Bevacizumab

Bevacizumab, sold under the trade name **Avastin**, is an angiogenesis inhibitor, a drug that slows the growth of new blood vessels.

Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A).[2] VEGF-A is a chemical signal that stimulates angiogenesis in a variety of diseases, especially in cancer. Bevacizumab was the first clinically available angiogenesis inhibitor in the United States.[3]

Bevacizumab was approved by the U.S. Food and Drug Administration (FDA) for certain metastatic cancers. It received its first approval in 2004, for combination use with standard chemotherapy for metastatic colon cancer.[4] It has since been approved for use in certain lung cancers, renal cancers, ovarian cancers, and glioblastoma multiforme of the brain. It had been approved for breast cancer, but that approval was withdrawn when later studies showed no evidence of effectiveness.[5] It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[6] It is listed for its use in treating certain eye diseases.[6]

1 Medical uses

1.1 Colorectal cancer

Bevacizumab was approved by the FDA in February 2004 for use in metastatic colorectal cancer when used with standard chemotherapy treatment (as first-line treatment) and with 5-fluorouracil-based therapy for second-line metastatic colorectal cancer.

Bevacizumab has also been examined as an add on to other chemotherapy drugs in people with non-metastatic colon cancer undergoing surgical removal. The data from two large randomized studies showed no benefit in preventing the cancer from returning and a potential to cause harm in this setting.[7]

It was approved by the EMA in January 2005 for use in colorectal cancer.

1.2 Lung cancer

In 2006, the FDA approved bevacizumab for use in first-line advanced nonsquamous non-small cell lung cancer in combination with carboplatin/paclitaxel chemotherapy. The approval was based on the pivotal study E4599 (conducted by the Eastern Cooperative Oncology Group), which demonstrated a 2-month improvement in overall survival in patients treated with bevacizumab (Sandler, et al. NEJM 2004). A preplanned analysis of histology in E4599 demonstrated a 4-month median survival benefit with bevacizumab for patients with adenocarcinoma (Sandler, et al. JTO 2010); adenocarcinoma represents approximately 85% of all non-squamous cell carcinomas of the lung. A subsequent European clinical trial, AVAiL, was first reported in 2009 and confirmed the significant improvement in progression-free survival shown in E4599 (Reck, et al. Ann. Oncol. 2010). An overall survival benefit was not demonstrated in patients treated with bevacizumab; however, this may be due to the more limited use of bevacizumab as maintenance treatment in AVAiL versus E4599 (this differential effect is also apparent in the European vs US trials of bevacizumab in colorectal cancer: Tyagi and Grothey, Clin Colorectal Cancer, 2006). As an anti-angiogenic agent, there is no mechanistic rationale for stopping bevacizumab before disease progression. Stated another way, the survival benefits achieved with bevacizumab can only be expected when used in accordance with the clinical evidence: continued until disease progression or treatment-limiting side effects. Another large European-based clinical trial with bevacizumab in lung cancer, AVAPERL, was reported in October 2011 (Barlesi, et al. ECCM 2011). First-line patients were treated with bevacizumab plus cisplatin/pemetrexed for four cycles, and then randomized to receive maintenance treatment with either bevacizumab/pemetrexed or bevacizumab alone until disease progression. Maintenance treatment with bevacizumab/pemetrexed demonstrated a 50% reduction in risk of progression vs bevacizumab alone (median PFS: 10.2 vs 6.6 months, HR 0.50, $p<0.001$). The National Comprehensive Cancer Network recommends bevacizumab as standard first-line treatment in combination with any platinum-based chemotherapy, followed by maintenance bevacizumab until disease progression. Higher doses are usually given with carboplatin-based chemotherapy, whereas the lower dose is usually given with cisplatin-based chemotherapy.

1.3 Breast cancer

In December 2010, the FDA removed the breast cancer indication from bevacizumab, saying that it had not

been shown to be safe and effective in breast cancer patients. The combined data from four different clinical trials showed that bevacizumab neither prolonged overall survival nor slowed disease progression sufficiently to outweigh the risk it presents to patients. This only prevented Genentech from marketing bevacizumab for breast cancer. Doctors are free to prescribe bevacizumab off label, although insurance companies are less likely to approve off-label treatments.[8][9] In June 2011, an FDA panel unanimously rejected an appeal by Roche. A panel of cancer experts ruled for a second time that Avastin, the best-selling cancer drug in the world, should no longer be used in breast cancer patients, clearing the way for the U.S. government to remove its endorsement from the drug. The June 2011 meeting of the FDA's oncologic drug advisory committee was the last step in an appeal by the drug's maker. The committee concluded that breast cancer clinical studies of patients taking Avastin have shown no advantage in survival rates, no improvement in quality of life, and significant side effects. Patient support groups were disappointed by the committee's decision.[10]

On October 11, 2011, the U.S. Food and Drug Administration (FDA) announced that the agency is revoking the agency's approval of the breast cancer indication for bevacizumab after concluding that the drug has not been shown to be safe and effective for that use.

