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Cancer Chemotherapy Update

Docetaxel and Cisplatin Regimen for 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@aol.com; 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: Docetaxel and cisplatin (DC)

Origin of name: The regimen is named for the 2 drugs it contains: **d**ocetaxel and **c**isplatin. Alternative names include: DP (**d**ocetaxel and cis**p**latin), TC (docetaxel [***T**axotere*] and **c**isplatin), and TP (***T**axotere* and cis**p**latin).

COMMENTS

Cisplatin-based doublets are recommended for adjuvant and neoadjuvant treatment of potentially operable non-small cell lung cancer (NSCLC) and first-line therapy for advanced or metastatic NSCLC.[1] Some studies indicate that the doxcetaxel and cisplatin (DC) regimen is equal or superior to vinorelbine-containing regimens.[2-5]

INDICATION(S)

The DC regimen (see **Table 1**) has been studied as initial therapy for advanced,[2-4,6-11,] locally advanced,[12-14] metastatic,[5,8] and recurrent[9] NSCLC. The DC regimen is currently recommended for adjuvant and neoadjuvant chemotherapy of NSCLC and first-line chemotherapy for advanced and metastatic NSCLC.[1]

DRUG PREPARATION

Follow institutional policies for preparation of hazardous medications when preparing and dispensing docetaxel and cisplatin.

A. Docetaxel

1. Use docetaxel injection, 10 mg/mL or 20 mg/mL, or the 40 mg/mL formulation, which requires an initial dilution before addition to the infusion bag.
2. If the 40 mg/mL formulation is used:
   a. Dilute the docetaxel to a concentration of 10 mg/mL with the provided diluent.
   b. Caution should be used to prevent medication errors:
      (1) The Institute for Safe Medication Practices (ISMP) has reported instances of errors in which the diluent was accidentally dispensed instead of the reconstituted drug, because the label on the diluent vial emphasizes the name of the active drug.[15]
      (2) Errors in reconstitution of docetaxel, related to overfill in the drug and diluent vials, also have been reported. The 20 and 80 mg vials contain 23.6 and 94.4 mg of docetaxel, respectively. The diluent vials are also overfilled. When reconstituted properly, the final solution contains 10 mg/mL of docetaxel. The proper volume needed to obtain the required dose should be measured, rather than merely withdrawing the entire contents of the vial.[16]

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Table 1. Docetaxel and cisplatin regimen[2-5,8,10-12]

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Doxetaxel	75 mg/m^2	IV	1	75 mg/m^2
Cisplatin	75 mg/m^2	IV	1	75 mg/m^2
Cycle repeats: every 3 weeks				
Variations				
1. Docetaxel 60 mg/m^2 and cisplatin 80 mg/m^2 on day 1 every 21 days.[6,9]				
2. Docetaxel 100 mg/m^2 on day 1 and cisplatin 80 mg/m^2 on day 2 every 3 weeks.[7]				
3. Docetaxel 40 mg/m^2 and cisplatin 40 mg/m^2 on days 1, 8, 29, and 36.[13,14]				

Note: IV = intravenous.

3. The 10 mg/mL or 20 mg/mL formulation does not require pre-mixing prior to dilution for infusion. However the 20 mg/mL formulation is twice the concentration (20 mg/mL) of the original (10 mg/mL) product. Admixture errors could occur due to the concentration difference between the new formulation (20 mg/mL) and the old formulation (10 mg/mL).
4. Dilute with 0.9% sodium chloride injection or 5% dextrose injection. The final concentration should be 0.3 to 0.9 mg/mL.
5. Contact of undiluted docetaxel with plasticized polyvinyl chloride (PVC) equipment or devices is not recommended. Docetaxel solutions should be dispensed in glass, polypropylene, or polyolefin containers.

