Trastuzumab for Small HER-2+ Breast Cancer: Small Tumor, Big Decision

PRESENTATION OF THE CASE

A 53-year-old postmenopausal woman was found to have a new area of microcalcification at the 10 o'clock position of her right breast during a routine screening mammogram. Ultrasound-guided core biopsy revealed a grade 2 invasive ductal carcinoma, estrogen receptor (ER)+ (90%), progesterone receptor positive (20%), and human epidermal growth factor receptor (HER)-2+ (3+ by immunohistochemistry). A right breast lumpectomy and sentinel node biopsy were performed. The invasive tumor measured 0.7 cm, no lymphovascular space invasion was identified, surgical margins were uninvolved, and the sentinel lymph nodes were negative for tumor. She was evaluated postoperatively in the medical oncology clinic to discuss an adjuvant treatment strategy.

The question for our colleagues is: should she be offered adjuvant chemotherapy and trastuzumab prior to adjuvant radiation and 5 years of hormonal therapy?

PRO

By Roisin M. Connolly
The Johns Hopkins Sidney Kimmel
Comprehensive Cancer Center

*Roisin M.
Connolly*

The challenging case presented here reflects a clinical dilemma that is increasingly being discussed in multidisciplinary breast tumor boards—adjuvant decision making in a patient with a HER-2+ breast cancer <1 cm. The introduction of mammographic screening led to an increase in the detection of such small breast cancers, and unfortunately there are few data to support a specific adjuvant treatment strategy in these cases. The most up to date National Comprehensive Cancer Network (NCCN) recommendations suggest consideration of adjuvant chemotherapy, with or without trastuzumab, for women with lymph node-negative tumors that are 0.6–1 cm in size [1]. The guidelines note that the decision to administer adjuvant trastuzumab in this setting must “balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.”

Increased expression of HER-2 or amplification of the *HER-2/neu* gene has been associated with a worse prognosis than with other breast cancer phenotypes [2]. Reassuringly, a number of clinical trials have indicated that the addition of 1 year of trastuzumab to adjuvant chemotherapy regimens in HER-2+ breast cancer patients results in an ~50% lower breast cancer recurrence rate and 35% lower mortality rate. However, certain caveats relating to the adjuvant trastuzumab studies are evident. As Dr. Bardia correctly highlights, only the recent publication by Slamon et al. [3] included patients with tumors <1 cm.

CON

By Aditya Bardia
Massachusetts General Hospital Cancer
Center, Harvard Medical School

Aditya Bardia

Overexpression of HER-2, a transmembrane tyrosine kinase receptor, is reported to occur in 20%–30% of invasive breast cancers and is an independent predictor of relapse and worse survival among patients with breast cancer [1, 2]. Trastuzumab (Herceptin®) is a humanized monoclonal antibody that binds to the extracellular domain IV of HER-2, inhibiting HER-2 signaling and proliferation of HER-2+ tumors [3].

Multiple large, randomized clinical trials have consistently shown that adjuvant trastuzumab-based therapy results in superior disease-free survival (DFS) and overall survival outcomes among women with localized HER-2+ tumors [4–8]. However, patients with tumors <1 cm were excluded from most of these trials (Table 1), and the clinical management of such tumors is subject to much debate. National consensus guidelines, such as those of the NCCN, do not provide a recommendation in favor or against adjuvant trastuzumab use for patients with such tumors and leave the decision up to the treating oncologist, as pointed out by Dr. Connolly.

Let us consider the prognosis of patients with small HER-2+ tumors to better understand the role of adjuvant trastuzumab therapy for such tumors. Whereas patients with pT1a/b breast cancers (<1 cm) in general have an excellent prognosis, those with small HER-2+ tumors have worse prognosis than those with HER-2– tumors. For example, in a large

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And so we ask ourselves the question: what evidence or rationale is there to support the administration of adjuvant chemotherapy and trastuzumab (in addition to 5 years of adjuvant hormonal therapy) in this woman with a small ER+ HER-2+ tumor who would likely not have been offered this approach in the not too recent past? Can we extrapolate from the adjuvant trastuzumab trials to say that it is likely that patients who have T1a/b (<1 cm) node-negative tumors would benefit similarly from treatment with trastuzumab? Despite small numbers in the T1a/b subgroup ($n = 148$) in the Slamon et al. [3] trial, a disease-free survival (DFS) benefit was observed with the addition of trastuzumab to chemotherapy [3]. The traditional view has been that patients with T1a/b breast cancers have an excellent long-term outcome, therefore not benefiting from adjuvant therapy. Web-based adjuvant decision-making tools such as Adjuvant! Online disappoint in this setting because they do not yet include HER-2 status as a prognostic or predictive marker [4]. The commercially available gene expression signatures, such as Oncotype DX® (Genomic Health, Inc., Redwood City, CA) and MammaPrint® (Agendia Inc., Irvine, CA), also offer little help in clinical decision making for women with ER– or HER-2+ disease [5].