1.4 Renal cancers

In certain renal (kidney) cancers, bevacizumab improves the progression free survival time but not survival time. In 2009, the FDA approved bevacizumab for use in metastatic renal cell cancer (a form of kidney cancer).[11][12] following earlier reports of activity[13] EU approval was granted in 2007.

1.5 Brain cancers

Bevacizumab slows tumor growth but does not affect overall survival in people with glioblastoma multiforme.[14]

The FDA granted accelerated approval for the treatment of recurrent glioblastoma multiforme in May 2009.[15] A 2014 Cochrane review deemed there to not be enough evidence for its use in recurrences.[14]

1.6 Eye disease

Many diseases of the eye, such as age-related macular degeneration (AMD) and diabetic retinopathy, damage the retina and cause blindness when blood vessels around the retina grow abnormally and leak fluid, causing the layers of the retina to separate. This abnormal growth is caused by VEGF, so bevacizumab has been successfully used to inhibit VEGF and slow this growth.

Bevacizumab has recently been used by ophthalmologists in an off-label use as an intravitreal agent in the treatment of proliferative (neovascular) eye diseases, particularly for choroidal neovascular membrane (CNV) in AMD. Although not currently approved by the FDA for such use, the injection of 1.25-2.5 mg of bevacizumab into the vitreous cavity has been performed without significant intraocular toxicity.[16] Many retina specialists have noted impressive results in the setting of CNV, proliferative diabetic retinopathy, neovascular glaucoma, diabetic macular edema, retinopathy of prematurity[17] and macular edema secondary to retinal vein occlusions.

Some reviews conclude that similar results are obtained using either bevacizumab or ranibizumab.[18][19] Others found a higher rate of adverse events[20][21][22] such as thromboembolism with bevacizumab or were unable to reach firm conclusions based on the limited data available.[23]

1.7 Drug administration

Bevacizumab is usually given intravenously every 14 days. In colon cancer, it is given in combination with the chemotherapy drug 5-FU (5-fluorouracil), leucovorin, and oxaliplatin or irinotecan. Clinical trials are underway to test an intra-arterial technique for delivering the drug directly to brain tumors, bypassing the blood–brain barrier.[24][25] For treatment of eye diseases it is injected intravitreously.

2 Adverse effects

Bevacizumab inhibits the growth of blood vessels, which is part of the body's normal healing and maintenance. The body grows new blood vessels in wound healing, and as collateral circulation around blocked or atherosclerotic blood vessels. One concern is that bevacizumab will interfere with these normal processes, and worsen conditions like coronary artery disease or peripheral artery disease.[26]

The main side effects are hypertension and heightened risk of bleeding. Bowel perforation has been reported.[27] Fatigue and infection are also common.[28] In advanced lung cancer, less than half of patients qualify for treatment.[29][30] Nasal septum perforation and renal thrombotic microangiopathy have been reported.[31] In December 2010, the FDA warned of the risk of developing perforations in the body, including in the nose, stomach, and intestines.

In 2013, Hoffmann-La Roche announced that the drug was associated with 52 cases of necrotizing fasciitis from 1997 to 2012, of which 17 patients died.[32] About 2/3 of

cases involved patients with colorectal cancer, or patients with gastrointestinal perforations or fistulas.

These effects are largely avoided in ophthalmological use since the drug is introduced directly into the eye thus minimizing any effects on the rest of the body.

