Cancer Chemotherapy Update

Gemcitabine and Carboplatin (Renally Dosed) Regimen for Bladder 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: Gemcitabine and carboplatin
Synonym: GCarbo or CaG
Origin of name: GCarbo and CaG are acronyms for the 2 medications in the regimen: **gem**citabine and **carb**oplatin or **carb**oplatin.

INDICATION(S)

The GCarbo regimen (Table 1) has been studied in metastatic bladder cancer¹⁻⁶ and is recommended as an alternative regimen to first-line chemotherapy in metastatic disease.⁷ The GCarbo regimen has also been studied as perioperative chemotherapy, specifically neoadjuvant chemotherapy, in locally advanced bladder cancer prior to cystectomy.^{8,9} Current bladder cancer guidelines, however, recommend against the substitution of carboplatin for cisplatin in the setting of perioperative chemotherapy and suggest consideration of split-dose administration of cisplatin for patients with renal dysfunction, although efficacy of this adjustment remains unproven.⁷

CARBOPLATIN DOSE CALCULATION

Carboplatin doses are commonly calculated using an equation based on the method of Calvert

et al.¹⁰ Calvert's group showed that the carboplatin dose in milligrams can be calculated using a desired area under the time versus concentration curve (AUC) and the patient's glomerular filtration rate (GFR). Calvert measured GFR by clearance of chromium-51-EDTA. The equation is: carboplatin dose (mg) = AUC × [GFR + 25].

If radiopharmaceutical clearance is not used to measure GFR, creatinine clearance (CrCl) estimated by the Cockcroft-Gault method¹¹ is commonly used to estimate GFR. Appropriate patient weight and serum creatinine should be used when estimating GFR for use in the Calvert equation. The following guidelines are recommended:

1. If the patient is not obese (body mass index [BMI] < 25), actual body weight should be used.^{12,13}
2. If the patient is overweight or obese (BMI ≥ 25), an adjusted body weight (ABW) should be used.^{14,15} Although a number of different formulae for calculating ABW are available, the most commonly used formula is: ABW = [(Actual Body Weight – Ideal Body Weight)(0.4)] + Ideal Body Weight. Ideal Body Weight (IBW) is most commonly calculated as¹⁶:
IBW = 50 kg + 2.3 kg/inch >60 inch (Men)
IBW = 45.5 kg + 2.3 kg/inch >60 inch (Women)

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Table 1. Gemcitabine and carboplatin (GCarbo) regimen¹⁻⁴

Drug	Dose	Route of Administration	Administered on day(s)	Total dose/cycle
Gemcitabine	1,000 mg/m ²	IV	1, 8	2,000 mg/m ²
Carboplatin	AUC 4 to 5	IV	1	AUC 4 to 5

Cycle repeats every 21 days

Variations:

1. Gemcitabine 1,250 mg/m² day 1 and 8 and carboplatin AUC 5 on day 2 of 21-day cycle.⁵
2. Gemcitabine 1,000 mg/m² on day 1, 8, 15 and carboplatin AUC 5 on day 2 of 21-day cycle.⁶
3. Gemcitabine 800 mg/m² on day 1, 8, and 15 and carboplatin AUC 4 on day 2 of 21-day cycle.⁸
4. Gemcitabine 1,000 mg/m² on day 1, 8, and 15 and carboplatin AUC 5 on day 2 of 21-day cycle.⁹

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

3. If the patient has a serum creatinine less than 0.8 mg/dL, round the serum creatinine up to 0.8 mg/dL.^{15,17} The Gynecologic Oncology Group has suggested rounding values less than 0.7 mg/dL up to 0.7 mg/dL.¹⁸
4. Use of GFR values higher than 125 mL/min to calculate carboplatin doses by Calvert's method may be appropriate in selected patients. Calvert reported measured GFRs as high as 180 mL/min and used measured GFRs up to 136 mL/min to calculate carboplatin doses.¹⁰ The US Food and Drug Administration (FDA) recommends that CrCl greater than 125 mL/min, as estimated by the Cockcroft-Gault method, should not be used to calculate carboplatin doses in the Calvert equation.¹⁹

DRUG PREPARATION

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

A. Gemcitabine

1. Use gemcitabine hydrochloride injection, 38 mg/mL; or powder for injection.
2. Reconstitute the lyophilized powder to a concentration of 38 mg/mL with 0.9% sodium chloride injection (NS), 5% dextrose in water (D5W), or sterile water for injection (SWFI).
 - a. When reconstituted according to the manufacturer's recommendation, the final concentration is 38 mg/mL, not 40 mg/mL.
 - b. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution and should be avoided.
3. Dilute with 50 to 250 mL NS for infusion.

