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Bevacizumab in Non-Small Cell Lung Cancer

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Abstract

Lung cancer continues to be the leading cause of cancer death in Western countries. The median survival time for advanced non-small cell lung cancer (NSCLC) remains poor and chemotherapy is the treatment of choice for most patients with metastatic NSCLC. Platinum-based chemotherapy has long been the standard of care for advanced NSCLC. The formation of new blood vessels (angiogenesis) is needed for the growth and invasiveness of primary tumours, and plays an important role in metastatic growth. Vascular endothelial growth factor (VEGF) has emerged as a key potential target for the pharmacological inhibition of tumour angiogenesis. This review discusses current data and the future potential of bevacizumab, a recombinant humanized monoclonal antibody that binds VEGF, in the treatment of NSCLC.

Results from a phase II study showed that the addition of bevacizumab to the first-line chemotherapy with paclitaxel and carboplatin (CP) may increase the overall survival (OS) and the time to progression in advanced NSCLC. Based on these promising results, a randomized phase III trial compared the combination of bevacizumab with CP versus CP alone in the treatment of advanced non-squamous NSCLC. The combination of CP plus bevacizumab led to a statistically significant increase in median OS and progression-free survival (PFS) compared with CP alone, with a response rate (RR) in the CP arm of 15% compared with 35% in the bevacizumab plus CP arm ($p < 0.001$). More recently, the randomized AVAIL (Avastin in Lung Cancer) study, which evaluated cisplatin with gemcitabine plus bevacizumab in two different dosages versus chemotherapy alone in 1043 patients with recurrent or advanced non-squamous NSCLC, reported a significant increase of PFS, RR and duration of response for both of the bevacizumab-containing arms. Bevacizumab has also been investigated in combination with erlitonib as second-line treatment in two small early phase trials, with interesting results.

Bevacizumab was generally well tolerated in clinical trials; the main treatment-associated adverse events were neutropenia and haemorrhage, especially in the lung, but also at other sites. Several trials that incorporate bevacizumab in combination with new active drugs in NSCLC are ongoing and should further help to define the place of bevacizumab in the therapy of NSCLC.

Non-small cell lung cancer (NSCLC) represents the leading cause of cancer death in Western countries.[1] Approximately 50% of patients have advanced/metastatic disease at diagnosis, and the only treatment option is palliative therapy, with the aim of prolonging overall survival (OS) and improving disease-related symptoms and quality of life (QOL). In 1980, with best supportive care (BSC), the median survival was about 4–6 months and 2-year survival was <5%. In 1995, a meta-analysis of randomized clinical trials indicated that cisplatin-based chemotherapy was able to induce a modest but significant survival advantage over BSC alone in patients with advanced NSCLC.[2] Within the past decade, a number of randomized trials have showed the efficacy, in terms of survival and toxicity profile, of platinum-based therapy combined with third-generation drugs, such as vinorelbine, gemcitabine and taxanes.[3-5]

To identify the best chemotherapy regimen, several randomized phase III trials comparing the different platinum-based doublets have been completed worldwide.[6-9] Schiller et al.[7] compared three chemotherapy regimens (cisplatin plus gemcitabine, cisplatin plus docetaxel, and carboplatin plus paclitaxel) with a standard reference regimen of cisplatin plus paclitaxel. All of these regimens showed a comparable efficacy; no differences in response rate (RR), median and 1-year survival were found among treatment arms, being 17–22%, 7.4–8.1 months and 31–36%, respectively. Only the toxicity profile varied among the different regimens. Therefore, regimens that combine platinum agents plus taxanes, vinorelbine or gemcitabine have been considered the standard option for treatment of advanced NSCLC and four to six cycles should be offered to all patients with a good performance status, aged <70 years and with no significant comorbidities.[10]

