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Bevacizumab (Antineoplastic)

Updated: September 26, 2017.

OVERVIEW

Introduction

Bevacizumab is a humanized monoclonal antibody to human vascular endothelial growth factor (VEGF) and an anti-angiogenesis agent used in the therapy of colorectal, ovarian, renal and brain cancers. Bevacizumab has not been linked to serum enzyme elevations during therapy or to idiosyncratic acute liver injury. Bevacizumab may be partially protective against the vascular hepatic damage caused by other chemotherapeutic agents.

Background

Bevacizumab (be" va siz' ue mab) is a recombinant humanized monoclonal IgG1 antibody which is directed at and binds avidly to circulating vascular endothelial growth factor (VEGF). Receptors for VEGF (Flt-1 and KDR) are present on endothelial cells, and the engagement of VEGF with these receptors promotes angiogenesis. Inhibition of VEGF decreases formation of new blood vessels, which plays an important role in growth and spread of cancer cells. When used in combination with other antineoplastic agents, bevacizumab has been shown to extend both recurrence-free as well as overall patient survival in several forms of advanced cancer. Bevacizumab was approved in the United States in 2004 for use in metastatic colon cancer. Indications were subsequently extended to selected forms of non-small cell lung cancer, breast and renal cancer and glioblastoma. However, the indication for use in breast cancer was withdrawn in 2011 because of lack of evidence that bevacizumab extended overall patient survival. Bevacizumab is available vials of 100 or 400 mg (25 mg/mL) under the brand name Avastin. The typical dose is 5 to 10 mg/kg intravenously every 2 weeks or 7.5 to 15 mg every three weeks, usually in combination with other antineoplastic agents. Bevacizumab should be administered only by physicians with experience in using antineoplastic agents and managing their major complications. Bevacizumab has significant adverse side effects. Common adverse events include epistaxis, headache, dizziness, fatigue, hypertension, rhinitis, dry skin, back pain, excessive bleeding and skin rash. Rare complications include bowel, stomach or nasal septum perforation, poor wound healing, hemorrhage, thrombosis, renal dysfunction and ovarian failure.

Hepatotoxicity

In large clinical trials, serum aminotransferase elevations were no more frequent in patients receiving bevacizumab than in those on placebo or receiving comparator agents. Subsequent to its approval and general use, bevacizumab has not been implicated in cases of idiosyncratic adult liver injury. Bevacizumab is generally given with other potent antineoplastic agents and to patients with hepatic metastases which makes it difficult to attribute serum enzyme elevations or clinically apparent liver injury to a specific agent being used. Nevertheless, significant liver injury from bevacizumab must be quite rare, if it occurs at all.

Because bevacizumab inhibits angiogenesis, it has the potential to inhibit hepatic regeneration and wound healing after hepatic surgery. However, when used in conjunction with other antineoplastic agents before resection for colorectal hepatic metastases, bevacizumab has been associated with less hepatic toxicity from the other antineoplastic agents (such as oxaliplatin, fluorouracil and irinotecan) and has not been associated with an increase in perioperative complications or operative mortality. Thus, inhibition of angiogenesis by bevacizumab may be beneficial in ameliorating the hepatic vascular injury caused by other antineoplastic agents. Indeed, bevacizumab has been reported to decrease the frequency of sinusoidal obstruction syndrome in patients receiving chemotherapy for colorectal liver metasstases.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which bevacizumab might cause liver injury is unclear. It is a recombinant protein and unlikely to be inherently hepatoxic, being metabolized to small polypeptides or amino acids by many cells and having no effect on activity of drug metabolizing enzymes or hepatic transporter molecules. Because it is an inhibitor of angiogenesis, it might be benefical in ameliorating hepatic vascular injury caused by other antigenoplastic agents.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

See also: Macular Degeneration Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Bevacizumab – Avastin®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Bevacizumab	**216974-75-3**	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 26 September 2017

Zimmerman HJ. Drugs used to treat rheumatic and musculospastic disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 517-54.

(Expert review of hepatotoxicity published in 1999; well before the availability of most monoclonal antibody therapies).

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 569-91

(Review of hepatotoxicity of immunosuppressive agents mentions that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists").

Chabner BA, Barnes J, Neal J, Olson E, Mujagiv H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-53.

(Textbook of pharmacology and therapeutics).

Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350: 2335-42. PubMed PMID: 15175435.

(Among 813 patients with metastatic colorectal cancer treated with irinotecan, fluorouracil and leucovorin [FOLFIRI] with or without bevacizumab, patient survival was longer with bevacizumab, but adverse events were similar in the two groups; no mention of ALT elevations or hepatotoxicity).

