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., 2004). 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/m² body surface area, the incidence of congestive heart failure is 0.14%. This incidence increases to 7% at a dose of 550 mg/m² body surface area and to 18% at a dose of 700 mg/m² 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 VEGFα and FDA approved for lung, colorectal, breast and brain cancers. Treatment with Bevacizumab increases the incidence of 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, e.g., 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 1st, 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 1st, 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, e.g., 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$^2$) 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 leucrile 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$^2$), 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$^2$), 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$^2$) 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.

References

Abaid LN1, Lopez KL, Micha JP, et al (2010). Bevacizumab, paclitaxel and carboplatin for advanced ovarian cancer: low risk of gastrointestinal and cardiovascular toxicity. *Eur J Gynaecol Oncol*, 31, 308-11.

Alam M, Ratner D (2001). Cutaneous squamous-cell carcinoma. *N Engl J Med*, 344, 975-83.

Bleomycin in advanced squamous cell carcinoma: A random controlled trial (1976). Report of Medical Research Council Working Party on Bleomycin. *Br Med J*, 1, 188-90.

Bristol-Myers Squibb Company: Sprycel (Dasatinib) prescribing information. Princeton, NJ, 2006.

Chen HX, Mooney M, Boron M, et al. Phase II multicenter trial of bevacizumab plus fluorouracil and leucovorin in patients with advanced refractory colorectal cancer: an NCI Treatment Referral Center Trial TRC-0301. *J Clin Oncol*, 24, 3354-60.

Clayman GL, Lee JH, Holsinger FC, et al (2005). Mortality risk from squamous cell skin cancer. *J Clin Oncol*, 23, 759-65.

Lippman SM, Parkinson DR, Itri LM et al. 13-cis-retinoic acid from squamous cell skin cancer. *J Clin Oncol*, 13, 975-83.

D’Adamo DR, Anderson SE, Albritton K, et al (2005). Phase II study of doxorubicin and bevacizumab for patients with metastatic soft-tissue sarcomas. *J Clin Oncol*, 23, 7135-42

Deng QQ, Huang YE, Ye LH, et al (2013). Phase II trial of Loubo® (Lobaplatin) and pemetrexed for patients with metastatic breast cancer not responding to anthracycline or taxanes. *Asian Pac J Cancer Prev*, 14, 413-7.

Deng W, Long L, Li JL, et al (2014). Mortality of major cancers in guangxi, china: sex, age and geographical differences from 1971 and 2005. *Asian Pac J Cancer Prev*, 15, 1567-74.

Ewer MS, Lippman SM (2005). Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol*, 23, 2900-2.
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Fan JH, Wang JB, Jiang Y, et al (2014). Attributable Causes of Liver Cancer Mortality and Incidence in China. Asian Pac J Cancer Prev, 14, 7251-6.

Fujisawa Y, Umeyabashi Y, Ichikawa E, et al (2006). Chemoradiation using lowdose cisplatin and 5-fluorouracil in locally advanced squamous cell carcinoma of the skin: A report of two cases. J Am Acad Dermatol, 55, S81-5.

Gui S, Talibert S, Chinot O, et al (2008). Bevacizumab/irinotecan. An active treatment for recurrent high grade gliomas: preliminary results of an ANOCEF Multicenter Study. Rev Neurol, 164, S88-94.

Goldberg H, Tsalik M, Bernstein Z, et al (1994). Cisplatin-based chemotherapy for advanced basal and squamous cell carcinomas. Harefuah, 127, 217-21.

Guthrie TH Jr, McElveen JJ, Porubsky ES, et al (1985). Cisplatin and doxorubicin. An effective chemotherapy combination in the treatment of advanced basal cell and squamous carcinoma of the skin. Cancer, 55, 1629-32.

Guthrie TH Jr, Porubsky ES, Luxenberg MN, et al (1990). Cisplatin-based chemotherapy in advanced basal and squamous cell carcinomas of the skin: Results in 28 patients including 13 patients receiving multimodality therapy. J Clin Oncol, 8, 342-6.

Han A, Ratner D (2007). What is the role of adjuvant radiotherapy in the treatment of cutaneous squamous cell carcinoma with perineural invasion? Cancer, 109, 1053-9.

Hao ZF, Ao JH, Zhang J, et al (2013). APT3 activates Stat3 phosphorylation through inhibition of p53 expression in skin cancer cells. Asian Pac J Cancer Prev, 14, 7439-44.

