Optimizing Adjuvant Chemotherapy: Ongoing Trials and Recent Results

Two taxane-containing regimens have demonstrated improved efficacy in recent studies—dose-dense, every two-week AC + paclitaxel with growth factor support, and TAC (docetaxel, doxorubicin, and cyclophosphamide). Because of the relatively high rate of febrile neutropenia, growth factor support is required for the TAC regimen. Indirect comparison of databases suggests similar efficacy and tolerability, and both have demonstrated an overall survival advantage in randomized trials. Another taxane-containing regimen — AC followed by docetaxel — is commonly utilized in the adjuvant setting, but has only been reported in a major randomized trial in the neoadjuvant setting. While the benefits in terms of disease-free and overall survival observed in CALGB-9741 are clear, it is unclear whether the advantage observed from dose-dense scheduling is related to the AC portion of the regimen or paclitaxel scheduling.

CALGB-9741: ADJUVANT DOSE-DESI SCHEDULE CHEMOTHERAPY

This study, designed with input from all members of the Breast Intergroup and coordinated by the CALGB, had a two-by-two factorial design. The two parameters were dose density — giving drugs every two weeks with G-CSF instead of every three weeks — and combination sequential versus therapeutic. The doses were derived from previous clinical trial experience. The only difference was the schedule. This trial, which accrued more than 2,000 patients, showed improved, decreased death rates and reduced toxicity. I believe in dose-dense therapy because I’ve seen its evolution in the laboratory and the clinic for 25 years. It has a solid evidence base.

LARRY MARTELL, MD

SWISS-0221: DOARES DENSE VERSUS CONTINUOUS CHEMOTHERAPY

In this study, AC is administered in either a dose-dense manner with pegfilgrastim or what might be described as a therapeutic schedule with filgrastim. Both schedules are then followed by paclitaxel. We chose six cycles of AC and paclitaxel in the control arms for several reasons. By imposing similar durations of treatment in all arms, we avoid wondering later whether an inferior outcome in any arm reflected the duration of treatment. Data suggest six cycles is superior, although this is still controversial. This more continuous schedule may provide a good chemotherapy base upon which to add other antangiogenic approaches. Evidence suggests that with the maximum tolerated dose schedule a burst of angiogenesis occurs between cycles. Hematopoietic growth factors possibly augment that, but it is unclear whether that occurs with weekly dosing and daily cyclophosphamide.

G. THOMAS BUDD, MD

USE OF ADJUVANT TAC

Taxane with AC is the only two chemotherapy regimen in the adjuvant setting, typically utilizing a six-cycle TAC regimen. The disease-free and overall survival of dose-dense therapy and TAC are similar. Growth factor support, used in conjunction with TAC, reduces the rate of febrile neutropenia to that seen in CALGB-9741.

— Denise A. Talbot, MD

INTERVENTING DOSE DENSITY INTO CLINICAL TRIAL

CALGB-40101 incorporates the every-two-week schedule comparing paclitaxel to AC in patients with high-risk, node-negative breast cancer. It also compares four cycles versus six, and although many clinicians think they already know which is better, this is the first point-on testament. It’s not so difficult to believe that therapy every two weeks is better than every three weeks. One may question whether it’s worth the effort, but because treatment is completed faster and it lowers the risk of neutropenic fever, I believe it is worthwhile.

— Clifford Hudis, MD

NSABP TRAIL B-38

NSABP-B38 will compare two anthracycline/taxane regimens with a new combination in the paclitaxel phase. It’s a good trial design because in addition to determining which phase of the breast cancer risk is more important, it combines the two parameters in the phase. It’s a good trial design because in addition to determining which phase of the breast cancer risk is more important, it combines the two parameters in the phase. It’s a good trial design because in addition to determining which phase of the breast cancer risk is more important, it combines the two parameters in the phase. It’s a good trial design because in addition to determining which phase of the breast cancer risk is more important, it combines the two parameters in the phase. It’s a good trial design because in addition to determining which phase of the breast cancer risk is more important, it combines the two parameters in the phase. 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— Shams E. Thomas, MD