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REVIEW ARTICLE

Safety and Tolerability of Bevacizumab across Tumour Types

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ABSTRACT

Bevacizumab is one of the novel pharmacological agents used for the treatment of multiple tumour types including metastatic colorectal cancer, non–small-cell lung cancer, metastatic breast cancer, glioblastoma multiforme, and metastatic renal carcinoma. A humanised monoclonal antibody, bevacizumab is a vascular endothelial growth factor inhibitor. Key clinical trial data confirm its efficacy in improving progression-free survival and overall survival across multiple cancers. Several adverse events including hypertension, proteinuria, increased risks of bleeds, wound healing complications, gastrointestinal perforations and thromboembolic events have been associated with bevacizumab treatment. This paper outlines the aetiology and risk factors associated with their development in bevacizumab-treated patients. Importantly, practical clinical management of adverse events arising from bevacizumab treatment is also presented. Given the favourable bevacizumab efficacy data, a good understanding of the potential adverse events, together with practical strategies to avoid and / or manage these, can help clinicians make appropriate clinical management decisions to maximise benefits for cancer patients.

Key Words: *Adverse effects; Bevacizumab; Drug toxicity; Safety; Vascular endothelial growth factors*

中文摘要

Bevacizumab對於不同腫瘤的安全性及耐受性

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Bevacizumab是其中一種嶄新的藥物製劑，可醫治不同種類的腫瘤，包括轉移性結直腸癌、非小細胞肺癌、轉移性乳腺癌、膠質母細胞瘤、及轉移性腎臟癌。Bevacizumab是一種擬人化單克隆抗體，用作抑製血管內皮生長因子。重要的臨床數據顯示bevacizumab可以有效改善患有不同腫瘤的病人的無惡化生存期及總體存活率。但同時亦發現以下的副作用與bevacizumab相關，包括高血壓、蛋白尿、出血風險上升、傷口癒合併發症、胃腸道穿孔及血栓事件。本文概述接受bevacizumab治療的病人出現副作用的病因及風險因素，並重點討論有關這藥物副作用的實用臨床治理。由於資料顯示bevacizumab有臨床效用，了解其潛在副作用, 及用以避免及治理這些副作用 的策略有助醫生制定適當的臨床決定，以確保癌症病人得到最大利益。

INTRODUCTION

According to the Hospital Authority's latest statistical report, cancer is the leading cause of death in Hong Kong.[1] Together, lung, colorectal cancer (CRC), and breast cancers account for about 45% of all newly diagnosed cancers in the territory.[2]

Over the last decade, there have been significant improvements in the availability of pharmacological options for the treatment of cancers. This has led to

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improved survival and quality of life. It should be noted that new chemotherapeutic agents and biological therapies contribute greatly to this.

Bevacizumab is one of the novel chemotherapeutic agents used for the treatment of metastatic colorectal cancer (mCRC), non–small-cell lung cancer (NSCLC), metastatic breast cancer, glioblastoma multiforme (GBM), and metastatic renal cell carcinoma. Bevacizumab is a humanised monoclonal antibody that specifically inhibits vascular endothelial growth factor (VEGF).[3]

BEVACIZUMAB AND VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITION

Angiogenesis is a fundamental process required for tumour growth and metastasis, and is mediated primarily through the interaction between VEGF and VEGFR-2 (receptor tyrosine kinase of the VEGF receptor family).[4,5] Direct and continuous targeting of VEGF is an important anti-tumour strategy based on continuous expression of VEGF throughout the tumour life cycle as well as proposed genetic stability of VEGF and endothelial cells.[5,6] Given the central role of angiogenesis in tumour development, anti-angiogenic agents can play a pivotal role in cancer treatment.

Bevacizumab directly inhibits VEGF extracellularly and may therefore cause angiogenesis inhibition without disrupting targets outside the VEGF pathway.[3,5,7,8] Key clinical trials of bevacizumab have proven efficacy in improving progression-free survival (PFS) and overall survival (OS) across multiple cancers.[9-14]

Bevacizumab's direct inhibition of VEGF allows for greater precision than other means of targeting the VEGF pathway. As a result, unwanted inhibitory effects on non–VEGF-mediated functions could be avoided. Nevertheless, several adverse reactions with bevacizumab use have been described, including:

- Common adverse events (AEs): hypertension, proteinuria, bleeding;
- Uncommon, 'class-related' AEs: wound healing complications (WHCs), gastrointestinal (GI) perforation, arterial thromboembolic events (ATE) / venous thromboembolic events (VTE); and
- Rare (but serious) AEs: congestive heart failure, reversible posterior leukoencephalopathy, fistulae, hypersensitivity, and infusion reactions.

