

## RESEARCH ARTICLE

# Anti-VEGF Therapy with Bevacizumab - Limited Cardiovascular Toxicity

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### Abstract

**Purpose:** This analysis was conducted to evaluate cardiovascular toxicity of commonly used anti-VEGF therapeutic agent, bevacizumab, in treating patients with cancer. **Methods:** Clinical studies evaluating the efficacy and safety of bevacizumab-based regimens on response and safety for patients with cancer were identified using a predefined search strategy, allowing cardiovascular toxicity and other side effects of treatment to be estimated. **Results:** In bevacizumab based regimens, 4 clinical studies including 282 patients with advanced cancer (including gliomas, cervical, breast and ovarian cancer) were considered eligible for inclusion. These bevacizumab-based regimens included docetaxel, irinotecan and carboplatin. Systematic analysis suggested that, of 282 patients treated by bevacizumab based regimens, hypertension and thrombo-embolism occurred in 2.5% (7/282), while only 3 patients reported cardiovascular events (1.1%). No treatment related death occurred in bevacizumab based treatment. **Conclusion:** This systemic analysis suggests that bevacizumab based regimens are associated with reasonable and accepted cardiovascular toxicity when treating patients with gliomas, cervical, breast and ovarian cancer.

**Keywords:** Anti-VEGF therapy - bevacizumab - cardiovascular toxicity

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### Introduction

Many therapies for cancer have been associated with the development of cardiovascular disease. The cumulative dose, the administration schedule, the intervals between doses, and the concomitant use of other cardiotoxic therapies determine the likelihood for certain chemotherapies to cause cardiovascular disease (Yeh et al., 2006).

Anthracycline-induced cardiovascular disease is one of the most extensively studied form of drug-induced cardiovascular disease. Cardiotoxicity of anthracyclines (eg., doxorubicin, daunorubicin, and epirubicin) is usually cumulative and dose dependent (Yeh et al., 2004). At total doses of less than 400 mg/m<sup>2</sup> body surface area, the incidence of congestive heart failure is 0.14%. This incidence increases to 7% at a dose of 550 mg/m<sup>2</sup> body surface area and to 18% at a dose of 700 mg/m<sup>2</sup> body surface area (Von Hoff et al., 1979). Several alkylating drugs (cyclophosphamide, ifosfamide, cisplatin, mitomycin) have been associated with the development of cardiovascular disease (Yeh et al., 2004).

In contrast to anthracyclines, the cardiotoxicity of cyclophosphamide seems to be related to the total dose given at an individual time point, rather than the cumulative dose (et al., 20). In recent years, several tyrosine kinase inhibitors have been associated with increased risk of the

development of cardiac dysfunction. Sunitinib is used for the treatment of renal cell carcinoma and gastrointestinal tumors. A small study showed that 11% of patients receiving Sunitinib developed LV dysfunction (Motzer et al., 2006). Similarly, Imatinib, a small-molecule inhibitor of the fusion protein Bcr-Abl, has been associated with the development of heart failure. Evidence from animal studies suggests that the inhibition of c-Abl is causally linked with cardiotoxicity (Kerkela et al., 2006). Dasatinib also targets Bcr-Abl as well as other tyrosine kinases. Although its cardiotoxicity is less well described, this drug has also been associated with the development of LV dysfunction (Bristol-Myers et al., 2006).

Bevacizumab, an anti-angiogenic agent, is a humanized monoclonal antibody directed against VEGFA and FDA approved for lung, colorectal, breast and brain cancers. Treatment with Bevacizumab increases the incidence hypertension when compared to patients treated with chemotherapy alone (11% versus 2.3%) (Hurwitz et al., 1998). In a study, 16.4% of patients experienced bevacizumab-associated hypertension that required new or changes in baseline antihypertensive medication (Hedrick et al., 2006). Hypertension associated with bevacizumab is likely related to VEGF inhibition, which decreases endothelial nitric oxide production. In patients treated with bevacizumab, the most clinically significant side effect was thrombosis, in both the venous and the arterial territory

(Kabbinavar et al., 2003; Chen et al., 2006). However, no large clinical trial was published to evaluate cardiovascular toxicities of commonly used anti-VEGF therapy, eg., bevacizumab, in treating patients with cancer. On this background, we report a pooled analysis on cardiovascular toxicity of bevacizumab in treating patients with selected refractory or relapsed solid tumors.

