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Cancer Chemotherapy Update

Carboplatin (Renally Dosed) and Etoposide Regimen for Small-Cell Lung 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.

Regimen Name: CE

Origin of Name: CE is an acronym for the 2 medications in the regimen: carboplatin and etoposide.

COMMENTS

Carboplatin doses are commonly calculated using equations based on the method of Calvert et al.[1] Calvert's group showed that the carboplatin dose in milligrams can be calculated using a selected carboplatin area under the curve (AUC) and the patient's glomerular filtration rate (GFR) as determined by clearance of a radiopharmaceutical, chromium-51-EDTA. Calvert's equation is expressed as carboplatin $dose_{mg} = AUC \times [GFR + 25]$. A common practice is to substitute the GFR of the Calvert equation with a calculated creatinine clearance (CrCl) determined with the Cockcroft-Gault equation.

INDICATION(S)

The CE regimen has been studied and is recommended for primary treatment of both limited and extensive-stage small-cell lung cancer (SCLC) (**Table 1**).[2-12]

DRUG PREPARATION

Follow institutional policies for preparation of hazardous medications when preparing carboplatin and etoposide.

A. Carboplatin

1. Use carboplatin injection 10 mg/mL, or powder for reconstitution.
2. Reconstitute the powder to a concentration of 10 mg/mL with sterile water for injection (SWFI), 5% dextrose in water (D5W), or 0.9% sodium chloride (NS).
3. Dilute with 100 to 1,000 mL of D5W or NS.
4. Carboplatin is less stable in saline solutions, with up to 5% degradation within 24 hours.[13]
5. If the drug is prepared in a saline diluent, the solution should be used within 8 hours.

B. Etoposide

1. Use etoposide injection, 20 mg/mL.
2. Dilute with D5W 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.

DRUG ADMINISTRATION

A. Carboplatin: Administer by intravenous (IV) infusion over 30 to 60 minutes.

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Table 1. Carboplatin (renally dosed) and etoposide regimen[2-8]

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Carboplatin	AUC 5	IV	1	AUC 5
Etoposide	80-140 mg/m^2	IV	1-3	240-420 mg/m^2
Cycle repeats: every 3 to 4 weeks				
Variations				
1. Carboplatin AUC 6 IV day 1 and etoposide 100 mg/m^2 IV days 1-3 every 3 weeks.[9,11]				
2. Carboplatin AUC 5 IV day 1 and etoposide 100 mg/m^2 IV days 1-5 every 4 weeks.[10]				

Note: AUC = area under the time vs concentration curve; IV = intravenous.

B. Etoposide:

1. Administer by IV infusion over 45 to 60 minutes.
2. Infusion over less than 30 minutes greatly increases the incidence of hypotension.

SUPPORTIVE CARE

A. Acute and Delayed Emesis Prophylaxis: The CE regimen is predicted to cause acute emesis in 30% to 90% of patients.[14] The studies reviewed reported grade 3 nausea or vomiting in 0.2% to 9% of patients.[2,3,5-7,9,10]

Appropriate acute emesis prophylaxis includes a serotonin antagonist and a corticosteroid plus or minus a neurokinin antagonist in selected patients.[15-18] One of the following regimens is suggested:

1. Ondansetron 16 to 24 mg and dexamethasone 12 mg orally (PO) ± aprepitant 125 mg PO 30 minutes before day 1 of CE.
2. Granisetron 1 mg to 2 mg and dexamethasone 12 mg PO ± aprepitant 125 mg PO 30 minutes before day 1 of CE.
3. Dolasetron 100 mg and dexamethasone 12 mg PO ± aprepitant 125 mg PO 30 minutes before day 1 of CE.
4. Palonosetron 0.25 mg IV and dexamethasone 12 mg PO ± aprepitant 125 mg PO 30 minutes before day 1 of CE.

The antiemetic therapy should continue for at least 2 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 a steroid and dopamine antagonist combination most appropriate for follow-up therapy.[19] One of the following regimens is suggested:

1. Dexamethasone 8 mg PO once daily for 2 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 CE.
2. Dexamethasone 8 mg PO once daily for 2 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 CE.
3. Dexamethasone 8 mg PO once daily for 2 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 CE.

If a neurokinin antagonist is used on day 1 of CE, then aprepitant 80 mg PO once daily for 2 days should be added to one of the regimens above, starting on day 2 of CE.