Despite the recent advances, by using chemotherapy, the median OS has only improved to about 8 months and 2-year survival to 10–15%. Treatment for cancer is now moving beyond traditional chemotherapy, and with the advent of targeted therapy, much research is focused on developing treatments that are based on inhibiting tumour angiogenesis. Tumours cannot grow beyond 2 mm in diameter without developing a vascular supply, but remain dormant and are unable to metastasize.[11] Angiogenesis, the formation of new blood vessels from existing capillaries, is a crucial step for tumour cell survival, growth and metastasis. Tumours secrete a range of angiogenic factors that favour angiogenesis and, as consequence, their development and metastasis.[11] Angiogenesis is a multi-step process that is stimulated by a number of angiogenic factors and the most important target for antitumour therapy is vascular endothelial growth factor (VEGF). VEGF promotes angiogenesis through several mechanisms, including an increased survival and proliferation of vascular endothelial cells, increased migration and invasion of endothelial cells, and increased permeability of existing vessels; moreover, VEGF is an antiapoptotic signal and may promote tumour invasion and metastasis.[12]

Bevacizumab is a recombinant humanized IgG monoclonal antibody that binds to VEGF and neutralizes its activity. As a humanized monoclonal antibody, bevacizumab has a high degree of specificity, prolonged drug half-life and low immunogenicity (approximately 93% of the amino acid sequence is derived from human IgG_1 and 7% of the sequence is derived from murine antibody). Bevacizumab became the first antiangiogenic agent to be approved for the treatment of cancer by the US FDA. The addition of bevacizumab to standard chemotherapy improved time to progression (TTP) and OS in patients with metastatic colorectal cancer[13] and progression-free survival (PFS) in metastatic breast cancer patients.[14]

The rationale for combining antiangiogenic agents with standard chemotherapy is based on the hypothesis that the simultaneous attack on the major pathways in tumour growth (cell proliferation and neoangiogenesis) may provide better antitumour activity.[15] Furthermore, the antiangiogenic drugs are not expected to contribute to drug resistance, because endothelial cells, the key target of these drugs, are considered to be genetically more stable than tumour cells. Tumour blood vessels are structurally

Table I. Phase II/III trials with chemotherapy ± bevacizumab (BEV) in treatment-naive advanced non-small cell lung cancer patients (pts)

Study	Treatment	Phase (no. of pts randomized)	No. of evaluable pts	RR (%)	Median duration of response (mo)	TTP or PFS (mo)	OS (mo)
Johnson et al.[21]	CP	II (99)	32	31.3	5.2	5.9	14.9
	CP + BEV 7.5 mg/kg/q3w		32	21.9	5.1	4.1	11.6
	CP + BEV 15 mg/kg/q3w		35	40.0	8.2	7.0	17.7
Sandler et al.[22]	CP	III (878)	444	12.9	4.5	4.8	10.3
	CP+ BEV 15 mg/kg/q3w		434	29.0	6.2	6.4	12.3
Manegold et al.[23]	CisG	III (1043)	NA	20	NA	6.1	NA
	CisG + BEV 7.5 mg/kg/q3w			34		6.7	
	CisG + BEV 15 mg/kg/q3w			30		6.5	

CisG = cisplatin plus gemcitabine; **CP =** carboplatin plus placlitaxel; **NA** = not available; **OS** = overall survival; **PFS** = progression-free survival; **q3w** = every 3 weeks; **RR** = response rate; **TTP** = time to progression.

and functionally abnormal, VEGF inhibition generates a normalization of tumour vasculature that creates a better delivery of chemotherapeutic drugs. The role of angiogenesis is well established in the progression of lung cancer, and high microvessel density has been studied as a prognostic factor; the majority of studies support correlation between angiogenic factors, microvessel density and poor prognosis, although their role remains controversial.[16-18] VEGF is expressed in 61–92% of patients with NSCLC.[19,20] This review evaluates the results of clinical trials (independent and sponsored) of bevacizumab plus chemotherapy in NSCLC.

1. Bevacizumab in Chemotherapy-Naive Non-Small Cell Lung Cancer (NSCLC) Patients

1.1 Phase II Trials

A randomized phase II trial[21] evaluated the combination of carboplatin (area under the concentration-time curve [AUC] = 6) plus paclitaxel (200 mg/m^2) without (control arm) or with bevacizumab 7.5 or 15 mg/kg every 3 weeks in 99 patients with advanced/metastatic NSCLC. Study endpoints were efficacy (TTP, RR, OS), safety, and pharmacodynamic and pharmacokinetic analyses (table I and figure 1).

