Cancer Chemotherapy Update: Bevacizumab, Etoposide, and Cisplatin Regimen for Refractory Brain Metastases

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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, email: 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, email: waddfour@charter.net.

Regimen Name: Bevacizumab, etoposide, and cisplatin (BEEP)

Origin of Name: The regimen is named for the medications it contains: bevacizumab, etoposide, and cisplatin.

Comments

Use of systemic chemotherapy against central nervous system (CNS) tumors is limited by the inability of the drugs to cross the blood-brain barrier. Despite this limitation, the combination of cisplatin plus etoposide has demonstrated moderate overall response in breast cancer patients with brain metastases who have not received whole brain radiation.^{1,2} The addition of bevacizumab, a humanized recombinant monoclonal antibody active against vascular endothelial growth factor, has been shown to induce vascular normalization of brain metastases and potentiate the combined cisplatin and etoposide antitumor effect.³⁻⁵

Indications

The bevacizumab, etoposide, and cisplatin (BEEP) regimen (see Table 1) has been studied as salvage treatment for breast cancer–induced refractory brain metastases.³⁻⁵ Variations of the 3-drug regimen are also used to treat extensive-stage small cell and advanced non–small cell lung cancer.⁶⁻⁸ Current guidelines do not list BEEP as a recommended treatment for CNS metastases.⁹

Drug Preparation

Follow institutional policies for preparation of hazardous medications when preparing BEEP.

A. Bevacizumab

1. Use bevacizumab, 25 mg/mL injection.
2. Dilute in 100 to 250 mL of 0.9% sodium chloride (NS) solution.

3. Do not mix or administer with dextrose-containing solutions. Bevacizumab may precipitate rapidly when bevacizumab is diluted with or mixed in a dextrose-containing solution.¹⁰
4. Solutions diluted in NS are stable for up to 8 hours under refrigeration.

B. Etoposide

1. Use etoposide injection, 20 mg/mL.
2. Dilute with 5% dextrose in water or NS to a final concentration of 0.2 mg/mL to 0.4 mg/mL.
3. Concentrations greater than 0.4 mg/mL are not stable and may precipitate during infusion.
4. Stability varies based on concentration; 0.2 mg/mL solutions are stable for 96 hours at room temperature, and 0.4 mg/mL solutions are stable for 24 hours at room temperature.
5. Do not refrigerate.
6. Etoposide injection contains polysorbate 80 which may cause leaching of diethylhexyl phthalate. Etoposide solutions should be dispensed in glass or polyolefin containers.

C. Cisplatin

1. Use cisplatin injection, 1 mg/mL.

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Table 1. Bevacizumab, Etoposide, and Cisplatin Regimen for Refractory Brain Metastases.³⁻⁵

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Bevacizumab	15 mg/kg	IV	1	15 mg/kg
Etoposide	70 mg/m ²	IV	2, 3, 4	210 mg/m ²
Cisplatin	70 mg/m ²	IV	2	70 mg/m ²

Cycle repeats: every 3 weeks for 6 cycles.

Variations

1. Cisplatin 60 mg/m² IV on day 1, etoposide 120 mg/m² IV on days 1 through 3, and bevacizumab 15 mg/kg IV on day 1, every 3 weeks for up to 4 cycles.⁶
2. Cisplatin 30 mg/m² IV on days 1 through 3, etoposide 50 mg/m² PO on days 1 through 15, and bevacizumab 5 mg/kg IV on day 3, every 3 weeks.⁷
3. Cisplatin 25 mg/m², etoposide 100 mg/m² IV on days 1 through 3, bevacizumab 7.5 mg/kg IV day 1, every 3 weeks for 6 cycles.⁸

Note. IV = intravenous; PO = Oral.

2. Dilute in 250 to 1000 mL of NS or a saline/dextrose solution.
3. To ensure stability, cisplatin infusion concentration must have a final chloride ion concentration of at least 0.2%.
4. Stability varies based on chloride ion concentration.

Drug Administration

A. Bevacizumab

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

B. Etoposide

1. Administer by intravenous (IV) infusion over 45 to 60 minutes.
2. Use a 0.22-μm inline filter to reduce precipitate risk.
3. Infusions with a duration less than 30 minutes greatly increase the incidence of hypotension.

C. Cisplatin is usually administered as a 30-minute to 1 hour IV infusion.

Supportive Care

A. Acute and Delayed Emesis Prophylaxis

The BEEP regimen is predicted to cause acute emesis in greater than 90% of patients.¹¹ However, the expected emetogenicity of the BEEP regimen varies according to the day of the regimen. The studies reviewed reported mild to moderate (grade 1 or 2) nausea or vomiting in 15% to 27%

of completed cycles^{3,4}; severe (grade 3 or 4) nausea or vomiting was reported in 1%.³

On day 2, when cisplatin and etoposide are administered, or days 3 and 4, when etoposide alone is administered, the risk of nausea or vomiting is higher than on day 1 when only bevacizumab is administered.¹¹ One of the following regimens is suggested:

Day 1:

For most patients, prophylactic antiemetic therapy, particularly with a serotonin antagonist, is not required.¹²⁻¹⁴ However, patients who do experience nausea or vomiting on day 1 will require a prophylactic antiemetic regimen for subsequent cycles of therapy.

Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category added to the previous prophylactic antiemetic regimen.¹¹⁻¹⁴ One of the following regimens is recommended:

1. Patients who received a steroid only—Add a dopamine antagonist.
2. Patients who received a dopamine antagonist only—Add a steroid.
3. Patients who received a steroid and dopamine antagonist—Substitute a serotonin antagonist for the dopamine antagonist.

Day 2:

Appropriate acute emesis prophylaxis includes a serotonin antagonist, a corticosteroid, and a neurokinin (NK₁) antagonist.¹²⁻¹⁴ One of the following regimens is recommended:

1. Ondansetron 16 mg to 24 mg, dexamethasone 12 mg, 30 minutes before BEEP on day 2.
2. Granisetron 2 mg, dexamethasone 12 mg, before BEEP on day 2.

3. Dolasetron 100 mg, dexamethasone 12 mg, PO 30 minutes before BEEP on day 2.
4. Palonosetron 0.25 mg IV, dexamethasone 12 mg, PO 30 minutes before BEEP on day 2. Palonosetron should not be used if given earlier in the cycle.

One of the following neurokinin antagonist options should be used with one of the above regimens:

1. Aprepitant 125 mg PO day 2, 80 mg PO days 3 and 4.
2. Fosaprepitant 150 mg IV.
3. Rolapitant 180 mg PO (increase dexamethasone to 20 mg).

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

4. Netupitant 300 mg/palonosetron 0.5 mg PO, dexamethasone 12 mg PO 30 minutes before BEEP on day 2. The netupitant/palonosetron combination drug should not be used if palonosetron was given previously during the current cycle.

The antiemetic therapy should continue for at least 3 days. A meta-analysis of several trials of serotonin antagonists recommends against prolonged (greater than 24 hours) use of these agents, making a steroid, or steroid and dopamine antagonist combination most appropriate for follow-up therapy.¹⁵ One of the following regimens is recommended:

1. Dexamethasone 4 mg PO twice a day for 3 days, $\pm$ aprepitant 80 mg PO every morning for 2 days, $\pm$ metoclopramide 0.5 to 2 mg/kg PO every 4 to 6 hours, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 3 of BEEP.
2. Dexamethasone 4 mg PO twice a day for 3 days, $\pm$ aprepitant 80 mg PO every morning for 2 days, $\pm$ prochlorperazine 10 mg PO every 4 to 6 hours, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 3 of BEEP.
3. Dexamethasone 4 mg PO twice a day for 3 days, $\pm$ aprepitant 80 mg PO every morning for 2 days, $\pm$ promethazine 25 to 50 mg PO every 4 to 6 hours, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 3 of BEEP.

Patients who do experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.¹¹⁻¹⁴ 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 generally not recommended.¹⁶⁻²⁰

Cisplatin in doses of $>50 \text{ mg/m}^2$ (either as a single dose or cumulative over consecutive days) is reported to cause

delayed nausea in 78% of patients and delayed emesis in 61% of patients. Delayed nausea or emesis may begin as soon as 16 hours after cisplatin administration, reach their peak of severity at 48 to 72 hours after cisplatin administration, and usually abate between 96 and 168 hours after cisplatin administration.²¹

B. Breakthrough Nausea and Vomiting¹¹⁻¹⁴

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.

Patients who do experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.¹¹⁻¹⁴ 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.¹⁶⁻²⁰

C. Hydration

Cisplatin can cause irreversible kidney damage by acute tubular necrosis. Maintenance of a urine output of greater than or equal to 75 to 100 mL/h for several hours before and after each cisplatin dose is the best prophylaxis against cisplatin-induced nephrotoxicity. A wide variety of hydration and diuretic regimens for this purpose have been reported. Cornelison and Reed reported that, with the possible exception of the first treatment cycle, diuretics add nothing to vigorous hydration for prevention of cisplatin nephrotoxicity.²² Kintzel noted the mechanism of action of diuretics intuitively supports their use to prevent cisplatin-induced nephrotoxicity, but there is no evidence to recommend their use over vigorous hydration.²³

A suggested hydration regimen is 5% dextrose/0.9% sodium chloride injection or 0.9% sodium chloride injection, infused at 250 mL/h for 2 to 4 hours before and after each cisplatin dose. Oral hydration regimens are also used, but the increased chloride from IV sodium chloride injections may offer better renal protection.²²

D. Hematopoietic Growth Factors

Accepted practice guidelines and pharmacoeconomic analysis suggest that antineoplastic regimens have a greater than 20% incidence of febrile neutropenia before prophylactic use of colony-stimulating factors is warranted. For regimens with an incidence of febrile neutropenia between 10% and 20%, use of colony-stimulating factors should be considered. For regimens with an incidence of febrile neutropenia less than 10%, routine prophylactic use of colony-stimulating factors is not recommended.^{24,25}

Lu et al reported febrile neutropenia in 2% of treatment cycles.³ In studies reviewed, severe (grade 3 or 4) neutropenia was found in up to 57% of cycles.^{3,4} As febrile neutropenia was reported in only 2% of patients in the trials of BEEP, prophylactic use of colony-stimulating factors is not recommended.^{25,26} Colony-stimulating factors should be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of BEEP.