B. Breakthrough Nausea and Vomiting[15-18]: Patients should receive a prescription for an antiemetic to treat breakthrough nausea. One of the following regimens is suggested:

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

D. Hydration: If carboplatin doses are reduced appropriately for diminished renal function (as in AUC dosing), no prophylactic hydration or diuretic use is required. [20]

F. Hematopoietic Growth Factors: Accepted practice guidelines and pharmaco-economic 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.[21,22]

Since febrile neutropenia (grade 3 or 4) was reported in 3% to 14% of patients in the trials of CE, primary prophylactic use of CSFs may be considered if the patient has had febrile neutropenia or grade 4 neutropenia in a prior cycle of CE or has other known risk factors for febrile neutropenia.[21,22]

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:** Unspecified cardiac events (grade 4) 6%.[10]
B. **Dermatologic:** Alopecia (all grades) 34%,[2] (grade 3) 10%,[11] (grade 4) 2% to 33%[7,11]; "almost universal" 100%.[9]
C. **Gastrointestinal:** Diarrhea (grade 3) 1% to 6%,[3,5,6] (grade 3 or 4) 0.2%[2]; esophagitis (grade 3) 10%[9]; mucositis (grade 3) 3%[10]; nausea (grade 3) 1% to 9%,[3,5-7,9,10] (grade 4) 1%,[5] (grade 3 or 4) 0.2%[2]; vomiting (grade 3) 2% to 6%,[3,6,9,10] (grade 3 or 4) 1%.[2]
D. **Hematologic:** Leukopenia (grade 3) 16% to 56%,[3,5,6,8,9,11] (grade 4) 3% to 26%,[3,5,6,8,9,11] (grade 3 or 4) 8%[2]; neutropenia (grade 3) 20% to 47%,[3,6-8,10,11] (grade 4) 26% to 53%,[3,6-8,10,11] (grade 3 or 4) 47% to 69%[2,4]; febrile neutropenia (grade 3) 7% to 14%,[5,6] (grade 4) 3% to 4%,[5-7] (grade 3 or 4) 4% to 5%[2,9]; thrombocytopenia (grade 3) 9% to 41%,[3,5-11] (grade 4) 3% to 29%,[3,5-11] (grade 3 or 4) 10% to 29%[2,4]; anemia (grade 3) 3% to 35%,[3,5,6,8-11] (grade 4) 2% to 6%,[5,6,9-11] (grade 3 or 4) 7% to 19%.[2,4]
E. **Hepatic:** Hyperbilirubinemia (grade 3) 3%[8]; alanine aminotransferase/aspartate aminotransferase (ALT/AST) elevations (grade 3) 3%.[3,8]
F. **Neurologic:** Asthenia/fatigue (grade 3 or 4) 3% to 27%.[2,4]
G. **Renal:** Serum creatinine increase (grade 3) 3%.[10]
H. **Other:** Hyponatremia (grade 3) 6%,[3,8] (grade 4) 9% to 10%,[3,8] (grade 3 or 4) 1%[2]; increased arterial O_2 pressure (grade 3) 6% to 9%,[3,8] (grade 4) 1%[3]; infection (grade 3) 5% to 14%,[3,5,6] (grade 4) 3%,[3,8] (grade 3 or 4) 12%[4]; unspecified lung toxicity (grade 3) 6%.[9]
I. **Treatment-related mortality:** Bacterial infection 4%,[5] septic multi-organ failure 3%,[6] hemoptysis 3%,[8] septic shock 9%.[10]

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
2. Serum creatinine

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. White blood cell count (WBC):
   a. Greater than or equal to 4,000 cells/mcL.[3,5,6,8]
   b. Greater than 2,000 cells/mcL.[7]
   c. Greater than 3,500 cells/mcL.[9]
   d. Greater than 3,000 cells/mcL.[11]
2. Absolute neutrophil count (ANC):
   a. Greater than 2,000 cells/mcL.[4,11]
   b. Greater than 1,500 cells/mcL.[10]
3. Platelet count:
   a. Greater than or equal to 100,000 cells/mcL.[3-6,8-11]
   b. Greater than 150,000 cells/mcL.[7]
4. Serum creatinine:
   a. Less than or equal to 1.5 mg/dL.[3,11]
   b. Less than 1.4 mg/dL.[4]
   c. Less than 1.25 times upper limit of normal (ULN).[5,6]
   d. Less than 2 times ULN.[7]
5. Blood urea nitrogen (BUN) and serum creatinine:
   a. Less than 2 times ULN.[8]
   b. Less than or equal to 1.5 times ULN.[11]
6. CrCl:
   a. Greater than or equal to 50 mL/min.[3]
   b. Greater than or equal to 30 mL/min.[8]
   c. Greater than 60 mL/min.[9]
   d. Greater than 20 mL/min.[10]

7. Serum bilirubin:
   a. Less than or equal to 1.5 mg/dL.[3,8,11]
   b. Less than 1.25 times ULN.[5,6]
8. Hemoglobin:
   a. Greater than or equal to 9 g/dL.[3,6,8]
   b. Greater than 10 g/dL.[9,11]
9. AST/ALT:
   a. Less than or equal to 2 times ULN.[3,8]
   b. AST less than or equal to 2.5 times ULN or less than or equal to 5 times ULN if liver metastases present.[11]

In clinical practice, a pretreatment absolute neutrophil count (ANC) of 1,000 cells/mcL and platelets of 75,000 cells/mcL are usually considered acceptable.

