Cancer Chemotherapy Update

Paclitaxel, Carboplatin, and Trastuzumab

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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, carboplatin, and trastuzumab

Origin of Name: The regimen is named for the 3 drugs it contains.

COMMENTS

The paclitaxel, carboplatin, and trastuzumab regimen was designed to couple the antitumor activity shown by the combination of paclitaxel and carboplatin¹⁻³ with the synergistic activity seen between trastuzumab and other platinum agents.⁴ Both weekly^{3,5-9} and every 3 week^{3,7,10,11} administrations of the paclitaxel, carboplatin, and trastuzumab regimen have been studied. The weekly regimen is the focus of this review (Table 1).

INDICATIONS

The paclitaxel, carboplatin, and trastuzumab regimen has been studied in locally advanced⁵⁻⁷ and metastatic HER2+ breast cancer.^{3,8-11} Current guidelines recommend it for the treatment of HER2+ recurrent or metastatic breast cancer.¹²

CARBOPLATIN DOSE CALCULATION

Carboplatin doses are commonly calculated using an equation based on the method of Calvert et al.¹³

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 x [GFR + 25].

If radiopharmaceutical clearance is not used to measure GFR, creatinine clearance (CrCl) estimated by the Cockcroft-Gault method¹⁴ 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.^{15,16}
2. If the patient is overweight or obese (BMI ≥ 25), an adjusted body weight (ABW) should be used.^{17,18} 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 as¹⁹:
$$IBW = 50\ kg + 2.3\ kg/inch > 60\ inch\ (Men)$$

$$IBW = 45\ kg + 2.3\ kg/inch > 60\ inch\ (Women)$$

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Table 1. Paclitaxel, carboplatin, and trastuzumab regimen^{3,7,9}

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Paclitaxel	80 mg/m ²	IV	1, 8, 15	240 mg/m ²
Carboplatin	AUC=2	IV	1, 8, 15	AUC=6
Trastuzumab	4 mg/kg	IV	Cycle 1, day 1	4 mg/kg
	2 mg/kg	IV	Cycle 1, day 8, 15	4 mg/kg
	2 mg/kg		Cycle 2+, days 1, 8, 15, 22	8 mg/kg

Cycle repeats: every 28 days

Variations:

1. Sonke et al used paclitaxel 70 mg/m², carboplatin AUC = 3, and trastuzumab 2 mg/kg (loading dose 4 mg/kg) weekly for 24 weeks. In weeks 7, 8, 15, 16, 23, and 24, only trastuzumab was given.⁶
2. Conlin et al used paclitaxel 100 mg/m², carboplatin AUC = 2, and trastuzumab 2 mg/kg (loading dose 4 mg/kg) with the same schedule as the standard regimen for 6 cycles.⁸
3. Sikov et al used weekly paclitaxel 80 mg/m² and trastuzumab 2 mg/kg (loading dose 4 mg/kg) weekly for 16 weeks, carboplatin AUC = 6 every 4 weeks.⁵
4. Yu et al used paclitaxel 175 mg/m², carboplatin AUC = 6, and trastuzumab 6 mg/kg (loading dose 8 mg/kg) every 3 weeks for 4 cycles.⁷
5. Fountzilias et al used paclitaxel 175 mg/m² and carboplatin AUC = 6 every 3 weeks and trastuzumab 2 mg/kg (loading dose 4 mg/kg) weekly for 6 cycles.¹⁰
6. Robert et al used paclitaxel 175 mg/m² and carboplatin AUC = 6 every 3 weeks with weekly trastuzumab 2 mg/kg (loading dose 4 mg/kg) for 6 cycles.¹¹

Note: AUC = area under the time vs 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.^{20,21} The Gynecologic Oncology Group has suggested rounding values less than 0.7 mg/dL up to 0.7 mg/dL.²²
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.¹³ 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.²³

DRUG PREPARATION

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

A. Paclitaxel

1. Use paclitaxel injection 6 mg/mL.
2. Dilute to a concentration of 0.3 to 1.2 mg/mL with 0.9% sodium chloride (NS), 5% dextrose in water (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.

