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Cancer Chemotherapy Update

Carboplatin and Liposomal Doxorubicin 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: Carboplatin plus PLD (pegylated liposomal doxorubicin), CD

Origin of name: The regimen is named for the 2 drugs it contains: **c**arboplatin and pegylated liposomal **d**oxorubicin. PLD is the acronym for pegylated liposomal doxorubicin, often shortened to liposomal doxorubicin.

COMMENTS

Patients who relapse at greater than 6 months after chemotherapy treatment are good candidates for re-treatment with platinum-taxane combinations; however, these patients are also at a higher risk for developing adverse events such as neuropathy due to cumulative paclitaxel doses.[1] The use of carboplatin plus liposomal doxorubicin (PLD) in ovarian cancer was intended to decrease toxicities such as neurotoxicity, myelotoxicity, alopecia, and cardiotoxicity while demonstrating similar efficacy to carboplatin and paclitaxel.[1,2] The regimen has demonstrated comparative efficacy to carboplatin and paclitaxel with lower incidences of neuropathy and carboplatin hypersensitivity.[1-3]

INDICATIONS

The CD regimen has been studied primarily for initial therapy of relapsed, platinum-sensitive ovarian cancer.[1-16] It has also been studied as first-line therapy for newly diagnosed ovarian cancer[2,17] and as second-line therapy for relapsed ovarian cancer.[3] Current guidelines list the CD combination for platinum-sensitive patients with recurrence occurring later than 6 months after completion of initial chemotherapy.[18]

CARBOPLATIN DOSE CALCULATION

Carboplatin doses are commonly calculated using an equation based on the method of Calvert et al.[19] 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 method[20] 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.[21,22]
2. If the patient is overweight or obese (BMI ≥25), an adjusted body weight (ABW) should be used.[23,24] Although a number of different formulae for

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Table 1. Carboplatin plus pegylated liposomal doxorubicin regimen[1,3-5,8,10,12-17]

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Liposomal doxorubicin	30 mg/m^2	IV	1	30 mg/m^2
Carboplatin	AUC = 5	IV	1	AUC = 5
Cycle repeats every 28 days				

Variations

1. Pignata et al. used the above regimen, but reduced the cycle interval to every 3 weeks for 6 cycles.[2]
2. Liposomal doxorubicin 40 mg/m^2 and carboplatin AUC = 6 every 4 weeks.[6]
3. Liposomal doxorubicin 40 mg/m^2 and carboplatin AUC = 5 or 6 every 4 weeks.[8]
4. Liposomal doxorubicin 50 mg/m^2 and carboplatin AUC = 5 every 4 weeks.[10]
5. Liposomal doxorubicin 45 mg/m^2 and carboplatin AUC = 5 every 4 weeks.[12]

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

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 as[25]:
IBW = 50 kg + 2.3 kg/inch >60 inch (Men)
IBW = 45.5 kg + 2.3 kg/inch >60 inch (Women)

3. If the patient has a serum creatinine less than 0.8 mg/dL, round the serum creatinine up to 0.8 mg/dL.[24,26] The Gynecologic Oncology Group has suggested rounding values less than 0.7 mg/dL up to 0.7 mg/dL.[27]
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.[19] 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.[28]

DRUG PREPARATION

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

A. Liposomal Doxorubicin

1. Use liposomal doxorubicin injection (2 mg/mL).
2. Doses of 90 mg or less should be diluted in 250 mL of 5% dextrose in water (D5W).
3. Doses exceeding 90 mg should be diluted in 500 mL of D5W.
4. Do not:
   a. Mix in diluents other than D5W.
   b. Mix in diluents containing preservatives.
   c. Filter.
5. Solutions diluted for administration:
   a. Should be used within 24 hours of preparation.
   b. Solutions diluted for infusion may be stored under refrigeration [2°C to 8°C (36°F to 46°F)] for up to 24 hours.