The three arms were well balanced for main prognostic factors, although in the low-dose bevacizumab group, there were more frequent squamous histological type and stage IV patients, while in the high-dose bevacizumab group, more female patients were enrolled. However, the study was not powered to define a relationship between dose of bevacizumab and results. The RR showed a trend towards improved response for patients receiving bevacizumab (40.0% for the high-dose group vs 21.9% for low-dose group vs 31.3% for control group). There were better results in terms of TTP in the high-dose bevacizumab arm compared with the control arm (7.4 vs 4.2 months). In the high-dose bevacizumab arm, median OS was 17.7 months, which was better than the control arm (14.9 months) and the low-dose arm (11.6 months). Nevertheless,

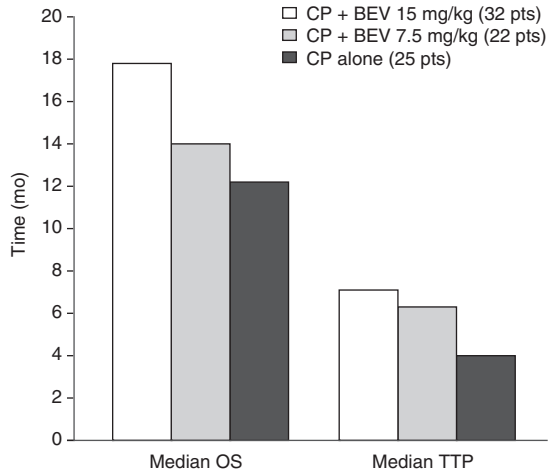

Fig. 1. Results in patients (pts) with non-squamous cell histology in a phase II trial of bevacizumab (BEV).[21] Response rates for carboplatin plus paclitaxel (CP), CP plus BEV 7.5 mg/kg and CP plus BEV 15 mg/kg were 20%, 32% and 50%, respectively. Median time to progression (TTP) was 4, 6.3 (p = 0.29) and 7.1 months (p = 0.01), respectively. Median overall survival (OS) was 12.2, 14.0 (p = 0.32) and 17.8 months (p = 0.57), respectively.

in this trial the median OS in the chemotherapy alone arm was longer than that of published results with carboplatin plus paclitaxel (median OS range 8–9.9 months).[6,8]

A total of 19 patients in the control group with progressive disease were allowed to crossover to receive high-dose bevacizumab monotherapy; in this group, five patients obtained stable disease (SD) for >6 months and survival at 12 months was 47.7%.[21] This better result in median OS may be explained, in part, by the fact that 59% of patients in the chemotherapy alone arm received bevacizumab at progression of disease.

In this study,[21] nine patients died from treatment-related toxicity. The main causes were major haemoptysis, pulmonary haemorrhage, liver failure, *Aspergillus* lung abscess, chronic obstructive pulmonary disease, aspiration pneumonia and sepsis. Haemoptysis occurred in six patients treated with bevacizumab (9%), and in four patients it was fatal. All patients had centrally located tumours close to important blood vessels. The incidence of hypertension was 15.6% and 17.6% in low- and high-dose bevacizumab arms, respectively, and 3.1% with chemotherapy alone. However, grade 3 hypertension (which required new or increased antihypertensive therapy) occurred only in the high-dose bevacizumab arm. Age and hypertension were found to be associated with an increased incidence of proteinuria. Thrombosis (venous and arterial) was slightly increased among the patients receiving bevacizumab (ten vs three events, respectively). Since the association between life-threatening bleeding and squamous cell histology was seen in this study, the authors conducted a retrospective analysis excluding those patients. Data from this analysis confirm that high-dose bevacizumab in combination with carboplatin and paclitaxel improve RR, TTP and OS in patients with advanced NSCLC[21] (figure 1).

