A US Registry–Based Assessment of Use and Impact of Chemotherapy in Stage I HER2-Positive Breast Cancer

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Abstract

Background: Despite the paucity of evidence supporting chemotherapy in the treatment of node-negative, HER2-positive breast cancer measuring <2 cm, use of trastuzumab-based chemotherapy has increased over the past decade. Therefore, we used the National Cancer Database to evaluate the use and impact of chemotherapy on survival in this population. **Methods:** We identified female patients aged 18 to 70 years with node-negative, HER2-positive breast cancer measuring <2 cm. A propensity-matched cohort model was used to control for risk factors known to influence survival. Primary end points assessed were receipt of chemotherapy and overall survival (OS). **Results:** In our propensity-matched cohort model (n=8,222), adjuvant chemotherapy (ACT) was associated with a lower 5-year OS rate in T1mi breast cancer (n=626; 89.1% [95% CI, 81.8%–93.5%] vs 99.1% [96.6%–99.8%]), no significant effect in T1a disease (n=2,901; 95.4% [93.2%–96.9%] vs 96.9% [94.1%–98.3%]), and improved 5-year OS in T1b (n=2,340; 97.1% [95.1%–98.4%] vs 92.3% [88.5%–94.9%]) and T1c tumors (n=2,355; 95.9% [93.5%–97.5%] vs 91.5% [88.4%–93.9%]). In the entire cohort of 21,148 patients who met the inclusion criteria, ACT was associated with lower 5-year OS in T1mi (89.6% [83.7%–93.4%] vs 98.1% [96.6%–98.9%]) and T1a tumors (94.9% [92.9%–96.3%] vs 96.5% [94.6%–97.7%]), and improved 5-year OS in T1b (96.8% [95.6%–97.7%] vs 92.3% [88.7%–94.8%]) and T1c tumors (95.8% [94.9%–96.5%] vs 91.6% [88.5%–93.9%]). Increased use of ACT was observed over the study period. From 2010 to 2013, annual treatment rates were 71.5%, 72.4%, 73.3%, and 74.4%, respectively (trend test, *P*<.0001). **Conclusions:** Our data support the use of ACT for HER2-positive, node-negative T1b and T1c breast cancer, whereas no benefit was observed for ACT in T1mi and T1a HER2-positive, node-negative breast cancer. Although use of ACT is increasing in node-negative, HER2-positive breast cancer <2 cm, our findings caution against its use in the smallest of these tumors (T1mi and T1a) due to lack of survival benefit.

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No definite preferred standard of care exists for adjuvant chemotherapy (ACT) in patients with node-negative, HER2-positive breast cancers measuring <2 cm.[1] Prior to the advent of HER2-directed therapy, *HER2* overexpression was a marker of poor prognosis, and is currently found in 15% to 20% of all invasive breast cancers. Approximately 10% of small, node-negative invasive breast cancers will also overexpress *HER2*.[2–4] Trastuzumab is a monoclonal antibody that targets an extracellular domain of the *HER2* oncogene. Trastuzumab with ACT has been shown to improve disease-free survival (DFS) and overall survival (OS) in previous trials, and has become the standard of care in patients with high-risk node-negative or node-positive breast cancer.[5–7] However, these landmark trials often excluded or underrepresented patients with node-negative breast cancer measuring <2 cm.

For patients with node-negative, HER2-positive

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breast cancers ≤1 cm, NCCN used expert opinion (category 2B) to recommend consideration of trastuzumab-containing ACT regimens, and category 1 evidence to support its use in patients with tumors >1 cm.[8] Data supporting use of chemotherapy for node-negative, HER2-positive breast cancers ≤1 cm are limited by the small, single-armed, or observational nature of the studies.[9–12] Patients with node-negative tumors that are 1 to 2 cm are underrepresented in the prospective randomized trials, which showed improvements in relative risk reduction but less clear absolute benefits.[7,13,14] Despite the lack of robust evidence, a significant increase in the use of trastuzumab-based chemotherapy has occurred in patients with node-negative, HER2-positive breast cancers ≤1 cm in the past decade.[15] Because trastuzumab-based chemotherapy has both short- and long-term adverse effects, the question should be asked whether there is a tumor size below which treatment has little value or is even detrimental in terms of overall outcome. Therefore, we used the National Cancer Database (NCDB) to evaluate the use and impact of ACT on OS in patients with node-negative, HER2-positive breast cancers <2 cm.

Methods

Data Source

Access was granted to the NCDB Participant Use Data File (PUF) for patients diagnosed with breast cancer from 2004 through 2014. Patients were identified based on International Classification of Diseases for Oncology, Third Edition (ICD-O-3) site codes C50.0 through C50.9.[16] The NCDB is a nationwide, facility-based, comprehensive, clinical surveillance resource oncology data set, started jointly in 1989 by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, that integrates hospital registry data collected in >1,500 CoC-accredited facilities. The data represent approximately 70% of all newly diagnosed cancer cases nationwide annually. The NCDB PUF is a HIPAA-compliant data file. Institutional Review Board approval was not required for this study because the PUF is deidentified.

