Oncology Pharmacy Newsletter

Volume 1, Issue 12, December 16, 2015

Management of Antiangiogenic Therapy-Induced Hypertension

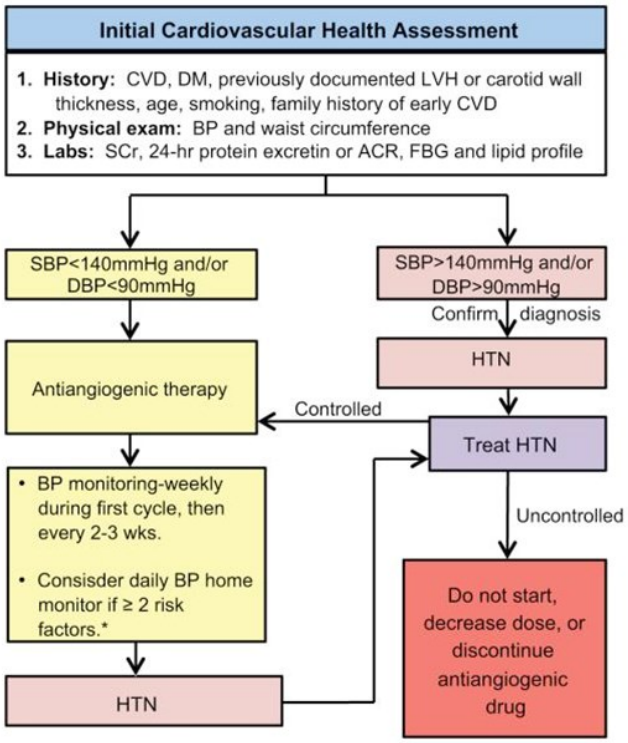
Robert Ambrose, UConn Pharm. D. Candidate 2016

Introduction

Angiogenesis, the formation of new blood vessels, is essential for tumor growth and metastasis.[1] It is controlled by proangiogenic mediators released from the tumor, including vascular endothelial growth factor (VEGF). In turn, there are drugs that block these mediators, the most common being bevacizumab, which starve the tumor of nutrients (see last page). The most common toxicity of these therapeutic drugs is hypertension. A recent meta-analysis reported the incidence is about 20%.[2-4]

Pathophysiology

Although the exact mechanism for antiangiogenic therapy induced hypertension is not known, some evidence exists indicating that it may be caused by endothelin 1 (ET-1).[7] ET-1 levels have increased in rodents when therapy is started, and normalization of ET-1 has occurred upon stopping the drug. Several preclinical models have prevented the rise in blood pressure with co-administration of an ET-1 antagonist (ambrisentan, bosentan, macitentan, sitaxentan).[8] ET-1 antagonist are currently used in the management of pulmonary arterial hypertension.



CV Assessment Before Starting Therapy

The National Cancer Institute recommends patients should have a full cardiovascular (CV) health assessment before starting antiangiogenic therapy.[5] The adjacent diagram describes the algorithm for angiogenic induced hypertension treatment. They suggest stratifying patients based on specific risk factors: low risk, 0 risk factors; high risk, 1 risk factor; higher risk, ≥ 2 risk factors. Major risk factors include systolic BP >160 mmHg or diastolic >100 mmHg, history of diabetes or CV diseases, established/ subclinical renal disease, subclinical end-organ damage, smoking, dyslipidemia, glucose intolerance, age, family history of early CV disease, and abdominal obesity. The number of risk factors does not indicate the degree of hypertension or how it's treated but rather assesses the risk for developing it. For example, someone with 3 risk factors is more likely to develop hypertension then someone with only 1 risk factor but both will be treated/monitored in the same fashion.

BP Goals and Monitoring

The National Cancer Institute recommends using Joint National Committee (JNC) guidelines for blood pressure goals. Blood pressures should be <140/90 mmHg unless they have diabetes and/or kidney disease, then <130/80 mmHg is preferred.

Once antiangiogenic therapy is started, blood pressure should be monitored every week during the first cycle, and then every 2-3 weeks.

Therapeutic Interventions

At this time, no clinical evidence favors one antihypertensive over another in the treatment of antiangiogenic therapy induced hypertension. The most common anti-hypertensives being used are dihydropyridine calcium channel blockers (DHP CCBs), such as amlodipine, and renin angiotensin system inhibitors, which include angiotensin converting enzyme inhibitors (ACE-I), such as lisinopril, and angiotensin receptor blockers (ARBs), such as valsartan.[9] Dihydropyridine CCBs appear to be best for first- line therapy because they directly act on the arterial smooth muscle cell contractility.[10] However, ACE-I and ARBs are good in the setting of proteinuria or when 2 agents are required. Beta-blockers and thiazide diuretics can also be used, although they appear to be less effective than CCBs, ACE-Is, and ARBs.

What to Do?

