VOLUME 30 · NUMBER 18 · JUNE 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Decline in the Use of Anthracyclines for Breast Cancer

Sharon H. Giordano, Yu-Li Lin, Yong Fang Kuo, Gabriel N. Hortobagyi, and James S. Goodwin

See accompanying article on page 2179

From The University of Texas MD Anderson Cancer Center, Houston; and The University of Texas Medical Branch, Galveston, TX.

Submitted October 17, 2011; accepted March 23, 2012; published online ahead of print at www.jco.org on May 21, 2012.

Supported in part by National Institutes of Health Grants No. 2P30 CA016672 and K05 CA134923, ACS RSGI-09-149-01-CPHPS from the American Cancer Society, and CPRIT RP101207-P02 from the Cancer Prevention Research Institute of Texas.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Sharon Giordano, MD, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 1354, Houston, TX 77030; e-mail: sgiordan@mdanderson.org.

0732-183X/12/3018-2232/$20.00

DOI: 10.1200/JCO.2011.40.1273

ABSTRACT

Purpose
To determine the patterns of use of anthracycline- and taxane-based chemotherapy for breast cancer treatment.

Methods
Claims from a 5% national Medicare sample and from a nationally representative claims database (Marketscan) from 1998 to 2009 were used. Patients with International Classification of Diseases (ICD), ninth revision, codes indicating breast cancer, ICD and Common Procedural Terminology codes indicating breast surgery, and claims for chemotherapy between 3 months before and 12 months after surgery comprised the study cohort. Chemotherapy was classified as anthracycline-based or taxane-based, and the percentages of use were calculated. Piecewise regression models were used to identify the inflection points in the rates of chemotherapy use. The effect of patient characteristics on receiving different types of chemotherapy was estimated by multivariable logistic regression models.

Results
A total of 4,458 patients were included in the Medicare cohort and 30,422 in the private insurance cohort. After 2005, a sharp increase in the use of taxane-based chemotherapy and a decline in anthracycline-based chemotherapy was seen. By 2008 in the Medicare cohort, 51% of patients received taxane-based and 32% received anthracycline-based chemotherapy. By the end of 2008, the majority of patients younger than 65 years were also receiving taxane-based chemotherapy. Patients younger than 35 years were less likely to be treated with a taxane-based regimen, whereas patients who underwent 21-gene recurrence score testing and those treated with trastuzumab were more likely to receive taxane-based chemotherapy.

Conclusion
The use of anthracycline-based chemotherapy has declined, and the majority of patients with breast cancer are instead receiving taxane-based chemotherapy. The potential impact on patient outcomes is unknown.

J Clin Oncol 30:2232-2239. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Anthracyclines are among the most active chemotherapeutic agents for the treatment of breast cancer. Multiple trials in the 1980s and 1990s demonstrated that anthracycline-based chemotherapy was associated with lower rates of breast cancer recurrence and improved survival when compared with nonanthracycline chemotherapy regimens, such as cyclophosphamide, methotrexate, and fluorouracil.[1] Given these data, the use of adjuvant anthracyclines increased across the United States through the 1990s. By the year 2000, more than 80% of women younger than 70 years with node-positive breast cancer and more than 70% of women younger than 70 years with node-negative breast cancer received an anthracycline-based chemotherapy regimen.[2]

However, the use of anthracyclines has remained the source of some controversy as a result of cardiac toxicity. A small percentage of patients treated with anthracyclines will develop cardiac dysfunction as a result of treatment.[3] Although rare, the congestive heart failure associated with anthracyclines is largely irreversible and may increase over time since the completion of treatment.[3,4]

The comparable efficacy of anthracyclines and taxanes for women with metastatic breast cancer led to the investigation of taxane-based regimens for early breast cancer.[5] In 2005, the results of two phase III randomized studies were presented at the San Antonio Breast Cancer Symposium, both of which suggested that taxane-based regimens may provide an alternative to anthracycline-based regimens.[6,7] The first study, US Oncology Research Trial 9735,

compared docetaxel plus cyclophosphamide (TC) with a first-generation anthracycline regimen (doxorubicin plus cyclophosphamide, or AC) and reported superior overall survival for the patients treated with TC.[6] However, how the TC regimen will compare with more current third-generation regimens, which incorporate both an anthracycline and taxane and are significantly more effective than AC, is still unknown, and the pivotal studies are ongoing. The second study, Breast Cancer International Research Group (BCIRG) 006, focused on human epidermal growth factor receptor 2 (HER2) –positive breast cancer and demonstrated statistically equivalent results between AC followed by docetaxel and trastuzumab and a non–anthracycline-containing regimen of docetaxel, carboplatin, and trastuzumab (TCH).[7]

We hypothesized that these two studies, which provided nonanthracycline chemotherapy options for both HER2-positive and HER2-negative breast cancer, may have resulted in changes in the treatment patterns of breast cancer. Therefore, we analyzed data from Medicare and from an employer-based claims database (Marketscan) to determine patterns of chemotherapy use for breast cancer.

