No Gains in Efficacy Observed by Adding Gemcitabine to Adjuvant Therapy for Lymph Node-Positive Breast Cancer

Researchers have published the final results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-38 trial confirming that outcomes are not improved by adding gemcitabine to standard adjuvant chemotherapy, and that no efficacy differences exist between the 2 optimal adjuvant chemotherapy regimens (J Clin Oncol. 2013;31:3197-3204).

“This trial adds to the existing data and shows that there are multiple effective options for the adjuvant treatment of breast cancer,” says Sandra Swain, MD, medical director of the Washington Cancer Institute at MedStar Washington Hospital Center and professor of medicine at Georgetown University, both in Washington, DC. “The dialogue with the patient is important to discuss the different toxicities of each to tailor the appropriate treatment for that patient.”

In previous clinical trials, the addition of gemcitabine (G) to paclitaxel (P) was shown to improve outcomes in patients with metastatic breast cancer, and therefore the researchers set out to determine whether this benefit translated into the adjuvant setting. Furthermore, doxorubicin (adriamycin [A]) and cyclophosphamide (C) followed by P (AC→P) on a dose-dense schedule, as well as the regimen of docetaxel, doxorubicin, and cyclophosphamide (TAC), have been shown to be effective adjuvant chemotherapy regimens. The current study design allowed for these 2 regimens to be compared, which they previously had not been, in a single, prospective, randomized study.

Dr. Swain and her coinvestigators randomized 4894 women with lymph node–positive early breast cancer who underwent mastectomy or lumpectomy to 1 of 3 adjuvant chemotherapy regimens: 1) 6 cycles of TAC (T at a dose of 75 mg/m², A at a dose of 50 mg/m², and C at a dose of 500 mg/m² every 3 weeks); 2) dose-dense AC→P (4 cycles of A at a dose of 60 mg/m² plus C at a dose of 600 mg/m² every 2 weeks followed by 4 cycles of P at a dose of 175 mg/m² every 2 weeks); or 3) dose-dense AC→PG (AC every 2 weeks for 4 cycles followed by 4 cycles of P plus G at a dose of 2000 mg/m² every 2 weeks).

All patients received primary prophylaxis for neutropenia with filgrastim or pegfilgrastim. Patients who underwent a lumpectomy were required to have a plan for radiation therapy after chemotherapy, and all patients underwent analysis of their hormone receptor status before entering into the study. After 1 year, the protocol was amended so that patients who were found to be positive for human epidermal growth factor receptor 2 (HER2) (HER2+) were excluded. However, any patient who was enrolled before this amendment and found to be HER2+ could receive trastuzumab along with the chemotherapy.
The distribution of HER2+ patients was fairly even between the trial arms, and 80% of patients in each arm had tumors that were hormone-receptor positive. The majority of patients (approximately 90% in each arm) were able to complete the chemotherapy regimen as written in the protocol.

“This trial has no major weaknesses, but because 80% of patients had [estrogen receptor-positive] ER+ disease, more than half of the disease-free survival events have not yet occurred. Statistically it is a definitive report, but clinically it is not,” says Kathy Miller, MD, associate professor and coleader of the breast cancer program at the Indiana University Simon Cancer Center in Indianapolis, Indiana. However, despite this, she does not believe the overall efficacy results will be affected with longer follow-up.

Study Results
After a median follow-up of 64 months, 941 disease-free survival (DFS) events were reported (327 in the TAC arm, 294 in the dose-dense AC→T arm, and 320 in the dose-dense AC→TG arm). DFS events were defined as local, regional, or distant breast cancer recurrence; second primary cancer; or death. No significant differences were observed with regard to efficacy endpoints between the regimens. The 5-year DFS rate for dose-dense AC→PG compared with dose-dense AC→P was 80.6% versus 82.2%. The DFS rate for dose-dense AC→PG compared with TAC was 80.6% versus 80.1%. Furthermore, the hazards ratio for DFS of dose-dense AC→P versus TAC was 0.87 (P = .07). No significant differences in overall survival were observed between the treatment arms, with each arm demonstrating a 5-year survival rate of approximately 90%.

Furthermore, there were no differences in survival noted between the treatment arms in any ER or lymph node status subset. Multiple Cox proportional hazards models were performed adjusting for age, number of positive lymph nodes, ER status, receipt of radiation therapy, and type of surgery. No significant differences were seen between arms with these adjustments.

No new safety issues were noted, with the reported toxicities being typical for the regimens used. There were, however, some significant differences in toxicities between treatment arms. Grade 3 or 4 febrile neutropenia was significantly more common in the TAC arm compared with the AC→P or AC→PG arms (9%, 3%, and 3%, respectively), while grade 3 or 4 sensory neuropathy was significantly lower with the TAC regimen compared with the AC→P or AC→PG arms (less than 1%, 7%, and 6%, respectively). In addition, the occurrence of grade 3 or 4 diarrhea was significantly higher in the TAC arm, with a rate of 7% versus 2% for the other 2 arms.

Furthermore, a hemoglobin level of less than 10 mg/dL was observed in 12% of patients receiving TAC, 26% of patients receiving AC→P, and 33% of patients receiving AC→PG. This translated to significantly more patients receiving transfusions and erythropoietin-stimulating agents on the dose-dense arms. An unplanned exploratory analysis showed no difference in second cancers or DFS between the patients who received erythropoietin-stimulating agents and those who did not.

Future Directions
The authors conclude that because the efficacy among standard triplet anthracycline-based and taxane-based regimens for patients with early-stage breast cancer is similar in this large phase 3 trial, clinicians and patients can choose based on the toxicity profile and schedule. “Future studies that explore the addition of other cytotoxic chemotherapy agents, or make changes in dosage or scheduling to current triplet regimens, are unlikely to be fruitful,” says Dr. Swain.

Dr. Miller concurs and states that the time for large and broad adjuvant trials has passed. “To reap larger gains in efficacy, future efforts at improving adjuvant regimens must concentrate on the biology in the subset of patients who truly need chemotherapy,” she says. She adds that it is possible many of the patients with ER+ disease in the NSABP-38 trial may not have needed chemotherapy.

In this regard, Dr. Swain points out that there are ongoing studies examining gene profiling in lymph node-positive patients with low recurrence-risk scores to determine if they really do need chemotherapy. There is also an ongoing study on the effect of adding everolimus to standard hormonal therapy in patients with hormone receptor-positive disease with high recurrence-risk scores. These types of studies will have the greatest impact on how the adjuvant treatment of breast cancer is improved and refined.

doi: 10.3322/caac.21206