Bevacizumab for Renal Cell Carcinoma, Glioblastoma, and Other Solid Tumors

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In July 2009, the US Food and Drug Administration (FDA) granted approval for use of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab (Avastin) in combination with interferon alfa for treatment of patients with metastatic renal cell carcinoma (RCC).

Indications
Renal cell carcinoma
In July 2009, the US Food and Drug Administration (FDA) granted approval for use of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab (Avastin) in combination with interferon alfa for treatment of patients with metastatic renal cell carcinoma (RCC). Approval was based on results from the BO17705 trial, which demonstrated a 5-month improvement in median progression-free survival (PFS) in the patients treated with bevacizumab.[1] In addition, there were positive published results from the Cancer and Leukemia Group B (CALGB) 90206 trial, a randomized, open-label North American study of bevacizumab plus interferon alfa-2b compared with interferon alfa-2b alone in patients with metastatic RCC. CALGB investigators reported a median progression-free survival (PFS) time of 8.4 months for patients treated with the bevacizumab combination, compared with a PFS time of 4.9 months for patients who received single-agent interferon alfa-2b. An overall survival improvement was not observed.[1] Toxicity with combined bevacizumab and interferon alfa-2b was increased and more severe compared with interferon alfa-2b alone.[2] Proteinuria occurred in 20% of patients with a median onset of 5.6 months, and median time to resolution was 6.1 months.

Glioblastoma
In May 2009, the FDA approved bevacizumab as a single agent for treatment of patients with glioblastoma progressing despite treatment with other therapies. Glioblastoma multiforme tumors have a high expression of VEGF, which is produced both by the tumor and by the microenvironment, or stroma. While this overexpression is associated with a poor prognosis, it also provides a target that can be blocked by bevacizumab.[1] Approval of bevacizumab for use in selected patients with glioblastoma was based on the results of two single-arm trials, AVF3708g and NCI 06-C-0064E, that showed durable objective responses to treatment including this drug. AVF3708g was an open-label, randomized multicenter trial in patients previously treated with radiotherapy and temozolomide (Temodar). Patients received bevacizumab (10 mg/kg IV) alone or with irinotecan every 2 weeks until disease progression or unacceptable toxicity was noted. Only efficacy data from the bevacizumab monotherapy arm (85 patients) were used to support drug approval. Responses (based on World Health Organization [WHO] radiographic criteria) were observed in 25.9% of the patients, with a median response duration of 4.2 months.
NCI 06-C-0064E was a single-arm, single-site study of bevacizumab for the treatment of patients with previously treated gliomas. All 56 patients had documented disease progression after receiving temozolomide and radiation therapy. Patients received bevacizumab (10 mg/kg IV) every 2 weeks...
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until disease progression or unacceptable toxicity was noted. The objective response rate was 19.6% (using the same WHO radiologic response criteria as in AVF3708g). Median response duration was 3.9 months.

Experience with another pan-VEGF receptor inhibitor, cediranib (AZD2171, Recentin), showed that there was immediate blockade of the VEGFR pathway in many patients, but when patients relapsed, two unexpected pathways then took over, providing angiogenesis for the tumor. This suggested that, ultimately, a multidrug regimen would be required for optimal treatment.[3]

Other solid tumors
Bevacizumab is already used to treat several types of solid tumors. It was first approved by the FDA in February 2004, for use with intravenous, fluorouracil (5-FU)-based chemotherapy to treat metastatic colorectal cancer. In October 2006, it was approved to treat unresectable locally advanced or metastatic nonsquamous, non-small-cell lung cancer (NSCLC) in combination with carboplatin and paclitaxel, and in February 2008, it was approved for use with paclitaxel for patients who have not received chemotherapy for metastatic HER2-negative breast cancer. (It is not indicated for patients whose breast cancer has progressed following anthracycline and taxane chemotherapy administered for metastatic disease.][4]

Mechanism of Action
Bevacizumab binds to (VEGF) so that it cannot bind to its receptors Flt-1 and KDR on the endothelial cell surface.[4] Normally, VEGF would bind to these receptors and stimulate the endothelial cells to proliferate and migrate to the tumor to develop a new blood supply for the tumor. Tumors are unable to grow beyond 1–2 mm, the diffusion distance of oxygen, without having new blood vessels to bring in oxygen and remove cellular waste products. It is theorized that bevacizumab, in combination with chemotherapy, normalizes tumor blood vessels so that concomitantly administered chemotherapy can enter and reach all parts of the tumor to exert an antitumor effect.[5] Malignant blood vessels are tortuous, with many blind endings and different diameters, so some areas of the tumor receive little, if any, blood supply, and the vasculature has holes, or fenestrations, through which drugs leak out of the tumor.

Metabolism
Drug serum half-life is approximately 20 days (range, 11–50 days), with a predicted time to steady state of 100 days. Drug clearance is higher in males and patients with a higher tumor burden, but there is no evidence that this results in inferior responses.

Drug Preparation
Drug is available in single-use 4 mL 100-mg vials and in 16 mL 400-mg vials.
Aseptically withdraw ordered dose from appropriate vial(s) and dilute to a total volume of 100 mL 0.9% Sodium Chloride Injection USP. Discard any remaining drug, as it has no preservatives.