DOSAGE MODIFICATIONS

A. Renal Function

1. Carboplatin: If doses are calculated according to the patient's renal function, additional dose adjustments for renal insufficiency are not necessary. It is common practice to calculate doses utilizing AUC methods based on the Calvert equation [Carboplatin dose in mg = AUC x (GFR + 25), where GFR is determined by radiopharmaceutical clearance].[1] If radiopharmaceutical clearance is not used to determine GFR, CrCl estimated by the Cockcroft-Gault equation is commonly substituted for GFR in the Calvert equation. Great care should be taken with the patient weight and serum creatinine data used when the Cockcroft-Gault equation is substituted for GFR in the Calvert equation. The following guidelines are suggested:
   a. If the patient is not obese (body mass index [BMI] $<$ 25), studies suggest that actual body weight should be used.[23,24]
   b. If the patient is overweight or obese (BMI $\geq$ 25), studies suggest that 40% adjusted ideal body weight should be used.[25,26]
   c. If the patient has a serum creatinine value less than 0.8 mg/dL, round the serum creatinine up to 0.8 mg/dL.[26,27] The Gynecologic Oncology Group has suggested rounding values less than 0.7 mg/dL up to 0.7 mg/dL.[28]
   d. The US Food and Drug Administration advised in 2010 that Cockcroft-Gault–estimated CrCl of greater than 125 mL/min should not be substituted for GFR in the Calvert equation.[29] Calvert et al reported successful treatment of patients with GFRs determined by radiopharmaceutical clearance up to 136 mL/min and observed GFRs determined by radiopharmaceutical clearance as high as 180 mL/min.[1]
2. Etoposide[30]:
   a. Reduce dose by 15% if CrCl is greater than or equal to 45 mL/min and less than 60 mL/min.
   b. Reduce dose by 20% if CrCl is greater than or equal to 30 mL/min and less than or equal to 45 mL/min.
   c. Reduce dose by 25% if CrCl is less than or equal to 30 mL/min.

B. Liver Function[31,32]

1. Etoposide: Reduce dose by 50% if:
   a. Serum bilirubin is less than or equal to 1.5 mg/dL and greater than or equal to 3 mg/dL.
   b. AST is greater than 3 times ULN.

C. Myelosuppression

1. Carboplatin:
   a. Grade 4 neutropenia or leukopenia lasting 4 days or more, reduce dose from AUC 5 to AUC 4 on day 1 of next cycle.[3]
   b. Grade 4 hematologic toxicity, reduce dose from AUC 5 to AUC 4 on day 1 of next cycle. If grade 4 toxicity persists, reduce dose to AUC 3.2 on day 1 of next cycle. If grade 4 toxicity persists, stop carboplatin.[4]
   c. Thrombocytopenia less than or equal to 20,000 cells/mcL or neutropenia less than or equal to 1,000 cells/mcL, reduce dose from AUC 5 to AUC 4. If thrombocytopenia or neutropenia persists, reduce dose to AUC 3.[5,6]
   d. Grade 4 neutropenia greater than 7 days, febrile neutropenia or thrombocytopenia, reduce dose from AUC 5 to AUC 4.[7]
   e. Day 28 WBC count less than 1.5 x 10^9/L and/or platelet count less than 100 x 10^9/L, delay treatment by 1 week.[7]
   f. Grade 3 or 4 hematologic toxicity, delay treatment up to maximum of 15 days until recovery, then administer 75% of original dose.
   g. Grade 4 neutropenia or thrombocytopenia, reduce dose by 33%.[10]
   h. Neutropenic fever and more than 10 days of neutropenia, reduce dose by 25%.[11]
2. Etoposide:
   a. Grade 4 neutropenia or leukopenia lasting 4 days or more, reduce dose from 80 mg/m^2 to 60 mg/m^2 for 3 days.[3]

b. Grade 4 hematologic toxicity, reduce dose from 140 mg/m^2 to 110 mg/m^2 next cycle. If grade 4 toxicity persists, reduce dose to 90 mg/m^2 at subsequent cycle. If grade 4 toxicity persists, stop etoposide.[4]
c. Grade 4 neutropenia greater than 7 days or febrile neutropenia, reduce dose by 25%.[7]
d. Grade 4 leukopenia, neutropenia, or thrombocytopenia, reduce dose by 25% for subsequent cycle. If same hematologic toxicity persists despite dose reduction, stop etoposide.[8]
e. Grade 3 or 4 hematologic toxicity, delay treatment up to a maximum of 15 days until recovery, then administer 75% of original dose.
f. Grade 3 or 4 thrombocytopenia, give 50% of dose.[9]
g. Grade 4 neutropenia or thrombocytopenia, reduce dose by 20%.[10]
h. Neutropenic fever and more than 10 days of neutropenia, reduce dose by 25%.[11]

D. Other

1. Grade 4 non-hematologic toxicities:
   a. Reduce both agents by 20%.
   b. If grade 4 non-hematologic toxicities persist in the next cycle, reduce by another 20%.[4]
2. Grade 3 or 4 non-hematologic toxicities, delay treatment until resolution.[11]

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