Cancer Chemotherapy Update

Nab-Paclitaxel and Carboplatin (Nab-PC) Regimen for Advanced 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: Nab-Paclitaxel and Carboplatin

Synonym: Nab-PC

Origin of Name: Nab-PC is an acronym for the 2 medications in the regimen: nab-paclitaxel and car-boplatin.

INDICATIONS

The nab-PC regimen has been studied in advanced non-small-cell lung cancer (NSCLC).¹⁻⁶ Current guidelines recommend the nab-PC regimen as first-line therapy in patients with advanced NSCLC and good performance status (Table 1).⁷

CARBOPLATIN DOSE CALCULATION

Carboplatin doses are commonly calculated using an equation based on the method of Calvert et al.⁸ 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 method⁹ 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.^{10,11}
2. If the patient is overweight or obese (BMI ≥ 25), an adjusted body weight (ABW) should be used.^{12,13} 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 as¹⁴: 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.^{15,16} The Gynecologic Oncology Group has suggested rounding values less than 0.7 mg/dL up to 0.7 mg/dL.¹⁷
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

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Table 1. Nab-paclitaxel and carboplatin (nab-PC) regimen¹⁻⁶

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Nab-paclitaxel	100 mg/m ²	IV	1, 8, 15	300 mg/m ²
Carboplatin	AUC 6	IV	1	AUC 6

Cycle repeats every 21 days.

Variations:

1. Nab-paclitaxel 225 mg/m² and carboplatin AUC 6 given on day 1 of a 21-day cycle.⁴
2. Nab-paclitaxel 260 mg/m² and carboplatin AUC 6 given on day 1 of a 21-day cycle.⁴
3. Nab-paclitaxel 300 mg/m² and carboplatin AUC 6 given on day 1 of a 21-day cycle.⁴
4. Nab-paclitaxel 340 mg/m² and carboplatin AUC 6 given on day 1 of a 21-day cycle.⁴
5. Nab-paclitaxel 140 mg/m² on day 1 and 8, and carboplatin AUC 6 on day 1 of a 21-day cycle.⁴
6. Nab-paclitaxel 100 mg/m² on day 1, 8, and 15, and carboplatin AUC 6 on day 1 of a 21-day cycle.⁴
7. Nab-paclitaxel 125 mg/m² on day 1, 8, and 15, and carboplatin AUC 6 on day 1 of a 21-day cycle.⁴

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

measured GFRs as high as 180 mL/min and used measured GFRs up to 136 mL/min to calculate carboplatin doses.⁸ 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.¹⁸

DRUG PREPARATION

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

A. Nab-paclitaxel

1. Use nab-paclitaxel powder for injection.
2. Reconstitute the lyophilized powder with 0.9% sodium chloride injection (NS) to a concentration of 5 mg/mL.
 - a. To prevent foaming, avoid rapid injection of fluid or vigorous shaking of the vial.
 - b. Allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake.
 - c. Gently swirl and/or invert the vial slowly until the particles are evenly dispersed.
3. Dispense in an empty, sterile intravenous (IV) bag.

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), 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.¹⁹
5. If the drug is prepared in a saline diluent, the solution should be used within 8 hours.

DRUG ADMINISTRATION

A. Nab-paclitaxel

1. The manufacturer recommends the drug be given as a 30- to 40-minute IV infusion.
2. Infusion over 30 minutes has been associated with grade 3 or 4 peripheral neuropathy. Administering the drug over 2 hours has been shown to decrease the average severity of grade 2 or greater peripheral neuropathy without affecting survival.²⁰

B. Carboplatin: Administer by IV infusion over 30 to 60 minutes.

SUPPORTIVE CARE

A. Acute and Delayed Emesis Prophylaxis: The nab-PC regimen is predicted to cause vomiting in 30% to 90% of patients on day 1 and in 10% to 30% of patients on day 8 and day 15.²¹⁻²³ The studies reviewed reported nausea in 24% to 68%¹⁻³ of patients, grade 3 to 4 nausea in less than 1% to 11%^{1-3,5,6} of patients, and vomiting in 33% of patients.¹ Appropriate acute emesis prophylaxis includes a serotonin antagonist and a corticosteroid plus or minus a neurokinin antagonist in selected patients.²¹⁻²³ One of the following regimens is suggested:

1. Ondansetron 16 to 24 mg and dexamethasone 12 mg orally (PO) $\pm$ aprepitant 125 mg PO 30 minutes before day 1 of nab-PC.
2. Granisetron 1 mg to 2 mg and dexamethasone 12 mg PO $\pm$ aprepitant 125 mg PO 30 minutes before day 1 of nab-PC.
3. Dolasetron 100 mg and dexamethasone 12 mg PO $\pm$ aprepitant 125 mg PO 30 minutes before day 1 of nab-PC.
4. Palonosetron 0.25 mg IV and dexamethasone 12 mg PO $\pm$ aprepitant 125 mg PO 30 minutes before day 1 of nab-PC.

