Cancer Chemotherapy Update

Irinotecan and Carboplatin (IC) Regimen for Small-Cell Lung Cancer and Non-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: IC

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

INDICATION(S)

The IC regimen (Table 1) has been studied and is recommended for treatment of limited, extensive-stage, and relapsed small-cell lung cancer (SCLC).¹⁻¹⁵ The IC regimen has also been studied in untreated and advanced non-small-cell lung cancer (NSCLC).¹⁶⁻¹⁹

DRUG PREPARATION

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

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.²⁰
5. If the drug is prepared in a saline diluent, the solution should be used within 8 hours.

B. Irinotecan

1. Use irinotecan for injection 20 mg/mL.
2. Dilute in 250 to 500 mL of 0.9% sodium chloride injection or D5W to a final concentration of 0.12 to 2.8 mg/mL.

DRUG ADMINISTRATION

- A. Carboplatin:** Carboplatin was administered as an intravenous (IV) infusion over 30 to 120 minutes in the trials reviewed.^{1-6,10-12,14,16-18}
- B. Irinotecan:** In the trials reviewed, irinotecan was administered as a 30- to 90-minute IV infusion.^{1-6,8,10-12,16,17}

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Table 1. Irinotecan and carboplatin (IC) regimen^{1-5,16,17}

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Carboplatin	AUC 5	IV	1	AUC 5
Irinotecan	50 mg/m ²	IV	1, 8, 15	150 mg/m ²
<i>Cycle repeats: every 28 days</i>				
Variations				
1. Carboplatin AUC 5 IV day 1 and irinotecan 50 mg/m ² IV days 1 and 8 every 21 days. ^{6,11,12}				
2. Carboplatin AUC 4 IV day 1 and irinotecan 175 mg/m ² IV day 1 every 21 days. ⁷				
3. Carboplatin AUC 5 IV day 1 and irinotecan 200 mg/m ² IV day 1 every 21 days. ^{8,18}				
4. Carboplatin AUC 5 IV day 1 and irinotecan 150 mg/m ² IV day 1 every 21 days. ⁸				
5. Carboplatin AUC 5 IV day 1 and irinotecan 60 mg/m ² IV days 1, 8, and 15 every 28 days. ⁹				
6. Carboplatin AUC 2 IV days 1 and 8 and irinotecan 50 mg/m ² IV days 1 and 8 every 21 days. ¹⁰				
7. Carboplatin AUC 4 IV day 1 and irinotecan 60 mg/m ² IV days 1, 8, and 15 every 28 days. ¹³				
8. Carboplatin AUC 2 IV days 1, 8 and 15 and irinotecan 50 mg/m ² IV days 1, 8, and 15 every 28 days. ¹⁴				
9. Carboplatin AUC 2.5 IV days 1 and 8 and irinotecan 65 mg/m ² IV days 1 and 8 every 21 days. ¹⁹				

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

SUPPORTIVE CARE

A. Acute and Delayed Emesis Prophylaxis: The IC regimen is predicted to cause acute emesis in 60% to 90% of patients.²¹ The studies reviewed reported nausea and vomiting (all grades) in 1% to 45% of patients and severe (grade 3 or 4) nausea or vomiting in only 1% to 18% of patients.^{1-6,8,10-14,16-18} Although carboplatin is reported to cause delayed nausea or emesis similar to cisplatin, the mechanism of action and clinical course of carboplatin-induced nausea and vomiting differ from cisplatin.^{22,23} Analysis of urinary 5-hydroxyindole acetic acid (5-HIAA) excretion indicates carboplatin causes a lower peak level, but more prolonged release, of serotonin than cisplatin. The clinical course of carboplatin-induced emesis reflects this pattern of serotonin release. Carboplatin-induced emesis usually begins 6 to 7 hours after drug administration and may persist for up to 120 hours. Although not well documented in the literature, some clinicians divide the daily antiemetic dose into 2 doses on days when carboplatin is administered. Appropriate acute emesis prophylaxis includes a serotonin antagonist and a corticosteroid plus or minus a neurokinin antagonist in selected patients.²⁴⁻²⁶ One of the following regimens is suggested:

1. Ondansetron 16 mg to 24 mg, dexamethasone 12 mg orally (PO) ± aprepitant 125 mg given PO 60 minutes before IC on day 1.
2. Granisetron 1 mg to 2 mg, dexamethasone 12 mg PO ± aprepitant 125 mg given PO 60 minutes before IC on day 1.
3. Dolasetron 100 mg to 200 mg, dexamethasone 12 mg PO ± aprepitant 125 mg given PO 60 minutes before IC on day 1.
4. Palonosetron 0.25 mg IV and dexamethasone 12 mg PO ± aprepitant 125 mg given PO 60 minutes before IC on day 1.

The antiemetic therapy should continue for an additional 2 days. Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.²⁴⁻²⁶ A meta-analysis of several trials of serotonin antagonists recommends against prolonged (greater than 24 hours) use of these agents, making a steroid and dopamine antagonist combination most appropriate for follow-up therapy.²⁷ 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 IC.
2. Dexamethasone 8 mg PO once daily for 2 days, ± prochlorperazine 10 mg PO every 4

to 6 hours, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of IC.

3. Dexamethasone 8 mg PO once daily 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 2 of IC.

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

B. Breakthrough Nausea and Vomiting²⁴⁻²⁶: 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, $\pm$ 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.

A few small studies suggest that higher doses of granisetron (3 mg IV or 40 mcg/kg to 240 mcg/kg)²⁸⁻³² may be effective in treating breakthrough nausea, however none of these reports found the improvement to be statistically significant.

C. Diarrhea: Diarrhea is a frequent consequence of irinotecan therapy and can be severe and potentially fatal. Severe cases of irinotecan-induced diarrhea have been documented in individuals with Gilbert's syndrome, which is caused by homozygosity for polymorphisms of the UDP-glucuronyltransferase gene: UGT1A1*28.³³⁻³⁶ In the studies reviewed, patients possessing these polymorphisms demonstrated an increased rate of hematologic toxicity and more severe diarrhea.^{1,11,12,18} Irinotecan may cause 2 severe, life-threatening forms of diarrhea. Early diarrhea usually occurs during the first 24 hours of receiving irinotecan and is characterized by cholinergic symptoms, such as increased salivation, diaphoresis, and abdominal cramping. This early form is usually responsive to IV atropine (0.25 mg to 1 mg). Late diarrhea, occurring more than 24 hours after treatment, may lead to dehydration,

electrolyte imbalances, or sepsis. This late form of diarrhea should be treated with loperamide.³⁷

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 after each unformed stool, or as often as every 2 hours for 24 hours.³⁸ Patients should be counseled to³⁹:

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 (>4 hours) grade 1 or 2 diarrhea or grade 3 diarrhea (increase of >7 stools per day or incontinence or symptoms of dehydration).
4. Discontinue loperamide when they have been diarrhea-free for at least 12 hours.

The studies reviewed reported grade 3 or 4 diarrhea in 2% to 23% of patients.^{1-14,16-19}

D. 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.^{40,41} In the IC trials reviewed, febrile neutropenia was reported in 1% to 19% of patients^{1,2,4,8,9,13,16,18,19}; severe neutropenia (grade 3 or 4) was reported in 2% to 55% of patients.^{2,6,8-10,14,16,18,19} Therefore, prophylactic use of CSFs should be considered with the IC regimen.^{40,41}

E. Hydration: If carboplatin doses are reduced appropriately for diminished renal function (as in area under the curve [AUC] dosing), no prophylactic hydration or diuretic use is required.⁴²

F. Hypersensitivity Precautions: No special precautions are usually required.^{43,44} There was one treatment-related death due to anaphylactic shock after IV administration of carboplatin¹⁷ and several reports of allergic reactions (grade 1-2) 1% to 4%¹⁰ and rash (grade 1-2) 2%¹⁶ in the studies reviewed.

