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ORIGINAL ARTICLE

Use of bevacizumab as a first-line treatment for metastatic breast cancer

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ABSTRACT

Objective

During clinical practice, it can be challenging, given the lack of response biomarkers, to identify the patients with metastatic breast cancer (mBCa) who would benefit most from the addition of bevacizumab to first-line standard chemotherapy. The aim of the present review was to summarize the relevant scientific evidence and to discuss the experience of a group of experts in using bevacizumab to treat mBCa.

Methods

A panel of 17 Spanish oncology experts met to discuss the literature and their experience in the use of bevacizumab as first-line treatment for mBCa. During the meeting, discussions focused on three main issues: the profile of the patients who could benefit most from bevacizumab, the optimal bevacizumab treatment duration, and the safety profile of bevacizumab.

Results

The subset of mBCa patients who would benefit the most from the addition of bevacizumab to first-line standard chemotherapy are those with clinically defined aggressive disease. Treatment with bevacizumab should be maintained until disease progression or the appearance of unacceptable toxicity. In the mBCa setting, the toxicity profile of bevacizumab is well known and can be managed in clinical practice after adequate training.

Conclusions

This expert group recommends administering bevacizumab as first-line treatment in patients with clinically aggressive disease.

KEY WORDS

Bevacizumab, metastatic breast cancer, clinical practice

1. INTRODUCTION

Breast cancer is the most common cancer among women; it also contributes to a substantial proportion of the global cancer burden[1]. At diagnosis, metastatic breast cancer (mBCa) accounts for 5%–10% of all breast cancers[2].

Molecular subtyping is essential when choosing a treatment for mBCa. The most commonly used biomarkers of treatment response are the estrogen and progesterone hormone receptors and HER2 (human epidermal growth factor receptor 2). For tumours with enriched HER2 expression, the choice of first-line treatment has been clear since the introduction of anti-HER2 targeted therapies[2]. It is also well established that endocrine therapy is preferred for mBCa that expresses hormone receptors (estrogen receptor– or progesterone receptor–positive, or both)[2]. However, treatment selection is not that straightforward for certain molecular subtypes of breast cancer that are unsuitable for targeted or endocrine therapy and that lack response biomarkers.

Bevacizumab is a humanized monoclonal antibody that inhibits angiogenesis by binding to the vascular endothelial growth factor A. In the mBCa context, varying regulatory decisions based on the

same evidence have led to a controversial scenario. In Europe, where bevacizumab is approved for the first-line treatment of mBCa[3], local reimbursement restrictions vary from one region to another. In contrast, the U.S. Food and Drug Administration (FDA) revoked its approval for bevacizumab in mBCa, but Medicare is reimbursing bevacizumab as an off-label drug for that indication.

From a clinical perspective, the fact that no biomarker of treatment response has been identified for bevacizumab makes it difficult to judge the suitability of the drug for a particular patient when making treatment decisions, which are strongly driven by molecular subtyping.

Because the current economic situation is imposing restrictions on clinical practice, our expert group considered it necessary to review the most controversial issues concerning bevacizumab for mBCa—namely, the selection of patients who could benefit the most, the toxicity profile of bevacizumab in breast cancer, and the duration of treatment.

2. METHODS

Our objective was to review bevacizumab for the treatment of mBCa in daily clinical practice, combining the evidence reported so far in relevant clinical studies with the clinical experience of our expert group.

For the purpose of the review, a panel of 17 Spanish oncology experts was assembled. To encourage dynamic participation, the experts were divided into three groups. Each group met once in April 2013. Before each meeting, participants were each assigned an issue of interest and were asked to prepare a brief summary based on both the published evidence and their personal clinical experience. During the meetings, the members discussed the reviewed literature and their personal clinical experience with administering bevacizumab for mBCa. The main issues discussed during each meeting were the profile of the patients who could benefit most from bevacizumab, the optimal duration of bevacizumab treatment, and the safety profile of bevacizumab.

Each meeting was coordinated by two panel members. A medical writer attended all three meetings. The medical writer drafted outlines of the issues covered during the discussions at each meeting. Those outlines were then reviewed by all the experts, who provided further comments. A complete first draft of the manuscript was then produced by the medical writer. That manuscript was distributed to the experts, who provided commentary on the text until a final version was approved by the entire panel of experts.