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 sterile water for injection, NS, or D5W.
3. Dilute in 100 to 1000 mL of D5W or NS.
4. Carboplatin is less stable in saline solutions, with up to 5% degradation within 24 hours.²⁴
5. If the drug is prepared in a saline diluent, the solution should be used within 8 hours.

C. Trastuzumab

1. Use trastuzumab powder for injection.
2. Reconstitute with 20 mL bacteriostatic water for injection (BWFI) to a concentration of 21 mg/mL.
3. Dilute in 250 mL NS.
4. Trastuzumab is reported to be incompatible with dextrose solutions.²⁵

5. Solutions diluted in NS are reported to be stable for up to 28 days at room temperature or refrigerated.
6. The manufacturer recommends that diluted solutions be used within 24 hours.²⁶
7. Since the provided diluent (BWFI) contains a preservative, partially used vials may be stored under refrigeration (2°C - 8°C [36°F - 46°F]) for up to 28 days.

DRUG ADMINISTRATION

- A. **Paclitaxel** is administered as an intravenous (IV) infusion over 1 to 3 hours through a non-PVC (low-sorbing) infusion set with a 0.22 micron filter.
- B. **Carboplatin** is usually administered as a 30- to 60-minute IV infusion. Perez et al administered carboplatin as a 15-minute infusion.³
- C. **Trastuzumab**
 1. Trastuzumab is usually administered as an IV infusion over 30 to 90 minutes.
 2. Do not administer as an IV bolus or push.

SUPPORTIVE CARE

- A. The paclitaxel, carboplatin, and trastuzumab regimen is predicted to cause acute emesis in 30% to 90% of patients.²⁷⁻³⁰ The studies reviewed reported mild to moderate (grade 1 or 2) vomiting in 35% of patients and severe vomiting (grade 3) in 5% to 8% of patients.^{3,9} No grade 4 vomiting was reported in any of the studies reviewed.^{3,7,9} Mild nausea (grade 1 or 2) was experienced by 33% of patients, while severe nausea (grade 3 or 4) was experienced by 8% to 13% of patients, respectively.^{3,9}

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.^{31,32} Analysis of urinary 5-hydroxyindole acetic acid (5-HIAA) excretion indicates that 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. Prophylactic antiemetic therapy with a serotonin antagonist is recommended²⁸⁻³⁰ but may not be required in all patients. One group suggests that the addition of a neurokinin (NK₁) antagonist may be appropriate in some patients.²⁸ One of the following regimens given 30 minutes prior to therapy is recommended:

1. Ondansetron 8 mg to 16 mg orally (PO), ±dexamethasone 12 mg PO, given 30 minutes before paclitaxel, carboplatin, and trastuzumab on days 1, 8, and 15.
2. Granisetron 1 mg to 2 mg PO, ±dexamethasone 12 mg PO, given 30 minutes before paclitaxel, carboplatin, and trastuzumab on days 1, 8, and 15.
3. Dolasetron 100 mg PO, ±dexamethasone 12 mg PO, given 30 minutes before paclitaxel, carboplatin, and trastuzumab on days 1, 8, and 15.
4. Palonosetron 0.25 mg IV and dexamethasone 12 mg PO, given 30 minutes before paclitaxel, carboplatin, and trastuzumab on days 1, 8, and 15.

The antiemetic therapy should continue for at least 3 days. A meta-analysis of several trials of serotonin antagonists recommends against prolonged (>24 hours) use of these agents, making a steroid, or steroid and dopamine antagonist combination, most appropriate for follow-up therapy.³³ One of the following regimens is recommended:

1. Dexamethasone 4 mg PO twice a day for 3 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 days 2, 9, and 16 of paclitaxel, carboplatin, and trastuzumab.
2. Dexamethasone 4 mg PO twice a day for 3 days, ±prochlorperazine 10 mg PO every 4 to 6 hours, ±diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on days 2, 9, and 16 of paclitaxel, carboplatin, and trastuzumab.
3. Dexamethasone 4 mg PO twice a day for 3 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 days 2, 9, and 16 of paclitaxel, carboplatin, and trastuzumab.