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 (SWFI), D5W, or 0.9% sodium chloride (NS).
3. Dilute with 100 to 1,000 mL of D5W, NS, or a dextrose-saline solution.
4. Carboplatin has been reported to be less stable in saline solutions, with up to 10% degradation within 24 hours.[29] A recent report indicates it is stable for at least 7 days in saline solutions.[30]

DRUG ADMINISTRATION

A. Pegylated liposomal doxorubicin is administered as an intravenous infusion over 1 hour.

B. Carboplatin

1. Is administered intravenously, usually as a 30- to 60-minute infusion.
2. One study infused it over a minimum of 15 minutes.[4]
3. In most of the CD studies that stated the order in which the drugs were infused, the carboplatin was administered after the liposomal doxorubicin.[3,5-11]

4. The liposomal doxorubicin was administered after the carboplatin in 2 of the trials reviewed.[2,17]

SUPPORTIVE CARE

A. Acute and Delayed Emesis Prophylaxis The carboplatin plus PLD regimen is predicted to cause acute emesis in 30% to 90% of patients.[31-34] The studies reviewed reported nausea in 28% to 86% and vomiting in 43% to 49% of patients.[1,3-5,8,10,14,16] Severe (grade 3 or 4) nausea or vomiting was reported in 3% to 10% of patients.[3-5,8,10,14,16] Prophylactic antiemetic therapy with a serotonin antagonist and a corticosteroid is recommended. One of the following regimens given 30 minutes prior to PLD is recommended for acute emesis prophylaxis.[31-34]

1. Ondansetron 16 mg to 24 mg orally (PO) and dexamethasone 12 mg PO ± 125 mg aprepitant PO, given 30 minutes before CD on day 1.
2. Granisetron 1 mg to 2 mg PO and dexamethasone 12 mg PO ± 125 mg aprepitant PO, given 30 minutes before CD on day 1.
3. Dolasetron 100 mg or 200 mg PO and dexamethasone 12 mg PO ± 125 mg aprepitant PO, given 30 minutes before CD on day 1.
4. Palonosetron 0.25 mg IV and dexamethasone 12 mg PO ± 125 mg aprepitant PO, given 30 minutes before CD on day 1.

Antiemetic therapy should continue for at least 2 additional 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.[35] If a neurokinin antagonist is used on day 1, then aprepitant 80 mg PO once daily for 2 days should be added to one of the regimens above, starting on day 2. One of the following regimens is recommended:

1. Dexamethasone 8 mg PO once daily for 2 days, aprepitant 80 mg PO every morning for 2 days, ± metoclopramide 0.5 to 2 mg/kg PO every 4 to 6 hours as needed, ± diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of CD.
2. Dexamethasone 8 mg PO once daily for 2 days, aprepitant 80 mg PO every morning for 2 days, ± prochlorperazine 10 mg PO every 4 to 6 hours as needed, ± diphenhydramine 25 to 50 mg PO every 6 hours if needed starting on day 2 of CD.
3. Dexamethasone 8 mg PO once daily for 2 days, aprepitant 80 mg PO every morning for 2 days, ± promethazine 25 to 50 mg PO every 4 to 6 hours as needed, ± diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of CD.

Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacological category.[31-34] 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.[36-40]

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.[41,42] 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.

B. Breakthrough Nausea and Vomiting[31-34]: 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, ± 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.

Prophylactic use of a neurokinin (NK1) antagonist may be added for moderately emetogenic regimens if a serotonin antagonist and steroid combination was not effective in the previous treatment cycle.

