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Review

The Use of Bevacizumab in Non-Small Cell Lung Cancer: An Update

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Abstract. *Lung cancer is the leading cause of cancer-related death worldwide, with approximately 1.2 million deaths annually. The standard-of-care in patients with advanced disease is platinum-based doublet chemotherapy. Recent advances in the understanding of biological mechanisms of tumor growth have allowed for identification of some molecular targets for cancer treatment, such as vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR). VEGF is a pro-angiogenetic factor, which binds membrane receptors, and whose intra-cytoplasmatic domain presents tyrosine kinase activity. Pathological angiogenesis promotes tumor growth and metastasis. Targeted action against angiogenesis can lead to regression or normalization of neovascular structures and to inhibition of new blood vessel growth. The most commonly used mechanism is mediated by bevacizumab, a monoclonal antibody that selectively binds to VEGF and prevents interaction with its receptor. Currently bevacizumab is the only anti-angiogenic agent approved for the first-line treatment of non-small cell lung cancer (NSCLC) in selected patients. In the present review, we discuss the most important trials that demonstrate the efficacy and safety of bevacizumab. We also present an overview of the types of patients eligible for this treatment and a cost-effectiveness analysis. In conclusion, the possibility of administering a treatment with bevacizumab must be carefully analyzed case by case. It is important to identify those patients who can really benefit from the use of this drug, through the identification of specific response markers.*

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Lung cancer is the leading cause of cancer-related death worldwide, with approximately 1.2 million deaths annually. More than 80% of lung cancer cases are of non-small cell cancer (NSCLC). Approximately 51% of patients present with advanced disease at diagnosis (1).

Currently, the treatment of NSCLC is undergoing significant progress due to the continuous evolution of chemotherapy drugs and the introduction of new targeted agents. However, most patients cannot benefit from the most effective therapeutic combinations because of several factors, such as age, which is often advanced, and their general clinical condition (2). The standard-of-care in patients with advanced disease is platinum-based doublet chemotherapy. Various studies comparing different platinum-based doublets have been conducted, without finding superiority of one schedule with respect to any other. The addition of a third cytotoxic agent increases toxicity and does not provide for additional clinical benefit (3). Even if chemotherapy has improved the outcome and the quality of life of patients, prognosis remains unfavorable, with a median survival time that does not exceed 10 months (1).

Recent advances over the understanding of biological mechanisms of tumor growth have allowed identification of certain molecular targets for cancer treatment. In particular, in NSCLC, we have sharpened knowledge regarding specific growth factors such as vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) (4).

VEGF is a pro-angiogenetic factor which binds membrane receptors, and whose intra-cytoplasmatic domain has tyrosine kinase activity. Angiogenesis is the growth of new microvessels from pre-existing vessels. Many different cells are involved in this process, such as macrophages, endothelial cells and pericytes, and these are coordinated by a fine balance between pro-angiogenic and anti-angiogenic factors (5, 6). Pathological angiogenesis promotes tumor growth and metastasis. (7) Tumor angiogenesis is characterized by the formation of abnormal, tortuous, dilated, poorly-organized vessels with altered permeability (8-10). These vascular abnormalities lead to formation of a

microenvironment characterized by interstitial hypertension, hypoxia and acidosis, with a consequent increased production of VEGF (11, 12).

Targeted action against angiogenesis can lead to regression or normalization of neovascular structures and the inhibition of new blood vessel growth. This can be obtained by acting on the VEGF pathway by inhibiting its ligand or its receptor (13). The most commonly used method uses a monoclonal antibody that selectively binds VEGF and prevents interaction with its receptor. This antibody is called bevacizumab. It is currently indicated in combination with platinum-based chemotherapy in the first-line treatment of unresected, advanced, metastatic or recurrent NSCLC with non-squamous cell histology. (14)

Efficacy Results

Bevacizumab is the only anti-angiogenic agent approved for the first-line treatment of NSCLC in selected patients (13, 14). Bevacizumab efficacy was recently demonstrated in a number of important clinical trials (15-17, 19-22) (Table I).