2.1 Regulatory Context

The European Medicines Agency approved bevacizumab in combination with paclitaxel or capecitabine for the first-line treatment of mBCa[3]. In 2008, the FDA approved bevacizumab for the same indication under its accelerated approval program; in 2011, it revoked that decision, arguing that the lack in overall survival did not outweigh the risk of adding bevacizumab to the backbone chemotherapy[4]. Subsequently, and using argumentation similar to that used by the FDA, Health Canada also revoked its approval of bevacizumab as a treatment for mBCa[5]. In both countries, the United States and Canada, bevacizumab remains available for other cancer indications. In contrast, at that time and also after reviewing its initial decision, the European Medicines Agency continued to recommend bevacizumab in combination with paclitaxel for patients with mBCa[6].

The decisions by the FDA and Health Canada were based on follow-up reports from two randomized clinical trials, AVADO[7] and RIBBON-1[8], which demonstrated statistically significant increases in progression-free survival (PFS)—though less relevant than the increase reported in the E2100 trial[9] (Table I)—and failed to demonstrate a benefit in overall survival (OS)[4,5]. The revocations started a debate that divided opinion in the oncologist community, as revealed in a worldwide survey in which 52% of responding oncologists disagreed with the FDA decision[12]. The key point in the debate is whether the main therapeutic objective should be the same for all malignancies, or whether it should vary depending on the aggressiveness of the disease and the chance of receiving further treatments, which differs across settings. Because subsequent treatments and crossovers are highly common after first-line treatment in mBCa, the observed OS will be similar in the long term, regardless of first-line treatment[13]. Therefore, in the first-line treatment of mBCa, PFS is preferred over OS as the primary efficacy outcome, given the difficulty of measuring an unbiased OS in this indication. The simulation model developed by Broglio and Berry[14], consistently shows that, for diseases with a long median survival after progression (>12 months), the lack of a statistically significant difference in OS does not always mean lack of an improvement in OS. Most of the randomized clinical trials of bevacizumab in mBCa were therefore designed and statistically powered to assess PFS rather than OS.

All trials of bevacizumab in mBCa have reported a significant improvement in PFS in favour of bevacizumab[7–11] (Table I). To date, the only randomized clinical trial designed to assess OS as a primary objective was the TURANDOT noninferiority trial (bevacizumab–capecitabine vs. bevacizumab–paclitaxel)[11]. The only results currently available for that trial are preliminary, and in the planned interim efficacy analysis, they showed no clinically relevant difference in the OS primary endpoint (Table I)[11]. The non-interventional studies performed in the clinical practice setting report a PFS that is consistent with the PFS observed in clinical trials (median: 9–12 months), with an overall response rate of 52%–63%, a median

TABLE I Randomized clinical trials of bevacizumab as a first-line treatment for metastatic breast cancer (MBCa)

Reference (study name)	*Study design*	*Disease type*	*Pts (*n*)*	*Treatment groups (*N *analyzed/*N *randomized)*	*Primary endpoint*	*HR*	*95% CI*[a]
Miller *et al.,* 2007[10], Gray *et al.,* 2009[9] (E2100)	Phase III, open label	HER2-negative, LR/MBCa	722	Paclitaxel + bevacizumab (368/368) Paclitaxel (354/354)	PFS (independent review facility)	0.48	0.39 to 0.61
Robert *et al.,* 2011[8] (RIBBON)	Phase III, double-blind	HER2-negative, LR/MBCa	1237	Capecitabine cohort: capecitabine + bevacizumab (409/409); capecitabine + placebo (206/206)	PFS	0.69	0.56 to 0.84
				Paclitaxel/A cohort: Paclitaxel/A + bevacizumab (415/415) Paclitaxel/A + placebo (207/207)		0.64	0.52 to 0.80
Miles *et al.,* 2010[7] (AVADO)	Phase III, double-blind	HER2-negative, LR/MBCa	736	Docetaxel + bevacizumab 15 mg/kg (247/247)	PFS	0.67	0.54 to 0.83
				Docetaxel + bevacizumab 7.5 mg/kg (248/248)		0.80	0.65 to 1.00
				Docetaxel + placebo (241/241)			
Lang *et al.,* 2013[11] (TURANDOT)	Phase III, open label noninferiority	HER2-negative, MBCa	564	Bevacizumab + capecitabine (265/279) Bevacizumab + paclitaxel (268 /285)	OS (interim report)	1.04	97.5% CI: $-\infty$ to 1.69[b] (p=0.59)
					PFS	1.36	1.09 to 1.68

[a] Unless otherwise specified.
[b] Non-inferiority criterion for the interim analysis (α=0.00105) was not met.
Pts = patients; HR = hazard ratio; CI = confidence interval; LR = locally recurrent; PFS = progression-free survival; paclitaxel/A = paclitaxel/anthracycline; OS = overall survival.

