National PBM Drug Monograph
Bevacizumab (Avastin™)
August 2004

VA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

FDA-approved indication: Bevacizumab is a humanized monoclonal antibody that binds to circulating Vascular Endothelial Growth Factor (VEGF). Bevacizumab is approved for use in combination with intravenous 5-fluourouracil-based chemotherapy for first-line treatment of metastatic colorectal carcinomas.

Dosing: The dose of bevacizumab is 5mg/kg diluted in 100ml of 0.9% sodium chloride (infusions should not be admixed with dextrose solutions). The first dose is infused over 90 minutes following chemotherapy. If there are no infusion reactions, the second dose is given over 60 minutes. If this is tolerated, subsequent doses are infused over 30 minutes. The dose is repeated every 14 days until disease progression or toxicity. There are no recommended dose modifications; therapy may be interrupted temporarily as needed.

Efficacy: The registration trial was a phase III trial comparing standard bolus IFL (Saltz regimen) plus placebo to IFL plus bevacizumab. A third arm of leucovorin/5-fluorouracil plus bevacizumab was stopped after a pre-planned interim analysis found acceptable toxicities in the IFL plus bevacizumab arm. The primary endpoint was survival, and median survival in the IFL + bevacizumab arm was 20.3 months versus 15.5 months in the IFL + placebo arm ($p<0.001$). Supporting trials include 2 phase II trials, one comparing leucovorin/5-fluorouracil to leucovorin/5-fluorouracil + bevacizumab and the other evaluated IFL plus bevacizumab. Second line therapy with bevacizumab plus FOLFOX has only published safety data at this time. Phase II data is also available for other solid tumors: pancreatic carcinoma, renal cell carcinoma, breast cancer, and NSCLC.

Safety: Common adverse events attributed to bevacizumab include epistaxis, hypertension, headache, and proteinuria. Hypertension may require therapy or adjustment of previous antihypertensive drugs. Serious events include leukopenia, neutropenia, hypertension, hemorrhage, GI perforations/wound dehiscence sometimes accompanied by abdominal abscess, nephrotic syndrome, CHF, and arterial thromboembolic events. Recently, the manufacturer announced warnings of an increased risk in arterial thromboembolic events, some fatal, during bevacizumab therapy. High-risk patients included those with a history of arterial thromboembolism, those over 65 years of age, and bevacizumab therapy.

Conclusion: Bevacizumab improves survival when added to bolus IFL therapy in metastatic colorectal carcinomas through a unique mechanism of action. Bolus IFL therapy had been the standard of care at the time this study was initiated. Other current first-line therapies may also offer increased survival comparable to bevacizumab plus IFL. Recent safety concerns will need to be evaluated in our population who are at high risk for arterial thromboembolism due to age.

Recommendation: Bevacizumab should be available for use in veteran patients with metastatic colorectal cancer as one choice for first-line therapy. Patients should be carefully evaluated for risk factors and exclusion criteria to avoid inappropriate prescribing.

Introduction

The purpose of this monograph is to review the efficacy and safety of bevacizumab, a monoclonal antibody used in combination with 5-fluorouracil-based chemotherapy in the treatment of metastatic carcinoma of the colon or rectum.

Pharmacology/Pharmacokinetics[1,2]

Vascular endothelial growth factor (VEGF) is expressed in multiple cell types (tumor cells, macrophages, T-cells, smooth muscle cells, kidney cells, etc.). VEGF is involved in vascular permeability and proliferation in the angiogenesis cascade. Binding of VEGF to two receptor tyrosine kinases (RTKs) on endothelial cells sends a pro-angiogenic signal to downstream targets that initiate the signal cascade.

Bevacizumab is a humanized monoclonal antibody that binds to and inhibits circulating VEGF from binding to the receptor tyrosine kinases. In animal models VEGF inhibition prevented growth of human tumor xenografts and decreased tumor vessel density but did not affect the growth of malignant cells in vitro. Tumor VEGF expression has prognostic value in a variety of solid tumors (breast, esophagus, colorectal, ovarian, and lung) and in one liquid tumor (acute myelogenous leukemia). In colorectal carcinomas VEGF expression has been shown to be higher in metastatic disease.