The incidence of AEs which are grade 3 or above in severity are consistent across phase III and observational studies (Table 1[9,10,13-20]). These data are further supported by experience gained from the use of bevacizumab in over 1 million patients.

From phase III clinical studies, the rates of 60-day and AE-related mortality are not significantly different.[9-14] This shows that the occurrence of a serious AE does not increase the risk of death in bevacizumab-treated patients.

Vascular regression, as a result of bevacizumab therapy, has translated into significant improvements in tumour response.[9,11,15,20,21] Given the favourable bevacizumab efficacy data, a good understanding of the potential AEs, together with practical strategies to avoid and/or manage these AEs, can help clinicians make appropriate clinical management decisions in order to maximise the benefit of bevacizumab for cancer patients.

AETIOLOGY, RISK FACTORS, AND MANAGEMENT OF BEVACIZUMAB-RELATED ADVERSE EVENTS

Hypertension

It is not known what causes hypertension, but VEGF stimulates nitric oxide (NO) production which normally decreases vascular resistance and blood pressure.[22,23] By the same reasoning, VEGF inhibition may well decrease NO production and cause a rise in blood pressure. Reduced NO may also decrease renal sodium excretion, further contributing to hypertension.[24]

In the absence of formal risk factors, physicians should also consider patient lifestyles and family histories. The frequency of hypertension in bevacizumab-treated

Table 1. Frequency of grade ≥3 adverse events from phase III and observational studies.

Selected grade ≥3 AEs	Phase III trials (%)[9,10,13-15]	Observational studies (%)[16-20]
Hypertension	3-15	4-22*
Proteinuria	1-7	1-3
Bleeding	2-4	1-4
WHC	≤1	≤1
GI perforation	1-2	<1-2
ATE/VTE	≤8	2-8

Abbreviations: AE = adverse events; WHC = wound healing complications; GI = gastrointestinal; ATE/VTE = arterial / venous thromboembolic events.

* Higher cumulative incidence of hypertension in BRiTE related to bevacizumab treatment duration.

patients is of the order of 3 to 20% from data across clinical studies.[9,10,13,15-19]

In the Bevacizumab Regimens: Investigation of Treatment Effects and Safety (BRiTE) study, of the 22% of patients who developed *de novo* hypertension, 68% were well managed with only one antihypertensive agent. With the addition of a second antihypertensive, clinicians managed to control blood pressure in 95% of affected patients.[25]

It should be noted that only 1% of patients in BRiTE discontinued bevacizumab due to uncontrolled hypertension.[25] A subanalysis of this study also showed that all classes of antihypertensives were effective in controlling bevacizumab-related hypertension.

Management

The suggested management of bevacizumab-related hypertension is shown in Table 2.[26,27] As a general rule, blood pressure measurements should be conducted on each patient prescribed bevacizumab prior to each treatment cycle. If diastolic blood pressure was below 100 mm Hg, bevacizumab treatment may be commenced but patients may need to take antihypertensive treatment. However, in those whose diastolic blood pressure exceeds 100 mm Hg, treatment with antihypertensives should be used to control the blood pressure prior to starting bevacizumab.[26]

Proteinuria

Glomerular endothelial cells may require VEGF signalling for efficient cell repair.[28] Defective cell repair could, in turn, lead to ineffective renal filtration and consequently, proteinuria.[26] The incidence of grade 3 or higher proteinuria is 1 to 3%, based on data from clinical and observational studies, while the frequency of nephrotic syndrome is 0.5%.[9,10,13,15-19]

There are currently no known risk factors for proteinuria. However, clinicians should be cautious using bevacizumab in patients with existing renal disease.[26]

Management

In clinical trials, proteinuria was not associated with renal dysfunction and rarely was the reason for discontinuation of bevacizumab. Clinicians should measure urinary protein by dipstick analysis before initiating bevacizumab at least once per month while patients remain on the treatment.