We can start by referring ourselves to a number of retrospective analyses that have highlighted the significant risk for recurrence associated with this subgroup of patients with HER-2+ node-negative tumors. The retrospective MD Anderson Cancer Center study evaluating the outcome of patients with T1a/b tumors describes how women with HER-2+ disease had a worse 5-year recurrence-free survival (RFS) rate (77.1%) than those with HER-2– disease (93.7%). None of the women had received adjuvant chemotherapy or trastuzumab. Among the women with HER-2+ disease, similar rates of recurrence (21%) were observed between those with hormone receptor (HR)+ breast cancer and those with HR– breast cancer, despite the fact that half of the former had received adjuvant hormonal therapy [6].

European investigators identified a larger cohort of 2,130 patients with T1a/b lymph node-negative early breast cancer, 150 (7%) of whom had HER-2+ disease. No patients received adjuvant trastuzumab. At a median follow up of 4.6 years, patients with HR– disease had similar 5-year DFS rates whether they were HER-2– or HER-2+ (92% versus 91%). For patients with HR+, the 5-year DFS rate were 99% if the tumor was HER-2– and 92% if the tumor was HER-2+. Of note, 65% of the patients with HR+ HER-2+ disease received hormonal therapy alone, with a further 24% receiving hormonal therapy plus chemotherapy. Crosstalk between ER and HER-2 and the resultant endocrine resistance may account for the worse prognosis observed in those with HR+ HER-2+ disease. Less benefit from hormonal therapy in those with HER-2+ disease was previously noted in both neoadjuvant and adjuvant hormonal studies [7, 8]. Reassuringly, data from the Herceptin® Adjuvant trial indicate that both patients with HR+ and those with HR– disease benefit from adjuvant trastuzumab, with the greatest benefit for HR+ patients being seen in those with intermediate strength ER positivity (Allred score, 3–5), versus strong ER positivity (Allred score, 6–8) [9]. Of interest, the earlier recurrence pattern for HR– HER-2– patients

Table 1. Randomized trials investigating the efficacy of adjuvant trastuzumab-based therapy among women with localized human epidermal growth factor receptor 2–positive breast cancers

Study	Regimen	Sample size	Efficacy	Inclusion criteria
Joensuu et al. [4]	Adjuvant docetaxel or vinorelbine, with or without trastuzumab	1,010	3-yr DFS, 89% versus 78%; HR, 0.42; $p = .01$	Positive axillary node or node-negative breast cancer ≥ 2 cm
Piccant-Gebhart et al. [5]	Neoadjuvant or adjuvant chemotherapy, with or without trastuzumab	1,694	2-yr DFS, 85.8% versus 77.4%; HR, 0.54; $p < .0001$	Positive axillary node or node-negative breast cancer > 1 cm
Romond et al. [6]	Doxorubicin and cyclophosphamide followed by paclitaxel every 3 wks (AC-T), with (AC-TH) or without trastuzumab	3,676	3-yr DFS, 87.1% versus 75.4%; HR, 0.48; $p < .0001$	Positive axillary node or node-negative breast cancer > 1 cm if hormone receptor negative or > 2 cm if hormone receptor positive
Spielmann et al. [7]	Adjuvant anthracycline-based chemotherapy with or without docetaxel, with or without trastuzumab	3,010	3-yr DFS, 80.9% versus 77.9%; HR, 0.86; $p = .41$	Node-positive breast cancer
Slamon et al. [8]	Adjuvant doxorubicin and cyclophosphamide followed by docetaxel (AC-T), the same regimen plus 52 wks of trastuzumab (AC-TH), or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH).	3,222	5-yr DFS, 75% for AC-T, 84% for AC-TH, and 81% for TCH; HR, 0.47; $p = .003$ for AC-TH; HR, 0.64; $p = .06$ for TCH	High-risk node-negative or node-positive breast cancer (stage T1, T2, or T3)

