



Bevacizumab in clinical practice

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Abstract

The development of targeted therapies and especially angiogenesis inhibitor drugs is undoubtedly a major advancement in the treatment of cancer in the 21st century. Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor that was approved for the treatment of multiple solid tumors, we have reviewed the side effects cited in clinical trials of bevacizumab and the guidelines for their management and we can conclude that bevacizumab, is generally well tolerated but is associated with increase in some

adverse side effects for which monitoring is required particularly vascular and renal side effects including hypertension, proteinuria, thromboembolic events and hemorrhage. The better understanding of bevacizumab toxicity profile and the guidelines for their optimal management as well as the education of patients may allow prolonged therapy and thus improved clinical outcomes.

Keywords

Angiogenesis, bevacizumab, hypertension, proteinuria, safety, toxicity

Introduction

Angiogenesis represents an important step in the pathogenesis, invasion, progression and development of metastatic cancer and is regulated by pro-angiogenic factors such as vascular endothelial growth factor (VEGF).⁽¹⁾ Bevacizumab is a humanized immunoglobulin monoclonal antibody that binds to and inhibits the activity of VEGF, which leads to the regression of existing tumor micro-vasculature, normalization of surviving tumor vasculature and inhibition in the formation of new vasculature.⁽²⁾ Bevacizumab is the subject of several trials and has shown clinical benefits and efficacy in multiple types of malignancies including metastatic colorectal cancer, non-small-cell lung cancer, breast cancer, as well as renal cell cancer, recurrent glioblastoma multiforme and recently in ovarian cancer. Toxicities associated with bevacizumab across the trials have been consistent, although chemotherapy toxicities differ. They were generally mild to moderate in intensity and generally manageable⁽³⁾ but can occasionally be serious, even lethal and require monitoring and specific management.

In this context, we have reviewed the side effects cited in clinical trials of bevacizumab and the

guidelines for their optimal management to make this document simplified and practice for use by the different medical professionals.

Hypertension: Hypertension is the most common side effect of bevacizumab therapy. The incidence varies across indications. The cause is not entirely clear, but it may be due to decreased production of the vasodilator nitric oxide (NO) by blockade of the VEGF receptors.⁽⁴⁾ Reduced NO production also leads to reduced renal sodium excretion which may contribute to hypertension.⁽⁵⁾ Hypertension can occur at any time during the course treatment and blood pressure should, therefore, be monitored at least once a week during treatment and before every dose. In addition, pre-existing hypertension should be adequately controlled before starting avastin treatment, however prophylactic antihypertensive therapy is not recommended. Hypertension grade 2 according to the NCI-CTCAE v3.0 can generally

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be well controlled with monotherapy that must be initiated in case of persistent and/or symptomatic hypertension with standard antihypertensive therapy; typically angiotensin–converting enzyme (ACE) inhibitors, beta–blockers calcium channel blockers, angiotensin receptor blockers or diuretics. Currently ACE inhibitors may be a more logical choice due to their added benefit of decreasing bevacizumab–associated proteinuria.⁽⁶⁾

Concerning patients with severe (grade 3) hypertension, temporary interruption of Avastin is recommended until adequate control is achieved with more than one antihypertensive drug. If hypertension cannot be controlled, Avastin should be permanently discontinued as well as if grade 4 hypertension occurs, including: hypertensive crisis, hypertensive encephalopathy or reversible posterior leukoencephalopathy syndrome (RPLS). (see Table 1) Moreover, discontinuation of Avastin is rarely required due to hypertension. Besides, much evidence was suggested recently that bevacizumab–induced hypertension might be predictive of the effect of bevacizumab.⁽⁷⁾

Proteinuria: Proteinuria is an established side effect of bevacizumab therapy. It is usually asymptomatic and grade 3 and 4 are rare (1–3%).^(8,9) The mechanism of this adverse event is not fully understood, but it may be due to the fact that VEGF maintains the glomerular and peritubular capillary network in the kidney. Use of anti VEGF agent may

therefore perturb this network of blood vessels leading to glomerular dysfunction and proteinuria.⁽¹⁰⁾ Monitoring is recommended prior to each cycle. 24–hour urine collection should be used before the next treatment if the dipstick reading is $\geq 2+$ (3+ on second and subsequent occurrences). Thereafter, bevacizumab should be interrupted if urine protein levels are $\geq 2\text{g}/24\text{h}$ and can be restarted once levels are $<2\text{g}/24\text{h}$ and when levels are $<1\text{g}/24\text{h}$ the monitoring can be resumed to dipstick urinalysis. For grade 3 proteinuria, avastin must be discontinued until 24 hour urine collection decreases to $< 2\text{g}/24\text{h}$ (see Table 2). Proteinuria is generally reversible but in case of nephrotic syndrome treatment should be stopped permanently.⁽¹¹⁾ It has been suggested recently that higher dosages of bevacizumab was associated with increased risk for proteinuria, however there was no significant correlation between the risk for high grade proteinuria and clinical outcomes of bevacizumab based treatment.⁽¹²⁾

Bleeding/hemorrhage: VEGF is a major factor regulating vascular endothelial cell mitogenesis; disruption of this process by anti VEGF agents may decrease the renewal capacity of endothelial cells in response to trauma.⁽¹³⁾ Bevacizumab has been associated with an increased risk of bleeding of all grades, although most bleeding events are mild, self–limited, and frequently mucosal without need for medical intervention or bevacizumab permanent discontinuation except in patients who experience a repeat grade 3 or a new grade 4 bleeding.