On day 8 and day 15, one of the following pre-medications is suggested: dexamethasone 8 to 12 mg PO^{21,22} or metoclopramide 10 to 40 mg PO^{21,23} or prochlorperazine 10 mg PO.^{21,23} A single dose of an oral serotonin antagonist may also be considered.^{21,23}

The antiemetic therapy should continue for at least 2 days after day 1. A meta-analysis of several trials of serotonin antagonists recommends against prolonged (greater than 24 hours) use of these agents, making a steroid or a steroid and dopamine antagonist combination most appropriate for follow-up therapy.²⁴ One of the following regimens is suggested:

1. Dexamethasone 8 mg PO once daily for 2 days, $\pm$ 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 day 2 of nab-PC.
2. Dexamethasone 8 mg PO once daily 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 day 2 of nab-PC.
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 nab-PC.

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

- B. Breakthrough Nausea and Vomiting²¹⁻²³:** 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.

- C. Hematopoietic Growth Factors:** Accepted practice guidelines and pharmacoeconomic analysis suggest that antineoplastic regimens have a greater than 20% incidence of febrile neutropenia before prophylactic use of colony stimulating factors (CSF) is warranted. For regimens with an incidence of febrile neutropenia between 10% and 20%, use of CSF should be considered. For regimens with an incidence of febrile neutropenia less than 10%, routine prophylactic use of CSF is not recommended.²⁵

In the trials reviewed, neutropenia was reported in 83% to 94%¹⁻³ of patients and grade 3 to 4 neutropenia in 45% to 69%¹⁻⁶ of patients. Febrile neutropenia was reported in 3% to 11%.^{1,3} Prophylactic use of CSF is not recommended with this regimen. CSF should be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of nab-PC.

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. Constitutional:** Fatigue (all grades) 33% to 74%,¹⁻³ (grade 3 or 4) 3% to 6%.^{2,3,5,6}
- B. Dermatologic:** Alopecia (all grades) 49% to 100%,¹⁻³ (grade 3 or 4) 1%^{3,6}

- C. Gastrointestinal:** Anorexia (all grades) 16% to 69%,¹⁻³ (grade 3 or 4) 1% to 17%^{1-3,5,6}; constipation (all grades) 54%,² (grade 3 or 4) 1%²; nausea (all grades) 24% to 68%,¹⁻³ (grade 3 or 4) 1% to 11%^{1-3,5,6}; vomiting (all grades) 33%.¹
- D. Hematologic:** Anemia (all grades) 86% to 98%,¹⁻³ (grade 3 or 4) 16% to 32%^{1,3-6}; febrile neutropenia (all grades) 3% to 11%,^{1,3} (grade 3 or 4) less than 1% to 11%^{1,3,5,6}; leukopenia (all grades) 89% to 93%,^{1,2} (grade 3 or 4) 24% to 50%^{1,2,4}; neutropenia (all grades) 83% to 94%,¹⁻³ (grade 3 or 4) 45% to 69%¹⁻⁶; thrombocytopenia (all grades) 61% to 81%,¹⁻³ (grade 3 or 4) 14% to 23%.²⁻⁶
- E. Musculoskeletal:** Arthralgia (all grades) 15% to 66%¹⁻³; myalgia (all grades) 8% to 61%,¹⁻³ (grade 3 or 4) 1%³
- F. Neurologic:** Sensory neuropathy (all grades) 44% to 64%,¹⁻³ (grade 3 or 4) 2% to 7%^{1-3,5,6}; peripheral neuropathy (grade 3 or 4) 8%.⁴

PRETREATMENT LABORATORY STUDIES NEEDED

- A. Baseline**
1. Complete blood count (CBC) with differential
 2. Serum creatinine
 3. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT)
 4. Total bilirubin
 5. Conjugated bilirubin
- B. Prior to Each Treatment**
1. CBC with differential
 2. Serum creatinine
- C. Recommended Treatment Values:** The minimally acceptable pretreatment CBC values required to begin a cycle with full-dose therapy were not stated in the protocols reviewed. 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. Carboplatin: Refer to carboplatin dose calculations.
 2. Nab-paclitaxel: No dose adjustment required.²⁶
- B. Hepatic Function**
1. Carboplatin, no dose adjustment required.²⁶

2. Nab-paclitaxel²⁷:
 - a. Bilirubin 1.26 to 2 times the upper limit of normal (ULN) and AST/ALT less than 10 times the ULN, reduce dose by 25%.
 - b. Bilirubin 2.01 to 5 times the ULN and AST/ALT less than 10 times the ULN, reduce dose by 50%.
 - c. Bilirubin greater than 5 times the ULN and/or AST/ALT greater than 10 times the ULN, do not give the drug.

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