Adjuvant trastuzumab with or without chemotherapy in stage 1 pT1N0 HER2+ breast cancer: a National Cancer Database analysis

Lifen Cao1,2,3,4 · Robert Shenk2,3 · Nickolas Stabellini4 · Megan E. Miller2,3 · Christopher W. Towe3,5 · Alberto J. Montero1,6

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Abstract

Purpose Approximately 20% of all breast cancers (BC) are HER2 amplified. In the APT trial, weekly paclitaxel/trastuzumab in node negative HER2+ BC with tumors < 3 cm was associated with a 7-year invasive disease-free survival of 93%. However, this was in the context of a non-randomized trial, and for pT1N0 HER2+ BC it remains unclear whether HER2 monotherapy would provide similar clinical outcomes to chemo-HER2 therapy. We hypothesized that adjuvant chemo-HER2 therapy would be associated with a modestly improved overall survival compared to HER2 monotherapy in patients with tumors < 2 cm.

Methods In the National Cancer Database (2004–2017), patients with a primary diagnosis of pT1N0M0 HER2+ BC, were separated into two groups: (i) HER2 monotherapy, i.e., trastuzumab, and (ii) chemo-HER2 therapy. A 3:1 propensity match was performed to balance patient selection bias between the two different cohorts. Long-term overall survival (OS) was compared between both groups.

Results A total of 23,281 patients met the criteria. 22,268 (96.7%) received chemo-HER2 therapy and 1013 (4.4%) received HER2 monotherapy. Propensity match identified 1995 patients who received chemo-HER2 therapy, and 666 who received HER2 monotherapy. After matching, adjuvant chemo-HER2 therapy was associated with a modest survival advantage over HER2 monotherapy (5-year OS 94.1% vs. 90.6%, \(P = 0.041\)).

Conclusions Even though there is a modest OS advantage favoring adjuvant chemo-HER2 therapy in patients with pT1N0 HER2+ BC, HER2 monotherapy was associated with 5-year OS > 90%. Therefore, in select patients who have contraindications for cytotoxic chemotherapy, or decline adjuvant chemotherapy altogether, adjuvant trastuzumab monotherapy appears to be a reasonable alternative.

Keywords Breast cancer · Immunotherapy · Chemotherapy · HER2 positive · HER2 breast · NCDB
Introduction

Breast cancer (BC) is the most commonly occurring cancer and leading cause of cancer death among women worldwide. In the U.S. alone, an estimated 281,550 new cases of invasive BC will be diagnosed in 2021 [1]. HER2-positive BC represents 20–25% of BC worldwide [2], and have a distinctive biology, which prior to the development of HER-2 targeting agents was associated with a higher risk of recurrence and poorer clinical outcomes [3–6].

The development of trastuzumab, a humanized monoclonal HER-2-specific antibody was considered a landmark achievement in the field of targeted therapy in the 1990s [7]. When combined with chemotherapy, trastuzumab improves progression-free survival and overall survival in HER2-positive BC [8, 9] and therapies inhibiting HER2 signaling together with chemotherapy have become the standard of care [10].

Trastuzumab-based therapy is well-established for early-stage HER2+ breast cancer, however in patients with small stage 1 tumors, the data are limited since they were excluded from the initial pivotal adjuvant trastuzumab trials [11]. The APT trial examined a less intensive chemotherapy regimen in a non-randomized phase 2 trial [12]. This study enrolled patients with HER2+ node negative cancers <3 cm who all received weekly paclitaxel with trastuzumab, and reported 3-year and 7-year invasive disease-free survival rates (iDFS) of 98.7% and 93%, respectively [11, 12]. Preliminary data with single agent trastuzumab in metastatic breast cancer indicate that the overall response rate was modest ranging from 15 to 25% [13], there are no randomized adjuvant trials that compare trastuzumab with or without chemotherapy in patients with node negative HER2-positive breast cancer.