C. Hydration: If carboplatin doses are reduced appropriately for diminished renal function (as

in AUC dosing), no prophylactic hydration or diuretic use is required.[43]

D. **Hypersensitivity Precautions**
   1. Pegylated liposomal doxorubicin: Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with liposomal doxorubicin.[44,45] In most patients, these reactions resolve over the course of several hours once the infusion is terminated. Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.[44,45]
   2. Carboplatin: Hypersensitivity reactions to carboplatin are reported in up to 12% of patients. The median number of platinum (carboplatin or cisplatin) courses when the first episode occurred was 8 (range, 6-21). When 3 of these patients were rechallenged with carboplatin 1 month later following premedication with diphenhydramine and dexamethasone, 2 of the patients again experienced hypersensitivity reactions. Patients who experience hypersensitivity reactions to carboplatin should receive a prophylactic steroid and antihistamine prior to subsequent cycles.[46] For severe or repeated reactions, desensitization to carboplatin may be done.[47,48]

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.[49] 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.[49,50] Since febrile neutropenia was reported in 2% to 10% of patients in the trials reviewed,[1,3,4,10,14,16] prophylactic use of CSFs is not recommended. CSFs should be considered if a patient develops febrile neutropenia grade 4 in a prior cycle of CD.[49,50]

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, 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:** Arrythmia (grade 2) 2%,[10] (grade 3 or 4) 1%[10]; unspecified cardiac reactions 11%,[1] (grade 2) 2%,[14] (≥grade 2) 7%,[1] (grade 3 or 4) 1%.[14]

B. **Central Nervous System:** Anxiety (grade 3 or 4) 3%.[5]

C. **Constitutional:** Asthenia (grade 1) 26%,[3] (grade 2) 33% to 37%,[3,10] (grade 3) 8%,[3] (grade 3 or 4) 5%[10]; fatigue 49% to 78%,[1,5] (grade 2) 30% to 32%,[14,16] (≥grade 2) 37%,[1] (grade 3) 2%,[8] (grade 3 or 4) 3% to 9%,[5,14,16] (grade 4) 2%[8]; fatigue/malaise/lethargy (grade 3) 10%.[4]

D. **Dermatologic:** Alopecia 3% to 34%,[1,5] (grade 1) 21%,[3] (grade 2) 3% to 16%[3,8,10,14,16]; (≥grade 2) 7%,[1] (grade 4) 11%[13]; rash 14%.[5]

E. **Endocrine/Metabolic:** Hypokalemia (grade 3) 2%,[8] (grade 4) 2%[8]; hypomagnesemia (grade 3) 3%[4,8]; hyponatremia (grade 3) 3%.[4]

F. **Gastrointestinal:** Anorexia (grade 3) 3%[8]; asitia 63%,[5] (grade 3 or 4) 3%[5]; constipation 26% to 55%,[1,5] (grade 1) 11%,[3] (grade 2) 12% to 21%,[3,10,14,16] (≥grade 2) 22%,[1] (grade 3) 10%[8]; (grade 3 or 4) 2% to 3%[14,16]; constipation/bowel obstruction (grade 3) 6%[4]; diarrhea 11% to 23%,[1,5] (grade 1) 9%,[3] (grade 2) 3% to 5%,[3,10,14,16] (≥grade 2) 5%,[1] (grade 3) 2%,[8] (grade 3 or 4) 1% to 3%[5,10,14,16]; mucositis 39%,[1] (grade 1) 10%,[3] (grade 2) 8% to 15%,[3,14,16] (≥grade 2) 14%,[1] (grade 3) 4%,[3] (grade 3 or 4) 2%[14,16]; nausea 78% to 86%,[1,5] (grade 2) 28% to 32%,[14,16] (≥grade 2) 35%,[1] (grade 3) 3% to 6%,[4,8] (grade 3 or 4) 3% to 8%[5,14,16]; nausea/vomiting (grade 1) 28%,[3] (grade 2) 25% to 29%,[3,10] (grade 3) 3% to 7%[3,4]; stomatitis 54%,[5] (grade 2) 25%,[10]

(grade 3) 2%[8]; vomiting 43% to 49%,[1,5] (grade 2) 15% to 20%,[14,16] (≥grade 2) 23%,[1] (grade 3) 3%,[8] (grade 3 or 4) 3% to 10%.[5,10,14,16]