If a neurokinin antagonist is used, one of the following regimens is recommended:

1. Dexamethasone 4 mg PO twice a day for 3 days, 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 days 2, 9, and 16 of paclitaxel, carboplatin, and trastuzumab.
2. Dexamethasone 4 mg PO twice a day for 3 days, 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 days 2, 9, and 16 of paclitaxel, carboplatin, and trastuzumab.
3. Dexamethasone 4 mg PO twice a day for 3 days, 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 days 2, 9, and 16 of paclitaxel, carboplatin, and trastuzumab.

Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.¹³⁻¹⁶ 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.³⁴⁻³⁸

B. Breakthrough Nausea and Vomiting²⁷⁻³⁰: 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.

C. Hydration: If carboplatin doses are reduced appropriately for diminished renal function (as in AUC dosing), no prophylactic hydration or diuretic use is required.³⁹

D. Hypersensitivity Precautions: Paclitaxel injection produces hypersensitivity reactions in about

10% of patients.⁴⁰ Routine prophylactic premedications should be given prior to paclitaxel administration. One of the following regimens is suggested⁴¹:

1. Ranitidine 150 mg
2. Dexamethasone 10 mg or 20 mg
3. Diphenhydramine 50 mg

All given PO over 30 minutes prior to paclitaxel.

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

All given IV over 30 minutes prior to paclitaxel.

E. Hematopoietic Growth Factors: Accepted practice guidelines and pharmacoeconomic 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.^{42,43}

Since febrile neutropenia (grade 3 or 4) was reported in only 2% of patients in the trials reviewed, prophylactic use of CSFs is not recommended.³ CSFs should be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of paclitaxel, carboplatin, and trastuzumab.

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. Gastrointestinal: Diarrhea (grade 1 or 2) 33%,⁹ (grade 3) 5%⁹; nausea (grade 1 or 2) 33%,⁹

(grade 3) 8%⁹; vomiting (grade 1 or 2) 30%,⁹ (grade 3) 5% to 8%.^{3,9}

B. Hematologic: Anemia (grade 1 or 2) 70%,⁹ (grade 3) 6% to 8%^{3,9}; febrile neutropenia 2%³; leukopenia (grade 3) 27% to 31%^{3,7}; neutropenia (grade 1 or 2) 78%,⁹ (grade 3) 20% to 42%,^{3,7,9} (grade 4) 5% to 10%^{3,7,9}; thrombocytopenia (grade 1 or 2) 10%,⁹ (grade 3) 3% to 4%.^{3,9}

C. Hypersensitivity: (grade 3) 6%.³

D. Miscellaneous: Dehydration (grade 3) 2%³; fatigue (grade 3) 17%³; mucositis (grade 1 or 2) 30%,⁹ (grade 3) 8%.⁹

E. Neuromuscular and skeletal: Arthralgia (grade 3) 8%,³ asthenia (grade 1 or 2) 38%,⁹ (grade 3) 5%,⁹ myalgia (grade 3) 4%,³ neuropathy (grade 1 or 2) 43%,⁹ neurosensory (grade 3) 2%.³

F. Respiratory: Dyspnea (grade 3) 6%.³

PRETREATMENT LABORATORY STUDIES NEEDED

A. Baseline

1. Aspartate aminotransferase/alanine aminotransferase (AST/ALT)
2. Total bilirubin
3. Serum creatinine
4. Complete blood count (CBC) with differential

B. Prior to Each Treatment

1. 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. Hemoglobin: Greater than or equal to 10 g/dL.^{7,9}
2. Absolute neutrophil count (ANC): Greater than or equal to 1,500 cells/mcL.^{3,7,9}
3. Platelet count: Greater than or equal to 100,000 cells/mcL.^{3,7,9}
4. Serum creatinine:
 - a. Less than or equal to 1.5 times the upper limit of normal (ULN).³
 - b. Less than 110 micromol/L.⁷
 - c. Creatinine clearance greater than or equal to 65 mL/min.⁹
5. Serum bilirubin:
 - a. Greater than or equal to 1.25 times the ULN.⁹
 - b. Greater than or equal to 1.5 times the ULN.^{3,7}

