ORIGINAL REPORT

Disparities in Use of Human Epidermal Growth Hormone Receptor 2–Targeted Therapy for Early-Stage Breast Cancer

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ABSTRACT

Purpose

Trastuzumab is a key component of adjuvant therapy for stage I to III human epidermal growth factor receptor 2 (HER2)–positive breast cancer. The rates and patterns of trastuzumab use have never been described in a population-based sample. The recent addition of HER2 information to the SEER-Medicare database offers an opportunity to examine patterns of trastuzumab use and to evaluate possible disparities in receipt of trastuzumab.

Methods

We examined a national cohort of Medicare beneficiaries with incident stage I to III HER2-positive breast cancer diagnosed in 2010 and 2011 (n = 1,362). We used insurance claims data to track any use of trastuzumab in the 12 months after diagnosis as well as to identify chemotherapy drugs used in partnership with trastuzumab. We used modified Poisson regression analysis to evaluate the independent effect of race on likelihood of receiving trastuzumab by controlling for clinical need, comorbidity, and community-level socioeconomic status.

Results

Overall, 50% of white women and 40% of black women received some trastuzumab therapy. Among women with stage III disease, 74% of whites and 56% of blacks received trastuzumab. After adjustment for tumor characteristics, poverty, and comorbidity, black women were 25% less likely to receive trastuzumab within 1 year of diagnosis than white women (risk ratio, 0.745; 95% CI, 0.60 to 0.93).

Conclusion

Approximately one half of patients 65 years of age and older with stage I to III breast cancer do not receive trastuzumab-based therapy, which includes many with locally advanced disease. Significant racial disparities exist in the receipt of this highly effective therapy. Further research that identifies barriers to use and increases uptake of trastuzumab could potentially improve recurrence and survival outcomes in this population, particularly among minority women.

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INTRODUCTION

In the past two decades, the monoclonal antibody trastuzumab has dramatically changed the treatment paradigm and prognosis of human epidermal growth factor receptor 2 (HER2)–positive breast cancer.[1-4] Since its approval for adjuvant use in the United States in 2004, trastuzumab has been rapidly adopted as a standard of care for women with stage II to III HER2-positive disease and is offered to many women with stage I breast cancer. Although the benefits of trastuzumab are uncertain among some patients (eg, those with very small cancers and frail elderly patients),[5] most women with HER2-positive breast cancer benefit from trastuzumab-based systemic therapy, which has been shown in long-term follow-up studies to improve overall survival in this patient population by 37%.[4] However, noninitiation and nonadherence studies have shown in the other primary targeted therapy—endocrine therapy in hormone receptor–positive breast cancer—that highly effective drug therapy is not always delivered consistently across patient populations. The actual uptake of trastuzumab in community settings and the extent to which trastuzumab is used or underused in US populations, particularly among vulnerable groups such as minority and elderly women, are unknown.

The study of disparities in trastuzumab use has been complicated by the lack of large

population-based cohorts with known HER2 status. To date, available observational data sources have been limited to single-institution series and pooled data from academic centers and have been focused primarily on the impact of trastuzumab-based therapy on outcomes among women with stage I tumors.[6-10] To our knowledge, no prior study has described predictors of trastuzumab use among eligible women with HER2-positive breast cancer in a large population-based cohort.

Beginning in 2010, HER2 status became a required data element for cancer registries that participate in the SEER network of the National Cancer Institute, and these data have been made available for cases diagnosed in 2010 and 2011. To date, this information has been used only to describe the epidemiology of breast cancer with regard to the triple phenotype (the combination of estrogen receptor [ER], progesterone receptor [PR], and HER2 status) in breast cancer.[11] Linkage of SEER data with fee-for-service Medicare administrative claims offers an opportunity to examine potential racial disparities in trastuzumab use among a national cohort of women with HER2-positive breast cancer. We examined racial variation in trastuzumab use among Medicare beneficiaries with newly diagnosed nonmetastatic HER2-positive breast cancer who are candidates for adjuvant trastuzumab-based therapy.

