CLINICAL VIGNETTE

Toxicity of Bevacizumab (bev): The First in Class Anti-Angiogenesis Agent in Oncology

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Normal blood vessel production during embryogenesis involves both vasculogenesis, the development of a primitive vascular network with endothelial cells derived from mesodermal precursors, and angiogenesis, the evolution of a more intricate network of blood vessels associated with vascular smooth muscle and pericytes as well[1]. After birth, angiogenesis continues during normal growth and wound repair, and, in females, during the processes of menstruation and embryo implantation[1]. Angiogenesis also plays a critical role in the growth of cancers. All progressive cancers require an angiogenic switch, during which the proliferating collection of cancer cells must begin to generate new blood vessels to supply oxygen and nutrients to the growing tumor mass, which has outstripped the existing blood supply[2]. Hence, targeting angiogenesis in malignancy has been an active area of research and drug development for years.

Preclinical models and subsequent clinical studies have established that Vascular Endothelial Growth Factor A (VEGF-A) is the primary mediator of angiogenesis (3). VEGF-A, with 2 main isoforms of 121 and 165 amino acids (AAs), is part of a family of ligands including VEGF- B, C, D and placental growth factor. VEGF-A is the main ligand binding to VEGF-receptor 2 (VEGF-R2), the predominant signal for angiogenesis. VEGF-A/ VEGF-R2 signaling stimulates endothelial mitogenesis, endothelial cell survival, increased vascular permeability and increased levels of enzymes that degrade the extra-cellular matrix[3]. Bevacizumab, a humanized monoclonal antibody, binds VEGF-A with high affinity and a prolonged half life in vivo of 17 to 21 days in humans[4].

When combined with standard chemotherapy, bev has been shown to improve response rates, progression free survival (PFS) and/ or overall survival (OS) in several advanced malignancies, including colorectal cancer[5], non-squamous, non-small cell lung cancer[6], renal cell cancer[7] and glioblastoma multiforme[8], the most common primary brain tumor in adults. In addition to inducing sustained tumor ischemia, bev may initially augment the efficacy of chemotherapy by transiently increased blood flow to the tumor mass by "pruning" leaky and inefficient tumor vessels and so allowing increased of chemotherapy to interior, previously poorly perfused cancer cells[9]. Bev is the first FDA approved anti-angiogenic agent in cancer therapy and remains the agent with the most FDA approved indications.

Despite the lack of challenging cytotoxic CT toxicities, like nausea and vomiting and myelosuppression, bev has several recognized side effects. Many of these are seen with the other anti-angiogenic agents and so appear to be class effects, including hypertension (HTN), proteinuria, venous and arterial thromboembolic events (VTEs, ATEs), bleeding, congestive heart failure (CHF), and rare reversible posterior leukoencephalopathy (RPLS)[10]. Toxicities more specific to bev include monoclonal antibody type infusion reactions, headache, hoarseness, gastrointestinal (GI) perforation and poor wound healing, likely exacerbated by the long half life of bev[10].

While usually manageable and reversible, bev toxicities result in a modestly increased rate of fatal adverse events (FAEs). A meta-analysis involving 10,297 cancer patients from 16 randomized clinical trials (RCTs) of CT with or without bev demonstrated 2.5% FAEs with bev and 1.7% without, for a relative risk (RR) of 1.46[11]. The improvement in PFS and/ or OS with the addition of bev to standard CT clearly outweighs the risk of dying from bev-induced complications. To optimize the relative benefit of bev, however, it is essential for medical oncologists to monitor for and to intervene early to treat bev-related side effects.

Phase 1 dose escalation studies of bev established 5 mg/kg/wk as standard, given dose limiting headache at 10 mg/kg/wk[12]; the one exception is first line metastatic colorectal cancer, with a 2.5 mg/kg/wk dose of bev[5]. There are no data to support dose reduction of bev to manage side effects, so intervention requires either effective supportive

therapy, like anti-hypertensives for HTN, or stopping bev. Severe or life-threatening toxicity generally requires permanent discontinuation.

HTN is easily recognized and relatively common, with 6 to 15% grade 3 HTN reported in clinical trials[13]. While the precise mechanism is not known, inhibition of nitric oxide, the most potent in-vivo vasodilator, may be involved[14]. Any blood pressure (BP) greater than 140/90 (grade 1) merits increased monitoring, and, if persistent (grade 2), requires anti-hypertensive therapy. No specific agent or class of anti-hypertensive is recommended. A diastolic BP > 110 or a systolic BP > 180 (grade 3) merits holding bev and initiating treatment. Bev can be resumed if HTN reaches grade 2. Finally, hypertensive crisis (grade 4) requires permanently stopping bev.