Pharmacokinetics	Bevacizumab
Clearance	Males 0.262 L/day Females 0.207 L/day High tumor burden 0.249 L/day Low tumor burden 0.199 L/day
Half-life	20 days (11-50)

Renal Impairment/Hepatic dysfunction: No studies have been conducted in patients with either renal impairment of hepatic dysfunction.

FDA Approved Indication(s) and Off-label Uses

Bevacizumab in combination with intravenous 5-fluorouracil-based chemotherapy is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

Off Label: second-line treatment in combination with chemotherapy for metastatic colorectal carcinomas, renal cell carcinomas, metastatic breast cancer, pancreatic cancer, non-small cell lung cancer.

Dosage and Administration

In metastatic colon or rectal carcinoma, the recommended dose of bevacizumab is 5mg/kg given as an IV infusion once every 14 days until disease progression.

Therapy with bevacizumab should not be initiated for at least 28 days following major surgery and only after the surgical incision is completely healed.

Dose Modifications:
There are no recommended dose reductions. Bevacizumab may be discontinued or temporarily suspended as needed.

Permanent discontinuation: in patients who develop GI perforation, wound dehiscence requiring medical intervention, serious bleeding, nephrotic syndrome, or hypertensive crisis.

Temporary suspension: in patients with evidence of moderate to severe proteinuria pending further evaluation and in patients with severe hypertension not controlled with medical management. Therapy should be suspended at least several weeks prior to elective surgery and resumed when incision is healed. The appropriate interval between the last dose and elective surgery is unknown.

Mixing/stability/storage:
Bevacizumab should be diluted in 100ml of 0.9% sodium chloride injection. **Infusions should not be administered or mixed with dextrose solutions.** Polyvinyl chloride and polyethylene bags are acceptable. Diluted solutions may be stored under refrigeration (2-8°C) for up to 8 hours.

Bevacizumab vials must be refrigerated and vials should be protected from light. Vials contain no preservatives.

Administration:
The first dose should be administered over 90 minutes following chemotherapy. If no infusion-related reactions (fever and/or chills), the second dose may be administered over 60 minutes. If this is well tolerated, subsequent doses may be administered over 30 minutes.

In clinical trials, standard premedications for chemotherapy were administered. In cases of infusion reactions (<3%with first dose) the use of acetaminophen, diphenhydramine, and meperidine was allowed.

In the phase III trial, bevacizumab was administered every 2 weeks regardless of chemotherapy dosing delays as long as there were no contraindications to continue.

Efficacy Measures

Primary: Survival
Secondary: Progression-free survival
Objective response rate
Duration of response
Safety

Clinical Trials

Metastatic Carcinoma of the Colon or Rectum

First-line Therapy:

Phase III in combination with IFL[3]

Multicenter, randomized, double-blind study comparing IFL (irinotecan, 5-fluorouracil, leucovorin) to IFL + bevacizumab. A third arm used 5-fluorouracil and leucovorin + bevacizumab but was discontinued after a pre-specified interim analysis showed safety in the IFL + bevacizumab arm. Patients were excluded if they received prior chemotherapy or biologic therapy for metastatic disease, adjuvant fluoropyrimidines with leucovorin or levamisole within the previous 12 months, radiation within the past 14 days, had CNS metastasis, bleeding diathesis or coagulopathy, regular use of aspirin (>325mg/day) or other nonsteroidal anti-inflammatory agents, proteinuria at baseline, clinically detectable ascites, or a major procedure within 28 days. In addition, patients with clinically significant cardiovascular disease in the past 12 months were excluded. Baseline characteristics were similar.

Outcome	IFL + Placebo (N =411)	IFL + Bevacizumab (N = 402)
Overall Survival*		
Median (months)	15.6	20.3
Hazard ratio		0.66
Progression-Free Survival*		
Median (months)	6.2	10.6
Hazard ratio		0.54
Overall Response Rate**		
Rate (%)	35%	45%
CR	2.2	3.7
PR	32.6	41.0
Duration of Response		
Median (months)	7.1	10.4
Hazard ratio		0.62

* p< 0.001
**p =0.004

The median duration of treatment was 27.6 weeks in the IFL plus placebo arm and 40.4 weeks in the IFL plus bevacizumab arm.