Carboplatin hypersensitivity reactions generally develop in patients who have been extensively pre-treated with the agent.⁴⁵ With more prolonged use (ie, >6 courses), or if utilized in previously treated patients, the incidence of reactions is likely to be considerably greater.⁴⁵ Carboplatin is reported to cause hypersensitivity reactions in 12% to 19% of patients.⁴⁶ One study reported the incidence as high as 27% in patients with gynecologic cancers receiving 7 or more courses of carboplatin.⁴⁵ Mild hypersensitivity reactions, consisting of localized itching, and mild erythema of the palms and/or soles necessitates stopping the infusion and possible administration of an antihistamine and/or a corticosteroid before continuing the infusion.⁴⁷ Upon symptom resolution, these patients may resume treatment. Moderate to severe reactions, consisting of more severe itching, diffuse erythema, rigor, facial swelling, throat and/or chest tightness, tachycardia, bronchospasm, hypertension, or hypotension usually require permanent discontinuation of carboplatin treatment and prompt administration of parenteral corticosteroids and antihistamines.⁴⁷ The decision to re-challenge or discontinue treatment after a moderate to severe reaction occurs is dependent upon the severity of the reaction and other clinical factors.⁴⁶

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://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 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:** Dehydration (grade 3) 3% to 12%,^{2,12,13,18} (grade 4) 3%²; thrombosis (grade 3) 2%¹²; unspecified cardiac toxicity (grade 3) 2%,¹² (grade 4) 2%.¹²
- B. **Central Nervous System (CNS):** Confusion (grade 3) 2%,¹² dizziness (grade 3) 2% to 10%,^{12,18} pain (grade 3) 2% to 12%,^{12,13,18} syncope (grade 3) 2%,¹² unspecified CNS toxicity (grade 3) 4%.⁶
- C. **Constitutional:** Fatigue/asthenia (grade 3) 2% to 21%,^{4,11-13,18} malaise (grade 3) 5%.¹⁸
- D. **Dermatologic:** Alopecia (grade 3) 4% to 6%,^{5,16} skin rash (grade 3) 3%.¹⁶
- E. **Endocrine/Metabolic:** Elevated serum calcium (grade 4) 2%,¹⁰ hyperglycemia (grade 3) 2%,¹⁸ hyponatremia (grade 3) 3% to 15%,^{11,13} unspecified potassium abnormality (grade 3) 3%.¹¹
- F. **Gastrointestinal:** Abdominal pain (grade 3) 2%,¹² (grade 4) 2%¹⁰; anorexia (grade 3) 2% to 15%,^{12,13} (grade 4) 8%⁴; constipation (grade 3) 2% to 9%,^{5,10,12} (grade 4) 4%¹⁰; mucositis (grade 3) 2%⁵; nausea (grade 3) 3% to 18%,^{1-5,10-14,16-18} (grade 4) 1% to 3%,^{1,10,14} (grade 3 or 4) 8% to 13%⁸; rectal/perirectal pain (grade 3) 2%¹²; vomiting (grade 3) 3% to 18%,^{2,3,5,10,12-14,18} (grade 4) 2% to 3%,^{10,14} (grade 3 or 4) 8% to 13%.⁸
- G. **Hematologic:** Anemia (grade 3) 2% to 43%,^{1-6,10-14,16-18} (grade 4) 2% to 25%,^{3,5,6,10,11,17,18} (grade 3 or 4) 5% to 15%^{7,8}; febrile neutropenia (grade 3) 3% to 5%,^{2,4,13} (grade 4) 1% to 19%,^{2,4,16,18} (grade 3 or 4) 3% to 10%,^{1,8,9,19} leukopenia (grade 3) 4% to 42%,^{1-6,10,11,13,14,16,17} (grade 4) 2% to 17%,^{1-6,10,11,13,14,16} (grade 3 or 4) 32%⁷; neutropenia (grade 3) 2% to 46%,^{2-6,10-14,16-18} (grade 4) 3% to 47%,^{2-4,6,10-14,16-18} (grade 3 or 4) 30% to 55%^{8,9,19}; thrombocytopenia (grade 3) 2% to 50%,^{1-6,11-14,16-18} (grade 4) 1% to 22%,^{1-4,6,11-14,16-18} (grade 3 or 4) 15% to 23%.^{7,8,19}
- H. **Hepatic:** Alanine aminotransferase (ALT) elevations (grade 3) 2% to 7%,^{4,10,11,14,17} aspartate aminotransferase (AST) elevations (grade 3) 2% to 7%,^{4,10,11,17} hyperbilirubinemia (grade 3) 3%,⁴ unspecified liver dysfunction (grade 3) 5%.¹⁰
- I. **Infection:** Unspecified infection (grade 3) 1% to 20%.^{1,2,4,6,11,12,14,18}
- J. **Neurologic:** Motor neuropathy (grade 3 or 4) 2%,¹⁰ sensory neuropathy (grade 3) 2%.¹⁰
- K. **Pulmonary:** Dyspnea (grade 3) 6% to 17%,^{12,13,18} (grade 4) 4%¹⁰; pneumonitis (grade 3) 2%¹⁷; unspecified pulmonary toxicity (grade 3) 2% to 4%,^{6,12} (grade 4) 2%.¹²
- L. **Renal:** Elevated serum creatinine (grade 3) 3%,¹¹ (grade 4) 4%.¹⁰
- M. **Treatment-Related Mortality:** Anaphylaxis 2%,¹⁷ arrhythmia 2%,¹² infection or sepsis 2% to 5%,^{4,6,8,10,14,18,19} obstructive airway disease 3%,¹³ respiratory failure 3%,¹³ spontaneous tension pneumothorax 2%,¹⁰ toxic colitis 2%,² transfusion-related lung injury 3%.¹⁸