METHODS

Data Source and Study Population

We used data from the SEER-Medicare–linked data set for the period 2009 to 2013. SEER data represent approximately 28% of the US cancer population. For those ages 65 years and older and insured by fee-for-service Medicare, approximately 97% are successfully linked by the National Cancer Institute. The SEER Medicare data are linked by using an iterative, deterministic approach that has been described previously.[12] Data elements include demographic characteristics, timing and type of cancer diagnosis, staging, and insurance-reimbursed treatment. Our preliminary sample included female patients who received a diagnosis in 2010 and 2011 of a first primary stage I to III HER2-positive invasive breast cancer at age 66 years or older (to allow for assessment of comorbidity in the prior year) and who survived at least 365 days from diagnosis. SEER registries use an algorithm to assign HER2 status that combines available results from immunohistochemistry, fluorescence in situ hybridization, and chromogenic in situ hybridization tests.[13]

Patients were required to have continuous enrollment in fee-for-service Medicare parts A and B from 12 months before to 12 months after diagnosis to ensure full capture of all treatment of comorbid conditions as well as the first course of primary breast cancer treatment. Patients enrolled in health maintenance organization plans were excluded due to incomplete ascertainment of claims. Patients were required to have a primary breast cancer surgery (either breast-conserving surgery or mastectomy) within 6 months of diagnosis from a previous methodology[14] (Data Supplement). Patients with borderline, unknown, or missing information for both ER and PR status were excluded because they could not be classified into a tumor phenotype (n ≤ 11). A CONSORT diagram is shown in Figure 1.

Primary Outcome

The primary outcome was receipt of trastuzumab, which was defined as at least one claim for trastuzumab within the year after diagnosis (Healthcare Common Procedure Classification System code J9355). Trastuzumab exposure could occur at any time between diagnosis and day 365 postdiagnosis, which included both neoadjuvant and adjuvant sequencing. Chemotherapies given concurrently with trastuzumab were examined and categorized by analyzing all claims for chemotherapy agents given to patients within 1 year of diagnosis and categorizing as follows: doxorubicin, cyclophosphamide, taxane (ACTH) regimen; docetaxel, carboplatin (TCH) regimen; some doxorubicin or carboplatin use that did not meet the definition of ACTH or TCH; taxane agents with or without cyclophosphamide; all other chemotherapy partners; and trastuzumab as a single agent. Detailed definitions of chemotherapy regimens can be found in the Data Supplement. For patients who did not receive trastuzumab, use of any chemotherapy within 1 year was also captured.

Primary Exposure and Covariates

Our primary exposure of interest was race as recorded by Medicare enrollment files, which are based on information from the Master Beneficiary Record of the Social Security Administration.[15-17] We obtained key covariates from the SEER Patient Entitlement and Diagnosis Summary File, which included diagnosis date, age, race (white, black, other), tumor characteristics, and ER and PR status. Tumor grade, primary tumor size, and nodal involvement were defined according to American Joint Committee on Cancer Staging VII criteria.[17a]

Additional covariates defined based on claims-based algorithms were type of breast surgery, receipt of radiation,[14] and comorbidity as defined by the Klabunde modification of the Charlson comorbidity index.[18] Contextual socioeconomic variables were taken from American Communities Survey data and included the proportion of people living in poverty in the patients' census tracts.[19] We controlled for geographic variation in trastuzumab use by the four-category grouping of SEER regions (northeast, south, north central, and west).

Statistical Analysis

To identify predictors of trastuzumab use, we used modified multivariable Poisson regression analysis with sandwich standard errors[20] by using the GENMOD procedure of SAS version 9.4 software (SAS Institute, Cary, NC). Covariates for the final model were determined a priori on the basis of clinical judgment and literature that has identified common factors associated with variations in breast cancer treatment. Patient-level covariates of interest were chosen based on literature that breast cancer treatment and outcomes may vary by marital status,[21] comorbidity,[22] socioeconomic status,[23] and geographic region.[24] Year of diagnosis was included based on literature that adoption of treatment innovations increases over time.[25] Disease-related variables were chosen based on clinical judgment about their use in treatment decision making and prognostication, which includes tumor size, nodal status, tumor grade, and hormone receptor status. Local therapy approach was included based on clinical judgment that differences in local treatment preferences might be associated with differences in systemic treatment preferences. We present unadjusted and adjusted risk ratios (RRs) and 95% CIs for all models.