Drug Administration
Administer initial infusion over a period of 90 minutes; administer subsequent infusions over a 60-minute time period if the initial infusion is well tolerated, and all subsequent infusions over a 30-minute period if the second 60-minute infusion is well tolerated. Do not administer intravenous push (IVP) or intravenous (IV) bolus.
Initiate bevacizumab at least 28 days following major surgery and after surgical wound is fully healed. Reidy et al.[6] demonstrated that bevacizumab 5 mg/kg could be safely administered at 0.5 mg/kg/min (10 minutes). Three hundred seventy patients received a total of 2,311 doses with 1.6% of patients developing symptoms of mild hypersensitivity reactions. This dosage is not recommended by the manufacturer, however.

Metastatic Renal Cell Carcinoma
10 mg/kg IV every 2 weeks with interferon alfa
Glioblastoma
10 mg/kg IV every 2 weeks
Metastatic Colorectal Cancer
5 mg/kg IV every 2 weeks with bolus-IFL (irinotecan plus 5-FU, leucovorin); 10 mg/kg IV every 2 weeks with FOLFOX4 (oxaliplatin [Eloxatin], leucovorin, 5-FU)
Nonsquamous Non-small-cell Lung Cancer (NSCLC)
15 mg/kg IV every 3 weeks with carboplatin/paclitaxel
Metastatic Breast Cancer
10 mg/kg IV every 2 weeks with paclitaxel

Adverse Reactions to Bevacizumab by Body System (boldface type indicates more
common events, and effects are influenced by any concomitant chemotherapy
CNS: Dizziness, headache, rare reversible posterior leukoencephalopathy syndrome
CV: Hypertension, congestive heart failure (rare)
ENT: Epistaxis, rhinitis, lacrimation disorder
GI: Diarrhea, constipation, GI perforation, rectal hemorrhage (rare), stomatitis, taste alterations
GU: Proteinuria, nephritic syndrome (rare)
Hematologic: GI hemorrhage, deep vein thrombosis, neutropenia, leucopenia, arterial thrombotic events, rare pulmonary embolism
Musculoskeletal: Myalgia
Reproductive: Potential for fetal harm
Respiratory: Dyspnea, upper respiratory infection
Skin: Dry skin, exfoliative dermatitis
Other: Asthenia, abdominal pain, rare infusion reactions

Patient Education
Teach the patient to:
• Expect routine blood pressure monitoring, when the nurse gives bevacizumab. An antihypertensive medicine may be prescribed if blood pressure is elevated.
• Report immediately any unusual bleeding, high fever, chills or rigors, sudden onset or worsening of neurological function, persistent or severe abdominal pain that may be associated with constipation and/or vomiting.
• Expect drug will be stopped at least 4 weeks before surgery, and held until after the surgical wound has healed, as drug causes an increased risk of wound healing complications during and after bevacizumab treatment.
• Report immediately changes in neurological function, chest pain, difficulty breathing, or other changes, as drug may increase risk of an arterial thromboembolic event.
• Use effective contraception during treatment and for at least 6 months after treatment ends, as bevacizumab may damage the fetus if pregnancy occurs.
• Ensure that patient has name and telephone number(s) of healthcare provider(s) who should be contacted if any of the previously described problems develop.

Drug Interactions
Chemotherapy and bevacizumab: increased risk of neutropenia. Paclitaxel, carboplatin, and bevacizumab: substantially lower paclitaxel serum levels after four cycles of treatment (day 63) vs those of patients not receiving bevacizumab. Incompatible with dextrose solution.

Special Considerations
Discontinue bevacizumab in cases of:
• Gastrointestinal (GI) perforation, fistula formation involving an internal organ or GI tract.
• Wound dehiscence and wound healing complications requiring medical intervention.
• Serious hemorrhage requiring medical intervention.
• Severe arterial thromboembolic events.
• Hypertensive crisis or hypertensive encephalopathy.
• Reversible posterior leukoencephalopathy syndrome (RPLS).
• Nephrotic syndrome.

Temporarily suspend bevacizumab:
• At least 4 weeks prior to elective surgery.
• In cases of severe hypertension not controlled with medical management.
• When patient has moderate to severe proteinuria pending further evaluation (urine protein equal to or greater than 2 grams/24 hours).
• If severe infusion reactions develop.

Drug is teratogenic, so patients should be counseled to continue effective contraception for at least 6 months after treatment ends; in addition, the drug should not be given to nursing mothers. Hapani et al.[7] completed a meta-analysis of gastrointestinal perforation in patients receiving bevacizumab, and found the risk was dependent on dose (with lowest risk at a dose of 2.5 mg/kg/weekly, which was not statistically significant, vs 5 mg/kg/week, which carried a significantly higher risk) as well as tumor type (higher in patients with renal cell cancer, relative risk [RR] of 5.67, followed by those with metastatic colorectal cancer, RR 3.10).

Contraindications/Precautions
No contraindications. Patients with glioblastoma may develop dehiscence at the craniotomy site, owing to the compound effects of irradiation together with those of bevacizumab, and this usually
requires reoperation.[8] If patients with glioblastoma develop a thromboembolic event, it is unknown whether therapeutic anticoagulation would increase the risk of hemorrhage into the glioblastoma.[9]

**References:**


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