Abbreviations: DFS, disease-free survival; HR, hazard ratio.

retrospective review of patients with T1a/b N0M0 breast cancers diagnosed at MD Anderson Cancer Center ($n = 965$), of which, 10% ($n = 98$) were HER-2+, a worse 5-year relapse-free survival (RFS) rate (77.1%) was reported among patients with HER-2+ tumors compared with HER-2– tumors (93.7%) [9]. Other authors have reported similar findings [10–12]. Thus, it appears that patients with small HER-2+ tumors have a worse prognosis than those with HER-2– tumors. However, does this imply that adjuvant trastuzumab therapy should be given to all patients with small HER-2+ tumors? I tend to disagree.

Scientific evidence justifying the use of adjuvant trastuzumab in patients with small HER-2+ tumors is limited and weak. Rodriques et al. [13] reported institutional results for patients with pT1a/b, pN0, HER-2+ positive breast cancer diagnosed in 2002–2008 at three comprehensive cancer centers in France. Patients with adverse prognostic features (a negative hormone receptor (HR) status, high Elston grade, moderate or high mitotic index) were treated with adjuvant trastuzumab along with chemotherapy (93%). During a median overall follow-up time of 29 months, there was not a significant difference in the RFS rate with adjuvant trastuzumab-based therapy ($p = .11$). More recently, Slamon et al. [8] reported results from a large randomized trial (Breast Cancer International Research Group 006) comparing adjuvant doxorubicin, cyclophosphamide, and paclitaxel (AC-T) with AC-T plus trastuzumab (AC-TH) and with docetaxel, cyclophosphamide, and trastuzumab (TCH) among women with localized HER-2+ tumors. The authors reported that, among the pa-

was mirrored in the observation arm of that trial, wherein the 3-year DFS rate was 70.3% for those with ER– disease (Allred score, 0–2) and 82.8% for those with strong ER positivity; these figures were all improved by the addition of 1 year of trastuzumab to adjuvant chemotherapy [9].

More recently, a Kaiser Permanente group identified 237 patients with T1a/b HER-2+ tumors, 25% of whom received adjuvant chemotherapy (8.9% in addition received adjuvant trastuzumab). The 5-year RFS rates were 96.2% and 91.1%, respectively. Those authors concluded that the recurrence risk for T1a (≤ 0.5 cm) HER-2+ tumors was too low to justify adjuvant chemotherapy or trastuzumab, supporting the NCCN treatment recommendations. They also suggested that more aggressive local therapy may be necessary for these patients because almost half of the invasive recurrences were local only [10]. Finally, in a French retrospective multicenter series in 2000–2008, 97 patients with T1a/b HER-2+ tumors were identified and 43% received adjuvant chemotherapy ($n = 42$), 37 of these with trastuzumab, and three patients received trastuzumab alone. With a 41-month median follow-up duration, there were no recurrences in patients treated with trastuzumab and eight of the 56 patients treated without trastuzumab experienced recurrent disease (with three deaths during this time), a finding that was statistically significant [11].

Although no prospective data exist at this time, the clear benefits observed in the adjuvant trastuzumab trials as well as the significant recurrence risk for patients with T1a/b HER-2+ tumors provide a strong rationale for treating these patients with adjuvant chemotherapy and trastuzumab. Of course, one must always weigh up the pros and cons of a particular treatment strategy, in particular in a curative setting such as that being discussed. Dr. Bardia points out the risk for cardiotoxicity associated with adjuvant trastuzumab administration. Recently, an independent adjudication of the National Surgical Adjuvant Breast and Bowel Project B-13 and North Central Cancer Treatment Group N9831 clinical trials confirmed a 2% incidence of symptomatic heart failure in trastuzumab-treated patients, versus 0.45% in patients treated with chemotherapy alone [12]. Reassuringly, the majority of these patients had recovery of heart function with appropriate therapy.

It is doubtful that randomized trials comparing chemotherapy alone with chemotherapy plus trastuzumab will be performed in this population. However, the predominantly anthracycline and taxane chemotherapy backbone used in the adjuvant trials may not be necessary for all patients, in particular those with tumors < 1 cm or with negative lymph nodes. Trials evaluating trastuzumab in combination with single-agent taxanes [13] or docetaxel and cyclophosphamide [14], for example, may provide alternative treatment strategies for this subgroup of patients. In addition, whether or not some women may gain the most benefit from an adjuvant approach that uses anti-HER-2 therapy alone is of great interest, and clinical trials are currently being designed to evaluate this question.