Study Population

After obtaining permission from the NCDB, we queried the 2014 NCDB PUF for patients who were diagnosed with histologically confirmed invasive breast cancer from 2010 to 2013. We limited our analysis to 2010 through 2013 because the NCDB began requiring HER2 reporting in 2010. Vital status information is not included for patients diagnosed in 2014 because of the limited follow-up for these patients. Follow-up ranged from 6 years for patients diagnosed in 2010 to 3 years for those diagnosed in 2013. The PUF data do not include cause of death information, and therefore cause-specific survival cannot be calculated. In our analysis, we included adults aged ≥18 and ≤70 years to maximize the number of patients treated with chemotherapy and minimize the non–cancer-related deaths. We selected female patients with node-negative, HER2-positive invasive breast cancer <2 cm. Patients had to have undergone definitive surgery (lumpectomy with radiation or mastectomy) with negative margins. We excluded those who were HER2-negative or had unknown HER2 status, whose survival time was missing, and who did not receive definitive surgery. Figure 1 depicts the CONSORT diagram.

Stratification of patients into treated and untreated groups was complicated by the fact that the NCDB does not provide drug-specific data. For patients diagnosed between 2010 and 2012, some biologic agents, including trastuzumab and pertuzumab, were classified as chemotherapy. In 2013, the NCDB announced a change in classification for trastuzumab and pertuzumab, and these agents were reclassified as immunotherapy for cases diagnosed starting January 1, 2013. This change impacted our data set, and we opted to include patients who received chemotherapy with or without explicitly noted immunotherapy treatment in our treatment group. For the purposes of this study, the term "chemotherapy" will be used to include systemic chemotherapy, with anti-HER2 therapy including trastuzumab and pertuzumab. The nontreatment group included only patients without explicitly noted immunotherapy who did not receive chemotherapy. The small group of patients recorded as receiving immunotherapy without chemotherapy were excluded.

Statistical Methods and Analysis

We assessed potential associations between sociodemographic, stage, estrogen receptor (ER)/progesterone receptor (PR) status, and tumor and treatment characteristics using Pearson chi-square or Fisher exact tests. Survival analysis using Kaplan-Meier curves

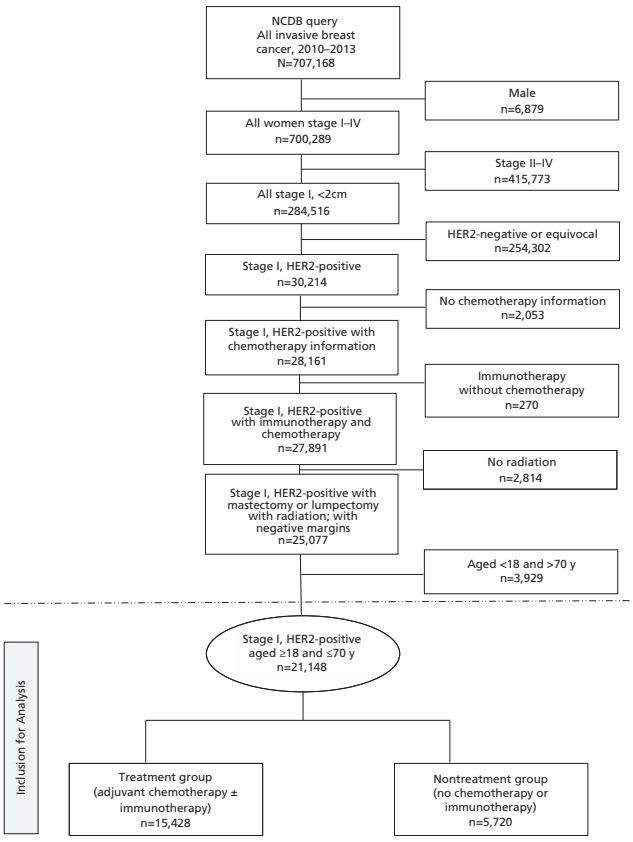

Figure 1. CONSORT diagram of the study population.
Abbreviation: NCDB, National Cancer Database.

and the log-rank test were used to compare OS between the treatment and nontreatment groups. Additionally, both a multivariate Cox proportional hazards regression model and propensity score–matched univariable Kaplan-Meier curves were constructed to control for clinicodemographic differences between the study groups. For the multivariate Cox model, variables were selected in a stepwise fashion from the pool of candidate variables that displayed significant univariable associations with treatment status. During the selection process, $P<.20$ was required for initial inclusion in the model and $P<.10$ was required to remain in the model. The propensity score model of treatment receipt was based on a multivariate logistic regression model, and used a variable selection process similar to the Cox model variable selection process. Treated and untreated patients were matched 1:1 on propensity score, with a maximum allowed difference in propensity score of ±2%. Statistical analysis was performed using SAS 9.4 (SAS Institute Inc.), and $P<.05$ was considered statistically significant for all comparisons.