There are also limited data comparing the impact of dual HER2 antibody therapy to trastuzumab mono-therapy, which is still a relevant question for lower risk node negative stage 1 HER2+ patients. Based on the Aphinity trial, the addition of pertuzumab to standard adjuvant therapy in HER2+ early BC should be limited to patients with node-positive disease [14–16]. Even in the preoperative setting, pertuzumab-containing regimens should be administered only to HER2+ breast cancer patients with ≥cT2 or ≥cN1 [16].

A recently published non-inferiority trial investigated the relative value of adjuvant trastuzumab monotherapy in older women with stages I–III HER2+ early breast cancer [17]. Although the primary objective of non-inferiority for trastuzumab monotherapy was not met, less than a percentage point difference in 3 year overall survival was observed between trastuzumab-chemotherapy and trastuzumab monotherapy groups (97.2% vs. 96.6%; (HR 1.07; 95% CI 0.36 to 3.19)). However, this trial was not designed to address the question of the relative value of chemotherapy added to trastuzumab mono-therapy in pT1N0 HER2+ BC at the lower end of the risk spectrum regardless of age.

Using the National Cancer Database (NCDB)—the largest source of BC data in the United States—our research aim was to determine whether adjuvant HER2 antibody monotherapy (i.e., trastuzumab) was associated with similar overall survival rates compared to chemo plus trastuzumab in patients with pT1N0M0 HER2+ BC. Prior to 2003, the NCDB categorized trastuzumab as chemotherapy. From 2003 onwards, trastuzumab and pertuzumab were categorized as immunotherapy. Pertuzumab was not FDA approved as adjuvant therapy for HER2+ breast cancer until 2017 [18]. Therefore, we confined our query to 2003–2017 when adjuvant immunotherapy for pT1N0 HER2+ breast cancer would have only included trastuzumab. We hypothesized that the combination of chemotherapy and trastuzumab (chemo-HER2 therapy) would result in only a very modest survival advantage over trastuzumab monotherapy, and which if true, would provide real world evidence supporting the use of trastuzumab as adjuvant monotherapy in patients who are not ideal candidates for adjuvant chemotherapy.

Methods

Data collection and data elements

A retrospective cohort study of the National Cancer Database (NCDB) was performed. Jointly sponsored by the American College of Surgeons and the American Cancer Society, NCDB is a clinical oncology database sourced from hospital registry data representing more than 70% of newly diagnosed cancer cases nationwide. The database covers more than 1500 Commission on Cancer (CoC)-accredited facilities. Definition of the database variables are available from the dictionary of NCDB Participant Use Data File (http://ncdbpuf.facs.org). The CoC’s NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Patient cohort and data analysis

The NCDB was queried to analyze patients with HER2+pT1N0M0 BC who received surgery from 2013–2017. Pathological staging data for the cohort was based on TNM classification in American Joint Committee on Cancer (AJCC) 7th edition [19]. Patients were excluded if they had: metastases, had hormone receptor-positive cancers but did not
receive endocrine therapy, or were missing critical study information (e.g., pathologic stage or HER2 status).

The cohort was categorized by treatment status: (i) immunotherapy alone (HER2 monotherapy) or (ii) immunotherapy plus chemotherapy (chemo-HER2 therapy). In the context of stage 1 HER2+ breast cancer, the only immunotherapy agent that patients could have received was trastuzumab, since pertuzumab was not FDA approved for use as adjuvant therapy for HER2+ breast cancer until 2017. The primary outcome was overall survival.

Analysis included univariate comparison of patient factors associated with chemo-HER2 therapy vs. HER2 monotherapy. To compare the two groups, Wilcoxon rank-sum test was utilized for continuous variables and chi-square for categorical data. Multivariable logistic regression determined the association between adjuvant chemotherapy and demographic/tumor factors. Overall survival (OS) differences between the two groups was analyzed using Kaplan–Meier survival estimates and compared by utilizing a log-rank test. To control for confounding effects, Cox proportional hazard analysis was also performed. To further account for differences between patient cohorts receiving chemo-HER2 therapy vs. HER2 monotherapy, a 3:1 propensity match was performed, correcting for: age, race, Charlson comorbidity score, income, facility, tumor grade, hormone receptor status, mastectomy procedures, lymph nodes removed, lympho-vascular invasion status, and sub pathological T1 stage (T1a, T1b, T1c). The propensity match dropped observations of patients receiving HER2 monotherapy whose propensity score as higher than the maximum or less than the minimum score of the controls (chemo-HER2 therapy). 3:1 nearest neighbor matching replacement was used, with the caliper set to 0.01. Standardized differences before and after matching were reported and graphed during the analysis of propensity matching. Differences in survival among the matched pairs were analyzed using a stratified log-rank test and Cox proportional hazard regression analysis using a clustered “sandwich” robust variance estimator to account for clustering within the matched pairs.