At the 2007 American Society of Clinical Oncology (ASCO) meeting, Patel et al.[24] presented the results of a phase II trial in patients with non-squamous NSCLC (stage IIIB/IV) treated with pemetrexed (500 mg/m^2), carboplatin (AUC = 6) and bevacizumab (15 mg/kg) every 21 days. A total of 39 patients of 50 planned were enrolled in this trial; median age was 64 years (range 41–80 years) and 19 patients were female. Approximately 66% of patients completed at least six cycles of chemotherapy. A total of 38 patients were evaluable for response with one complete response and 20 partial response (PR) [RR 55%; 95% CI 43, 75]. There were no grade 4 haematological toxicities, while grade 3 haematological toxicities were anaemia (5%) and thrombocytopenia (3%). Non-haematological toxicity included proteinuria grade 3 (3%), venous thrombosis grade 3 (3%), infection grade 4 (3%) and diverticulitis grade 3–4 (11%). One patient with diverticulitis experienced bowel perforation that required surgical intervention; the presence of diverticulitis was identified as a risk factor for perforation. We concur with Patel et al.[24] that the combination of pemetrexed and carboplatin plus bevacizumab is feasible with an acceptable toxicity profile.

Preliminary results were presented by Davila et al.[25] at the 2006 ASCO meeting using the combination GEMOX (gemcitabine 1000 mg/m^2 plus oxaliplatin 130 mg/m^2) plus bevacizumab (15 mg/kg) in patients with stage IIIB/IV non-squamous NSCLC. They analysed 26 patients of 50 planned: there were 17 male patients, median age was 65 years, 8 patients had a performance status of 0, and 23 had stage IV disease. A total of 22 patients were evaluable for response: 31% obtained a PR and 36% SD. No bleeding complications were reported. One patient died of liver failure after one cycle. Twenty-four patients were evaluable for toxicity: haematological toxicity was minimal (one patient had neutropenia grade 3, one patient had neutropenia grade 3 and piastrinopenia grade 4), but selected non-haematological toxicity was reported (one patient had ischaemic bowel after the first cycle, three patients had diarrhoea grade 3, two patients had nausea/vomiting grade 3).

Groen et al.[26] reported results from a trial that evaluated the combination of bevacizumab (15 mg/kg every 3 weeks) plus erlotinib (150 mg/day) in patients with advanced NSCLC. This trial included

33 patients evaluable for toxicity and 32 for efficacy. The RR was 20% and toxicity (any grade) included rash (32%), diarrhoea (18%), haemorrhage (2.6%), hypertension (2.7%) and thrombosis (2.7%).

1.2 Phase III Trials

The Eastern Cooperative Oncology Group (ECOG) 4599 trial randomized 878 patients with stage IIIB/IV or recurrent NSCLC to receive carboplatin (AUC = 6) plus paclitaxel (200 mg/m^2) every 3 weeks for six cycles alone (control arm) or in combination with bevacizumab 15 mg/kg every 3 weeks until disease progression or unacceptable toxicity.[22] Based on events seen in phase II trials, patients with squamous cell histology, a history of haemoptysis or CNS metastases were excluded from this trial. Both treatment groups were well balanced, but there was a higher proportion of males in the control group. No crossover was allowed at progression; the primary endpoint was OS and secondary objectives were RR, TTP and toxicity (table I).

The addition of bevacizumab led to a statistically significant increase of OS compared with carboplatin plus paclitaxel alone. The median OS was 10.3 months in the control arm and 12.3 in the bevacizumab arm ($p = 0.003$; hazard ratio [HR] 0.79; 95% CI 0.67, 0.92). The median PFS was 4.5 versus 6.2 months ($p < 0.001$; HR 0.66; 95% CI 0.57, 0.77), and the 24-month survival rate was 15% and 23% in control and bevacizumab arms, respectively. Analyzing the survival benefit by considering patient subgroups (e.g. disease stage, weight loss, prior radiotherapy, race, performance status, age, gender), there was a consistent benefit in patients aged >65 years, in patients with weight loss of ≥5% in the 6 months prior to randomization and in males where the histology was not specified. This exploratory analysis can only give some indications that should be verified with *ad hoc* trials. The RR in the control arm was 15% compared with 35% in the bevacizumab arm ($p < 0.001$).[22]

