Coping with uncertainty: T1a,bN0M0 HER2-positive breast cancer, do we have a treatment threshold?

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Background: Recent retrospective studies have suggested that patients with T1a,bN0M0 human epidermal growth factor receptor 2 (HER2)-positive breast cancer are at a higher risk for recurrence and might benefit from adjuvant trastuzumab. The absolute benefits associated with treating this subgroup are uncertain.

Design: We reviewed recent studies examining the prognostic value of HER2 in patients with node-negative T1a,b HER2-positive breast cancer. We calculated the number needed to treat (NNT) using baseline risk estimates for untreated T1a,bN0M0 breast cancer and the number needed to harm (NNH) using the incidence of cardiac events in each of the adjuvant trastuzumab clinical trials.

Results: Several studies were identified, each with limitations inherent to retrospective database analyses: small cohort sizes, lack of systematic HER2 testing in older specimens, variations in the use of adjuvant therapy and definitions of study endpoints, and lack of information relating to comorbidities. The 5-year disease-free survival in the pre-trastuzumab era ranged from 77% to 95%. Comparisons between small HER2-positive and small HER2-negative cancers showed numerically worse outcome for the HER2-positive cohort in some but not all studies. In many instances, the NNH was larger (26–250) than the NNT (13–35); however, in a subset of patients, the NNH was lower (6) than the NNT (13–35).

Conclusions: Better prediction tools to estimate more precisely the risk for death due to comorbid illness versus breast cancer are needed. In some patients, the risks of therapy could outweigh the benefits. Treatment selection for T1a,bN0 HER2-positive cancers remains in the transition area between evidence- and subjective judgment-based medicine.

Key words: adjuvant therapy, breast cancer, HER2 positive, small HER2-positive cancers, T1a,bMON0

Patients enrolled in clinical trials often do not match the individual presenting for treatment, who may have more or less severe disease, comorbid conditions, or different demographic characteristics. As a result, uncertainty, debate, and ultimately variations in how these patients are managed occur [1]. An example is the treatment of T1a (>1 and ≤5 mm) and T1b (>5 and ≤10 mm), lymph node-negative, human epidermal growth factor receptor 2 (HER2)-positive breast cancer [2, 3]. Six large randomized, controlled trials (RCTs) have demonstrated significant improvements in breast cancer recurrence and death associated with the addition of trastuzumab to chemotherapy in the adjuvant setting [4–8]. These trials enrolled predominately patients with node-positive disease and, with the exception of the Breast Cancer International Research Group-006 trial, excluded patients with tumors ≤1 cm in diameter. Historically, the prognosis for patients with T1a,bN0M0 breast cancers (including both HER2-positive and HER2-normal cases) is good. The overall probability of death at 10 years from breast cancer is considerably lower than that from other causes, especially among women >50 years of age [9]. However, recent studies have suggested that patients with HER2-positive T1a,bN0M0 cancers may be at a higher risk for recurrence [10–12].

