Capecitabine, Oxaliplatin, and Bevacizumab (BCapOx) Regimen for Metastatic Colorectal Cancer

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The complexity of cancer chemotherapy requires pharmacists be familiar with the complicated regimens and highly toxic agents used. This column reviews various issues related to preparation, dispensing, and administration of antineoplastic therapy, and the agents, both commercially available and investigational, used to treat malignant diseases. Questions or suggestions for topics should be addressed to Dominic A. Solimando, Jr, President, Oncology Pharmacy Services, Inc, 4201 Wilson Blvd #110-545, Arlington, VA 22203, e-mail: OncRxSvc@comcast.net; or J. Aubrey Waddell, Professor, University of Tennessee College of Pharmacy; Oncology Pharmacist, Pharmacy Department, Blount Memorial Hospital, 907 E. Lamar Alexander Parkway, Maryville, TN 37804, e-mail: waddfour@charter.net. The information presented in this review is based on published data and clinical expertise and includes information not included in the product labeling. Incorporation of such published data provides a more robust assessment of the drugs and assists pharmacists in evaluation of orders for off-label use of these agents.

Regimen Name: BCapOx

Origin of Name: The regimen is named for the 3 drugs it contains: **Bevacizumab** (*Avastin*), **Capecitabine** (*Xeloda*), and **Oxaliplatin** (*Eloxatin*)

Indications

BCapOx (see Table 1) has been studied as primary therapy for advanced, recurrent, or metastatic colorectal cancer (mCRC)¹⁻⁹ and primary therapy for adenocarcinoma of the small bowel or ampulla of Vater.¹⁰ Current guidelines recommend BCapOx as first- or second-line therapy for advanced or mCRC and first-line neoadjuvant therapy for colon cancer with unresectable synchronous liver and/or lung metastases.^{11,12}

Drug Preparation

Follow institutional policies for preparation of hazardous medications when preparing bevacizumab and oxaliplatin and dispensing capecitabine.

A. Capecitabine

1. Capecitabine is available as 500-mg and 150-mg tablets.
2. Capecitabine tablets are unscored and film-coated; breaking or cutting the tablets is difficult and not recommended.

B. Oxaliplatin

1. Use oxaliplatin injection 5 mg/mL, or powder for injection.
2. Reconstitute the powder to a concentration of 5 mg/mL with sterile water for injection or 5% dextrose in water (D5W).

3. Dilute in 250 mL to 500 mL D5W.
4. Oxaliplatin is incompatible with chloride ion. Avoid saline or dextrose/saline diluents.

C. Bevacizumab

1. Use bevacizumab 25 mg/mL injection.
2. Dilute in 100 mL 0.9% sodium chloride injection.

Drug Administration

A. Capecitabine

1. Capecitabine is administered orally (PO), usually in 2 divided doses daily.
2. Tablets should be swallowed with water within 30 minutes after a meal.
3. The dose is often prescribed as the *total daily dose*, which is *twice the individual dose* (eg, 2000 mg/m²/day = 1000 mg/m² twice a day).

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Table 1. Capecitabine, Oxaliplatin, and Bevacizumab Regimen.^{1-5,10}

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Capecitabine	1000 mg/m ² twice daily	PO	1 through 14	28 000 mg/m ²
Oxaliplatin	130 mg/m ²	IV	1	130 mg/m ²
Bevacizumab	7.5 mg/kg	IV	1	7.5 mg/kg

Cycle repeats: every 21 days

Variations

1. Capecitabine 1500 mg/m²/day days 1-14; oxaliplatin 85 mg/m² day 1, bevacizumab 5 mg/kg day 1, every 14 days.⁶
2. Capecitabine 1700 mg/m²/day days 1-14; oxaliplatin 130 mg/m² day 1, bevacizumab 7.5 mg/kg day 1, every 14 days.⁷
3. Capecitabine 2000 mg/m²/day days 1-14; oxaliplatin 85 mg/m² day 1, bevacizumab 10 mg/kg day 1, every 14 days.⁸
4. Capecitabine 1500 mg/m²/day days 1-14; oxaliplatin 130 mg/m² day 1, bevacizumab 7.5 mg/kg day 1, every 21 days.⁹

Note. IV = intravenous; PO = oral.