Additional sub-group analyses were performed to evaluate the effects of risk factors on survival benefits. Trends by each baseline risk factor for the primary outcome of overall survival and for the secondary outcome of progression-free survival were consistent with the results of the whole population. When treatment was adjusted for risk factors, the subanalysis found reductions in the hazard ratios for overall survival and progression-free survival, and an increase in the odds ratio for response rate in patients treated with bevacizumab.[4]

The most frequent adverse events of all grades in the bevacizumab arms included: asthenia, pain, vomiting, anorexia, constipation, headache, stomatitis, dyspepsia, GI hemorrhage, dizziness, hypertension, dyspnea, respiratory infection, epistaxis, alopecia, and proteinuria.

The most frequent grade 3 or 4 events in both arms included: diarrhea, leukopenia, neutropenia, and any thromboembolic events.

Serious events included: gastrointestinal perforation (6 of 392 with bevacizumab + IFL, 4/109 with 5-FU/LV + bevacizumab) some with a fatal outcome. Wound dehiscence occurred in 2 of 396 with IFL, 4/392 with bevacizumab + IFL, and 1/109 with 5FU/LV + bevacizumab.

Phase III 5-Fluorouracil/Leucovorin (5FU/LV) + Bevacizumab[5]

A pre-specified interim analysis occurred after approximately 100 patients were randomized into each group. This arm of the trial was then discontinued because IFL + bevacizumab was shown to be safe.

Outcome	IFL/Placebo (N= 101)	IFL + bevacizumab (N= 103)	5FU/LV + bevacizumab (N= 110)
Median survival (months)	15.1	20.5	18.3
Hazard ratio		0.72	0.82
P value		0.066	0.2521
Median PFS (months)	6.7	10.9	8.8
Hazard ratio		0.66	0.86
P value		0.0382	0.4192
ORR (CR + PR)	36.6%	45.6	40
P value		0.2119	0.6556
Median duration of response (months)	7.2	11.7	8.5

PFS=Progression Free Survival

The safety profile with 5-fluorouracil/leucovorin + bevacizumab showed less neutropenia and alopecia but more skin toxicity, diarrhea, and hypertension.

Phase II 5FU/LV versus 5FU/LV + bevacizumab[6]

A multi-center, randomized trial of 5FU/LV alone compared to 5FU/LV + bevacizumab (5 or 10mg/kg). Exclusion criteria included prior chemotherapy (except for adjuvant therapy > 12 months from day 0), radiotherapy or major surgery within 28 days, patients with serious non-healing wounds, ulcers, or bone fractures, and clinically significant cardiovascular or peripheral vascular disease. Recurrent use of anticoagulants, except to maintain central lines, or aspirin was not allowed. 5-fluorouracil and leucovorin were administered weekly according to the Roswell Park regimen (LV 500mg/m^2 over 2 hours once a week for 6 weeks per cycle; 5-fluorouracil 500mg/m^2 IV bolus 1 hour after starting leucovorin infusion). Bevacizumab was administered following chemotherapy.

Outcome	5FU/LV (N=36)	Bevacizumab 5mg/kg (N=33)	Bevacizumab 10mg/kg (N=33)
Time to progression			
Median (months)	5.2	9.0	7.2
Hazard ratio, unadjusted		0.46	0.66
95% CI	3.5 – 5.6	5.8 – 10.9	3.8 – 9.2
P value		0.005	0.217
Response Rate (%)	17	40	24
95% CI	7-34	24 – 58	12 – 43
P value		0.029	0.434
Survival			
Median (months)	13.8	21.5	16.1

Safety: Five patients died from causes other than disease progression, including respiratory distress (5mg/kg) and pulmonary embolism (10mg/kg). The incidence and severity of known 5FU/LV toxicities was similar when bevacizumab was added. Bevacizumab patients also experienced fever, headache, rash, epistaxis, and chills that were generally mild to moderate. Bleeding, hypertension, and thrombosis occurred more often in the bevacizumab patients. The most common bleeding was epistaxis lasting less than 5 minutes. Proteinuria occurred more often in bevacizumab patients

Phase II Bevacizumab plus IFL (ECOG 2200)[7]

Primary outcomes were evaluation of PFS, response rate, and toxicity of combination therapy in previously untreated patients with metastatic disease. Exclusion criteria included prior adjuvant therapy with irinotecan, adjuvant therapy <12 months from start of study, patients receiving therapeutic anticoagulation. The treatment regimen was standard IFL plus bevacizumab 10mg/kg. In 2001, the IFL regimen was dose reduced because of toxicities with IFL in two other clinical trials.