In the absence of level I evidence supporting the use of adjuvant trastuzumab-based chemotherapy in this population, the management of these patients remains controversial. The American Society of Clinical Oncology 2007 recommendations did not advise HER2 testing of the primary tumor ‘for solely determining a patient’s prognosis’ [13]. While the predictive role of HER2 is well established, a systematic review of the literature in 2001 concluded that HER2 was a weak to moderate prognostic factor and advised against its use when making decisions regarding adjuvant systemic therapy [14]. The main
Table 1. Retrospective studies examining the prognostic role of HER2 in T1a,bN0M0 breast cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design, patient, and treatment characteristics</th>
<th>No. of patients with T1a,bN0M0 HER2-positive breast cancer</th>
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<th>Results (for T1a,bN0M0 HER2-positive cases only)</th>
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<tr>
<td>Curigliano et al.</td>
<td>Design: nested case–control; objective: assess prognostic role of HER2 overexpression/amplification in patients with pT1a,bN0M0 breast cancer. Patients diagnosed from 1999 to 2006 with T1a,bN0M0 HER2-positive breast cancer matched by hormone receptor (HR) status, age, year of surgery. Mean age: HR-negative, HER2-positive breast cancer = 54.3 years and HR-positive HER2-positive cancer = 51.6 years. Treatment of HER2-positive disease: 34% (51/150) received chemotherapy, 0% received trastuzumab, 89% (70/79) of HR-positive HER2-positive disease received endocrine.</td>
<td>150</td>
<td>4.6</td>
<td>5-year DFS in HR positive/HER2 positive (n = 79) 92% (95% CI 86% to 99%); 5-year DFS in HR negative/HER2 positive (n = 71) 91% (95% CI 84% to 99%); 5-year DFS in HR-positive/HER2-positive T1a 88% (95% CI 67% to 96%); 5-year DFS in HR-positive/HER2-positive T1b 95% (95% CI 82% to 99%); 5-year DFS in HR-negative/HER2-positive T1a: 93% (95% CI 72% to 98%); 5-year DFS in HR-negative/HER2-positive T1b: 85% (95% CI 60% to 95%)</td>
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<td>Gonzalez-Angulo et al.</td>
<td>Design: retrospective cohort; objective: assess risk for recurrence in patients with T1a,bN0M0 HER2-positive breast cancer. Patients diagnosed from 1990 to 2002 with T1a,bN0M0 HER2-positive breast cancer or HER2-negative breast cancer comprised study cohort. Median age: HER2-positive breast cancer = 51.5 years. Treatment of HER2-positive disease: 0% received trastuzumab, 0% received chemotherapy, 52% (31/60) with HR-positive HER2-positive disease received hormone therapy.</td>
<td>98</td>
<td>6.2</td>
<td>5-year RFS: 77% (95% CI 67% to 85%); 5-year DRFS: 86% (95% CI 77% to 92%)</td>
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<td>Gonzalez-Angulo et al.</td>
<td>Design: retrospective cohort (presented with above study); objective: validation cohort for above study; patients: T1a,bN0M0 HER2-positive and HER2-negative breast cancer. Median age 60 years. Treatment of HER2-positive disease:</td>
<td>21</td>
<td>NR</td>
<td>5-year RFS 87.4% (95% CI 57.7% to 96.8%); 5-year DRFS 92.3% (95% CI 56.6% to 98.9%)</td>
<td>5-year RFS was worse for T1a,bN0M0 HER2-positive compared with HER2-negative breast cancer (P = 0.043). There was no difference in 5-year DRFS for T1a,bN0M0 HER2-positive (92.3%) compared with HER2-negative</td>
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<td>Park et al. [12]</td>
<td>Design: retrospective cohort; objective: identify risk factors for systemic recurrence in patients with tumors ≤1 cm. Patients diagnosed from 1994 to 2004 with T1a,bN0M0 breast cancer. Median age 48 years (22–81 years). Patients grouped into (i) HER2-positive group (HER2 positive and HR negative) 8.8%; (ii) HR-positive group (ER and/or PR positive and HER2 positive or negative) 82%; (iii) triple-negative breast cancer (ER negative, PR negative, and HER2 negative) 9.3%. Adjuvant chemotherapy: HER2-positive group = 25% (94/370), HR-positive group = 17% (53/306), triple-negative group = 65% (20/31); adjuvant hormonal therapy: HR-positive subgroup = 89% (272/306), no trastuzumab administered.</td>
<td>54</td>
<td>5</td>
<td>T1a,b: DRFS in T1a,b HER2-positive subgroup (HER2 positive, HR negative) 92%; DRFS in T1a,b HR-positive (HR positive and HER2 positive or negative) 98%. T1b: DRFS in T1b HER2-positive subgroup (HER2 positive, HR negative) 90%; DRFS in T1b HR-positive (HR positive and HER2 positive or negative) 98%. T1a,b: DRFS for HER2 positive, ER positive versus HER2 positive, ER negative: 95% versus 88% (log-rank test $P = 0.46$)</td>
<td>T1a,bN0M0 cancers (97.0%) $P = 0.449$. DRFS and OS were extrapolated directly from Kaplan–Meier curves shown in the article.</td>
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<td>Chia et al. [23]</td>
<td>Design: retrospective cohort; objective: assess HER2 as a prognostic factor in node-negative breast cancer. Patients diagnosed with node-negative breast cancer from 1986 to 1992. Median age: NR for pT1aN0 and 13 patients with T1bN0M0 and 13 patients with T1bN0M0 HER2-positive breast cancer received no treatment.</td>
<td>T1a = 16; T1b = 13</td>
<td>12.4</td>
<td>10-year BCSS for T1aN0M0 breast cancer 93.3% (1 event/16); 10-year RFS for T1bN0M0 68.4% (4 events/13)</td>
<td>The 10-year relapse-free survival and breast cancer-specific survival for T1a,bN0M0 breast cancer without HER2 overexpression was not significantly different from T1a,bN0M0 HER2-positive breast cancer.</td>
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<td>Ioensu et al. [24]</td>
<td>Design: retrospective cohort study; objective: assess value of 10 prognostic factors in pT1N0M0</td>
<td>T1a moderately or poorly differentiated = 12; T1b</td>
<td>9.5</td>
<td>9-year DDFS for T1a and T1b 67%</td>
<td>Of 852 women with T1N0M0 breast cancer, HER2 staining by IHC was unavailable in 33% (283/852) and</td>
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utility of HER2 is to guide whether a patient should receive trastuzumab therapy [15]. As women are living longer with their disease, the long-term treatment effects of therapy, comorbid conditions, and competing causes of death assume increasing importance. This issue is recognized by the National Comprehensive Cancer Network, which considers trastuzumab as an option for HER2-positive tumors between 0.6 and 1 cm, but ‘the prognosis of patients with T1a and T1b tumors that are node negative is generally favorable even when HER2 is amplified or overexpressed, and the decision to use trastuzumab must be balanced with the known toxicities, such as cardiac toxicity, and the uncertain absolute benefits that may exist with trastuzumab therapy’. This recommendation was coded as category 3 indicating that it is not based on high-level evidence but on expert opinion and generated substantial disagreement between panel members [16].

