Dose-dense Adjuvant Chemotherapy

A number of randomized trials — including NSABP B-22 and other studies using autologous stem cell support — have failed to demonstrate an advantage to dose-intensive chemotherapy. A dose-dense chemotherapy regimen involves a strategy where closer than normal dosing intervals are utilized, often facilitated by hematopoietic growth factor support, i.e. filgrastim. Several Phase II trials have assessed different dose-dense regimens as adjuvant therapy in women with node-positive breast cancer. As a result, two major Phase III randomized trials are evaluating the role of dose-dense adjuvant chemotherapy. CALGB 9741 is closed to accrual, and initial results will be reported at this meeting, suggesting a disease-free and survival advantage in the dose-dense randomization arm. CAN-NCC-MA21 is actively accruing patients.

**PHASE III RANDOMIZED STUDY OF SEQUENTIAL CHEMOTHERAPY USING DOXORUBICIN, PACLITAXEL, AND CYCLOPHOSPHAMIDE OR CONCURRENT DOXORUBICIN AND CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL AT 14- AND 21-DAY INTERVALS IN WOMEN WITH NODE-POSITIVE STAGE II OR IIIA BREAST CANCER — Closed Protocol Protocol IDs: CLB-5741, E-57341, NCTC-5741, SWOG-5741 Projected Accrual: 2,100 patients

**Eligibility:** Operable, stage II or IIIA adenocarcinoma of the breast (T3a, N1, and M0) surgically treated by either a modified radical mastectomy or a ‘segmental mastectomy plus axillary node dissection

**ARM 1**
- Doxorubicin (A) q3w x 4
- Paclitaxel (T) q3w x 4
- Cyclophosphamide (C) G-CSF days 3-10 after each cycle of chemotherapy.

**ARM 2**
- Doxorubicin (A) q3w x 4
- Paclitaxel (T) q3w x 4
- Cyclophosphamide (C) G-CSF days 3-10 after each cycle of chemotherapy.

**ARM 3**
- Doxorubicin (A) q3w x 4
- Paclitaxel (T) q3w x 4
- Cyclophosphamide (C) G-CSF days 3-10 after each dose of chemotherapy.

**SELECT PHASE II Dose-Dense Adjuvant Chemotherapy TRIALS**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Eligibility</th>
<th>Number of Patients</th>
<th>Chemotherapy Regimen</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hudis 1999</td>
<td>T+ positive lymph nodes</td>
<td>71</td>
<td>A q 21 days x 4 + C q 14 days x 3 + (filgrastim days 3-10 of each cycle)</td>
<td>5 years: 52% DFS, 60% OS</td>
</tr>
<tr>
<td>Hudis 1999</td>
<td>T+ positive lymph nodes</td>
<td>42</td>
<td>A q 14 days x 3 + C q 14 days x 3</td>
<td>4 years: 78% DFS</td>
</tr>
<tr>
<td>Fountzilas 2001</td>
<td>T+; T0, no positive lymph nodes</td>
<td>49</td>
<td>C q 2 wks x 3 + T q 10 wks x 3 + G-CSF 2 wks x 3</td>
<td>3 years: 72% DFS, 95% OS</td>
</tr>
<tr>
<td>Ellis 2002</td>
<td>HER2+ or ERBB2- or ERBB2-</td>
<td>62</td>
<td>C q 24 wks + I or 20-24 wks + T</td>
<td>5 years: 85% DFS, 86% OS</td>
</tr>
</tbody>
</table>

**BIOLOGIC RATIONALE FOR DOSE-DENSE CHEMOTHERAPY**

- The delivery of multiple cycles of chemotherapy using the shortest possible intervals is therefore hypothesized to minimize tumor regrowth between one cycle and the next. This is called ‘dose-dense’ chemotherapy, wherein an increase in dose-intensity is obtained by shortening the intervals between treatments and not, as has been done previously, by simply increasing dose levels.

- “The concept of ‘dose intensity’ (DI) in the management of breast cancer has been widely explored by medical oncologists during the last decade... DI can be increased either by dose escalation or by reducing the interval between cycles, a concept termed ‘dose density’ The administration of drugs at an adequate dosing at shorter time intervals, i.e. every 2 weeks, became feasible with the introduction of hematopoietic growth factors into the clinical practice... Sequential chemotherapy and dose-dense chemotherapy are two concepts that greatly influenced the design of adjuvant clinical trials in breast cancer during the last decade. The design of such trials was mostly empirical although it was based on mathematical and experimental evidence stressing the superiority of dose-dense sequential chemotherapy over conventional chemotherapy.”


**ADJUVANT A + C**

- “Our pilot study of doxorubicin followed by cyclophosphamide demonstrates the safety and feasibility of the sequential dose-dense plan. Long-term follow-up, although noncomparative, is promising... Because the sequential plan can decrease overlapping toxicities, it is an appropriate platform for the addition of newer active agents, such as taxanes or monoclonal antibodies.”


**ADJUVANT E = T + C MF**

- “The E-CMF regimen is well tolerated, as adjuvant treatment, in patients with operable breast cancer with promising activity and deserves further evaluation in phase III studies.”


**ADJUVANT WEEKLY AC**

- “Continuous dose-dense chemotherapy with G-CSF support produced encouraging results, which seem to be superior to those expected with ‘standard’ doxorubicin and cyclophosphamide chemotherapy. It deserves a test in the form of a randomized trial where this approach to anthracycline-based treatment is compared with intermittent administration.”


**SELECT PUBLICATIONS**