In the arm receiving bevacizumab, the rates of hypertension, proteinuria, bleeding, neutropenia, febrile neutropenia, thrombocytopenia, hyponatraemia, rash and headache were higher than in the control arm. The bleeding events (grade ≥3) were 4.4% in those receiving bevacizumab versus 0.7% in those who did not ($p < 0.001$). The bleeding events were mainly represented by pulmonary haemorrhage, gastrointestinal bleeding, CNS haemorrhage and epistaxis. In 1.9% of patients, these events were fatal versus 0.2% in the control arm. An analysis of clinical and radiographic risk factors was conducted to evaluate possible predictive factors. Although this analysis included a small number of patients, the presence of cavitation in intra-thoracic lesions at baseline and recent haemoptysis were noted as potential risk factors. In the bevacizumab arm, the incidence of grade 4 neutropenia was higher than in the control arm (25.5% vs 16.8%; $p = 0.002$). Grade ≥3 febrile neutropenia was 5.2% in the bevacizumab arm and 2.0% in the control arm, including five fatal cases all in the bevacizumab arm. Patients aged >65 years appeared to be at a greater risk of grade 4 neutropenia, leukopenia, diarrhoea (grade ≥3) and fatigue. Other grade ≥3 toxicities in the bevacizumab and control arms, respectively, included headache (3.0% vs 0.5%), hyponatraemia (3.5% vs 1.1%), hypertension (7.0% vs 0.7%), proteinuria (3.1% vs 0%) and rash (2.3% vs 0.5%). The rate of these adverse events was significantly higher in the bevacizumab arm.

An analysis of this trial that included only patients with performance status 0 or 1 who were aged >70 years reported that, in this subset of patients, the addition of bevacizumab to the carboplatin plus paclitaxel regimen did not improve PFS and OS. The incidence of toxicity and deaths related to the treatment were greater among elderly patients (aged >70 years) compared with younger patients.[27] This result in elderly patients should be verified with the necessary careful patient selection.

The AVAIL (Avastin in Lung Cancer) study evaluated the efficacy of bevacizumab at two doses (7.5 mg/kg or 15 mg/kg every 3 weeks) plus cisplatin (80 mg/m^2 on day 1) and gemcitabine (1250 mg/m^2 on day 1 and 8) every 3 weeks for a maximum of six cycles.[23] This study randomized 1043 chemotherapy-naive patients with inoperable stage IIIB/IV

or recurrent non-squamous NSCLC and no brain metastases to receive control chemotherapy with cisplastin and gemcitabine plus bevacizumab (low or higher dose) or control chemotherapy plus placebo. The primary endpoint was PFS. Both doses of bevacizumab significantly improved PFS versus placebo (low dose 6.7 months, high dose 6.5 months and placebo 6.1 months, p = 0.0004 and p = 0.0125, respectively). A difference in PFS based on geographical region, gender, disease stage, performance status, age, histology and race was noted. RR was 20% in the chemotherapy alone arm, and 34% and 30% in two bevacizumab arms. Although OS data was not presented, the AVAIL study demonstrated a significant increase in PFS for both arms with bevacizumab compared with chemotherapy alone, for both RR and response duration.

The rate of haemoptysis was lower than observed in the ECOG 4599 trial using bevacizumab 15 mg/kg. There were no significant differences in adverse events between the two doses of bevacizumab and placebo. However, there was a more frequent toxicity of grade ≥3 bleeding, hypertension and proteinuria in the bevacizumab arms. Pulmonary haemorrhage was 4.9% for controls, 7% for patients receiving low-dose bevacizumab and 9.7% for patients receiving high-dose bevacizumab. These included fatal haemorrhages in 1.2% of patients in the low-dose bevacizumab arm and 0.9% in the high-dose bevacizumab arm versus 0.3% receiving control. The magnitude of benefit was less evident in the AVAIL trial than in the ECOG 4599 trial, thus bevacizumab may be more effective with some chemotherapy regimens than with others. The AVAIL trial did not clarify the best dosage of bevacizumab (low or high).[22,23]