Trastuzumab-induced cardiotoxicity is idiosyncratic, is unrelated to dose, displays a wide range of severity, and is reversible in most cases but not all cases [17]. However, in the absence of long-term safety data, it remains an important issue [18–20]. Despite prospective monitoring and exclusion of women with various cardiac conditions in the adjuvant trials, the incidence of cardiotoxicity was significantly higher in the trastuzumab-treated arms with up to 4% developing severe congestive heart failure and a larger number developing asymptomatic decreases in left ventricular ejection fraction (LVEF), the long-term significance of which is unknown [21, 22].

Several retrospective studies have examined the role of HER2 as a prognostic marker in T1a,bN0M0 breast cancer (Table 1).

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<td>CISH was unavailable in 36% (304/852); the overall DDFS for T1N0M0 case with available HER2 status was 73% (95% CI 62% to 85%) and 72% (95% CI 60% to 85%) for overexpression and amplification; patients with tumor size 0.1–0.5 cm (n = 49) had a 9-year DDFS of 100%.</td>
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Abstracts and studies that grouped T1c in with T1a,bN0M0 cancers were not included.

CI, confidence interval; CISH, chromogenic in situ hybridization; DDFS, distant disease-free survival; DFS, disease-free survival; DRFS, distant recurrence-free survival; IHC, immunohistochemistry; NR, not reported; OS, overall survival; RFS, recurrence-free survival.

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Definition of a cardiac event (CE) by each trial—HERA: severe congestive heart failure (CHF), which does not include death from cardiac causes, defined as New York Heart Association (NYHA) class III or IV functional class confirmed by a cardiologist and a decrease in LVEF of at least 10% below baseline and to <50%. Symptomatic CHF was defined as symptomatic congestive heart failure confirmed by a cardiologist and LVEF <50% and a decrease in LVEF of at least 10% from baseline [29, 30]. NSABP B31: defined as NYHA class III or IV CHF or possible/probable cardiac death [28]. NCCTG N9831: defined as grade 3/4 arrhythmia (grade 3 CHF is symptomatic CHF responsive to treatment, LVEF between 20% and 39%; grade 4 CHF is refractory CHF, LVEF < 20%) [31].

Tan-Chiu et al. [32] analysis of cardiac dysfunction in the NSABP B31 trial reported that among the 48 patients of age 50 years with LVEF ≤ 54%, 9 experienced CHF, all within 7 months of initiating trastuzumab (cumulative incidence = 20%; 95% CI 11% to 36%).

AC-DH, doxorubicin, cyclophosphamide-docetaxel, trastuzumab; AC-TH, doxorubicin, cyclophosphamide-paclitaxel, trastuzumab; CI, confidence interval; CT-H, chemotherapy-trastuzumab; DFS, disease-free survival; DRFS, distant recurrence-free survival; HR, hormone receptor; LVEF, left ventricular ejection fraction; NNH, number needed to treat harm one patient; NNT, number needed to treat for one patient to benefit; RFS, recurrence-free survival; TCH, docetaxel, carboplatin, trastuzumab.

Table 2. Number of patients with T1a,bN0M0 HER2-positive breast cancer needed to treat or harm

<table>
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<tr>
<th>Study</th>
<th>NNT (95% CI)</th>
<th>NNH</th>
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<tbody>
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<td>Curigliano et al. [10]</td>
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<td>5-year DFS</td>
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<tr>
<td>HR positive</td>
<td>35 (19–264)</td>
<td>30</td>
<td>26</td>
<td>125</td>
<td>53</td>
<td>250</td>
<td>62.5</td>
<td>6</td>
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<tr>
<td>HR negative</td>
<td>31 (17–264)</td>
<td>30</td>
<td>26</td>
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<td>53</td>
<td>250</td>
<td>62.5</td>
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<td>Gonzalez-Angulo et al. [11]</td>
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<tr>
<td>HR positive</td>
<td>13 (9–18)</td>
<td>30</td>
<td>26</td>
<td>125</td>
<td>53</td>
<td>250</td>
<td>62.5</td>
<td>6</td>
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<tr>
<td>HR negative</td>
<td>20 (13–34)</td>
<td>30</td>
<td>26</td>
<td>125</td>
<td>53</td>
<td>250</td>
<td>62.5</td>
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<tr>
<td>Collaborators [11]</td>
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<tr>
<td>5-year DRFS</td>
<td>35 (7–240)</td>
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When benefits from therapy are uncertain (e.g. due to uncertain baseline risk estimates), the risks for adverse events from treatment, patient preferences, and cost-effectiveness become increasingly important in decision making.