Two new drugs for colon cancer. Med Lett Drugs Ther 2004; 46 (1184):46-8. PubMed PMID: 15184808.

(Concise review of mechanism of action, clinical efficacy, and cost of bevacizumab and cetuximab, two antineoplastic monoclonal antibodies, shortly after their approval in the US; adverse effects of bevacizumab include gastrointestinal bleeding or perforation, hypertension, pulmonary hemorrhage, thrombosis and asthenia; no mention of hepatotoxicity).

Donadon M, Vauthey JN, Loyer EM, Charnsangavej C, Abdalla EK. Portal thrombosis and steatosis after preoperative chemotherapy with FOLFIRI-bevacizumab for colorectal liver metastases. World J Gastroenterol 2006; 12: 6556-8. PubMed PMID: 17072991.

(61 year old woman with colorectal liver metastases received 6 courses of irinotecan, fluorouracil, leucovirin [FOLFIRI] and bevacizumab and CT scan showed portal branch thrombosis and fatty liver that required stopping chemotherapy and alteration of plans for resection of the metastasis).

Sanborn RE, Sandler AB. The safety of bevacizumab. Expert Opin Drug Saf 2006; 5: 289-301. PubMed PMID: 16503749.

(Review of the safety of bevacizumab focusing on hypertension, bleeding, thrombosis, proteinuria, neuropathy and gastrointestinal perforations; no discussion of ALT elevations or hepatotoxicity).

Ribero D, Wang H, Donadon M, Zorzi D, Thomas MB, Eng C, Chang DZ, et al. Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. Cancer 2007; 110: 2761-7. PubMed PMID: 17960603.

(Among 105 patients with metastatic colorectal cancer undergoing preoperative chemotherapy [fluorouracil and oxaliplatin] before hepatic resection, the incidence and severity of hepatic sinusoidal dilation was less in those who also received bevacizumab [n=62; 27% any grade, 8% severe] than in those who did not [n=43; 54% any grade, 28% severe]).

D'Angelica M, Kornprat P, Gonen M, Chung KY, Jarnagin WR, DeMatteo RP, Fong Y, et al. Lack of evidence for increased operative morbidity after hepatectomy with perioperative use of bevacizumab: a matched case-control study. Ann Surg Oncol 2007; 14: 759-65. PubMed PMID: 17103075.

(Among 32 patients who underwent hepatic resection of colorectal cancer metastases who had received bevacizumab, perioperative complications and survival were similar to those of a matched, historical control group).

Bilchik AJ, Hecht JR. Perioperative risks of bevacizumab and other biologic agents for hepatectomy: theoretical or evidence based? J Clin Oncol 2008; 26: 1786-8. PubMed PMID: 18398144.

(Editorial on the concerns over the adverse effects of bevacizumab on wound healing and regeneration, mentioning that medical evidence is lacking on its specific adverse effects in using it with chemotherapy before hepatic resection of colorectal metastases).

Zorzi D, Chun YS, Madoff DC, Abdalla EK, Vauthey JN. Chemotherapy with bevacizumab does not affect liver regeneration after portal vein embolization in the treatment of colorectal liver metastases. Ann Surg Oncol 2008; 15: 2765-72. PubMed PMID: 18636296.

(Among 65 patients with metastatic colorectal cancer undergoing chemotherapy before portal vein embolization, liver remnant volume [measured by CT], hypertrophy in response to embolization, complications and outcomes were not different between the 26 who received bevacizumab and the 17 who did not).

Bevacizumab (Avastin) for metastatic breast cancer. Med Lett Drugs Ther 2008; 50 (1287): 42-3. PubMed PMID: 18509265.

(Concise review of the role of bevacizumab for metastatic breast cancer shortly after its approval for this indication by the FDA mentions that it may prolong recurrence free survival, but has not been shown to prolong overall survival; discussion of adverse events does not mention hepatotoxicity or ALT elevations).

Klinger M, Eipeldauer S, Hacker S, Herberger B, Tamandl D, Dorfmeister M, Koelblinger C, et al. Bevacizumab protects against sinusoidal obstruction syndrome and does not increase response rate in neoadjuvant XELOX/FOLFOX therapy of colorectal cancer liver metastases. Eur J Surg Oncol 2009; 35: 515-20. PubMed PMID: 19200687.

(Among 106 patients with metastatic colorectal cancer undergoing preoperative chemotherapy before hepatic resection, bevacizumab therapy [n=50] was associated with less sinusoidal dilatation [both frequency and severity], but rates of steatosis, fibrosis and tumor response were similar in the two groups).