4. Care should be taken to ensure the intended daily dose is not taken twice a day.

B. Oxaliplatin is administered as an intravenous (IV) infusion over 2 hours on day 1.

C. Bevacizumab

1. Infuse the first dose over 90 minutes.
2. If the first dose is tolerated well, infuse the second dose over 60 minutes.
3. If the second dose is tolerated well, all subsequent doses may be infused over 30 minutes.
4. Should not be administered within 28 days of major surgery or until the surgical wound is fully healed.

Supportive Care

A. Acute and Delayed Emesis Prophylaxis: The BCapOx regimen is predicted to cause acute emesis in 30% to 90% of patients.¹³⁻¹⁶ The studies reviewed reported nausea from 1% to 59% and vomiting from 3% to 32%, with grade 3 or 4 nausea in 1% to 2% of patients and grade 3 or 4 vomiting in 3% to 7%.¹⁻⁴ Prophylactic antiemetic therapy with a steroid and serotonin antagonist is recommended.¹³⁻¹⁶ One group suggests addition of a neurokinin (NK₁) antagonist may be appropriate in some patients.¹³ One of the following regimens given 30 minutes prior to therapy is recommended:

1. Ondansetron 8 mg to 16 mg PO, dexamethasone 20 mg PO, given 30 minutes before oxaliplatin.
2. Granisetron 1 mg to 2 mg PO, dexamethasone 20 mg PO, given 30 minutes before oxaliplatin.
3. Dolasetron 100 mg PO, dexamethasone 20 mg PO, given 30 minutes before oxaliplatin.
4. Palonosetron 0.25 mg IV on day 1 only and dexamethasone 20 mg PO, given 30 minutes before oxaliplatin.

If a neurokinin antagonist is used, one of the following regimens is recommended:

1. Netupitant 300 mg/palonosetron 0.5 mg PO, dexamethasone 12 mg PO.
2. Aprepitant 125 mg PO day 1 and 80 mg PO on days 2 and 3, combined with one of the regimens above (decrease dexamethasone to 12 mg).
3. Fosaprepitant 150 mg IV, combined with one of the regimens above (decrease dexamethasone to 12 mg).
4. Rolapitant 180 mg PO, combined with one of the regimens above.

All given 30 minutes before chemotherapy, except rolapitant which is given 1 to 2 hours before chemotherapy.

The antiemetic therapy should continue for at least 3 days. A meta-analysis of several trials of serotonin antagonists recommends against prolonged (>24 hours) use of these agents, making a steroid or steroid and dopamine antagonist combination most appropriate for follow-up therapy.¹⁷ One of the following regimens is recommended:

1. Dexamethasone 4 mg PO twice a day for 3 days, ±metoclopramide 0.5 to 2 mg/kg PO every 4 to 6 hours, ±diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of BCapOx.
2. Dexamethasone 4 mg PO twice a day for 3 days, ±prochlorperazine 10 mg PO every 4 to 6 hours, ±diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of BCapOx.
3. Dexamethasone 4 mg PO twice a day for 3 days, ±promethazine 25 to 50 mg PO every 4 to 6 hours, ±diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of BCapOx.

Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.¹³⁻¹⁶ There is no evidence that substituting granisetron for ondansetron in subsequent treatment cycles, or increasing the dose, even to very high doses, is effective. This approach is not recommended.¹⁷⁻²²

B. Breakthrough Nausea and Vomiting¹³⁻¹⁶: Patients should receive a prescription for an antiemetic to

treat breakthrough nausea. One of the following regimens is recommended:

1. Metoclopramide 0.5 to 2 mg/kg PO every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed.
2. Prochlorperazine 10 mg PO every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed.
3. Prochlorperazine 25 mg rectally every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 4 to 6 hours if needed.
4. Promethazine 25 to 50 mg PO every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 4 to 6 hours if needed.

C. Hypersensitivity Precautions: Oxaliplatin is reported to cause hypersensitivity reactions in 8% to 13% of patients, with the incidence of moderate to severe reactions ranging from <1% to 7%. The most common symptoms are flushing and swelling of the face and hands, itching, sweating, lacrimation, skin rash, hives, rigors, dyspnea, and fever. Such reactions usually occur during the second or subsequent cycles, but one study suggests that the reactions most often occur around cycle 9 or 10.²³⁻²⁵

