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A systematic review of bevacizumab efficacy in breast cancer

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ABSTRACT

Angiogenesis is a key component of cancer growth, invasion and metastasis. Therefore, inhibition of angiogenesis is an attractive strategy for the treatment of cancer.

We systematically describe phase II and III clinical trials of bevacizumab for the treatment of breast cancer.

Methods: A computer-based literature search was carried out using PUBMED and conference databases. Original phase II and III studies reporting ⩾15 patients who received bevacizumab were included.

Results: 41 phase II trials were identified in the metastatic setting. Most trials found bevacizumab treatment feasible. Response rates (RR) varied from 0% to 76.5%, time to progression (TTP)/progression free survival (PFS) from 2.4 to 25.3 months and overall survival from 11.5 to more than 38 months. 14 phase III trials including more than 4400 patients with MBC unanimously showed increased RR and PFS, however, no trials demonstrated an OS benefit. In the neoadjuvant setting 23 phase II and III trials were identified. All studies found increased pCR/tpCR but no benefit in terms of OS could be demonstrated. The only study conducted in the adjuvant setting failed to show any survival benefit of bevacizumab.

Conclusion: Despite increased response rates in both the metastatic and neoadjuvant setting, bevacizumab has failed to show any OS benefit. Future trials should include identification of robust predictive biomarkers in order to improve our understanding of molecular biomarkers and mechanisms.

Introduction

Neovascularization is one of the hallmarks of tumor invasion and metastasis and is a prerequisite for progression of solid tumors [1]. For this reason, the inhibition of angiogenesis is regarded an attractive therapeutic approach.

Bevacizumab is a recombinant humanized monoclonal antibody that binds to the VEGF-A ligand and prevents it from binding to its receptors [2,3]. Few drugs have generated as much discussion in both the medical literature and the popular press as bevacizumab for metastatic breast cancer (MBC). The decision in 2011 of the US Food and Drug Administration (FDA) to withdraw full approval for the drug in first-line MBC after having granted accelerated approval 3 years earlier renewed the debate not only about the approval process, but also about how to measure clinical outcome and how to evaluate risk benefit of a new drug.

This review focusses on efficacy of bevacizumab in phase II and III trials in the (neo)adjuvant and the metastatic setting.

Methods

We systematically searched PUBMED for phase II and III studies using the following search terms: bevacizumab AND breast cancer with the clinical trial filter activated. We repeated the search without the clinical trial filter, using the same search terms AND (neo)adjuvant/metastatic breast cancer to ensure that all relevant articles were retrieved. Full articles were obtained and references were checked for additional material when appropriate. In addition, abstracts from 2009 to 2013 annual meetings of the American Society of Clinical Oncology (ASCO) and San Antonio Breast Cancer Symposium 2009–2013 were retrieved for relevant abstracts using similar search terms. The reference list was updated in December 2013 (Fig. 1).

The following criteria were applied: Studies reporting ⩾15 evaluable patients, studies reporting efficacy parameters of at least response rate (RR) or time to progression (TTP)/progression free survival (PFS) in the metastatic setting, pathological response (pCR) (breast tumor/breast tumor and lymph nodes) in the neoadjuvant or disease free survival (DFS) in the adjuvant setting and papers in English were included.

Two authors independently surveyed the literature ((neo)adjuvant: OGC and DLN; MBC: IB and DN). In case of unclarity or

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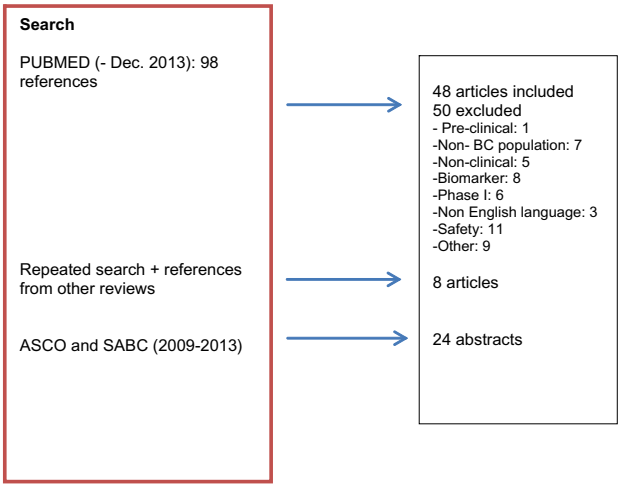

Fig. 1. Diagram of included articles.

disagreement, the complete paper was analyzed and a verdict was reached by consensus.

Results

Our search identified 22 phase II and 2 phase III trials in the neoadjuvant setting and 1 phase III trial in the adjuvant setting. One reference was retrieved by searching in prior reviews. In the metastatic setting 41 phase II and 14 phase III trials were retrieved.

Bevacizumab in predominantly human epidermal growth factor receptor 2 (HER2)-negative MBC

Phase II studies

Several combinations of bevacizumab and chemotherapy have been investigated in the metastatic setting both as first-line treatment as well as in subsequent treatment-lines. Phase II trials are summarized in Table 1. Taxanes are the drugs most often studied in combination with bevacizumab. Two trials of bevacizumab in combination with docetaxel demonstrated RR of approximately 50% with median PFS/TTP of 7.5 and 9.3 months, respectively [4,5]. Addition of capecitabine in two other studies produced similar results with RR of 49% and 61%, respectively, and TTP of 11 months in both studies [6,7]. Furthermore, several studies have reported on combinations of taxanes and various other drugs, all showing RRs and PFS/TTP in the same range [8–24]. Studies not including taxanes have shown modest activity although there are only few trials [25,26].

