Chemotherapy with or without trastuzumab

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Introduction

HER2 is amplified and/or overexpressed in ~20% of breast cancers. HER2 is a poor prognostic marker associated with aggressive breast cancer behaviour, with high rates of recurrence and mortality in the absence of systemic therapy [1]. Positive HER2 status often correlates with high grade, high proliferation and lack of hormone receptor expression. HER2-positive status is a predictive marker for response to anti-HER2 therapy.

Trastuzumab, a humanized monoclonal antibody, binds to the HER2 extracellular domain and blocks the receptor signalling cascade. Trastuzumab benefit is evident as monotherapy and in combination with chemotherapy. Initially, a prospective phase III trial demonstrated benefit of trastuzumab in combination with chemotherapy in metastatic disease in terms of improved response rates, time to progression (TTP) and overall survival (OS) [2]. Subsequently, six prospective adjunct trials have been reported comparing trastuzumab with no trastuzumab given during and/or after chemotherapy [3–7] (Table 1). Five of the trials reported marked benefit of trastuzumab for disease-free survival (DFS) and OS. Recurrence and mortality were reduced by ~20–40%. Outcome was significantly improved with concurrent and sequential trastuzumab over chemotherapy alone, with a trend favouring the concurrent arm. Only the PACS04 trial failed to show significant improvement in outcome [8]. Based on these results, trastuzumab has emerged as standard of care for HER2-positive breast cancer.

An outstanding issue for clinicians is determination of which patients will benefit from trastuzumab therapy. Most patients in the adjuvant trials had HER2-positive, node-positive disease. All six trials included node-positive patients and four included patients with high risk node-negative disease. Of the node-negative patients, only NCIC 006 enrolled patients with a primary tumour <10 mm in size (Table 1). Thus, at present, exhaustive data for trastuzumab for small node-negative tumours are lacking.

Trastuzumab is currently indicated only in HER2-positive disease. This presumes that HER2 detection methods and thresholds identify a sensitive population, and equally presumes no benefit in HER2-negative disease by current criteria. In the adjuvant trials, positive HER2 status was defined as strong and complete cell membrane staining by immunohistochemistry (IHC) of >10% of invasive tumour cells or gene amplification determined by a FISH ratio of HER2 gene copy number to chromosome 17 centromeres (CEP17) of >2.0. These criteria are less restrictive than those currently advised by the American Society of Clinical Oncology and the College of American Pathologists (ASCO-CAP) guidelines in which HER2 positivity is defined by uniform intense and complete membrane staining by IHC in ≥30% of cells or a HER2/CEP17 ratio by FISH ≥2.2 [9].

This review will focus on these two outstanding clinical issues: the benefit of anti-HER2 therapy in pT1N0M0 disease and the challenge in determination of HER2 status.
benefit of anti-HER2 therapy in HER2-positive pT1N0M0 disease

With routine mammographic screening and use of breast magnetic resonance imaging, it is more common that women present for consideration of adjuvant systemic therapy for small, node-negative tumours. A percentage will have HER2-positive disease, raising the question of anti-HER2 treatment. As with any adjuvant therapy, the prime considerations are (i) estimated risk of disease recurrence; (ii) potential benefit of intervention; and (iii) potential treatment toxicities.

estimated risk of recurrence of HER2-positive pT1N0M0 disease

In biologically unselected populations, patients with small (<20 mm), node-negative tumours have an excellent prognosis. Most are cured by locoregional therapy alone. Some reports show long-term DFS in >90% of patients [10].

Results from biologically unselected populations are seldom transferrable to an individual. Due to heterogeneity in disease biology, breast cancers have a diverse prognosis and response to therapy. It must be a clinically priority to refine risk estimation and treatment benefit within this biological framework. For most individuals with stage I breast cancer the prognosis is excellent. However, some individuals, despite small tumour size and lack of nodal involvement, will have disease recurrence. Ten-year DFS rates (without therapy) of <75% are reported for some stage I cohorts [10]. Reported poor prognostic factors in T1a,bN0M0 disease include high grade, lymphovascular invasion, young age (<35 years) and high proliferation [10, 11].