3 Chemistry

Bevacizumab was originally derived from a mouse monoclonal antibody generated from mice immunized with the 165-residue- form of recombinant human vascular endothelial growth factor. It was humanized by retaining the binding region and replacing the rest with a human full light chain and a human truncated IgG1 heavy chain, with some other substitutions. The resulting plasmid was tranfected into Chinese Hamster Ovary cells which are grown in industrial fermentation systems.[33]:4

4 History

Bevacizumab is a recombinant humanized monoclonal antibody and in 2004 it became the first clinically used angiogenesis inhibitor.[34] Its development was based on the discovery of human vascular endothelial growth factor (VEGF), a protein that stimulated blood vessel growth, in the laboratory of Genentech scientist Napoleone Ferrara.[35][36][37] Ferrara later demonstrated that antibodies against VEGF inhibit tumor growth in mice.[38] His work validated the hypothesis of Judah Folkman, proposed in 1971, that stopping angiogenesis might be useful in controlling cancer growth.[37]

4.1 Approval

The first approved indication came in 2004[34] for metastatic colorectal cancers, which remains a cancer type that responds well to Avastin. The overwhelming data of trials for usage of Avastin with a fluoropyrimidine demonstrates its efficacy and safety, which continually extends survival for this group of patients.

At one point bevacizumab was approved for breast cancer by the FDA, but the approval was revoked on 18 November 2011.[39][40] The approval for breast cancer was revoked because, although there was evidence that it slowed progression of metastatic breast cancer, there was no evidence that it extended life or improved quality of life, and it caused adverse effects including severe high blood pressure and hemorrhaging. In 2008, the FDA gave bevacizumab provisional approval for metastatic breast cancer, subject to further studies. The FDA's advisory panel had recommended against approval.[41] In July 2010, after new studies failed to show a significant benefit, the FDA's advisory panel recommended against the indication for advanced breast cancer. Genentech requested a hearing, which was granted in June 2011. The FDA ruled to withdraw the breast cancer indication in November 2011. FDA approval is required for Genentech to market a drug for that indication. Doctors may sometimes prescribe it for that indication, although insurance companies are less likely to pay for it.[39] The drug remains approved for breast cancer use in other countries including Australia.[42] It has been funded by the English NHS Cancer Drugs Fund but in January 2015 it was proposed to remove it from the approved list.[43]

5 Society and culture

5.1 Costs

In countries with national health care systems (such as the UK and Canada), many of those national health services have restricted bevacizumab on the basis of cost-benefit calculations; in the U.K., for example, the National Institute for Health and Clinical Excellence has taken the position that bevacizumab should not be funded by the NHS because it costs nearly £21,000 per patient but only minimal benefit in many cancers.[44] In 2006, the Scottish Medicines Consortium recommended against the NHS funding Avastin for first-line treatment of metastatic carcinoma of the colon or rectum, due to estimated costs of £24,000 to £93,000 per quality-adjusted life year (QALY).[45]

The addition of bevacizumab to standard treatment can prolong the lives of breast and lung cancer patients by several months, at a cost of $100,000 a year in the United States.[46] For colorectal cancer, Robert J. Mayer wrote in the New England Journal of Medicine that bevacizumab extended life by 4.7 months (20.3 months vs. 15.6 months) in the initial study, at a cost of $42,800 to $55,000.[47] Costs in other countries vary; in Canada it is reported to cost $40,000 CAD per year.[48]

5.2 Use for macular degeneration

When bevacizumab is used in the treatment of wet age-related macular degeneration (wet AMD), only tiny and relatively inexpensive doses (compared to amounts used in colon and other cancers) are required. Some investigators believe that bevacizumab at a cost of around $42 a dose is as effective as ranibizumab at a cost of over $1,593 a dose.[49][50]

As of April 2015, there was a fierce debate in the UK and other European countries concerning the choice of prescribing bevacizumab or ranibizumab (Lucentis) for wet AMD.[51] In the UK, part of the tension was between on the one hand, both the European Medicines Agency and the Medicines and Healthcare Products Regulatory Agency which had approved Lucentis but not Avastin for wet AMD, and their interest in ensuring that doctors to

do not use medicines off-label when there are other, approved medications for the same indication, and on the other hand, NICE in the UK, which sets treatment guidelines, and has been unable so far to appraise Avastin as a first-line treatment, in order to save money for the National Health Service.[51] Novartis and Roche (which respectively have marketing rights and ownership rights for Avastin) had not conducted clinical trials to get approval for Avastin for wet AMD and had no intention of doing so.[51] Further, both companies lobbied against treatment guidelines that would make Avastin a first-line treatment, and when government-funded studies comparing the two drugs were published, they published papers emphasizing the risks of using Avastin for wet AMD.[51]

5.3 Breast cancer approval

In 2010, before the FDA announcement, The National Comprehensive Cancer Network (NCCN) updated the NCCN Clinical Practice Guidelines for Oncology (NCCN Guidelines) for Breast Cancer to affirm the recommendation regarding the use of bevacizumab (Avastin, Genentech/Roche) in the treatment of metastatic breast cancer.