Outcome	Full Dose IFL N=19	Reduced Dose IFL N=67	Overall
Progression-free survival			10 months
Median follow-up			16.7 months
CR	7%	6%	6%
PR	50%	42%	43%

Safety: The most common adverse event was grade 1 epistaxis. Thrombosis occurred in 13% including pulmonary embolism in 3 patients. Tolerability improved when IFL doses were reduced.

Second-line therapy Bevacizumab plus FOLFOX4 (E3200)[8]

Multi-center, randomized trial comparing bevacizumab 10mg/kg alone to FOLFOX4 alone and bevacizumab 10mg/kg + FOLFOX4 in previously treated patients with metastatic colorectal cancer. Exclusion criteria included patients with prior bevacizumab or oxaliplatin therapy, hypertension not on a stable anti-hypertensive regimen, history of thrombotic or hemorrhagic events, therapeutic anticoagulation, and anti-platelet therapy (except for aspirin <325mg/day). Only safety data is available at this time.

Adverse Event	Bevacizumab + FOLFOX (N=262)	FOLFOX (N=265)	Bevacizumab (N=230)
Hematologic			
Platelets			
G3	0	0	0
G4	<1%	0	0
Neutrophils			
G3	2	1%	0
G4	13	17	<1%
Gastrointestinal			
Diarrhea			
G3	13	12	2
G4	1	<1	0
Vomiting			
G3	8	3	3
G4	2	<1	0
Stomatitis			
G3	1	1	<1
G4	0	0	0
Hemorrhagic			
Hematemesis			
G3	1	0	2
G4	0	0	0
Hematuria			
G3	0	0	2
G4	0	0	0
Other			
G3	4	0	1
G4	0	0	0
Other			
Thrombosis/embolism			
G3	3	1	0
G4	0	2	<1
Hypertension			
G3	5	2	6
G4	1	<1	0
Proteinuria			
G3	<1	0	<1
G4	0	0	0

Bowel Perforations: Bevacizumab + FOLFOX (2) Bevacizumab alone: (3) (one death in patient with inoperable perforation)

Possible Treatment Related Deaths:
Bevacizumab + FOLFOX: Pneumonitis/infiltrates (1)
Sudden death (2) Probably PE
CNS hemorrhage (1) patient with thrombosis that bled following anticoagulation

Bevacizumab alone: Bowel perforation (1)

Other

Pancreatic Cancer

Bevacizumab plus Gemcitabine[9]
A multicenter phase II trial of bevacizumab 10mg/kg plus standard gemcitabine in 40 patients with advanced pancreatic cancer resulted in partial response in 24% lasting a median of 9.2 months. The median time to progression was 5.3 months and the median survival was 12.4 months. Grade 3/4 adverse events included leukopenia (28%), neutropenia (25%), thrombocytopenia (5%), thrombosis (10%), hypertension (3%), and proteinuria (3%). One GI bleed and one GI perforation resulted in death.

Renal Cell Carcinoma

Bevacizumab versus placebo Phase II[10]
A phase II randomized, double-blinded study in patients with measurable metastatic disease who had received IL-2 or were ineligible for IL-2. Patients were randomized to placebo, bevacizumab 3mg/kg or 10mg/kg every two weeks after an initial loading dose of 150% of the assigned dose.

Outcome	Placebo (N=39)	Bevacizumab 3mg/kg (N=37)	Bevacizumab 10mg/kg (N=40)
TTP (months) P value Hazard ratio	2.5	3 p=0.041 1.26	4.8 p<0.001 2.55
Patients free of progression (%) 4 months after randomization 8 months after randomization	 20 5	 39 14	 64 30
Response rate PR	 0	 0	 10

TTP=Time To Progression

The most common adverse effects included proteinuria, hypertension, malaise, and epistaxis. There were no grade IV adverse events or deaths due to bevacizumab therapy.