Evidence is emerging for the power of HER2 as an independent predictor of poor prognosis in stage I disease [11–18] (Table 2). HER2 positivity is uncommon in stage I breast cancer, accounting for <10% of cases, but, when present, it is associated with much higher recurrence rates than HER2-negative disease. Rates are higher than those for populations selected by size and nodal status alone. Most data come from small, retrospective studies, with variability in follow-up duration and adjuvant therapy use [11–18].

HER2 has predictive implications beyond its prognostic significance. It is necessary to establish the impact of HER2 positivity on clinical outcomes for patients with stage I disease, and whether blockade of HER2-enhanced signalling has a similar benefit in these patients compared with those with larger, node-positive tumours.

A retrospective analysis of 852 T1N0M0 tumours from the Finnish Cancer Registry assessed a panel of 10 potential prognostic factors [12]. Grade 1 and T1a tumours showed excellent outcome, with 9-year distant disease-free survival (DDFS) of 95% and 100%, respectively. HER2 overexpression was strongly associated with increased recurrence risk. In a subset with grade 2 or 3 tumours <10 mm, HER2 amplification was associated with worse 9-year DDFS (92% versus 67%, $P = 0.006$).

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<tbody>
<tr>
<td>Duration of trastuzumab</td>
<td>1 year/2 years</td>
<td>1 year</td>
<td>1 year</td>
<td>1 year</td>
<td>9 weeks</td>
</tr>
<tr>
<td>Eligibility</td>
<td>Node positive</td>
<td>Node positive</td>
<td>Node positive</td>
<td>Node positive</td>
<td>Node positive</td>
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<tr>
<td>Tumour size (% of patients) ≥20 mm</td>
<td>49</td>
<td>58</td>
<td>60</td>
<td>51</td>
<td>65</td>
</tr>
<tr>
<td>Nodal status (% of patients) node negative</td>
<td>32</td>
<td>29</td>
<td>6</td>
<td>0</td>
<td>11</td>
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ACT, adriamycin, cyclophosphamide followed by taxane; D, docetaxel; ED, epirubicin and docetaxel; ER, oestrogen receptor; FEC, fluorouracil, epirubicin and cyclophosphamide; PgR, progesterone receptor; TC, docetaxel and carboplatin; Vin, vinorelbine.

**Table 1.** Patient characteristics from the trastuzumab adjuvant chemotherapy trials: HER2-positive patients
**Table 2.** Studies assessing the impact of HER2 status on outcome for individuals with pT1N0M0 breast cancer

