Initiation of Trastuzumab by Women Younger Than 64 Years for Adjuvant Treatment of Stage I–III Breast Cancer

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Abstract

Purpose: Studies have reported disparities by age and race in the initiation of adjuvant trastuzumab for the initial treatment of older women with early-stage breast cancer, but less is known about its initiation in younger patients. Therefore, we assessed temporal trends and clinical and demographic factors associated with trastuzumab initiation in a large, population-based cohort of patients aged <64 years in 5 states. **Methods:** Using a cancer registry and claims-linked data set of 13,398 women with incident invasive breast cancer from 2006 to 2011, we identified 934 patients aged <64 years with HER2-positive stage I–III breast cancer. We assessed trastuzumab initiation within the first 9 months after diagnosis and conducted logistic regression analyses to assess sociodemographic and clinical factors associated with trastuzumab initiation. **Results:** From 2006 to 2011, trastuzumab initiation steadily increased in patients with node-positive (from 65% to 91%) and node-negative (from 39% to 75%) breast cancers. Several tumor-related factors were associated with trastuzumab initiation, including high histologic grades (adjusted odds ratio [aOR], 6.43; 95% CI, 3.27–12.65; and aOR, 3.25; 95% CI, 1.66–6.36, for grades 3 and 2, respectively), node-positive status (aOR, 1.88; 95% CI, 1.28–2.78; $P=.001$), tumor size >2 cm (aOR, 1.50; 95% CI, 1.04–2.16; $P=.03$), and hormone receptor–negative status (aOR, 1.51; 95% CI, 1.01–2.26; $P=.04$). We found a null effect of race. **Conclusions:** Adjuvant trastuzumab therapy for early-stage breast cancer has been widely disseminated among women aged <64 years. The initiation of this targeted therapy was associated with higher-risk features, consistent with practice guidelines.

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Background

The administration of trastuzumab, a humanized monoclonal antibody targeting HER2 on the surface of cancer cells, significantly improves survival among patients with HER2-positive breast cancer. Based on results from a joint analysis of 2 large randomized trials showing a 52% and 33% reduction in recurrence and mortality, respectively, trastuzumab was FDA-approved in

November 2006 as adjuvant treatment for patients with early-stage, HER2-positive, node-positive breast cancer in combination with cytotoxic chemotherapies.¹ In January 2008, trastuzumab was approved for use as single-agent therapy after standard adjuvant chemotherapy for early-stage, HER2-positive breast cancer, independent of nodal status, based on data from the Herceptin Adjuvant (HERA) trial demonstrating a 46% reduction in

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recurrence.² Since 2006, NCCN has recommended trastuzumab for patients with HER2-positive and node-positive breast cancer, or for those with a tumor >1 cm and node-negative disease.³ In 2010, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) expanded the recommendation for considering trastuzumab to women with node-negative breast cancer whose tumors measured 0.6 to 1 cm with grade 2 or 3 disease.⁴ These expanded recommendations demonstrate the increased role trastuzumab plays in the care of women with stage I–III HER2-positive breast cancer.

Although professional guidelines have recommended trastuzumab for stage I–III breast cancer since 2005, data on its use in clinical practice are very limited. This is especially true for women aged <65 years due to lack of sufficiently comprehensive, linked data sources that include this population. Of the 231,840 women diagnosed with invasive breast cancer each year, >133,000 are aged <65 years.^{5,6} Compared with older patients, these younger patients have a higher percentage of HER2-positive cancers (20% vs 13% for age <65 years and >65 years, respectively)⁷ and often have more aggressive tumors that require adjuvant chemotherapy.^{8,9} Thus, it is particularly important to assess the dissemination of trastuzumab treatment in this young population. We evaluated temporal trends and clinical and sociodemographic factors associated with trastuzumab initiation among women with breast cancer aged <64 years.

Methods

Data Sources

We linked data between cancer registries from 5 states (California, Georgia, Kentucky, New York, and Ohio) and administrative claims consisting of medical and pharmacy records for members enrolled in Anthem-affiliated plans maintained by HealthCore (Wilmington, DE), an independently operated, wholly owned subsidiary of Anthem. Anthem is an independent licensee of Blue Cross Blue Shield Association and serves members in 14 states. We obtained HER2 status from the cancer registry data. Each cancer registry started collecting HER2 statuses in 2005 for California, 2008 for Kentucky, and 2009 for New York, Ohio, and Georgia. More details of the data linkage can be found in previous publications.¹⁰