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 Common Terminology Criteria for Adverse Events (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities, but make, or consider, 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: Cerebellar infarction (grade 3 or 4) 1%³; hemorrhage (grade 1 or 2) 2%³; hypertension (grade 1 or 2) 14% to 37%,^{3,4} (grade 3 or 4) 1%.^{3,4}

B. Hematologic: Anemia (grade 1 or 2) 40% to 50%,^{3,4} (grade 3 or 4) 7%^{3,4}; febrile neutropenia (grade 3 or 4) 2%³; leukopenia (grade 1 or 2) 37%,³ (grade 3 or 4) 16%³; lymphocytopenia (grade 1 or 2) 35%,⁴ (grade 3 or 4) 23%⁴; neutropenia (grade 1 or 2) 28% to 35%,^{3,4} (grade 3 or 4) 23% to 57%³; thrombocytopenia (grade 1 or 2) 30% to 39%,^{3,4} (grade 3 or 4) 4% to 8%.^{3,4}

C. Gastrointestinal: Epigastralgia (grade 1 or 2) 11%³; nausea (grade 1 or 2) 27%³; vomiting (grade 1 or 2) 15%,³ (grade 3 or 4) 1%.³

D. Hepatic: Increased aspartate aminotransferase/alanine aminotransferase (AST/ALT) (grade 1 or 2) 20% to 23%,^{3,4} (grade 3 or 4) 1% to 8%.^{3,4}

E. Renal: Increased creatinine (grade 1 or 2) 5%³; proteinuria (grade 1 or 2) 15% to 27%,^{3,4} (grade 3 or 4) 0%.^{3,4}

F. Metabolic/endocrine: Hypokalemia (grade 1 or 2) 10%,³ (grade 3 or 4) 4%³; hyponatremia (grade 1 or 2) 4% to 12%,^{3,4} (grade 3 or 4) 7% to 23%.^{3,4}

G. Infection: Infection with mild to moderate neutropenia (grade 1 or 2) 3%,³ (grade 3 or 4) 15%³; infection with moderate to severe neutropenia (grade 3 or 4) 6%.³

H. Other: Fatigue (grade 1 or 2) 12%³; tracheoesophageal fistula (grade 3 or 4) 1%.³

Pretreatment Laboratory Studies Needed

A. Baseline and Prior to Each Treatment

1. AST/ALT
2. Total bilirubin
3. Serum creatinine
4. Complete blood count with differential
5. Blood pressure
6. Urine analysis

B. Recommended Pretreatment Values

The reviewed studies required adequate hematologic, renal, and hepatic functions to initiate therapy but did not specify specific values used.^{3,4} In clinical practice, a pretreatment absolute neutrophil count of 1000 cells/ μ L and platelets of 75 000 cells/ μ L are usually considered acceptable.

Dosage Modifications

A. Renal Function

1. Bevacizumab: No adjustment required²⁷
2. Etoposide: Creatinine clearance:
 - a. >50 mL/min—No adjustment required^{28,29}
 - b. 15 mL/min to 50 mL/min—Give 75% dose²⁹
 - c. 10 mL/min to 50 mL/min—Give 75% dose²⁸
 - d. <10 mL/min—Give 50% dose²⁸
 - e. <60 mL/min—Give 85% dose³⁰
 - f. 45 mL/min—Give 80% dose³⁰
 - g. 30 mL/min—Give 75% dose³⁰
3. Cisplatin:
 - a. Creatinine $\geq$ 1.5 mg/dL or Blood Urea Nitrogen (BUN) $\geq$ 25 mg/dL—Do not give drug³¹
 - b. Creatinine clearance:
 1. >50 mL/min—No adjustment required²⁸
 2. 10 mL/min to 50 mL/min—Give 75% dose²⁸
 3. <10 mL/min—Give 50% dose²⁸
 4. <60 mL/min—Give 75% dose³⁰
 5. <45 mL/min—Give 50% dose³⁰
 6. <30 mL/min—Do not give drug³⁰

B. Hepatic

1. Bevacizumab: No information available³⁰
2. Etoposide:
 - a. Bilirubin 1.5 mg/dL to 3 mg/dL—Give 50% dose³²

- b. Bilirubin >3 mg/dL—Do not give drug.³²
- c. AST/ALT 60 units to 180 units—Give 50% dose.³²
- d. AST/ALT >180 units—Do not give drug.³²
- e. Bilirubin 1.5 mg/dL to 3 mg/dL and AST >3 times the upper limit of normal—Give 50% dose.³³
- f. Bilirubin 1.5 mg/dL to 3 mg/dL and AST >180 units—Give 50% dose.³⁴

3. Cisplatin: No information available³¹

C. Myelosuppression

Grade 3 or 4 hematologic toxicity: Reduce etoposide and cisplatin dose to 60 mg/m².³

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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