<table>
<thead>
<tr>
<th>Author/patient cohort</th>
<th>T1N0M0 n, T inclusion</th>
<th>T1N0M0 HER2+ n (%)</th>
<th>Central HER2 method</th>
<th>Median follow-up (years)</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Joensuu/Finnish Cancer Registry [12]</td>
<td>852, T1a–c</td>
<td>65 (8%)</td>
<td>Yes; IHC; CISH</td>
<td>9.5</td>
<td>Overall DDFS 88%</td>
</tr>
<tr>
<td>Gonzalez-Angulo/M.D. Anderson Cancer Centre [13]</td>
<td>965, T1a,b</td>
<td>98 (10%)</td>
<td>Yes: IHC; FISH</td>
<td>6.2</td>
<td>Overall 5-year DRFS 96%</td>
</tr>
<tr>
<td>Curigliano/European Institute of Oncology [14]</td>
<td>2130, T1a,b</td>
<td>150 (7%)</td>
<td>Yes; IHC; FISH</td>
<td>4.5</td>
<td>5-year DFS hormone receptor positive: HER2 positive 92% (95% CI 86% to 99%); HER2 negative 99% (95% CI 96% to 100%)</td>
</tr>
<tr>
<td>Chia/Canadian Cancer Registry [15]</td>
<td>1248, T1a–c</td>
<td>117 (9%)</td>
<td>Yes; IHC; FISH</td>
<td>12.4</td>
<td>10-year DRFS: HER2 positive 78%; HER2 negative 86%; P = 0.095 ER positive: HER2 positive 87% (95% CI 71% to 94%); HER2 negative 87% (95% CI 84% to 89%) ER negative: HER2 positive 73% (95% CI 61% to 82%); HER2 negative 84% (95% CI 78% to 88%)</td>
</tr>
<tr>
<td>Tovey/Glasgow Royal Infirmary [16]</td>
<td>230, T1a–c, grade 1 or 2</td>
<td>16 (7%)</td>
<td>Yes; IHC; FISH</td>
<td>6.5</td>
<td>Relapse HER2 positive: HR 8.99 (95% CI 3.0–27.0, P = 0.000)</td>
</tr>
<tr>
<td>Black/MA General Hospital and Dana Farber Cancer Institute [17]</td>
<td>134, T1a-c/30, T2</td>
<td>134/30</td>
<td>No</td>
<td>5</td>
<td>5-year DFS: T1a,b 90.5%; T1c 89.5%; T2 79.5%</td>
</tr>
<tr>
<td>Park/Korean Breast Cancer Registry [18]</td>
<td>370, T1a,b</td>
<td>31 (8%)</td>
<td>Yes; IHC; FISH</td>
<td>5</td>
<td>DRFS HER2-positive subgroup (defined as HER2 positive, hormone receptor negative): HR 5.7 (95% CI 1.04–31.5, P = 0.045)</td>
</tr>
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Table 2. (Continued)

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<thead>
<tr>
<th>Author/patient cohort</th>
<th>T1N0M0 n, T inclusion</th>
<th>T1N0M0 HER2+ n (%)</th>
<th>Central HER2 method</th>
<th>Median follow-up (years)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rakhit/MD Anderson Cancer Centre [11]</td>
<td>1369, T1a,b</td>
<td>123 (9%)</td>
<td>Yes: IHC; FISH</td>
<td>6.2</td>
<td>HER2 positive subgroup</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(defined as HER2 positive regardless of hormone receptor status) DRFS</td>
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<td>5 years: HR 4.66 (95% CI 2.47–8.8, P &lt;0.0001)</td>
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CI, confidence interval; CISH, chromogenic in situ hybridization; DDFS, distant disease-free survival; DFS, disease-free survival; DRFS, distant relapse-free survival; ER, estrogen receptor; IHC, immunohistochemistry; HR, hazard ratio.

An M.D. Anderson Cancer Center study assessed 965 T1a,bN0M0 patients [13]. Patients were excluded if they had received adjuvant chemotherapy or trastuzumab. For all patients, 5-year recurrence-free survival (RFS) was 92%. However, RFS varied substantially according to HER2 status (HER2 positive 77% versus HER2 negative 94%, P <0.001). In multivariate analysis, HER2-positive status was associated with higher risk of local and distant recurrence compared with HER2-negative disease. A similar trend for outcome based on HER2 status was seen in 350 patients from two other institutions.

The largest published analysis of HER2-positive, T1a,bN0M0 disease included 150 patients from the European Institute of Oncology, Milan [14]. Approximately 50% of patients with hormone receptor-negative disease had received chemotherapy. Compared with a cohort matched for hormone receptor status, age and year of surgery, HER2 positivity was associated with higher recurrence [hazard ratio (HR) 2.4, 95% confidence interval (CI) 0.9 – 6.5, P = 0.09]. For patients with a hormone receptor-positive tumour, 5-year DFS was better for HER2-negative than HER2-positive tumours (99% versus 92%). In contrast, DFS for patients with a hormone receptor-negative lesion was similar for HER2-positive and -negative disease (91% versus 92%). Eighty-five tumours were T1a. For patients with a T1a hormone receptor-positive tumour, HER2 positivity was associated with worse 5-year DFS than HER2 negativity (97% versus 88%), whereas for hormone receptor-negative disease, DFS was 87% and 93%, respectively.