All statistical analysis was performed using STATA/MP, version 16.0 (Stata Corp LLC, College Station, TX). Institutional Review Board (IRB) approval was exempted by the University Hospitals Cleveland Medical Center IRB as all data are de-identified.

Results

Clinical and demographic details

The final analytic cohort included 23,281 patients with a pathological diagnosis of pT1N0M0 stage BC (Table 1). 22,268 (96.7%) received adjuvant chemo-HER2 therapy and 1013 (4.4%) received HER2 monotherapy. As expected, older patients were more likely to receive HER2 monotherapy (median age 66 years vs. 57, \(P < 0.001\)). Only 1.94% of women under 50 received HER2 monotherapy, compared to 5.28% of women 50 and older (Supplemental Table 1, \(P < 0.001\)). Patients who received adjuvant chemo-HER2 therapy were more likely to have higher grade tumors (poorly or non-differentiated (53.2% vs. 45.7%, \(P < 0.001\)), and present with lympho-vascular invasion (13.9% vs. 9.7%, \(P < 0.001\)) compared to patients who received HER2 monotherapy. Patients who received chemo-HER2 therapy were more frequently non-white (18.2% vs. 15.0%, \(P = 0.027\)), had private insurance (65.6% vs. 43.0%, \(P < 0.001\)), and treated at academic/integrated facilities (49.2% vs. 45.5%, \(P = 0.001\)). There were no differences in comorbidity, distance to the hospital, or community designation. By contrast, patients who received HER2 monotherapy were more likely to have smaller tumors \((P = 0.019\)), that were more often HR+ and received adjuvant endocrine therapy \((P < 0.001\)).

Significant differences in the types of breast surgery were observed between the two different adjuvant therapy groups. Patients who received HER2 monotherapy, were significantly more likely to undergo a partial mastectomy \((P < 0.001\)), and had fewer axillary lymph nodes removed \((P < 0.002\)) compared to patients who received adjuvant chemo-HER2 therapy.

Factors associated with chemo-HER2 therapy

A multivariable logistic regression was performed to determine clinical factors independently associated with receipt of chemo-HER2 therapy (Table 2). Patients with pT1b and pT1c BC were more likely to receive chemotherapy as compared to those with pT1a disease (OR 1.468 and OR 1.885, \(P \leq 0.001\)). Other factors significantly associated with an increased likelihood of receiving adjuvant chemo-HER2 therapy included: treatment at an academic/integrated facility or comprehensive community cancer program, poorly differentiated or undifferentiated histology. Older age (OR 0.924, \(P < 0.001\)) and hormone receptor-positive cancers with endocrine therapy (OR 0.659, \(P < 0.001\)) were less likely to receive chemo-HER2 therapy.