OS of 20–29 months, and a 1-year survival proportion of 73%–83% (Table II).

Based on the foregoing evidence, guidelines from the U.S. National Comprehensive Cancer Network include the combination of bevacizumab–paclitaxel as an option for patients with MBCa[18]. The international consensus guidelines for advanced breast cancer state the need to further assess the benefit of bevacizumab in the MBCa setting and recommend considering bevacizumab only for selected cases[19]. Recent guidelines from the American Society for Clinical Oncology go a step further and define "selected cases" as those involving life-threating disease or severe symptoms, for which they recommend adding bevacizumab to single-agent chemotherapy[20].

The discordance across regulatory decisions remains surprising. The positive European regulatory decision was based mainly on the E2100 trial[9], which was questioned by the FDA because of the absence of a placebo control group[12]. That methodologic flaw (which was quite common at the time E2100 was undertaken) will be outweighed by the currently ongoing placebo-controlled MERIDIAN trial[21]. However, regardless of the limitations that each individual study might have, a review of the evidence pertaining to bevacizumab in MBCa as a whole shows that the improvement in PFS obtained when bevacizumab is added to paclitaxel or capecitabine in the first-line setting is consistent across studies.

2.2 Patient Profile

During clinical practice, treatment decision-making for MBCa is based on molecular subtyping of the tumour and clinical risk factors, such as extensive or symptomatic visceral involvement (Figure 1)[2,22].

Several *post hoc* subanalyses have explored the efficacy of bevacizumab regimens for various subsets

TABLE II Observational studies of bevacizumab plus paclitaxel as first-line treatment for metastatic breast cancer (MBCa)

Reference (study name)	*Study design*	*Disease type*	*Pts (n)*	*Treatment*	*Median follow-up (months)*	*Primary objective*	*Results*
Smith *et al.,* 2011[15] (ATHENA)	Prospective single-arm	HER2-negative LR/MBCa	2251	Standard bevacizumab first-line chemotherapy	12.7	Safety	Grade 3 or greater: neutropenia, 5.4%; hypertension, 4.4%; thromboembolism, 3.2%; proteinuria, 1.7%; bleeding, 1.4% Overall response rate: 52% Median TTP: 9.5 months (95% CI: 9.1 months to 9.9 months)[a]
Klare *et al.,* 2011[16]	Longitudinal single-arm cohort	HER2-negative MBCa	786	Standard bevacizumab first-line chemotherapy	NR	Safety, efficacy	Grade 3 or greater: pain, 9.0%; hypertension, 5.0%; thromboembolism, 1.4%; sensory neuropathy, 2.7%; infection, 1.1%; proteinuria, 0.5%; gastrointestinal perforation, 0.8% Overall response rate: 62% Median PFS: 9.3 months (95% CI: 8.9 months to 10.2 months) 1-Year survival: 73% (95% CI: 70% to 77%)
Marcos Sánchez *et al.,* 2013[b]	Retrospective single-arm cohort	MBCa	56	Standard bevacizumab chemotherapy	NR	Descriptive	Hypertension, 1.8%; thromboembolism, 5.4%; grade 1 or 2 proteinuria, 16.1%; grade 1 or 2 bleeding, 28.6% Overall response rate: 57% Median PFS: 12 months Median OS: 29 months (95% CI: 24.93 months to 33.06 months)
Ruiz de Lobera *et al.,* 2012[c]	Retrospective single-arm cohort	HER2-negative MBCa	66	Standard bevacizumab chemotherapy	NR	Descriptive	Grade 3 or greater: neutropenia, 31.8%; febrile neutropenia, 21.2%; asthenia, 21.2%; Infection, 9.1%; onycholysis, 6.1% Overall response rate: 57.5% Median PFS:11.7 months Median OS: 19.7 months
Manso *et al.,* 2013[17] (AVALOX)	Cross-sectional	HER2-negative MBCa	219	Standard bevacizumab first-line chemotherapy	NA	Descriptive	Overall response rate: 62.7% DFS of 12 months or more: 82.8%

[a] At data cut-off, 72% of the patients were still alive. Survival follow-up is therefore ongoing.