Study Population

We first identified incident invasive breast cancer diagnosed from January 1, 2006, through December 31, 2011 (N=13,398) and followed through April 30, 2012 (Figure 1). We then excluded patients diagnosed with stage IV breast cancer or missing stage information (n= 843), and those with negative (n=5,072), borderline (n=142), or unknown (n=6,258) HER2 status, which was mostly due to lack of registry reporting of HER2 status in earlier years. We also excluded women who did not have any medical coverage during the first 9 months after diagnosis (n=111). We excluded 38 more women who were aged 64 years at the time of diagnosis because HealthCore claims data do not include complete information on drug use when women become eligible for Medicare at age 65 years. The final study population included 934 women aged <64 years when diagnosed with AJCC-defined stage I–III HER2-positive breast cancer.¹¹ A total of 778 (83.3%) of the women had continuous coverage during the first 9 months after diagnosis; most of the 156 women without continuous coverage had ≥6 months of coverage after their breast cancer diagnosis.

Measures

The outcome of the study was receipt of trastuzumab as adjuvant therapy for stage I–III HER2-positive breast cancer, defined as initiation of trastuzumab within the first 9 months after diagnosis. We chose this 9-month cutoff to balance the time patients may need to complete surgery and/or adjuvant chemotherapy before initiating trastuzumab, and to avoid

Figure 1. Flow diagram of study patient selection.

including patients who may have experienced disease progression and are receiving trastuzumab for metastatic disease. From registry data, we obtained patients' sociodemographic factors (age at diagnosis, race/ethnicity, marital status, and state of residence) and cancer-related characteristics, including nodal status; AJCC stage; estrogen receptor (ER), progesterone receptor (PR), and HER2 status; tumor size; histologic grade; and history of cancer before breast cancer diagnosis. Information on TNM staging was obtained from registry data using the AJCC Breast Cancer Staging (version 6 or 7, depending on year of diagnosis).¹¹ Based on NCCN Guidelines and tumor size information available in our dataset, we defined women as high risk (for recurrence) if they had either positive lymph nodes or a tumor >2 cm (T2–T4).^{3,4} Because of lack of specific tumor size information in our data, we were unable to determine which patients had node-negative disease and tumors 1 to 2 cm and would also have been eligible for trastuzumab. From the claims data maintained by HealthCore, we obtained patients' median household income and percentage of college education completion derived from census tract data based on their residential address. Using longitudinal medical records available in the claims data, we assessed the presence of 30 comorbidities included in the Elixhauser comorbidity index score¹² the year before breast cancer diagnosis. We grouped those 30 comorbidities into cardiovascular (congestive heart failure, hypertension, peripheral vascular disorders, and diabetes) or other comorbidities.

Statistical Analysis

We first described the characteristics of patients with HER2-positive breast cancer and their use of trastuzumab in the total population. We then conducted a logistic regression with trastuzumab use as the dependent variable to identify patient demographic and clinical characteristics associated with trastuzumab use in the total population. Variable selection was based on expert opinions and consideration of the model fitting process. For example, we adjusted for regional (state-level) differences in practice patterns and first year of HER2 status reporting. We combined prior cardiovascular history with other comorbidities due to small sample size in separate categories and very similar estimates with trastuzumab use. Third, we calculated predicted probability of new trastuzumab users

within the first 9 months of their breast cancer diagnosis by calendar year to examine the temporal trend of trastuzumab initiation by nodal status and clinical indication. We also conducted a sensitivity analysis among women who had continuous coverage in the first 9 months after breast cancer diagnosis.

Results

Population Characteristics and Their Trastuzumab Use

This study included a total of 934 patients with stage I–III HER2-positive breast cancer diagnosed from 2006 to 2011. Overall, 680 (73%) of the participants initiated trastuzumab within 9 months of diagnosis. Among trastuzumab users, the median time to trastuzumab initiation was 70 days from diagnosis. Among 680 trastuzumab users, 448 had continuous medical coverage for at least 1 year and 84% of these completed a 1-year course of trastuzumab as recommended.

Table 1 describes the demographic and clinical characteristics of our study cohort. Most patients were aged 40 to 59 years (72%) and were non-Hispanic white (76%). Most women had tumors that were ≤ 2 cm (53%), node-negative (61%), either ER- and/or PR-positive (68%), and of poorly or undifferentiated histologic grade (56%).