METHODS

Data Sources

We used data from Medicare beneficiaries and from a nationally representative employer-based claims database (Marketscan). The Marketscan database contains information on medical claims and prescription drug claims for employees, spouses, and their dependants from approximately 45 large employers and over 100 payers. All data are de-identified.

For the Medicare analyses, claims from the year 1998 to 2009 for a 5% representative national sample of Medicare beneficiaries were used, including Medicare enrollment files, Medicare Provider Analysis and Review files, Outpatient Standard Analytic Files, and Medicare Carrier files. For the Marketscan analyses, claims from the year 1998 to 2009 were used.

Study Cohort

Female patients with breast cancer (International Classification of Disease, ninth revision [ICD-9] codes 174.x) who received mastectomy (ICD-9 codes 85.41, 85.42, 85.43, 85.44, 85.45, 85.46, 85.47, 85.48; Common Procedural Terminology [CPT] codes 19,180, 19,182, 19,200, 19,220, 19,240, 19,303, 19,304, 19,305, 19,306, 19,307), conservative surgery (ICD-9 codes 85.20, 85.21, 85.22, 85.23, 85.25; CPT codes 19,110, 19,120, 19,125, 19,126, 19,160, 19,162, 19,301, 19,302), or axillary lymph node dissection[1,2] (ICD-9 code 40.3; CPT codes 38,740, 38,745,38,525) during January 1999 through December 2008 were selected (n = 32,931 for Medicare population, age $\geq$ 66 years; and n = 100,277 for Marketscan population, age $\leq$ 64 years).[8-10] This algorithm for identifying cases was adapted from previously validated algorithms with specificity of greater than 99%.[8-10] For patients with codes for both mastectomy and breast-conserving surgery, if the mastectomy happened within 3 months of breast-conserving surgery, then patients were considered to have had mastectomy.

Medicare patients who died, were ever enrolled in health maintenance organizations, or had an interruption in Medicare Parts A and B enrollment during 12 months before and 12 months after the procedure month were removed (n = 5,082), leaving 27,849 patients. Among these 27,849 patients, only those who had received chemotherapy drugs within 3 months before and 12 months after the procedure month (including the procedure month) were kept in the study cohort (n = 4,458). Marketscan patients who were not continuously covered from 3 months before to 12 months after the procedure month were removed (n = 29,706), leaving 70,571 patients. Among these patients, only those who had received chemotherapy drugs within 3 months before and 12 months after the procedure month (including the procedure month) were kept in the study cohort (n = 30,422). Claims for receiving chemotherapy drugs were identified by HCPCS codes J8520, J8521, J8530, J8540, J8560, J8597, J8610, J8999, J9000–J9999, except J9003, J9165, J9175, J9202, J9209, J9212-J9226, J9240, J9395.

Measures

Two types of chemotherapy were studied: anthracycline-based and taxane-based. Anthracycline-based chemotherapy was defined using Healthcare Common Procedure Coding System (HCPCS) codes J9000, J9001, J9010, J9178, and J9180. Patients who had claims with such HCPCS codes within 3 months before and 12 months after the procedure month (including the procedure month) were classified into this category. Taxane-based chemotherapy was defined as no anthracycline chemotherapy and the presence of at least one HCPCS code for paclitaxel (J9265), docetaxel (J9170), or nab-paclitaxel (J9264) within the aforementioned time period. Patients who were in the anthracycline-based chemotherapy arm could have also received a taxane in addition to an anthracycline, because our primary interest was in cases in which taxanes were substituted for anthracyclines.

Charlson comorbidity index was calculated for the Medicare patients using claims from the year before the procedure. We did not calculate comorbidities for the patients in Marketscan due to shorter periods of continuous enrollment. When we restricted the data set to patients who had a year of continuous enrollment before diagnosis, we lost an additional 34% of patients. Because this is a young population, we elected to omit the comorbidity data in order to include a more comprehensive cohort of patients. Trastuzumab use for those who had surgery during 2005 to 2008 was identified by claims with HCPCS code J9355. Medicare does not have information on prescription drug use for all the years in this study. For Marketscan patients, the use of hormonal therapy was identified by National Drug Code codes for tamoxifen, anastrozole, letrozole, and exemestane. The Marketscan data do not include information on patient race. Twenty-one–gene recurrence score (Oncotype DX) testing claims were identified by the unique physician identification number (Y06495) or national provider identifier (1215003603) in Medicare and the code S3854 in the Marketscan data.