[b] Marcos Sánchez RA, Rodríguez CA, Gómez–Bernal A, *et al.* Efficacy and safety of chemotherapy and bevacizumab treatment in metastatic breast cancer in the clinical practice setting. Efficacy and safety results. Presented at the IX Simposio Internacional de GEICAM; Valencia, Spain; April 17–19, 2013.

[c] Ruiz de Lobera A, Sancho A, Carrera S, *et al.* Clinical benefit of the use of bevacizumab plus chemotherapy in the treatment of metastatic breast cancer. Presented at the 2012 San Antonio Breast Cancer Symposium; San Antonio, TX, U.S.A.; December 4–8, 2012.

Pts = patients; LR = locally recurrent; TTP = time to progression; CI = confidence interval; NR = not reported; PFS = progression-free survival; OS = overall survival; NA = not applicable; DFS = disease-free survival.

of MBCa patients. In randomized clinical trials, the benefit of adding bevacizumab to standard chemotherapy was maintained across most subgroups, such as the hormone receptor–positive subgroup and the subgroup with clinically aggressive disease—that is, patients with visceral metastasis (Figure 2)[23]. Subgroup analyses have also been reported in observational settings. In the ATHENA cohort, the median time to progression was 10.4 months [95% confidence interval (CI): 8.8 to 11.8 months] for the subgroup of patients 70 years of age and older ($n = 175$)[24] and 7.2 months (95% CI: 6.6 to 7.8 months) for the triple-negative breast cancer (TNBCa) subgroup ($n = 585$)[25]. The small size of the elderly and TNBCa subgroups in the randomized clinical trials might explain the absence of a statistically significant improvement in those groups (Figure 2).

Considering the literature review, it appears that most subgroups benefit in terms of PFS when

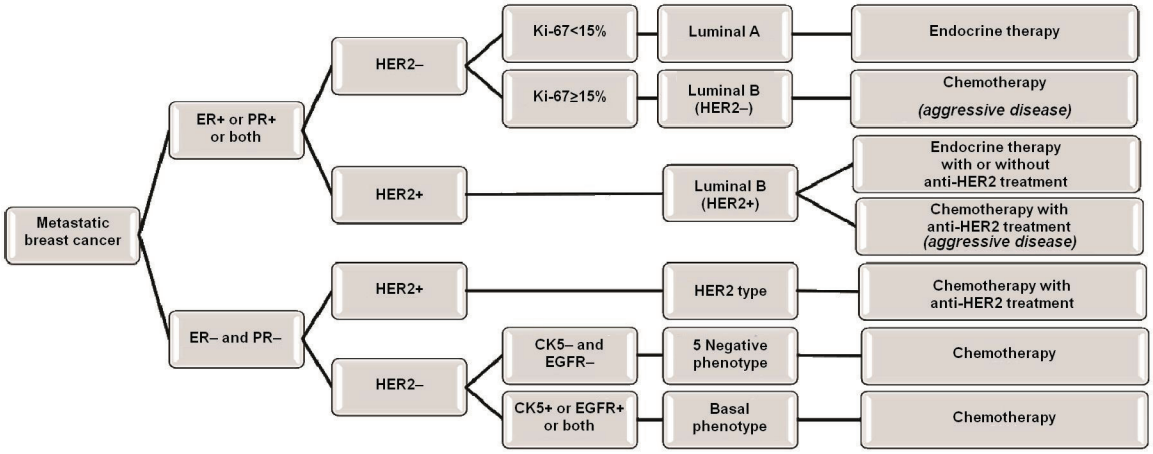

FIGURE 1 Molecular subtyping and recommended treatments for metastatic breast cancer. Adapted from Cardoso et al.*, 2012[2], and Engstrom* et al.*, 2013[22]. ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; CK5 = cytokeratin 5; EGFR = epidermal growth factor receptor 1.*

