**Hosp Pharm** 2014;49(1):18–22

www.hospital-pharmacy.com
doi: 10.1310/hpj4901-18

# *Cancer Chemotherapy Update*

# *nab*-Paclitaxel Plus Gemcitabine Regimen for Pancreatic 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*-P + G

*Origin of Names:* The regimen is named for the 2 medications in the regimen: *nab*-paclitaxel and gemcitabine.

## INDICATION(S)

*nab*-P + G (**Table 1**) is used for the treatment of locally advanced or metastatic pancreatic adenocarcinoma.[1-4]

## DRUG PREPARATION

Follow institutional policies for preparation and dispensing of hazardous medications when dispensing *nab*-paclitaxel and gemcitabine.

**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. Gemcitabine**

1. Use gemcitabine hydrochloride injection 38 mg/mL or powder for injection.
2. Reconstitute the lyophilized powder to a concentration of 38 mg/mL with NS, 5% dextrose in water (D5W), or sterile water for injection (SWFI).
   a. When reconstituted according to the manufacturer's recommendation, the final concentration is 38 mg/mL, not 40 mg/mL.
   b. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution and should be avoided.
3. Dilute with 50 to 250 mL NS for infusion.

## DRUG ADMINISTRATION

**A. *nab*-paclitaxel**

1. The manufacturer recommends that the drug be given as a 30- to 40-minute IV infusion.[5]
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 and grade ≥2 peripheral neuropathy without affecting survival.[6]

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**Table 1.** *nab*-P + G regimen[3,4]

| Drug | Dose | Route of administration | Administered on days | Total dose/ cycle |
|---|---|---|---|---|
| *nab*-paclitaxel | 125 mg/m$^2$ | IV | 1, 8, 15 | 375 mg/m$^2$ |
| Gemcitabine | 1,000 mg/m$^2$ | IV | 1, 8, 15 | 3,000 mg/m$^2$ |
| Cycle repeats: every 28 days | | | | |
| *Variation:* Zhang et al gave *nab*-paclitaxel 120 mg/m$^2$ IV and gemcitabine 1,000 mg/m$^2$ IV, both given on day 1 and 8 every 21 days.[2] | | | | |

*Note:* IV = intravenous.

**B. Gemcitabine**

1. In the studies reviewed, the drug was given as a 30- to 40-minute IV infusion.[2]
2. Infusion times greater than 60 minutes have been associated with increased grade 3 or 4 hematologic toxicity due to accumulation of the active metabolite gemcitabine triphosphate.[7]

## SUPPORTIVE CARE

**A. Acute Emesis Prophylaxis:** According to accepted models for predicting emetogenicity, the *nab*-P + G regimen has a low (10% to 30%) risk of causing nausea or vomiting.[8] In the studies reviewed, nausea or vomiting was reported in 67%,[2] nausea in 48%,[3] and vomiting in 36% of patients,[3] suggesting that the regimen is more emetogenic than predicted by the models. The studies reviewed reported grade 3 or 4 nausea in 2% of patients and grade 3 or 4 vomiting in 7% of patients.[3] Prophylactic antiemetic therapy with a serotonin antagonist is recommended,[8-10] but may not be required in all patients. One group suggests that the addition of a neurokinin ($NK_1$) antagonist may be appropriate in some patients.[8] One of the following regimens given 30 minutes prior to therapy is suggested:

1. Ondansetron 8 mg to 16 mg orally (PO), ± dexamethasone 12 mg PO.
2. Granisetron 1 mg to 2 mg PO, ± dexamethasone 12 mg PO.
3. Dolasetron 100 mg PO, ± dexamethasone 12 mg PO.
4. Palonosetron 0.25 mg IV, ± dexamethasone 12 mg PO.

Prophylactic use of an $NK_1$ antagonist is recommended for moderately emetogenic regimens if the 2-drug combination was not effective in the previous treatment cycle.[8-10] One of the following regimens given 30 minutes prior to therapy is recommended:

1. Ondansetron 8 mg to 16 mg, dexamethasone 12 mg, and aprepitant 125 mg PO.
2. Granisetron 1 mg to 2 mg, dexamethasone 12 mg, and aprepitant 125 mg PO.
3. Dolasetron 100 mg, dexamethasone 12 mg PO, and aprepitant 125 mg PO.
4. Palonosetron 0.25 mg IV, dexamethasone 12 mg, and aprepitant 125 mg PO.

The antiemetic therapy should continue for at least 3 days. A meta-analysis of several trials of serotonin antagonists recommends against prolonged (greater than 24 hours) use of these agents, which makes a steroid, or steroid and dopamine antagonist combination, most appropriate for follow-up therapy.[11] 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 day 2 of *nab*-P + G.
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 day 2 of *nab*-P + G.
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 day 2 of *nab*-P + G.

If an $NK_1$ 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, ± 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 *nab*-P + G.

2. Dexamethasone 4 mg PO twice a day for 3 days, aprepitant 80 mg PO every morning 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 *nab*-P + G.
3. Dexamethasone 4 mg PO twice a day for 3 days, aprepitant 80 mg PO every morning 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 *nab*-P + G.

Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.[8-10,12] 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.[13-17]

**B. Breakthrough Nausea and Vomiting[8-10]:** Patients should receive an antiemetic prescription to treat breakthrough nausea and vomiting. 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 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 6 hours if needed.