RESULTS

We identified 1,362 women with HER2-positive breast cancer (85% white, 7.6% black, 7% other races). Table 1 shows clinical and demographic characteristics of the cohort. Around one half of patients were younger than 75 years, and 69% had node-negative disease. Seventy-three percent of patients had triple-positive (hormone-receptor and HER2-positive) breast cancer. More than one half of patients (52%) had high-grade tumors, and 42% had tumors ≥ 2 cm, which reflects the relatively aggressive biology of HER2-positive cancer. In bivariable analyses, patients who received trastuzumab were significantly younger, more likely to have hormone receptor–negative disease, and more likely to be treated surgically with mastectomy than patients who did not receive trastuzumab.
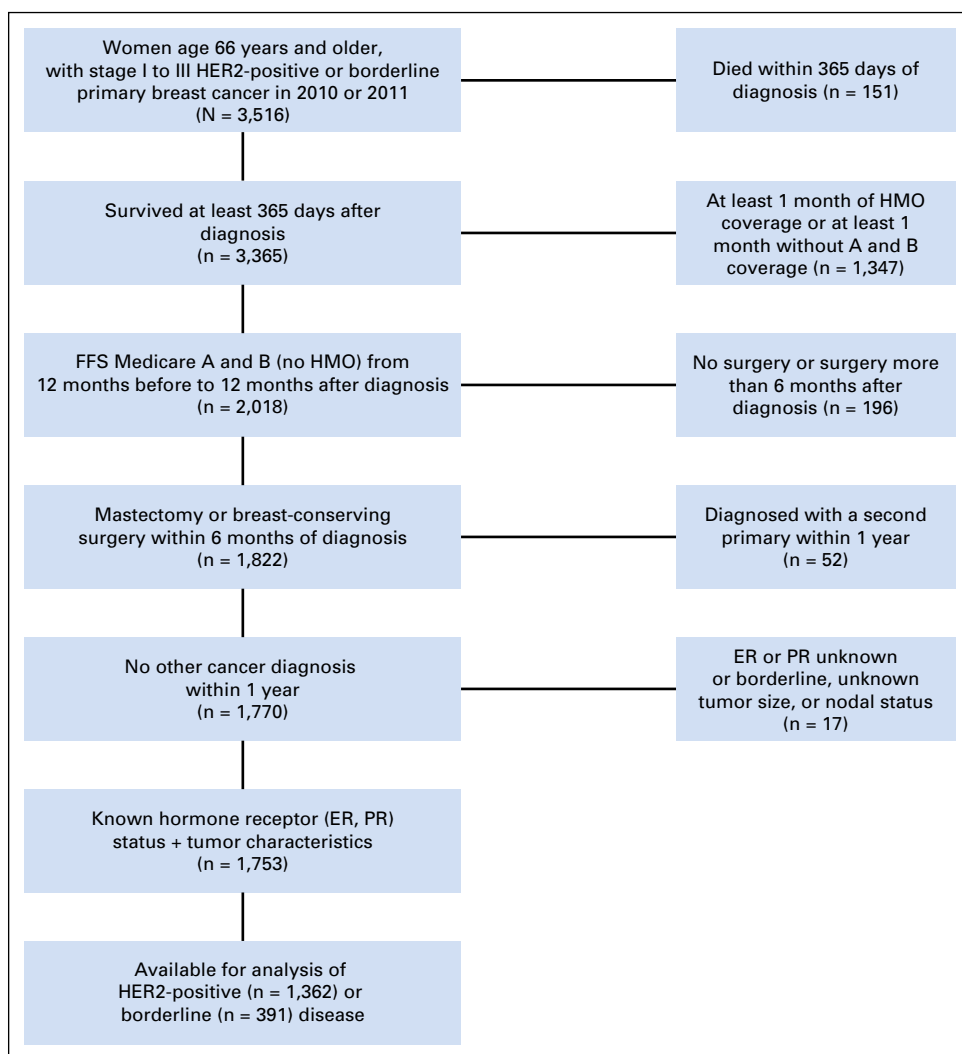
Fig 1. CONSORT diagram for study cohort. ER, estrogen receptor; FFS, fee for service; HER2, human epidermal growth factor receptor 2; HMO, health maintenance organization; PR, progesterone receptor.

We examined unadjusted rates of trastuzumab use by race. Overall, trastuzumab use within 1 year of diagnosis was 50% among whites (n = 1,162), 40% among blacks (n = 104), and 52% among other minorities (n = 96; data not shown). Use among blacks compared with whites lagged at every stage (Fig 2), with 56% of blacks and 74% of whites receiving trastuzumab for stage III disease. Due to cell sizes <11 in black women, exact numbers are not displayed.

Predictors of Trastuzumab Use

After adjustment for the covariates age, comorbidity, and disease characteristics as well as type of locoregional therapy and neighborhood-level poverty, black women were 25% less likely to receive trastuzumab within 1 year of diagnosis than white women (RR, 0.75; 95% CI, 0.60 to 0.93; Table 2). Disease characteristics that predicted a greater likelihood of receiving trastuzumab were large tumor size (all T sizes greater than T1a), node positivity, and moderately or poorly differentiated tumors compared with well-differentiated tumors. Age older than 74 years and the presence of medical comorbidity measured by a Charlson comorbidity score > 1 were associated with a lower likelihood of receiving trastuzumab.