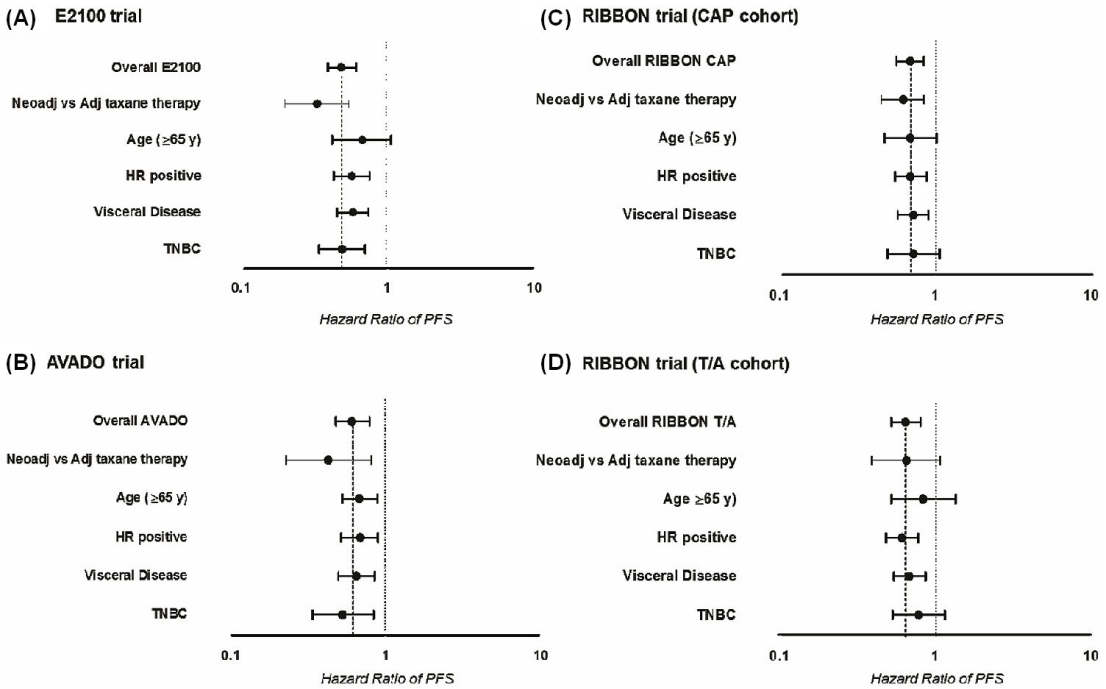

FIGURE 2 Efficacy of bevacizumab plus paclitaxel as first-line therapy for metastatic breast cancer. Hazard ratios for overall study results are stratified using the stratification factors applied at randomization. Hazard ratios for the subgroup analyses are unstratified. (A) Gray et al.*, 2009 (E2100 trial)[9]. (B) Miles* et al.*, 2010 (AVADO)[7]. (C,D) Robert* et al.*, 2011 (RIBBON)[8]. Neoadj = neoadjuvant; Adj = adjuvant; HR = hormone receptor; TNBC = triple-negative breast cancer; PFS = progression-free survival; CAP = capecitabine; T/A = taxane–anthracycline.*

bevacizumab is added to standard chemotherapy, regardless of the backbone chemotherapy. To more accurately select the patients that would benefit most from the addition of bevacizumab, biomarkers of tumour response to bevacizumab have to be identified. Based on preliminary subanalyses[26,27], several ongoing projects are prospectively evaluating the potential role of genetic variants of the vascular endothelial growth factor pathway in predicting response to bevacizumab[28]. Although some results are divergent, two randomized clinical trials in breast cancer[29,30] and a meta-analysis of six randomized controlled trials in various malignancies[31–33] could lead to a hypothesis about vascular endothelial growth factor A as a potential marker of response to bevacizumab. The predictive value of plasma vascular endothelial growth factor A is currently being evaluated in the MERIDIAN trial, for which patient enrollment began in August 2012. Primary outcome measures will be available in June 2016, and completion is expected in January 2019[21].

The angiotensin II receptor type 1 has also recently been hypothesized to be a marker predictive of response to bevacizumab[34,35]. Hypertension has also been suggested to be a predictive marker of bevacizumab efficacy, and a retrospective analysis suggested a predictive value of hypertension as a marker of response to bevacizumab[36]. In contrast, an analysis of seven phase III trials[37] and the results of a phase II trial[38] reject that hypothesis. A group of Spanish oncologists are currently conducting a prospective study to explore the potential role of hypertension in predicting the efficacy (in terms of PFS) of bevacizumab associated with chemotherapy in patients with breast or colorectal cancer (see http://www.clinicaltrials.gov/show/NCT01733628).