No treatment is required for bevacizumab-related grade 1 proteinuria. In patients who develop grade 2 proteinuria, clinicians should monitor urinary protein over 24 hours. Treatment may be continued if urinary protein levels are below 2 g/24 hours. However, bevacizumab should be withheld in patients with urinary protein excretion exceeding 2 g/24 hours, but may be resumed once urinary protein levels drop below 2 g/24 hours (Table 2).[26]

Bleeding

VEGF is required for the survival and maintenance of immature blood vessels as well as the repair of existing vessels.[29] Inhibition of VEGF may therefore reduce the ability of blood vessels to heal after trauma or damage.[30]

Clinicians should exercise caution when using bevacizumab for patients who have inherited or acquired

Table 2. Suggested management strategies for bevacizumab-related adverse events.[26,27]

	Grade 1	Grade 2	Grade 3	Grade 4
Hypertension	Continue bevacizumab treatment, no therapy required	Discontinue bevacizumab and treat with oral hypertensive medication, resume bevacizumab once hypertension is under control		Oral hypertensive medication and permanently discontinue bevacizumab
Proteinuria	1+ proteinuria: continue bevacizumab treatment, no therapy required	≥2+ proteinuria: monitor 24-hour urine; <2 g continue treatment; >2 g hold bevacizumab	Nephrotic syndrome: permanently discontinue bevacizumab	
Bleeding	Use standard first aid or medical procedure as appropriate, continue bevacizumab treatment		Permanently discontinue bevacizumab treatment	
Thromboembolic events: VTE	Closely monitor patients: use anticoagulation therapy and withhold bevacizumab for 2 weeks for grade 3 events (no increased risk of bleeding)[26,27]			Permanently discontinue bevacizumab
Thromboembolic events: ATE	Permanently discontinue bevacizumab; prophylactic low-dose aspirin can be considered for patients at risk[27]			

Abbreviations: VTE = venous thromboembolic event; ATE = arterial thromboembolic event.

coagulopathy, or are receiving anticoagulations.[26] From clinical and observational studies, the frequency of bleeds at or above grade 3 in severity are between 1 and 4%.[9,10,13,15-19]

Phase II clinical trial data show that squamous cell histology and central tumour location are major risk factors for severe pulmonary haemorrhage.[31] In subsequent trials, the exclusion of patients with these characteristics has reduced the frequency of severe pulmonary haemorrhage from 9% to below 1.5%.[32]

In the treatment of NSCLC patients, bevacizumab should only be used in patients with unresectable, advanced, metastatic, or recurrent tumours with non-squamous histology. In patients with NSCLC, the major risk factors for bleeding include[26]:

- previous haemoptysis (>1 teaspoon at a time);
- squamous cell histology (risk increases to 99% when bevacizumab is used); and
- centrally located tumours (with an infiltrating tumour, it is best to avoid bevacizumab).

Management

Most bleeding events are grade 1-2, mucocutaneous in origin and could be well managed with standard treatment.[26]

Grade 1 bleeds (e.g. nose bleeds) are very common and may occur in approximately one in two patients on bevacizumab. Standard first aid or medical procedures are effective management strategies. Bevacizumab does not need to be discontinued in these patients. However, bleeding can be serious (grades 3 and 4 bleeds) in which case bevacizumab therapy should cease (Table 2), and not be restarted until there have been appropriate interventions to address the cause of the serious bleeds.

Wound Healing Complications

WHCs may include wound dehiscence, ecchymosis, and bleeding.[26] As the VEGF pathway is important for normal wound healing,[33] VEGF inhibition may disrupt the wound healing process by preventing growth and development of new blood vessels.[26] WHCs are rare (<1% across studies),[9,10,13,15-19] and associated risk factors have not yet been identified.

Management

In bevacizumab-treated patients having major elective surgery, the drug should be withdrawn five to eight weeks prior to elective surgery and restarted four weeks later.[34] For minor surgeries, it could be restarted about one week post-surgery. These strategies markedly reduce the risk of developing WHCs.

If WHCs occur, bevacizumab should be withheld until they are completely resolved.[34] Bevacizumab should be permanently discontinued if a fistula or intra-abdominal abscess is diagnosed. Wound dehiscence is also another valid reason to permanently discontinuing the treatment.[26]

Gastrointestinal Perforation

GI perforations are more common in patients with colorectal or ovarian cancers than in patients who have GBM, lung or breast cancers. Bowel perforations may occur as a tumour embedded in the intestinal wall shrinks in response to therapy.[26] Non-tumour site perforations may be related to delayed would healing caused by the cytotoxic chemotherapy backbone.[21]

While no baseline risk factors have been identified, underlying intra-abdominal inflammation often accompanies GI perforations. In patients treated with bevacizumab plus chemotherapy, the frequency of GI perforations is rare (≤2% across studies).[9,10,13,15-19]

From the BRiTE study,[35] it was observed that radiation to the pelvic region mildly increases the frequency as does the use of non-steroidal anti-inflammatory drugs including aspirin.