Hormone receptor positivity was not an independent predictor of trastuzumab use after controlling for other tumor characteristics. Women who received breast-conserving surgery and radiation as their locoregional therapy were somewhat less likely to receive trastuzumab (RR, 0.73; 95% CI, 0.63 to 0.86) than those treated with mastectomy.

To address the concern that cardiac as opposed to overall comorbidity may exert a stronger effect on the likelihood of trastuzumab receipt and may attenuate the independent effects of race and age, we performed sensitivity analyses for measures of cardiac comorbidity derived from the Medicare Chronic Conditions Warehouse in combination with and substituted for the modified Charlson comorbidity score. The estimated effect of race and age on likelihood of trastuzumab receipt remained stable regardless of the approach to comorbidity modeling. Full results of this analysis are presented in the Data Supplement.

Patterns of Chemotherapy Use With Trastuzumab

We performed descriptive analyses to determine the most common chemotherapy partners for patients who received trastuzumab. By using their pattern of chemotherapy drug claims, we

2005

	Total (n = 1,362)		Treated (n = 672)		Untreated (n = 690)		
	No.	%	No.	%	No.	%	P
Age-group							< .001
65-69 years	354	26.0	212	31.5	142	20.6	
70-74 years	362	26.6	222	33.0	140	20.3	
75-84 years	501	36.8	216	32.1	285	41.3	
≥ 85 years	145	10.6	22	3.3	123	17.8	
Race							.1511
Black	104	7.6	42	6.3	62	9.0	
Other	96	7.0	50	7.4	46	6.7	
White	1,162	85.3	580	86.3	582	84.3	
State buy-in for 12 months before diagnosis							.0861
No	1,163	85.4	585	87.1	578	83.8	
Yes	199	14.6	87	12.9	112	16.2	
SEER region							.797
North central	172	12.6	81	12.1	91	13.2	
Northeast	274	20.1	141	21.0	133	19.3	
South	350	25.7	169	25.1	181	26.2	
West	566	41.6	281	41.8	285	41.3	
Marital status							< .001
Married	554	40.7	255	37.9	299	43.3	
Other	808	59.3	417	62.1	391	56.7	
Comorbidity score							< .001
0	844	62.0	451	67.1	393	57.0	
1	288	21.1	126	18.8	162	23.5	
≥ 2	230	16.9	95	14.1	135	19.6	
Residents below poverty level							.1397
< 5.0%	289	21.2	160	23.8	129	18.7	
5.0%-9.99%	373	27.4	178	26.5	195	28.3	
10.0%-19.99%	439	32.2	212	31.5	227	32.9	
≥ 20.0%	261	19.2	122	18.2	139	20.1	
Diagnosis year							.0581
2010	684	50.2	320	47.6	364	52.8	
2011	678	49.8	352	52.4	326	47.2	
AJCC tumor size							< .001
T1a	139	10.2	25	3.7	114	16.5	
T1b	203	14.9	71	10.6	132	19.1	
T1c	452	33.2	235	35.0	217	31.4	
T2	452	33.2	271	40.3	181	26.2	
T3	67	4.9	35	5.2	32	4.6	
T4	49	3.6	35	5.2	14	2.0	
AJCC nodes involved							< .001
N0	942	69.2	386	57.4	556	80.6	
N1	282	20.7	185	27.5	97	14.1	
N2/N3	138	10.1	101	15.0	37	5.4	
Tumor grade							< .001
Well differentiated	124	9.1	25	3.7	99	14.3	
Moderately differentiated	484	35.5	192	28.6	292	42.3	
Poorly differentiated	703	51.6	439	65.3	264	38.3	
Unknown	51	3.7	16	2.4	35	5.1	
Hormone receptor status							.0091
Positive	990	72.7	467	69.5	523	75.8	
Negative	372	27.3	205	30.5	167	24.2	
Surgery type							< .001
Mastectomy	574	42.1	305	45.4	269	39.0	
Breast conserving	324	23.8	201	29.9	123	17.8	
Breast conserving and radiation	397	29.1	127	18.9	270	39.1	
Mastectomy and radiation	67	4.9	39	5.8	28	4.1	

Table 1. Cohort Characteristics

Abbreviation: AJCC, American Joint Committee on Cancer.