Aussilhou B, Dokmak S, Faivre S, Paradis V, Vilgrain V, Belghiti J. Preoperative liver hypertrophy induced by portal flow occlusion before major hepatic resection for colorectal metastases can be impaired by bevacizumab. Ann Surg Oncol 2009; 16: 1553-9. PubMed PMID: 19363584.

(Measurement of hepatic volume before and after portal vein embolization in preparation for resection of hepatic colorectal metastasis found that 13 patients who received bevacizumab and extended chemotherapy had less hypertrophy in response to embolization that those who did not receive bevacizumab).

Vauthey JN, Zorzi D. In search of the black sheep: is it bevacizumab or extended chemotherapy? Ann Surg Oncol 2009; 16: 1463-4. PubMed PMID: 19357926.

(Editorial in response to Aussilhou [2009] questioning whether bevacizumab or extended chemotherapy with oxaliplatin or irinotecan was responsible for the finding of impaired liver regeneration after portal embolization in reparation for hepatic resection of metastases).

Scoggins CR, Campbell ML, Landry CS, Slomiany BA, Woodall CE, McMasters KM, Martin RC. Preoperative chemotherapy does not increase morbidity or mortality of hepatic resection for colorectal cancer metastases. Ann Surg Oncol 2009; 16: 35-41. PubMed PMID: 18987915.

(Among 186 patients with metastatic colorectal cancer who underwent hepatic resection between 1996 and 2006 at a single US referral center, there were no differences in complications, mortality or overall survival between the 112 who received preoperative chemotherapy and the 74 who did not).

Di Fiore F, Van Cutsem E. Acute and long-term gastrointestinal consequences of chemotherapy. Best Pract Res Clin Gastroenterol 2009; 23: 113-24. PubMed PMID: 19258191.

(Review of acute liver adverse events from cancer chemotherapy focusing on the effects of preoperative chemotherapy for colorectal cancer metastases and effects of irinotecan and oxaliplatin).

Cleary JM, Tanabe KT, Lauwers GY, Zhu AX. Hepatic toxicities associated with the use of preoperative systemic therapy in patients with metastatic colorectal adenocarcinoma to the liver. Oncologist 2009; 14: 1095-105. PubMed PMID: 19880627.

(Review of toxicities of preoperative chemotherapy for metastatic colorectal cancer including steatohepatitis after irinotecan [4-20%] and sinusoidal dilatation after oxaliplatin [10-78%], as well as the relative safety of bevacizumab and data showing that it may protect against sinusoidal damage and concerns over whether it may interfere with hepatic regeneration).

Rubbia-Brandt L, Lauwers GY, Wang H, Majno PE, Tanabe K, Zhu AX, Brezault C, et al. Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. Histopathology 2010; 56: 430-9. PubMed PMID: 20459550.

(Among 274 patients with metastatic colorectal cancer undergoing preoperative chemotherapy [oxaliplatin] before hepatic resection, moderate to severe sinusoidal dilatation and injury was less common in those who received bevacizumab [n=70; 31%] than in those who did not [n=204; 62%], as was nodular regenerative hyperplasia [11% vs 29%] and centrilobular fibrosis [31% vs 52%], and these hepatic abnormalities were not found in 110 patients who did not undergo preoperative chemotherapy).

Zalinski S, Bigourdan JM, Vauthey JN. [Does bevacizumab have a protective effect on hepatotoxicity induced by chemotherapy?]. J Chir (Paris) 2010; 147 Suppl 1: S18-24. PubMed PMID: 20172201.

(Commentary on the possibility that antiangiogenesis effects of bevacizumab might affect wound healing and hepatic regeneration after resection of hepatic metastases, suggesting that the surgery be delayed until 5 weeks after completion of chemotherapy).

Pessaux P, Panaro F, Casnedi S, Zeca I, Marzano E, Bachellier P, Jaeck D, Chenard MP. Targeted molecular therapies (cetuximab and bevacizumab) do not induce additional hepatotoxicity: preliminary results of a case-control study. Eur J Surg Oncol 2010; 36: 575-82. PubMed PMID: 20452168.

(Among 36 patients with colorectal cancer undergoing hepatic resection after chemotherapy, steatohepatitis was less frequent in 21 patients who received bevacizumab than matched controls [5% vs 33%], and sinusoidal obstruction syndrome was less frequent in 15 patients given cetuximab than controls [0% vs 33%]).