A Canadian Cancer Registry study confirmed HER2 as an independent poor prognostic factor for relapse and death in >2000 node-negative patients [15]. Seventy percent of the patients never received adjuvant therapy and 1248 patients had stage I disease. HER2 positivity was detected in 21 of 328 patients with a T1a,b tumour and in 96 of 920 patients with a T1c tumour. For stage I disease, HER2 overexpression showed a trend for worse outcome in terms of distant RFS, but not for DFS or OS. However, within stage I oestrogen receptor (ER)-negative disease, HER2 positivity was an independent prognostic factor for DFS. Conversely in ER-positive patients, DFS seemed independent of HER2 status. Only 21 patients had an HER2-positive T1a,bN0M0 tumour, limiting assessment of the prognostic power of HER2 in this cohort.

Retrospective analysis by Tovey et al. identified 362 patients with ‘low-risk’ breast cancer, defined by grade 1 or 2, node-negative disease [16]. Only 22 patients had HER2-positive tumours, which were more likely to be grade 2 and ER negative. The overall HR for HER2 positivity was 5.65 (95% CI 2.4–13.1). Five-year breast cancer-specific survival rates were 96% and 68% for HER2-negative and -positive disease, respectively (P <0.001). Of 230 patients with stage I disease, 16 had HER2-positive tumours with an HR of 8.99 (95% CI 3.0–27.0).

A study by Black et al. reviewed 164 patients with T1–2, node-negative, HER2-positive breast cancer; 134 had T1 disease [17]. In 74 patients with a T1a,b HER2-positive tumour, ~30% of whom received chemotherapy, recurrence risk at 5 years was 9.5%.

Two studies assessed breast cancer outcomes in T1a,bN0M0 tumours by IHC-defined breast cancer subtypes [11, 18]. A Korean single-centre retrospective analysis of 370 patients showed HER2-positive [ER−/progesterone receptor (PgR)−/HER2+] and triple-negative (ER−/PgR−/HER2−) subgroups to be independent risk factors of recurrence [18]. For the HER2-positive subgroup, the RFS HR was 7.2 (95% CI 2.02–25.7, P = 0.002). Another study identified 1369 patients with T1a,bN0M0 disease diagnosed over a 30-year period [11]. In the group of 123 patients with HER2-positive disease (HER2 positive, regardless of hormone receptor status), RFS was significantly worse (HR 5.19, 95% CI 3.21–8.39, P <0.0001) compared with the group of patients with ER-positive HER2-negative breast cancer.

Thus in terms of prognosis, breast cancer patients with stage I HER2-positive disease tumours have a significant risk of relapse. In trials including patients who received chemotherapy, HER2 status still predicted poor outcome. This suggests that, despite chemosensitivity in HER2-positive disease, chemotherapy alone did not substantially improve patient outcome [14, 17, 18].

The potential benefit of trastuzumab in pT1N0M0 disease

Incremental benefit from trastuzumab in stage I is unknown. Prospective data are missing and there are neither clear nor consistent guidelines. HER2 signalling appears critical in defining the poor prognosis in stage I disease and, thus, despite lack of direct evidence, one may anticipate benefit from HER2 blockade. Targeting biological pathways, rather than treatment
based on tumour size and nodal status, is exemplified by the use of endocrine therapy. A prospective randomized trial showed tamoxifen benefit in T1a,b ER-positive tumours, despite small tumour size [19].

