Doxorubicin and cyclophosphamide (AC) followed by weekly paclitaxel (T) chemotherapy for adjuvant treatment of breast cancer[1]

Cycle length: AC is given every 21 days for four cycles; paclitaxel is given every seven days of a 28 day cycle for three cycles.

Drug	Dose and route	Administration	Given on days
Doxorubicin	60 mg/m^2 IV	Dilute with normal saline (NS) to a final concentration of 2 mg/mL and administered as an IV bolus over three to five minutes into a free flowing IV infusion of NS or 5 percent dextrose in water (D5W). The presence of local erythematous streaking along the vein as well as facial flushing may be signs that administration is too rapid. If needed, doxorubicin can be further diluted after reconstitution in NS or D5W and given as a slow IV infusion administered over 15 to 60 minutes[2].	Day 1
Cyclophosphamide	600 mg/m^2 IV	Dilute with 250 to 500 mL NS or D5W and administer over 30 to 60 minutes. Rapid infusions may produce nasal burning or congestion that is relieved by slowing the rate.	Day 1
After completion of AC, administer:			
Paclitaxel	80 mg/m^2 IV	Dilute in 250 mL NS or D5W to a final concentration of 0.3 to 1.2 mg/mL and administer over one hour*.	Days 1, 8, 15, and 22

Pretreatment considerations:

- **Hydration:** Patients receiving cyclophosphamide should maintain adequate oral hydration (2 to 3 L/day during administration and for one to two days thereafter) and void frequently to reduce the risk of hemorrhagic cystitis[3].
- **Emesis risk:** HIGH (>90 percent frequency of emesis). Refer to UpToDate topic on "Prevention and treatment of chemotherapy-induced nausea and vomiting in adults".
- **Prophylaxis for infusion reactions:** Paclitaxel may cause severe hypersensitivity reactions. Premedication regimen should include dexamethasone (either 20 mg orally twelve and six hours before, or 20 mg IV 30 minutes before drug administration) plus both an H1 (diphenhydramine 25 to 50 mg IV) and an H2 receptor antagonist (ranitidine 50 mg or famotidine 20 mg IV) 30 to 60 minutes prior to paclitaxel administration. Severe infusion reactions (eg, skin rash, flushing, dyspnea, urticaria, back pain, hypotension, chest pain, tachycardia) occur primarily during the first and second infusions, typically within the first hour after the start of the infusion. Further information on infusion reactions, including management, is available. Refer to UpToDate topic on "Infusion reactions to systemic chemotherapy".
- **Vesicant/irritant properties:** Doxorubicin is a vesicant and can cause significant tissue damage if an extravasation occurs. For peripheral infusions, the IV line should be recently placed into a large, intact vein, with good blood return established immediately prior to starting the infusion. The IV or catheter site should be continuously monitored throughout drug administration infusion. If extravasation occurs, apply ice to the site and consider use of dexrazoxane. Paclitaxel can cause significant tissue damage; avoid extravasation. Refer to UpToDate topic on "Extravasation injury from chemotherapy and other non-antineoplastic vesicants".
- **Infection prophylaxis:** Not applicable.
- **Dose adjustment for baseline liver or renal dysfunction:** Dose adjustment is not necessary for doxorubicin or paclitaxel in renal impairment. The need for cyclophosphamide dose reduction in renal insufficiency is controversial. For patients with preexisting hepatic impairment, dose adjustments in doxorubicin, cyclophosphamide, and paclitaxel may be needed. Refer to UpToDate topics on "Chemotherapy-related nephrotoxicity and dose modification in patients with renal insufficiency" and "Chemotherapy hepatotoxicity and dose modification in patients with liver disease".
- **Cardiac issues:** A baseline assessment of LVEF is recommended, with periodic reassessment of during therapy. The risk of doxorubicin-associated cardiac dysfunction is related to cumulative dose. The risk is increased in patients with underlying heart disease, when anthracyclines are used concurrently with other cardiotoxic agents or radiation, and in patients previously treated with mediastinal or chest wall irradiation. Doxorubicin is contraindicated for patients with recent myocardial infarction, severe myocardial dysfunction, severe arrhythmia, or previous therapy with high cumulative doses of doxorubicin[2]. Further information on anthracycline-associated cardiotoxicity, including discussion about prevention and treatment, is available. Refer to UpToDate topic on "Cardiotoxicity of anthracycline-like chemotherapy agents".

Monitoring parameters:

- CBC with differential and platelet count every two weeks prior to each treatment cycle.
- Serum electrolytes and liver and renal function tests every two weeks prior to each treatment cycle.
- Assess changes in neurologic function prior to each treatment cycle of paclitaxel.
- During treatment with doxorubicin or paclitaxel, assess line site periodically during infusion of chemotherapy for signs and symptoms of extravasation.

Suggested dose alterations for toxicity:

- **Myelotoxicity:** Subsequent cycles should be delayed until the absolute neutrophil count is greater than 1000/microL and platelet count greater than 100,000/microL. If there is more than a three week delay in treatment, a dose reduction of 25 percent is recommended[1]. Refer to UpToDate topic on "Use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation".
- **Neurologic toxicity:** For patients who develop severe neuropathy (grade 3 or 4) that persists for a week or longer, the dose of paclitaxel should be reduced by 20 percent for subsequent courses of paclitaxel; hold if severe toxicity persists after dose reduction[4]. Refer to UpToDate topic on "Overview of neurologic complications of non-platinum cancer chemotherapy".
- **Dose adjustment for hepatic or renal dysfunction:** Guidelines for managing doxorubicin, cyclophosphamide, and paclitaxel in patients who have changes in kidney or liver function during therapy are addressed in detail separately. Refer to UpToDate topics on "Chemotherapy-related nephrotoxicity and dose modification in patients with renal insufficiency" and "Chemotherapy hepatotoxicity and dose modification in patients with liver disease".

If there is a change in body weight of at least 10 percent, dose should be recalculated for all drugs.

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy. The clinician is expected to use his or her independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; LVEF: left ventricular ejection fraction; CBC: complete blood count.
* Paclitaxel can be administered in NS, D5W, or NS/D5W at varying concentrations between 0.3 to 1.2 mg/mL. Use glass or polypropylene bottles or polypropylene or polyolefin plastic bags, and administer through polyethylene-lined administration sets with a microporous membrane 0.22 microns or less.

References:

1. *Sparano JA, et al. N Engl J Med 2008; 358:1663.*
2. *Doxorubicin hydrochloride injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 19, 2011).*
3. *Cyclophosphamide injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 19, 2011).*
4. *Paclitaxel injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 19, 2011).*