Results

Patient Characteristics

A total of 21,148 patients identified in the database between 2010 and 2013 met inclusion criteria. Baseline patient characteristics are summarized in Table 1. Most were white (82.2%), were aged ≥50 years (71.3%), had good performance status (87.1% with Charlson/Deyo score of 0), had some form of insurance (96.9%), had no other prior malignancy (87.9%), had ductal carcinoma histology (92.9%), and had T1c stage disease at diagnosis (48.2%). Between 2010 and 2013, marked shifts occurred in the number of patients classified as receiving ACT alone compared with ACT combined with immunotherapy (Table 2). Associations between stage and clinicodemographic characteristics are summarized in Table 3.

Association Between Treatment Receipt and Tumor and Sociodemographic Characteristics

An increased use of ACT occurred during the study period. The annual treatment rates from 2010 to 2013 were 71.5%, 72.4%, 73.3%, and 74.4%, respectively (trend test, $P<.0001$). Increasing rates of ACT were primarily driven by increased treatment rates for T1b and T1c tumors (trend test, $P<.0001$ and $P<.0001$, respectively), whereas treatment rates for T1a tumors did not change significantly (trend test, $P=.64$) and rates decreased slightly in T1mi tumors (trend test, $P=.03$). Practice patterns in use of ACT reflected NCCN recommendations, in that use increased from T1mi to T1c (26.1%, 46.3%, 77.5%, 88.2%; trend test, $P<.0001$) and from well-differentiated to poorly/undifferentiated tumors (48.4% to 82.5%; $P<.0001$). Younger patients were more likely to receive treatment (87.0% for <40 years of age vs 67.4% for 60–70 years of age; $P<.0001$). ER/PR status was not associated with receipt of chemotherapy. A total of 82% of all patients with ER-positive breast cancer received endocrine therapy. Patients with malignant cells in regional lymph nodes that measured <0.2 mm (N0i+ or N0mol+) were more likely to receive ACT than those without malignant cells in regional lymph nodes N0 (including N0i– or N0mol–).

Table 1. Baseline Demographic and Clinical Characteristics

Characteristics	Received Chemotherapy, n (%) N=15,428	No Chemotherapy, n (%) N=5,720	*P* Value
Age, y			<.0001
<40	955 (6)	143 (2)	
40–49	3,867 (25)	1,095 (19)	
50–59	5,557 (36)	2,043 (36)	
60–70	5,049 (33)	2,439 (43)	
PR status			<.0001
Negative/Borderline	7,045 (45)	2,597 (45)	
Positive	8,364 (54)	3,098 (54)	
Not done/unknown	19 (1)	25 (1)	
ER status			.0002
Negative/Borderline	4,650 (29)	1,587 (28)	
Positive	10,766 (70)	4,121 (72)	
Not done/unknown	12 (0)	12 (<1)	
AJCC T stage			<.0001
T1mi	379 (2)	1,073 (19)	
T1a	1,939 (13)	2,245 (39)	
T1b	4,117 (27)	1,199 (21)	
T1c	8,993 (58)	1,203 (21)	
Node status			<.0001
N0 (i+ or m+)	619 (4)	117 (2)	
N0 (i– and m–)	14,809 (96)	5,603 (98)	
Histology type			.0005
Ductal	14,371 (93)	5,282 (93)	
Lobular	362 (2)	189 (3)	
Other	695 (5)	249 (4)	
Grade (differentiation)			<.0001
Well	724 (5)	773 (14)	
Moderate	5,843 (38)	2,497 (44)	
Poor	7,951 (51)	1,687 (29)	
Not determined	910 (6)	763 (13)	
Surgery type			.0001
Lumpectomy	8,609 (56)	2,945 (51)	
Mastectomy	6,819 (44)	2,775 (49)	
Surgery ± radiation			<.0001
Lumpectomy + radiation	8,609 (56)	2,945 (52)	
Mastectomy + radiation	937 (6)	76 (1)	
Mastectomy alone	5,882 (38)	2,699 (47)	
Primary payer			<.0001
Not insured	316 (2)	109 (2)	
Private insurance	11,233 (73)	3,793 (66)	
Medicaid	1,085 (7)	364 (6)	
Medicare	2,437 (16)	1,307 (23)	
Other government	187 (1)	82 (2)	
Unknown	170 (1)	65 (1)	
Income			.82
<$38,000	1,992 (13)	762 (13)	
$38,000–$47,999	3,008 (19)	1,129 (20)	
$48,000–$62,999	4,096 (27)	1,485 (26)	
≥$63,000	6,293 (41)	2,332 (41)	
Unknown	39 (<1)	12 (<1)	
Education less than high school			.0009
≥21%	2,034 (13)	878 (15)	
13%–20.9%	3,405 (22)	1,276 (22)	
7%–12.9%	5,195 (34)	1,841 (32)	
<7%	4,756 (31)	1,714 (31)	
Unknown	38 (<1)	11 (<1)	
Charlson/Deyo score			.006
0	13,490 (87)	4,925 (86)	
1	1,701 (11)	677 (12)	
2	237 (2)	118 (2)	
Previous cancer			<.0001
Yes	1,696 (11)	865 (15)	
No	13,732 (89)	4,855 (85)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

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Table 1. Baseline Demographic and Clinical Characteristics (cont.)