G. Hematologic: Anemia 66% to 97%,[1,5] (grade 2) 28% to 40%,[14,16] (grade 3) 7% to 16%,[4,8] (grade 3 or 4) 3% to 17%[1,3,5,10,13,14,16]; bleeding (grade 3 or 4) 1%[1,14]; febrile neutropenia (grade 3) 10%,[4] (grade 3 or 4) 2% to 4%[1,3,10,14,16]; leukopenia 100%,[5] (grade 2) 48%,[16] (grade 3) 3% to 26%,[4,8] (grade 3 or 4) 8% to 46%,[3,5,10,16] (grade 4) 3%[4]; neutropenia 80% to 91%,[1,5] (grade 2) 26% to 27%,[14,16] (grade 3) 21% to 29%,[4,8] (grade 3 or 4) 27% to 83%,[1,3,5,10,13,14,16] (grade 4) 19%[4]; thrombocytopenia 38% to 97%,[1,5] (grade 2) 8% to 16%,[14,16] (grade 3) 10% to 29%,[4,8] (grade 3 or 4) 12% to 51%,[1,3,5,10,13,14,16] (grade 4) 7% to 10%.[4,8]

H. Hepatic: Ascites (grade 3) 5%.[8]

I. Hypersensitivity: 6% to 16%,[1,5] (grade 2) 1% to 7%,[10,14,16] (≥grade 2) 6%[1]; (grade 2 to 3) 4%,[13] (grade 3) 2% to 3%[3,8]; (grade 3 to 4) 3%.[14,16]

J. Infection: 20%,[1] (grade 1) 5%,[3] (grade 2) 11% to 18%,[3,14,16] (grade 3) 2%[3]; (grade 3 or 4) 3% to 5%[1,10,14,16]; catheter-related (grade 3) 3%[4]; with grade 3 or 4 neutropenia (grade 3) 6%[4]; respiratory (grade 3) 3%.[4]

K. Musculoskeletal: Arthralgia/myalgia 22%,[1] (grade 2) 4% to 5%,[14,16] (≥grade 2) 4%,[1] (grade 2 to 3) 3%,[13] (grade 3 or 4) 1%.[16]

L. Neurologic: Motor neuropathy 7%,[1] (grade 2) 2%,[14,16] (≥grade 2) 2%,[1] (grade 3 or 4) 1%,[16] palmar-plantar erythrodysesthesia 39% to 46%,[1,5] (grade 1) 21%,[3] (grade 2) 10% to 16%,[3,10,14] (≥grade 2) 12%,[1] (grade 2 to 3) 14%,[13] (grade 3) 2% to 5%,[4,8,16] (grade 3 or 4) 1% to 2%[10,14,16]; sensory neuropathy 40%,[1] (grade 2) 2% to 4%,[14,16] (≥grade 2) 5%,[1] (grade 2 to 3) 10%[13]; (grade 3 or 4) 2%,[16] unspecified neuropathy 17%,[5] (grade 1) 21%,[3] (grade 2) 6% to 9%,[3,10] (grade 3) 1%.[3]

M. Pain: Abdominal pain (grade 3) 14%[8]; abdominal pain/craping (grade 3) 3%[4]; unspecified (grade 2) 11%,[16] (grade 3 or 4) 3%.[16]

N. Pulmonary: Dyspnea (grade 3) 3%.[4]

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
5. EKG
6. Left ventricular ejection fraction (LVEF)

B. Prior to Each Treatment

1. CBC with differential
2. Serum creatinine

C. Recommended Pretreatment Values: The minimally acceptable pretreatment laboratory values required to begin a cycle with full dose therapy in the studies reviewed were:

