

## BEVACIZUMAB

Thi T. Nguyen

4th Year Pharmacy Student, UCSF

Bevacizumab (Avastin-Genentech) is a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF) and is the first drug in a new class of anticancer treatments known as angiogenesis inhibitors. Bevacizumab is FDA approved as a first-line treatment in combination with fluorouracil-based chemotherapy for patients with metastatic colorectal cancer.

### PHARMACOLOGY

Angiogenesis, the process of generating new blood vessels is essential for normal physiologic processes such as embryogenesis and wound healing, but also plays a role in cancer growth and metastasis.<sup>1,4</sup> A novel approach to treatment of solid tumors is to target the growth of new blood vessels. Without a rich blood supply, tumor cell growth is reduced.<sup>1</sup>

VEGF is responsible for angiogenic activity and is also an anti-apoptotic factor for newly formed blood vessels.<sup>1,3</sup> Increased levels of VEGF have been found in most human tumors, including lung, gastrointestinal tract, kidney, thyroid, bladder, ovary, and cervix and have been associated with a poor prognosis.<sup>1,4</sup> Bevacizumab binds to VEGF and prevents the interaction of VEGF with its receptors on the surface of endothelial cells therefore interfering with tumor blood supply.<sup>5</sup>

### PHARMACOKINETICS

Bevacizumab is administered as an intravenous infusion. The volume of distribution is 0.046 L/kg.<sup>6</sup> Clearance of bevacizumab varies from 0.003-0.005 L/kg/day.<sup>4,6</sup> Bevacizumab is metabolized by the same pathways as IgG. The estimated half-life of bevacizumab is approximately 20 days with a range of 11 to 50 days.<sup>4,5</sup>

### CLINICAL TRIALS

The first phase II study of bevacizumab in colorectal cancer evaluated a combination with fluorouracil (FU) and leucovorin (LV). One hundred four previously untreated patients with colorectal cancer were randomly assigned to receive standard chemotherapy consisting of intravenous FU 500 mg/m<sup>2</sup> and LV 500 mg/m<sup>2</sup>, or standard chemotherapy plus either bevacizumab (5 mg/kg every 2 weeks) or bevacizumab (10 mg/kg every 2 weeks). Overall response rate was 17% vs 40% vs 24% in the standard chemotherapy, low-dose bevacizumab, and high-dose bevacizumab groups respectively. Median time to disease progression in the low-dose arm was a median of 9 months vs 5.2 months with standard chemotherapy. Median survival was 13.8 months for standard chemotherapy, 21.5 months for the low-dose bevacizumab arm, and 16.1 months for the high-dose arm. These differences in median survival were not statistically significant.<sup>7</sup>

In an unpublished multi-center phase III study involving more than 900 previously untreated metastatic colorectal cancer patients, 815 patients were randomized to receive either bevacizumab plus the IFL regimen consisting of irinotecan, FU, and LV or IFL regimen alone. Median time to disease progression increased from 6.2 months to 10.6 months. Median survival increased from 15.6 months to 20.3 months. Overall response rates improved from 35% to 45%.<sup>8</sup>

In a phase II trial of bevacizumab in 116 patients with metastatic renal cell cancer, there was an increase in time to disease progression in those who received 10 mg/kg of bevacizumab when compared with placebo.<sup>9</sup> In the final analysis there were no clinically important differences in overall survival between the two groups. Trials with bevacizumab are also being conducted in non-small-cell lung, breast, prostate, and colorectal cancer.<sup>7</sup>

### ADVERSE EFFECTS

A boxed warning states that bevacizumab is associated with three uncommon but serious adverse events, which include gastrointestinal perforation, hemorrhage, and impaired wound healing.<sup>5</sup> Due to the possibility of impaired wound healing, bevacizumab should not be given for at least 28 days following major surgery and should be discontinued prior to any surgery. The time between termination of bevacizumab and subsequent surgery has not been determined but should take into account the approximate 20-day half-life of the drug. Serious hemorrhage occurred mostly in those with non-small cell lung cancer. In a phase III study, only severe hypertension was much more frequent in the bevacizumab group, but thromboembolism, bleeding, proteinuria, and gastrointestinal perforation also occurred.<sup>8</sup>

### DOSAGE AND COST

The recommended dose of bevacizumab is 5 mg/kg once every 14 days as an intravenous infusion until the cancer progresses.<sup>5</sup> The average patient will use one 400 mg vial every other week. The median duration of treatment of bevacizumab in clinical trials was 10.6 months. The UCSD cost of bevacizumab is as follows:

	UCSD Outpatient Cost	UCSD Inpatient Cost
Bevacizumab		
100 mg	\$ 449	\$ 550
400 mg	\$1,798	\$ 2,118

### SUMMARY

Bevacizumab is a monoclonal antibody that may offer metastatic colorectal cancer patients who have not been previously treated about

a four month delay in cancer progression at an average drug acquisition cost of \$3600 to \$4200/month. In addition to its high cost, the drug has important potential side effects.