To help weigh these benefits and risks, we estimated the number needed to treat (NNT) to save one patient from a breast event and the number needed to harm (NNH) by causing one adverse cardiac event (CE) (Table 2). We assumed that the relative risk (RR) reduction associated with trastuzumab-based therapy would be the same across all prognostic risk levels based on tumor size. We used the RRs from the Dahabreh et al. [21] meta-analysis. Absolute differences in outcome were calculated using [exp (RR × ln (control survival)) – control survival] [33] and the NNT was calculated as follows: NNT = 1/absolute benefit [34].

The NNH was calculated using the incidence of CE’s in the trastuzumab arm of each adjuvant trastuzumab RCT and assuming the incidence of a CE would be zero in an untreated group (the incidence of a CE according to definitions given in Table 2 range from 0% to 0.7% in the trastuzumab–untreated arms). Table 2 shows that in many instances the NNH (26–250) is much larger than the NNT (13–35). However, in certain populations, particularly among those with borderline-normal LVEF (50%–54%) and >50 years of age, the NNH is substantially lower (6) than the NNT (13–35). Figure 1 shows that as the absolute risk reduction decreases, the NNT increases and more studies that included patients who mostly received some form of adjuvant therapy report the lowest recurrence rates. The majority of studies report survival rates ~90% (Table 1). Studies that report on comparison of outcome between small HER2-positive and similarly small HER2-negative cancers tend to report a numerically worse outcome for the HER2-positive cohorts, which reaches statistical significance in some but not all studies. To put these results into a broader context, based on surveillance, epidemiology and end results data, for patients with T1a,bN0M0 breast cancers including both HER2-positive and HER2-negative cases treated according to community standards between 1988 and 2001, the 10-year all-cause mortality and breast cancer-specific mortality rates were 24% and 4%, respectively [9]. In younger women (≤50 years), the breast cancer-specific mortality can be as high as 11%.

There is no hint from any of the numerous RCTs that the efficacy (i.e. the antitumor activity) of trastuzumab, endocrine therapy, or chemotherapy would depend on tumor size [4, 25, 26]. Therefore, <1 cm tumors are expected to derive the same relative benefit from these adjuvant treatment modalities as larger cancers. Consequently, even the smallest invasive cancer that has the slightest risk for recurrence has a chance that it could benefit from adjuvant systemic therapy. The absolute benefit would vary greatly depending on the baseline risk for recurrence, which is influenced by tumor size among others.
patients are exposed to the adverse effects of therapy. As the risk for a CE increases due to comorbid conditions or advancing age, the NNH falls (Figure 2) and at some point the NNH and the NNT overlap (Figure 3). These results highlight the need for careful medical judgment when selecting patients with T1a,bN0M0 cancer for adjuvant trastuzumab.

A blanket recommendation to treat all small HER2-positive breast cancer with trastuzumab-based therapy will almost certainly lead to clinically significant cardiotoxicity in some without any benefit in breast cancer recurrence. Similarly, withholding this form of adjuvant therapy from all small HER2-positive cancers will result in some otherwise avoidable breast cancer recurrence. Unfortunately, today we do not have accurate tools to identify precisely the subset of patients for whom the risks of trastuzumab outweigh the benefits. Currently available data suggest that the patient population in whom the risk/benefit ratio of trastuzumab-based adjuvant chemotherapy is the least favorable includes women who are >50 years of age and/or have borderline LVEF (50%–54%).

Shared medical decision making should incorporate estimates of the risk for a CE using risk calculators similar to Adjuvant! online [35], e.g. http://www.americanheart.org/gglRisk/locale/en_US/ or http://www.cardiosmart.org/, and these risks should also be discussed and explored with patients in order for them to make informed choices based on their own perspectives and risk tolerance levels, and if trastuzumab-based therapy is considered, regimens with lowest risk of cardiotoxicity should be considered [36, 37].

It is unlikely that an RCT would ever be conducted for this subset to establish or refute the benefit from adjuvant trastuzumab. Estimates of the risk/benefit ratio could be further optimized by the development of molecular predictors of prognosis within the HER2-positive disease [38]. In addition, it would be very important to develop better prediction tools to estimate more precisely the risk for death from comorbid illnesses and in particular the risk for cardiac death. Until such a multivariate adverse event prediction tool becomes available, treatment selection for T1a,bN0M0 HER2-positive cancers remains at the transition zone of evidence- and subjective judgment-based-medicine.

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references