## Materials and Methods

### Search strategy

We searched PUBMED, by using the following search term: (bevacizumab) and (cardiovascular toxicity). All clinical studies evaluating the impact of bevacizumab on the occurrence of cardiovascular toxicities published in English prior to November 1<sup>st</sup>, of 2014 were identified. If samples of two studies overlap, only the latest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

### Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (1) Clinical studies, bevacizumab could be combined with paclitaxel or carboplatin; (2) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified metastatic and/or locally advanced cancers, bevacizumab was prescribed at 7.5-15 mg/kg, a performance status (WHO) 2, age < 18 years. Studies were excluded if one of the following existed: (1) duplicate data; (2) no sufficient data were reported.

### Data collection and analysis

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors; the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion.

Data was extracted by independent authors. The following recorded data were extracted: author, publication data, and country of the first or corresponding author, the number of patients.

## Results

There were 66 papers relevant to the search words by the end of November 1<sup>st</sup>, of 2014. Via steps of screening the title and reading the abstract, 4 studies were identified (Guiu et al., 2008; Monk et al., 2009; Abaid et al., 2010; Pivot et al., 2011) when bevacizumab was used in combination with paclitaxel or carboplatin. These studies had been carried out in Europe, and in the United States. The following outcomes were presented in all studies and extracted for combined analysis: grade 3 or 4 adverse events at least possibly related to bevacizumab included

hypertension (7/282), thrombo-embolism (7/282), myocardial infarction (1/282) and pulmonary embolism (2/282).

## Discussion

Cardiovascular disease and cancer are the main causes of death in China (Deng et al., 2014; Fan et al., 2014). Although development in prevention and treatment, these two diseases are still a great burden to patients. Results from previous reports are available for the diagnosis and treatment of heart disease and cancer. Cardiovascular disease and cancer are frequently diagnosed in similar clinical setting, because of the high prevalence of both diseases, and because some forms of cardiovascular disease are caused by cancer and the related treatment. Cardiovascular disease and cancer diagnosed in the same patient often complicates treatment, because therapy for one disease could negatively affect the outcome of the other disease. In addition, guidelines for the treatment of cancer are often based on studies which exclude patients who have cardiovascular disease. Therefore, generally accepted strategies for the diagnosis and therapy of cancer may not always apply to patients with cardiovascular disease. Two forms of chemotherapy-related cardiovascular disease have been proposed. Type I chemotherapy-related disease is often irreversible, dose related, mediated by free radical formation, and associated with ultrastructural changes. One example of type I chemotherapy-related disease is the cardiotoxic side effects of doxorubicin. In contrast, type II chemotherapy-related disease is frequently reversible, not dose dependent, mediated by blocked ErbB2 signaling, and usually not associated with ultrastructural changes (Ewer et al., 2005). Furthermore, tyrosine kinase inhibitors, eg., imatinib, induce another form of ultrastructural changes including mitochondrial abnormalities and accumulation of membrane whorls in both vacuoles and in the sarco- (endo-) plasmic reticulum (Kerkela et al., 2006).

Bevacizumab is a recombinant humanized monoclonal antibody that is part of the combination therapy with fluorouracil-based regimens for metastatic colorectal cancer (Shih et al., 2006). The combination therapy of bevacizumab and doxorubicin increases the rate of cardiomyopathy to a greater extent than expected just from the treatment with doxorubicin in patients who had not received prior chest radiotherapy or high doses of alkylating agents (two risk factors for increasing the risk of anthracycline-associated cardiomyopathy) (D'Adamo et al., 2005). Besides, there are several other clinical studies evaluating the efficacy and safety of bevacizumab based regimens on response and safety for patients with cancer. An American group conducted a phase II trial to assess the efficacy and tolerability of bevacizumab, eligible patients had recurrent cervical cancer, measurable disease, and GOG performance status < or = 2. Treatment consisted of bevacizumab 15 mg/kg intravenously every 21 days until disease progression or prohibitive toxicity. Primary end points were progression-free survival at 6 months and toxicities. As their results, 46 patients were enrolled (median age, 46 years); 38 patients (82.6%) received prior