2. Bevacizumab in Chemotherapy Pretreated Patients

2.1 Phase II Trials

The epidermal growth factor signalling pathway is known to play a pivotal role in cancer cell proliferation. Herbst et al.[28] treated 40 patients with non-squamous stage IIIB/IV NSCLC with the combination of bevacizumab 15 mg/kg every 3 weeks plus erlotinib (100 or 150 mg/day). Median age was 59 years (range 36–72 years) and 21 patients were female. All patients had received one or more prior chemotherapy regimens. Eight patients (20%) had PR and 26 (65%) had SD. The median OS was 12.6 months and PFS was 7 months (table II). The most common toxicities were rash, diarrhoea, infection, haematuria and proteinuria. All adverse events were rarely more than mild to moderate and were easily managed, suggesting that this combination is feasible and well tolerated. No pharmacokinetic interactions were observed between the two agents.

More recently, Herbst et al.[29] reported results from a multicentre, randomized, phase II trial that evaluated the activity of bevacizumab (15mg/kg every 3 weeks) added to erlotinib or chemotherapy (docetaxel or pemetrexed), compared with chemotherapy alone as second-line treatment for advanced non-squamous NSCLC (table II). 122 patients were enrolled. The median PFS for chemotherapy alone, bevacizumab plus chemotherapy and bevacizumab plus erlotinib was 3.0, 4.8 and 4.4 months, respectively; median OS was 8.6, 12.6 and 13.7 months; and the 1-year survival rates were 33.1%, 53.8% and 57.4%, respectively. The improvement in PFS and OS demonstrated an advantage for the combination of bevacizumab with either chemotherapy or erlotinib over chemotherapy alone in the second-line

Table II. Phase II trials with chemotherapy ± bevacizumab (BEV) in pretreated advanced non-small cell lung cancer patients (pts)

Study	Treatment	Phase (no. of pts)	No. of evaluable pts	RR (%)	PFS (mo)	OS (mo)
Herbst et al.[28]	Erlotinib + BEV 15 mg/kg/q3w	I/II (40)	40	20.0	6.2	12.6
Herbst et al.[29]	CT + placebo	III (120)	41	12.2	3.0	8.6
	CT + BEV 15 mg/kg/q3w		40	12.5	4.8	12.6
	Erlotinib + BEV 15 mg/kg/q3w		39	17.9	4.4	13.7

CT = pemetrexed or docetaxel; **OS** = overall survival; **PFS** = progression-free survival; **q3w** = every 3 weeks; **RR** = response rate.

Table III. Ongoing trials with bevacizumab (BEV) in advanced non-small cell lung cancer patients (pts)

Study	Phase	No. of pts planned	Treatment	Endpoints
ATLAS/multicentre in the US[30]	III	1150	CMT + BEV followed by BEV + erlotinib or BEV + placebo	PFS, OS, safety
PASSPORT (brain metastases)[31]	II	110	BEV + CMT, BEV to start no sooner than 4 wk after completion CNS RT	OS, safety
BRIDGE/multicentre in the US[32]	Pilot	40	CP alone followed by CP + BEV followed by BEV alone	PFS, safety

CP = carboplatin plus paclitaxel; **CMT** = chemotherapy; **OS** = overall survival; **PFS** = progression-free survival; **RT** = radiotherapy.

setting, with a 22.4% increase in 1-year survival rate (55.5% vs 33.1%). The RR was 12.2% in chemotherapy alone, 12.5% in the chemotherapy plus bevacizumab arm and 17.9% in bevacizumab plus erlotinib arm. The incidence of severe adverse events was higher in the chemotherapy-containing arms (55% in chemotherapy alone, 41% in bevacizumab plus chemotherapy and 33% in bevacizumab plus erlotinib arms). The incidence of haemorrhage grade ≥3 in bevacizumab-treated patients was 5.1% (four patients) versus one event with chemotherapy alone. There were six treatment-related deaths, three due to pulmonary haemorrhage in bevacizumab arms. Diarrhoea (grade <3), epistaxis (grade <3) and hypertension (all grades) were more frequent in the bevacizumab-containing arms; whereas, anaemia and neutropenia (all grades) were more frequent in the chemotherapy arms. In the bevacizumab plus erlotinib arm, only 13% of patients prematurely withdrew from the trial versus 24% in the chemotherapy alone arm and 28% in the bevacizumab plus chemotherapy arm.