For mild reactions, the oxaliplatin infusion is stopped and an antihistamine and a corticosteroid may be administered. Moderate to severe reactions usually require administration of parenteral corticosteroids. One report suggests that lengthening the oxaliplatin infusion time from 2 to 6 hours reduces the incidence of hypersensitivity reactions and may be appropriate for some patients. Premedication with corticosteroids and antihistamines does not prevent subsequent hypersensitivity reactions.²³ If the reaction to oxaliplatin is determined to be anaphylactic, a desensitization regimen may be necessary for future doses.²⁵

D. Hematopoietic Growth Factors: Accepted practice guidelines and pharmacoeconomic analysis suggest that an antineoplastic regimen have a greater than 20% incidence of febrile neutropenia before prophylactic use of colony-stimulating factors (CSFs) is warranted. For regimens with an incidence of febrile neutropenia between 10% and 20%, use of CSFs should be considered. For regimens with an incidence of febrile neutropenia less than 10%, routine prophylactic use of CSFs is not recommended.^{26,27} Because febrile neutropenia was reported in 1% to 2% of patients and grade 3 or 4 neutropenia was reported in 4% to 22% of patients in the trials reviewed,¹⁻⁴ primary prophylactic use of CSFs is not recommended.¹⁻⁴ CSFs should be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of BCapOx.

E. Diarrhea: Diarrhea is a frequent consequence of capecitabine administration.

Diarrhea is usually mild to moderate, responding to conventional therapy. Occasionally, the problem can be severe or dose-limiting.

Patients should receive a prescription for an antidiarrheal agent for use at the onset of diarrhea. The standard recommendation is loperamide 4 mg PO at the onset of diarrhea, followed by 2 mg PO every after each unformed stool, or as often as every 2 hours for 24 hours.²⁸ Patients should be counseled to²⁹:

1. Monitor bowel movements.
2. Treat grade 1 or 2 diarrhea (increase of <7 stools per day or nocturnal stools) with loperamide and oral rehydration.
3. Immediately seek advice from their physician, pharmacist, or nurse for persistent (>24 hours) grade 1 or 2 diarrhea, or grade 3 diarrhea (increase of ≥ 7 stools per day or incontinence or symptoms of dehydration).

F. Neurotoxicity: Neurotoxicity was reported in 1% to 83% of patients receiving BCapOx,¹⁻⁵ with grade 3 or 4 neurotoxicity reported in 8% to 26% of patients.¹⁻⁵

Oxaliplatin causes acute neurotoxicity consisting of cold-induced or cold-exacerbated paresthesias/dysesthesias and muscle contractions. It also causes chronic neurotoxicity that can impair quality of life. Preclinical data suggest the acute neurotoxicity may be due to oxaliplatin's effects on voltage-dependent sodium channels and/or chelation of intracellular calcium by the oxaliplatin metabolite, oxalate.³⁰

IV infusion of 1 g each of calcium gluconate and magnesium sulfate before and after the oxaliplatin infusion was reported to significantly reduce the incidence of neurotoxicity.³¹⁻³³ Recent data indicate that this is not effective. The use of calcium gluconate and magnesium sulfate is no longer recommended.³⁴

Major Toxicities

Most of the toxicities listed below are presented according to their degree of severity. Higher grades represent more severe toxicities. Although there are several grading systems for cancer chemotherapy toxicities, all are similar. One of the frequently used systems is the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (<http://ctep.info.nih.gov>). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities but make, or consider making, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence values are rounded to the nearest whole percent unless incidence was less than or equal to 0.5%.

A. Cardiovascular: Angina (grade 3 or 4) 1%³; bleeding from colostomy (grade 1 or 2) 1%³; bleeding gums (grade 1 or 2) 1%³; bloody stool (grade 1 or 2) 1%³; epistaxis (all grades) 1% to 12%³; gastrointestinal

hemorrhage (all grades) 1% to 2%,¹ (grade 3 or 4) 2%;¹ rectal bleeding (grade 1 or 2) 1%;³ unspecified bleeding (all grades) 1% to 8%;^{2,5} (grade 3 or 4) 6%;² hypertension (all grades) 1% to 28%;^{1,5} (grade 3 or 4) 1% to 11%;^{1,3} thromboembolic events (all grades) 1% to 9%,^{1,3,5} (grade 3 or 4) 1% to 6%.^{1,3}