In subgroup analyses, trastuzumab efficacy appears consistent across tumour size and nodal status. BCIRG 006 showed DFS and OS benefit for AC-TH (adriamycin plus cyclophosphamide followed by docetaxel and trastuzumab) over AC-T (adriamycin plus cyclophosphamide followed by docetaxel) regardless of tumour size and nodal involvement [4]. A HERA DFS subgroup analysis showed trastuzumab benefit for node-negative disease (HR 0.51, 95% CI 0.30–0.87) and tumours of 10–20 mm (HR 0.59, 95% CI 0.39–0.88) [20]. These results for consistent trastuzumab proportional risk reduction are in line with results from the EBCCTG Overview that proportional benefits from systemic therapy are independent of tumour size and nodal status [21].

**trastuzumab toxicity**

The anticipated absolute benefit of trastuzumab makes it worthy of consideration in Stage I disease. Patients will accept treatment and potential toxicity for a small absolute benefit [22]. Trastuzumab is generally well tolerated, associated however with potential cardiotoxicity. Cardiotoxicity may be influenced by concurrent or sequential chemotherapy/trastuzumab scheduling and type of chemotherapy. In adjuvant trials, class III/IV congestive heart failure (CHF) or cardiac-related deaths ranged from 0% to 4.1% [3–7]. Direct trial comparisons are difficult due to differences in definition of a cardiac event and duration of follow-up. In HERA, after 2 years of follow-up, severe cardiac events (class III/IV CHF, not including cardiac death) were reported in 0% and 0.6% of patients treated with chemotherapy and chemotherapy plus trastuzumab, respectively (P < 0.0001); incidence of symptomatic CHF was 0.1% versus 2.0%, respectively (P < 0.0001) [20]. In BCIRG 006, class III/IV CHF was detected in 0.4%, 1.9% and 0.4% for AC-T, AC-TH and docetaxel, carboplatin and trastuzumab (TCH), respectively, with no cardiac deaths [4]. In PACS04, in which cardiotoxicity was defined by reductions in left ventricular ejection fraction (LVEF), higher anthracycline dose in Fluorouracil, epirubicin and cyclophosphamide (FEC) compared with epirubicin and docetaxel (ED) had a higher rate of severe cardiac toxicity (14% versus 8.0%, respectively) [7]. Three-year cumulative incidence of symptomatic CHF or sudden cardiac death in N9831 was 0.3% for chemotherapy alone, 2.8% for sequential trastuzumab and 3.3% for concurrent trastuzumab [23]. Thus trastuzumab may be more cardiotoxic when used concurrently and with anthracyclines.

**current guidelines**

The ASCO guidelines state that HER2 should be evaluated in any primary breast cancer [24]. HER2 will identify patients that may benefit from anti-HER2 therapy. No comment is made regarding tumour size. The 2009 San Gallen Expert Panel posed the question: ‘What justifies the use of anti-HER2 therapy?’ [25]. The guidelines advise anti-HER2 therapy in HER2-positive disease ‘for all but the very lowest risk invasive tumours’. Whilst recognizing that some evidence supports HER2 as a poor prognostic marker, even in tumours <10 mm,
should be considered, even if associated with slight loss of efficacy.

**intratumoural HER2 heterogeneity**

Trastuzumab is indicated only for patients with HER2-positive disease. What qualifies as HER2 positive is thus critical, as it dictates who will or will not receive potentially efficacious treatment. The challenge for any HER2 guidelines is that, whilst the decision for therapy requires a yes/no answer, HER2 status derives from a continuum of gene copy number and protein expression.

The widely adopted ASCO-CAP HER2 guidelines aim to improve detection reliability, accuracy and reproducibility [24]. They are stricter than thresholds applied in the pivotal trials, selecting a narrower population for trastuzumab. However, they do not consider heterogeneity of intratumoural HER2 status and histological types (Figure 2A and B). HER2 amplification or overexpression may be detected in discrete focal clones of cells or in individual cells diffusely scattered on a dominant background of HER2-negative/equivocal expression (Figure 2C and D). In both cases, the tumour may be HER2 negative by current criteria. The prognostic and therapeutic implications are unclear.