B. Cisplatin

1. Use cisplatin injection, 1 mg/mL.
2. Dilute in 250 to 1,000 mL of 0.9% sodium chloride or a saline/dextrose solution.
3. To ensure the stability of cisplatin, the infusion solution must have a final chloride concentration of at least 0.2%.

DRUG ADMINISTRATION

A. Docetaxel is administered as a 1-hour intravenous (IV) infusion.

B. Cisplatin is administered as a 30-minute to 1-hour IV infusion.

SUPPORTIVE CARE

A. Acute and Delayed Emesis Prophylaxis

The DC regimen is predicted to cause acute emesis in greater than 90% of patients.[17-20] The studies reviewed reported mild (grade 1 or 2) nausea or vomiting in 15% to 65% of patients[5,12] and severe (grade 3 or 4) nausea or vomiting in 5% to 13% of patients.[2-5,12] Cisplatin in doses greater than 50 mg/m^2 (either as a single dose or cumulative over consecutive days) is reported to cause delayed nausea in 78% of patients and delayed emesis in 61% of patients. Delayed nausea or emesis may begin as soon as 16 hours after cisplatin administration, reach their peak of severity at 48 to 72 hours after cisplatin administration, and usually abate between 96 to 168 hours after cisplatin administration.[21]

Appropriate acute emesis prophylaxis includes a serotonin antagonist, a corticosteroid, and a neurokinin (NK_1) antagonist.[17-20] One of the following regimens is suggested:

1. Ondansetron 16 mg to 24 mg, dexamethasone 12 mg, and aprepitant 125 mg given orally (PO) 30 minutes before docetaxel.
2. Granisetron 2 mg, dexamethasone 12 mg, and aprepitant 125 mg given PO 30 minutes before docetaxel.
3. Dolasetron 100 mg to 200 mg, dexamethasone 12 mg, and aprepitant 125 mg given PO 30 minutes before docetaxel.
4. Palonosetron 0.25 mg IV, dexamethasone 12 mg, and aprepitant 125 mg given PO 30 minutes before docetaxel 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 (more than 24 hours) use of these agents, making a steroid, or steroid and dopamine antagonist combination, most appropriate for follow-up therapy.[22] One of the following regimens is suggested:

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 DC regimen.

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 DC regimen.
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 DC regimen.

Patients who do experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.[17-20] There is no evidence that substituting granisetron for ondansetron in subsequent treatment cycles or increasing the dose, even to very high doses, are effective. These approaches are generally not recommended.[23-27]

B. Breakthrough Nausea and Vomiting[17-20]: 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, ±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.

C. Hydration: Cisplatin can cause irreversible kidney damage by acute tubular necrosis. Maintenance of a urine output greater than or equal to 75 to 100 mL/h for several hours before and after each cisplatin dose is the best prophylaxis against cisplatin-induced nephrotoxicity. A wide variety of hydration and diuretic regimens for this purpose have been reported. Cornelison and Reed reported that, with the possible exception of the first treatment cycle, diuretics add nothing to vigorous hydration for prevention of cisplatin nephrotoxicity.[28] Kintzel noted the mechanism of action of diuretics intuitively supports their use to prevent cisplatin-induced nephrotoxicity, but there is no evidence to recommend their use over vigorous hydration.[29]

A suggested hydration regimen is 5% dextrose/0.9% sodium chloride injection or 0.9% sodium chloride injection infused at 250 mL/h for 2 to 4 hours before and after each cisplatin dose. Oral hydration regimens are also used, but the increased chloride from intravenous sodium chloride injections may offer better renal protection.[28]

D. Hypersensitivity Precautions[30,31]: The manufacturer recommends administration of dexamethasone 8 mg PO twice daily for 3 days, beginning the day *before* the docetaxel infusion. Some clinicians administer a histamine$_2$ antagonist ± a histamine$_1$ antagonist in addition to the steroid. If additional prophylaxis against hypersensitivity is chosen, the following regimen is suggested:

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

All are given intravenously over 30 minutes prior to docetaxel.