B. Carboplatin

1. Use carboplatin injection 10 mg/mL, or powder for reconstitution.

2. Reconstitute the powder to a concentration of 10 mg/mL with SWFI, D5W, or NS.
3. Dilute with 100 to 1,000 mL of D5W or NS.
4. Carboplatin is stable in saline solutions stored at room temperature at concentrations of 0.5 mg/mL, 2 mg/mL, and 4 mg/mL for 3 days, 5 days, and 7 days, respectively, and for up to 7 days at all concentrations when stored at 4°C.²⁰

DRUG ADMINISTRATION

A. Gemcitabine

1. In the studies reviewed, gemcitabine was given as a 30-minute intravenous (IV) infusion.¹⁻⁴
2. Infusion times greater than 60 minutes have been associated with increased grade 3 or 4 hematologic toxicity due to accumulation of the active metabolite gemcitabine triphosphate.²¹

B. Carboplatin: In the studies reviewed, carboplatin was given as a 30- to 60-minute²⁻⁴ IV infusion.

SUPPORTIVE CARE

A. Acute and Delayed Emesis Prophylaxis: The GCarbo regimen is predicted to cause vomiting in 30% to 90% of patients on day 1 and in 10% to 30% of patients on day 8 and day 15.^{22,23} The studies reviewed reported nausea in 14%,⁶ nausea and vomiting in 10% to 47%,^{2,8,9} grade 3 to 4 nausea and vomiting in 7% to 65%,^{2,5} vomiting in 32%,³ and grade 3 or 4 vomiting in 7% of patients.³ Appropriate acute emesis prophylaxis includes a serotonin antagonist and a corticosteroid plus or minus a neurokinin antagonist in selected patients.^{22,23} 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 GCarbo.
2. Granisetron 1 mg to 2 mg and dexamethasone 12 mg PO ± aprepitant 125 mg PO 30 minutes before day 1 of GCarbo.
3. Dolasetron 100 mg and dexamethasone 12 mg PO ± aprepitant 125 mg PO 30 minutes before day 1 of GCarbo.
4. Palonosetron 0.25 mg IV and dexamethasone 12 mg PO ± aprepitant 125 mg PO 30 minutes before day 1 of GCarbo.

The antiemetic therapy should continue for at least 2 days after day 1. 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.²⁴ 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 GCarbo.
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 GCarbo.
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 GCarbo.

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

The GCarbo regimen is predicted to cause vomiting in 10% to 30% of patients on days 8 and 15.²² On days 8 and 15, a single dose of one of the following premedications is suggested: dexamethasone 12 mg PO or metoclopramide 10 to 40 mg PO or prochlorperazine 10 mg PO. A single dose of an oral serotonin antagonist may also be considered.

B. Breakthrough Nausea and Vomiting^{22,23}: Patients should receive a prescription for an antiemetic to treat breakthrough nausea. One of the following regimens is suggested:

1. Metoclopramide 10 to 40 mg 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 12.5 to 25 mg PO every 4 to 6 hours if needed, ± diphenhydramine 25 to 50 mg PO every 4 to 6 hours if needed.

C. 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 (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.²⁵

In the trials reviewed, neutropenia was reported in 50% to 100%^{1-3,6,8,9} of patients and grade 3 to 4 neutropenia in 7% to 70%^{1-6,8,9} of patients. Febrile neutropenia was reported in 3% to 25% of patients.^{1,3,4,8,9} Prophylactic use of CSFs is recommended with this regimen.