Hedrick E, Kozloff M, Hainsworth J, et al. Safety of bevacizumab plus chemotherapy as first-line treatment of patients with metastatic colorectal cancer: updated results from large observational registry in the US (BRiTE). J Clin Oncol 2006, 24 (suppl), 155s (abstract 3536).

Hurwitz H, Fehrenbacher L, Novotny W, et al (1999). Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med, 340, 2335-42.

Ikegawa S, Saïda T, Obayashi H, et al (2013). Cisplatin combination chemotherapy in squamous cell carcinoma and adenoid cystic carcinoma of the skin. J Dermatol, 36, 227-30.

Joseph MG, Zuluetta WP, Kennedy PJ, et al (1992). Squamous cell carcinoma of the skin of the trunk and limbs: The incidence of metastases and their outcome. Aust NZ J Surg, 62, 697-701.

Jambusaria-Pahlajani A, Miller CJ, Quon H, et al (2009). Surgical monotherapy versus surgery plus adjuvant radiotherapy in high-risk cutaneous squamous cell carcinoma: A systematic review of outcomes. Dermatol Surg, 35, 574-85.

Kabbinavar F, Hurwitz HJ, Fehrenbacher L, et al (2003). Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol, 21, 60-5.

Kerkela R, Grazette L, Yacobi R, et al (2006). Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nat Med, 12, 908-16.

Kphansur T, Kennedy A (1991). Cisplatin and 5-fluorouracil for advanced locoregional and metastatic squamous cell carcinoma of the skin. Cancer, 67, 2030-32.

Merimsky O, Neudorfer M, Spitzer E, et al (1992). Salvage cisplatin and Adriamycin for advanced or recurrent basal or squamous cell carcinoma of the face. Anticancer Drugs, 3, 481-4.

Miller AB, Hoogstraten B, Staquet M, et al (1981). Reporting results of cancer treatment. Cancer, 47, 207-24.

Miller DL, Weinstock MA, et al (1994). Nonmelanoma skin cancer in the United States: Incidence. J Am Acad Dermatol, 30, 774-8.

Minton TJ, et al (2008). Contemporary Mohs surgery applications. Curr Opin Otolaryngol Head Neck Surg, 16, 376-80.

Mohs F, et al (1978). Chemosurgery: Microscopically Controlled Surgery for Skin Cancer. Springfield, Ill.: Charles C. Thomas, 153-64.

Monk BJ, Sill MW, Burger RA et al (2009). Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol, 27, 1069-74.

Motzer RJ, Michaelson MD, Redman BG, et al (2006). Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. J Clin Oncol, 24, 16-24.

Nakamura K, Okuyama R, Saida T, et al (2013). Platinum and anthracycline therapy for advanced cutaneous squamous cell carcinoma. Int J Clin Oncol, 18, 506-9.

Pivot X, Schneeweiss A, Verma S et al (2011). Efficacy and safety of bevacizumab in combination with docetaxel for the first-line treatment of elderly patients with locally recurrent or metastatic breast cancer: results from AVADO. Eur J Cancer, 47, 2387-95.

Sadek H, Azli N, Wendling JL, et al (1990). Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin. Cancer, 66, 1692-9.

Shih T, Lindley C (2006). Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. Clin Ther, 28, 1779-802.

Shin DM, Glisson BS, Khuri FR, et al (2002). Phase II and biologic study of interferon alfa, retinoic acid, and cisplatin in advanced squamous skin cancer. J Clin Oncol, 20, 364-70.

Veness MJ, Morgan GJ, Palme CE, et al (2005). Surgery and adjuvant radiotherapy in patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph nodes: Combined treatment should be considered best practice. Laryngoscope, 115, 870-5.

Von Hoff DD, Layard MW, Basa P, et al (1979). Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med, 91, 710-7.

Wu Q, Zhao YB, Sun ZH, et al (2013). Clinical application of endoscopic inguinal lymph node resection after lipolysis and liposuction for vulvar cancer. Asian Pac J Cancer Prev, 14, 7121-6.

Yeh ET. Cardiotoxicity induced by chemotherapy and antibody therapy. Circulation, 109, 47-54.

Yeh ET, Tong AT, Lenihan DJ, et al (2004). Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation, 109, 3122-31.