A trial of pegylated liposomal doxorubicin and bevacizumab as first-line treatment in locally recurrent and MBC was stopped prematurely due to toxicity after the enrolment of 43 patients [27].

A study of bevacizumab in combination with vinorelbine and capecitabine in recurrent inflammatory breast cancer showed RR of 46.4% [28].

Preclinical studies have suggested that metronomic chemotherapy has anti-angiogenic properties [29]. Bevacizumab in combination with metronomic chemotherapy consisting of cyclophosphamide and capecitabine or methotrexate demonstrated clinical benefit (CRB) rates of 64–68% with PFS of 8–9 months in patients who had previously received anthracyclines and taxanes [30,31]. A randomized trial of bevacizumab in combination with metronomic chemotherapy demonstrated a near three-fold increase in RR (10% versus (vs.) 29%) and TTP (2.0 vs. 5.5 months). The results are preliminary and from 2005. No updates or final publication have been identified, nevertheless, these results have prompted the initiation of several phase III trials evaluating metronomic chemotherapy and bevacizumab in both early and MBC (NCT00925652, NCT01131195, NCT01112826) [32,33].

Phase III

Results of phase III trials are given in Table 2. The pivotal open-label E2100 trial randomized 722 patients (90% HER2-negative) to paclitaxel +/− bevacizumab as first-line therapy. An increased RR (21% vs. 37%, $P < 0.001$) and a doubling in median PFS (5.9 vs. 11.8 months, $P < 0.001$) were demonstrated. The median OS, however, was similar in the two groups (25.2 vs. 26.7 months, $P = 0.16$) [34,35]. Unfortunately, data on treatment administered after progression were not collected, precluding an exploratory analysis of the influence of cross over between treatment arms and subsequent therapy on OS.

Results from the placebo-controlled AVADO trial including 736 patients randomized to first-line treatment with docetaxel + placebo, docetaxel + bevacizumab (7.5 mg/kg) or docetaxel + bevacizumab (15 mg/kg) revealed a modest yet statistically significant increased RR (46.4% vs. 55.2% vs. 64.1%) and PFS 8.2 vs. 9.0 vs. 10.1 months, though seemingly to a lesser extent than the bevacizumab plus paclitaxel combination. The median OS was similar in the three groups [36].

In the initial registration study AVF2119g the addition of bevacizumab to capecitabine in patients with advanced, pretreated MBC was rather disappointing. Despite a doubling of the RR in the combination arm (19.8% vs. 9.1%) PFS did not improve (4.8 vs. 4.2 months) nor did OS (15.1 vs. 14.5 months) [37]. Because of these results, the FDA required a third arm including capecitabine in the following RIBBON-1 trial.

The RIBBON-1 trial evaluated first-line chemotherapy (taxane, capecitabine or anthracycline-based) +/− bevacizumab. Among 1237 patients the addition of bevacizumab resulted in a significant improvement in RR and PFS. A prespecified subgroup analysis showed that the efficacy of bevacizumab was independent of prior therapy and hormone-receptor (HR) status. However, no significant OS advantage was demonstrated [38].

A pooled subgroup analysis of 2447 individual patients included in E2100, AVADO and RIBBON-1 was undertaken. The analysis showed a PFS of 9.2 months with bevacizumab and 6.7 months without (Hazard ratio (HR) 0.64; 95% confidence interval (CI) 0.57–0.71). The one-year median OS rate was increased (71% vs. 65%). However, OS was not different (26.7 vs. 26.4 months) (HR 0.97; 95% CI 0.86–1.08). The magnitude of benefit was similar in all patient subgroup irrespective of baseline characteristics [39].

The RIBBON-2 trial assessed the efficacy of bevacizumab plus non-anthracycline-based, second-line chemotherapy. The addition of bevacizumab significantly improved PFS. Nevertheless, OS was not significantly different [40]. Of note, an exploratory subgroup analysis of 159 (23%) triple-negative breast cancer (TNBC) patients demonstrated significant improvements in RR (41% vs. 18%; $P = 0.0078$), PFS (6.0 vs. 2.7 months; (HR 0.494; 95% CI 0.33–0.74; $P = 0.0006$) and median OS (17.9 vs. 12.6 months; HR 0.624, 95% CI 0.39–1.007; $P = 0.0534$). Despite the small sample size, there was a trend toward improved OS among this subset of patients [41].

The TURANDOT trial evaluated the combination of bevacizumab plus paclitaxel vs. bevacizumab plus capecitabine. Results from an interim OS analysis after inclusion of 564 patients showed that the non-inferiority criterion was not met and OS results were inconclusive, although PFS was better and more patients experienced response in the paclitaxel arm [42]. Final results are expected in 2014. A one year survival of 78% was reported among 63 TNBC patients receiving bevacizumab plus paclitaxel [43]. A randomized study of bevacizumab plus taxane +/− capecitabine was stopped after the first interim analysis showing no PFS benefit but