Cancer Chemotherapy Update

Paclitaxel and Trastuzumab for Breast Cancer

Thomas Lehmann, PharmD, BCPS*; Dominic A. Solimando, Jr, MA, FAPhA, FASHP, BCOP; and J. Aubrey Waddell, PharmD, FAPhA, BCOP

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 trastuzumab, or TP

Origin of Name: The regimen is named for the 2 drugs it contains: paclitaxel and trastuzumab.

INDICATION(S)

This regimen (Table 1) has been studied for neo-adjuvant¹ and initial therapy for advanced²⁻⁴ and metastatic⁵⁻⁸ breast cancer and salvage therapy for metastatic breast cancer.⁹⁻¹² Current guidelines recommend TP for HER₂-expressing invasive breast cancer after treatment with doxorubicin and cyclophosphamide (AC).¹³

DRUG PREPARATION

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

A. Paclitaxel

1. Use paclitaxel injection (6 mg/mL).
2. Dilute in 250 to 1,000 mL of 0.9% sodium chloride (NS), 5% dextrose in water (D5W), or a saline/dextrose solution to a final concentration of 0.3 to 1.2 mg/mL.
3. Contact of undiluted paclitaxel with plasticized PVC equipment or devices is not recommended.

4. Paclitaxel solutions should be dispensed in glass, polypropylene, or polyolefin containers.

B. Trastuzumab

1. Use trastuzumab powder for injection.
2. Reconstitute with 20 mL of the supplied diluent to a concentration of 21 mg/mL.
3. Dilute in 250 mL NS.
4. Trastuzumab is reported to be incompatible with dextrose solutions.¹⁴
5. Solutions diluted in NS are reported to be stable for up to 28 days at room temperature or refrigerated. The manufacturer recommends that solutions be used within 24 hours.¹⁵
6. Because the provided diluent 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 infusion over 1 to 3 hours through a non-PVC (low-sorbing) infusion set with a 0.22 micron filter.

B. Trastuzumab

1. Trastuzumab is usually administered as an intravenous (IV) infusion over 30 to 90 minutes.
2. Do not administer as an IV bolus or push.

*Dr. Lehmann is the Chief of Pharmacy at the Andrew Rader US Army Health Clinic in Ft. Myer, Virginia. At the time this article was written, he was a Pharmacy Practice (PGY-1) Resident at Walter Reed National Military Medical Center, Bethesda, Maryland.

Table 1. Paclitaxel and trastuzumab regimen

Drug	Dose	Route of administration	Administered on day(s)	Total dose/month
Paclitaxel	80 mg/m ²	IV	Weekly	320 mg/m ²
Trastuzumab	4 mg/kg 2 mg/kg	IV	Week 1 Weekly	10 mg/kg Cycle 1, then 8 mg/kg
<i>Cycle repeats: every 4 weeks^{3,4,10}</i>				
OR				
Paclitaxel	175 mg/m ²	IV	1	175 mg/m ²
Trastuzumab	4 mg/kg 2 mg/kg	IV	Week 1, Cycle 1 Weekly	6 mg/kg
<i>Cycle repeats: every 3 weeks^{5,8,10}</i>				

Variations

- Horiguchi et al used paclitaxel 90 mg/m² weekly for 3 weeks, then on week off for 4 cycles and trastuzumab 4 mg/kg for the first dose followed by 2 mg/kg weekly for 16 weeks.¹
- Fountzilas et al used paclitaxel 90 mg/m² weekly immediately followed by trastuzumab 4 mg/kg the first week, then 2 mg/kg weekly for 12 weeks.²
- Seidman et al used paclitaxel 90 mg/m² weekly for 6 weeks with trastuzumab 4 mg/kg loading dose followed by 2 mg/kg every week.⁶
- Leyland-Jones et al used paclitaxel 175 mg/m² every 3 weeks for 7 cycles. Trastuzumab was given 8 mg/kg the day after the first paclitaxel dose, and then 6 mg/kg every 3 weeks on the same day as the paclitaxel dose. Trastuzumab was continued in responding patients until disease progression or patient withdrawal.⁷
- Gori et al used paclitaxel 60 to 90 mg/m² depending on prior treatment weekly for 6 months. Trastuzumab was given 4 mg/kg the day before the first paclitaxel dose, and then 2 mg/kg weekly after paclitaxel.⁹
- John et al used paclitaxel 90 mg/m² weekly given over two 6-week blocks with a 14-day break. Trastuzumab was given as 4 mg/kg loading dose and then 2 mg/kg weekly thereafter.¹¹
- Romond et al used paclitaxel 175 mg/m² every 3 weeks for 4 cycles plus trastuzumab 4 mg/kg with the first dose of paclitaxel followed by weekly doses of 2 mg for 51 weeks in one group, and paclitaxel 80 mg/m² weekly for 12 doses with trastuzumab 4 mg/kg with the first dose of paclitaxel followed by weekly doses of 2 mg for 51 weeks.