In 2004, Johnson *et al*. conducted a randomized phase II trial comparing the chemotherapy doublet carboplatin-paclitaxel *versus* the same chemotherapy regimen plus bevacizumab, at a dose of 7.5 or 15 mg/kg. Patients who received high-dose bevacizumab compared to those who received chemotherapy-alone had a higher response rate (RR) (31.5% *vs*. 18.8%), longer time-to-progression (TTP) (74 months *vs*. 4.2 months; p=0.023) and increased overall survival (OS) (17.7 months *vs*. 14.9 months; p=0.63). In this trial, a higher rate of hemoptysis was observed among patients treated with bevacizumab. It was apparently associated with squamous cell histology, cavitated lesions, centrally-located tumors, or close proximity to major blood vessels (15).

In 2006, the Eastern Cooperative Oncology Group (ECOG) conducted a large randomized phase III trial (E4599), enrolling 878 patients with stage IIIB-IV non-squamous NSCLC. Patients were treated with carboplatin-paclitaxel every three weeks for six cycles with or without bevacizumab at 15 mg/kg. Bevacizumab was then administered as maintenance therapy until evidence of disease progression or unacceptable toxicity occurred. In patients treated with bevacizumab overall survival (OS) was significantly longer (12.3 months *vs*. 10.3 months; p=0.003), increased progression-free survival (PFS) (6.2 months *vs*. 4.5 months; p<0.001) and a higher objective RR (35% *vs*. 15%; p<0.001). The experimental regimen was well-tolerated, although more major bleeding episodes were observed than in the control group (4.4% *vs*. 0.7%) (16).

In the phase III AVAiL trial (Avastin in Lung trial), patients were randomized to receive a chemotherapeutic treatment with cisplatin and gemcitabine, with or without bevacizumab at two different doses, 15 mg/kg and 7.5 mg/kg. This study showed a significant improvement in the primary end-point of PFS with the addition of high-dose bevacizumab compared to chemotherapy-alone (6.5 months *vs*. 6.1 months; p=0.03), or by the addition of low-dose bevacizumab (6.7 months *vs*. 6.1 months; p=0.003). The RR in the group of patients receiving high-dose or low-dose bevacizumab or placebo of 30.4%, 34.1% and 20.1% respectively. The results in terms of OS were not statistically significant in the chemotherapy group or in the high-dose bevacizumab group (13.1 months *vs*. 13.4 months; p=0.761), nor in the low-dose bevacizumab group (13.1 months *vs*. 13.6 months; p=0.42) (17). A retrospective analysis on data of this study showed a benefit in terms of PFS using bevacizumab maintenance monotherapy compared to the control group (4.6 months *vs*. 3.2 months), but did not show a benefit in terms of OS (18). Adverse events appeared more frequently in the groups treated with bevacizumab. These were, more frequently, hypertension (7% in the low-dose group and 9% in the high-dose group *vs*. 2% in the control group), proteinuria (2% and 3% *vs*. 0%) and bleeding (4% and 5% *vs*. 2%) (17).

The efficacy of bevacizumab was also studied by Patel *et al*. in a phase II study published in 2009. In that study, patients with NSCLC received a first-line treatment with pemetrexed, carboplatin, and bevacizumab, followed by maintenance therapy with the doublet pemetrexed-bevacizumab. Patel *et al*. enrolled 49 patients and obtained an RR of 55%, a PFS of 7.8 months and an OS of 14.1 months (19). In light of the data from this study, the phase III POINTBREAK trial was conducted, in which 939 patients were randomized into two treatment arms. In the first arm, patients were treated with pemetrexed-carboplatin-bevacizumab, followed by pemetrexed plus bevacizumab in maintenance therapy. In the second arm, patients were, however, treated according to the scheme paclitaxel-carboplatin-bevacizumab followed by maintenance therapy with bevacizumab alone. This study did not reach statistical significance for the primary end-point of OS (12.6 months *vs*. 13.4 months, p=0.949), although in the group treated with pemetrexed and bevacizumab in maintenance therapy, an increased PFS was reported (6 months *vs*. 5.6 months, p=0.012) (20, 21).

Another important phase III trial was AVAPERL, in which after four cycles of chemotherapy with cisplatin, pemetrexed, and bevacizumab, patients were randomized to receive maintenance therapy with bevacizumab alone or with pemetrexed and bevacizumab. This trial showed an advantage over the primary end-point of PFS in the group receiving maintenance therapy with the doublet of drugs (6.6 months *vs*. 10.2 months, p<0.001). There was also an improvement in OS in patients treated with pemetrexed and bevacizumab in maintenance therapy (19.8 months *vs*. 15.9 months; p=0.39), but the result was not statistically significant (22, 23).