categorized patients as having received one of the following: ACTH OR TCH, some exposure to anthracycline or carboplatin-based agents without meeting the predetermined criteria for ACTH or TCH, taxane agents only, single-agent trastuzumab, and other chemotherapy agents. Complete descriptions of the chemotherapy algorithms are provided in the Data Supplement. Among trastuzumab users (n = 672), the most common chemotherapy regimen was TCH (42% of treated patients [n = 285]) followed by taxane-only
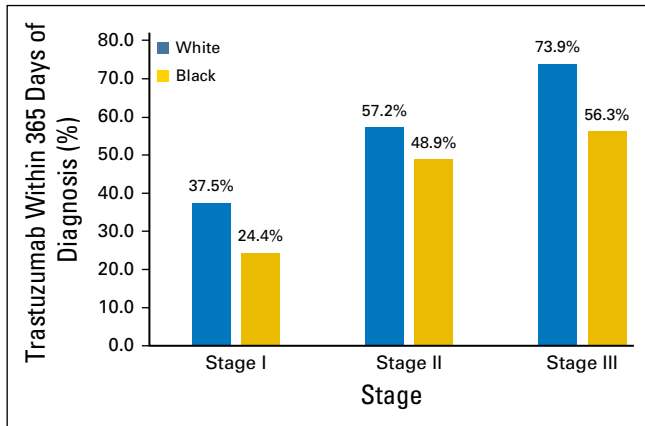
Fig 2. Receipt of trastuzumab among women with human epidermal growth factor receptor 2–positive breast cancer by stage and race.

regimens (21% [n = 141]) and ACTH (9% [n = 58]). A small number of women had one or more claims for an anthracycline (3% [n = 20]) or carboplatin (8% [n = 55]) but did not clearly receive ACTH or TCH. In this sample, 94 women received trastuzumab as a single agent, and 19 received it in combination with another nonstandard chemotherapeutic agent. The distribution of chemotherapy regimens is illustrated in Figure 3. Due to small sample sizes for most regimens in minority women, racial differences in chemotherapy type were not systematically examined.

DISCUSSION

This study found that approximately one half of women with HER2-positive breast cancer insured by Medicare did not receive adjuvant HER2-targeted therapy and that black women were 25% less likely than clinically similar white women to receive such therapy. These findings have several troubling implications. First, although this study did not examine survival outcomes, the low overall rates of use and low rates among patients with stage II and III disease raise concerns for widespread underuse of trastuzumab in this age-group. Second, the racial findings suggest that the presence of a clear biologic predictor of treatment benefit, in this case the HER2 marker, does not mitigate the overall pattern of treatment disparity observed among black women with breast cancer.[26] Finally, this pattern is observed during a recent time period (2010 to 2011) and suggests that gaps in breast cancer treatment continue to be problematic despite widespread awareness of the problem and efforts to improve access to care among minority women.[27-30]

We found that older patients and those with a higher comorbidity burden were less likely to receive trastuzumab-based therapy following a long-standing pattern observed in studies of systemic breast cancer treatment. In some cases, such variation may be appropriate because small gains in recurrence-free survival from targeted therapy may be attenuated or lost in patients with significant competing mortality risks. However, given the sizeable benefit of trastuzumab, the overall aggressive biology of this subtype, and extensive literature documenting undertreatment of even healthy older patients,[31] the hypothesis that age is used