Survival analyses

Initial Kaplan–Meier estimates demonstrated that among patients who underwent definitive breast surgery those who received adjuvant HER2 monotherapy had a significantly lower OS rate when compared to patients who received adjuvant chemo-HER2 therapy \((P < 0.001)\). Both 3-year OS (98.7% vs. 97.0%) and 5-year OS (96.7% vs. 90.6%) were higher in patients who received chemo-HER2 therapy. A Kaplan Meier estimate of OS is shown in Fig. 1.
| Characteristics                                      | HER2 monotherapy (n=1013) | Chemo-HER2 therapy (n=22,268) | P value |
|----------------------------------------------------|---------------------------|-------------------------------|---------|
| Number (%), Age (years)                            |                           |                               |         |
| 66 (35–90)                                         | 57 (29–90)                |                               |         |
| P value                                             |                           |                               | <0.001  |
| Race                                               |                           |                               |         |
| White                                              | 859 (85.05)               | 18,076 (81.81)                | 0.027   |
| Black                                              | 92 (9.11)                 | 2557 (11.57)                  |         |
| Asian and other                                     | 59 (5.84)                 | 1463 (6.62)                   |         |
| Charlson-Deyo Score                                |                           |                               | 0.283   |
| 0                                                  | 851 (84.01)               | 19,141 (85.96)                |         |
| 1                                                  | 128 (12.64)               | 2543 (11.42)                  |         |
| 2                                                  | 26 (2.57)                 | 430 (1.93)                    |         |
| 3                                                  | 8 (0.79)                  | 154 (0.69)                    |         |
| Insurance                                          |                           |                               | <0.001  |
| Public                                             | 564 (56.23)               | 7251 (32.83)                  |         |
| Private                                            | 431 (42.97)               | 14,483 (65.58)                |         |
| Not insured                                        | 8 (0.8)                   | 352 (1.59)                    |         |
| Facility type                                      |                           |                               | 0.001   |
| Community cancer program                           | 110 (11.1)                | 1658 (8.13)                   |         |
| Comprehensive community cancer program             | 430 (43.39)               | 8701 (42.69)                  |         |
| Academic/research program                          | 333 (33.6)                | 6933 (34.02)                  |         |
| Integrated network cancer program                  | 118 (11.91)               | 3090 (15.16)                  |         |
| Facility area                                      |                           |                               | 0.755   |
| Metro                                              | 848 (86.71)               | 18,897 (86.94)                |         |
| Urban                                              | 113 (11.55)               | 2524 (11.61)                  |         |
| Rural                                              | 17 (1.74)                 | 314 (1.44)                    |         |
| Distance to the hospital (miles)                   |                           |                               | 0.089   |
| 0.1/20                                             | 651 (74.23)               | 14,146 (74.48)                |         |
| 20.1/40                                            | 111 (12.66)               | 2833 (14.92)                  |         |
| 40.1/60                                            | 52 (5.93)                 | 895 (4.71)                    |         |
| 60.1/max                                           | 63 (7.18)                 | 1115 (5.87)                   |         |
| Grade                                              |                           |                               | <0.001  |
| Well-differentiated                                | 79 (8.09)                 | 1115 (5.21)                   |         |
| Moderately differentiated                          | 451 (46.21)               | 8905 (41.61)                  |         |
| Poorly differentiated                              | 445 (45.59)               | 11,353 (53.04)                |         |
| Undifferentiated                                   | 1 (0.1)                   | 30 (0.14)                     |         |
| Lympho-vascular invasion                           |                           |                               | <0.001  |
| Not present                                        | 807 (90.27)               | 16,271 (76.08)                |         |
| Present                                            | 87 (9.73)                 | 2631 (24.02)                  |         |
| Hormone receptor                                   |                           |                               | <0.001  |
| Not present                                        | 230 (22.7)                | 6172 (27.72)                  |         |
| Present                                            | 783 (77.3)                | 16,096 (72.28)                |         |
| Sub T stage                                        |                           |                               | <0.001  |
| 1a                                                 | 170 (17.38)               | 3222 (15.21)                  |         |
| 1b                                                 | 285 (29.14)               | 5688 (26.85)                  |         |
| 1c                                                 | 523 (53.48)               | 12,272 (57.94)                |         |
| Breast surgery type                                |                           |                               | <0.001  |
| Partial mastectomy                                 | 725 (71.57)               | 13,871 (62.29)                |         |
| Unilateral mastectomy                              | 188 (18.56)               | 4552 (20.44)                  |         |
| Bilateral mastectomy                               | 100 (9.87)                | 3845 (17.27)                  |         |
| Axillary surgery type                              |                           |                               | <0.001  |
| SLNB (1–5 lymph nodes)                             | 871 (86.49)               | 18,391 (82.93)                |         |
| ALND (>5 lymph nodes)                              | 109 (10.82)               | 3288 (14.83)                  |         |
| No nodes or no Axillary Surgery                    | 27 (2.68)                 | 497 (2.24)                    |         |
Additionally, when we divided the patient population into age < 50 and age > 50 (Supplemental Fig. 1), the Kaplan–Meier OS curves the former are completely overlapping, while in the older population there is more separation of curves between both groups with HER2 monotherapy demonstrating a significantly worse OS (P < 0.001, Supplemental Fig. 1B).

