

Network Guidance Document

Guidelines for Bevacizumab Induced Hypertension

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1.0 Overview

Bevacizumab may cause hypertension in patients that are treated with the drug. This is due to the mechanism of action of bevacizumab and its effects on the vascular endothelial growth factor signalling pathway and angiogenesis.

An increased incidence of hypertension (all grades) of up to 34% was observed in bevacizumab-treated patients in clinical trials compared with up to 14% in those treated with comparator. Grade 3 and 4 hypertension (requiring oral anti-hypertensive medicines) in patients receiving bevacizumab ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with bevacizumab and chemotherapy compared to up to 0.2% of patients treated with the same chemotherapy alone.

Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting treatment with bevacizumab.

2.0 Management of Bevacizumab induced Hypertension

Hypertension is generally adequately controlled with oral anti-hypertensives such as angiotensin-converting enzyme (ACE) inhibitors, diuretics and calcium-channel blockers. However, if patients are to receive a cisplatin containing chemotherapy regime, then the use of diuretics is not recommended for managing hypertension.

Key steps for management:

1. Conduct and document a formal risk assessment for potential cardiovascular complications before treatment with bevacizumab is initiated. This should include standardised blood pressure measurements – at least two separate sessions
2. Recognise that pre-existing hypertension will be common in cancer patients and should be identified and addressed before treatment with bevacizumab is initiated.
3. Actively monitor blood pressure throughout treatment with more frequent assessments during the first cycle.
4. The goal for hypertension control is a maximum blood pressure of 140/90 mmHg. However, if a patient has additional risk factors e.g. diabetic or chronic kidney disease, then the target blood pressure of less than 130/80 mmHg is the current recommendation.
5. Manage blood pressure elevations aggressively to avoid the development of complications associated with excessive/prolonged elevations. Seek advice from Cardiology colleagues if necessary.
6. If medically significant hypertension cannot be controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy, bevacizumab should be permanently discontinued.

Taking into account data information from various papers it would appear that the best classes of antihypertensive drugs to treat hypertension caused by bevacizumab would be ACE inhibitors, Angiotensin II inhibitors and calcium channel blockers.

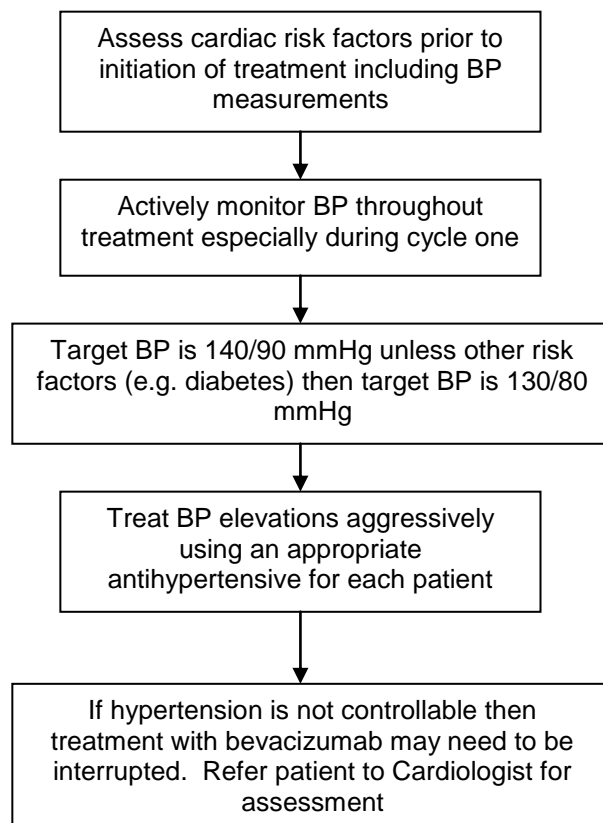
Points to consider when selecting an antihypertensive drug:

Class of Drug	Cancer specific cautions or reasons to avoid	Basis for preferred selection	General cautions and contraindications
ACE inhibitors	Co-administration /titration with renal clearance dependent agents (e.g. cisplatin & pemetrexed), hyperkalaemia	Left ventricular systolic dysfunction, diabetic nephropathy	Renovascular disease, peripheral vascular disease, renal impairment
Angiotensin II inhibitors	Co-administration /titration with renal clearance dependent agents (e.g. cisplatin & pemetrexed), hyperkalaemia	Intolerance of other agents, especially ACE inhibitors, Left ventricular systolic dysfunction, diabetic nephropathy	Renovascular disease, peripheral vascular disease, renal impairment
Beta blockers	Asthenia, malaise, fatigue, QT interval prolonging drugs	Angina, history of myocardial infarction, anxiety	Bradycardia/heart block, diabetes (risk for hypoglycaemia), asthma/COPD (wheezing), decompensated heart failure
Calcium channel blockers (e.g. dihydropyridines)	Lower extremity swelling	Elderly patients, isolated systolic hypertension	Pre-existing oedema, slow onset of action
Thiazide diuretics	Gout, hyperuricaemia, hypokalaemia, young patients (age ≤45yrs), QT interval prolonging drugs	Elderly patients, isolated systolic hypertension, secondary stroke prevention, typically least expensive	Gout, documented sulfa allergy

2.1 Duration of treatment

The hypertensive effects of bevacizumab should dissipate when bevacizumab is discontinued. Ensure that blood pressure is monitored closely on discontinuation of treatment and that the doses of any prescribed antihypertensive drugs are monitored and reduced as appropriate.

2.2 Summary



If a patient develops hypertension that cannot be controlled to consistently < 180/110mmHg, bevacizumab should be withheld and the patient referred to a hypertension specialist.

References

Avastin® Summary of Product Characteristics accessed online 3rd May 2011. Last updated 04/04/2011

Maitland ML et al. Initial Assessment, Surveillance, and Management of Blood Pressure in Patients Receiving Vascular Endothelial Growth Factor Signaling Pathway Inhibitors. *J Natl Cancer Inst* 2010; 102: 596–604

Miles D et al. Using bevacizumab to treat metastatic cancer: UK consensus guidelines. *British Journal of Hospital Medicine*, December 2010, Vol 71, No 12.

Document Administration

Approval Record

Approval		
Date	Name / Title	Signature
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Enquiries

All enquiries relating to this document should be addressed to:

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Document Location

The document is located in the Kent and Medway Cancer Network office, in hardcopy and electronic format. Also mention here if it can be found on any of the Network websites

DATE OF NEXT REVIEW

This item is next to be reviewed in November 2015

Revision History

Date	Version	Status	Author	Summary of Changes
July 2011	0.1	Draft	K Miller/ Colorectal NOG	New document
October 2011	1	Final	K Miller/ Colorectal NOG	Published
November 2013				Reviewed by Colorectal NOG – no changes.

MEASURES ADDRESSED BY THIS EVIDENCE ITEM

This item of evidence is submitted against the following measures:

ORIGINATORS OF THIS EVIDENCE ITEM

K Miller / Colorectal NOG