Cancer Chemotherapy Update

Paclitaxel and Carboplatin (TC) Regimen for Ovarian 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: Paclitaxel and Carboplatin

Synonym: TC

Origin of Name: TC is an acronym for the 2 medications in the regimen: paclitaxel (*T*axol) and carboplatin.

INDICATION(S)

The TC regimen (Table 1) has been studied as adjuvant therapy in ovarian cancer¹⁻⁸ and primary treatment of relapsed platinum-sensitive ovarian cancer.⁹ Current guidelines recommend TC as primary adjuvant therapy for all stages of ovarian cancer, as therapy for recurrent platinum-sensitive tumors, and as neo-adjuvant therapy for patients with bulky stage III/IV ovarian cancer who are poor surgical candidates.¹⁰

DRUG PREPARATION

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

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.¹¹
5. If the drug is prepared in a saline diluent, the solution should be used within 8 hours.

B. Paclitaxel

1. Use paclitaxel injection 6 mg/mL.
2. Dilute to a concentration of 0.3 to 1.2 mg/mL with NS, D5W, or a saline/dextrose solution.
3. Contact of undiluted paclitaxel with plasticized polyvinyl chloride (PVC) equipment or devices is not recommended.
4. Paclitaxel solutions should be dispensed in glass, polypropylene, or polyolefin containers.

DRUG ADMINISTRATION

- A. **Carboplatin:** Administer by intravenous (IV) infusion over 30 to 60 minutes.
- B. **Paclitaxel** is administered by IV infusion over 3 hours through a non-PVC (low-sorbing) infusion set and a 0.22 micron filter.

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Table 1. Paclitaxel and carboplatin (TC) regimen^{1-4,6,8,9}

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Paclitaxel	175 mg/m ²	IV	1	175 mg/m ²
Carboplatin	AUC 5 to AUC 6	IV	1	AUC 5 to AUC 6

Cycle repeats every 21 days

Variations:

1. Paclitaxel 175 mg/m² IV and carboplatin AUC 7 IV, both on day 1, cycle repeats every 21 days.⁵
2. Paclitaxel 185 mg/m² IV and carboplatin AUC 6 IV, both on day 1, cycle repeats every 21 days.⁷

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

SUPPORTIVE CARE

A. Acute and Delayed Emesis Prophylaxis: The TC regimen is predicted to cause acute emesis in 30% to 90% of patients.¹²⁻¹⁴ The studies reviewed reported vomiting (all grades) in 33% to 45%,^{3,4,6,7,9} severe (grade 3 or 4) vomiting in 4%,¹ nausea or vomiting (all grades) in 59%,⁸ and severe nausea or vomiting (grade 3 or 4) in 1% of patients.⁵ Appropriate acute emesis prophylaxis includes a serotonin antagonist and a corticosteroid plus or minus a neurokinin antagonist in selected patients.¹²⁻¹⁴ 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 TC.
2. Granisetron 1 mg to 2 mg and dexamethasone 12 mg PO ± aprepitant 125 mg PO 30 minutes before day 1 of TC.
3. Dolasetron 100 mg and dexamethasone 12 mg PO ± aprepitant 125 mg PO 30 minutes before day 1 of TC.
4. Palonosetron 0.25 mg IV and dexamethasone 12 mg PO ± aprepitant 125 mg PO 30 minutes before day 1 of TC.

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.¹⁵ 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 TC.

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 TC.
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 TC.

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

B. Breakthrough Nausea and Vomiting¹²⁻¹⁴: 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.

C. Hydration: If carboplatin doses are adjusted appropriately for renal function (as in AUC dosing), no prophylactic hydration or diuretic use is required.¹⁶

D. Hypersensitivity Precautions: Paclitaxel injection produces hypersensitivity reactions in about 10% of patients.^{17,18} Routine prophylactic premedications should be given prior to paclitaxel

administration. The following regimen is suggested¹⁹:

1. Ranitidine 50 mg
2. Dexamethasone 10 or 20 mg
3. Diphenhydramine 50 mg

All given IV over 30 minutes prior to paclitaxel.

- 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 (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.^{20,21}

In the trials reviewed, severe (grade 3 or 4) neutropenia was reported in 37% to 88% of patients,^{1,2,4-7,9} severe (grade 3 or 4) granulocytopenia was reported in 58% to 70% of patients,^{3,8} and febrile neutropenia was reported in 4% to 8% of patients.^{3,6,7,9} Prophylactic use of CSFs is not recommended with this regimen. CSFs should be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of TC.

