Hormone Receptor Status Affects Locoregional Control in HER2-Positive Breast Cancer Treated With Trastuzumab

A recent study suggests for the first time that treatment with trastuzumab lowers the risk of locoregional recurrence (LRR) in patients with hormone receptor–positive (HR+) / human epidermal growth factor receptor 2 (HER2)-positive (HER2+) breast cancer, but does not confer the same benefit in patients with HR-negative (HR−) / HER2+ disease (Cancer. 2012; doi:10.1002/cncr.27502).

“Our study suggests that there is an interaction between hormone receptor status, HER2 status, and the locoregional benefit of their corresponding targeted therapies,” say authors Thomas Buchholz, MD, chair of radiation oncology, and Michelle Kim, MD, radiation oncology resident, both at MD Anderson Cancer Center in Houston, Texas.

According to the authors, although there are multiple studies showing survival benefit for adjuvant trastuzumab in early-stage HER2+ breast cancer and tumor response in advanced-stage HER2+ breast cancer regardless of hormone receptor (HR) status, there has not been research regarding locoregional benefits in relation to HR positivity or negativity. Their team, therefore, set out to study the relationship between HER2 and HR status with trastuzumab treatment and the effects on locoregional control, because locoregional recurrence directly influences survival in early stage breast cancer.

The researchers included 5683 women with invasive breast cancer and confirmed HR and HER2 status treated with definitive locoregional and systemic therapy at MD Anderson Cancer Center between 2000 and 2008. Estrogen receptor (ER) and progesterone receptor (PR) status was considered positive if 1% or more positive tumor nuclei were seen on immunohistochemical staining. HR was considered positive if either or both ER and PR were positive. HER2 was considered positive if immunohistochemistry was scored 3+ or was positive by fluorescence in situ hybridization. Patients were divided into 6 subgroups: HER2+/HR+ or HER2+/ HR− with or without trastuzumab treatment, HER2−/ HR+, and HER2−/HR− (triple negative) disease. Relapse in the ipsilateral breast or chest wall, and/or ipsilateral axillary, internal mammary, or supraclavicular nodes was considered LRR without regard to systemic recurrence.

Locoregional Benefit From Trastuzumab May Depend on More Than HER2

Patients with triple-negative disease had the highest 5-year LRR rate and those with HER2−/HR+ had the lowest, at 9% and 2%, respectively. Among the 4 subgroups of patients with HER2+ tumors, LRR rate varied. In patients with HER2+/HR+ disease, the 5-year LRR rate was 3% in patients who received trastuzumab and 6% in those who did not. In patients with HER+/ HR− disease, the 5-year LRR rate was 6% regardless of treatment with trastuzumab. On univariate and multivariate analyses LRR rates were similar in the HER2−/HR+ cohort and HER2+/HR+ trastuzumab-treated cohort. All other cohorts had significantly higher LRR rates on both analyses. Multivariate analysis of the interaction between receptor subgroup and type of locoregional treatment showed that the LRR rate was independent of surgery type or radiation treatment among the cohorts.

“Since the very first report by the NSABP [National Surgical Adjuvant Breast and Bowel Project] and the North American Intergroup, it has been apparent that adjuvant trastuzumab lowers the risk of locoregional recurrence, along with improving disease-free and overall survival, in women with HER2-positive breast cancer,” says Harold Burstein, MD, PhD, associate professor of medicine at Harvard Medical School in Boston, Massachusetts. “This study suggests that the lion’s share of the locoregional benefit is in tumors that also express hormone receptor.” He adds that it is unclear why the effects of trastuzumab should differ between subgroups in locoregional recurrence when other studies show benefit of trastuzumab regardless of ER status when it comes to disease-free survival.

The findings of the current study suggest that LRR risk among patients who are HR− is elevated, even for those with HR−/HER2+ disease treated with trastuzumab, as
compared to patients who are HR+. The authors state that there have been 5 prospective studies of adjuvant trastuzumab with chemotherapy, but only the combined analysis of the B-31 and N9831 trials looked at the effect of HR status on the outcomes. In this analysis, there was no effect of HR status on the survival benefit of trastuzumab in HER2+ patients, but no LRR data according to HR status was included (N Engl J Med. 2005;353:1673-1684). Further, a combined analysis of 3 studies showed no effect of HR status on time to progression or response rate in HER2+ patients with metastatic disease treated with trastuzumab either alone or in conjunction with chemotherapy (Clin Breast Cancer. 2005;6:247-252).

Besides the inherent weaknesses of a retrospective study, other limitations that may have affected these findings include: no analysis according to level of HR expression, the low overall LRR rate, and the shorter time of follow-up of the patients with HER2+ treated with trastuzumab.

“While our findings suggest an interaction between hormone receptor status, HER2 status, and trastuzumab treatment, it is important to note that overall, locoregional recurrence [LRR] rates were relatively low in this cohort of patients, which limits the ability to detect small differences between patient subgroups according to locoregional therapy,” Dr. Kim says. “In addition, varying degrees of estrogen and/or progesterone receptor expression may also influence reported outcomes in these studies.” She added that future studies including a quantitative assessment of the impact of ER and PR expression on locoregional and systemic disease control may clarify the benefit of trastuzumab in relation to HR status and the complex interrelationship that exists between these signaling pathways.

To the authors’ knowledge, this is the first study to look at LRR risk among receptor subgroups before and after the introduction of trastuzumab around 2004. They found that treatment with trastuzumab lowered the LRR risk by 50% in patients with HER+/HR+ disease, but those who were HER2+/HR− had the same rate of LRR regardless of trastuzumab treatment. It suggests that further strategies may be needed for locoregional control in this subset of patients and that future studies should look at this interaction. “The novel findings in our study are hypothesis-generating, and should help direct future studies that identify and characterize factors mediating the efficacy of trastuzumab on clinical outcomes among patients with HER2-positive disease,” Dr. Kim says.

Dr. Burstein says he hopes that this retrospective, single-center study will prompt investigators associated with the 7 randomized trials of adjuvant trastuzumab to analyze their local recurrence outcomes by HR status. “Meanwhile, patients with HER2-positive breast cancer should continue to receive high-quality, multidisciplinary care regardless of hormone receptor status,” he says. ■

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