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, major Phase III randomized trials are evaluating the role of dose-dense adjuvant chemotherapy. CALGB 9741 is closed to accrual, and initial results were presented at the San Antonio Breast Cancer Symposium in December, suggesting a disease-free and survival advantage in the dose-dense randomization arms.

Three-year results of CALGB 9741, a phase III randomized study comparing dose-dense versus conventional scheduling and sequential versus combination adjuvant chemotherapy for node-positive breast cancer

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Dose-dense Scheduling</th>
<th>Conventional Scheduling</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td>85%</td>
<td>81%</td>
<td>RR = 0.74 (p = 0.007)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>92%</td>
<td>90%</td>
<td>RR = 0.69 (p = 0.014)</td>
</tr>
</tbody>
</table>

DEFINITION OF 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 suggesting the superiority of dose-dense sequential chemotherapy over conventional chemotherapy.”


INTERGROUP TRIAL 9741

This study was designed with input from all members of the breast Intergroup and coordinated by the CALGB. It had a two-by-two factorial design. The two parameters were dose-density — giving drugs every two weeks instead of every three weeks using G-CSF — and combination versus sequential therapy. The doses were the same optimal doses derived from previous clinical trial experience. The only difference was the schedules.

—Larry Norton, MD

CLINICAL APPLICABILITY OF DOSE-DENSE ADJUVANT CHEMOTHERAPY

Dose-dense adjuvant chemotherapy in a nonprotocol setting is a reasonable option. This trial, which accrued over 2,000 patients, shows improved efficacy, decreased death rates and reduced toxicity; therefore, there’s no reason not to use dose-dense chemotherapy at this time. I believe in dose-dense therapy because I’ve seen its evolution in the laboratory and the clinic for 25 years, and I believe it has a solid basis. However, no individual can stand up and say this is the new standard of care. We have to see how people are going to utilize this in the community. I would not be shocked to find this approach widely accepted and used, but whether it becomes a new standard of care needs to be defined by the community.

—Larry Norton, MD

ACCEPTANCE OF DOSE DENSITY IN CLINICAL PRACTICES

Dose-dense therapy is definitely a therapeutic option for high-risk patients with breast cancer at this time. I always present patients with their options, and I like to hear what they have to say. In general, patients want to receive the treatment quickly — in fact, that’s one of the most common reasons patients express for wanting dose-dense therapy. I was initially embargoed from revealing the results of CALGB 9741, but now I discuss it with patients. I give them my take on the literature and my recommendation. I’ve been surprised how positively dose-dense therapy has been received. As I talk to physicians, I find they are often already using or at least considering it.

—Marc Citron, MD