Table I. *Results from phase II and III trials of bevacizumab in combination with chemotherapy as first-linetreatment.*

Reference	Phase	Primary endpoint	Regimen	No. of patients	RR (%)	PFS (months)	OS (months)	Maintenance
Johnson *et al*. 2004 (15)	II	TTP	CBDCA + PTX	32	18.8	(TTP) 4.2	14.9	No
			CBDCA + PTX + Bev (7.5 mg/kg)	32	28.1	(TTP) 4.3	11.6	
			CBDCA + PTX + Bev (15 mg/kg)	35	31.5	(TTP) 7.4	17.7	
Patel *et al*. 2009 (19)	II	PFS	CBDCA + Pem + Bev (15 mg/kg)	49	55	7.8	14.1	Yes
Reynolds *et al*. 2009 (32)	II	RR	nabPTX + CBDCA + Bev (15 mg/kg)	50	31	9.8	16.8	No
Sandler *et al*. 2006 (16)	III	OS	CBDCA + PTX	444	15	4.5	10.3	Yes
			CBDCA + PTX + Bev (15 mg/kg)	434	35	6.2	12.3	
Reck *et al*. 2009 (17)	III	OS	CDDP + Gem	327	20.1	6.1	13.1	Yes
			CDDP + Gem + Bev (15 mg/kg)	329	30.4	6.5	13.4	
			CDDP + Gem + Bev (7.5 mg/kg)	330	34.1	6.7	13.6	
Barlesi *et al*. 2011 (22)	III	PFS	CDDP + Pem +Bev (7.5 mg/kg) → Pem+Bev	125	-	10.2	19.8	Yes
			CDDP + Pem + Bev (7.5 mg/kg) → Bev	128	-	6.6	15.9	
Patel *et al*. 2012 (20, 21)	III	OS	CBDCA + Pem +Bev (15 mg/kg) → Pem+Bev	524	-	6	12.6	Yes
			CBDCA + PTX + Bev (15 mg/kg) → Bev	522	-	5.6	13.4	

RR: Response rate; PFS: progression-free survival; TTP: time-to-progression; OS: overall survival; Bev: bevacizumab; CBDCA: carboplatin; CDDP: cisplatin; Gem: gemcitabine; PTX: paclitaxel; TXT: docetaxel; Pem: pemetrexed.

There are also several studies that evaluated the association of bevacizumab with platinum-based doublets in first-line treatment (24-40). Some of these were combined with bevacizumab regimes different from those generally used. For example, Reynolds *et al*. analyzed the association nabpaclitaxel-carboplatin-bevacizumab in a phase II study on 50 patients, obtaining a 50% RR, 9.8 months of PFS and 16.8 months of OS (32).

Interesting studies were recently conducted using bevacizumab in lines subsequent to the first, such as the study of Ohyangi *et al*. who analyzed the association between taxotere and bevacizumab in second line or more, obtaining a disease control rate (DCR) of 96% (41). Habib *et al*., instead, analyzed weekly paclitaxel (80 mg/m^2) in combination with bevacizumab every 21 days until disease progression or unacceptable toxicity in fourth-line treatment or more, obtaining 40% partial responses, 35% stable disease and 25% progression disease (42).

In the ongoing phase IIIb AvaALL trial, bevacizumab is used as maintenance therapy after disease progression. Expected results showed an OS beyond PD of 10.1 months in the experimental arm, receiving bevacizumab plus a second-line agent between pemetrexed, docetaxel or erlotinib, versus 7.9 months in the control arm, receiving only the second-line agent chosed by the investigator (43).

Bevacizumab was studied in combination with erlotinib in a phase II trial conducted by West *et al*. (38), with S-1, an oral fluoropyrimidine, in two studies conducted by Yoshino *et al*. (39) and Kaneda *et al*. (40). In these studies, good results in terms of RR, DCR and PFS were obtained, with an acceptable toxicity profile. These associations, however, require additional clinical trials to confirm the results.

In conclusion, treatment with bevacizumab in selected patients with NSCLC was effective in terms of PFS and OS, although of only a few months. It is also possible to perform a maintenance treatment with bevacizumab, resulting in an advantage in terms of survival and quality of life. Clinical trials are on-going to determine the efficacy of maintenance bevacizumab-alone or in combination with pemetrexed. Furthermore, several studies aim to demonstrate the efficacy of bevacizumab in combination with drugs other than those classically used, or in lines of treatment subsequent to the first. The promising results obtained, however, require for additional clinical studies.