Breast Cancer

Study	Population	Drug Doses	Results
Phase I/II Cob Leigh, et al.	Relapsed MBC	Bevacizumab 3mg/kg (N=18), 10mg/kg (N=41), 20mg/kg (N=16) every other week	ORR 9.3% 1 CR at 10mg/kg
Phase II Burstein, et al.	Refractory MBC	Bevy 10mg/kg q 2 weeks Vinorelbine 25mg/m^{2}q week	ORR 30% 1 CR 16 PR
Phase II Ramaswamy, et al.	Previously treated or untreated MBC	Bev 10mg/kg q 2 weeks Docetaxel 30mg/m^2 q week for 3 weeks; repeat every 28 days	ORR 54% 7 CR
Phase III Hillan, et al. Miller, et al.	Relapsed MBC	Bev 15mg/kg q 3 weeks Capecitabine 2500mg/m^2/day For 2 weeks of every 3 week cycle alone or with bevacizumab	Capecitabine ORR 9.1% Bev + capecitabine ORR 19.8% Did not achieve primary efficacy endpoint of PFS

MBC=metastatic breast cancer; Bev=bevacizumab

NSCLC

Bevacizumab plus Paclitaxel Phase II
Front-line treatment for metastatic NSCLC.
Carboplatin (AUC 6) and paclitaxel 200mg/m^2 every 3 weeks for 6 cycles (Control Arm)
Low dose bevacizumab (7.5mg/kg every 3 weeks) plus carboplatin and paclitaxel
High dose bevacizumab (15mg/kg every 3 weeks) plus carboplatin and paclitaxel

Outcome	Control (N=32)	Low dose (N=32)	High dose (N=35)
RR (CR + PR)	31.3%	21.9%	40%
Median TTP (months)	6	3.9	7
Median survival (months)	14.9	11.6	17.7

Six cases of pulmonary hemorrhage were documented; four were fatal. All were considered tumor-related bleeding from centrally located tumors close to major blood vessels. Potential risk factors identified include squamous cell histology and central, cavitary tumors.

Adverse Effects (Safety Data).[2]

Most common adverse events (any severity): asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea, vomiting, anorexia, stomatitis, constipation, upper respiratory infection, epistaxis, dyspnea, exfoliative dermatitis, proteinuria

Most common severe (NCI-CTC Grade 3-4) adverse events: asthenia, pain, hypertension, diarrhea, leukopenia.

Most serious adverse events: Gastrointestinal perforations/wound healing complications, hemorrhage, nephrotic syndrome, CHF, arterial thromboembolic events

NCI-CTC Grade 3-4 Adverse Events (≥2%)

Adverse Events	IFL + Placebo (N=396)	IFL + Bevacizumab (N=392)
Body as a whole		
Asthenia	7%	10%
Abdominal pain	5	8
Pain	5	8
Cardiovascular		
DVT	5	9
Hypertension	2	12
Intra-abdominal thrombosis	1	3
Syncope	1	3
Digestive		
Diarrhea	25	34
Constipation	2	4
Heme/Lymphatic		
Leukopenia	31	37
Neutropenia	14	21

NCI-CTC Grade 1-4 Adverse Events (≥5%)

Adverse Events	IFL + Placebo (N=98)	IFL + Bevacizumab (N= 102)	5FU/LV + Bevacizumab (N=109)
Body as a whole			
Asthenia	70%	74%	73%
Pain	55	61	62
Abdominal pain	55	61	50
Headache	19	26	26
Cardiovascular			
Hypertension	14	23	34
Hypotension	7	15	7
DVT	3	9	6
Digestive			
Vomiting	47	52	47
Anorexia	30	43	35
Constipation	29	40	29
Stomatitis	18	32	30
GI Hemorrhage	6	24	19
Hematologic			
Thrombocytopenia	0	5	5
Metabolic			
Hypokalemia	11	12	16
Bilirubinemia	0	1	6

Musculoskeletal			
Myalgia	7	8	15
Nervous system			
Dizziness	20	26	19
Confusion	1	1	6
Abnormal gait	0	1	5
Respiratory			
URI	39	47	40
Dyspnea	15	26	25
Epistaxis	10	35	32
Skin			
Alopecia	26	32	6
Dry skin	7	7	20
Exfoliative dermatitis	3	3	19
Special Senses			
Taste alteration	9	14	21
Excess lacrimation	2	6	18
Urogenital			
Proteinurea	24	36	36
Urinary frequency/urgency	1	3	6

Mucocutaneous Hemorrhage: Serious and non-serious hemorrhage occurred at a higher incidence in bevacizumab-treated patients. Epistaxis was most common, but generally mild. Gastrointestinal hemorrhage (24% vs 6%), minor gum bleeding, and vaginal bleeding were mild to moderate.

