Bevacizumab treatment for cancer patients with cardiovascular disease: a double edged sword?

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Received 3 July 2008; accepted 25 July 2008; online publish-ahead-of-print 1 September 2008

Recently, bevacizumab, the novel humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), has shown promising preclinical and clinical anti-cancer activity. However, concerns have been raised regarding a possible increased risk for arterial thrombo-embolic events associated with its administration, especially in patients with pre-existing cardiovascular disease. On the other hand, bevacizumab treatment is associated with an increased bleeding risk that may be augmented by the co-administration of anti-platelet drugs such as aspirin and clopidogrel. In this paper, we present the available data, identify controversies and unresolved issues, and suggest solutions regarding the administration of bevacizumab to cancer patients with cardiovascular disease.

Keywords Bevacizumab • Thrombosis • Bleeding

In recent years, bevacizumab, the novel humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), has shown promising preclinical and clinical anti-cancer activity in various malignancies.1–6 Bevacizumab acts by inhibiting angiogenesis which plays a central role in both local and metastatic tumour expansion. It also improves delivery of chemotherapy by altering tumour vasculature and decreasing the elevated interstitial pressure in the malignant tissue.1–6 It has been found to improve survival of patients with metastatic colon cancer1–3 or with nonsquamous non-small cell lung carcinoma4 and progression-free survival of patients with metastatic breast cancer5,6 especially when combined with conventional chemotherapy regimens.

Recently, concerns have been raised regarding a possible increased risk of arterial thromboembolic events associated with bevacizumab treatment, especially in patients with pre-existing cardiovascular diseases, or in those with multiple risk factors of atherosclerosis.1–9 The mechanism for this pro-thrombotic effect is likely to be multi-factorial and remains to be fully elucidated. It appears that the administration of bevacizumab is associated with up to 30% risk of developing hypertension,1–9 which appears to be related to a decreased production of endothelial nitric oxide (NO) that is a potent vasodilator.10 Furthermore, decreased levels of NO are associated with increased platelet aggregation and adhesion to the vascular endothelium.11,12 It has been demonstrated that VEGF blockade results in endothelial injury and sub-endothelial collagen exposure with subsequent tissue factor activation8 and increased expression of pro-inflammatory genes, including genes for cyclooxygenase-2 and E-selectin.10 All these effects can activate the coagulation system and lead to in situ thrombus formation. Finally, due to the key role of VEGF in angiogenesis it may be speculated that bevacizumab impairs the development of collaterals, which is an important mechanism to compensate for obstructive coronary disease. This issue is further complicated by the cancer-associated hypercoagulable state that in itself increases the risk of cardiovascular events.

On the other hand, bevacizumab treatment is associated with increased bleeding risk1,6 secondary to tumour necrosis and decreased renewal capacity of endothelial cells.7,8 This bleeding risk may be augmented by co-administration of anti-platelet drugs such as aspirin and clopidogrel in patients with cardiovascular disease. The increasing popularity of bevacizumab and the improved survival associated with its administration may make these issues even more relevant in the future.

Among the different placebo-controlled trials comparing the combined treatment of bevacizumab and chemotherapy vs. chemotherapy alone, several have demonstrated trends for increased risk of arterial thromboembolic complications.1,3,4,6 However, the event rate was relatively low and these trends did not reach statistical significance. Most of these trials excluded patients with history of stroke or myocardial infarction, unstable angina, serious cardiac arrhythmias and clinically significant congestive heart failure or peripheral vascular disease within 6–12 months.
prior to enrolment. Patients treated with anti-platelet drugs, except for low dose aspirin (<325 mg/day), or with full dose anti-coagulation were excluded as well.

A pooled analysis of five randomized controlled trials including a total of 1745 patients with different metastatic malignancies demonstrated an increased risk of arterial thromboembolic events with combination treatment of bevacizumab and chemotherapy compared with chemotherapy alone (HR = 2.0, 95% CI = 1.05–3.75, P = 0.031). The absolute event rates were 5.5 and 3.1 events per 100 person-years and the median time for the first event were 2.1 and 2.6 months in the chemotherapy plus bevacizumab combination therapy and chemotherapy alone, respectively. Most thromboembolic events were coronary or cerebrovascular and the number of events that resulted in death did not differ statistically between the two groups. Among the different baseline characteristics, only history of a prior arterial did not differ statistically between the two groups. Among the cerebrovascular and the number of events that resulted in death most thromboembolic events were coronary or was 2.1 and 2.6 months in the chemotherapy plus bevacizumab combination therapy and chemotherapy alone, respectively.

The rate of grade 3 and 4 bleeding events per 100 person-years of follow-up was 5.3 and 3.3 in the chemotherapy plus bevacizumab combination therapy and chemotherapy alone, respectively (HR = 1.6, 95% CI = 0.86–2.97, P = 0.13). No significant increased risk of bleeding events was observed in aspirin users compared with non-users in either the control or bevacizumab-treated patients. Finally, significant improvement in overall survival was associated with bevacizumab treatment in both the overall population and in all subgroups. This survival benefit persisted but to a lesser extent in the subgroup with both major risk factors (age ≥65 years and history of an arterial thromboembolic event).

The available data regarding the thromboembolic complications of bevacizumab have several limitations. First, the information is derived from a relatively small number of studies focusing on different malignancies that were treated with bevacizumab combined with different chemotherapy regimens. Secondly, these studies were designed to evaluate the efficacy of bevacizumab, and the occurrence of thromboembolic and bleeding events were secondary outcomes. Thirdly, the increased survival and delayed time to progression associated with the administration of bevacizumab may supersede the risk of an arterial thromboembolic or a bleeding event compared with the placebo group. Finally and perhaps most importantly, due to the strict exclusion criteria of all these studies, patients with significant or recent cardiovascular disease (those at highest risk of bevacizumab-associated thromboembolic complications) were not enrolled.

Currently, according to the limited clinical experience to date, it appears that cancer patients <65 years with multiple risk factors of atherosclerosis but no prior thromboembolic event may be treated with bevacizumab without an obvious increased risk of cardiovascular complications. The risk of cardiovascular complications is highest in patients ≥65 years with a history of a prior thromboembolic event. However, even in this high risk group, treatment with bevacizumab seems to be associated with an obvious survival benefit. Furthermore, existing evidence suggests that co-administration of low dose aspirin reduces the risk of cardiovascular events associated with bevacizumab.

Although co-administration of low dose aspirin was not found to significantly increase the risk of major bleeding events in bevacizumab-treated patients, there are no reports regarding co-administration of clopidogrel and bevacizumab. Therefore it seems reasonable that patients undergoing coronary angioplasty who require stenting and in whom bevacizumab treatment is planned should be treated with bare-metal stents that require a shorter duration of clopidogrel treatment.

Finally, based on the limited available experience it appears that the administration of bevacizumab may be associated with improved outcomes, even in patients with pre-existing cardiovascular diseases. However, the relatively scant data regarding possible thrombotic and bleeding complications associated with bevacizumab emphasize the critical need for multi-centre collaborative registries and post-marketing surveillance to studies to collect and follow a large number of cancer patients treated with bevacizumab. More extensive follow-up studies will enable physicians to more accurately identify cancer patients in whom the risk of atherothrombotic or bleeding complications may overcome the anti-cancer effect of bevacizumab.

Conflict of interest: none declared.

References