Doxorubicin and Cyclophosphamide Followed by Docetaxel

**CONSTITUENT DRUGS**
- Doxorubicin (*Adriamycin*)
- Cyclophosphamide (*Cytoxan*)
- Docetaxel (*Taxotere*)

**SYNONYMS**
- AC followed by D (AC → D)

**USES**
- Adjuvant therapy of operable breast cancer
- Neoadjuvant therapy of operable breast cancer
- Treatment of metastatic breast cancer

**SUPPORTIVE CARE**

**Emetogenicity**
- Predicted:
  - AC: > 90% (high) (see p. 520)
  - D: 10% to 30% (mild) (see p. 518)

**Hydration**
- Cyclophosphamide (see p. 521)

**Hypersensitivity Precaution**
- Doxorubicin (see p. 521)
- Docetaxel (see p. 521)

**Myeloid Growth Factors**
- Prophylactic use not recommended during AC phase but recommended during D phase (see p. 522).
- Febrile neutropenia
  - AC: 2% to 7% (2,4,6,7,9)
  - D: 1% to 27% (2,4,6,7,9)
- Neutropenia (grade 3 or 4)

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### Doxorubicin and Cyclophosphamide Followed by Docetaxel[^2-8]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Route</th>
<th>Total dose/ cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>60 mg/m² IV</td>
<td>60 mg/m²</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>600 mg/m² IV</td>
<td>600 mg/m²</td>
</tr>
</tbody>
</table>

Repeated every 21 days for 2 to 4 cycles, followed by:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Route</th>
<th>Total dose/ cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>100 mg/m² IV</td>
<td>100 mg/m²</td>
</tr>
</tbody>
</table>

Repeated every 21 days for 2 to 4 cycles

**Alternatives:**
1. Reverse sequence of D given first for 2 to 4 cycles, followed by AC for 2 to 4 cycles has been used.[6,7,9]
2. In operable breast cancer, timing of AC followed by D in regard to breast cancer surgery has the following variations:
   a. AC followed by D as neoadjuvant therapy.[2-5]
   b. AC as neoadjuvant therapy and D as adjuvant therapy.[5]
   c. D as neoadjuvant therapy and AC as adjuvant therapy.[6]
Extravasation
- Doxorubicin (see p. 522)

Pulmonary
- Docetaxel (see p. 524)

TOXICITIES

Common (> 50%)
- Dermatologic
  - Alopecia
    - Grade 1 or 2: 100% (AC)\(^3\); 100% (D)\(^3\)
    - Grade 3 or 4: 60% to 89% (AC)\(^2,4\); 45% to 94% (D)
  - Stomatitis
    - Grade 1 or 2: 67% (AC)\(^2\); 66% (D)\(^3\)
    - Grade 3 or 4: 1% to 3% (AC)\(^2,6,9\); 3% to 8% (D)\(^2,4,6,9\)
  - Hematologic
    - Anemia
      - Grade 1 or 2: 45% (AC)\(^3\); 71% (D)\(^3\)
      - Grade 3 or 4: 14% (AC)\(^6\); 2% to 3% (D)\(^5,8\)
    - Leukopenia
      - Grade 3 or 4: 4% to 50% (AC)\(^4,9\); 10% to 66% (D)\(^4,8\)
    - Neutropenia
      - Grade 1 or 2: 29% (AC)\(^2\); 11% (D)\(^3\)
      - Grade 3 or 4: 14% to 86% (AC)\(^3,4,6,7,9\); 20% to 93% (D)\(^3,4,6,7,9\)
  - Gastrointestinal
    - Nausea
      - Grade 1 or 2: 67% (AC)\(^2,3\); 29% (D)\(^3\)
      - Grade 3 or 4: 2% to 4% (AC)\(^4\); 1% to 3% (D)\(^2,6,9\)
    - Stomatitis
      - Grade 1 or 2: 67% (AC)\(^2\); 66% (D)\(^3\)
      - Grade 3 or 4: 1% (AC)\(^2,4\); 3% to 8% (D)\(^2,4,6,9\)
- Neurologic
  - Asthenia
    - Grade 1 or 2: 29% (AC)\(^3\); 53% (D)\(^3\)
    - Grade 3 or 4: 2% to 7% (AC)\(^3,9\); 3% to 9% (D)\(^3,6,9\)
- Pulmonary
  - Dyspnea
    - Severe: 20% (D)\(^8\)

Frequent (20% to 50%)
- Cardiovascular
  - Fluid retention: 5% to 23% (D)\(^4,7\)
  - Thrombotic events: 20% (D)\(^8\)
- Gastrointestinal
  - Diarrhea
    - Grade 1 or 2: 12% (AC)\(^3\); 24% (D)\(^3\)
    - Grade 3 or 4: 0.4% (AC)\(^2,4,6\); 1% to 7% (D)\(^2,4,6,9\)
  - Vomiting
    - Grade 1 or 2: 26% (AC)\(^3\)
    - Grade 3 or 4: 2% to 4% (AC)\(^2,3,6,9\); 1% to 3% (D)\(^2,9\)
- hematologic
  - Febrile neutropenia
    - 2% to 7% (AC)\(^2,4,6,7,9\)
    - 1% to 27% (D)\(^2,4,6,7,9\)
  - Hypersensitivity
    - All grades: 19% to 27% (D)\(^7,8\)
    - Grade 1 or 2: 5% (D)\(^3\)
    - Grade 3 or 4: 0.3% to 4% (D)\(^2,6\)
  - Neurologic
    - Musculoskeletal pain
      - All grades: 20% (D)\(^8\)
    - Myalgias
      - Grade 1 or 2: 24% (D)\(^3\)
    - Neurosensory toxicity
      - Grade 1 or 2: 7% (AC)\(^3\); 37% (D)\(^3\)
      - Grade 3 or 4: 2% (D)\(^8\)
  - Pulmonary
    - Dyspnea
      - Severe: 20% (D)\(^8\)