B. Constitutional: Fatigue (all grades) 4% to 62%,^{1,3,5} (grade 3 or 4) 4% to 16%.^{1,3,5}

C. Dermatologic: Alopecia (grade 1 or 2) 2%,¹ skin hyperpigmentation (grade 1 or 2) 2% to 43%.¹

D. Gastrointestinal: Anorexia (all grades) 3% to 34%,^{1,3} (grade 3 or 4) 3% to 13%;¹ diarrhea (all grades) 1% to 62%,^{1,5} (grade 3 or 4) 1% to 16%;^{2,4} dysgeusia (grade 1 or 2) 6% to 28%;¹ gastrointestinal perforation (all grades) 1% to 2%,^{1,3,5} (grade 3 or 4) 1%;^{3,4} nausea (all grades) 1% to 59%,^{1,4} (grade 3 or 4) 1% to 2%;^{1,3,4} stomatitis/mucositis (all grades) 2% to 49%,^{1,4} (grade 3 or 4) 2% to 3%;^{1,3,4} vomiting (all grades) 3% to 32%,^{1,4} (grade 3 or 4) 3% to 7%;^{2,3} weight loss (all grades) 4% to 12%.³

E. Hematologic: Anemia (all grades) 2% to 80%,^{1,4} (grade 3 or 4) 2% to 6%;^{1,2} febrile neutropenia (all grades) 1% to 2%,^{1,3} (grade 3 or 4) 2%;¹ leukopenia (all grades) 4% to 42%,^{1,2} (grade 3 or 4) 3% to 4%;^{1,2} neutropenia (all grades) 4% to 56%,^{1,4} (grade 3 or 4) 4% to 22%;^{1,4} thrombocytopenia (all grades) 1% to 58%,^{1,4} (grade 3 or 4) 1% to 6%.^{1,4}

F. Hepatic: Alanine aminotransferase (ALT) elevation (all grades) 2% to 31%,^{1,2} (grade 3 or 4) 2% to 19%;¹ aspartate aminotransferase (AST) elevation (all grades) 2% to 40%,^{1,2} (grade 3 or 4) 2% to 22%;¹ alkaline phosphatase elevation (all grades) 2% to 42%,¹ (grade 3 or 4) 2%;¹ hyperbilirubinemia (all grades) 2% to 21%,^{1,2} (grade 3 or 4) 2%.¹

G. Hypersensitivity: Hypersensitivity/allergy (grade 1 or 2) 2% to 6%;^{1,2} injection site reaction (grade 1 or 2) 1% to 8%.^{2,3}

H. Neurologic: Abdominal pain (all grades) 1% to 12%,³ (grade 3 or 4) 3%;³ hand-foot syndrome (all grades) 2% to 58%,^{1,5} (grade 3 or 4) 2% to 8%;^{1,4} neurotoxicity (grade 1 or 2) 9% to 25%;³ paraesthesia (grade 1 or 2) 3% to 19%;³ peripheral neuropathy (grade 1 or 2) 38% to 45%;¹ sensory neuropathy (all grades) 8% to 83%,^{2,5} (grade 3 or 4) 14%;² unspecified neuropathy (all grades) 4% to 45%,^{3,4} (grade 3 or 4) 4% to 18%.^{3,4}

I. Renal: Increased serum creatinine (all grades) 2% to 21%,¹ (grade 3 or 4) 2%;¹ proteinuria (all grades) 1% to 36%,^{1,5} (grade 3 or 4) 1% to 6%.^{2,4}

J. Treatment-Related Death: Gastrointestinal perforation 1%,³ cardiac event 2%.⁴

Pretreatment Laboratory Studies Needed

A. Baseline

1. AST/ALT

2. Total bilirubin
3. Serum creatinine
4. Complete blood count (CBC) with differential

B. Prior to Each Treatment

1. CBC with differential

C. Recommended Pretreatment Values: The minimally acceptable pretreatment CBC values required to begin a cycle with full-dose therapy in the protocols reviewed were:

1. Absolute neutrophil count (ANC), greater than or equal to 1500 cells/mcL.^{1,3,5,10}
2. White blood cell (WBC) count, greater than or equal to 3,000 cell/mcL.²
3. Hemoglobin, greater than or equal to 9 g/dL.^{1,3,5}
4. Platelet count, greater than or equal to 100 000 cells/mcL.^{2,3,5,10}
5. Renal function
 - a. Serum creatinine, within normal institutional limits^{2,4} or less than or equal to 1.5 times the upper normal limit (ULN)^{1,3} or less than or 2 mg/dL.⁵
 - b. Creatinine clearance, greater than or equal to 50 mL/min or greater than or equal to 30 mL/min.^{2,3,5}
 - c. Proteinuria, less than grade 1¹ or less than 2+ for protein¹¹ or urine protein creatinine ratio less than or equal to 1.⁵
6. Hepatic function
 - a. Total bilirubin, less than or equal to 2 mg/dL¹ or less than or equal to 1.5 times the UNL.^{2,3,5,10}
 - b. ALT/AST, less than or equal to 2.5 times the upper limit of normal^{1,3,5,10} or less than or equal to 5 times the UNL if liver metastases were present.^{1,3,5}
 - c. Alkaline phosphatase, less than or equal to 2.5 times the UNL^{5,10} or less than or equal to 5 times the UNL if liver metastases were present or less than or equal to 10 times the UNL if bone metastases were present.⁵

