Adjuvant Chemotherapy and Trastuzumab Is Safe and Effective in Older Women With Small, Node-Negative, HER2-Positive Early-Stage Breast Cancer

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Abstract

The benefit of adjuvant trastuzumab with chemotherapy in breast cancer is well-established; however, its impact on outcomes for older women with small, node-negative, human epidermal growth factor receptor 2-positive disease is less clear and unlikely to be addressed in prospective studies. This retrospective, sequential cohort study suggests adjuvant trastuzumab with chemotherapy results in excellent breast cancer outcomes with few cardiac events in this population.

Introduction: The benefit of adjuvant trastuzumab with chemotherapy is well established for women with higher risk human epidermal growth factor receptor 2-positive ($HER2^+$) breast cancer. However, its role in older patients with smaller, node-negative tumors is less clear. We conducted a retrospective, sequential cohort study of this population to describe the impact of trastuzumab on breast cancer outcomes and cardiac safety. **Patients and Methods:** Women $\geq$ 55 years with $\leq$ 2 cm, node-negative, $HER2^+$ breast cancer were identified and electronic medical records reviewed. A no-trastuzumab cohort of 116 women diagnosed between January 1, 1999 and May 14, 2004 and a trastuzumab cohort of 128 women diagnosed between May 16, 2006 and December 31, 2010 were identified. Overall survival and distant relapse-free survival were estimated by Kaplan-Meier methods. **Results:** The median ages of the trastuzumab and no-trastuzumab cohorts were 62 and 64 years, respectively. More patients in the trastuzumab cohort had grade III ($P = .001$), lymphovascular invasion ($P = .001$), or estrogen receptor-negative ($P < .001$) cancers. The majority of the trastuzumab cohort received chemotherapy versus one-half of the no-trastuzumab cohort (98% vs. 53%; $P < .0001$). The median follow-up was 4 versus 9 years in the trastuzumab versus no-trastuzumab cohorts; therefore, outcomes at 4 years are reported. Despite the higher-risk tumor features in the trastuzumab group, the 4-year overall survival was 99% in both cohorts; the distant relapse-free survival was 99% versus 97% in the trastuzumab versus no-trastuzumab cohorts. Four (3.1%; 95% confidence interval, 1.0%-7.8%) women in the trastuzumab cohort and 1 in the no-trastuzumab cohort developed symptomatic heart failure. There were no cardiac-related deaths in either arm. **Conclusion:** Following adjuvant trastuzumab with chemotherapy, selected older women with small, node-negative, $HER2^+$ breast cancers have excellent disease control. The rate of cardiac events is low.

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Introduction

In breast cancer, gene amplification or protein overexpression of human epidermal growth factor receptor 2 (HER2) is associated with an aggressive biologic phenotype, which confers a significant risk of distant recurrence, even in the setting of lymph node-negative disease.[1] However, this risk has been largely ameliorated by the successful development of the anti-HER2 monoclonal antibody trastuzumab.[2] Specifically, when administered in combination with adjuvant chemotherapy in multiple adequately powered, prospectively conducted randomized studies, trastuzumab dramatically improved disease-specific outcomes for women with HER2-positive ($HER2^+$) disease.[3-6] In these pivotal studies, however, older women and those with lower-risk, node-negative disease, were underrepresented. Subsequent studies have since indicated that both populations appear to derive benefit from adjuvant trastuzumab with chemotherapy,[7-9] although the benefits in older women may be offset by increased treatment-related hospital admission rates[7] and higher rates of trastuzumab-mediated cardiotoxicity.[10-13]

We have previously reported 2 retrospective, single-institution studies demonstrating the potential benefit of adjuvant trastuzumab-based therapy in women with small, node-negative breast cancers.[9,14] Other investigators have since demonstrated consistent results.[15,16] However, 65% of new breast cancer diagnoses occur in patients over 55 years of age,[17] and the risk of cardiotoxicity from trastuzumab increases above 50 years of age.[18,19] Furthermore, patients (including those with larger tumors and node-positive disease) in the meta-analysis of the pivotal III trials of adjuvant trastuzumab had a median age of 49 years.[2] Hence, the risks and benefits of trastuzumab with chemotherapy in older women with node-negative $HER2^+$ disease have not been fully defined. Although there is no single definition of "older" patients, we focused on women aged $\geq$ 55 years and conducted a retrospective, single-institution, sequential cohort study of patients with small, node-negative, $HER2^+$ breast cancer who did or did not receive adjuvant trastuzumab.