Focal HER2 amplified clones (FHACs) are reported in an N9831 substudy [34]. FHAC cases were defined as having 2–40% of cells with unequivocal amplification (cells with >10 HER2 signals or HER2/CEP17 ratio >5, regardless of overall HER2/CEP17 ratio). FHACs were detected particularly in tumours with discordance between HER2 status by IHC and FISH (21% of IHC 0–1/FISH-amplified and 30% of IHC2+/FISH-amplified cases contained FHACs). The therapeutic implications of this finding were explored in 91 patients from N9831 with FHAC compared with 1571 patients with diffuse HER2-amplified disease. HRs within FHACs and within diffusely HER2-amplified disease were 0.50 (P = 0.30) and 0.59 (P <0.0001) respectively, suggesting similar trastuzumab DFS benefit for patients with HER2 amplification, whether diffuse or focal. Notably, most of the 91 patients with FHAC were HER2 positive by standard criteria and were eligible for trastuzumab.

**Figure 1.** Considerations in the decision-making process for trastuzumab in HER2-positive pT1N0M0 disease. Current options for trastuzumab are omission or use in combination with chemotherapy. In this cohort with potential intermediate risk of relapse, cardiotoxicity may be lessened, perhaps with some loss of efficacy, by sequential trastuzumab. Future evidence may support the options of short course or endocrine therapy plus trastuzumab. *Confirmatory trials for short-course trastuzumab awaited. **Current lack of evidence for this approach in early disease. Promising results from the metastatic setting, but further trials are required for early disease.

**Figure 2.** (A) Invasive ductal carcinoma showing both HER2-positive and HER2-negative areas. (B) Invasive carcinoma of the breast with a lobular HER2-negative component and a ductal HER2-positive component. (C) Individual HER2-positive cells scattered on a dominant background of HER2-negative tumour. (D) FISH of the case show in (C) confirming amplification in the scattered HER2-positive cells as detected by immunohistochemistry.
The clinical and therapeutic significance of FHAC in tumours defined as HER2 negative by standard criteria remains unknown. A provocative N9831 substudy, with centralized HER2 restesting, revealed trastuzumab benefit beyond the HER2-positive population [36]. Trastuzumab benefit was seen in patients with normal gene copy number (relative risk for DFS 0.40; 95% CI 0.18–0.89, \( P = 0.026 \)) or FISH negative with IHC staining of \(< 3+\) (relative risk for DFS 0.34, 95% CI 0.14–0.80, \( P = 0.014 \)). Potential mechanisms are either intratumoural HER2 heterogeneity, such as FHACs, or mechanisms of trastuzumab action beyond the HER2 receptor. Another possibility is the incorrect interpretation of chromosome 17 rearrangement as polysomy. We [37] and others [38] have shown that true polysomy of chromosome 17 (i.e. the occurrence in a nucleus of extra copies of chromosome 17) is a rare event, while genetic aberrations, in particular involving its long arm, with increase or amplification of the centromeric region (CEP17) may occur quite commonly. In these cases the HER2/CEP17 ratio determined by FISH with dual-colour probes could lead to false-negative results. The significance of HER2 positivity within a predominantly HER2-negative tumour requires further exploration.

**conclusions**

- T <1 cm tumours: HER2 positive = generally worse outcome than HER2 negative.
- No reason to expect a lower proportional benefit from trastuzumab, and more generally from systemic therapies, in the case of small tumours (shown in a HERA substudy, BCIRG 006 substudy and EBCTCG Overview).
- Nevertheless, balance benefit with risks, particularly in the case of patients with pT1a.
- Patient involvement in decision making is important.
- If treatment, consider less cardiotoxic options.
- Ongoing trials might identify short trastuzumab regimens for these patients.

**disclosures**

Angelo Di Leo receives honoraria from Roche and GSK for a consultant/advisory role and is a speaker at sponsored symposia.

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