Characteristics	Received Chemotherapy, n (%) N=15,428	No Chemotherapy, n (%) N=5,720	*P* Value
Facility type			<.0001
Community cancer program	1,458 (9)	658 (11)	
Comprehensive cancer program	7,029 (46)	2,633 (46)	
Academic research program	5,230 (34)	1,877 (33)	
Integrated cancer program	1,711 (11)	552 (10)	
Case volume			<.0001
Highest quartile	9,453 (62)	3,282 (57)	
Second/third quartiles	5,116 (33)	2,097 (37)	
Lowest quartile	859 (5)	341 (6)	
Facility location			<.0001
New England	1,046 (7)	439 (8)	
Middle Atlantic	2,520 (16)	921 (16)	
South Atlantic	3,316 (21)	1,257 (22)	
East North Central	2,817 (18)	897 (16)	
East South Central	937 (6)	365 (6)	
West North Central	1,214 (8)	421 (7)	
West South Central	1,036 (7)	459 (8)	
Mountain	689 (5)	215 (4)	
Pacific	1,853 (12)	746 (13)	
County type			.72
Metropolitan	13,104 (85)	4,832 (85)	
Urban	1,793 (12)	692 (12)	
Rural	102 (1)	42 (1)	
Unknown	429 (2)	154 (2)	
Race			.23
White	12,700 (82)	4,694 (82)	
Black	1,708 (11)	611 (11)	
Other	905 (6)	360 (6)	
Unknown	115 (1)	55 (1)	
Ethnicity			.029
Non-Hispanic	14,068 (91)	5,176 (90)	
Mexican/Chicano	117 (1)	49 (1)	
Other Hispanic	715 (5)	252 (5)	
Unknown	528 (3)	243 (4)	
Year of diagnosis			.0005
2010	3,436 (22)	1,369 (24)	
2011	3,846 (25)	1,468 (26)	
2012	4,016 (26)	1,460 (26)	
2013	4,130 (27)	1,423 (25)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

Patients residing in areas with low educational attainment (≥21% of the population without a high school degree), with poor performance status (Charlson/Deyo score of ≥2), or a history of previous cancer were less likely to receive ACT. Academic/Research and integrated network program facilities were associated with higher rates of treatment (73.6% and 75.6%, respectively) compared with community cancer programs (68.9%; *P*<.0001). Likewise, facilities with a higher breast cancer case volume had higher treatment rates compared with those in the lowest quartile (74.2% vs 70.9%; *P*<.0001). Treatment rates varied by geographic location and insurance type; race, median household income, and type of county (metropolitan, rural, urban, missing) were not associated with use of ACT.

Table 2. Reporting in the NCDB

Year	Only ACT Noted, n (%)[a]	ACT + Immunotherapy Noted, n (%)	Neither ACT nor Immunotherapy Noted, n (%)
2010	3,366 (70)	70 (1)	1,369 (28)
2011	3,766 (71)	80 (2)	1,468 (28)
2012	3,581 (65)	435 (8)	1,460 (27)
2013	1,058 (19)	3,072 (55)	1,423 (26)
Total	11,771	3,657	5,720

Abbreviations: ACT, adjuvant chemotherapy; NCDB, National Cancer Database.
[a]Includes patients whose immunotherapy status was recorded as "unknown" (n=27).

Overall Survival

In the entire cohort (n=21,148), ACT was associated with decreased 5-year OS rates in patients with T1mi (n=1,452; 89.6% [95% CI, 83.7%–93.4%] vs 98.1% [96.6%–98.9%]; log-rank *P*<.0001) and