6. AST/ALT:

- a. Less than 1.5 times the ULN.⁷
- b. Less than 2.5 times the ULN.⁹
- c. Less than or equal to 3 times the ULN.³
- d. Less than 5 times the ULN in patients with hepatic involvement.³

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. Paclitaxel: No adjustment is required.^{44,45}
2. Carboplatin:
 - a. Use a pharmacokinetic formula to calculate the dose.⁴⁵
 - b. CrCl: If the dose is based on body surface area rather than a pharmacokinetic formula:⁴⁶
 - 1) Less than or equal to 50 mL/min and greater than or equal to 10 mL/min, reduce dose by 50%.
 - 2) Less than 10 mL/min, reduce dose by 75%.

B. Liver Function

1. Paclitaxel:
 - a. Bilirubin less than 1.5 mg/dL and/or ALT/AST greater than 2 times the ULN, reduce the dose by 25%.^{47,48}
 - b. Bilirubin greater than or equal to 1.6 mg/dL and less than or equal to 3 mg/dL, reduce dose by 60%.^{47,48}
 - c. Bilirubin greater than 3 mg/dL, reduce dose by 75%.^{47,48}
 - 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.⁴⁴
2. Carboplatin: No adjustment is required.⁴⁴

C. Myelosuppression

1. ANC less than 1,500 cells/mcL or platelet count less than 100,000 cells/mcL, delay treatment for a maximum of 2 weeks.⁹
2. Grade 4 neutropenia, grade 3 or 4 febrile neutropenia or sepsis and grade 4 thrombocytopenia, maximum of 2 dose reductions allowed.³
 - a. Paclitaxel: Reduce dose from 80 mg/m² to 70 mg/m² and then to 60 mg/m².
 - b. Carboplatin: Reduce dose from an AUC of 2 mg/mL per minute to 1 mg/mL per minute and then discontinue.

3. Grade 4 febrile neutropenia, grade 4 neutropenia lasting more than 5 days, or grade 4 thrombocytopenia (grade 3 if evidence of bleeding), 2 dose reductions allowed.⁹
 - a. Paclitaxel: Initially reduce dose by 25% and then by 20% if the patient is experiencing a second toxicity but still benefiting from the regimen.
 - b. Carboplatin: Initially reduce dose by 25% and then by 20% if the patient is experiencing a second toxicity but still benefiting from the regimen.

D. Other

1. Grade 3 or 4 arthralgia or myalgia, and grade 2 through 4 neuropathy, maximum of 2 dose reductions allowed.⁹
 - a. Paclitaxel: Reduce dose from 80 mg/m² to 70 mg/m², and then to 60 mg/m².
2. Grade 3 or 4 nonhematological toxicity, or grade 2 cardiac toxicity:⁹
 - a. Paclitaxel: Reduce dose by 25%.
 - b. Carboplatin: Reduce dose by 25%.