**C. 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 (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.[18] In the studies reviewed, febrile neutropenia was reported in 1% to 8% of patients.[2-4] Therefore, prophylactic use of CSF is not recommended. The incidence of grade 3 or 4 neutropenia was in 17% to 73% of patients, so prophylactic use of CSF may be advisable in some patients.[2-4] CSF may be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of *nab*-P + G.

## 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:/ctep.info.nih.gov). 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. Dermatologic:** Alopecia (grade 1 or 2) 58%,[2] (all grades) 50%.[4]

**B. Gastrointestinal:** Diarrhea (grade 1 or 2) 8% to 30%,[2,3] (grade 3 or 4) 2% to 6%[2-4]; nausea (grade 1 or 2) 45%,[3] (grade 3 or 4) 2%,[3] (all grades) 49%[4]; nausea/vomiting (grade 1 or 2) 67%[2]; vomiting (grade 1 or 2) 30%,[3] (grade 3 or 4) 7%.[3]

**C. Hematologic:** Anemia (grade 1 or 2) 50% to 84%,[2,3] (grade 3 or 4) 13 to 14%[2-4]; febrile neutropenia (grade 3 or 4) 2% to 8%,[2-3] (all grades) 3%[4]; leukopenia (grade 1 or 2) 34%,[3] (grade 3 or 4) 31% to 55%[3,4]; neutropenia (grade 1 or 2) 16% to 58%,[2,3] (grade 3 or 4) 17% to 73%[2-4]; thrombocytopenia (grade 1 or 2) 17% to 61%,[2,3] (grade 3 or 4) 8% to 27%.[2-4]

**D. Infection:** Sepsis (all grades) 5%.[4]

**E. Metabolic:** Fatigue (grade 1 or 2) 42% to 53%,[2,3] (grade 3 or 4) 17% to 27%.[2-4]

**F. Neurologic:** Neuropathy (grade 1 or 2) 8% to 55%,[2,3] (grade 3 or 4) 8% to 20%.[2-4]

**G. Pulmonary:** Pneumonitis (all grades) 4%.[4]

**H. Treatment-Related Deaths:** (Any cause) 4%.[4]

## PRETREATMENT LABORATORY STUDIES NEEDED

**A. Baseline and Prior to Each Treatment**

1. Aspartate aminotransferase/alanine aminotransferase (AST/ALT)
2. Total bilirubin
3. Complete blood count (CBC)

**B. Recommended Pretreatment Values:** The minimally acceptable pretreatment CBC values required to begin a cycle with full-dose therapy in the protocols reviewed were:

1. Absolute neutrophil count (ANC) greater than or equal to 1,500 to 2,000 cells/mcL.[2,4]

2. Platelet count greater than or equal to 100,000 cells/mcL. [2]
3. Hemoglobin greater than or equal to 9 g/dL.[4]
3. Total bilirubin less than or equal to 1.5 mg/dL.[2]
4. AST and ALT less than or equal to 100 IU/L.[2]

In clinical practice, a pretreatment ANC of 1,000 cells/mcL and platelets of 75,000 cells/mcL is usually considered acceptable.

## DOSAGE MODIFICATIONS

**A. Renal Function**

1. *nab*-paclitaxel: No adjustment required.[5]
2. Gemcitabine: No adjustment required.[19-21]

**B. Liver Function**

1. *nab*-paclitaxel:
   a. AST less than 10 times the upper limit of normal (ULN) and total bilirubin 1.26 to 2 times ULN, reduce dose by 25%.[22]
   b. AST less than 10 times ULN and total bilirubin 2.01 to 5 times ULN, reduce dose by 50%.[22]
   c. AST greater than or equal to 10 times ULN and/or total bilirubin greater than 5 times ULN, use is not recommended.[5,22]
2. Gemcitabine: No adjustment required.[21,23]

**C. Myelosuppression**

1. *nab*-paclitaxel
   a. ANC:
      (1) Less than 1,000 cells/mcL on day 8 of therapy, stop current cycle and proceed to next cycle with 20% dose reduction.[2]
      (2) Less than 1,000 cells/mcL on day 8 or 15 of therapy, continue current cycle and proceed with 20% dose reduction.[5]
   b. Platelets:
      (1) Less than 100,000 cells/mcL on day 8 of therapy[2]:
         (a) Stop current cycle.
         (b) Reduce dose 20% in the next cycle.
      (2) Less than 75,000 cells/mcL on day 8 or 15 of therapy[5]:
         (a) Continue current cycle.
         (b) Reduce dose 25% in the next cycle.
2. Gemcitabine
   a. ANC
      (1) Less than 1,000 cells/mcL on day 8 of therapy[2]:
         (a) Stop current cycle.
         (b) Reduce dose 25% in the next cycle.
      (2) Less than 1,000 cells/mcL on day 8 or 15 of therapy[5]:
         (a) Continue current cycle.
         (b) Reduce dose 20%.
   b. Platelets
      (1) Less than 100,000 cells/mcL on day 8 of therapy[2]:
         (a) Stop current cycle.
         (b) Reduce dose 25% in the next cycle.[2]
      (2) Less than 75,000 cells/mcL on day 8 or 15 of therapy[5]:
         (a) Continue current cycle.
         (b) Reduce dose 20%.

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