Table 2. Results of Multivariable Model

Parameter and Level	Risk Ratio	95% CI	P
Age-group			
65-69 years	1.00	Reference	
70-74 years	0.98	0.88 to 1.09	.7349
75-84 years	0.74	0.65 to 0.84	< .001*
≥ 85 years	0.25	0.17 to 0.37	< .001*
Race			
Black	0.75	0.60 to 0.93	.0097*
Other	1.01	0.86 to 1.20	.8855
White	1.00	Reference	
Marital status			
Married	1.00	Reference	
Not married	0.93	0.84 to 1.03	.1537
SEER region			
North central	0.90	0.77 to 1.06	.2038
Northeast	1.04	0.91 to 1.17	.5917
South	0.98	0.87 to 1.11	.7772
West	1.00	Reference	
Below poverty			
< 5.0%	1.00	Reference	
5.0%-9.99%	0.85	0.75 to 0.97	.0155†
10.0%-19.99%	0.87	0.77 to 0.99	.0377†
≥ 20.0%	0.88	0.76 to 1.02	.0965
Comorbidity score			
0	1.00	Reference	
1	0.90	0.80 to 1.02	.1063
≥ 2	0.84	0.73 to 0.97	.0187†
Diagnosis year			
2010	1.00	Reference	
2011	1.12	1.02 to 1.23	.0176†
Hormone receptor status			
Positive	1.00	Reference	
Negative	1.04	0.94 to 1.15	.4832
AJCC tumor size			
T1a	1.00	Reference	
T1b	1.72	1.18 to 2.51	.0047*
T1c	2.19	1.54 to 3.12	< .001*
T2	2.30	1.62 to 3.28	< .001*
T3	2.04	1.36 to 3.05	< .001*
T4	2.58	1.75 to 3.81	< .001*
AJCC nodes involved			
N0	1.00	Reference	
N1	1.27	1.14 to 1.41	< .001*
N2/N3	1.36	1.19 to 1.55	< .001*
Tumor grade			
Well differentiated	1.00	Reference	
Moderately differentiated	1.68	1.19 to 2.38	.0034*
Poorly differentiated	2.30	1.63 to 3.23	< .001*
Unknown	1.48	0.90 to 2.44	.1199
Surgery type			
Mastectomy	1.00	Reference	
Breast conserving only	1.15	1.04 to 1.28	.0075*
Breast conserving and radiation	0.73	0.63 to 0.86	< .001*
Mastectomy and radiation	1.02	0.83 to 1.25	.8797

Abbreviation: American Joint Committee on Cancer.
*Significant at P < .01.
†Significant at P < .05.

inappropriately to withhold trastuzumab-based therapy deserves further exploration. The availability of large patient cohorts that represent the entire age spectrum of patients with HER2-positive disease will be key to such research.

Several aspects of trastuzumab therapy may contribute to its underuse among minority women. First, standard use of this biologic agent requires combination with chemotherapy, and
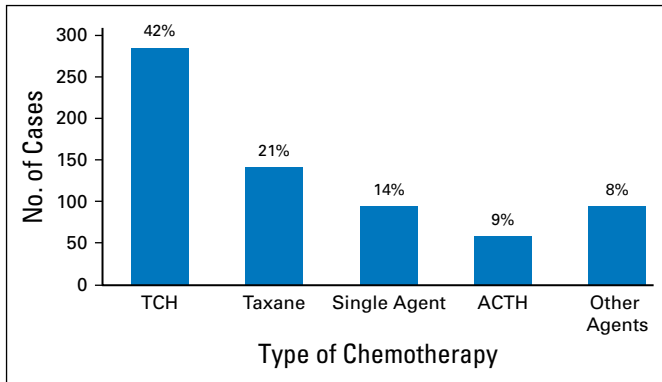
Fig 3. Chemotherapies received with trastuzumab (n = 672). ACTH, doxorubicin, cyclophosphamide, taxane; TCH, docetaxel, carboplatin.

evidence for the effectiveness of less-intensive single-agent taxane regimens for use in patients with HER2-positive breast cancer has only recently been presented[32] and was not available during this study period. The pairing of trastuzumab with intensive chemotherapy and the long duration of treatment may be a barrier to the treatment of patients with unreliable sources of transportation, job insecurity, or poor social support, and providers may perceive such women as less able to tolerate prolonged intensive treatment. Although we controlled for poverty at the neighborhood level, a complete accounting for such complex social factors is not possible in a claims-based analysis. Second, trastuzumab is a costly infused therapy. Although the patients in the present sample were uniformly insured by Medicare, the generosity of supplemental plans for outpatient expenses and the affordability of shared costs likely vary by race and could influence uptake. Third, the decision to use trastuzumab-based adjuvant therapy in patients with stage I breast cancer is made in the context of limited evidence,[5] with many patients falling into a gray zone of risk and benefit. Patients' ways of considering and weighing this imperfect evidence may vary by race, and minority patients may also be treated by providers who are less comfortable with applying the current evidence to recommend treatment with uncertain or marginal benefit. Fourth, trastuzumab therapy is a lengthy course of treatment that involves 1 year of infused therapy. Previous studies have suggested that black women are more likely to discontinue adjuvant trastuzumab therapy early,[10] and this protracted treatment course may similarly be a disincentive to initiation of treatment of minority patients with limited resources for obtaining and adhering to treatment. Finally, trastuzumab is a relatively new adjuvant therapy for breast cancer, and we and others have previously demonstrated that the adoption of cancer treatment innovations lags among minority patients.[25,33,34]

Not surprisingly, we found that clinically appropriate information, such as tumor size and nodal status, influenced the receipt of trastuzumab. We also found an indication of increasing use at a tumor size as small as 6 mm (T1b disease), which suggests that providers may define this as the appropriate cut point for considering HER2-directed therapy. Furthermore, hormone receptor status was not an independent predictor of trastuzumab use in adjusted analysis despite known differences in recurrence risk between patients with hormone receptor–positive/HER2-positive and hormone receptor–negative/HER2-positive disease and the availability of additional targeted therapy, specifically endocrine therapy in the

former. However, given that hormone receptor status was associated with trastuzumab use in bivariable analysis, the inclusion of multiple other disease characteristics, such as grade and tumor size, in the model likely attenuated the independent effect of hormonal status because hormone receptor–positive tumors would also be expected to present at a lower grade and smaller size.