radiation as well as either one ( $n = 34$ ) or two ( $n = 12$ ) prior cytotoxic regimens for recurrent disease. Grade 3 or 4 adverse events at least possibly related to bevacizumab included hypertension ( $n = 7$ ), thrombo-embolism ( $n = 5$ ), GI ( $n = 4$ ), anemia ( $n = 2$ ), other cardiovascular ( $n = 2$ ), vaginal bleeding ( $n = 1$ ), neutropenia ( $n = 1$ ), and fistula ( $n = 1$ ). One grade 5 infection was observed. Eleven patients (23.9%; two-sided 90% CI, 14% to 37%) survived progression free for at least 6 months, and five patients (10.9%; two-sided 90% CI, 4% to 22%) had partial responses. (Monk et al., 2009). A French study published in 2011 reported efficacy and safety of bevacizumab in combination with docetaxel in treating patients with locally recurrent or metastatic breast cancer (Pivot et al., 2011). In this study, patients with HER2-negative, locally recurrent or mBC were randomised to 3-weekly docetaxel (100mg/m<sup>2</sup>) with placebo, bevacizumab 7.5mg/kg or bevacizumab 15 mg/kg, for 9 cycles or until disease progression or unacceptable toxicity. Patients had no prior chemotherapy for mBC. Pivot et al. reported that progression-free survival was similar in the elderly and overall populations. Overall response rates for docetaxel plus placebo, bevacizumab 7.5 mg/kg and 15 mg/kg were 44.7%, 36.6% and 50.0%, respectively. Bevacizumab was well tolerated in elderly patients, the most common adverse effects were neutropenia and febrile neutropenia; there was no excess of grade-3 cardiovascular events. There was no clear correlation between baseline hypertension and its development during study treatment (Pivot et al., 2011).

A study from Hoag Cancer Center evaluated cardiovascular toxicity of bevacizumab, paclitaxel and carboplatin for patients with advanced ovarian cancer (Abaid et al., 2010). The first 20 patients were treated with six cycles of paclitaxel (175 mg/m<sup>2</sup>), carboplatin (AUC of 5 i.v.), and bevacizumab (15 mg/kg of body weight); q21 days per an independent protocol. The subsequent patients ( $n = 12$ ) were administered weekly paclitaxel (80 mg/m<sup>2</sup>), carboplatin (AUC of 5 i.v.) every four weeks, and bevacizumab (10 mg/kg of body weight) every two weeks for six cycles according to a separate, independent protocol. Bevacizumab was not added to either chemotherapy regimen until cycle 2. In both groups patients who achieved a complete response, partial response or stable disease at the conclusion of induction therapy received bevacizumab (10 mg/kg) and paclitaxel (135 mg/m<sup>2</sup>) q21 days as maintenance therapy. A total of 170 cycles (median = 6; range 3-6) of primary induction chemotherapy, 140 of which contained bevacizumab, were administered. And, 206 cycles (median = 9; range 1-12) of maintenance chemotherapy have been delivered to 28 patients thus far. There was no incidence of GI perforation and only two patients demonstrated clinically significant hypertension (Abaid et al., 2010).

Another French study reported the experience using the bevacizumab-irinotecan combination in treating patients with recurrent high-grade gliomas (Guiu et al., 2008). In this study, eight centers were involved. Bevacizumab-irinotecan was delivered by a commonly described method. Totally, 77 patients were treated (median age: 52 years; median Karnofsky score: 70) for a recurrent high-grade glioma (49 grade IV, 28 grade

III). At two months, the response rates were objective response=36%; stable disease=39%; progressive disease=13%; patients not evaluable because of a rapid fatal clinical deterioration=12%. Improvement was noted in 49% of patients. Among the main toxicities, we noted; intratumoral hemorrhage ( $n=5$  with spontaneous regression in three) and thromboembolic complications including venous thrombophlebitis ( $n=4$ ), pulmonary embolism ( $n=2$ ), myocardial infarction ( $n=1$ ), grade III-IV hematotoxicity ( $n=2$ ), reversible leukoencephalopathy ( $n=1$ ) (Guiu et al., 2008). One possible mechanism for the cardiotoxic effects of bevacizumab is its anti-angiogenic properties, which may lead to myocardial damage and subsequent cardiac dysfunction (D'Adamo et al., 2005).

Our pooled analysis suggested that in bevacizumab based regimens, when 4 clinical studies which including 282 patients with advanced cancer (gliomas, cervical, breast and ovarian cancer) were included, hypertension and thrombo-embolism occurred in 2.5% of patients (7/282), only 3 patients reported cardiovascular events (1.1%). No treatment related death occurred in bevacizumab based treatment. In conclusion, we suggests that bevacizumab based regimens are associated with reasonable and accepted cardiovascular toxicity when treating patients with gliomas, cervical, breast and ovarian cancer.

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