Start with a single agent as above and titrate up to an effective dose. If blood pressure is still uncontrolled at the maximum dose, add another agent (for example, if you started with a CCB, then add an ACE-I or ARB). The VEGF inhibitor can be continued as long as blood pressure is kept controlled in regard to JNC guidelines.[5] If systolic BP is >160mmHg, diastolic BP is >100mmHg, a hypertensive crisis occurs (>180/120mmHg), or if anti-hypertensives can not provide appropriate BP control, then VEGF inhibitor therapy should be decreased or held until antihypertensive therapy is titrated effectively. The VEGF inhibitor can be restarted once blood pressure is controlled.

Still to Come.....

Future therapeutic considerations include use of an ET-1 receptor antagonist. Clinically they are already approved for pulmonary hypertension, but no data exists on their effectiveness with antiangiogenic therapy. Because increase levels of ET-1 is the proposed mechanism of action of VEGF induced hypertension, it would make sense that these agents may play a role in the future.

References

1. Kerbel RS. Tumor angiogenesis. N Engl J Med. 2008;358:2039–2049.
2. Wu S, Chen JJ, Kudelka A, Lu J, Zhu X. Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. Lancet Oncol. 2008;9:117–123.
3. Zhu X, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis. Acta Oncol. 2009;48:9–17.
4. An MM, Zou Z, Shen H, Liu P, Chen ML, Cao YB, Jiang YY. Incidence and risk of significantly raised blood pressure in cancer patients treated with bevacizumab: an updated meta-analysis. Eur J Clin Pharmacol. 2010;66:813–821.
5. Maitland ML, Bakris GL, Black HR, Chen HX, Durand JB, Elliott WJ, Ivy SP, Leier CV, Lindenfeld J, Liu G, Remick SC, Steingart R, Tang WH. 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.
6. Humphreys, Jesus-Gonzalez BD, Nilka, Moslehi, Javid, Robinson, Emily. Management of antiangiogenic therapy-induced hypertension. Am Heart Assoc J. 2012;60:607-615.
7. Kappers MH, van Esch JH, Sluiter W, Sleijfer S, Danser AH, van den Meiracker AH. Hypertension induced by the tyrosine kinase inhibitor sunitinib is associated with increased circulating endothelin-1 levels. Hypertension. 2010;56:675–681

8. de Jesus-Gonzalez N, Robinson ES, Penchev RR, von Mehren M, Heinrich MC, Tap W, Demetri GD, George S, Humphreys BD. Regorafenib induces rapid and reversible changes in plasma nitric oxide and endothelin-1. Am J Hypertens. July 12, 2012. DOI: 10.1038/ajh.2012.97

9. Curwen JO, Musgrove HL, Kendrew J, Richmond GH, Ogilvie DJ, Wedge SR. Inhibition of vascular endothelial growth factor-a signaling induces hypertension: examining the effect of cediranib (recentin; azd2171) treatment on blood pressure in rat and the use of concomitant antihypertensive therapy. Clin Cancer Res. 2008;14:3124–3131

10. Abernethy DR, Schwartz JB. Calcium-antagonist drugs. N Engl J Med.

Drug	Indication	FDA approval
Bevacizumab (Avastin)	• Cervical cancer • Metastatic colorectal cancer • Metastatic renal cell carcinoma • Nonsquamous non-small cell lung cancer • Ovarian cancer	2004 colorectal cancer 2006 lung cancer 2009 renal cell
Lapatinib (Tykerb)	• Breast cancer, advanced or metastatic, in combination with capecitabine • Breast cancer, post menopausal, in combination with letrozole	2007 breast cancer 2010 post menopausal breast cancer
Sunitinib (Sutent)	• GI stromal tumor • Neuroendocrine tumor • Renal cell carcinoma, advanced	2006 GI stromal tumor and renal cell 2011 pancreatic neuroendocrine
Sorafenib (Nexavar)	• Liver carcinoma, unresectable • Tumor of thyroid gland • Renal cell carcinoma, advanced	2007 liver cancer 2005 renal cancer 2013 tumor of the thy-
Axitinib (Inlyta)	• Renal cell carcinoma, advanced	2012
Pazopanib (Votrient)	• Renal cell carcinoma, advanced • Soft tissue sarcoma, advanced	2009 renal cell and soft tissue sarcoma
Vandetanib (Caprelsa)	• Medullary thyroid carcinoma	2011
Ponatinib	• Chronic myeloid leukemia • Philadelphia chromosome-positive acute lymphoblastic leukemia	2012 for both
Regorafenib	• Gastrointestinal stromal tumor • Metastatic colorectal cancer	2012 colorectal cancer 2013 GI stromal
Cabozantinib	• Medullary thyroid carcinoma	2012
Ramucircumab	• Gastric cancer • Malignant neoplasm of cardio-esophageal junction of stomach • Metastatic colorectal cancer • Non-small cell lung cancer	2014 gastric, cardio-esophageal junction and non-small cell lung 2015 colorectal
Lenvatinib	• Malignant tumor of thyroid gland	2015
Ziv-alfibrecept	• Metastatic colorectal cancer	2012