Thromboembolism: The following thromboembolic events occurred more often in patients treated with bevacizumab-IFL versus placebo-IFL: Cerebrovascular events, MI, DVT, and intra-abdominal thrombosis. Pulmonary embolism was higher in the IFL-placebo group.

Some patients receiving IFL-bevacizumab who received full-dose warfarin developed bleeding complications associated with marked increases in the INR. Although there are speculations as to how bevacizumab causes both bleeding and thromboembolism, in a small number of patients in phase II trials, bevacizumab did not increase PT, aPTT, d-dimer levels, or alter platelet function. It was associated with increased levels of Factor VIII and the von Willebrand factor.[11]

Note: In August of 2004 Genetech sent out a Dear Healthcare Provider Letter with new warnings concerning the risk of thromboembolism. There is new evidence of an increased risk of serious arterial thromboembolic events (stroke, myocardial infarction, transient ischemic attacks, and angina) related to the use of bevacizumab. The risk of fatal thromboembolic events has also increased. If patients experience an arterial thromboembolic event, bevacizumab treatment should be discontinued permanently. Risk factors for the development of arterial thromboembolic events include a history of arterial thromboembolism prior to bevacizumab treatment, age 65 years and above, and bevacizumab therapy.

Precautions/Contraindications

Contraindications: There are no known contraindications to bevacizumab.

Warnings:

Gastrointestinal perforations/Wound healing complications:
Gastrointestinal perforation and wound dehiscence, sometimes complicated by intra-abdominal abscesses, occurred at an increased incidence in patients receiving bevacizumab. In some instances, gastrointestinal perforation was fatal.

The appropriate time interval between surgery and initiation of bevacizumab therapy has not been defined. Patients in clinical trials could not receive therapy for at least 28 days after surgery. In one patient, dehiscence at the anastomotic site occurred when bevacizumab was initiated 2 months after the surgery.

The appropriate time interval between discontinuation of bevacizumab and subsequent elective surgery has not been determined. The longest interval between the last dose of the drug and dehiscence was 56 days.

A sub-analysis of patients in the phase III trial was performed to exam the post-operative wound healing and bleeding complications in patients who underwent major surgery 1) 28-60 days before starting bevacizumab therapy and 2) on therapy, after receiving bevacizumab.

Post-surgical bleeding complications[12]

Type of hemorrhage	**IFL/placebo N=180**	**IFL + Bev N=173**	**5FU/LV + Bev N=45**
GI	2.8%	0.6%	2.2%
Rectal	0	0.6	0
Non-GI	0	0.6	0

Post-surgical Wound Healing Complications within 60 days

Type of wound complication	**IFL/placebo N=180**	**IFL + Bev N=173**	**5FU/LV + Bev N=45**
Abscess	0	0	0
Large intestine perforation	0	0.6%	0
Small intestine perforation	0	0.6	0
Perforation of stomach ulcer	0	0.6	0

Wound Healing Complications while receiving bevacizumab

Type of wound complication	**IFL/placebo N=29**	**IFL + Bev N=46**	**5FU/LV + Bev N=18**
Anastomotic bowel dehiscence	0	2	0
Thoracotomy dehiscence	0	1	0
Hemothorax after lung resection	0	1	0
Ecchymosis and bleeding along incision after colostomy revision	0	0	1

In patients with gastrointestinal perforation or wound dehiscence requiring medical therapy, bevacizumab should be discontinued.

Hemorrhage:
Two distinct patterns have been observed. Of the minor hemorrhages, grade 1 epistaxis is most common. Serious hemorrhage, sometimes fatal, occurred primarily in patients with non-small cell lung cancer. Many patients with life-threatening pulmonary hemorrhage have centrally located tumors with cavitation or necrosis. These serious hemorrhages occurred suddenly with the onset of major hemoptysis.

One patient with a CNS metastasis experienced CNS bleeding in a phase I trial. In subsequent trials, patients with CNS metastases were excluded; therefore use in this population has not been evaluated.