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## NITAZOXANIDE

**Kristen Knocke, Pharm.D.**

Pediatric Pharmacy Resident  
Children's Hospital of San Diego

Nitazoxanide (Alinia—Romark Laboratories) is an oral synthetic antiprotozoal agent for the treatment of cryptosporidiosis and giardiasis. Nitazoxanide is the first drug specifically approved for the treatment of cryptosporidiosis. Nitazoxanide oral suspension was approved for use in children from 12 months to 11 years in November 2002 for infectious diarrhea.

## PHARMACOLOGY

The exact mechanism of action of nitazoxanide is unknown. It is believed that the antiprotozoal effects of nitazoxanide are due to interference with the pyruvate: ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction, which is essential to anaerobic energy metabolism in protozoa. Studies of *Giardia lamblia* have shown that the PFOR enzyme from this organism directly reduces nitazoxanide by transfer of electrons in the absence of ferredoxin. The DNA-derived PFOR protein sequence of *Cryptosporidium parvum* appears to be similar to that of *Giardia lamblia*. Interference with the PFOR enzyme-dependent electron transfer reaction may not be the only pathway by which nitazoxanide exhibits antiprotozoal activity.<sup>1</sup>

## SPECTRUM AND RESISTANCE

In the US, the most common causes of cryptosporidiosis and giardiasis are *Cryptosporidium parvum* and *Giardia lamblia*, respectively. Resistance mechanisms to nitazoxanide by *Cryptosporidium parvum*, *Giardia lamblia* or other protozoa have not been examined.<sup>1</sup> Nitazoxanide has microbiological characteristics similar to those of metronidazole but without an apparent problem of resistance. It has been reported to be effective in treating metronidazole-resistant giardiasis.<sup>2</sup> Nitazoxanide has also been effective in treating diarrhea due to other protozoa such as *Giardia duodenalis*, *Giardia intestinalis* and *Entamoeba histolytica*, *Balantidium coli*, *Enterobius vermicularis*, *Ascaris lumbricoides*, *Ancylostoma duodenale*, *Trichuris trichiura*, *Strongyloides stercoralis*, and *Hymenolepis nana*.<sup>3,4</sup>

## PHARMACOKINETICS

Following oral administration of a single dose of nitazoxanide suspension with food, the drug is rapidly hydrolyzed to the active metabolite, tizoxanide (desacetyl-nitazoxanide) which then undergoes conjugation primarily to tizoxanide glucuronide. Nitazoxanide is transformed into tizoxanide during passage through the intestinal tract and in plasma. Therefore, the parent drug nitazoxanide is not detected in plasma, urine, or feces.<sup>2</sup> Once in the systemic circulation,

tizoxanide is >99% bound to plasma proteins. Maximum plasma concentrations of tizoxanide and tizoxanide glucuronide occur within 1 to 4 hours and the bioavailability is substantially increased by food.<sup>5,6</sup> Approximately 33% of an oral dose is excreted in urine and 67% in feces. Tizoxanide is found in plasma, urine, and feces and tizoxanide glucuronide is found in plasma and urine.<sup>2</sup> The pharmacokinetics of nitazoxanide in patients with hepatic and/or renal impairment has not been studied.<sup>1</sup>

## CLINICAL TRIALS

In a prospective, randomized, double-blind, placebo-controlled study conducted in 50 adults and adolescents (aged 12-65) and 50 children (aged 1-11) from the Nile delta of Egypt, diarrhea resolved in 39 (80%) of the 49 patients in the nitazoxanide treatment group, compared with 20 (41%) of the 49 in the placebo group. The study medication was given as follows: adults and adolescents received one 500 mg tablet twice daily for 3 days; the children received either 100 mg (aged 1-3 years) or 200 mg (aged 4-11 years) of nitazoxanide oral suspension. Diarrhea resolved in most patients receiving nitazoxanide within 3 or 4 days of treatment initiation, and reduced the duration of both diarrhea and oocyst shedding.<sup>7</sup>