Table 3. Associations Between Stage and Clinicodemographic Characteristics

Variable	Stage T1mi, n (%) N=1,452	Stage T1a, n (%) N=4,184	Stage T1b, n (%) N=5,316	Stage T1c, n (%) N=10,196	*P* Value
Age, y					<.0001
<40	65 (4)	233 (6)	233 (4)	567 (6)	
40–49	411 (28)	1,015 (24)	1,177 (22)	2,359 (23)	
50–59	574 (40)	1,552 (37)	1,901 (36)	3,573 (35)	
60–70	402 (28)	1,384 (33)	2,005 (38)	3,697 (36)	
PR status					<.0001
Negative/Borderline	992 (68)	2,219 (53)	2,299 (43)	4,132 (41)	
Positive	444 (31)	1,957 (47)	3,007 (57)	6,054 (59)	
Not done/unknown	16 (1)	8 (<1)	10 (<1)	10 (<1)	
ER status					<.0001
Negative/Borderline	727 (50)	1,446 (35)	1,424 (27)	2,640 (26)	
Positive	721 (50)	2,732 (65)	3,889 (73)	7,545 (74)	
Not done/unknown	4 (<1)	6 (<1)	3 (<1)	11 (<1)	
Node status					<.0001
Positive	40 (3)	130 (3)	148 (3)	418 (4)	
Negative	1,412 (97)	4,054 (97)	5,168 (97)	9,778 (96)	
Histology type					<.0001
Ductal	1,380 (95)	3,949 (95)	4,899 (92)	9,425 (92)	
Lobular	14 (1)	95 (2)	165 (3)	277 (3)	
Other	58 (4)	140 (3)	252 (5)	494 (5)	
Grade (differentiation)					<.0001
Well	42 (3)	367 (9)	490 (9)	598 (6)	
Moderate	357 (25)	1,883 (45)	2,314 (44)	3,786 (37)	
Poor	538 (37)	1,575 (38)	2,201 (41)	5,324 (52)	
Not determined	515 (35)	359 (8)	311 (6)	488 (5)	
Chemotherapy sequence					<.0001
Neoadjuvant	240 (17)	807 (19)	692 (13)	1,034 (10)	
Adjuvant	128 (9)	1,084 (26)	3,287 (62)	7,653 (75)	
None	1,084 (75)	2,293 (55)	1,337 (25)	1,509 (15)	
Primary payer					<.0001
Not insured	18 (1)	96 (2)	98 (2)	213 (2)	
Private insurance	1,109 (76)	3,041 (73)	3,781 (71)	7,095 (70)	
Medicaid	115 (8)	276 (7)	305 (6)	753 (7)	
Medicare	185 (13)	671 (16)	1,010 (19)	1,878 (18)	
Other government	17 (1)	46 (1)	69 (1)	137 (1)	
Unknown	8 (1)	54 (1)	53 (1)	120 (1)	
Income					<.0001
<$38,000	153 (10)	565 (14)	656 (13)	1,380 (14)	
$38,000–$47,999	271 (19)	748 (18)	1,023 (19)	2,095 (21)	
$48,000–$62,999	375 (26)	1,089 (26)	1,429 (27)	2,688 (26)	
≥$63,000	650 (45)	1,774 (42)	2,194 (41)	4,007 (39)	
Unknown	3 (<1)	8 (<1)	14 (<1)	26 (<1)	
Education less than high school					.0031
≥21%	207 (14)	550 (13)	713 (13)	1,442 (14)	
13%–20.9%	271 (19)	919 (22)	1,124 (21)	2,367 (23)	
7%–12.9%	490 (34)	1,392 (33)	1,832 (35)	3,322 (33)	
<7%	481 (33)	1,316 (32)	1,633 (31)	3,040 (30)	
Unknown	3 (<1)	7 (<1)	14 (<1)	25 (<1)	
Charlson/Deyo score					.036
0	1,282 (88)	3,688 (88)	4,613 (87)	8,832 (86)	
1	157 (11)	426 (10)	605 (11)	1,190 (12)	
2	13 (1)	70 (2)	98 (2)	174 (2)	
Previous cancer					.0002
Yes	177 (12)	516 (12)	725 (14)	1,143 (11)	
No	1,275 (88)	3,668 (88)	4,591 (86)	9,053 (89)	
Facility type					<.0001
Community cancer program	127 (9)	376 (9)	587 (11)	1,026 (10)	
Comprehensive cancer program	556 (38)	1,876 (45)	2,451 (46)	4,779 (47)	
Academic research program	620 (43)	1,486 (36)	1,729 (33)	3,272 (32)	
Integrated cancer program	149 (10)	446 (11)	549 (10)	1,119 (11)	
Case volume					<.0001
Highest quartile	946 (65)	2,622 (63)	3,175 (60)	5,992 (59)	
Second/Third quartiles	432 (30)	1,372 (33)	1,811 (34)	3,598 (35)	
Lowest quartile	74 (5)	190 (4)	330 (6)	606 (6)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

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Table 3. Associations Between Stage and Clinicodemographic Characteristics (cont.)