Other serious bleeding events reported included GI hemorrhage, subarachnoid hemorrhage, and hemorrhagic stroke.

If hemorrhage necessitates medical intervention, discontinue bevacizumab. Patients with hemoptysis should not receive bevacizumab.

Hypertension:
Incidence in the Phase III trial

Outcome	**IFL + placebo (n=394)**	**IFL + bevacizumab (N=392)**	**5FU/LV + bevacizumab (N=109)**
Hypertension (>150/100 mmHg)	43%	60%	67%
Severe Hypertension (>200/110 mmHg)	2	7	10

Any patient who develops hypertension, as above, should be treated with anti-hypertensive medications, or have their pre-existing medications adjusted. Patients developing severe hypertension that is not controlled with medication should have bevacizumab discontinued. Patients with hypertensive crisis should have bevacizumab discontinued.

Proteinuria
The incidence and severity of proteinuria (urine dipstick reading of 1+ or greater) was increased in the bevacizumab groups. Five of 1032 patients in clinical trials experienced nephrotic syndrome with one fatality. In three patients, proteinuria decreased after discontinuation of bevacizumab with normalization of levels. Bevacizumab should be discontinued in patients with nephrotic syndromes. Therapy should be interrupted if ≥2gm protein/24 hours, and resumed when proteinuria is <2gm in 24 hours.

Congestive Heart Failure
CHF grades 2-4 were reported in 2% of patients in all trials. The incidence was higher in patients receiving concurrent anthracyclines (14%) and in patients who received prior anthracyclines or chest wall irradiation (4%). The safety of continuing bevacizumab in patients with CHF has not been studied.

Precautions
Infusion reactions: Reactions during the infusion of the first dose were uncommon (<3%). Patients with reactions can develop stridor, wheezing, or grade 3 hypersensitivity reactions and have occurred with the first dose as well as subsequent doses. All patients with severe infusion reactions should have bevacizumab interrupted and appropriate medical care should be given. There is currently no data on how to identify patients who may be safely retreated.

Cardiovascular Disease: The safety of bevacizumab in patients with clinically significant cardiovascular disease has not been adequately studied.

Pregnancy Category C: Bevacizumab is teratogenic in rabbits when administered in doses two-fold greater than the recommended human dose. Angiogenesis is critical to fetal development and inhibition is likely to result in adverse effects on pregnancy although there are no studies in pregnant women. Bevacizumab should be used with caution during pregnancy or in any women not using adequate contraception if the benefits justify the risk to the fetus.

Drug Interactions

There have been no formal drug interaction studies. In patients receiving irinotecan, the concentration of its active metabolite SN38 was 33% higher in patients receiving concomitant bevacizumab.

Acquisition Costs

Drug	Dose	Cost/Infusion/patient ($)	Cost/4 weeks/patient ($)
Bevacizumab	5mg/kg	1646.75 (80kg person)	3293.50

Bevacizumab 100mg vial (25mg/ml): FSS price $411.69
Bevacizumab 400mg vial (25mg/ml): FSS price $1646.75

Conclusions

Efficacy:

In a phase III trial comparing standard IFL chemotherapy to IFL plus bevacizumab as first-line therapy for metastatic colorectal cancer, the addition of bevacizumab statistically significantly increased overall survival, progression-free survival, and response rate across all sub-groups.

In a small phase II trial comparing 5FU/LV alone to 5FU/LV plus bevacizumab at 2 doses as first-line therapy for metastatic colorectal cancer, the addition of bevacizumab 5mg/kg, but not the 10mg/kg, increased the Time To Progression and response rate. Overall survival was increased, but was not a primary outcome.

The efficacy results in second-line therapy in combination with FOLFOX4 have not been reported yet.

In pancreatic cancer, bevacizumab plus gemcitabine produced partial responses with a median survival of 12.4 months.

In renal cell cancer, low-dose and high-dose bevacizumab increased Time To Progression, increased the percentage of patients free of disease progression at 4 and 8 months compared to placebo, and the 10mg/kg dose produced partial responses.

In metastatic breast cancer, bevacizumab alone produced few responses. Response rates were higher when added to chemotherapy, such as vinorelbine, docetaxel, or capecitabine. Survival was not reported.