In a randomized, double-blind, placebo-controlled study of nitazoxanide conducted in 89 adults and adolescents for the treatment of diarrhea caused by *Giardia intestinalis* or *Entamoeba histolytica*/*E. dispar*, 38 of 47 (81%) patients' diarrhea resolved within 7 days compared to 17 of 42 (40%) patients in the placebo group.<sup>8</sup>

Two further studies reported their results using nitazoxanide for the treatment of intestinal protozoan and helminthic infections. The first study was conducted in Mexico, and the second study was an open label, multicenter, clinical study conducted in Egypt.<sup>3,4</sup> Results from both studies found treatment with nitazoxanide was 71-100% effective in eliminating a broad spectrum of mixed intestinal parasitic infections.

Comparative studies in children conclude that nitazoxanide is as effective as other current therapy options, including metronidazole, in the treatment of intestinal protozoa and helminthic infections. One study found that when a total of 110 children from Northern Peru presenting with diarrhea were randomized to treatment with either a 3-day course of nitazoxanide (100 mg every 12 hours, age range 2-3 years; 200 mg every 12 hours, age range 4-11 years) or a 5-day course of metronidazole (125 mg every 12 hours, age range 2-5 years; 250 mg every 12 hours age range 6-11 years), diarrhea resolved in 47 out of 55 (85%) children in the nitazoxanide group, compared to 44 out of 55 (80%) for metronidazole.<sup>2</sup>

## ADVERSE REACTIONS

Nitazoxanide is well tolerated, with the most frequent reported side effects being abdominal pain, diarrhea, vomiting and headache. These are typically mild and transient in nature. Gastrointestinal side effects may be increased with higher doses. In placebo controlled clinical trials, adverse events reported by patients in the nitazoxanide treatment groups were substantially identical to those reported by patients receiving placebo. None of the patients discontinued therapy because of adverse events.<sup>1</sup>

Animal studies have revealed no evidence of impaired fertility or harm to the fetus due to nitazoxanide. There are no adequate and well-controlled studies in pregnant women. It is not known whether nitazoxanide is excreted in human milk and caution should be exercised when is administered to a nursing mother.<sup>1</sup>

## COST

The following is a cost comparison of antiprotozoals used to treat cryptosporidiosis and giardiasis. Nitazoxanide is available as a 100 mg/5 mL oral suspension.

Drug	Dosage	UCSD Cost/Treatment
Nitazoxanide	200 mg q 12 h x 3d	\$49.69
Metronidazole	250 mg q 12 h x 5d	\$ 8.50
Furazolidone	37.5 mg q 6 h x 7-10d	\$54.00

## DOSAGE

The dose for children ages 12-47 months is 5 mL (100 mg nitazoxanide) every 12 hours for 3 days. The dose for children ages 4-11 years is 10 mL (200 mg nitazoxanide) every 12 hours for 3 days. The oral suspension should be taken with food. The dose of children under 1 year has not been established. In clinical trials, the dose of nitazoxanide used in adults and adolescents (12 years and over) was 500 mg every 12 hours for 3 days.<sup>2,7,9</sup>

## SUMMARY

Nitazoxanide is a broad-spectrum antiparasitic which can be used in the treatment of patients with intestinal protozoan and helminthic infec-

tions in both adults and children. In 1998, the drug manufacturer pursued approval to market nitazoxanide in the United States for treating infectious diarrhea in patients with acquired immunodeficiency syndrome but was rejected due to problems with the enrollment of the trial.<sup>10</sup> The U.S. Food and Drug Administration has not approved nitazoxanide 500 mg tablets for any indication but is seeking approval in treating enteric protozoal and helminthic infections in adults and adolescents. Nitazoxanide tablets are expected to be approved in the summer of 2004.

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## DESIRUDIN

William Van Le  
UCSF Pharmacy Student

Desirudin (Iprivask=Aventis) is a specific inhibitor of human thrombin. It is a recombinant analog of r-hirudin, which is secreted by the medicinal leech *Hirudo medicinalis*. The FDA approved it in April 2003 for prophylaxis of deep vein thrombosis (DVT) in patients undergoing elective hip replacement surgery.