In the scenario of MBCa tumours for which chemotherapy is indicated (Figure 1), it would be reasonable on several grounds to add bevacizumab to improve efficacy. First, bevacizumab has been shown to increase PFS, with an acceptable toxicity profile. Second, if patients do not receive bevacizumab as first-line treatment, the potential benefit of bevacizumab is lost because bevacizumab is available only as a first-line treatment for MBCa. Therefore, for all cases in which chemotherapy is indicated, there is no clinical reason to restrict bevacizumab therapy to a subset of patients. However, if bevacizumab has to be restricted because of economic considerations, those considerations should not affect patients with a poor prognosis and aggressive disease.

In the latter context, patients with TNBCa constitute a well-known subgroup with a poor prognosis. In addition, during the ATHENA study, a subgroup of patients with hormone receptor–positive MBCa and a clinical profile suggesting poor prognosis (disease-free interval of ≤24 months, liver metastasis, or ≥3 metastatic organ sites and prior neoadjuvant anthracycline or taxane therapy) was recently identified as high-risk, with a short OS expectancy, resembling the prognosis observed for patients with TNBCa (Figure 3)[39]. Identification of further specific subsets of responders to bevacizumab therapy awaits the results of ongoing research into molecular subtyping and biomarkers of response, and the associated assessments of the applicability of the results. In the meantime, in the absence of validated biomarkers, the clinical risk factors that currently constitute the other main component of the treatment decision-making algorithm (Figure 1) play a key role in deciding whether chemotherapy is indicated and therefore whether bevacizumab has to be added[39]. The clinical factors that define the aggressiveness of the disease include, but are not limited to, symptomatic disease, visceral metastasis (liver, lung, and central nervous system), rapidly progressive disease, premature relapse, and a short disease-free interval.

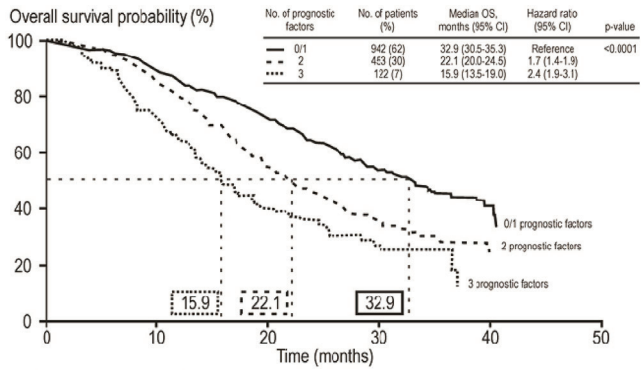

*FIGURE 3 Overall survival in the hormone receptor–positive subgroup (*n *= 1517) from Llombart–Cussac* et al.[39]. *OS = overall survival; CI = confidence interval.*

2.3 Treatment Duration

In MBCa, it is recommended that treatment with bevacizumab continue until disease progression or unacceptable toxicity occurs[3]. Randomized clinical trials were designed to treat patients with bevacizumab while clinical benefit continued, and to our knowledge, no available evidence supports the opposite approach. Therefore, there is no clinical reason to discontinue bevacizumab therapy once all chemotherapy cycles have been completed. However, in clinical practice, bevacizumab is sometimes discontinued once chemotherapy stops, although scientific evidence for cessation is lacking. On the contrary, long-term treatment with bevacizumab seems to improve survival outcomes in the clinical setting[a,b]. In the ATHENA observational study, median OS was 30 months (95% CI: 28.5 to 32.7 months) in patients who continued treatment with bevacizumab after discontinuation of chemotherapy (n = 1205); those who discontinued bevacizumab at the same time as chemotherapy (n = 1058) experienced reduced OS (median: 18.4 months; 95% CI: 17.2 to 19.7 months)[40]. More recently, the LORENA study found that long-term treatment with bevacizumab (>15 months) was significantly associated with longer PFS[41].

Another increasingly common issue in clinical practice is whether hormonal therapy should be added to long-term bevacizumab treatment for hormone-positive MBCa. A recent non-interventional study showed that, compared with long-term bevacizumab treatment, the addition of hormonal therapy was associated with a significantly longer PFS[42].

[a] Ruiz de Lobera A, Sancho A, Carrera S, *et al.* Clinical benefit of the use of bevacizumab plus chemotherapy in the treatment of metastatic breast cancer. Presented at the 2012 San Antonio Breast Cancer Symposium; San Antonio, TX, U.S.A.; December 4–8, 2012.