In 2008, the FDA approved Bevacizumab for use in breast cancer. A panel of outside advisers voted 5 to 4 against approval, but their recommendations were overruled. The panel expressed concern that data from the clinical trial did not show any increase in quality of life or prolonging of life for patients — two important benchmarks for late-stage cancer treatments. The clinical trial did show that bevacizumab reduced tumor volumes and showed an increase in progression free survival time. It was based on this data that the FDA chose to overrule the recommendation of the panel of advisers. This decision was lauded by patient advocacy groups and some oncologists. Other oncologists felt that granting approval for late-stage cancer therapies that did not prolong or increase the quality of life for patients would give license to pharmaceutical companies to ignore these important benchmarks when developing new late-stage cancer therapies.[41]

On March 28, 2007, the European Commission approved bevacizumab in combination with paclitaxel for the first-line treatment of metastatic breast cancer.[52]

5.4 Counterfeit

On Tuesday, February 14, 2012, Roche and its U.S. biotech unit Genentech announced that counterfeit Avastin had been distributed in the United States.[53] The investigation is ongoing, but differences in the outer packaging make identification of the bogus drugs simple for medical providers. Roche analyzed three bogus vials of Avastin and found they contained salt, starch, citrate, isopropanol, propanediol, t-butanol, benzoic acid, di-fluorinated benzene ring, acetone and phthalate moiety, but no active ingredients of the cancer drug. According to Roche, the levels of the chemicals were not consistent; whether the chemicals were at harmful concentrations could not therefore be determined. The counterfeit Avastin has been traced back to Egypt, and it entered legitimate supply chains via Europe to the United States.[54][55]

5.5 Biosimilars

In July 2014, two pharming companies, PlantForm and PharmaPraxis, announced plans to commercialize a biosimilar version of bevacizumab made using a tobacco expression system in collaboration with the Fraunhofer Center for Molecular Biology.[56]

5.6 Specialty drugs

On September 16, 2014 Genentech reclassified bevacizumab as specialty drugs which are only available through specialty pharmacies. “Specialty drugs usually fall under the FDA’s Risk Evaluation and Mitigation Strategy (REMS) program, established for compounds like the testosterone... that may have unusual side effects; or for drugs that are unusually expensive.”[57] This has caused concern to hospitals as the price increased.[57] According to IMS Health, the average price charged by hospitals for bevacizumab is approximately $9000 compared to approximately $2300 when administered in a doctor’s office. As a result of the new distribution arrangement, many hospitals will no longer be eligible for the 51% discount to average wholesale price that was mandated by the Affordable Healthcare Act under the old distribution arrangement.[58]

6 Research

A study released in April 2009 found that bevacizumab is not effective at preventing recurrences of non-metastatic colon cancer following surgery.[59]

Bevacizumab has demonstrated activity in ovarian cancer[60][61] and glioblastoma multiforme,[62] a type of brain tumour, when used as a single agent.

In 2010, two phase III trials showed a 27% and 54% increase in progression-free survival in ovarian cancer.[63]

Bevacizumab has been investigated as a possible treatment of pancreatic cancer, as an addition to chemotherapy, but studies have shown no improvement in survival.[64][65][66] It may also cause higher rates of high blood pressure, bleeding in the stomach and intestine, and intestinal perforations.

The drug is also undergoing initial trials as an addition to established chemotherapy protocols and surgery in the

treatment of pediatric osteosarcoma[67] and other sarcomas, such as leiomyosarcoma.[68]

Bevacizumab has been studied as a treatment for cancers that grow from the nerve connecting the ear and the brain.[69]

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8 External links

- Avastin.com
- Berenson, Alex (February 15, 2006). "A Cancer Drug Shows Promise, at a Price That Many Can't Pay". *New York Times*.
- NCI Drug Information Summary on Bevacizumab for Patients
- NCI Drug Dictionary Definition for Bevacizumab
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- U.S. National Library of Medicine: Drug Information Portal — Bevacizumab
- NCCN Guidelines For Breast Cancer Updated; Bevacizumab Recommendation Affirmed
- Avastin Adverse Events Reported to the FDA Adverse Event Reporting System (AERS)

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