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. 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.[32,33]

Because febrile neutropenia was reported in 1% to 9% of patients in the trials of DC reviewed,[2-5,11] prophylactic use of CSFs is not recommended. CSFs should be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of DC therapy.

F. Pulmonary: Docetaxel can cause fluid retention, including pleural effusion, ascites, and peripheral edema, in up to 27% of patients.[30] In the DC trials reviewed, mild (grade 1 or 2) edema was reported in 95% of patients,[12] and severe (grade 3) edema was reported in 1% of patients.[12] Patients should be treated with a steroid (eg, dexamethasone 8 mg to 10 mg PO twice daily) for 3 to 5 days, beginning the day *before* docetaxel administration.[30,31]

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 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. Cardiovascular: Dehydration (grade 3 or 4) 3%[3]; edema 32%,[2] (grade 1 or 2) 95%,[12] (grade 3) 1%[12]; peripheral edema (all grades) 36%.[3]

B. Central Nervous System: Dizziness 7%,[4] (grade 3) 0.5%[4]; neurocerebellar effects (grade 2) 3%[5]; neurocortical effects (grade 2) 5%.[5]

C. Constitutional: Arthralgia (grade 1 or 2) 5%,[11] (grade 3) 1%[11]; asthenia (grade 1 or 2) 65%,[12] (grade 3) 6%,[12] (grade 3 or 4) 11% to 14%[2,3]; fatigue 49%,[4] (grade 1 or 2) 52%,[11] (grade 3) 6% to 20%[4,11]; fatigue/asthenia (grade 1) 15%,[5] (grade 2) 5%,[5] (grade 3) 10%[5]; pain (grade 1 or 2) 24%,[12] (grade 3) 1%,[12] (grade 3 or 4) 7% to 10%,[2,3] (grade 4) 1%[12]; abdominal pain 9%,[4] (grade 3) 0.5%[4]; pyrexia 9%,[4] (grade 1) 13%,[5] (grade 2) 13%,[5] (grade 3) 1%[4]; weight loss 18%.[4]

D. Dermatologic: Alopecia 58%,[4] (grade 1) 23%,[5] (grade 1 or 2) 16% to 85%,[11,12] (grade 2) 49%,[5] (grade 3) 2% to 3%,[5,11] (grade 1 to 3) 74%[2]; nail changes 14%[2]; rash (grade 1 or 2) 5%[11]; unspecified skin reactions (grade 1) 11%[5]; (grade 1 or 2) 21%,[11] (grade 3) 1%.[12]

E. Gastrointestinal: Anorexia 37%,[4] (grade 1 or 2) 32%,[11] (grade 3) 2% to 3%,[4,11] (grade 3 or 4) 5% to 7%[2,3]; constipation 18%,[4] (grade 3) 1%[4]; diarrhea 32%,[4] (grade 1) 15%,[5] (grade 1 or 2) 18% to 47%,[11,12] (grade 2) 8%,[5] (grade 3) 3% to 8%,[5,12] (grade 3) 6%,[4] (grade 3 or 4) 6% to 8%,[2,3] (grade 4) 1%[12]; dysgeusia 11%[4]; dyspepsia 3%[4]; mucositis/stomatitis 19%,[4] (grade 1) 5%,[5] (grade 1 or 2) 23%,[12] (grade 2) 8%,[8] (grade 3) 1%,[12] (grade 4) 1%[12]; nausea 60%,[4] (grade 1) 31%,[5] (grade 1 or 2) 65%,[12] (grade 2) 21%,[5] (grade 3) 5% to 12%,[4,5,12] (grade 3 or 4) 10%[2]; nausea or vomiting (grade 3 or 4) 12% to 13%[3]; vomiting 39% to 52%,[3,4] (grade 1) 15%,[5] (grade 1 or 2) 51%,[12] (grade 2) 18%,[5] (grade 3) 1% to 12%,[4,5,12] (grade 3 or 4) 8%,[2] (grade 4) 1%.[12]