[b] Marcos Sánchez RA, Rodríguez CA, Gómez–Bernal A, *et al.* Efficacy and safety of chemotherapy and bevacizumab treatment in metastatic breast cancer in the clinical practice setting. Efficacy and safety results. Presented at the IX Simposio Internacional de GEICAM; Valencia, Spain; April 17–19, 2013.

However, that finding has not been demonstrated in clinical trials, although it is frequently considered during clinical practice.

Once chemotherapy is discontinued, bevacizumab therapy should be given as a treatment *per se* rather than as a "maintenance therapy." Chemotherapy is administered for only a limited number of cycles because of its toxicity, but toxicity should not affect the continuity of bevacizumab. The term "maintenance" might lead to the misconception that bevacizumab is optional and not necessary. In the MBCa setting, the literature review and clinical experience indicate that there is a benefit for bevacizumab administration until disease progression or unacceptable toxicity, as recommended in the Summary of Product Characteristics for bevacizumab[3].

2.4 Safety Profile

Hypertension, proteinuria, thromboembolism, impaired wound healing, bleeding, and gastrointestinal perforation are the adverse events that have been most frequently associated with bevacizumab in various tumour types[43]. However, because the toxicity profile of bevacizumab varies across malignancies, we focus here on the evidence obtained in patients with breast cancer. In that context, a meta-analysis[44] of five randomized clinical trials in the locally recurrent and MBCa settings revealed that bevacizumab was significantly associated with proteinuria, hemorrhagic events, and left ventricular dysfunction (Figure 4). A significant association was also observed for hypertension, but with a high degree of statistical heterogeneity (Figure 4). Two additional meta-analysis reported an increased risk of left ventricular dysfunction[45] and congestive heart failure[46] in patients with breast cancer treated with bevacizumab. However, the cardiotoxicity of bevacizumab is likely to be reversible[47]. In addition, some methodology concerns have been raised about the plausibility of ascribing the reported cardiac events to bevacizumab exposure. First, data about cardiovascular risk factors were absent in the meta-analyses[13]. Second, the definition of congestive heart failure varied from one study to another and was not clearly stated in all studies, revealing the lack of a consensus definition for congestive heart failure already highlighted by some authors[48]. The methodology issues raised with respect to the data on cardiotoxicity are sufficient to warrant the need for further and more robust data that, at some point in the future, can bear on this question.

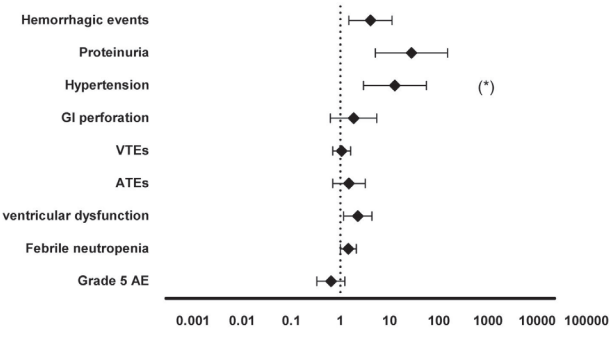

FIGURE 4 Grade 3 or greater adverse events (AEs) according to the U.S. National Cancer Institute's Common Toxicity Criteria*, after the addition of bevacizumab to the chemotherapy for first- or second-line treatment of metastatic or locally recurrent breast cancer. Pooled estimates of the odds ratios for AEs with chemotherapy plus bevacizumab compared with chemotherapy alone. * Statistical heterogeneity was observed for the pooled hypertension odds ratio (I2 = 70.1%;* p *= 0.010). No statistical heterogeneity was observed for the remaining pooled odds ratios. Adapted from Cortes* et al.*, 2011[44]. GI = gastrointestinal; VTEs = venous thrombolic events; ATEs = arterial thrombolic events.*

In clinical practice, long-term treatment does not seem to increase the risk of adverse events[40]. In the ATHENA observational study, a higher incidence of grades 3–5 adverse events was initially observed among patients treated for more than 1 year (65.8% vs. 57.6% in the overall population), but after accounting for the varied durations of treatment exposure, the mean number of such adverse events was lower for patients treated for more than 1 year (1.26 events per treatment–year) than for those treated for less than 1 year (4.13 events per treatment–year)[40].