IV = Intravenous

SUPPORTIVE CARE

A. Acute and Delayed Emesis Prophylaxis: The TP regimen is predicted to have a low (10% to 30%) risk of causing nausea or vomiting.¹⁶⁻¹⁹ However, the studies reviewed reported nausea or vomiting in 41%³ and vomiting in 6% to 21%^{3,4} of patients receiving weekly paclitaxel and nausea in 50%³ and vomiting in 2% to 37% of patients^{3,5} receiving paclitaxel every 3 weeks, suggesting that the regimen may be more emetogenic than predicted. Prophylactic antiemetic therapy with dexamethasone or a serotonin antagonist alone may be sufficient, particularly for patients receiving paclitaxel weekly.¹⁷⁻¹⁹ Because dexamethasone is generally part of the hypersensitivity prophylaxis for paclitaxel, additional dexamethasone as part of the antiemetic regimen is not needed. One of the following regimens is recommended:

- Ondansetron 8 mg to 16 mg orally (PO), given 30 minutes before TP.
- Granisetron 1 mg to 2 mg PO, given 30 minutes before TP.
- Dolasetron 100 mg PO, given 30 minutes before TP.
- Palonosetron 0.25 mg IV, given 30 minutes before TP on day 1 only.

Addition of a neurokinin (NK1) antagonist may be appropriate if the initial antiemetic regimen was not effective in the previous treatment cycle.¹⁷⁻¹⁹ One of the following regimens is recommended:

- Ondansetron 8 mg to 16 mg and aprepitant 125 mg, given PO 30 minutes before TP.
- Granisetron 1 mg to 2 mg and aprepitant 125 mg, given PO 30 minutes before TP.
- Dolasetron 100 mg and aprepitant 125 mg, given PO 30 minutes before TP.

4. Palonosetron 0.25 mg IV and aprepitant 125 mg, given PO 30 minutes before TP on day 1 only.

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, making a steroid, or steroid and dopamine antagonist combination, most appropriate for follow-up therapy.²⁰ One of the following regimens is recommended:

1. Dexamethasone 4 mg PO twice a day for 3 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 TP.
2. Dexamethasone 4 mg PO twice a day for 3 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 TP.
3. Dexamethasone 4 mg PO twice a day for 3 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 TP.

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 day 2 of TP.
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 day 2 of TP.
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 day 2 of TP.

Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.¹⁶⁻¹⁹ 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.²¹⁻²⁵

- B. Breakthrough Nausea and Vomiting¹⁶⁻¹⁹:** 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.

A few small studies suggest that higher doses of granisetron (3 mg IV or 40 mcg/kg to 240 mcg/kg)²¹⁻²⁵ may be effective in treating breakthrough nausea; however, none of these reports found the improvement to be statistically significant.

- C. Hypersensitivity Precautions:** Paclitaxel injection produces hypersensitivity reactions in about 10% of patients.^{26,27} Routine prophylactic premedications should be given prior to paclitaxel administration. The following regimen is suggested²⁸:

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

All should be 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 (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.^{28,29}

Because severe (grade 3 or 4) neutropenia was reported in up to 15%⁸ of patients in the TP trials reviewed and febrile neutropenia was reported in 1%⁸ of patients, 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 TP.

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. Weekly Paclitaxel (80 mg/m²)