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:** Coagulation (all grades) 2%,² (grade 3 or 4) 1%,² edema (all grades) 18% to 22%,^{4,7} (grade 3 or 4) 1% to 2%,^{4,7} hemorrhage (all grades) 4%,² thromboembolic events (all grades) 2%,³ upper intestinal hemorrhage (grade 3) 0.2%.¹
- B. Central Nervous System:** Anxiety (all grades) 8%,⁶ (grade 3 or 4) 1%⁶; headache (all grades) 17%,⁶ (grade 3 or 4) 1%⁶; insomnia (all grades) 20%,⁶ (grade 3 or 4) 0.3%.⁶
- C. Constitutional:** Asthenia (all grades) 23%,⁶ (grade 3 or 4) 2%⁶; fatigue (all grades) 28% to 82%,^{4,6,9} (grade 3 or 4) 4% to 7%^{1,4,6}; pain (all grades) 10% to 69%,^{1,4,6} (grade 3 or 4) 1% to 9%^{1,4,6}; back pain (all grades) 11%,⁶ (grade 3 or 4) 1%.⁶
- D. Dermatologic:** Alopecia (all grades) 72% to 98%,^{3,4,6,7,9} (grades 2, 3, or 4) 51%,¹ (grade 3 or 4) 28%⁶; hand and foot syndrome (all grades) 10%.⁹
- E. Endocrine/Metabolic:** Endocrine (any) (all grades) 6%²; hypokalemia (all grades) 36%,⁶ (grade 3 or 4) 6%⁶; second primary cancer during follow-up 4%.²
- F. Gastrointestinal:** Abdominal pain (all grades) 42% to 47%,^{3,6} (grade 3 or 4) 5%⁶; anorexia (all grades) 28% to 40%,^{3,6} (grade 3 or 4) 3%⁶; constipation (all grades) 38% to 58%,^{4,6,7,9} (grade 3 or 4) 2% to 15%^{4,6,7}; diarrhea (all grades) 23% to 35%,^{3,4,6,7,9} (grade 3 or 4) 1% to 3%⁴⁻⁷; nausea (all grades) 57% to 77%,^{3,4,6,7,9} (grade 3 or 4) 3% to 6%^{1,4,6,7}; nausea/ vomiting (all grades) 59%,⁸ (grade 3 or 4) 1% to 14%^{5,8}; vomiting (all grades) 33% to 45%,^{3,4,6,7,9} (grade 3 or 4) 3% to 4%^{1,4,6,7}; mucositis (all grades) 26%⁹; stomatitis (all grades) 5% to 37%^{3,6}; stomatitis/mucositis (all grades) 20% to 23%,^{4,7} (grade 3 or 4) 1%.^{4,7}
- G. Hematologic:** Anemia (all grades) 64% to 91%,^{2,4,6-9} (grade 3 or 4) 1% to 22%^{1,3,4-9}; granulocytopenia (all grades) 86%,⁸ (grade 3 or 4) 40% to 70%^{3,8}; leukopenia (all grades) 87% to 98%,^{2,4,6,7} (grade 3 or 4) 17% to 51%^{2,4-7}; neutropenia (all grades) 69% to 97%,^{2,4,6,7,9} (grade 3 or 4) 37% to 88%^{1,2,4-7,9}; febrile neutropenia (all grades) 4% to 8%,^{3,6,7,9} (grade 3 or 4) 2% to 4%^{1,4,6}; thrombocytopenia (all grades) 19% to 79%,^{2,4,6-9} (grade 3 or 4) 5% to 18%.¹⁻⁹
- H. Hepatic:** Hepatotoxicity (any) (all grades) 8%,⁴ (grade 3 or 4) 0.4% to 1%^{2,5}; total bilirubin (all grades) 12%,⁶ (grade 3 or 4) 4%.⁶
- I. Hypersensitivity:** (all grades) 9% to 35%,^{2-4,7,9} (grade 3 or 4) 1% to 4%.^{2,4,5,7}
- J. Infection/Fever:** Fever (all grades) 13% to 14%^{6,8}; infection (all grades) 20% to 47%,^{4,7,9} (grade 3 or 4) 3% to 36%^{5,7,9}; infection/fever (all grades) 9%.²

- K. Musculoskeletal:** Arthralgia (all grades) 29% to 48%,^{4,6} (grade 3 or 4) 1% to 5%^{4,6}; arthralgia/myalgia (all grades) 50% to 72%,^{7,9} (grade 3 or 4) 4% to 15%^{5,7}; myalgia (all grades) 29% to 64%,^{3,6} (grade 3 or 4) 1%.^{1,6}
- L. Neurologic:** Ataxia (all grades) 3%⁶; auditory/ototoxicity (all grades) 3% to 9%,^{2,4,7} (grade 3 or 4) 0.3% to 1%^{4,7}; central neuropathy (all grades) 18%,⁷ (grade 3 or 4) 2%⁷; hypoesthesia (all grades) 9%,⁶ (grade 3 or 4) 0.3%⁶; neuropathy (grades 2, 3, or 4) 14%¹; neuropathy motor (all grades) 13% to 20%,^{4,9} (grade 3 or 4) 2%⁴; neurosensory (all grades) 72% to 84%,^{3,4,7,9} (grade 3 or 4) 7%^{4,7}; neurotoxicity (all grades) 19% to 72%,^{2,8} (grade 3 or 4) 2% to 3%^{2,5,8}; paresthesia (all grades) 41%,⁶ (grade 3 or 4) 1%⁶; peripheral neuropathy (all grades) 41%,² (grade 3 or 4) 1%²; vertigo (all grades) 12% to 14%,^{4,6} (grade 3 or 4) 0.2% to 0.3%.^{4,6}
- M. Ocular/visual:** (any) (all grades) 8%.²
- N. Pulmonary:** Dyspnea (all grades) 16% to 28%,^{6,7} (grade 3 or 4) 1% to 6%^{6,7}; pharyngitis (all grades) 7%⁶; pulmonary (any) (all grades) 8%.²
- O. Renal:** Nephrotoxicity (any) (all grades) 5%⁷; serum creatinine elevations (all grades) 6%,⁴ (grade 3 or 4) 1%.⁴
- P. Treatment-Related Mortality:** Sepsis 0.5%.³