3. Ongoing Trials with Bevacizumab in NSCLC

Preliminary phase II and III trials reported that bevacizumab is generally well tolerated and in combination with chemotherapy significantly increases the clinical outcome (RR, PFS and OS) in patients with non-squamous NSCLC and good performance status. Studies are ongoing to clarify the appropriate use of bevacizumab in NSCLC. Table III illustrates the main ongoing trials with bevacizumab.

At the present, patients with brain metastases and squamous histology are not eligible for bevacizumab treatment. Two trials are ongoing for such patients who have been recandidated to this effective targeted therapy.

PASSPORT[31] is a multicentre US trial that includes patients with stage IV NSCLC with brain metastases or those who have developed brain metastases during or after completion of first-line therapy. This population of patients was excluded from the ECOG 4599 study. The chemotherapy regimens include cisplatin, carboplatin, paclitaxel, vinorelbine, docetaxel, pemetrexed and erlotinib plus bevacizumab (15 mg/kg every 3 weeks) for up to 12 months in the absence of disease progression or unacceptable toxicity. The enrolment begins post radiation therapy of the brain; systemic chemotherapy is allowed to begin >1 week after the end of CNS radiotherapy, while bevacizumab treatment is allowed to begin >4 weeks after the end of CNS radiotherapy.

BRIDGE[32] is a pilot study that evaluates the following three treatment intervals: (i) chemotherapy alone (cycle 1 and 2); (ii) chemotherapy plus bevacizumab (cycles 3–6); and (iii) bevacizumab alone (cycles >7). The chemotherapy used is carboplatin (AUC = 6) and paclitaxel (200 mg/m^2). This trial planned to enrol 40 patients with squamous cell histology, and the primary endpoints are safety and PFS.

Some very interesting clinical trials on the combination of bevacizumab and erlotinib are ongoing.

ATLAS[30] is a phase III trial that is evaluating first-line therapy with bevacizumab (15mg/kg every 3 weeks) plus chemotherapy for four cycles, followed by, as maintenance, bevacizumab plus erlotinib or bevacizumab plus placebo. This study includes patients with NSCLC (stage IIIB with malig-

nant pleural effusion, stage IV or recurrent disease), no prior chemotherapy for metastatic or locally advanced disease, and ECOG performance status 0–1. Patients with a predominant squamous cell histology or treated brain metastases are eligible under protocol-specified circumstances. The primary endpoints are PFS, OS and safety. It is planned to enrol 1150 patients.

The BETA lung trial[33] will evaluate erlotinib alone and in combination with bevacizumab in the second-line treatment of advanced non-squamous NSCLC. The primary endpoint is OS; secondary endpoints are PFS and the identification of an endothelial growth factor receptor marker that may predict outcome and safety.

Another important question is whether to continue bevacizumab after disease progression. The ECOG designed a phase II trial[34] in which patients treated with first-line therapy of platinum-based doublets plus bevacizumab, continue bevacizumab until disease progression. At progression, these patients receive, after randomization, second-line chemotherapy or chemotherapy plus bevacizumab.

Based on the results in advanced NSCLC, some ongoing studies are aimed at extending the benefit of bevacizumab into the adjuvant and neoadjuvant setting. A pilot study[35] of adjuvant bevacizumab in patients with resected IIIA NSCLC is being conducted to assess the safety and feasibility of the addition of bevacizumab to radiotherapy and chemotherapy; bevacizumab is administered with chemotherapy and radiotherapy, and then as maintenance therapy for 1 year. An US Intergroup trial, ECOG 1505, will compare cisplatin-based chemotherapy with cisplatin-based chemotherapy plus bevacizumab for 1 year in patients with resected stage IB, II and III NSCLC. In the BEACON (BEvacizumab And Chemotherapy for Operable NSCLC) trial,[36] patients with stage IB-IIIA NSCLC will receive bevacizumab plus chemotherapy before surgery; postoperatively all patients will receive maintenance bevacizumab for 1 year.