F. Hematologic: Anemia 88%,[4] (grade 1 or 2) 45% to 85%,[4,11,12] (grade 3) 4% to 12%,[4,11,12] (grade 3 or 4) 5% to 8%,[2,3] (grade 4) 7%[12]; leukopenia 77%,[4] (grade 3) 30%,[4] (grade 3 or 4) 71% to 82%%,[2,3] (grade 4) 5%[4]; neutropenia 77%,[4] (grade 1 or 2) 14% to 18%,[11,12] (grade 3) 15% to 20%,[4,11,12] (grade 3 or 4) 75%,[2] (grade 4) 7% to 50%[4,11,12]; febrile neutropenia 4% to 9%,[2,4,5] (grade 1 or 2) 1%,[11] (grade 3) 1%,[11] (grade 3 or 4) 3% to 8%,[3] (grade 4) 2%[11]; thrombocytopenia 32%,[4] (grade 1 or 2) 1% to 34%,[11,12] (grade 3) 0.5% to 7%,[4,11,12] (grade 3 or 4) 2% to 3%,[2,3] (grade 4) 3% to 7%.[11,12]

G. Hepatic: Increased aminotransferase (grade 1 or 2) 6%.[11]

H. Hypersensitivity: 12%,[2] (grade 1) 3%,[5] (grade 1 or 2) 25%,[12] (grade 2) 3%,[5] (grade 3) 1%,[12] (grade 4) 2%.[12]

I. Infection: (grade 1 or 2) 12%,[12] (grade 2) 3%,[5] (grade 3) 3% to 5%,[5,12] (grade 3 or 4) 8%,[2] (grade 4) 1%.[12]

J. Neurologic: Neuromotor reactions (grade 2) 3%,[5] (grade 3) 3%,[5] (grade 3 or 4) 2% to 6%,[3] (grade 4) 3%[5]; neurosensory reactions (grade 1) 15%,[5] (grade 1 or 2) 58%,[12] (grade 2) 3%,[5] (grade 3) 3%,[5,12] (grade 3 or 4) 2% to 7%[2,3]; paresthesia 8%[4]; peripheral neuropathy 16%[4]; unspecified reactions (grade 1 or 2) 13%,[11] (grade 3) 1%,[11] (grade 3 or 4) 9% to 16%.[3]

K. Otic: Tinnitus 3%.[4]

L. Pulmonary: Pneumonitis (grade 3) 1% to 3%[5,11]; unspecified pulmonary toxicity (grade 3 or 4) 8% to 12%.[2,3]

M. Treatment-related mortality: Gastrointestinal perforation 0.5%,[4] peritoneal infection 0.5%,[4] septic shock 0.5%,[4] unspecified cause 2%.[11]

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

B. Prior to each treatment

1. CBC with differential
2. Serum creatinine

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

1. Absolute neutrophil count:
   a. Greater than or equal to 1,500 cells/mcL[2,8]
   b. Greater than or equal to 2,000 cells/mcL[4,5,12]
2. Platelet count – greater than or equal to 100,000 cells/mcL[2,4,5,8,12]

3. Hemoglobin:
   a. Greater than or equal to 9 g/dL[2,8]
   b. Greater than or equal to 10 g/dL[12]
   c. Greater than 11 g/dL[4]
4. Hepatic function:
   a. ALT:
      (1) Less than 5 times the upper limit of normal (ULN)[8]
      (2) Less than 2.5 times the ULN[4,12]
      (3) Less than 1.5 times the ULN[2,5]
   b. Alkaline phosphatase:
      (1) Less than or equal to 5 times the ULN[2,12]
      (2) Less than 5 times the ULN[4]
   c. AST:
      (1) Less than 5 times the ULN[8]
      (2) Less than 2.5 times the ULN[4,12]
      (3) Less than 1.5 times the ULN[5]
   d. Hepatic enzymes – less than or equal to 2 times the ULN[2]
   e. Total bilirubin:
      (1) Less than the ULN[12]
      (2) Less than or equal to the ULN[2,4,5]
      (3) Less than or equal to 1.5 times the ULN[8]
5. Renal function:
   a. Serum creatinine:
      (1) Less than or equal to 1.5 mg/dL,[2,5,12] ***or*** creatinine clearance greater than or equal to 60 mL/min[2,12]
      (2) Less than or equal to the ULN, ***or*** creatinine clearance greater than or equal to 60 mL/min[4]
      (3) Less than 1.5 times the ULN[8]