- Cardiovascular:** Edema (grade 1 or 2) 35%,³ (grade 2) 29%,⁴ (grade 3) 5%,¹⁰ (grade 3 or 4) 2%,³ (grade 4) 1%¹⁰; left ventricular ejection fraction decline (grade 2) 6%,⁴ (grade 3) 6%.⁴
- Dermatologic:** Alopecia (grade 1 or 2) 94%,³ (grade 3 or 4) 18%³; erythema (grade 1 or 2) 5%,³ (grade 3 or 4) 2%³; onychopathy (grade 1 or 2) 22%,³ (grade 2) 18%,⁴ (grade 3 or 4) 8%³; rash (grade 1 or 2) 24%.³
- Gastrointestinal:** Diarrhea (grade 1 or 2) 30%,³ (grade 2) 6%,⁴ (grade 3) 5%,¹⁰ (grade 3 or 4) 3%³; heartburn (grade 2) 6%⁴; mucositis (grade 1 or 2) 22%,³ nausea (grade 1 or 2) 41%³; nausea/vomiting (grade 2) 6%⁴; vomiting (grade 1 or 2) 21%.³
- Hematologic:** Anemia (grade 2) 6%,⁴ (grade 3) 5% to 6%,^{4,10} (grade 4) <1%¹⁰; leukopenia (grade 2) 18%,⁴ (grade 3) 6%,¹⁰ (grade 4) 2%¹⁰; lymphocytopenia (grade 3) 15%,¹⁰ (grade 4) 4%¹⁰; neutropenia (grade 3) 5% to 13%,^{3,10} (grade 4) 3% to 6%^{4,10}; thrombocytopenia (grade 3) 1%,¹⁰ (grade 4) 1%.¹⁰
- Hepatic:** Hepatotoxicity (grade 1 or 2) 7%,³ (grade 3 or 4) 3%³; transaminitis (grade 2) 18%,⁴ (grade 3) 6%.⁴
- Hypersensitivity:** Infusion-related reactions 35%.⁴
- Infection:** Fever (grade 1 or 2) 30%³; flu (grade 1 or 2) 13%³; infection (grade 2)

41%,⁴ (grade 3) 3% to 24%,^{3,4,10} (grade 4) 1%.¹⁰

- Miscellaneous:** Fatigue (grade 3) 6%,¹⁰ (grade 4) <1%¹⁰; hyperglycemia (grade 3) 4% to 6%,^{4,10} (grade 4) 1%¹⁰; weight gain (grade 2) 35%,⁴ (grade 3) 6%.⁴
- Neurologic:** Asthenia (grade 1 or 2) 86%,³ (grade 3 or 4) 14%³; hearing impairment (grade 2) 12%⁴; neuromotor (grade 3) 9%¹⁰; peripheral neuropathy (grade 1 or 2) 95%,³ (grade 2) 18%,⁴ (grade 3) 24% to 29%,^{4,10} (grade 3 or 4) 5%,³ (grade 4) <1%.¹⁰
- Pulmonary:** Cough (grade 1 or 2) 13%³; dyspnea (grade 1 or 2) 13%,³ (grade 3) 5%,¹⁰ (grade 3 or 4) 3%,³ (grade 4) 2%.¹⁰

B. Paclitaxel every 3 weeks (175 mg/m²)

- Cardiovascular:** Congestive heart failure (grade 3) 1%,⁸ (grade 4) 1%,⁸ edema (grade 3) 1%¹⁰; heart failure (grade 1 or 2) 13%,⁵ (grade 3 or 4) 2%.⁵
- Dermatologic:** Alopecia (grade 1 or 2) 56%,⁵ (grade 3 or 4) 26%,⁵ rash (grade 1 or 2) 38%,⁵ (grade 3 or 4) 1%.⁵
- Gastrointestinal:** Abdominal pain (grade 1 or 2) 34%,⁵ (grade 3 or 4) 3%⁵; anorexia (grade 1 or 2) 24%,⁵ (grade 3 or 4) 1%⁵; constipation (grade 1 or 2) 25%⁵; diarrhea (grade 1 or 2) 45%,⁵ (grade 3) 2% to 3%,^{8,10} (grade 3 or 4) 1%¹⁰; nausea (grade 1 or 2) 50%,⁵ (grade 3 or 4) 3%⁵; nausea/vomiting (grade 3) 2%⁸; stomatitis (grade 1 or 2) 10%⁵; vomiting (grade 1 or 2) 37%,⁵ (grade 3 or 4) 9%.⁵
- Hematologic:** Anemia (grade 1 or 2) 14%,⁵ (grade 3) 2% to 3%,^{8,10} (grade 3 or 4) 1%⁵; leukopenia (grade 1 or 2) 24%,⁵ (grade 3) 8%,¹⁰ (grade 3 or 4) 6%,⁵ (grade 4) 1%¹⁰; lymphocytopenia (grade 3) 8%,¹⁰ (grade 4) 4%¹⁰; neutropenia (grade 3) 10% to 15%,^{8,10} (grade 4) 5% to 12%^{8,10}; thrombocytopenia (grade 3) 1% to 2%.^{8,10}
- Hypersensitivity:** Allergic reaction (grade 3) 2%.⁸
- Infection:** Chills (grade 1 or 2) 42%,⁵ (grade 3 or 4) 1%⁵; febrile neutropenia (grade 3) 1%⁸; fever (grade 1 or 2) 47%,⁵ (grade 3) 1%,⁸ (grade 3 or 4) 2%⁵; infection (grade 1 or 2) 46%,⁵ (grade 3) 2% to 4%,^{8,10} (grade 3 or 4) 1%.⁵
- Miscellaneous:** Back pain (grade 1 or 2) 36%,⁵ (grade 3 or 4) 8%⁵; chest pain (grade 1 or 2) 30%,⁵ (grade 3 or 4) 3%⁵; fatigue (grade 3)

