Should Elderly HER-2 Positive Breast Cancer Patients Without Pre-existing Cardiac Disease Receive Trastuzumab Targeted Therapy? Post-Print

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Date: 2019-03-11T00:00:00+00:00

Abstract

With population aging, the treatment of breast cancer must address an increasing number of elderly breast cancer patients. In recent years, targeted therapy for breast cancer, as a crucial systemic treatment modality for human epidermal growth factor 2 (HER2)-positive breast cancer, has assumed an increasingly prominent role in breast cancer management. The use of trastuzumab for targeted therapy in elderly HER2-positive breast cancer patients without pre-existing cardiac conditions remains controversial. Current evidence demonstrates that elderly HER2-positive breast cancer patients aged 60-70 years can benefit from trastuzumab therapy, with a low and reversible risk of cardiac events. For patients over 70 years of age, there is currently no evidence from large-scale trials to support its use. When selecting adjuvant treatment regimens, it is essential to balance benefits against risks, comprehensively considering the patient's preferences, physical status, and comorbid conditions to deliver individualized therapy. If trastuzumab is selected, concomitant use with anthracycline chemotherapy agents should be avoided, and cardiac function must be monitored to enable timely detection and management of cardiac events.

Full Text

Should Elderly HER-2 Positive Breast Cancer Patients Without Cardiac Comorbidities Receive Trastuzumab Targeted Therapy?

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Abstract

With global population aging, breast cancer treatment must address an increasing number of elderly patients. In recent years, targeted therapy for HER2-positive breast cancer has emerged as a crucial systemic treatment modality. However, controversy persists regarding whether elderly HER2-positive breast cancer patients without pre-existing cardiac disease should receive trastuzumab. Current evidence indicates that patients aged 60-70 years can benefit from trastuzumab with low and reversible cardiac risks, though large-scale trial data for patients over 70 remain lacking. Treatment decisions require balancing benefits against risks while considering patient preferences, physical condition, and comorbidities to enable individualized therapy. If trastuzumab is selected, concurrent anthracycline-based chemotherapy should be avoided, and cardiac function must be monitored to promptly detect and manage cardiac events.

Keywords: elderly; breast cancer; targeted therapy

Introduction

Breast cancer is the most common malignancy among women worldwide, accounting for 20% of all new female cancer cases with 1.68 million new cases annually [**?**]. The average age at breast cancer diagnosis is currently 61 years, with patients over 70 representing 30% of all breast cancer cases [**?**]. As population aging continues [**?**, **?**], clinicians face growing numbers of elderly breast cancer patients.

In recent years, targeted therapy has assumed an increasingly important role in the systemic treatment of HER2-positive breast cancer. The primary advantage of breast cancer targeted therapy lies in its ability to exploit specific genes or gene products expressed by tumor cells (with minimal or no expression in normal cells), creating relative or absolute targets that maximize tumor cell eradication while minimizing adverse effects. However, because certain cells in the cardiovascular system express antigens identical to those targeted by these therapeutic agents, cardiovascular injury can occur alongside tumor cell destruction. Whether trastuzumab can be safely administered to elderly breast cancer patients without underlying cardiovascular disease remains unresolved, a question that was extensively debated at the 2018 Geriatric Oncology Conference.

1. Characteristics of Elderly Breast Cancer Patients

Elderly breast cancer patients exhibit unique characteristics. The WHO projects that the global percentage of elderly individuals will double from 12% to 22% between 2015 and 2050 [**?**]. Additionally, elderly patients experience physiological decline, have multiple comorbidities such as hypertension, cardiovascular disease, and diabetes, demonstrate poor treatment compliance, and require chemotherapy dose adjustments. These factors inevitably influence breast cancer treatment selection, affect prognosis, and pose new challenges for individualized therapy [**?**].

Compared to younger patients, elderly breast cancer tends to be more frequently estrogen and progesterone receptor-positive, with or without HER2 positivity [**?**]. Literature reports indicate that both tumor size and lymph node involvement probability decrease with age, suggesting different tumor biology in elderly patients [**?**]. Notably, patients over 70 demonstrate significantly better prognosis than those aged 40-70 [**?**].

However, because elderly patients are frequently excluded from clinical trials, evidence for treatment selection in this population typically derives from trials conducted in younger cohorts [**?**], complicating precision treatment for elderly breast cancer patients and contributing to ongoing controversy regarding trastuzumab use.

2. Indications for Trastuzumab Therapy in Elderly HER2-Positive Breast Cancer Patients

Some experts advocate for trastuzumab targeted therapy in elderly HER2-positive breast cancer patients based on sufficient indications. According to the St. Gallen consensus, HER2-positive breast cancer patients without lymph node metastasis are classified as intermediate-risk [**?**], and ample evidence supports trastuzumab use in this population.

Four pivotal clinical studies in HER2-positive breast cancer (HERA, B006, N9831, B31) involving over 12,000 patients consistently demonstrated that trastuzumab significantly improved overall survival (OS) and disease-free survival (DFS), establishing 18 cycles (1 year) of adjuvant trastuzumab as the standard of care for early-stage HER2-positive breast cancer [**?**]. Extended follow-up analyses from the HERA trial (11 years) and N9831 trial (8.4 years) continued to show DFS and OS benefits [**?**, **?**].