In non-small cell lung cancer, high-dose bevacizumab plus carboplatin and paclitaxel increased response rates, median Time To Progression, and median survival versus carboplatin and paclitaxel alone. However, toxicities included some fatalities.

Safety:

Bevacizumab was generally well tolerated. In the phase III trial, approximately 4% of patients had a history of venous thrombosis, 12.2% a history of atherosclerosis, 43.2% a history of hypertension, and 13.1% a history of diabetes.[13]

Common adverse events particular to this drug include grade 1 epistaxis, proteinuria, and hypertension. Adjusting anti-hypertensive medications or starting anti-hypertensive therapy generally controlled hypertension. Epistaxis was controlled using conservative measures within 5 minutes for a majority of patients.

Some of the severe adverse events, common to chemotherapy, such as diarrhea and leukopenia, occurred at an increased incidence in the bevacizumab group.

There is a black box warning for gastrointestinal perforation/wound healing complications and for hemorrhage. Gastrointestinal perforation and wound dehiscence, sometimes associated with an intra-abdominal abscess, can occur any time throughout treatment and in some cases is fatal. Fatal hemoptysis was seen in patients with non-small cell lung cancer treated with bevacizumab plus chemotherapy, and was seen more often in patients with squamous cell histology, more likely to have centrally located cavitated tumors.

A new warning of an increased risk for arterial thromboembolic events, especially in high risk populations (prior arterial thromboembolic event, age >65, bevacizumab therapy), was recently sent out by the manufacturer.

Proteinuria was common, with 5 patients progressing to nephrotic syndrome and one fatality.

Congestive heart failure was seen at an increased incidence in patients receiving concurrent anthracyclines and patients who received prior anthracyclines or chest wall irradiation.

Infusion reactions (<3%) occurred during the first infusion and subsequent infusions. At this time, pre-treatment is not recommended.

Patients with clinically significant cardiovascular disease, CHF, CNS metastases, on full anticoagulation therapy, antiplatelet therapy, with clinically significant ascites, pre-existing hemoptysis or proteinuria were excluded from all studies.

Recommendations

Based on the results of the phase III trial, bevacizumab in addition to chemotherapy offers clinically significant outcomes in terms of progression-free survival and overall survival in first-line therapy of

metastatic colorectal cancer. It should be available in the VA as one choice for first-line therapy for metastatic colorectal cancer in patients who can tolerate therapy that is more intensive and do not meet any of the exclusion criteria listed below. Patients should be carefully screened and evaluated for risk of arterial thromboembolic events. The FDA recommended approval for use with all 5-flourouracil-based chemotherapy regimens. Currently, there is only safety data available with the combination of bevacizumab and FOLFOX4 (oxaliplatin, 5-fluorouracil, and leucovorin). The National Comprehensive Cancer Network (NCCN) recently added bevacizumab plus chemotherapy as a first-line therapy for metastatic colorectal cancer in their treatment guidelines.

The following conditions **exclude** patients from receiving bevacizumab because of toxicity or lack of safety data:

- Recent Hemoptysis
- CNS metastasis
- Non-small cell lung cancer
- Full anticoagulation
- Anti-platelet therapy with aspirin (>325mg/day) or other medications
- Major cardiovascular event within the previous 12 months (uncontrolled hypertension, myocardial infarction, unstable angina, serious cardiac arrhythmia requiring medication, or grade II or greater peripheral vascular disease)
- New York Heart Association (NYHA) grade II or greater Congestive Heart Failure
- Pre-existing proteinuria (>500mg urine protein/24 hours) or clinically significant impairment of renal function (serum creatinine >2 g/dL)
- Major surgery within the past 28 days
- Patients with a poor performance status (ECOG performance status of ≥2)
- Clinically detectable ascites

Use of bevacizumab in second-line therapy of colorectal cancer or in other solid tumors cannot be recommended at this time due to lack of evidence of efficacy and/or safety.

Blood pressure should be monitored every 2 weeks during therapy. Patients who develop hypertension or have a worsening of their hypertension may require more frequent monitoring. Urine should be dipsticked for protein at regular intervals. Patients with a 2+ or greater urine dipstick should be further assessed by a 24 hour urine collection. If urine protein is ≥2g/24 hours, interrupt therapy until the proteinuria is <2g/24 hours.

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