Propensity matching was performed, which generated 1995 chemo-HER2 and 666 HER2 monotherapy patients. Propensity matching effectively reduced selection bias between both groups (Fig. 2 and Supplemental Table 2). In the matched cohort, HER2 monotherapy was associated with poorer overall survival (P = 0.041, Fig. 3) compared to the adjuvant chemo-HER2 therapy group. The median follow-up time was 39.4 months vs. 38.9 months for HER2 monotherapy and chemo-HER2 therapy, respectively.

On multivariable Cox proportional hazard regression, the survival benefit of chemo-HER2 therapy was no longer statistically significant but trending (HR 0.659, P = 0.068, Table 3) when controlling for demographic, clinical pathologic, and tumor factors. African American (HR 1.995, P = 0.024) and high comorbidity (HR 4.320, P < 0.001) were significant predictors of increased mortality.

Discussion

For node negative early HER2+ BC, adjuvant weekly paclitaxel and trastuzumab has emerged as the preferred regimen [12]. The seven-year follow-up analysis of the APT trial reported a 7-year DFS and OS of 93% (95% CI 90.4 to 96.2) and 95% (95% CI 92.4 to 97.7), respectively [11]. More recently, the ATEMPT trial [20] in stage 1 HER2+ BC demonstrated that adjuvant therapy with the antibody drug conjugate trastuzumab emtansine (T-DM1) was associated with similar survival outcomes as paclitaxel plus trastuzumab (TH) but with important differences in treatment-related adverse events. However, since T-DM1 is antibody

Table 2 Multivariable logistic regressions for predictors of receipt of adjuvant chemo-HER2 vs. HER2 monotherapy in HER2+ pT1N0M0 breast cancer patients (NCDB 2013–2017)

| Chemo-HER2 vs. HER2 monotherapy | Odds ratio | 95% Conf. Int | p-value |
|----------------------------------|------------|---------------|---------|
| Age 0.924                         | 0.915      | 0.933         | <0.001  |
| Race: White Reference             |            |               |         |
| African American 1.040            | 0.808      | 1.339         | 0.760   |
| Asian or others 0.864             | 0.628      | 1.190         | 0.371   |
| Charlson-Deyo score 0 Reference   |            |               |         |
| 1 1.076                           | 0.869      | 1.332         | 0.502   |
| 2 1.116                           | 0.706      | 1.763         | 0.638   |
| 3 1.641                           | 0.711      | 3.785         | 0.245   |
| Facility type: Community Reference|            |               |         |
| Comprehensive 1.339                | 1.051      | 1.705         | 0.018   |
| Academic/integrate 1.329          | 1.044      | 1.692         | 0.021   |
| Insurance status: Public insurance|            |               |         |
| Private insurance 1.023           | 0.850      | 1.230         | 0.811   |
| Not insured 1.186                 | 0.516      | 2.724         | 0.688   |
| Grade: Well-differentated Reference|          |               |         |
| Moderately differentiated 1.159   | 0.872      | 1.541         | 0.309   |
| Poorly or undifferentiated 1.398  | 1.046      | 1.869         | 0.024   |
| HR 0.659                          | 0.550      | 0.791         | <0.001  |
| Lympho-vascular invasion 1.264    | 0.991      | 1.613         | 0.059   |
| Sub T stage: T1a 1.468            | 1.173      | 1.835         | 0.001   |
| T1b 1.885                         | 1.533      | 2.318         | <0.001  |
delivered chemotherapy, the question still remains what would expected outcomes be with trastuzumab monotherapy compared to chemo-HER2 therapy—either TP or T-DM1—in patients with pT1N0 HER2+ BC.