PRETREATMENT LABORATORY STUDIES NEEDED

- A. Baseline**
1. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT)
 2. Total bilirubin
 3. Serum creatinine
 4. Complete blood cell 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: Greater than or equal to 3,000 cells/mcL.^{2,8}
 2. Absolute neutrophil count: Greater than 1,500 cells/mcL.⁴⁻⁷
 3. Granulocyte count: Greater than 2,000 cells/mcL.³

4. Platelet count:
 - a. Greater than or equal to 100,000 cells/mcL.^{2,4-8}
 - b. Greater than 150,000 cells/mcL.³
5. Serum creatinine:
 - a. Less than or equal to 2 mg/dL.²
 - b. Less than the upper limit of normal (ULN).³
 - c. Less than 1.25 times ULN.^{4,7}
 - d. Less than 1.5 times ULN.⁶
 - e. Less than or equal to 120 micromole/L.⁸
6. Creatinine clearance:
 - a. Greater than or equal to 50 mL/min.⁶
 - b. Greater than or equal to 60 mL/min.⁸
7. Serum bilirubin:
 - a. Less than 1.5 times ULN.^{2,6}
 - b. Less than 1.25 times ULN.^{4,7}
 - c. Less than or equal to 25 micromole/L.⁸
8. AST/ALT: Less than or equal to 2.5 times ULN.⁶

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 – Carboplatin doses are commonly calculated using an equation based on the method of Calvert et al.²² 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 method²³ 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.^{24,25}
- b. If the patient is overweight or obese (BMI ≥ 25), an adjusted body weight (ABW) should be used.^{26,27} 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 as²⁸: $IBW = 50\ kg + 2.3\ kg/inch >60\ inch$ (men) $IBW = 45\ kg + 2.3\ kg/inch >60\ inch$ (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.^{29,30} The Gynecologic Oncology Group has suggested rounding values less than 0.7 mg/dL up to 0.7 mg/dL.³¹
- 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.²² 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.³²

2. Paclitaxel – no adjustment required.^{33,34}

B. Liver Function

1. Carboplatin – no dose adjustment required.³³
2. Paclitaxel – bilirubin and ALT/AST:
 - a. Bilirubin less than 1.5 mg/dL *and/or* ALT/AST greater than 2 times the ULN, reduce the dose 25%.^{35,36}
 - b. Bilirubin greater than or equal to 1.6 mg/dL and less than or equal to 3 mg/dL, reduce the dose 60%.^{35,36}
 - c. Bilirubin greater than 3 mg/dL, reduce the dose 75%.^{35,36}
 - d. Bilirubin greater than 5 times the ULN and/or ALT/AST greater than or equal to 10 times the ULN, do not give the drug.³³

C. Myelosuppression

1. Febrile neutropenia, granulocyte count less than 500 cells/mcL for more than 7 days, or platelets less than 25,000 cells/ mcL, reduce paclitaxel by 25 mg/m² and carboplatin by AUC 1.³
2. Grade 3 or 4 thrombocytopenia, reduce drug doses by 25% and 50%, respectively.⁵
3. Grade 4 neutropenia, Grade 4 thrombocytopenia, febrile neutropenia, or severe bleeding,

reduce paclitaxel to 135 mg/m² and carboplatin to AUC 4.⁹

D. Other

1. Grade 3 arthralgia or myalgia, reduce paclitaxel by 25 mg/m².³ Grade 4 arthralgia or myalgia, stop paclitaxel.³
2. Grade 4 anaphylaxis, stop chemotherapy.³
3. Grade 2 neurotoxicity, reduce paclitaxel by 25 mg/m².³ Grade 3 neurotoxicity, stop chemotherapy.³
4. Grade 2 through 4 neurotoxicity, stop chemotherapy.⁵
5. Grade 2 through 4 mucositis, reduce paclitaxel by 25 mg/m²,³ or 25% reduction of both paclitaxel and carboplatin.⁵
6. Severe hypersensitivity reactions, stop paclitaxel.⁵
7. Severe cardiac toxicity (symptomatic ventricular arrhythmias or more than 1st degree heart block), stop paclitaxel.⁵

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