Safety Results

Adverse events most frequently observed during treatment with bevacizumab include hypertension, nephrotic syndrome, bleeding, gastrointestinal perforation, heart failure and neutropenia (44).

Two large cohort studies focused on bevacizumab safety: the SAiL (Safety of Avastin in Lung) and ARIES (Avastin Registry: Investigation of Effectiveness and Safety) trials (45, 46). SAiL was a phase IV trial, performed on 2,212 patients, evaluating the safety of bevacizumab in first-line treatment at a dose of 7.5 mg/kg and 15 mg/kg, in combination with standard chemotherapy for a maximum of six cycles, followed by bevacizumab-alone until disease progression or unacceptable toxicity occurs. Significant adverse events (grade 3 or more) were rare: bleeding was observed in 80 cases (4%), pulmonary hemorrhages in 15 cases (1%), hypertension in 125 cases (6%), proteinuria in 67 cases (3%) and venous thromboembolism in 172 cases (8%) (45).

The ARIES trial was conducted on 1,518 patients with NSCLC, treated with first-line standard chemotherapy in combination with bevacizumab. In the studied population, hypertension was observed in 3.8% of cases, while bleeding of more than grade 3 was observed in 1.9% of cases (gastrointestinal in 1.1% of cases, pulmonary hemorrhage in 0.7% and CNS hemorrhage in 0.1%) (46).

The ATLAS trial on maintenance bevacizumab and erlotinib (47), the PASSPORT trial on bevacizumab in combination with chemotherapy in first- or second-line treatment (48) and the BeTa trial on bevacizumab and erlotinib in second-line treatment (49) included patients with treated brain metastases or in therapy with anti-coagulants. In these three trials, a low rate of adverse events was observed, proving that patients with treated brain metastases or patients taking anti-coagulants could be eligible for treatment with bevacizumab (47, 48). Besse *et al*. in the BRAIN trial enrolled patients affected by NSCLC with untreated and asymptomatic brain metastases. The results obtained showed adverse event rates comparable to those seen in previous studies on bevacizumab (50).

Therefore, we can conclude that bevacizumab is a safe drug with an acceptable toxicity profile. Reck *et al*., in a review published in 2012 in the Annals of Oncology, claim that the only exclusion criteria for treatment with bevacizumab are squamous histology and hemoptysis of grade 2 or more. Central location of the tumor, the presence of a cavitation, anti-coagulant treatment and the presence of brain metastases should not be considered contraindications to treatment with bevacizumab (51).

Patient Selection

The choice of a first-line treatment containing bevacizumab may mean choosing a therapeutic strategy that allows other drugs to be kept for use in successive lines of treatment, such as pemetrexed. Bevacizumab use has also the advantage of giving the patient the possibility of a maintenance therapy with monoclonal antibody alone. This opportunity is feasible if there is evidence of response or stability of disease at the end of first-line therapy. In this way, we can delay the progression of disease and the beginning of a second-line treatment. A therapeutic strategy containing bevacizumab is feasible in selected patients because of the toxicity related to the administration of bevacizumab (1).

The randomized phase II trial conducted by Johnson *et al*. in 2004 showed a high rate (9.1%) of severe pulmonary hemorrhage, fatal in some cases (15). This adverse event was more frequent in patients with tumors with squamous cell histology. Considering that squamous cell tumors are more likely centrally located and cavitated compared to adenocarcinoma, it is not clear whether this histology is an independent risk factor or a marker of increased risk (15). The phase II BRIDGE trial enrolled patients with squamous cell cancer and excluded patients with severe hemoptysis and cavitation. In only 3.2% of cases pulmonary hemorrhage occur. Bevacizumab use in squamous NSCLC remains experimental (52).

In many studies, squamous cell histology, a history of hemoptysis, the presence of thrombophilic or bleeding diathesis and the use of anti-coagulant agents became exclusion criteria for the administration of bevacizumab. With these restrictions, the incidence of bleeding was reduced to about 2% in the AVAiL trial. In that study, approximately 9% of the patients had started anticoagulant therapy during the treatment for the occurrence of deep venous thrombosis (17). In the phase IV SAiL trial, 15% of enrolled patients were receiving anticoagulant therapy (45). The incidence of bleeding in these two studies was similar in patients receiving anticoagulants *versus* those not receiving anticoagulant therapy (17, 45).