Hypertension is frequently associated with receipt of bevacizumab in the clinical setting. Hypertension seems to be an early adverse event, typically observed during the first year of treatment[46]. However, in our experience, hypertension is also likely to occur over the long term in treated patients, and in comparing earlier cycles with later cycles, the ATHENA study demonstrated no difference in the first onset of hypertension[40]. Blood pressure should be monitored regularly during bevacizumab treatment. Measurement of blood pressure is recommended before and after the first few doses of bevacizumab and then every 3 weeks. In patients with a blood pressure of 150/100 mmHg or more, bevacizumab should be discontinued until therapy restores normal pressure. Although this symptom can typically easily be managed with antihypertensive drugs, further expert advice is always worth obtaining. The best option is to refer hypertensive patients to specialized hypertension units, to internal medicine or cardiology specialists, or to the general practitioner, depending on availability.

In our experience, it is rare during clinical practice to discontinue bevacizumab therapy because of proteinuria in the MBCa setting. Generally, proteinuria associated with bevacizumab is not a common concern in MBCa patients. More frequently, its presence in association with other indications, such as ovarian cancer, can be explained by a longer duration of bevacizumab treatment in those settings. In the ATHENA study, the first onset of grade 3 or 4 proteinuria was consistently more frequent after 1 year of

treatment than during the 1st year[40]. To monitor proteinuria in patients undergoing treatment with bevacizumab, a dipstick urinalysis is recommended every 3–4 weeks. When a reading of 3+ is obtained (300 mg/dL), a 24-hour urine collection is recommended. For patients with either a dipstick reading of 4+ (400 mg/dL or more than 3 g/24 h, together with hypoalbuminemia and peripheral edema), treatment with bevacizumab should be discontinued[49].

With respect to the hemorrhagic events associated with bevacizumab, most such events are mild or moderate and can be managed with simple first-aid procedures[43,50,51]. In patients with grade 3 venous thromboembolism or pulmonary embolism, bevacizumab should be discontinued until recovery is achieved on a stable dose of anticoagulants. If grade 4 venous thromboembolism or any-grade arterial thromboembolism is detected, bevacizumab should be permanently discontinued[3]. In patients undergoing major surgery, 1 month without bevacizumab before and after surgery is recommended to prevent the increased risk of wound healing complications associated with bevacizumab. In patients undergoing minor surgery, the recommended bevacizumab-free period before and after surgery can be reduced to 1 week[43,50,52,53].

Bevacizumab added to first-line chemotherapy for the treatment of MBCa has shown an acceptable toxicity profile. The adverse events associated with bevacizumab are predictable and can easily be managed. That assessment has been demonstrated in the randomized clinical trials (individual data and meta-analyses) and in the non-interventional ATHENA study, and it is consistent with observations made during clinical practice.

3. CONCLUSIONS

In all the clinical trials performed in the MBCa setting, bevacizumab added to standard chemotherapy as first-line treatment has been shown to be associated with a significant improvement in PFS.

Given the absence of response biomarkers, clinical factors can be used to identify the specific subgroups of patients who could benefit from treatment with bevacizumab. Based on the clinical aggressiveness of disease, our group of experts recommends giving bevacizumab as a first-line treatment in patients with TNBCa or luminal disease with a poor prognosis.

For all patients in whom bevacizumab is expected to provide a clinical benefit, it should be continued until disease progression or unacceptable toxicity.

The toxicity profile of bevacizumab is inherent in its mechanism of action. With adequate training and knowledge, the toxicity of bevacizumab can be managed without complications.

4. ACKNOWLEDGMENTS

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5. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: All authors received fees from Roche Farma for their participation in the present work. LM has received consultancy fees from Roche Farma. RM has received fees for participation on advisory boards for Celgene. AA has received research grants from Roche. MA has received fees for participation on advisory boards for Celgene, Teva, Pfizer, Pierre Fabre, and AstraZeneca. AIB has participated on advisory boards for Roche, Bristol–Myers Squibb, GlaxoSmithKline, Grünenthal, Pfizer, Teva, Archimedes Pharma, and Celgene. AG has participated in meetings organized by Roche Farma and Grünenthal. ELM has received consulting fees from Celgene. MMA has participated on advisory boards for Teva, Celgene, and AstraZeneca. CO has received lecture fees from AstraZeneca. FM, BC, IC, MJE, SE, RGV, NMJ, and PZ declare no further conflicts of interest.

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