As with HTN, proteinuria occurs commonly, from 3 to 32%, in RCT of CT with or without bev[15]. HTN and proteinuria with bev treatment suggest a similar pathologic mechanism to pre-eclampsia, where decreased VEGF levels have been reported[16]. Patients receiving bev should have a urine dipstick performed with every treatment to screen for proteinuria. A level of 2+ or greater requires a 24 hour urine for protein. If >2 gm/ 24 hr is found, bev is held until follow up 24 hour collections demonstrate < 2 gm proteinuria at which point it can often be safely restarted. Nephrotic syndrome, even though generally reversible, triggers permanent cessation of bev.

ATEs, including cerebrovascular accidents (CVAs), transient ischemic attacks (TIAs), myocardial infarctions (MIs) and angina, occur more commonly in cancer patients receiving bev with CT. A pooled analysis of 1745 patients in CRC, NSCLC, and breast cancer studies of CT with or without bev showed 4.6% ATE rate with bev as opposed to 1.9% without[17]. Significant risk factors for ATE include age > 65 and a history of prior ATE[17]. Bev is stopped permanently after an ATE, even if successful medical therapy or surgical revascularization occurs. In addition, VTEs occur commonly in patients with advanced cancer. Whether bev increases the risk in cancer patients on CT is unclear. A 2006 meta-analysis of 7956 patients from 15 RCTs showed a RR or 1.33[18], but a more recent pooled analysis using individual patient data from 6055 patients in 10 RCT found no statistically significant increased risk of VTE[19].

Bev induces nasal epistaxis in up to 30% of patients but is generally mild and self-limited[20]. Major bleeding, requiring urgent medical intervention, occurs rarely. The major exception seen in the early development of bev was NSCLC patients receiving standard CT, where a randomized Phase 2 study showed 30% severe or even fatal hemoptysis in squamous cell cancers in contrast to less than 5% in patients with other NSCLC histologies[21]. Hence, the phase 3 study of bev with CT in NSCLC patients specifically excluded squamous subtypes[6]. An explanation for the dramatically higher risk of hemoptysis seen in squamous NSCLC remains elusive, although squamous cell cancers generally arise endobronchially and tumor necrosis may lead to more friable lesions that spontaneously bleed. In general, however, the risk of bleeding with bev is so small that post-marketing Phase 4 safety studies established that bev could be safely administered to cancer patients on stable, full dose anticoagulation[22].

Since angiogenesis is a critical component of tissue repair, bev treatment has not surprisingly been associated with impaired wound healing. A 3 fold increase in post-operative wound complications was seen in CRC patients who received bev within 28 days of major surgery[23], likely reflecting the prolonged inhibition of VEGF signaling due to the long monoclonal antibody half life. As a result, bev should not be given within 28 days of major surgery and should not be started or resumed until wound healing is complete.

Gastrointestinal (GI) perforation and fistula formation have been reported to be increased by bev. A meta-analysis of 12,294 patients with a variety of cancers receiving CT with or without bev from 17 RCT demonstrated 0.9% GI perforation, with a mortality rate of 21.2 % and representing a RR of 2.14[24]. Higher risks of GI perforation were seen in CRC, renal cell cancer and ovarian cancer. Any GI perforation or clinically significant fistula with bev therapy requires permanent discontinuation of bev.

Bev increases the risk of CHF. An overview of RCT involving 3784 patients with metastatic breast cancer on CT with or without bev demonstrated CHF in 1.6% with bev in contrast to 0.4% without[25]. Anthracycline CT, as with doxorubicin used commonly in early stage and advanced breast cancer, substantially increased the risk of CHF with bev[25]. This has led to interruption in early stage breast cancer trials involving treatment with both agents.

Reversible posterior leukoencephalopathy (RPLS) is an extremely rare clinical syndrome characterized by mild to severe HTN, headache, confusion, seizures, visual disturbance, vomiting and brain MRI evidence of white matter edema, often in the parietal or occipital lobes[26]. RPLS possibly represents the

failure of the careful regulation of cerebro-vascular pressures, perhaps exacerbated by VEGF inhibition[26]. This occurs in < 1% of bev treated patients and, although generally reversible within several days, requires permanent discontinuation of bev.

The management of other observed but non-life threatening complications of bev treatment depends on the severity of and persistence of symptoms. Side effects that can trigger stopping bev include monoclonal antibody type infusion reactions refractory to standard pre-medications, severe headache resistant to reasonable analgesic therapy, and progressive hoarseness that significantly affects the patient's quality of life.

Anti-angiogenic therapy in general and bev in particular represent a substantial therapeutic advance in oncology over the last decade. Adding bev to CT improves survival in several malignancies, including the first and third most common causes of cancer deaths in the US, NSCLC and CRC respectively. However, even an elegant biological therapy that avoids standard cytotoxic CT toxicities, like bev, has side effects that require awareness, appropriate monitoring and early intervention to optimize patient outcomes.

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