Variable	Stage T1mi, n (%) N=1,452	Stage T1a, n (%) N=4,184	Stage T1b, n (%) N=5,316	Stage T1c, n (%) N=10,196	*P* Value
Facility location					<.0001
New England	159 (11)	314 (8)	377 (7)	635 (6)	
Middle Atlantic	306 (21)	675 (16)	892 (17)	1,568 (15)	
South Atlantic	256 (18)	893 (21)	1,131 (21)	2,293 (22)	
East North Central	229 (16)	717 (17)	983 (18)	1,785 (18)	
East South Central	58 (4)	233 (6)	347 (7)	664 (7)	
West North Central	147 (10)	314 (8)	403 (8)	771 (8)	
West South Central	76 (5)	299 (7)	349 (7)	771 (8)	
Mountain	32 (2)	188 (4)	228 (4)	456 (4)	
Pacific	189 (13)	551 (13)	606 (11)	1,253 (12)	
County type					0.08
Metropolitan	1,251 (86)	3,589 (85)	4,508 (85)	8,588 (84)	
Urban	148 (10)	453 (11)	643 (12)	1,241 (12)	
Rural	8 (1)	23 (1)	39 (1)	74 (1)	
Unknown	45 (3)	119 (3)	126 (2)	293 (3)	
Race					<.0001
White	1,160 (80)	3,397 (81)	4,428 (83)	8,409 (82)	
Black	150 (10)	449 (11)	581 (11)	1,139 (11)	
Other	131 (9)	308 (7)	260 (5)	566 (6)	
Unknown	11 (1)	30 (1)	47 (1)	82 (1)	
Ethnicity					.35
Non-Hispanic	1,327 (91)	3,792 (91)	4,860 (91)	9,265 (91)	
Mexican/Chicano	15 (1)	38 (1)	34 (1)	79 (1)	
Other Hispanic	60 (4)	201 (5)	219 (4)	487 (5)	
Unknown	50 (4)	153 (3)	203 (4)	365 (3)	
Year of diagnosis					.047
2010	295 (20)	928 (22)	1,168 (22)	2,414 (24)	
2011	384 (26)	1,032 (25)	1,365 (26)	2,533 (25)	
2012	373 (26)	1,088 (26)	1,364 (25)	2,651 (26)	
2013	400 (28)	1,136 (27)	1,419 (27)	2,598 (25)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

T1a tumors (n=4,184; 94.9% [92.9%–96.3%] vs 96.5% [94.6%–97.7%]; *P*=.02). However, ACT was associated with improved 5-year OS rates in patients with T1b (n=5,316; 96.8% [95.6%–97.7%] vs 92.3% [88.7%–94.8%]; *P*<.0001) and T1c tumors (n=10,196; 95.8% [94.9%–96.5%] vs 91.6% [88.5%–93.9%]; *P*<.0001).

In our 1:1 propensity-matched cohort model (n=8,222), ACT was associated with a decreased 5-year OS rate in patients with T1mi tumors (n=626; 89.1% [95% CI, 81.8%–93.5%] vs 99.1% [96.6%–99.8%]; *P*=.0006) (Figure 2A), and no effect on 5-year OS was seen in patients with T1a tumors (n=2,901, 95.4% [93.2%–96.9%] vs 96.9% [94.1%–98.3%]; *P*=.059) (Figure 2B). It is important to note, however, that the overall number of events in patients with T1mi tumors was small, with 18 observed events in the ACT group and 2 observed events in the group that did not receive ACT. Patients with T1b (n=2,340) and T1c tumors (n=2,355) had improved 5-year OS rates with treatment (97.1% [95.1%–98.4%] vs 92.3% [88.5%–94.9%]; *P*=.0016 and 95.9% [93.5%–97.5%] vs 91.5% [88.4%–93.9%]; *P*=.0002, respectively) (Figure 2C, D, respectively).

Among the entire cohort, OS was poorer in patients with ER/PR-negative tumors compared with ER/PR-positive tumors (hazard ratio [HR], 1.51 [95% CI, 1.23–1.85]; *P*<.0001), regardless of tumor grade and/or chemotherapy treatment (poorly/undifferentiated vs moderately/well-differentiated: HR, 1.12 [0.92–1.40]; *P*=.25).

Discussion

To our knowledge, this is the largest registry-based study in the trastuzumab era examining the use and impact of ACT on OS in patients with node-negative, HER2-positive breast cancer measuring <2 cm. Our data support the use of ACT, showing an association with improved OS for patients with T1b and T1c node-negative, HER2-positive breast cancer. An association with decreased OS was observed for ACT in patients with T1mi, and no benefit was observed in patients with T1a node-negative, HER2-positive breast cancer. We observed an increasing use of chemotherapy during the study period.

Node-negative, HER2-positive breast cancer <2 cm is a challenging tumor type in which to conduct