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. Cisplatin: Creatinine clearance:
   a. Less than or equal to 45 mL/min and greater than or equal to 30 mL/min, reduce dose 50%.[34,35]
   b. Less than or equal to 45 mL/min and greater than 30 mL/min, reduce dose 50%.[35]
   c. Less than or equal to 30 mL/min, do not give drug.[35]
   d. Less than 30 mL/min, do not give drug. [35]
   e. Less than or equal to 50 mL/min and greater than or equal to 10 mL/min, reduce dose 25%.[36]
   f. Less than 10 mL/min, reduce dose 50%.[36]
   g. Less than 60 mL/min, reduce dose 25%.[35]
2. Doxetaxel: No adjustment required.[34]

B. Hepatic Function

1. Cisplatin: No adjustment required.[37,38]
2. Doxetaxel:
   a. Bilirubin greater than the ULN and AST/ALT greater than 1.5 times ULN, do not give drug.[34]
   b. ALT/AST:
      (1) Greater than or equal to 1.6 times the ULN and less than or equal to 6 times the ULN, reduce the dose 25%.[37]
      (2) Greater than or equal to 2 times the ULN and less than or equal to 3 times the ULN, reduce the dose 50%.[38]
      (3) Greater than 6 times the ULN, use clinical judgement.[37]
   d. Alkaline phosphatase greater than 2.5 times ULN, do not give drug.[34]

C. Myelosuppression

Reduce dose of both drugs 25% if[5]:

1. Nadir ANC is less than 500 cells/mcL for more than 7 days.
2. Platelets are less than 25,000 cells/mcL.
3. Fever is:
   a. Greater than 38.5°C for more than 3 days.
   b. Greater than or equal to 38°C 3 times in 24 hours.

D. Other

1. Cisplatin: Grade 2 neuropathy, reduce dose 20%.[12]
2. Docetaxel: Grade 3 or 4 diarrhea, ototoxicity, or cutaneous reaction, reduce dose 20%.[12]

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prepare students for the profession and may cover interviewing and other skills needed to enter the workforce, most simulation exercises are theoretical until a candidate needs the experience to model and understand workplace culture.

Our generation cannot assume that people coming into the profession today know how those who came before us entered the profession, nor how hard we worked to make our place in the field. If it's important for a new practitioner in your organization to know this path, share the stories and give them the opportunity to understand "how things used to be." The newer generations bring unique skills and abilities based on the factors that shaped their lives (parenting, technology, and economics), and we can learn from those differences. If you are hiring new graduates, be clear about your expectations but also attempt to meet them at least halfway by crafting your message to acknowledge their individuality and desire to contribute immediately to the organization.

Gen Y professionals are motivated by things that are considered less traditional than previous generations. If they are offered flexibility in their work schedules or the opportunity to work on a project, even if it is outside the normal work day, many will easily put in more hours without expecting additional compensation. Let them have a say in how things could work more efficiently and let them participate in the change process. If you hold back on telling a Gen Y professional how a problem must be solved, you may be pleasantly surprised at their unique approach and positive results.

Each generation is distinctive and brings a set of strengths to the workplace that should be recognized and celebrated. Our newest generation of professionals is optimistic, tenacious, willing to get involved, and hard working.

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