Our study has several limitations that are related to missing data not captured in large retrospective cohorts such as the NCDB. The database does not include local regional recurrence or disease-free survival; therefore, our analysis of long-term outcomes is limited only to OS. Similarly, granular details about chemotherapy or immunotherapy agents, doses, combinations, toxicities, and reasons behind decision-making are not included and therefore cannot be factored into our analyses. Another limitation is the absence of an untreated control group with no HER2 treatment. A study by O’Sullivan et al. did include this subgroup of patients and demonstrated that substantial DFS and OS benefit were provided from adjuvant trastuzumab among women with HER2-positive tumors ≤ 2 cm as well [21]. Finally, because the NCDB does not specify which HER-2 antibody was received, it is possible that reported outcomes with HER2 monotherapy may have included patients who received dual HER-2 therapy. However, since pertuzumab was not FDA approved for adjuvant use until 2017, and our analysis was limited to 2003–2017, it is reasonable to deduce that few if any patients could have received pertuzumab outside of a clinical trial.

Despite these limitations, this analysis provides real world data that indicate that even in pT1N0 HER2+ BC, there does seem to be a modest OS advantage with the addition of adjuvant chemotherapy to trastuzumab. Based on the very good outcomes observed with TH, the standard of care for pT1N0 HER2+ BC should remain adjuvant chemo-HER2 therapy with TH. The ATEMPT trial suggests that T-DM1 is an alternative. However, in patients who are considered unfit for adjuvant chemotherapy or who decline it altogether, these data provide evidence that trastuzumab alone is a viable alternative with 5-year OS rate of approximately 91%.
**Supplementary Information** The online version contains supplementary material available at [https://doi.org/10.1007/s10549-021-06411-4](https://doi.org/10.1007/s10549-021-06411-4).

**Declarations**

**Conflict of interests** CW Towe reports that he is a consultant for Zimmer Biomet, AstraZeneca, Atricure, and Medtronic, but that these relationships have not affected this manuscript or the accuracy of the data analysis. CW Towe reports that he has received unrelated research funding from Zimmer Biomet. All other authors have no disclaimers, sources of funding, or financial relationships to declare.

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### Table 3 Cox proportional hazard regression for overall survival of HER2+ pT1N0M0 patients among propensity-matched cohort

| Predictor                     | Hazard ratio | 95% Conf. Int | p-value |
|-------------------------------|--------------|---------------|---------|
| Chemotherapy-HER2 vs. HER2 monotherapy | 0.655        | 0.416–1.033   | 0.068   |
| Age                           | 1.031        | 0.999–1.064   | 0.060   |
| Race                          |              |               |         |
| White                         | Reference    |               |         |
| African American              | 1.995        | 1.096–3.635   | 0.024   |
| Asian or others               | 1.179        | 0.440–3.159   | 0.743   |
| Charlson-Deyo score           |              |               |         |
| 0                             | Reference    |               |         |
| 1                             | 1.648        | 0.929–2.925   | 0.088   |
| 2                             | 4.320        | 1.908–9.782   | <0.001  |
| 3                             | 2.464        | 0.274–22.178  | 0.421   |
| Facility type                 |              |               |         |
| Community                     | Reference    |               |         |
| Comprehensive                 | 0.722        | 0.374–1.394   | 0.332   |
| Academic                      | 0.614        | 0.318–1.185   | 0.146   |
| Integrated                    | 0.932        | 0.420–2.067   | 0.862   |
| Insurance status              |              |               |         |
| Public insurance              | Reference    |               |         |
| Private insurance             | 0.464        | 0.227–0.949   | 0.036   |
| Grade                         |              |               |         |
| Well-differentiated           | Reference    |               |         |
| Moderately differentiated     | 1.216        | 0.472–3.134   | 0.685   |
| Poorly or undifferentiated    | 1.039        | 0.395–2.736   | 0.938   |
| HR                            | 0.535        | 0.308–0.930   | 0.027   |
| Lympho-vascular invasion      | 1.089        | 0.498–2.381   | 0.830   |
| Sub T                         |              |               |         |
| T1a                           | Reference    |               |         |
| T1b                           | 0.910        | 0.459–1.802   | 0.786   |
| T1c                           | 0.849        | 0.451–1.597   | 0.611   |
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