Temporal Trends of Trastuzumab Use

There was a steadily increasing trend in trastuzumab initiation among patients with stage I–III HER2-positive breast cancer diagnosed between 2006 and 2011. Increased trastuzumab initiation was evident in patients with node-positive breast cancer (from 65% to 91%) and those with node-negative breast cancer (from 39% to 75%; Figure 2). Although trastuzumab initiation increased over time among women with a greater risk of recurrence, there was also an increased initiation in patients with node-negative tumors ≤ 2 cm (from 39% to 74%; Figure 3). We further examined histologic grade among women with node-negative tumors ≤ 2 cm and found that 95% of those using trastuzumab had tumors that were grade 2 or 3 (data not shown). The temporal effect of increased trastuzumab initiation remained after we adjusted for other patient characteristics (adjusted odds ratio [aOR], 2.04; 95% CI, 1.32–3.16 for a 2008–2009 diagnosis, and 4.03; 95% CI,

Table 1. Population Characteristics		
Population Characteristics	Total N (%)	Trastuzumab Use N (%)
Total	934 (100)	680 (73)
<i>Sociodemographic characteristics</i>		
Year of diagnosis		
2006–2007	246 (26)	141 (57)
2008–2009	261 (28)	196 (75)
2010–2011	427 (46)	343 (80)
Age at diagnosis, y		
24–39	106 (11)	82 (77)
40–49	300 (32)	225 (75)
50–59	370 (40)	266 (72)
60–63	158 (17)	107 (68)
Race/Ethnicity		
Non-Hispanic white	713 (76)	515 (72)
Non-Hispanic black	47 (5)	34 (72)
Hispanic	61 (7)	45 (74)
Asian and Pacific Islanders	100 (11)	75 (75)
All others	13 (1)	11 (85)
Marital status		
Married	665 (71)	482 (73)
Not married	258 (28)	190 (74)
Missing	11 (1)	8 (73)
State of residence		
California	623 (67)	437 (70)
Georgia	75 (8)	60 (80)
Kentucky	66 (7)	49 (74)
New York	82 (9)	63 (77)
Ohio	88 (9)	71 (81)
Area		
Rural	37 (4)	25 (68)
Urban	884 (95)	645 (73)
Missing	13 (1)	10 (77)
Median household income (quintiles) ^a		
Q1	140 (15)	104 (74)
Q2	176 (19)	121 (69)
Q3	185 (20)	139 (75)
Q4	204 (22)	151 (74)
Q5	216 (23)	155 (72)
Missing	13 (1)	10 (77)

^aData on median household income and percent completing college education are derived from census tract data.

(continued)

Table 1. Population Characteristics (cont.)		
Population Characteristics	Total N (%)	Trastuzumab Use N (%)
Completed college ^a		
<20%	169 (18)	127 (75)
20% to <30%	406 (44)	289 (71)
30% to <40%	227 (24)	166 (73)
≥40%	119 (13)	88 (74)
Unknown/Missing	13 (1)	10 (77)
<i>Clinical characteristics</i>		
Tumor size		
0	3 (0)	3 (100)
≤2 cm (T1)	497 (53)	325 (65)
>2 cm (T2–T4)	432 (46)	350 (81)
Missing	2 (0)	2 (100)
Stage at diagnosis		
Stage I	388 (42)	238 (61)
Stage II	378 (41)	300 (79)
Stage III	168 (18)	142 (85)
Lymph node status		
Positive	366 (39)	302 (83)
Negative	568 (61)	378 (67)
Estrogen or progesterone receptor status		
≥1 positive	633 (68)	439 (69)
Both negative	297 (32)	239 (81)
Both missing or 1 negative	4 (0)	2 (50)
Histologic grade		
1: Well differentiated	55 (6)	20 (36)
2: Moderately differentiated	304 (33)	200 (66)
3: Poorly or not differentiated	522 (56)	424 (81)
Missing	53 (6)	36 (68)
History of prior cancer		
No	900 (96)	656 (73)
Yes	34 (4)	24 (71)
Cardiovascular comorbidity		
No	892 (96)	649 (73)
Yes	42 (5)	31 (74)
Other comorbidity		
No	852 (91)	620 (73)
Yes	82 (9)	60 (73)

^aData on median household income and percent completing college education are derived from census tract data.

2.45–6.63 for a 2010–2011 diagnosis, compared with 2006–2007 diagnosis; $P<.001$; Table 2).