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. AST/ALT
2. Total bilirubin
3. Serum creatinine
4. 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. White blood cell count (WBC)
 - a. Greater than or equal to 4,000 cells/
mcL.^{1-3,10,11,16,17}
 - b. Greater than 4,000 cells/mcL and less
than 12,000 cells/mcL.^{6,14}
 - c. Greater than 3,000 cells/mcL.⁷
2. Absolute neutrophil count (ANC):
 - a. Greater than or equal to 1,500 g/
dL.^{4,5,8,10,12,13,18}
 - b. Greater than 2,000 cells/mcL.^{6,11,14}
3. Platelet count greater than or equal to
100,000 cells/mcL.^{1-8,11-14,16-18}
4. Serum creatinine
 - a. Less than or equal to 1.25 times upper
limit of normal (ULN).^{1,2,5}
 - b. Less than 1.5 mg/dL.^{4,6,11}
 - c. Creatinine clearance (CrCl) greater than
or equal to 50 mL/min.^{6,14}
 - d. Less than 1.5 times ULN.^{7,13}
 - e. Less than or equal to ULN.¹⁰
 - f. CrCl greater than or equal to 40 mL/
min.^{11,16}
 - g. Less than or equal to 2 mg/dL.¹²
 - h. Less than or equal to 1.2 mg/dL.¹⁴
 - i. Less than or equal to 2 mg/dL or CrCl
greater than 60 mL/min.¹⁸
5. Serum bilirubin
 - a. Less than or equal to 1.25 times ULN.^{1-3,5}
 - b. Less than or equal to 1.5 mg/dL.<sup>4,7,8,10,12-
14,16</sup>
 - c. Less than ULN.^{6,11}
 - d. Less than or equal to 25 micromol/L.¹⁷
 - e. Less than or equal to 1.5 times ULN.¹⁸
6. ALT/AST
 - a. Less than or equal to 2 times ULN.^{3,6,7,10,11,16,17}
 - b. Less than or equal to 3 times ULN.^{4,5}

- c. AST less than or equal to 2.5 times ULN
or less than 5 times ULN if liver metasta-
ses.^{8,12,13}
- d. AST/ALT less than or equal to 100 IU/L.¹⁴

7. Hemoglobin

- a. Greater than 9 g/dL.^{2,6,10-12}
- b. Greater than or equal to 10 g/dL.^{3,4,17}
- c. Greater than or equal to 9.5 g/dL.^{14,16}

8. Arterial oxygen pressure (PaO₂)

- a. Greater than or equal to 70 mm Hg.^{3,17}
- b. Greater than or equal to 60 mm Hg.^{6,11}