1. White blood cell count (WBC):
   a. Greater than 3,000 to 12,000 cells/mcL.[2,5]
   b. Greater than 4,000 cells/mcL.[3]
2. Absolute neutrophil count (ANC): Greater than 1,500 cells/mcL.[2,4,5]
3. Granulocyte count: Greater than 1,500 cells/mcL.[5]
4. Platelet count:
   a. Greater than equal to 100,000 cells/mcL.[2,4]
   b. Greater than equal to 75,000 cells/mcL.[5]
5. Hemoglobin: Greater than or equal to 10 g/dL.[4,5]
6. Serum creatinine:
   a. Less than or equal to 1.9 mg/dL.[4]
   b. Less than or equal to 1.5 times the upper limit of normal (ULN).[5]
   c. Less than or equal to 1.25 times the ULN.[3]
7. Serum bilirubin:
   a. Less than or equal to the ULN.[4]
   b. Less than or equal to 1.25 times the ULN.[3]
8. AST/ALT:
   a. Less than equal to 2 times the ULN.[4,5]
   b. Less than equal to 5 times the ULN with liver metastases.[3]
9. Alkaline phosphatase: Less than equal to 2 times the ULN.[4,5]
10. Left ventricular ejection fraction (LVEF): Greater than or equal to 50% measurement by echocardiogram if cumulative anthracycline dose exceeded 450 mg/m^2.[1,5]

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. Liposomal doxorubicin: No adjustment required.[51]
2. Carboplatin: Use a pharmacokinetic formula to calculate dosage.[52-54]

3. Creatinine clearance less than 60 mL/min, reduce carboplatin dose to AUC = 4.[14]

B. Liver Function

1. Liposomal doxorubicin: For bilirubin[51]:
   a. Greater than or equal to 1.2 mg/dL and less than or equal to 3 mg/dL, reduce dose 50%.
   b. Greater than 3 mg/dL, reduce dose 75%.
2. Carboplatin: No information available.[54]

C. Cardiotoxicity

1. Liposomal doxorubicin
   a. For LVEF:
      (1) less than 45%, do not give the drug.[4]
      (2) decreased greater than 5% to 20% from baseline, do not give the drug.[4,5]
      (3) any absolute decrease by 15%, eliminate from treatment.[5]
   b. For symptomatic arrhythmia or congestive heart disease, do not give the drug.[4,5]

D. Dermatologic Toxicity

1. Liposomal doxorubicin:
   a. Delay the dose 2 to 4 weeks for skin toxicity grade 2 or higher.[4]
   b. Reduce the dose by 25% for grade 3 or 4 skin toxicity that resolves to grade 1 or 2 within 2 to 4 weeks.[4]

E. Myelosuppression

1. Liposomal doxorubicin:
   a. Reduce dose to 25 mg/m^2 for[1,3]:
      (1) grade 4 neutropenia
      (2) febrile neutropenia
      (3) granulocyte count less than 500/mcL for greater than or equal to 7 days
      (4) granulocyte count less than 1,000/mcL for greater than or equal to 3 days
      (5) thrombocytopenia
      (6) severe bleeding.
   b. Hold dose until full recovery for[1]:
      (1) prolonged neutropenia
      (2) thrombocytopenia up to 14 days.
   c. Neutrophils less than 1,500 cells/mcL or platelets less than 50,000 cells/mcL for more than 7 days, reduce the dose of both drugs 20%.[17]
2. Carboplatin[1,3]:
   a. Reduce dose to AUC 4 for:
      (1) neutropenia
      (2) febrile neutropenia
      (3) thrombocytopenia
      (4) severe bleeding.

F. Neuropathy

1. Carboplatin: If peripheral neuropathy persists despite dose reduction, do not give the drug.[4]
2. Liposomal doxorubicin[17]:
   a. Palmar-plantar erythrodysesthesia
      (1) greater than or equal to grade 2, delay therapy for up to 2 weeks.
      (2) grade 3 or 4 that does not resolve in 2 weeks, reduce the dose 25%.

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