In clinical practice, a pretreatment ANC of 1000 cells/mcL and platelets of 75 000 cells/mcL are usually considered acceptable.

Dosage Modifications

A. Renal Function

1. Capecitabine: Creatinine clearance
 - a. 30 to 50 mL/min, reduce dose by 25%.^{3,5,35,36}
 - b. Less than 30 mL/min, do not give drug.³⁵
2. Oxaliplatin: Creatinine clearance
 - a. Greater than 20 mL/min, give 100% dose.³⁷
 - b. Greater than or equal to 30 mL/min, give 100% dose.³⁸

- c. Less than 30 mL/min, reduce dose by 25%.³⁸
- 3. Bevacizumab:
 - a. Creatinine clearance, no adjustment necessary.¹⁻⁵
 - b. Proteinuria:
 - 1. Patients with greater than grade 2 proteinuria without nephrotic syndrome, additional bevacizumab doses should be held until resolution.^{1,2,4,39}
 - 2. The manufacturer recommends:
 - a. Patients demonstrating a 2+ or greater dipstick reading should undergo further assessment with a 24-hour urine collection.⁴⁰
 - b. Bevacizumab should be held in patients demonstrating 2 g or greater proteinuria in a 24-hour period until proteinuria is less than 2 g in a 24-hour collection.⁴⁰

B. Liver Function

- 1. Capecitabine:
 - a. No information available.³⁶
 - b. No dosage adjustment required.⁴¹
- 2. Oxaliplatin:
 - a. No information available.³⁸
 - b. Dosage adjustments for elevated AST, ALT, and total bilirubin are not required, but regular assessments of liver function to monitor for oxaliplatin-induced hepatic injury are advised.^{42,43}
- 3. Bevacizumab:
 - a. No dosage adjustment required.¹
 - b. No information available.⁴⁰

C. Myelosuppression

- 1. Capecitabine and oxaliplatin:
 - a. Nadir ANC less than or equal to 500 cells/mcL or nadir platelet count less than or equal to 50 000 cells/mcL, decrease capecitabine dose by 25% to 50%¹ and oxaliplatin dose by 25% to 35%.¹
 - b. Delay treatment^{1,4} for ANC less than 1500 cells/mcL and platelets less than 75 000 cells/mcL
 - a. If ANC and platelets recover in 1 week, give original dose⁴
 - b. If ANC and platelets recover in 2 weeks, decrease dose by 25%.⁴
- 2. Bevacizumab: No dosage adjustment required^{1,4}

D. Nausea/Vomiting/Diarrhea

- 1. Capecitabine
 - a. Grade 3 or 4:
 - 1. Do not give drug.⁵

- 2. Decrease dose by 25%.^{1,4}
- 3. Decrease dose by 50%.¹

E. Hypertension

- 1. According to the manufacturer, if the patient develops hypertension, treat with appropriate antihypertensive therapy.⁴⁰
- 2. Further administration of bevacizumab should be temporarily suspended if hypertension cannot be medically controlled.^{2,4}
- 3. Bevacizumab should be discontinued in those patients with hypertensive crisis or hypertensive encephalopathy. Blood pressure should be monitored at regular intervals in patients with bevacizumab-induced or bevacizumab-exacerbated hypertension after discontinuation of bevacizumab.⁴⁰

F. Other

- 1. Oxaliplatin
 - a. Persistent grade 2 neuropathy (lasting greater than or equal to 15 days) or temporary grade 3 neuropathy (lasting 8-14 days), reduce dose to 25% to 35%.¹
- 2. Capecitabine
 - a. Grade 3 or 4 hand-foot syndrome, reduce dose by 25%.⁴
 - b. Grade 3 or 4 stomatitis, reduce dose 25%.⁴

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