REFERENCES

1. Fountzilas G, Dimopoulos AM, Papadimitriou C, et al. First-line chemotherapy with paclitaxel by three-hour infusion and carboplatin in advanced breast cancer (final report): A phase II study conducted by the Hellenic Cooperative Oncology Group. *Ann Oncol*. 1998;9(9):1031-1034.
2. Loesch D, Robert N, Asmar L, et al. Phase II multicenter trial of a weekly paclitaxel and carboplatin regimen in patients with advanced breast cancer. *J Clin Oncol*. 2002;20(18):3857-3864.
3. Perez E, Suman V, Rowland K, et al. Two concurrent phase II trials of paclitaxel/carboplatin/trastuzumab (weekly or every-3-week schedule) as first-line therapy in women with HER2-overexpressing metastatic breast cancer: NCCTG study 983252. *Clin Breast Cancer*. 2005;6(5):425-432.
4. Pegram MD, Lipton A, Hayes DF, et al. Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/neu monoclonal antibody plus cisplatin in patients with HER2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment. *J Clin Oncol*. 1998;16(8):2659-2671.
5. Sikov WM, Dizon DS, Strenger R, et al. Frequent pathologic complete responses in aggressive stages II to III breast cancers with every-4-week carboplatin and weekly paclitaxel with or without trastuzumab: A Brown University Oncology Group Study. *J Clin Oncol*. 2009;27(28):4693-700.
6. Sonke G, Mandjes I, Holtkamp M, et al. Paclitaxel, carboplatin, and trastuzumab in a neo-adjuvant regimen for HER2-positive breast cancer. *Breast J*. 2013;19(4):419-426.
7. Yu K, Liu G, Chen C, et al. Weekly paclitaxel/carboplatin/trastuzumab therapy improves pathologic complete remission in aggressive HER2-positive breast cancers, especially in luminal-B subtype, compared with a once-every-3-weeks schedule. *Oncologist*. 2013;18(5):511-517.
8. Conlin AK, Seidman AD, Bach A, et al. Phase II trial of weekly nanoparticle albumin-bound paclitaxel with carboplatin and trastuzumab as first-line therapy for women with HER2-overexpressing metastatic breast cancer. *Clin Breast Cancer*. 2010;10(4):281-287.
9. Ruiz M, Salvador J, Bayo J, et al. A phase-II study of weekly schedule of trastuzumab, paclitaxel, and carboplatin followed by a week off every 28 days for HER2+ metastatic breast cancer. *Cancer Chemother Pharmacol*. 2008;62(6):1085-1090.
10. Fountzilas G, Dafni U, Dimopoulos M, et al. A randomized phase III study comparing three anthracycline-free taxane-based regimens, as first line chemotherapy, in metastatic breast cancer: A Hellenic Cooperative Oncology Group study. *Breast Cancer Res Treat*. 2009;115(1):87-99.
11. Robert N, Leyland Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2006;24(18):2786-2792.
12. NCCN Clinical Practice Guidelines in Oncology – Breast Cancer. V.2.2014. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed March 30, 2014.
13. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. *J Clin Oncol*. 1989;7(11):1748-56.
14. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
15. Cathomas R, Harle A, Mead GM, et al. Glomerular filtration rate (GFR) in patients with stage I testicular seminoma treated with adjuvant carboplatin: A comparison of six formulae compared to a radioisotope gold standard. *J Clin Oncol*. 2007;25(18 suppl):abstract 15504.
16. Boumedien F, Arsenault Y, LeTarte N. Impact of weight and creatinine measurements in carboplatin dosing. *J Clin Oncol*. 2012;30(15 suppl):abstract e13027.
17. Ekhardt C, Rodenhuis S, Schellens JHM, Beijnen JH, Huitema ADR. Carboplatin dosing in overweight and obese patients with normal renal function. Does weight matter? *Cancer Chemother Pharmacol*. 2009;64(1):115-122.
18. Herrington JD, Tran HT, Riggs MW. Prospective evaluation of carboplatin AUC dosing in patients with a BMI ≥ 27 or cachexia. *Cancer Chemother Pharmacol*. 2006;57(2):241-247.
19. Devine BJ. Gentamycin therapy. *Drug Intell Clin Pharm*. 1974;8:650-655.
20. Kaag D. Carboplatin dose calculation in lung cancer patients with low serum creatinine concentrations using

CKD-EPI and Cockcroft-Gault with different weight descriptors. *Lung Cancer*. 2013;79(1):54-58.

21. Herrington JD, Tran HT, Riggs MW. Prospective evaluation of carboplatin AUC dosing in patients with a BMI $\geq$ 27 or cachexia. *Cancer Chemother Pharmacol*. 2006;57(2):241-247.

22. O'Cearbhaill R. New guidelines for carboplatin dosing. *Gyn Oncol Group Newsletter*. 2012;(Spring issue):5-6.

23. US Food and Drug Administration. Hematology/oncology (cancer) approvals & safety notifications 2010: Carboplatin dosing. US Food and Drug Administration Web site. <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductandTobacco/CDER/ucm228974.htm>. Accessed April 14, 2014.

24. Cheung YW, Craddock JC, Vishnuvajjala BR, Flora KP. Stability of cisplatin, iproplatin, carboplatin, and tetraplatin in commonly used intravenous solutions. *Am J Health Syst Pharm*. 1987;44(1):124-130.