Patients and Methods

Patients treated at Memorial Sloan Kettering Cancer Center (MSKCC) between January 1, 1999 and December 31, 2010 were identified through an institutional database, and electronic medical records were reviewed via an MSKCC institutional review board-approved waiver of informed consent. Women were included in this study if they met the following criteria: age $\geq$ 55 years, pathologically confirmed invasive breast cancer $\leq$ 2 cm without lymph node involvement (T1N0), $HER2^+$ disease defined as 3+ by immunohistochemistry and/or gene amplification ($\geq$ 2) by fluorescence in situ hybridization (FISH).

As previously described,[9,14] patients were identified as members of the no-trastuzumab or trastuzumab cohorts by use of adjuvant trastuzumab therapy, which was associated with the time of their initial diagnosis and treatment. Specifically, women treated before versus after the reporting of the first 2 pivotal phase III adjuvant trastuzumab trials in May 2005[20,21] were identified. Given the potential for variable clinical practice patterns in the immediate period after the May 2005 adjuvant trastuzumab clinical trials were reported, women treated between May 15, 2004 and May 15, 2005, who may have been offered delayed trastuzumab, were excluded. Hence, 2 cohorts of women were identified: those diagnosed between January 1, 1999 and May 15, 2004 (no trastuzumab) and those diagnosed between May 15, 2005 and December 31, 2010 (trastuzumab).

In most of the phase III studies, the planned duration of adjuvant trastuzumab was 1 year. However, because some data suggested a comparable benefit for a relatively short course of trastuzumab ($\leq$ 9 weeks) therapy, the duration of trastuzumab administration was not used to define eligibility for the current study.[4,22] Only women from the trastuzumab era who did not receive any anti-HER2 therapy were excluded. Other exclusion criteria, applicable to both cohorts, included current bilateral invasive breast cancer, a prior history of invasive breast cancer, or inadequate documentation of locoregional or systemic therapy. Electronic medical records were reviewed, and patient and tumor characteristics were recorded for all eligible patients. In addition, data on adjuvant therapy, including side of radiation, chemotherapy, and hormonal therapy, were collected.

Breast Cancer Outcomes

Breast cancer-specific outcomes were evaluated by administration of trastuzumab versus no administration of trastuzumab. Overall survival (OS) was defined as time from breast cancer diagnosis to date of death. Surviving patients were censored at the time of the most recent direct communication with MSKCC. Distant relapse-free survival (DRFS), distant metastatic disease or death from any cause, and ipsilateral/contralateral invasive breast cancers were defined from date of diagnosis to event as per Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials (STEEP) criteria.[23] Patients who did not have a recurrence event were censored at the date of the most recent assessment by relevant site-specific imaging or physical examination by a an MSKCC physician or nurse practitioner. OS and DRFS were analyzed using the Kaplan-Meier method, and 4-year estimates with 95% confidence intervals (CIs) were evaluated. The 4-year time point was chosen for our primary evaluation because this is the median follow-up for women in the trastuzumab group (the group with the shorter follow-up). No formal hypothesis testing is reported because of the low number of observed events in this low-risk patient population. Patient demographics and disease characteristics were tested by trastuzumab status using the χ^2 test or two-sample t test. Given the relatively small numbers of patients who developed ipsilateral and contralateral breast cancer, these events are reported descriptively.

Cardiac Outcomes

Electronic medical records were used to collect baseline cardiac risk factor data from time of breast cancer diagnosis, including smoking history, prior cardiac or cerebrovascular events, hypertension, hyperlipidemia, atrial fibrillation, diabetes mellitus, renal function, and body mass index. The occurrence of any cardiac event, defined as symptomatic heart failure or decline in left ventricular ejection fraction from time of diagnosis to most recent follow-up, was recorded. Attribution of heart failure was determined