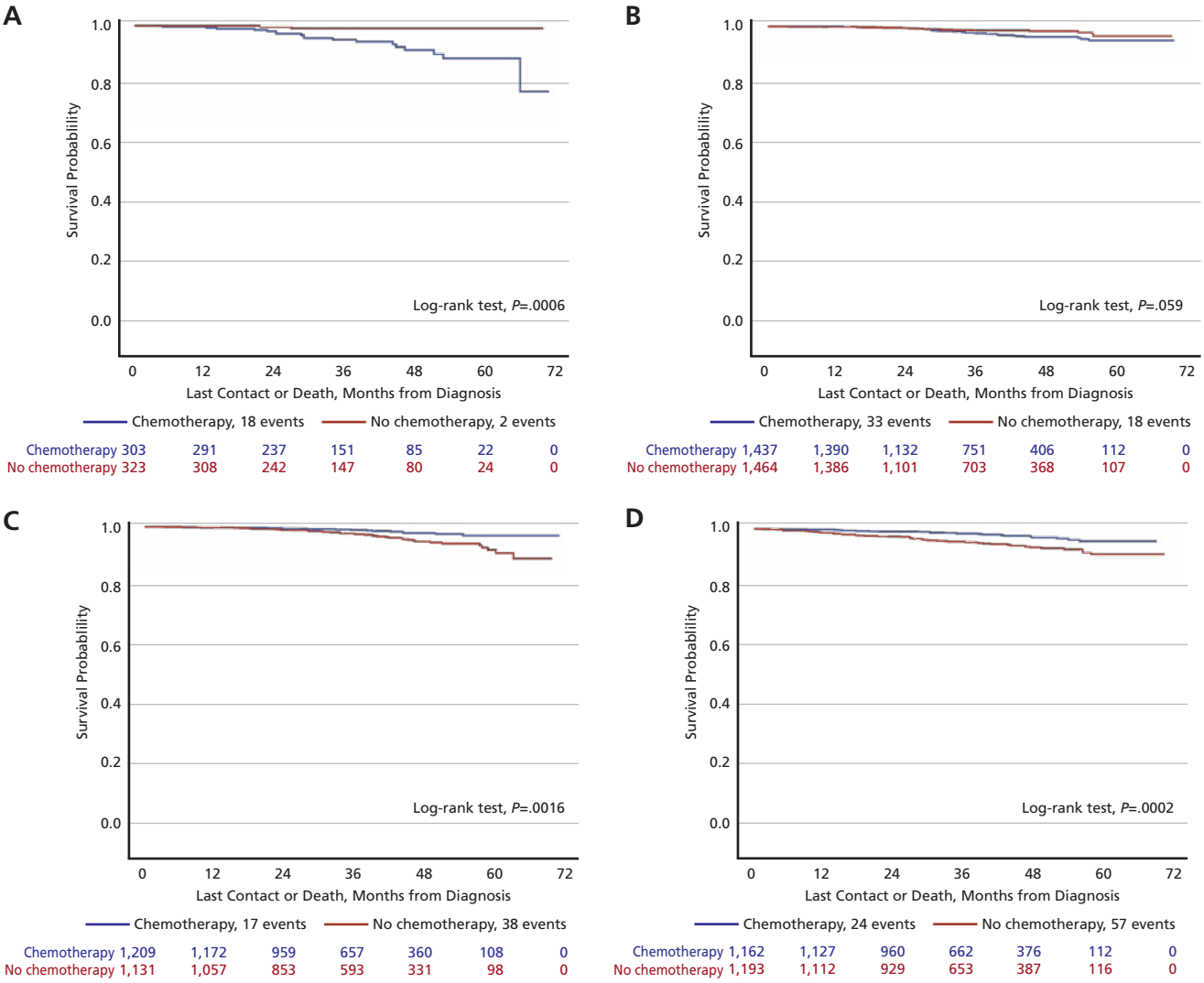

Figure 2. Stage-specific overall survival after treatment with versus without adjuvant chemotherapy for (A) T1mi, (B) T1a, (C) T1b, and (D) T1c tumors.

randomized clinical trials, given its low incidence, low event rate, and, as demonstrated in our report as well as others, small absolute benefit from chemotherapy. However, 5 of 6 large clinical studies in patients with HER2-positive tumors showed a consistent reduction in relapse with trastuzumab-based chemotherapy compared with observation.[5,6,14,17–19] A recent meta-analysis examined potential benefits for patients with tumors <2 cm and ≤1 positive lymph node[20]; however, across the 5 trials studied, only 75 patients had T1a–b, node-negative disease, and <600 patients had node-negative disease <2 cm. Per the study authors, the observed results were likely driven by the high proportion of patients with T1c disease and ≤1 positive lymph node. Due to underrepresentation, these large adjuvant studies provide no direct evidence regarding use of trastuzumab in patients with node-negative tumors <2 cm.[20]

Adding to the complex medical decision-making is the poor characterization of risk in patients with node-negative, HER2-positive breast cancer <2 cm. In a smaller Finnish registry (N=500; T1a/b=171, T1c=329), the risk of recurrence was characterized as high, with only 72% DFS at 9 years.[10] However, larger registry and national database reports have shown significantly lower rates of recurrence and favorable OS. In the MD Anderson series, 5-year DFS with pT1a and pT1b tumors was 92% for both groups, without ACT and trastuzumab.[4] In a pre-trastuzumab era report, a SEER regis-

try–based analysis of 51,246 patients with T1a or T1b, node-negative, HER2-positive breast cancer had a breast cancer–specific mortality of 4%.[21] Our NCDB assessment supports relatively high 5-year OS rates among patients with T1mi and T1a disease who did not receive ACT in both our overall and propensity-matched cohorts (T1mi: 98.1% [95% CI, 96.6%–98.9%] and 99.1% [96.6%–99.8%], respectively; T1a: 96.5% [94.6%–97.7%] and 96.9% [94.1%–98.3%], respectively). However, patients with T1b and T1c disease had a poorer outcome without ACT in both our overall and propensity-matched cohorts (T1b: 92.3% [88.7%–94.8%] and 92.3% [88.5%–94.9%], respectively; T1c: 91.6% [88.5%–93.9%] and 91.5% [88.4%–93.9%]). We could not assess DFS in the NCDB.