Infrequent (5% to 19%)
- Dermatologic
  - Nail changes
    - Grade 1 or 2: 2% (AC)\(^2\); 13% (D)\(^3\)
    - Grade 3 or 4: 0.2% (AC)\(^4\); 5% (D)\(^4\)
  - Skin changes
    - Grade 3 or 4: 1% (AC)\(^4\); 7% (D)\(^4\)
- Gastrointestinal
  - Appetite loss
    - Grade 3 or 4: 7% (AC)\(^4\)
  - Constipation
    - Grade 3 or 4: 5% (AC)\(^4\); 6% (D)\(^4\)
  - Nausea and vomiting
    - Grade 3 or 4: 1% to 13%\(^4\)
    - Grade 3 or 4: 13% (AC)\(^4\); 4% (D)\(^4\)
- Hematologic
  - Granulocytopenia
    - Grade 3 or 4: 6% (AC)\(^3\); 2% (D)\(^2\)
  - Thrombocytopenia
    - Grade 1 or 2: 10% (AC)\(^3\); 3% (D)\(^3\)
    - Grade 3 or 4: 1% to 7% (AC)\(^4,6\); 1% to 3% (D)\(^4,6,9\)
  - Infection
    - All grades: 10% (AC)\(^7\); 15% (D)\(^7\)
    - Grade 3 or 4: 2% (AC)\(^2,4\); 2% to 7% (D)\(^2,4,9\)
  - Metabolic
    - Fatigue
      - Grade 3 or 4: 10% (AC)\(^3\); 19% (D)\(^4\)
  - Neurologic
    - Neuromotor toxicity
      - Grade 1 or 2: 2% (AC)\(^3\); 5% (D)\(^3\)
      - Grade 3 or 4: 0.2% (AC)\(^3\); 2% (D)\(^2\)

Uncommon (1% to 4%)
• **Cardiovascular**
  ➢ Phlebitis or thromboembolism
    • Grade 3 or 4: 0.5% (AC); 1% (D)
• **Dermatologic**
  ➢ Skin rash
    • Grade 1 or 2: 3% (D)
• **Gastrointestinal**
  ➢ Anorexia
    • Grade 3 or 4: 4% (AC)
• **Neuropathy**
  ➢ Reduce doxorubicin and docetaxel doses by 25% for grade 3 or 4 mucositis.
• **Neurotoxicity**
  ➢ Reduce doxorubicin and docetaxel doses by 25% for grade 2 neuropathy.
  ➢ Discontinue docetaxel for grade 3 or 4 neurotoxicity.
• **Hypersensitivity**
  ➢ Discontinue docetaxel for grade 3 or 4 hypersensitivity reactions.
• **Diarrhea**
  ➢ Reduce doxorubicin dose by 25% and docetaxel and cyclophosphamide doses by 17% for grade 3 or 4 diarrhea.
• **Edema**
  ➢ Reduce docetaxel dose by 20% for grade 2 edema.
  ➢ Discontinue docetaxel for grade 3 or 4 edema.
• **Other**
  ➢ Reduce dose of all medications by 25% for any grade 3 or 4 nonhematologic toxicity.
  ➢ Reduce docetaxel dose by 25%, cyclophosphamide dose by 17%, and doxorubicin dose by 17% for grade 3 or 4 nausea or vomiting.
  ➢ Discontinue chemotherapy for a greater than 15% decrease in left ventricular ejection fraction to a level below 50%.

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**RECOMMENDED LABORATORY TESTS**

**Baseline**
- AST/ALT
- Total bilirubin
- Serum creatinine
- CBC with differential

**Prior to Each Treatment**
- CBC with differential

**Recommended Pretreatment Values**
- AGC ≥ 1,500 cells/mcL
- ANC ≥ 1,500 cells/mcL
- Platelets ≥ 100,000 cells/mcL
- An ANC of 1,000 cells/mcL and platelets of 75,000 cells/mcL are usually considered acceptable for treatment.

**DOSAGE MODIFICATIONS**

**Renal Function (see p. 526)**

**Liver Function (see p. 531)**
- **Docetaxel**
  ➢ Reduce dose by 25% for AST 2.5 to 5 times ULN.
  ➢ Omit dose for AST > 5 times ULN.
- **Neutrophils (AGC or ANC)**
  ➢ Hold treatment for up to 1 week for ANC < 1,500 cells/mcL
  ➢ Reduce doses of all medications by 17% to 25% for ANC < 500 cells/mcL
- **Platelets**
  ➢ Hold treatment for up to 1 week for platelets < 50,000 cells/mcL
  ➢ Reduce doses of all medications by 25% for platelets < 25,000 cells/mcL

**Mucositis**
- Hold treatment for up to 1 week for grade 2, 3, or 4 mucositis.

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**REFERENCES**