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 they 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: Edema (all grades) 17%,³ (grade 3 or 4) 7%.³

B. Constitutional: Asthenia (all grades) 73%,³ (grades 3 or 4) 19%³; fatigue (all grades) 6% to

35%,^{4,6} (grade 3 or 4) 3%⁶; lethargy (all grades) 29%.²

- C. **Dermatologic:** Alopecia (all grades) 9 to 63%.^{3,4,8}
- D. **Gastrointestinal:** Constipation (all grades) 7%⁶; mucositis (all grades) 3 to 24%,^{2,6} (grade 3 or 4) 1% to 13%^{2,5}; nausea (all grades) 14%⁶; nausea and vomiting (all grades) 10% to 47%,^{2,8,9} (grade 3 or 4) 7% to 65%^{2,5}; vomiting (all grades) 32%,³ (grade 3 or 4) 7%.³
- E. **Hematologic:** Anemia (all grades) 23% to 100%,^{2,3,5,8,9} (grade 3 or 4) 9% to 88%^{1-6,8,9}; febrile neutropenia (all grades) 3% to 25%^{1,3,4,8,9}; leukopenia (all grades) 93%,³ (grade 3 or 4) 29% to 44%^{3,5}; neutropenia (all grades) 50% to 100%,^{1-3,6,8,9} (grade 3 or 4) 7% to 70%^{1-6,8,9}; thrombocytopenia (all grades) 53% to 100%,^{2,3,6,8,9} (grade 3 or 4) 7% to 75%.^{1-6,8,9}
- F. **Hepatic:** Any toxicity (all grades) 37%.³
- G. **Infection:** (all grades) 39%,³ (grade 3 or 4) 2% to 15%.^{3,5}
- H. **Neurologic:** Peripheral neuropathy (all grades) 7%,³ (grade 3 or 4) 2% to 7%.^{3,5}
- I. **Renal:** Serum creatinine elevations (all grades) 49%,³ (grade 3 or 4) 2%.³
- J. **Treatment-Related Deaths:** Sepsis (any cause) 2% to 4%.^{3,4}

PRETREATMENT LABORATORY STUDIES NEEDED

- A. **Baseline**
 - 1. Complete blood count (CBC) with differential
 - 2. Serum creatinine
 - 3. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT)
 - 4. Total bilirubin
 - 5. Conjugated bilirubin
- B. **Prior to Each Treatment**
 - 1. CBC with differential
 - 2. Serum creatinine
- C. **Recommended Pretreatment Values:** The minimally acceptable pretreatment values required to begin a cycle with full-dose therapy were white blood cell count (WBC) of 3,500 cells/mcL,^{2,4} absolute neutrophil count (ANC) of 1,500 cells/mcL,^{1,2,4,6,8} platelet count of 100,000 cells/mcL,^{1-4,6,8} serum bilirubin less than 1.25 times upper limit of normal (ULN) or less than 1.5 mg/dL,^{3,6,8} CrCl greater than or equal to 30 to 60 mL/min,^{3,4,6,8} and serum creatinine less than 2 mg/dL.⁸

DOSAGE MODIFICATIONS

A. Renal Function

- 1. Gemcitabine – No adjustment required.^{26,27}
- 2. Carboplatin – Refer to carboplatin dose calculations.

B. Hepatic Function

- 1. Gemcitabine – No adjustment required.²⁸
- 2. Carboplatin – No adjustment required.²⁸

C. Myelosuppression

- 1. Gemcitabine
 - a. ANC
 - (1) Less than 1,500 cells/mcL on day 1 of therapy,¹⁻⁵ reduce dose by 75% or delay cycle 1 week.
 - (2) Less than 500 to 1,000 cells/mcL on day 8:
 - (a) Reduce dose by 50% or stop current cycle.¹⁻³
 - (b) Extend cycle to every 28 days.⁴
 - b. Platelets
 - (1) Less than 100,000 cells/mcL on day 1 of therapy,¹⁻⁵ reduce dose by 75% or delay cycle 1 week.
 - (2) Less than 50,000 to 90,000 cells/mcL on day 8 of therapy²:
 - (a) Reduce dose by 50% or stop current cycle.¹⁻³
 - (b) Extend cycle to every 28 days.⁴
- 2. Carboplatin
 - a. ANC less than 1,500 cells/mcL on day 1 of therapy,^{1,4} reduce dose by 50% or delay cycle 1 week.
 - b. Platelets less than 100,000 cells/mcL on day 1 of therapy,^{1,4} reduce dose by 75% or delay cycle 1 week.

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