Regarding efficacy, elderly patients over 60 in the B31/N9831 trials derived OS (HR 0.51, 95%CI 0.37-0.69) and DFS (HR 0.63, 95%CI 0.49-0.82) benefits consistent with the overall population [**?**]. The 11-year follow-up of the HERA study similarly showed consistent benefit trends for patients over 60 (HR 0.82, 95%CI 0.62-1.08) [**?**]. A meta-analysis incorporating HERA, N9831, and B31 trials confirmed that patients aged 60 and older benefit from trastuzumab (pooled HR: 0.53; 95% CI, 0.36-0.77) [**?**].

However, because these four landmark HER2-positive breast cancer studies excluded patients over 70, available data are limited to retrospective analyses of patients aged 60-70. The HERA trial showed consistent benefit trends for patients over 60 (HR 0.82, 95%CI 0.62-1.08), but lacked statistical power for age-based subgroup analysis as age stratification was not prospectively defined [**?**]. Current evidence supports trastuzumab benefit in patients aged 60-70, but insufficient data exist for those over 70.

3. Risks of Targeted Therapy in Elderly HER2-Positive Breast Cancer

Although cardiac toxicity from trastuzumab combined with chemotherapy cannot be ignored, it represents Type II chemotherapy-related cardiac dysfunction, which is notably reversible compared to Type I dysfunction [**?**, **?**]. Data show that severe cardiac damage from chemotherapy plus trastuzumab occurs infrequently and often resolves after treatment completion. In the B006 trial, left ventricular ejection fraction (LVEF) declines were observed within safe ranges and recovered after treatment [**?**]. The HERA study reported cardiac adverse events in 9.4% of patients in the 2-year treatment group and 5.2% in the 1-year group, with 87.2% recovering at a median of 7.2 months and 79.5% at a median of 6.6 months, respectively [**?**]. Notably, patients with cardiac risk factors were excluded from this study. The NSABP B31 trial reported cardiac events in 4% of the experimental group versus 1.3% in the control group at 7-year follow-up [**?**], though most patients recovered normal cardiac function after completing trastuzumab. Endomyocardial biopsies in some trastuzumab-treated patients revealed no significant abnormalities [**?**]. Other studies report severe heart failure rates of 1-4% with adjuvant trastuzumab [**?**].

A multicenter observational study of over 9,000 breast cancer patients aged 66 and older found that 23% received trastuzumab, with higher cardiac event rates compared to non-users ($p<0.01$). Multivariate analysis identified cardiac events as more common in patients over 80, those receiving weekly trastuzumab, and those with hypertension or coronary artery disease history, while elderly patients without cardiac comorbidities had relatively lower risk [**?**]. Another prospective observational study of 3,940 HER2-positive breast cancer patients across 339 institutions (2006-2012) included 507 patients aged 65-69 and 507 over 70, all receiving chemotherapy plus trastuzumab with annual follow-up, demonstrating good cardiac tolerability with predictable and manageable cardiac events [**?**]. The APT trial evaluating paclitaxel plus trastuzumab in node-negative HER2-positive breast cancer showed low cardiac risk, with 34% of enrollees over 60 and only 2 patients developing symptomatic congestive heart failure that resolved after trastuzumab discontinuation [**?**]. In summary, trastuzumab, particularly when combined with chemotherapy, carries cardiac toxicity, but risks remain within acceptable limits.

However, other experts argue that evidence for trastuzumab safety in elderly patients without cardiac comorbidities remains limited. The aforementioned mul-

ticenter study showed that while cardiac events were more common in patients over 80, those receiving weekly therapy, and those with hypertension or coronary disease, elderly patients without cardiac baseline disease still had higher risk than non-trastuzumab users [**?**]. Cardiac event risk increases significantly when targeted therapy is combined with chemotherapy, particularly anthracyclines. A 2011 NEJM study by Slamon et al. on anthracycline plus trastuzumab for advanced breast cancer showed delayed disease progression and reduced 1-year mortality, but 27% of 143 patients developed NCI CTCAE grade III or IV cardiac toxicity [**?**]. Another study of 47,806 breast cancer patients over 65 found cumulative congestive heart failure incidence of 5.5% in the first year and 15.5% at 5 years with anthracycline-trastuzumab combination, representing significantly increased risk compared to no chemotherapy/targeted therapy (HR 1.19, 95% CI 1.05-1.34) [**?**]. Anthracycline-trastuzumab combinations should be avoided in elderly breast cancer adjuvant therapy.

Clinical Consensus and Guidelines

The 2012 International Society of Geriatric Oncology and European Society of Breast Cancer Specialists consensus recommended trastuzumab for intermediate-risk elderly breast cancer patients without cardiac comorbidities [**?**]. The 2017 St. Gallen expert consensus stated that age alone should not determine treatment decisions for elderly breast cancer patients, emphasizing that individual disease factors, comorbidities, life expectancy, and patient preferences are key considerations. While optimal treatment duration remains unclear, evidence suggests good cardiac tolerability of trastuzumab in elderly patients [**?**]. The 2018 NCCN guidelines added T or TC regimen plus trastuzumab as adjuvant therapy for relatively low-risk HER2-positive breast cancer, avoiding anthracycline combination to reduce cardiac events [**?**].

Conclusion

Whether elderly HER2-positive breast cancer patients should receive adjuvant trastuzumab remains unresolved. Current evidence demonstrates that patients aged 60-70 benefit from trastuzumab with low and reversible cardiac risks, while large-scale trial data for patients over 70 are lacking. Treatment selection requires balancing benefits and risks through individualized therapy that incorporates patient preferences, physical condition, and comorbidities. If trastuzumab is chosen, concurrent anthracycline chemotherapy should be avoided, and cardiac function monitoring is essential for timely detection and management of cardiac events.

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