Grade	Description	Management
Grade 1	Asymptomatic, transient (<24hours) increase in blood pressure by >20mm Hg (diastolic) or to>150/100 mm Hg if previously within normal limits.	No intervention required
Grade 2	Recurrent or persistent (>24 hours) or symptomatic increase in blood pressure by >20mm Hg (diastolic) or to >150/100 mm Hg if previously within normal limits.	Initiate monotherapy and resume bevacizumab if blood pressure remains < 160/100
Grade 3	Requiring more than one drug or more intensive therapy than previously	Stop Bevacizumab until adequate control is achieved by antihypertensive medications.
Grade 4	Life–threatening (eg, hypertensive crisis)	Permanently discontinue the bevacizumab

Table 1. Guidelines for management of hypertension and grading according to the national Cancer Institute–Common Toxicity Criteria (NCI–CTC) version 3.0

Grade:	Description	Management
Grade 1	1+ protein on urinalysis or 0,15 to 1 g of protein in 24h urine collection	Continue bevacizumab
Grade 2	2+ to 3+ or 1 to 3,5 g/24hours	Give bevacizumab and collect 24 hour urine before the next cycle. – Resume bevacizumab only if < 2g/24h – If not < 2g/24h For 3 months discontinue bevacizumab
Grade 3	4+ or > 3,5 g/24hours	Hold and obtain 24h urine collection before the next cycle.
Grade 4	Nephrotic syndrome (3,5 g/24hours plus edema and hypertension)	Permanently discontinue the bevacizumab

Table 2. Guidelines for management of proteinuria and grading according to the national Cancer Institute–Common Toxicity Criteria (NCI–CTC) version 3.0

In the registry trial ARIES (n=1,970), there was no statistically significant association between tumor cavitation and risk for severe pulmonary hemorrhage.⁽¹⁴⁾ Data from literature also suggest that bevacizumab did not increase the risk of severe bleeding in cancer patients who received therapeutic anticoagulation.⁽¹⁵⁾ A notable toxicity in the E4599 NSCLC study was the occurrence of two deaths from hemoptysis, prompting the exclusion of patients with a history of significant hemoptysis and centrally located squamous cell tumors from receiving bevacizumab.⁽¹⁶⁾ It is noteworthy that the results of a retrospective analysis of more than 12,000 patients demonstrates that the risk of cerebral hemorrhage, in the presence of CNS metastases, is independent of bevacizumab therapy. The European Medicines Authority has thereafter, removed label restriction to allow patients with untreated CNS metastases to receive bevacizumab.⁽¹⁷⁾

Less frequently reported side effects:

Venous and arterial thromboembolic events: An increase in incidence of arterial thromboembolism is observed in patients treated with bevacizumab

compared with those receiving chemotherapy alone (4,5 vs. 2%).⁽²⁾ Besides, several factors have been identified including : a prior history of stroke/heart attack, patients with hypertension and those aged ≥ 65 years. Aspirin (<325mg) could be considered safely for suitable patients at high risk of arterial thromboembolic events.⁽¹⁸⁾ But if any grade of this side effect develop during bevacizumab therapy, the patient should be taken off–treatment. In addition, if any grade 3 or 4 venous thromboembolic events occur, the treatment should be held and restarted when anticoagulation parameters have stabilized in 2 to 3 weeks whereas patients with symptomatic pulmonary embolism must not be treated with bevacizumab.

Wound healing complications: Bevacizumab has a half–life of about twenty days. This suggest that wound healing complications risk declines considerably in patients who have a sufficient break in bevacizumab therapy, particularly twenty eight days surrounding surgery.⁽¹⁹⁾ However, the optimal interval has still to be defined.

Gastrointestinal perforation: Gastrointestinal perforation is a rare but serious complication of

bevacizumab therapy. ⁽²⁰⁾ Patients with abdominal carcinomatosis, acute diverticulitis, obstruction or with a history of pelvis/abdominal radiation are at an increased risk for complication and must be monitored for early symptoms and signs of perforation that must lead to bevacizumab discontinuation.

Reversible posterior leukoencephalopathy syndrome: This is a very rare neurological syndrome that is characterized by seizures, headaches, altered mental status, visual disturbance or cortical blindness and may also be associated with hypertension. If suspected the diagnosis is confirmed by MRI and bevacizumab must be stopped. ⁽²¹⁾

Conclusion

Bevacizumab is an all-or-none drug, so the dose is not to be titrated. The most frequent, usually mild, adverse events can be managed successfully with regular monitoring but can occasionally be serious and require temporary to permanent discontinuation. Hence, the better understanding of bevacizumab toxicity profile and the guidelines for their optimal management as well as the education of patients will be the key to administering it safely.

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