Pessaux P, Marzano E, Casnedi S, Bachellier P, Jaeck D, Chenard MP. Histological and immediate postoperative outcome after preoperative cetuximab: case-matched control study. World J Surg 2010; 34: 2765-72. PubMed PMID: 20652697.

(Among 26 patients with metastatic colorectal cancer undergoing preoperative chemotherapy who also received cetuximab, serum enzyme and bilirubin elevations were similar to 26 matched control patients, and liver histology showed no differences in rates of steatohepatitis, sinusoidal obstruction syndrome or fibrosis).

Chaudhury P, Hassanain M, Bouganim N, Salman A, Kavan P, Metrakos P. Perioperative chemotherapy with bevacizumab and liver resection for colorectal cancer liver metastasis. HPB (Oxford) 2010; 12: 37-42. PubMed PMID: 20495643.

(Among 35 patients with metastatic colorectal cancer who received bevacizumab before hepatic resection of liver metastases, 9 also received irinotecan, but only 4 developed steatohepatitis and 2 jaundice postoperatively, but relationship of these events to irinotecan was not provided).

Lehmann K, Rickenbacher A, Weber A, Pestalozzi BC, Clavien PA. Chemotherapy before liver resection of colorectal metastases: friend or foe? Ann Surg 2012; 255: 237-47. PubMed PMID: 22041509.

(Systematic review of literature on efficacy and safety of preoperative chemotherapy before resection of colorectal hepatic metastases concludes that downsizing chemotherapy may offer a chance of secondary resection in about a third of patients).

Robinson SM, Wilson CH, Burt AD, Manas DM, White SA. Chemotherapy-associated liver injury in patients with colorectal liver metastases: a systematic review and meta-analysis. Ann Surg Oncol 2012; 19: 4287-99. PubMed PMID: 22766981.

(Systematic review of literature on chemotherapy induced liver injury in patients with colorectal cancer; oxaliplatin regimens are associated with a higher rate of sinusoidal injury [17% vs 6%] but not steatosis [11.5% vs 9.8%], and rates are reduced by concurrent bevacizumab therapy).

Noguchi Y, Tsurushima M, Tamura Y, Aoyama K, Tokuyama Y, Uchiyama K, Shimizu Y. [A case of hepatitis B virus reactivation in a patient with prior resolved hepatitis B infection during bevacizumab plus FOLFIRI treatment]. Gan To Kagaku Ryoho 2013; 40: 1561-3. Japanese. PubMed PMID: 24231716.

(Abstract: 74 year old man with metastatic colorectal cancer who had anti-HBc without HBsAg in serum developed reactivation of hepatitis B 42 days after the 21st cycle of bevacizumab and FOLFIRI with HBsAg, HBeAg and high levels of HBV DNA progressing to acute liver failure and death).

Constantinidou A, Cunningham D, Shurmahi F, Asghar U, Barbachano Y, Khan A, Mudan S, et al. Perioperative chemotherapy with or without bevacizumab in patients with metastatic colorectal cancer undergoing liver resection. Clin Colorectal Cancer 2013; 12: 15-22. PubMed PMID: 23021126.

(Among 94 patients with metastatic colorectal cancer undergoing preoperative chemotherapy, rates of complications of hepatic resection were similar in those who had received bevacizumab [48% overall, 12% severe] and those who did not [54% overall, 13% severe].

Hubert C, Sempoux C, Humblet Y, van den Eynde M, Zech F, Leclercq I, Gigot JF. Sinusoidal obstruction syndrome (SOS) related to chemotherapy for colorectal liver metastases: factors predictive of severe SOS lesions and protective effect of bevacizumab. HPB (Oxford) 2013; 15: 858-64. PubMed PMID: 23458554.

(Retrospective analysis of 151 patients with colorectal cancer and hepatic metastases; some degree of sinusoidal obstruction syndrome occurred in 60 of 67 [90%] of those who received oxaliplatin and fluorouracil alone and was severe in 37 [55%], but arose in only 6 of 10 [60%] who also received bevacizumab and was severe in only 1 [10%]).

Maestraggi Q, Bouattour M, Toquet S, Jaussaud R, Kianmanesh R, Durand F, Servettaz A. Bevacizumab to treat cholangiopathy in hereditary hemorrhagic telangiectasia: be cautious: a case report. Medicine (Baltimore) 2015; 94: e1966. PubMed PMID: 26579805.

(61 year old woman with hereditary hemorrhagic telangiectasia treated with bevacizumab to inhibit angiogenesis developed hepatic vein thrombosis and multiple pulmonary emboli, possibly complications of the monoclonal antibody treatment).