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Phase III Trial Data Support Current Standard 12-month Adjuvant Trastuzumab for HER2-positive Breast Cancer

Nine weeks of trastuzumab may be sufficient for patients who receive higher dose of docetaxel

SAN ANTONIO — Disease-free survival (DFS) after nine weeks of adjuvant trastuzumab and standard chemotherapy was not comparable to DFS after 12 months of adjuvant trastuzumab and standard chemotherapy for women with early-stage HER2-positive breast cancer, supporting the current practice of extended trastuzumab treatment, according to data from the phase III Synergism or Long Duration (SOLD) clinical trial, presented at the 2017 San Antonio Breast Cancer Symposium, held Dec. 5–9.

The study, however, found no substantial difference in the secondary endpoints of distant disease-free survival (DDFS) and overall survival (OS) between the 12-month trastuzumab arm and the nine-week trastuzumab arm.

“The choice for one-year duration of trastuzumab administration in patients with HER2-positive breast cancer was arbitrary, and not based on research data,” said Heikki Joensuu, MD, professor in the Department of Oncology at the Helsinki University Hospital and University of Helsinki in Finland.

In all four large randomized trials that established the current standard treatment (chemotherapy plus trastuzumab), trastuzumab was given for one year and, therefore, the one-year duration became the standard, Joensuu explained. In two randomized trials with relatively limited statistical power, there was no statistical difference in DFS or OS between those who received nine weeks versus 12 months of trastuzumab.

“The current standard treatment is lengthy, costly, and occasionally associated with cardiac adverse events,” Joensuu said. While trastuzumab is well tolerated in general, the most important adverse effect is congestive heart failure (CHF). CHF occurred in less than 3 percent of the patients treated in the pivotal clinical trials, but the risk for trastuzumab-related CHF is likely higher in elderly patients who have pre-existing risk for CHF, he added.

Joensuu and colleagues studied whether it is sufficient to administer trastuzumab with chemotherapy only for a brief period of time (nine weeks) instead of the standard practice of administering trastuzumab both during chemotherapy (for nine weeks) and then as a single agent after stopping chemotherapy (for 12 months).

“We could not demonstrate that the experimental treatment [nine weeks of trastuzumab] is similar in efficacy as the standard treatment [12 months of trastuzumab] in terms of DFS,” said Joensuu. “There was, however, not much difference between the groups in two other important clinical endpoints, DDFS and OS, which were secondary objectives of the study.”

In SOLD, the investigators randomly assigned (1:1) 2,176 patients with early-stage HER2-positive breast cancer to the nine-week trastuzumab arm or the 12-month trastuzumab arm.

Patients in both arms received three cycles of docetaxel (80 mg/m^2 or 100 mg/m^2) and trastuzumab three times a week, followed by three cycles of chemotherapy. Patients in the nine-week arm received no further treatment while those in the 12-month arm received trastuzumab every three weeks for 14 cycles. Patients with estrogen receptor-positive cancer received appropriate endocrine treatment and radiation therapy per guidelines.

In the 12-month arm, DFS was 90.5 percent, compared with 88 percent in the nine-week arm. There was no substantial difference in DDFS and OS between the two arms: five-year DDFS was 93.2 percent in the nine-week arm and 94.2 percent in the 12-month arm; five-year OS was 94.7 percent in the nine-week arm and 95.9 percent in the 12-month arm.

“Interestingly, we detected a significant interaction between the dose of docetaxel given concomitantly with trastuzumab in preplanned subgroup analyses,” noted Joensuu.

Among patients who received 100 mg/m^2 docetaxel, DFS in the nine-week arm was similar to the DFS in the 12-month arm, but among those who received 80 mg/m^2 docetaxel, 12 months of trastuzumab yielded superior DFS than nine weeks, suggesting that the dose of docetaxel administered with trastuzumab may influence survival outcomes. “This, and brief dual inhibition of HER2 with trastuzumab and pertuzumab, each given with an adequate dose of a taxane, warrant further studies,” he said.

“The shorter trastuzumab treatment was safer to the heart than the longer treatment,” added Joensuu. Cardiac failure occurred in 3 percent and 2 percent of patients in the 12-month and nine-week arms, respectively. Patients in the nine-week arm had significantly higher cardiac left ventricle ejection fractions (LVEFs) than patients in the 12-month arm, but the absolute differences were small, and the LVEFs mostly returned to the baseline level within three years after the date of randomization, Joensuu said.

A limitation of the study is that because of cancer characteristics and some logistical issues, including not being able to reach the planned number of DFS events within a reasonable time frame, the study had lower statistical power than planned.

SOLD was funded by Pharmac (New Zealand), Sanofi, Novartis, the Academy of Finland, the Cancer Society of Finland, Helsinki University Hospital research funds, Sigrid Juselius Foundation, and Jane and Aatos Erkko Foundation. Joensuu is a scientific advisor for Neutron Therapeutics, has received consultation fees from Orion Pharma, and has stock ownership interest in Orion Pharma, Faron Pharmaceuticals, and Sartar Therapeutics.

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