While the history of peptic ulcer disease did not increase the frequency of GI perforations,[35] they can occur if patients have active peptic ulcers or diverticulitis. In such patients, bevacizumab should be withheld until the lesions have completely healed. BRiTE also showed that the majority of GI perforations occur within the first three months of bevacizumab treatment.[35]

Management

Bevacizumab should be permanently discontinued in patients who develop GI perforations while on treatment, and clinical management used should be in line with the severity of bevacizumab-related GI perforations. Clinicians should be mindful of the potential for WHCs if surgery is deemed required.[26]

Thromboembolic Events

VEGF inhibition may make endothelial cells susceptible to apoptosis leading to exposure of the basement membrane and the potential to induce clot

formation.[27,30,36,37] Risk factors of bevacizumab-related thromboembolic events include[25,27]:

- history of ATEs;
- age >65 years; and
- poor performance status.

Both ARIES (A Study of Avastin in Combination With Chemotherapy for Treatment of Colorectal Cancer and Non-Small Cell Lung Cancer[38]) and BRiTE[16] studies showed that age is not as important a risk factor as a history of ATEs and poor performance status. Across studies, the frequency of thromboembolic events of greater than grade 3 severity is less than 8%.[9,10,13,15-19]

Management

Clinicians should consider risk factors (as stated above) prior to initiating bevacizumab. All patients receiving bevacizumab treatment should be monitored for thromboembolic events.

Clinicians should closely monitor patients who develop VTEs of grade 3 or below in severity. Grade 3 VTEs should be treated with anticoagulants and bevacizumab should also be withheld for 2 weeks (Table 2).[26] Clinicians should wait for any coagulopathy to resolve before restarting bevacizumab. Bevacizumab should be permanently discontinued in the event of a grade 4 bevacizumab-related VTE (e.g. major pulmonary embolus).

Patients who develop any ATE (e.g. stroke, myocardial infarct) should permanently discontinue bevacizumab.[26]

EFFICACY AND SAFETY OF BEVACIZUMAB IN ELDERLY PATIENTS

Elderly patients are under-represented in clinical trials and frequently undertreated with standard therapy.[16] The median age of patients involved in phase III bevacizumab studies in CRC and lung cancer was 58 years. As such, these studies do not necessarily provide clinicians with a good indication of bevacizumab use in patients aged older than 65 years.

Data from observational studies include patients across age-groups and therefore give clinicians more information about the efficacy and safety of bevacizumab in this age-group.

Efficacy

ARIES was an observational study. It was designed to follow patients with metastatic or locally advanced and unresectable CRC, locally advanced or metastatic NSCLC (excluding those with predominant squamous histology) who were receiving bevacizumab in combination with first-line chemotherapy.[38] This was the first study to describe effects of second-line bevacizumab treatment for mCRC in a large population of elderly patients.

ARIES showed that elderly patients (aged ≥70 years) were less likely to receive 'intense' chemotherapy regimens than patients below 70 years of age. The frequency of bevacizumab-targeted AEs was similar in younger and elderly patients within first- and second-line cohorts. Within the second-line cohort, there were no significant differences between median OS and PFS in patients below 70 years and those aged 70 years or more. Within the first-line cohort, while PFS was similar across age-groups, the median OS in the elderly patients was significantly lower.[38]

ARIES demonstrated that bevacizumab also provided similar benefits in terms of OS and PFS in the elderly population.

In the BRiTE study, an observational cohort study, assessed the safety and efficacy of bevacizumab-based first-line therapy for metastatic CRC in a large number of elderly patients (896 patients ≥65 years). Median PFS (months) was similar across age cohorts (<65 years, 9.8; 65 to <75, 9.6; 75 to <80, 10.0; ≥80, 8.6). Median OS (months) decreased with age (<65 years, 26.0; 65 to <75, 21.1; 75 to <80, 20.3; ≥80, 16.2).[16]

Safety

Use of bevacizumab in post-progression regimens was found to decrease with age in BRiTE. The frequency of targeted AEs did not increase with age, except for ATEs, for which the Eastern Cooperative Oncology Group (ECOG) performance status, anticoagulation and arterial disease history were stronger predictors than age.[16] The increased frequency of ATEs in the elderly population may be correlated to a history of previous ATE as well as poor performance status. Notably, elderly bevacizumab patients with no history of ATEs and a normal performance status were at no higher risk of developing ATEs than their younger counterparts.