Risk stratification of T1a and T1b tumors based on clinicopathologic features, including hormone receptor status, tumor grade, and Ki-67 index, has been attempted in previous studies. ER status in node-negative, HER2-positive tumors <2 cm has not been associated with outcome in several prior trials.[4,10,22] To our knowledge, the only prior trial to show an effect based on hormone receptor status was the EIO series,[2] reporting a nonintuitive reduced DFS in patients with node-negative, ER-positive, HER2-positive tumors <2 cm (HR, 5.2 vs 2.4 for the whole HER2-positive population). Our analysis supports hormone receptor status as a predictive risk factor in node-negative breast cancer <2 cm, because patients with ER/PR-negative tumors had poorer survival overall than those with ER- or PR-positivity (HR, 1.51 [95% CI, 1.23–1.85]; *P*<.0001), regardless of tumor grade (poorly/undifferentiated vs moderately/well-differentiated: HR, 1.12 [0.92–1.40]; *P*=.25). In our entire cohort, receipt of endocrine therapy was also associated with improved OS. Ki-67 index and tumor grade have also been evaluated as clinicopathologic risk factors in HER2-positive breast cancer.[10,23] Although we could not report on Ki-67 because it is not a reported variable in the NCDB, tumor grade was assessed and found not to be associated with OS in our patient population.

Our 5-year OS data in patients who received ACT in both the overall and propensity-matched cohorts (T1b: 96.8% [95% CI, 95.6%–97.7%] and 97.1% [95.1%–98.4%]; T1c: 95.8% [94.9%–96.5%] and 95.9% [93.5%–97.5%]) are very similar to those from a phase II, prospective, nonrandomized study of weekly adjuvant paclitaxel in combination with trastuzumab for 12 weeks, followed by maintenance trastuzumab for 1 year in patients with node-negative, HER2-positive breast cancer ≤3 cm.[11] In that study, 201 of the 406 participants had pT1a/bN0 breast cancer, and the 3-year DFS rate was 98.7%, a proportion significantly higher than the historical data from the MD Anderson series,[4] among others. An update of this data set was reported with a median follow-up of 6.5 years, showing that the 7-year DFS was 93.3% (95% CI, 90.4%–96.2%) and 7-year OS was 95.0% (95% CI, 92.4%–97.7%).[24] More aggressive chemotherapy regimens may be unwarranted in node-negative, HER2-positive breast cancer <2 cm.

We did observe an association between decreased survival and receipt of ACT in patients with T1mi breast cancer in the propensity-matched cohort and in those with T1mi and T1a disease in the unmatched cohort. However, due to uncontrolled variables in the unmatched cohort, small sample size in the matched cohort (N=379 with mature 5-year OS data), and low number of events overall, we were not able to draw significant conclusions.

We showed an increasing use of ACT across all years in our overall cohort and in patients with T1b and T1c tumors. This finding is consistent with prior reports of increasing ACT use.[15] We observed relatively high use of ACT in patients with T1mi and T1a breast cancer (26.1% and 46.3%, respectively), and suggest selective use of chemotherapy in this subset given the lack of observed benefit in our report, potential risk of harm observed, and risk of toxicity.

Strengths of this study include the sample size afforded by the NCDB, allowing us to capture most patients in the United States with node-negative, HER2-positive, chemotherapy-eligible breast cancer <2 cm. We were able to construct a propensity-matched cohort and adjust for the known confounding patient, tumor, and facility factors that affect receipt of chemotherapy and OS.

Our study has limitations, including its retrospective design and relatively short follow-up. In addition, unobserved confounding factors can limit interpretation of study outcomes derived from observational data. Some misclassification and treatment underreporting are unavoidable in a large registry-based data set like the NCDB. The NCDB does not

provide drug-specific information regarding the chemotherapy administered, DFS, disease-specific survival, and local recurrence. There is a known underascertainment of immunotherapy in the NCDB as reported compared with linked databases such as the SEER-Medicare database.[25] Additionally, the change in coding of biologic agents in 2013 of trastuzumab and pertuzumab impacted our data set, limiting our ability to definitively identify patients receiving chemotherapy that included HER2-directed therapy. Due to these limitations, we could not assess the chemotherapy regimen recommended, the inclusion of HER2-directed therapy, breast cancer recurrences, or progression-free survival. Our OS data are limited to 5 years given the short duration of HER2 data in the NCDB, with reporting starting in 2010.

Conclusions

ACT was found to be associated with improved OS in T1b and T1c breast cancer and no benefit in T1mi and T1a tumors in a nationally representative cohort of chemotherapy-eligible women with node-negative, HER2-positive, breast cancer <2 cm in the trastuzumab era. During the study period, an increasing use of chemotherapy was observed. We support chemotherapy use in T1b and T1c node-negative, HER2-positive breast cancer <2 cm, but urge more judicious use in patients with T1mi and T1a disease. We caution that treatment recommendations need to be individualized in this patient population. Future investigations are warranted using this data set, with 10- and 15-year follow-up data when mature, as future randomized clinical trials are unlikely.

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