Finally, it is clear that molecular tools are urgently required to clarify the prognostic impact of HER-2 overexpression in patients with T1a/b, node-negative breast cancer and to guide our adjuvant decision making for these patients. Prospective data would

tients with HER-2+ tumors < 1 cm, women who received AC-TH (hazard ratio, 0.36; $p = .04$) but not those who received TCH (hazard ratio, 0.45; $p = .09$) had a significantly longer DFS interval than those treated with AC-T, as pointed out by Dr. Connolly. However, the association with overall survival was not reported and, interestingly, neither AC-TH nor TCH was associated with a longer DFS interval (as compared to AC-T) among patients with tumors < 1 cm but > 2 cm in size [hazard ratio, 0.88 ($p = .87$) and 1.11 ($p = .64$), respectively], suggesting that caution needs to be exerted in interpreting such subgroup analyses for clinical decision making.

Faced with the difficult scenario of limited evidence to support adjuvant trastuzumab therapy for patients with small HER-2+ tumors, I would recommend the need to personalize the decision making for an individual patient and consider three broad issues. First, it is important to consider the pathological characteristics of the HER-2+ tumor. All small HER-2+ tumors are not the same, and the prognosis varies based on features such as tumor size, grade, and lymphovascular invasion, among others. Second, the absolute benefit of adjuvant trastuzumab therapy needs to be weighed against the potential risks. For example, this patient has about a 20% recurrence risk [9]. Although the response to endocrine therapies is slightly lower for patients with HER-2+ tumors, one would still expect that the recurrence risk would be reduced to $\sim 10\%$ with adequate hormonal therapy. If we were to extrapolate the benefit of adjuvant trastuzumab with chemotherapy from the large adjuvant trials (Table 1), this risk could be reduced to about 5% with an adjuvant trastuzumab-based chemotherapy regimen, but it would include a risk up to 5% for cardiomyopathy and a cost of as much as \$50,000 (trastuzumab) to \$100,000 per year (with chemotherapy) [14]. Third, the pros and cons of various adjuvant trastuzumab regimens need to be carefully weighed. Trastuzumab without chemotherapy, although safer, does not have much efficacy as a single agent; on the other hand, trastuzumab with standard chemotherapy, such as dose-dense AC-T or TCH, has greater efficacy but also greater toxicity. An intermediate approach suggested is the use of adjuvant trastuzumab with weekly paclitaxel for a duration of 12 weeks followed by trastuzumab alone to complete a year of adjuvant therapy, and this approach is being investigated in a clinical trial (ClinicalTrials.gov identifier, NCT00542451). Although the results of this trial are eagerly awaited, it should be noted that the trial is a single-arm, nonrandomized trial and might not address the role of trastuzumab in patients with small HER-2+ tumors conclusively. Moving forward, the HER-2 field clearly needs predictive biomarkers that can accurately predict responsiveness to trastuzumab monotherapy versus combination chemotherapy (and type of chemotherapy). Certain biomarkers, such as topoisomerase II α (*TOP2A*) amplification, appear promising but need to be validated before they can be incorporated into clinical practice [8].

In conclusion, whereas patients with small HER-2+ tumors have a worse prognosis than those with HER-2– tumors, the absolute benefit of adjuvant trastuzumab therapy in reducing the slightly elevated risk is unclear and needs to be carefully weighed against the potential risks. Adjuvant trastuzumab with weekly

be welcomed relating to the optimal treatment strategy for patients in this setting. Until that time, however, I would favor administering adjuvant chemotherapy and trastuzumab to women with small HER-2+ tumors, such as in the case described, after a clear discussion of the potential risks and benefits of such an adjuvant treatment strategy.

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paclitaxel is a promising investigational regimen, but until the safety and efficacy results of the trial are known, the regimen cannot be recommended for routine practice outside a clinical trial. Biomarkers that can accurately predict patients who are most likely to recur (or not), as well as predict efficacy to various trastuzumab regimens, would greatly help in personalizing the optimal trastuzumab regimen for women with small HER-2+ tumors.

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