A phase II trial conducted by Johnson *et al*. suggested that a central tumor location may be a risk factor for pulmonary hemorrhage in bevacizumab-treated patients (15). Subsequent data do not support this result. For example, in the SAiL trial, the incidence of pulmonary hemorrhage of any grade was 8.1% in patients with central tumors and 8.6% in patients with no central tumor (53). In the the ARIES trial, the rate of grade 3 or more pulmonary hemorrhage was 1.2% in patients with centrally-located tumors compared to 0.5% in patients without central location. However, this result was not significantly associated with central location (54).

Sandler *et al*. in 2009 conducted a retrospective analysis of the E4599 study and they observed that the main risk factor for the occurrence of pulmonary hemorrhage was cavitation of the primary tumor and not central location of the cancer (55). Other data do not show a relationship between cavitation and pulmonary hemorrhage. Cavity formation occurred in approximately 16% of patients with no pre-existing cavitation and was more frequent in patients with squamous cell cancer and current smokers (56). This is due to the central necrosis of lesions after inhibition of angiogenesis (56). In accordance with this observation, hemoptysis was associated with tumor size, but not with cavitation (56).

Another widely analyzed aspect related to the risk of bleeding is that related to the presence of brain metastases, a factor long considered an exclusion criterion for treatment with bevacizumab. On this topic, several clinical trials have been conducted. For example the ATLAS, PASSPORT and BeTa trials included patients with treated brain metastases and recorded a low rate of CNS hemorrhage (47-49). Besse *et al*. published the results of a retrospective analysis conducted on the data of 17 studies on the use of bevacizumab in lung, breast, kidney and colorectal cancer in patients with untreated brain metastases. This retrospective

analysis showed that the use of bevacizumab in patients with brain metastases does not increase risk of bleeding (57). Besse *et al*. also conducted the phase II non-comparative BRAIN trial, enrolling patients with untreated brain metastases. In that study, they registered a rate of CNS hemorrhage comparable to that of previous bevacizumab studies, in which the presence of untreated brain metastases was an exclusion criterion (50).

Moreover, we have to take into account that bevacizumab is responsible for an increase in blood pressure, both in patients with a history of hypertension and in those with no history. The pathogenesis of hypertension must be related to the reduction of capillary network and to the blockade of human VEGF. It leads to a reduced production of nitric oxide and to reduced renal sodium excretion, finally resulting in an increased plasma volume (58, 59). In 2010, Dahlberg *et al*. published a retrospective analysis on the data of E4599 trial, suggesting a positive correlation between the occurrence of hypertension during treatment with bevacizumab and OS (15.9 months *vs*. 11.5 months) or PFS (7.0 months *vs*. 5.5 months) (60). Similar results, also reported in the CALGB 90206 trial, involving patients with metastatic renal cell carcinoma, were not confirmed by later studies (61).

Finally, we analyze the aspect of patient age. We can affirm that the risk of bleeding in elderly patients is not increased compared to younger patients. This statement is supported by the results of sub-group analysis of the AVAIL, SAiL and ARIES studies (51, 54, 62).

We can conclude, however, that in some studies many adverse events were observed during therapy with bevacizumab, the most recent studies showed that this drug is safe. Many of the factors previously considered exclusion criteria, such as anticoagulant treatment, central tumor location, the presence of cavitation, the presence of brain metastases and advanced age, are not currently valid. Currently, the only exclusion criteria are squamous histology and the presence of hemoptysis (51).

Cost-effectiveness Analysis

Bevacizumab is quite an expensive molecular targeted drug. Considering the growing necessity to reduce healthcare costs, several cost-effectiveness analysis of chemotherapy regimens containing bevacizumab in NSCLC were conducted. This question is much debated in literature and conclusive results have not yet been reached (63-66).

Here we present a review of literature of pharmaco-economical studies, comparing a bevacizumab-containing regimen with chemotherapy alone, for a maximum of six cycles and with the administration of bevacizumab as maintenance therapy in cases of response or disease stability until disease progression or unacceptable toxicity (63-66).