In descriptive analysis, we found that trastuzumab often was paired with chemotherapeutic agents other than ACTH and TCH, including a significant proportion of single-agent taxane regimens. Although weekly paclitaxel with trastuzumab is increasingly recognized as a regimen with good short-term outcomes in low-risk HER2-positive disease on the basis of data published in 2014,[32] the current findings suggest that a significant number of providers adopted such regimens in advance of the clinical evidence possibly as an attempt to compromise between clinical need and toxicity concerns. More of concern, we found that 14% of trastuzumab recipients received no chemotherapeutic agent of any type, an approach that has no evidence of efficacy in this setting. Although sample size did not permit exploration of chemotherapy partners by race or other patient-level factors, concerns that there may be disparities in treatment intensity as well as trastuzumab receipt deserve further exploration.

This study has several important limitations. First, we focused the analysis on women with HER2-positive cancer and excluded 391 with SEER-defined HER2 borderline phenotype. We hypothesized that in the early period of adoption of this mandatory data element, the borderline group would include both patients with truly borderline clinical results and patients for whom the registry has incomplete information with regard to HER2 status (eg, an immunohistochemical result of 2+ without a subsequent confirmatory test result). To explore this, we examined rates of trastuzumab use among the HER2-positive and HER2 borderline groups and found that overall use was 49% among HER2-positive group but only 6% among the borderline group, which reinforces concerns that the borderline group might include many patients who were not ultimately determined by their treating provider to have HER2-positive disease. Second, although we measured comorbidity by using a validated claims-based instrument for patients with cancer, this measure may not reflect less critical but relevant comorbidities, such as cardiac risk factors, that might affect chemotherapy decisions and vary by race. However, all patients were required to have primary breast surgery, which indicated at least some level of fitness for cancer therapy. As with other analyses that used SEER-Medicare data, the current findings may not represent treatment patterns among younger women or those in Medicare-managed care plans. Finally, in a claims-based analysis, we were not able to ascertain whether HER2-directed therapy was offered to a patient and in what context it was discussed. Further investigations that examine prescribing behavior at the provider level may help to clarify provider-level factors that influence disparities.

In conclusion, trastuzumab is an innovative and nontoxic biologic therapy with a clear biomarker for prediction of response and ample evidence of significant improvements in survival of patients with HER2-positive breast cancer. Its underuse among older, particularly black, women is a concerning finding that merits further study. System-level interventions that highlight patients eligible for HER2-directed therapy objectively and consistently as well as interventions that focus on removing barriers to therapy at

the patient level are needed to ensure that this effective treatment reaches all women who will benefit.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Final approval of manuscript: All authors

REFERENCES

1. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353: 1659-1672, 2005

2. Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353: 1673-1684, 2005

3. Slamon D, Eiermann W, Robert N, et al: Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365:1273-1283, 2011

4. Perez EA, Romond EH, Suman VJ, et al: Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: Planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol 32: 3744-3752, 2014

5. Reeder-Hayes KE, Carey LA: How low should we go? The search for balance in management of small human epidermal growth factor receptor 2-positive breast cancers. J Clin Oncol 32:2122-2124, 2014

6. Curigliano G, Viale G, Bagnardi V, et al: Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. J Clin Oncol 27:5693-5699, 2009

7. Gonzalez-Angulo AM, Litton JK, Broglio KR, et al: High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol 27:5700-5706, 2009

8. Fehrenbacher L, Capra AM, Quesenberry CP Jr, et al: Distant invasive breast cancer recurrence risk in human epidermal growth factor receptor 2-positive T1a and T1b node-negative localized breast cancer diagnosed from 2000 to 2006: A cohort from an integrated health care delivery system. J Clin Oncol 32:2151-2158, 2014

9. Vaz-Luis I, Ottesen RA, Hughes ME, et al: Outcomes by tumor subtype and treatment pattern in women with small, node-negative breast cancer: A multi-institutional study. J Clin Oncol 32:2142-2150, 2014

