

WEB EXCLUSIVES

Looking for the Optimal Treatment Schedule for Taxanes

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The first generation of studies involving a group of chemotherapy drugs known as taxanes established their role in the treatment of breast cancer. Now, a second generation of trials is investigating the optimal schedules for use of taxanes. Conflicting results from two large studies including the taxanes, NSABP B-30 and BCIRG 005, were presented at SABCS on Sunday morning. These studies assessed various combinations and sequences of Adriamycin (doxorubicin), Taxotere (docetaxel), and/or Cytosan (cyclophosphamide).

NSABP B-30 was a phase III trial involving women with operable, lymph node-positive breast cancer that compared three adjuvant treatments: Adriamycin/Taxotere (AT), Taxotere/Adriamycin/Cytosan (TAC), and Adriamycin/Cytosan followed by Taxotere, a sequential treatment. The primary outcome measure was overall survival. According to final data presented by Sandra Swain, MD, of the National Cancer Institute, sequential treatment decreased mortality by 14 percent compared with TAC and by 17 percent compared with AT. But only the latter was significantly significant.

In terms of disease-free survival, the sequential treatment schedule had an even stronger advantage over the other two regimens. Disease-free survival was 17 percent better with the sequential treatment compared with TAC, and 20 percent better compared with AT.

It should be noted that dosing was changed for the AT and TAC groups after the study was initiated. Because of toxicities, the doses of Adriamycin and/or Cytosan were decreased, and the dose of Taxotere was increased.

Swain reported that compared with the other treatment groups, patients receiving the sequential treatment had significantly higher rates of infection, stomatitis (inflammation of the mucous membranes in the mouth), and febrile neutropenia, which can increase the risk of infection. Compared with the AT group, patients in the sequential treatment arm had significantly higher rates of severe vomiting and diarrhea.

Separately, Swain and her colleagues analyzed the subgroup of women who were premenopausal at the time they entered the NSABP B-30 study. The researchers investigated whether there was any difference in survival between women who experienced a loss of their menstrual periods (amenorrhea) and those who did not. They found that, across all three treatment arms, women who had amenorrhea (six months or more during a period of two years) had significantly better overall survival and disease-free survival than those who had more frequent menstrual periods.

Patients receiving AT treatment had the lowest rate of amenorrhea, according to a presentation involving quality-of-life data from the NSABP B-30 trial by Patricia Ganz, MD, of the University of California at Los Angeles. "It's a double-edged sword," Ganz said in an interview with *CURE*. "We would have liked to have had women have preservation of their menstrual periods and still have the survival benefit, but that did not appear to be the case." In response to a question after the presentation, Ganz said that AT could be an alternative for women in whom "preservation of fertility is paramount over the modest improvement in survival."

"We think that in younger women who continue to menstruate there may be a higher risk of recurrence, particularly if they have hormone receptor-positive tumors," Ganz added. She explained that according to previous research, removing the ovaries of premenopausal women improves survival. "Some people speculate that what chemotherapy is doing in younger women is improving their survival by stopping their menstrual periods."

Ganz and colleagues found that after six months of treatment, quality-of-life and side effects were similar for patients in all three treatment arms. Younger women had more severe symptoms, depending on whether or not they experienced amenorrhea.

Another cooperative group phase III trial, BCIRG 005, compared the sequential treatment with TAC as therapy for women with HER2-negative, lymph node-positive, early-stage breast cancer. According to data presented by Wolfgang Eiermann, MD, of Red Cross Women's Hospital in Munich, Germany, the two regimens were equal with regard to disease-free survival. Eiermann noted that this was true even though the doses of all three drugs were higher in the sequential regimen than in TAC, and even though sequential treatment was given for eight cycles compared with six cycles for TAC.

The TAC regimen was associated with significantly greater rates of febrile neutropenia and more severe thrombocytopenia (low platelet count), compared with the sequential treatment. However, some side effects rated moderately severe or severe were significantly more common with sequential treatment, including joint pain, sensory neuropathy, fluid retention, hand-foot syndrome, and muscle pain.

Of note, the doses of TAC given to patients in the BCIRG 005 trial were higher than the doses given in NSABP B-30 after the investigators in the latter trial adjusted dosing due to toxicity. Swain acknowledged that patients on TAC in NSABP B-30 may have been undertreated.

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