Patient Characteristics Associated With Trastuzumab Use

Aside from year of diagnosis, several clinical factors were significantly associated with trastuzumab

receipt, including high histologic grade (aOR, 6.43; 95% CI, 3.27–12.65 for grade 3, and aOR, 3.25; 95% CI, 1.66–6.36 for grade 2, vs grade 1; $P<.001$), node-positive status (aOR, 1.88; 95% CI, 1.28–2.78; $P=.001$), both ER- and PR-negative status (aOR, 1.51; 95% CI, 1.01–2.26; $P=.04$), and tumor size

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Figure 2. Temporal trend of trastuzumab use (percentage and 95% CI) by nodal status for women aged <64 years with HER2-positive, stage I-III breast cancer.

Figure 3. Temporal trends of trastuzumab use (percentage and 95% CI) among patients with HER2-positive, stage I-III breast cancer by (1) node-positive or tumor >2 cm and (2) node-negative and tumor ≤2 cm.

>2 cm (aOR, 1.50; 95% CI, 1.04–2.16; $P=.03$; Table 2). Notably, trastuzumab initiation did not differ by race in this population (72% in white, 72% in black, 74% in Hispanic, 75% in Asian; aOR, 1.03; 95% CI, 0.68–1.56; $P=.88$ for nonwhite vs white population; Tables 1 and 2). In our sensitivity analysis among women with continuous 9 month coverage, we found the same predictors associated with trastuzumab use (see supplemental eTable 1, available with this article at JNCCN.org).

Discussion

Before the era of trastuzumab and other HER2-targeted therapies, HER2-positive breast cancers were associated with poor outcomes.^{13,14} Despite strong evidence showing the benefit of adjuvant trastuzumab initiation for women with HER2-positive breast cancer, no studies exist on its initiation in younger women, a patient subgroup with a higher percentage of HER2-positive cancer. In this study, we assessed trastuzumab initiation in a large and diverse population-based cohort treated in general clinical practice. We found that trastuzumab was well disseminated in young women with breast cancer, particularly among those with node-positive tumors. We also observed a large temporal increase in trastuzumab initiation among patients with node-negative tumors <2 cm, reflecting the evolution of clinical guidelines in expanding the indications for adjuvant trastuzumab over the past decade. We did not find racial differences in trastuzumab initiation in this young population as reported in prior studies of patients aged ≥65 years. The strongest clinical factors associated with trastuzumab

initiation were those that would be predicted based on practice guidelines during our study period and include node-positive status, high histologic grade, hormone receptor-negative disease, or larger tumors. Thus, our study effectively demonstrates the dissemination of adjuvant trastuzumab for HER2-positive stage I-III breast cancer among patients at the highest risk of breast cancer recurrence and mortality.

Two prior studies using the SEER-Medicare linked database demonstrated significant age and racial disparities in trastuzumab initiation among women aged ≥65 years with early-stage HER2-positive breast cancer in 2010 to 2011.^{15,16} One study reported that 50% of 1,162 white and 40% of 104 black women aged ≥65 years with HER2-positive early-stage breast cancer received adjuvant trastuzumab. Additionally, they found that black women were 25% less likely to start trastuzumab than white women even after adjusting for other sociodemographic and cancer-related characteristics. In another study of 770 women aged ≥66 years without a history of congestive heart failure, 56% of eligible women received trastuzumab, but non-Hispanic black women were 3-fold more likely to not receive trastuzumab than non-Hispanic white women (aOR, 3.14; 95% CI, 1.38–7.17). In contrast to these 2 prior studies, our study population, all diagnosed at ≤64 years of age, was more likely to have aggressive disease features. Freedman et al¹⁷ assessed receipt of trastuzumab by race/ethnicity among 1,190 women, 74% of whom were <60 years of age, receiving care from 8 medical centers. They found no significant differences by race/ethnicity in trastuzumab initiation. The lack of racial disparities in trastuzumab initiation in our