10. Freedman RA, Hughes ME, Ottesen RA, et al: Use of adjuvant trastuzumab in women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer by race/ethnicity and education within the National Comprehensive Cancer Network. Cancer 119:839-846, 2013

11. Howlader N, Altekruse SF, Li CI, et al: US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 106:dju055, 2014

12. Warren JL, Klabunde CN, Schrag D, et al: Overview of the SEER-Medicare data: Content, research applications, and generalizability to the United States elderly population. Med Care 40:IV-3-IV-18, 2002 (suppl)

13. SEER: Derived HER2 Recode (2010+). http://seer.cancer.gov/seerstat/databases/ssf/her2-derived.html

14. Reeder-Hayes KE, Meyer AM, Dusetzina SB, et al: Racial disparities in initiation of adjuvant endocrine therapy of early breast cancer. Breast Cancer Res Treat 145:743-751, 2014

15. Zaslavsky AM, Ayanian JZ, Zaborski LB: The validity of race and ethnicity in enrollment data for Medicare beneficiaries. Health Serv Res 47: 1300-1321, 2012

16. Arday SL, Arday DR, Monroe S, et al: HCFA's racial and ethnic data: current accuracy and recent improvements. Health Care Financ Rev 21:107-116, 2000

17. McBean AM: Improving Medicare's data on race and ethnicity. Medicare Brief 15:1-7, 2006

17a. Edge SB and Compton CC: The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17:1471-1474, 2010

18. Klabunde CN, Legler JM, Warren JL, et al: A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. Ann Epidemiol 17:584-590, 2007

19. United States Census Bureau: Geographic terms and concepts - census tract, 2010. https://www.census.gov/geo/reference/gtc/gtc_ct.html

20. Zou G: A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 159:702-706, 2004

21. Aizer AA, Chen MH, McCarthy EP, et al: Marital status and survival in patients with cancer. J Clin Oncol 31:3869-3876, 2013

22. Yancik R, Wesley MN, Ries LA, et al: Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 285: 885-892, 2001

23. Bigby J, Holmes MD: Disparities across the breast cancer continuum. Cancer Causes Control 16: 35-44, 2005

24. Schootman M, Jeffe DB, Lian M, et al: The role of poverty rate and racial distribution in the geographic clustering of breast cancer survival among older women: A geographic and multilevel analysis. Am J Epidemiol 169:554-561, 2009

25. Carpenter WR, Reeder-Hayes K, Bainbridge J, et al: The role of organizational affiliations and research networks in the diffusion of breast cancer treatment innovation. Med Care 49:172-179, 2011

26. Wheeler SB, Reeder-Hayes KE, Carey LA: Disparities in breast cancer treatment and outcomes: Biological, social, and health system determinants and opportunities for research. Oncologist 18: 986-993, 2013

27. Hershman DL, Unger JM, Barlow WE, et al: Treatment quality and outcomes of African American versus white breast cancer patients: Retrospective analysis of Southwest Oncology studies S8814/S8897. J Clin Oncol 27:2157-2162, 2009

28. Bickell NA, Wang JJ, Oluwole S, et al: Missed opportunities: Racial disparities in adjuvant breast cancer treatment. J Clin Oncol 24:1357-1362, 2006

29. Centers for Disease Control and Prevention (CDC): Vital signs: Racial disparities in breast cancer severity—United States, 2005-2009. MMWR Morb Mortal Wkly Rep 61:922-926, 2012

30. Rust G, Zhang S, Malhotra K, et al: Paths to health equity: Local area variation in progress toward eliminating breast cancer mortality disparities, 1990-2009. Cancer 121:2765-2774, 2015

31. Owusu C, Lash TL, Silliman RA: Effect of undertreatment on the disparity in age-related breast cancer-specific survival among older women. Breast Cancer Res Treat 102:227-236, 2007

32. Tolaney SM, Barry WT, Dang CT, et al: Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 372: 134-141, 2015

33. Black DM, Jiang J, Kuerer HM, et al: Racial disparities in adoption of axillary sentinel lymph node biopsy and lymphedema risk in women with breast cancer. JAMA Surg 149:788-796, 2014

34. Hassett MJ, Silver SM, Hughes ME, et al: Adoption of gene expression profile testing and association with use of chemotherapy among women with breast cancer. J Clin Oncol 30: 2218-2226, 2012

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disparities in Use of Human Epidermal Growth Hormone Receptor 2–Targeted Therapy for Early-Stage Breast Cancer

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