In clinical practice, a pretreatment 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.⁴⁸ Carboplatin doses are commonly calculated using an equation based on the method of Calvert et al.⁴⁹ Calvert's group showed that the carboplatin dose in milligrams can be calculated using a desired area under the time vs 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 x [GFR + 25]. If radiopharmaceutical clearance is not used to measure GFR, CrCl estimated by the Cockcroft-Gault method⁵⁰ 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:
 - a. If the patient is not obese (body mass index [BMI] < 25), actual body weight should be used.^{51,52}
 - b. If the patient is overweight or obese (BMI ≥ 25), an adjusted body weight (ABW) should be used.^{53,54} 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 as⁵⁵:

IBW = 50 kg + 2.3kg/inch >60 inch (Men)
 IBW = 45.5 kg + 2.3kg/inch >60 inch (Women)

- c. If the patient has a serum creatinine less than 0.8 mg/dL, round the serum creatinine up to 0.8 mg/dL.^{56,57} The Gynecologic Oncology Group has suggested rounding values less than 0.7 mg/dL up to 0.7 mg/dL.⁵⁸
- d. 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.⁴⁹ The US Food and Drug Administration 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.⁵⁹

2. Irinotecan: No specific guidelines are available, however a reduced dose should be considered in patients with renal dysfunction.⁶⁰

B. Hepatic Function

1. Carboplatin: No adjustment recommended.⁶¹
2. Irinotecan: Reduce dose by 25% if bilirubin is 1.5 to 3 mg/dL.⁶²

C. Myelosuppression

1. Carboplatin:
 - a. Dose reduced to AUC 4 if thrombocytopenia less than 20,000 cells/mcL after day 15 or leukopenia less than 1,000 cells/mcL.^{1,2}
 - b. Further dose reduce to AUC 3 if thrombocytopenia less than 20,000 cells/mcL after day 15 or leukopenia less than 1,000 cells/mcL despite initial dose reduction.^{1,2}
 - c. Dose reduced by 1 AUC if patient experienced grade 4 thrombocytopenia or received a platelet transfusion for grade 3 thrombocytopenia.^{6,16}
 - d. Dose reduced by 25% for severe or prolonged hematologic toxicity.⁷
 - e. Dose reduced to AUC 4 for grade 4 neutropenia and grade 3 to 4 thrombocytopenia when starting irinotecan dose equaled 150 mg/m².⁸
 - f. Dose reduced 20% from the previous cycle if nadir leukocyte count less than 1,000 cells/mcL, nadir neutrophil count less than 500 cells/mcL or nadir platelet count less than 20,000 cells/mcL.¹⁰

- g. Dose reduced by 1 AUC if grade 4 thrombocytopenia.¹¹
- h. Dose reduced 25% for ANC 1,000 cells/mcL to 1,499 cells/mcL and held for ANC less than 1,000 cells/mcL or platelets less than 75,000 cells/mcL or prior hospitalization for neutropenic fever.¹³
- i. Hold dose on days 8 or 15 if leukocyte count less than 3,000 cells/mcL or platelet count less than 100,000 cells/mcL.¹⁴

2. Irinotecan:

- a. Dose omitted on day 15 and all subsequent cycles if thrombocytopenia less than 20,000 cells/mcL before day 15.^{1,2}
- b. Dose omitted days 8 or 15 if leukocyte count less than 3,000 cells/mcL or platelets less than 100,000 cells/mcL.^{3,17}
- c. Dose omitted on days 8 or 15 if neutrophil count less than 1,500 cells/mcL.⁴
- d. Dose omitted day 8 if WBC count less than 3,000 cells/mcL or platelets less than 100,000 cells/mcL.⁶
- e. Dose reduced by 10 mg/m² if patient experienced grade 4 leukopenia or neutropenia lasting 3 days or longer or grade 4 thrombocytopenia.^{6,16}
- f. Dose reduced by 25% for severe or prolonged hematologic toxicity.⁷
- g. Dose reduced from 200 mg/m² to 150 mg/m² if grade 4 neutropenia or grade 3 to 4 thrombocytopenia.⁸
- h. Dose reduced 20% from the previous cycle if nadir leukocyte count less than 1,000 cells/mcL, nadir neutrophil count less than 500 cells/mcL or nadir platelet count less than 20,000 cells/mcL.¹⁰
- i. Dose held day 8 if neutrophil count less than 1,000 cells/mcL or if platelet count less than 75,000 cells/mcL.¹¹
- j. Dose reduced by 10 mg/m² if grade 4 leukopenia or neutropenia lasting 3 days or longer, grade 3 or 4 neutropenia associated with a fever higher than 38°C, grade 4 thrombocytopenia or if prior doses had been skipped.¹¹
- k. Dose reduced 25% for ANC 1,000 cells/mcL to 1,499 cells/mcL and held for ANC less than 1,000 cells/mcL or platelets less than 75,000 cells/mcL or prior hospitalization for neutropenic fever.¹³