Isla *et al*. analyzed different schemes, both of first- and second-line, and observed a reduction of direct costs using bevacizumab (67). Bischoff *et al*., who focused their attention on the comparison of cisplatin-gemcitabine-bevacizumab *vs*. cisplatin-pemetrexed, obtained similar results (64). Stanisic *et al*. analyzed indirect costs in addition to direct costs. They recorded a gain in terms of increased productivity (reduction of indirect costs) in the arm of patients treated with regimens containing bevacizumab. This can be attributed to the increase of PFS and the improvement of quality of life (69). Klein *et al*. analyzed first-line and maintenance regimens containing bevacizumab 15 mg/kg and concluded that these schemes are not cost-effective compared to pemetrexed-based regimens (70, 71). Giuliani *et al*. (72) and Ahn *et al*. (73) concluded that schemes based on bevacizumab at a dose of 7.5 mg/kg in combination with cisplatin and gemcitabine are convenient compared to schemes based on cisplatin and pemetrexed. Finally, Goulart and Ramsey analyzed the cost-effectiveness of cisplatin-pemetrexed alone or in combination with bevacizumab at a dose of 15 mg/kg. They concluded that regimens containing bevacizumab are not cost-effective (74).

Published studies are heterogeneous for different aspects such as the line of treatment, as certain studies included lines following the first, the dose of bevacizumab (7.5 mg/kg or 15 mg/kg), the analysis of the direct (cost of drugs, costs related to the management of adverse events and increased survival) and indirect costs (costs related to loss of productivity in terms of work, cost of caregiver, *etc*.). Regarding the question of the dose of bevacizumab, 7.5 mg/kg in some studies and 15 mg/kg in others, the discrepancy is probably due to an absence of clear guidelines. In fact the use of bevacizumab at the dose of 15 mg/kg has been approved by the Food and Drug Administration (FDA), based on the results of the E4599 trial, but the dosage of 7.5 mg/kg is not contraindicated by National Comprehensive Cancer Network (NCCN) guidelines, according to the results of AVAiL trial (63).

Despite the advantage in terms of increased OS and PFS, the data published in literature about cost-benefit analysis are not conclusive. A treatment containing bevacizumab is more expensive compared to chemotherapy alone due to the high cost of the drug, the longer duration of treatment, bevacizumab being indicated for maintenance therapy, an increased cost related to the longer OS, and the cost related to the management of side-effects (73).

Conclusion

The topic covered in this review is still under much debate and there is no common approach to first-line treatment with bevacizumab for NSCLC.

The results of pivotal studies, revealing an increase of OS and of PFS, although of only a few months, argue in favor of the use of this drug (15-17, 19-40). Other important

aspects are the possibility of practicing a maintenance treatment, increasing the time-to-disease progression and improving the quality of life; the possibility of delaying the start of a second-line treatment and the possibility of saving effective treatments for successive lines, such as those based on pemetrexed (1, 5).

On the other hand, the use of bevacizumab is related to some adverse events, such as bleeding, thromboembolism, hypertension and proteinuria. It is contraindicated in patients with squamous histology and with recent bleeding (51), but can be used with caution in patients receiving platelet aggregation inhibitors or anti-coagulants, with bleeding or thrombophilic diathesis, and in patients with untreated brain metastases. These categories of patients, in fact, have been excluded by the majority of previous clinical trials. Several recent trials, however, have focused on demonstrating the safety of this drug even in the categories of patients previously excluded from clinical trials (45, 47-60).

Bevacizumab leads to a gain of about two months in terms of OS. Therefore, it is not clear whether it is really appropriate to choose such an expensive treatment burdened by many side-effects to gain a rather small clinical benefit (1).

Another aspect to be taken into account is the absence of factors predictive of response to treatment with bevacizumab, differently to what occurs for other targeted agents, such as gefitinib. Such factors of treatment response would allow us to pursue a targeted therapeutic strategy, to reduce costs and to not administer a drug burdened by toxicity to patients who cannot benefit from it (63).

In conclusion, the possibility of practicing a treatment with bevacizumab must be carefully analyzed case by case. As a future perspective, it is important to identify patients who can really benefit from the use of this molecular-targeted drug, through identification of specific response markers and by the identification of specific patient characteristics associated with a best response to this treatment. Moreover, in light of the results of recent clinical trials, it is important to analyze new associations which could be effective and with acceptable toxicity and that can also be used in elderly patients and in therapy lines subsequent to the first.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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