## PHARMACOLOGY AND PHARMACOKINETICS

Desirudin is a direct inhibitor of thrombin. One molecule of desirudin binds to one molecule of thrombin and blocks the thrombogenic activity of thrombin. All thrombin-dependent assays are affected which include prolongation of activated partial thromboplastin time and thrombin time. Inhibition of thrombin activity by desirudin leads to bleeding as its main side effect. Desirudin has no effect on other enzymes of the hemostatic system.

Following administration of single dose of 0.1 to 0.75 mg/kg subcutaneously (SC), absorption of desirudin is complete with the peak plasma concentration reached in 1-3 hours. Its distribution is mainly in the extracellular space with a volume of distribution of 0.25 L/kg. Desirudin binds tightly to thrombin via noncovalent bonding to form a tight complex. Metabolism and elimination is mainly via the kidney; approximately 40-50% of an administered dose is excreted as

unchanged in the urine. Metabolites lack one or two C-terminal amino acids and have no pharmacological activity. Total clearance of desirudin is independent of dose. Mean elimination half-life is about 2 hours.<sup>1</sup>

## CLINICAL TRIALS

Desirudin was evaluated in two controlled, randomized, multicenter, clinical efficacy trials and in one controlled, double-blind, dose-finding study.

The first two multicenter efficacy studies compared desirudin 15 mg SC every 12 hours to unfractionated heparin 5000 IU SC d every 8 hours (n= 445) and to enoxaparin sodium 40 mg SC every 24 hours (n = 2049). Desirudin was started before the surgery and continued for 8 to 12 days postoperatively. Patients in the desirudin treatment group had a lower incidence of venous thromboembolic events (VTEs) and proximal deep vein thrombosis (DVT) than patients in the other two groups in both studies.<sup>2,3</sup>

A third multicenter study assessed desirudin at different doses (10 mg, 15 mg, 20 mg) administered SC every 12 hours in compare to unfractionated heparin 5,000 IU administered SC every 8 hours. At all dose levels, desirudin was more effective than heparin in pre-

# Discourse

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### DRUG INFORMATION ON-LINE

The UCSD Clinical Web Portal <http://www.ucsdhealth-care.ucsd.edu/clinical/default.asp> is a place where UCSD clinicians can find various types of information about medications. The Drug Information tab on the left of this web page has links to the excellent drug information database Clinical Pharmacology, the UCSD inpatient Formulary, and now has links to P&T Committee-approved guidelines for epoetin & darbepoetin, hypertonic saline and factor VIIa. From the link above, click on the Drug Information tab and select Guidelines.

For drug information questions that cannot be answered using these on-line sources, call the UCSD Drug Information Service at extension 54233.

venting proximal deep vein thrombosis.<sup>4</sup>

Other non-FDA approved indications include its use in patients with past or current heparin-induced thrombocytopenia (HIT), for treatment of acute coronary syndrome,<sup>5,6</sup> and for prevention of restenosis after percutaneous transluminal coronary angioplasty.<sup>7</sup>

### ADVERSE EFFECTS

Bleeding is the most common adverse reaction to desirudin administration. The frequency of serious and major bleeding was similar to that observed with heparin and enoxaparin. Other less frequent adverse reactions include thrombosis, hypotension, leg edema, fever, decreased hemoglobin, hematuria, dizziness, epistaxis, nausea, vomiting, impaired wound healing, cerebrovascular disorders, leg pain, and hematemesis.

Weak allergic reactions have been reported in patients receiving desirudin.<sup>8</sup> Rare fatal anaphylactoid reactions occurred during hirudin therapy. Other side effects include antibody formation, injection site reaction, wound secretion, anemia, and deep thrombophlebitis.

Desirudin is contraindicated in patients with known hypersensitivity to natural or recombinant hirudins, and in patients with active bleeding or irreversible coagulation disorder.<sup>1</sup>

### DOSAGE AND COST

For deep vein thrombosis prophylaxis in patients undergoing elective hip replacement surgery, the recommended dose is 15 mg SC every 12 hours with first dose given 5-15 hours before the surgery. Treatment duration is up to 12 days post surgery. Dosage reduction is recommended for patients with severe renal failure.<sup>9</sup>

### SUMMARY

Patients undergoing elective hip replacement surgery may benefit

from desirudin. It is more effective than enoxaparin and unfractionated heparin in the prevention of deep vein thrombosis. Although occurring at low frequency, anti-hirudin antibody production and fatal anaphylactoid reactions have been reported with desirudin use.<sup>1</sup> Due to its similar bleeding side effect profile to heparin and enoxaparin, desirudin can become a potential replacement for more experience heparin and enoxaparin.

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