoint [Patel *et al.* 2013]. A PFS benefit favored the combined maintenance arm, but no difference was seen for OS in the ITT analysis between these two arms (Table 2). However, when considering only the nonprogressing population after induction, a superiority of the pemetrexed/bevacizumab continuation maintenance arm was suggested.

Future directions

Bevacizumab beyond disease progression?

Nearly all patients treated with bevacizumab in the maintenance setting experience disease progression. Giving the mechanism of action of bevacizumab, there is a scientific rationale to continue the drug beyond progression (and to add a cytotoxic chemotherapy agent or a tyrosine-kinase inhibitor [TKI]), in order to maintain an angiogenesis blockade. This strategy is also supported by the results of ramucirumab (a monoclonal antibody directed against VEGFR2), and nintedanib (a TKI inhibiting VEGFR, PDGFR and FGFR) in the second-line setting [Garon *et al.* 2014; Reck *et al.* 2014]. Indeed, both drugs significantly improved the outcomes of previously-treated patients with NSCLC, when combined with docetaxel. The AvaALL study randomized advanced NSCLC patients with progressive disease after first-line chemotherapy and bevacizumab to continued bevacizumab with second-line (and subsequent lines) chemotherapy *versus* chemotherapy alone [Gridelli *et al.* 2011]. This study completed accrual in 2015, and results are

eagerly awaited to determine the benefits of bevacizumab beyond progression in NSCLC.

In addition, innovative combinations of bevacizumab are currently under study with two French clinical trials, whose results will be reported during the next annual meeting of the American Society of Clinical Oncology (ASCO). First, the IFCT BUCIL phase II trial was aimed to evaluate the following treatment sequence in previously untreated patients with advanced nonsquamous NSCLC: three cycles of cisplatin/pemetrexed/bevacizumab, then bevacizumab maintenance until disease progression; at the time of progression, three additional cycles of cisplatin/pemetrexed/bevacizumab, then bevacizumab/pemetrexed maintenance (EUDRACT 2012-002647-18). Second, the IFCT ULTIMATE phase III study randomized previously treated patients with nonsquamous NSCLC between docetaxel and bevacizumab/paclitaxel (EUDRACT 2012-004524-3).

Bevacizumab in patients with EGFR mutant NSCLC?

TKIs of the Epidermal Growth Factor Receptor (EGFR-TKIs), such as gefitinib [Mok *et al.* 2009], erlotinib [Rosell *et al.* 2012], and afatinib [Sequist *et al.* 2013], are nowadays the standard of care for previously untreated patients with EGFR-mutant advanced NSCLC. Recently, the role of bevacizumab in this population was specifically addressed in a randomized clinical trial comparing erlotinib/bevacizumab with erlotinib alone in the first-line setting [Seto *et al.* 2014]. This Japanese study demonstrated a significant PFS benefit with an addition of bevacizumab to erlotinib compared with erlotinib alone in patients with EGFR mutant NSCLC (median PFS of 16.0 months *versus* 9.7 months; HR = 0.54, 95% CI: 0.36–0.79; $p = 0.0015$). In a European population, combining erlotinib with bevacizumab in previously-untreated patients with EGFR-mutant advanced NSCLC resulted in a median PFS of 13.8 months [Stahel *et al.* 2015]. Based on these results, combinations of bevacizumab with EGFR-TKIs might be the standard of care in the future for the first-line treatment of stage IV EGFR-mutant NSCLC.

Predictive biomarker for bevacizumab efficacy?

To date, no clinically applicable predictive biomarker has been identified for bevacizumab in oncology [Jubb and Harris, 2010]. Predictive

biomarkers that have been investigated comprise physiological parameters such as hypertension, circulating parameters such as VEGF, soluble VEGF receptor or placental growth factor, genetic markers, and functional tumor imaging. Even the prospective ABIGAIL trial, which comprehensively investigated the correlation between plasma biomarkers and clinical outcomes in patients with advanced NSCLC, failed to identify any relation between angiogenic plasma biomarkers (plasma basic FGF, E-selectin, intercellular adhesion molecule-1, placental growth factor, VEGFR1, and VEGFR2) and tumor response to chemotherapy plus bevacizumab [Mok *et al.* 2014]. Only low (*versus* high) baseline levels of VEGF-A (the primary ligand targeted by bevacizumab) were significantly correlated with longer PFS and OS, demonstrating the potential of VEGF-A as a prognostic, or a predictive biomarker, with further investigation warranted.

Conclusion

The recognition of the VEGF pathway as a key regulator of angiogenesis in NSCLC has led to the study of several anti-angiogenic agents. Bevacizumab was the first drug to demonstrate a level of activity that drives OS in the treatment of advanced NSCLC and is now considered as an essential therapeutic component for eligible patients with stage IV nonsquamous NSCLC. However, several questions are still open, including the place of anti-VEGF therapy all along the disease treatment and the identification of predictive biomarkers for efficacy.

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