Table 2. Predictors of Herceptin Use			
Population Characteristics	Total N (%)	P Value	Overall P Value
<i>Sociodemographic characteristics</i>			
Year of diagnosis			
2006–2007	1.0 (Ref)		
2008–2009	2.04 (1.32–3.16)	.001	<.001
2010–2011	4.03 (2.45–6.63)	<.001	
Age at diagnosis, y			
24–39	1.41 (0.72–2.78)	.32	.61
40–49	1.33 (0.80–2.19)	.27	
50–59	1.10 (0.69–1.76)	.70	
60–63	1.0 (Ref)		
Race/Ethnicity			
White	1.0 (Ref)		
Nonwhite	1.03 (0.68–1.56)	.88	.88
Marital status			
Married	1.0 (Ref)		
Not married	1.05 (0.72–1.54)	.80	.80
State of residence			
California	1.0 (Ref)		
Georgia	0.94 (0.44–2.02)	.87	.63
Kentucky	0.71 (0.35–1.45)	.35	
New York	0.62 (0.31–1.21)	.16	
Ohio	0.92 (0.45–1.79)	.83	
Completed college ^a			
<20%	1.0 (Ref)		
20% to <30%	0.82 (0.50–1.35)	.44	.85
30% to <40%	0.84 (0.48–1.45)	.53	
≥40%	0.95 (0.51–1.79)	.89	
<i>Clinical characteristics</i>			
Tumor size			
≤2 cm (T1)	1.0 (Ref)		
>2 cm (T2–T4)	1.50 (1.04–2.16)	.03	.03
Lymph node status			
Positive	1.0 (Ref)		
Negative	1.88 (1.28–2.78)	.001	.001
Estrogen or progesterone receptor status			
≥1 positive	1.0 (Ref)		
Both negative	1.51 (1.01–2.26)	.04	.04
Histologic grade			
1: Well differentiated	1.0 (Ref)		
2: Moderately differentiated	3.25 (1.66–6.36)	<.001	<.001
3: Poorly or not differentiated	6.43 (3.27–12.65)	<.001	
Comorbidity within 1 year before breast cancer diagnosis			
No	1.0 (Ref)		
Yes	1.12 (0.65–1.94)	.69	.69

^aData on median household income and percent completing college education are derived from census tract data.

study may be partially due to some clinical factors in women aged <64 years that lead patients and providers to consider trastuzumab necessary, such as longer life expectancy and increased presence of higher-risk features for cancer recurrence. It is also possible that our small sample size of nonwhite women limited our power to detect any differences.

The temporal trends we observed are likely due to evolving evidence and practice guidelines that called for treating more subsets of women with stage I–III breast cancer, such as women with node-negative disease with tumors >1 cm beginning in 2006, and women with tumor size ≤1 cm but with high histologic grade (2 or 3) in 2010. Among 336 patients in our study with node-negative, grade 2 or 3 tumors that were ≤2 cm in size, trastuzumab initiation steadily increased from 49% in 2006 to 78% in 2011. This increase reflects practitioners’ adherence to clinical recommendations for trastuzumab initiation in this young population.

Dissemination of adjuvant trastuzumab was not perfect or universal. Our cohort consisted of 19% of women with higher-risk features who did not receive adjuvant trastuzumab. This may be partly due to age effects; our data showed that women aged 60 to 63 years accounted for 21% and 12% of the total cohort in the nontrastuzumab and trastuzumab groups, respectively. We investigated the possibility that comorbidity might help explain this result, because some studies have reported an association between trastuzumab initiation and an increased risk of heart failure.¹⁸ However, we did not observe that cardiovascular comorbidity was associated with decreased trastuzumab initiation among the 19% of patients with high-risk features of recurrence. This finding may also be partly due to the low prevalence (5%) of cardiovascular comorbidity in our study population.

This study is important in that it is among the first to report use patterns of trastuzumab initiation among patients <64 years diagnosed with stage I–III breast cancer. The study findings were limited to patients with commercial insurance. Because trastuzumab costs approximately \$70,000 USD for 1 year of treatment,^{19,20} out-of-pocket costs for women without any insurance pose serious financial barriers to its initiation. Subsequent studies comparing initiation of this targeted therapy in women with commercial versus public coverage would be desirable. Additionally, due to lack of exact tumor size data, we were

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unable to distinguish patients recommended for trastuzumab initiation (tumor size >1 cm, or tumors 0.6–1 cm graded as 2 or 3) from all patients with tumor size ≤2 cm. Therefore, we used conservative criteria and only counted patients diagnosed with tumors >2 cm as having high-risk features because these patients clearly met clinical recommendations for trastuzumab initiation. The time trend analyses are limited by the distinct time contribution and small sample size in most registries, except California. Because of the lack of data, this study is unable to assess the effect of different drivers on the initiation of trastuzumab, such as insurance type and patient and physician preferences.

Conclusions

Trastuzumab treatment is well disseminated among patients <64 years of age with stage I–III HER2-positive breast cancer. Our data did not find racial disparities in trastuzumab initiation, as reported in prior studies of women aged ≥65 years. This study found overall excellent adherence to professional recommendations regarding adjuvant trastuzumab initiation in clinical practice for women diagnosed at <64 years of age at high risk of recurrence after initial treatment for stages I–III, HER2-positive breast cancer.

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