- l. Hold dose on days 8 or 15 if leukocyte count less than 3,000 cells/mcL or platelet count less than 100,000 cells/mcL. Dose reduced 10 mg/m² for leukocyte nadir less than 1,000 cells/mcL, neutrophil nadir less than 500 cells/mcL or platelet nadir less than 25,000 cells/mcL.¹⁴
- m. Dose reduced by 20% if ANC nadir from previous cycle was less than 500 cells/mcL for greater than 7 days or if the patient experienced febrile neutropenia.¹⁸

D. Diarrhea

- 1. Carboplatin: Dose reduced 20% for greater than or equal to grade 2 diarrhea from previous cycle.¹⁰
- 2. Irinotecan:
 - a. Reduce by 20% for greater than or equal to grade 2 diarrhea persisting for greater than 3 days, despite treatment with loperamide and neomycin or in the case of grade 4 diarrhea.^{1,2}
 - b. Dose held on days 8 or 15 if patient experienced diarrhea on those days.^{3,17}
 - c. Dose omitted day 8 or 15 if greater than or equal to grade 2 diarrhea.^{4,6}
 - d. Dose reduced by 10 mg/m² if patient experienced diarrhea of grade 3 or higher.^{6,16}
 - e. Dose reduced to 100 mg/m² in cases of grade 3 to 4 diarrhea in the previous cycle.⁸
 - f. Dose reduced 20% for greater than or equal to grade 2 diarrhea from previous cycle.¹⁰
 - g. Dose reduced 10 mg/m² if grade 3 or higher diarrhea or doses had been skipped on both days 8 and 15.¹¹
 - h. Dose reduce 25% for grade 3 or 4 diarrhea during previous cycle.¹²
 - i. Dose reduced 10 mg/m² for grade 2 or greater diarrhea during previous course.¹⁴
 - j. Dose held on days 8 or 15 if grade 1 or higher diarrhea.¹⁶
 - k. Dose reduction of 15% for all subsequent cycles if grade 2 diarrhea. Dose reduced 25% for all subsequent cycles for grade 3 diarrhea or need for IV fluid support. Termination from study for all grade 4 diarrhea.¹⁸
- l. Hold dose on days 8 or 15 for grade 2 or higher diarrhea on previous course.¹⁴

E. Other

- 1. Carboplatin:
 - a. Drug dose reduced 25% or discontinued for grade 3 or higher non-hematologic toxicity (excluding nausea/vomiting, anorexia, constipation, diarrhea, alopecia and fatigue) at any time.^{11,13}
- 2. Irinotecan:
 - a. Dose reduced from 200 mg/m² to 150 mg/m² if nonhematologic toxicity was encountered in the previous cycle.⁸
 - b. Dose reduced 20% for grade 3 nonhematological toxicity (excluding diarrhea, nausea, vomiting, appetite loss, general fatigue or alopecia) from previous cycle.¹⁰
 - c. Drug discontinued for grade 3 or higher nonhematologic toxicity (excluding nausea/vomiting, anorexia, constipation, diarrhea, alopecia and fatigue) at any time.¹¹
 - d. Dose reduce 25% for grade 3 or 4 nonhematologic toxicity.¹³
 - e. Dose reduced by 15% for any/all grade 2 or 3 nonhematologic toxicity and 25% for any/all grade 4 nonhematologic toxicity.¹⁸

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