25. Kaiser J, Kramer I. Physicochemical stability of diluted trastuzumab infusion solutions in polypropylene infusion bags. *Int J Pharmaceut Compound*. 2011;15:515-520.

26. *Herceptin* [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2013.

27. Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol*. 1997;15(1):103-109.

28. NCCN Clinical Practice Guidelines - Antiemesis. V.1.2014. http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed March 31, 2014.

29. American Society of Clinical Oncology. Antiemetics: ASCO clinical practice guideline update. <http://www.asco.org/institute-quality/antiemetics-asco-clinical-practice-guideline-update>. Accessed April 10, 2014.

30. Multinational Association for Supportive Care in Cancer. Antiemetic guidelines. 2013. http://www.mascc.org/assets/documents/mascc_guidelines_english_2013.pdf. Accessed: April 10, 2014.

31. Martin M. The severity and pattern of emesis following different cytotoxic agents. *Oncology*. 1996;53(Suppl 1):26-31.

32. DuBois A, Vach W, Kiechle M, Cramer-Giraud U, Meerpohl HG. Pathophysiology, severity, pattern, and risk factors for carboplatin-induced emesis. *Oncology* 1996;53(Suppl 1):26-31.

33. Geling O, Eichler HG. Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications. *J Clin Oncol*. 2005;23(6):1289-1294.

34. Terrey JP, Aapro MS. The activity of granisetron in patients who had previously failed ondansetron antiemetic therapy. *Eur J Clin Res*. 1996;8:281-288.

35. Carmichael J, Keizer HJ, Cupissol D, Milliez J, Scheidel P, Schindler AE. Use of granisetron in patients refractory to previous treatment with antiemetics. *Anticancer Drugs*. 1998;9(5):381-385.

36. de Wit R, de Boer AC, vd Linden GH, Stoter G, Sparreboom A, Verweij J. Effective cross-over to granisetron after failure to ondansetron, a randomized double blind study in patients failing ondansetron plus dexamethasone during the first 24 hours following highly emetogenic chemotherapy. *Br J Cancer*. 2001;85(8):1099-1101.

37. Smith IE. A dose-finding study of granisetron, a novel antiemetic, in patients receiving cytostatic chemotherapy. The Granisetron Study Group. *J Cancer Res Clin Oncol*. 1993;119(6):350-354.

38. Soukop M. A dose-finding study of granisetron, a novel antiemetic, in patients receiving high-dose cisplatin. Granisetron Study Group. *Support Care Cancer*. 1994;2(3):177-183.

39. Cornelison TL, Reed E. Nephrotoxicity and hydration management for cisplatin, carboplatin, and ormaplatin. *Gynecol Oncol*. 1993;50(2):147-158.

40. Weiss RB, Donehower RC, Wiernik PH, et al. Hypersensitivity reactions from Taxol. *J Clin Oncol*. 1990;8(7):1263-1268.

41. Bookman MA, Kloth DD, Kover PE, Smolinski S, Ozols RF. Intravenous prophylaxis for paclitaxel-related hypersensitivity reactions. *Semin Oncol* 1997;24(19 Suppl):S19-13-S19-15.

42. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 Update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. *J Clin Oncol*. 2006;24(19):3187-3205.

43. NCCN Clinical Practice Guidelines in Oncology - Myeloid Growth Factors. V.1.2014. http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf. Accessed April 11, 2014.

44. Boyiadzis MM, Lebowitz PF, Frame JN, Fojo T. *Hematology-Oncology Therapy*. New York: McGraw-Hill; 2007: 570-578.

45. Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: Dosing guidelines for altered renal function. *Cancer Treat Rev*. 1995;21(1):33-64.

46. Aronoff GR, Bennett WM, Berns JS, Brier ME, Kasbekar N, Mueller BA, Pasko DA, Smoyer WE. *Drug Prescribing in Renal Failure*. 5th ed. Philadelphia: American College of Physicians; 2007.

47. Floyd J, Mirza I, Sachs, Perry MC. Hepatotoxicity of chemotherapy. *Semin Oncol*. 2006;33(1):50-67.

48. King PD, Perry MC. Hepatotoxicity of chemotherapy. *Oncologist*. 2001;6(2):162-176. ■