5%^{8,10}; hyperglycemia (grade 3) 7%,¹⁰ (grade 4) 1%¹⁰; pain (grade 1 or 2) 60%,⁵ (grade 3) 11%,⁸ (grade 3 or 4) 10%,⁵ (grade 4) 1%.⁸

8. **Musculoskeletal:** Arthralgia (grade 1 or 2) 37%,⁵ (grade 3 or 4) 9%⁵; myalgia (grade 1 or 2) 38%,⁵ (grade 3 or 4) 7%.⁵

9. **Neurologic:** Asthenia (grade 1 or 2) 62%,⁵ (grade 3 or 4) 8%⁵; headache (grade 1 or 2) 36%,⁵ (grade 3 or 4) 7%⁵; neuromotor (grade 4) 4%¹⁰; neuropathy (grade 3) 8% to 12%,^{8,10} (grade 4) 1%⁸; paresthesia (grade 1 or 2) 47%,⁵ (grade 3 or 4) 2%.⁵

10. **Pulmonary:** Cough (grade 1 or 2) 42%⁵; dyspnea (grade 1 or 2) 28%,⁵ (grade 3) 2%,⁸ (grade 3 or 4) 1%,⁵ (grade 4) 1% to 3%^{8,10}; pharyngitis (grade 1 or 2) 22%.⁵

PRETREATMENT LABORATORY STUDIES NEEDED

A. Baseline

1. Left ventricular ejection fraction
2. Complete blood count (CBC)
3. Total bilirubin
4. Hemoglobin
5. Aspartate aminotransferase/alanine aminotransferase (AST/ALT)
6. Serum creatinine

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. ANC: Greater than or equal to 1000 cells/mcL⁴
2. Platelet count: Greater than or equal to 100,000 cells/mcL.^{4,10}
3. Absolute granulocyte count (AGC):
  - a. At least 1,000 cells/mcL for 3-weekly paclitaxel.
  - b. At least 1,500 cells/mcL for weekly paclitaxel.

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

1. Paclitaxel – no adjustment required.^{30,31}
2. Trastuzumab – no adjustment required.¹⁵

B. Hepatic

1. Paclitaxel

a. Bilirubin:

- (1) Less than 1.5 mg/dL and ALT/AST greater than 2 times the upper limit of normal (ULN), reduce dose 25%.^{32,33}
- (2) Greater than or equal to 1.6 mg/dL and less than or equal to 3 mg/dL, reduce dose 60%.^{32,33}
- (3) Greater than 3 mg/dL, reduce dose 75%.^{32,33}

2. Trastuzumab – no adjustment required.³¹

C. Myelosuppression

1. Neutrophils:

- a. Greater than 500 cells/mcL and less than 1,000 cells/mcL³:
  - (1) Reduce paclitaxel dose 25%.
  - (2) Add filgrastim to subsequent cycles.
- b. Grade 4 or febrile neutropenia, reduce paclitaxel dose 25%.³
- c. Febrile neutropenia, add filgrastim 5 mcg/kg daily on day 2 and continue until ANC is >10,000/mm³.¹⁰
- d. Less than 500 cells/mcL:
  - (1) Delay therapy 1 week.³
  - (2) Add filgrastim 5 mcg/kg daily on day 2 and continue until ANC is >10,000/mm³.¹⁰

2. Platelets:

- a. Less than 75,000 cells/mcL, delay therapy 1 week.³
- b. Less than 25,000 cells/mcL:
  - (1) Every 3 week administration of paclitaxel, reduce dose to 150 mg/m², on recurrence reduce to 125 mg/m², then 105 mg/m², and finally 90 mg/m² with no dose reescalation.¹⁰
  - (2) Weekly administration of paclitaxel, reduce dose to 70 mg/m², on recurrence reduce to 60 mg/m², then 50 mg/m² and finally 40 mg/m² with no dose reescalation.¹⁰

3. WBC:

- a. Less than 1,000 mm³ for greater than or equal to 7 days, add filgrastim 5 mcg/kg daily on day 2 and continue until ANC is >10,000/mm³.¹⁰

D. Neurologic

1. Paclitaxel 80 mg/m² weekly

- a. Grade 2 toxicity, reduce paclitaxel dose to 60 mg/m².³

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