4. Conclusions

Significant improvements in median survival, TTP and QOL have been achieved in recent decades for patients with advanced/metastatic NSCLC by using platinum-based regimens with newer chemotherapy agents, but the long-term outcome is still dismal. However, recently, key molecules involved in signal transduction pathways and angiogenesis have been identified as therapeutic targets.

The combination of the VEGF inhibitor bevacizumab plus chemotherapy has proven to prolong PFS and OS in colorectal cancer, breast cancer and NSCLC.[12] Clinical trials in patients with advanced/metastatic NSCLC have demonstrated a significant advantage in RR, PFS, OS in chemotherapy-naive patients when they received carboplatin, paclitaxel and bevacizumab.[21,22] The ECOG 4599 trial showed about 2–2.5 months' improvement in median survival and about a 10% improvement in 1-year survival for patients treated with bevacizumab plus chemotherapy as compared with chemotherapy alone.[22] The AVAIL trial also confirms these results with an increase of 10–14% in terms of RR and better PFS, although the OS has not yet been presented.[23] The carboplatin plus paclitaxel chemotherapy regimen is more commonly used in the US, while cisplatin plus gemcitabine is more often used in Europe.

Bevacizumab is generally well tolerated with a little increase in the incidence or severity of typical chemotherapy toxicity (haematological adverse events), but adds novel toxicities; indeed, hypertension, thrombosis, proteinuria and bleeding events are more frequent in bevacizumab-treated patients. Concerning the risk of pulmonary haemorrhage in patients that received bevacizumab, Sandler et al.[37] reported a retrospective analysis of baseline risk factors associated with severe pulmonary haemorrhage in phase II and III trials. The number of patients is too small to indicate risk factors; a first hypothesis was that histology may be important, as baseline cavitation of the lung cancer and haemoptysis are markers of increased risk. At present, bevacizumab should be not used in patients with brain metastases and squamous histology.

Ongoing trials are investigating whether these patients can be recandidated to bevacizumab therapy.

Several phase II trails have shown that bevacizumab can be safety administered with erlotinib or other last-generation chemotherapeutic regimens, with very promising antitumour activity, even in second-line treatment. New trials that incorporate active drugs in NSCLC, such as gemcitabine and oxaliplatin, in combination with bevacizumab are ongoing.

Currently, biological and predictive factors for response under bevacizumab are not yet available for the treatment of lung cancer. Moreover, the role of bevacizumab in the adjuvant setting is undefined and its use must be limited to clinical trials. Ongoing trials are attempting to integrate bevacizumab in the treatment of early-stage NSCLC as adjuvant and neoadjuvant therapy (section 3).

Finally, a critical question for future trials is how long to continue treatment with bevacizumab after the bevacizumab plus chemotherapy induction. This is a critical point. At this time, we can suggest that bevacizumab should be given unless is there is progressive disease or toxicities; it is an empirical decision that is not based upon any hard scientific clinical data. Another question is what to do on relapse. Should we continue bevacizumab on relapse plus a new chemotherapy? Should we stop treatment?

A wide array of additional new antiangiogenic agents, in particular small-molecule inhibitors of the VEGF receptor, are also currently in development in combination with chemotherapy (e.g. vatalanib, cediramib [AZD2171], pazopanib [GW786034], sunitinib [SU 11248]) in patients with NSCLC.

In conclusion, these arguments and data suggest the use of bevacizumab in first-line treatment in combination with last-generation chemotherapeutic regimens in patients with advanced or metastatic NSCLC. Further trials are needed to evaluate the optimal dose, schedule and duration of treatment with bevacizumab, in combination with other biological agents or newer chemotherapy in advanced NSCLC, and in the adjuvant setting. Pharmacoeconomic data on the use of bevacizumab plus chemotherapy in lung cancer are not yet available. However, the inclusion of bevacizumab will result in an increase in treatment costs, which highlights the need to accurately identify those patients who will benefit.

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