BRiTE concluded that elderly patients receiving bevacizumab with first-line chemotherapy showed

treatment benefit, although there was reduced median survival with increasing age. There was no increased toxicity among elderly patients (>75 years old), except for an increased risk of ATEs.[16] This effect could be correlated to previous ATEs and poor performance status.[25]

Within the first three months of treatment, ARIES found that most AEs relating to bevacizumab use were likely to ensue. Similar to other patient groups, serious AEs were found to be unlikely in elderly patients.[38]

The Avastin Therapy for Advanced Breast Cancer (ATHENA) study involved patients with human epidermal growth factor receptor (EGFR)–2 negative, locally recurrent or metastatic BrCa who received first-line bevacizumab with standard chemotherapy until disease progression, unacceptable toxicity, or physician / patient decision to discontinue.[39] Only hypertension and proteinuria were more common in older than younger patients (grade ≥3 hypertension: 6.9% vs 4.2%; grade ≥3 proteinuria: 4.0% vs 1.5%). Above grade 3 thromboembolic events occurred in 2.9% of older versus 3.3% of younger patients.

Further analysis revealed no relationship between baseline presence and severity of hypertension and risk of developing hypertension during bevacizumab-containing therapy. These findings suggest that bevacizumab-containing therapy is tolerable and active in older patients aged 70 years or above. Hypertension was more common than in younger patients but was manageable.[39]

Authors of the ATHENA study found no evidence precluding the use of bevacizumab in older patients, including those with hypertension.[39]

The Safety of Avastin in Lung cancer (SAiL) study was undertaken to assess the safety and efficacy of first-line bevacizumab combined with standard chemotherapy regimens in patients with untreated locally advanced, metastatic, or recurrent non-squamous NSCLC.[18]

The frequency of clinically significant (≥grade 3) AEs was generally low. Thromboembolism occurred in 8% of patients, hypertension in 6%, bleeding in 4%, proteinuria in 3%, and pulmonary haemorrhage in 1% of bevacizumab-treated patients. The most common grade 3 or highly serious associated AE was pulmonary embolism (28 patients; 1%), and epistaxis, neutropenia, febrile neutropenia, and deep vein thrombosis all occurred in 1% of patients.[18]

Results from SAiL confirmed the manageable safety profile of first-line bevacizumab in combination with various standard chemotherapy regimens for the treatment of advanced non-squamous NSCLC.

CONCLUSIONS

These data indicate that elderly patients derive similar survival benefits from bevacizumab-based chemotherapy as younger patients. Generally, the survival benefits with bevacizumab-based chemotherapy are not associated with an increase in toxicity in this patient population, except for an increase in the frequency of ATEs.

As angiogenesis is fundamental for tumour growth, and VEGF is the pro-angiogenic factor central to the angiogenic pathway, continuous tumour expression of VEGF makes it a rational target for cancer therapy. Bevacizumab is a direct inhibitor of VEGF that exerts its anti-angiogenic effects through three key mechanisms:

1. regression of tumour vasculature,[40-42]
2. normalisation of surviving vasculature,[40,42,43] and
3. inhibition of new and recurrent tumour vessel growth.[43,44]

Clinical trials have firmly demonstrated that bevacizumab confers significant improvements in OS and / or PFS across multiple tumour types.[9-11,13-15] Class-related effects have been observed with bevacizumab treatment,[9-11,13-15] however, these are generally of low grade and manageable using standard medical management strategies. These class-related effects are also seen with other anti-angiogenic agents. Importantly, phase III clinical trials also show that the addition of bevacizumab to standard chemotherapy did not increase mortality rates.[9-11,13-15]

In order to maximise the clinical benefits of bevacizumab, treating clinicians can pre-empt these AEs by conducting pre-treatment investigations as well as employing appropriate management strategies should these events occur. Patient education is also important to ensure treatment success.[14]

Bevacizumab has proven efficacy across multiple tumour types. Practical management of AEs associated with bevacizumab can ensure that cancer patients are

given every opportunity to benefit from this form of treatment.

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