Trastuzumab and Congestive Heart Failure: What Can We Learn From Use in the Community?

Ann M. Geiger

Correspondence to: Ann M. Geiger, MPH, PhD, Division of Public Health Sciences, Wake Forest School of Medicine, Medical Center Boulevard, Winston Salem, NC 27157 (e-mail: ageiger@wakehealth.edu).

The development of trastuzumab for the treatment of non–metastatic invasive breast cancer tumors expressing HER2 has been lauded as an “elegant example of translational research” (1), representing an important step toward the “era of personalized oncology” (2). Multiple trials have documented clinically and statistically significant improvements in overall and disease-free survival for women receiving adjuvant treatment including trastuzumab vs women whose regimens do not include this agent (3). Trastuzumab for HER2-positive early (stages I and II) breast cancer also appears cost-effective at a threshold of $50 000 per quality-adjusted life year (4), a rare achievement for new cancer chemotherapies.

As is often true, the clear benefits of trastuzumab have been offset by important safety concerns, particularly the possibility of an increased risk of congestive heart failure. The recognition of this risk in trials of trastuzumab for metastatic breast cancer resulted in careful monitoring of cardiac function in subsequent trials in the early breast cancer setting (5). A pooled analysis of the early breast cancer trials suggests a fivefold increase in risk of congestive heart failure for women who receive trastuzumab vs those who do not. These results are consistent across varying treatment regimens (3).

In this issue of the Journal, Bowles et al. (6) describe the association of trastuzumab with congestive heart failure among women treated in the community outside clinical trials. They report a four- to sevenfold increased risk of congestive heart failure in women who received trastuzumab-containing chemotherapy regimens compared with those who did not receive chemotherapy, after adjusting for age and other factors. The authors appropriately acknowledge a number of limitations inherent to their study and all observational studies that use data gathered for purposes other than clinical research. Those limitations are unlikely to account for the strong association between trastuzumab and heart failure in this study. Although the magnitude of the association is somewhat greater than what has been reported in the trials, the results of the Bowles et al. study (6) and clinical trials (3) seem consistent, given the broader use of trastuzumab in the community.

What does the study by Bowles et al. (6) then add to our understanding of the association of trastuzumab with congestive heart failure? First, the median follow-up time of 4.4 years exceeds by 1 year the median follow-up time of 3.3 years of trials reported to date (3). The incidence of congestive heart failure appears to continue increasing over this additional year of follow-up, and there is no indication of a plateau. These results provide additional evidence that heightened risk of heart failure is a long-term effect of previous trastuzumab use rather than a short-term increase associated with current or recent use. This justifies long-term surveillance for congestive heart failure in women who have received trastuzumab, as well as extended follow-up of women enrolled in trials.

Second, the results from Bowles et al. (6) raise questions about the design of treatment and comparison arms in randomized controlled trials. Of the eight trials reported to date (3), seven included anthracycline in both treatment and comparison arms. Only two included an arm in which trastuzumab was combined with chemotherapy regimens not including anthracyclines. Just one trial used a comparison arm with no anthracycline administration (3). Yet Bowles et al. (6) in their observational study found that about 40% of women undergoing chemotherapy received regimens excluding anthracycline, likely due in part to the older age (>65 years) and higher comorbidity burden relative to participants in clinical trials. However, nearly a third of the women on nonanthracycline regimens in the Bowles et al. (6) study were younger than age 55 years and presumably quite comparable to trial participants with a median age of 49 years (3). Although we can debate the appropriateness of avoiding anthracycline use in younger women, treatment and control arms that reflect the actual choices of physicians and patients in the community would provide valuable information for younger women who are most likely to withstand trastuzumab toxicity and benefit in years of life saved.

Finally, roughly a quarter of the women who received adjuvant trastuzumab in the Bowles et al. (6) study were treated well in advance of the publication of peer-reviewed results of relevant randomized controlled trials [eg (7,8)]. Presumably these women were treated based on findings from trials in women with metastatic breast cancer, as well as presentation of preliminary data from the early breast cancer trials. The adoption of trastuzumab before the trial results were published is a concern, given interim findings were based on follow-up periods too short to account for the lengthier life expectancy of women with early breast cancer relative to women with metastatic disease. There are a number of cases in which new treatments disseminate based on preliminary reports of benefit, only to be withdrawn after additional safety data become available. Autologous bone marrow transplantation for breast cancer is a particularly egregious example. Patients, clinicians, and researchers must temper their enthusiasm about the benefits of new cancer therapies with the recognition that estimates of the long-term risk of adverse events are based on short-term observations among carefully selected clinical trial participants.
In conclusion, the study by Bowles et al. (6) suggests that the risk of congestive heart failure after trastuzumab treatment for women with non–metastatic invasive breast cancer tumors expressing HER2 in community-based settings is equivalent to or greater than the risk reported thus far by clinical trials. There is a need for ongoing monitoring for congestive heart failure in women who have received trastuzumab and continued prudence in the use of trastuzumab outside clinical trials. The Bowles et al. (6) study also illustrates how observational studies complement randomized controlled trials by capturing valuable information about treatment outcomes for the vast majority of women who are unable to access a trial.

References

Funding
National Cancer Institute, National Institutes of Health (CA155932-01A1 to AMG).

Notes
The author declares no conflict of interest.

Affiliation of author: Ann M. Geiger, Division of Public Health Sciences, Wake Forest School of Medicine, Winston Salem, NC.