Statistical Analysis

The percentages of use of anthracycline-based and taxane-based chemotherapy were calculated by month of surgery. Piecewise regression models were used to find the time point when the sharp increase/decrease of taxane/anthracycline-based chemotherapy began.[11] The location of the knot point was estimated by nonlinear least square regression. The percentage use of anthracycline and taxane chemotherapy was also calculated by procedure year and stratified by patient age, hormonal therapy use, and trastuzumab use. To study the regional variations in chemotherapy use, maps were constructed using ArcMap version 9.3. The effect of patient characteristics on receiving different types of chemotherapy was estimated by multivariable logistic regression models with adjustment for patient characteristics for those who had the procedure during 2005 and 2008 (n = 1,714 for the Medicare cohort and 19,370 for the Marketscan cohort). All analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Overall, 4,458 patients were included in the Medicare cohort and 30,422 in the Marketscan cohort. The distribution of patient characteristics is shown in Table 1. The Medicare cohort is limited to patients 66 years of age and older, and the Marketscan cohort is limited to patients younger than age 65 years. In both cohorts, among patients who were treated after 2005, which was when the adjuvant trastuzumab data became available, 22% were treated with trastuzumab. Also, after 2005, approximately 6% of patients received 21-gene recurrence score testing in both cohorts.

Figure 1 shows the trends in the use of anthracycline-based and taxane-based chemotherapy by month of surgery. We defined anthracycline-based chemotherapy as any chemotherapy regimen that contained an anthracycline, whether or not a taxane was also

JCO 2012;30:2233-2240

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Medicare Cohort No.	Medicare Cohort %	Marketscan Cohort No.	Marketscan Cohort %
Overall	4,458	100	30,422	100
Region				
Midwest	1,188	26.7	7,762	25.5
Northwest	763	17.1	2,371	7.8
South	1,795	40.3	15,400	50.6
West	677	15.2	4,759	15.6
US territories	35	0.8	130	0.4
Age, years				
< 35			980	3.2
35-44			5,843	19.2
45-54			12,639	41.6
55-64			10,960	36.0
66-70	1,998	44.8		
71-75	1,398	31.4		
76-80	809	18.2		
> 80	253	5.7		
Race				
White	3,934	88.3		
Black	382	8.6		
Other	142	3.2		
Medicaid eligibility	468	10.5		
Cardiac condition*	158	3.5		
Other comorbidity†	1,245	27.9		
Use of hormone therapy			15,295	50.3
Trastuzumab use‡	378	21.9	4,377	22.5
21-gene recurrence score test‡	105	6.1	1,214	6.2

*Congestive heart failure or myocardial infarction in the prior year.
†Charleson comorbidity excluding cardiac condition in the prior year.
‡Only for patients who had the procedure during 2005 through 2008.

given. Taxane-based chemotherapy was defined as a chemotherapy regimen in which patients received a taxane but no anthracycline. After 2005, there is a sharp increase in the use of taxane-based chemotherapy. Using piecewise regression models, we examined time trends for knots, or points when the rate of change in use of a drug either accelerated or decelerated. For taxane-based chemotherapy, the change occurred in December 2005 in both the Medicare and the Marketscan cohorts (95% CI for Medicare cohort, August 2005 to March 2006; for Marketscan cohort, October 2005 to February 2006). For the older patients in Medicare, the use of taxane-based chemotherapy surpassed the use of anthracycline-based chemotherapy in late 2007. In 2008, 51% of patients received taxane-based chemotherapy and 32% received anthracycline-based chemotherapy. For the younger patients in the Marketscan database, the use of taxane-based chemotherapy surpassed anthracycline chemotherapy in late 2008.

We next explored whether the increase in taxane-based chemotherapy was seen across different subsets of patients. Figure 2 shows the yearly trends in chemotherapy use, stratified by patient characteristics. The use of anthracycline-based chemotherapy is lower in patients older than age 75 years, but the increase in taxanes and decrease in anthracyclines is seen across all age groups (Fig 2A). We then evaluated the use of chemotherapy in the Marketscan cohort stratified by hormonal therapy use (Fig 2B), which was used as a surrogate for hormone receptor status. The increase in taxane-based chemotherapy was similar between patients who were prescribed hormonal therapy and those who were not. Figures 2C (Medicare) and 2D (Marketscan) show trends in chemotherapy use stratified by the use of trastuzumab. For both the older and younger patients, the switch to a taxane-based chemotherapy regimen occurred earlier among the trastuzumab-treated patients. Among the older patients, the majority of all women were receiving taxane-based chemotherapy by 2008. In contrast, among the younger women not treated with trastuzumab (ie, those with HER2-negative breast cancer), anthracycline-based chemotherapy was still more commonly used than taxane-based chemotherapy. Among younger women treated with trastuzumab (ie, those with HER2-positive breast cancer), taxane-based chemotherapy was more commonly used than anthracycline-based regimens.

Figure 3 shows the use of docetaxel versus paclitaxel among patients who received taxane-based chemotherapy. In the Medicare cohort, among trastuzumab users, the rate of docetaxel increased from 62.5% of patients in 2005 to 74.5% of patients in 2008. In patients who did not receive trastuzumab, 44.2% of women received docetaxel in 2005, which increased to 88.8% in 2008. In the Marketscan cohort of trastuzumab users, docetaxel increased from 34.4% of women in 2005 to 61.7% of

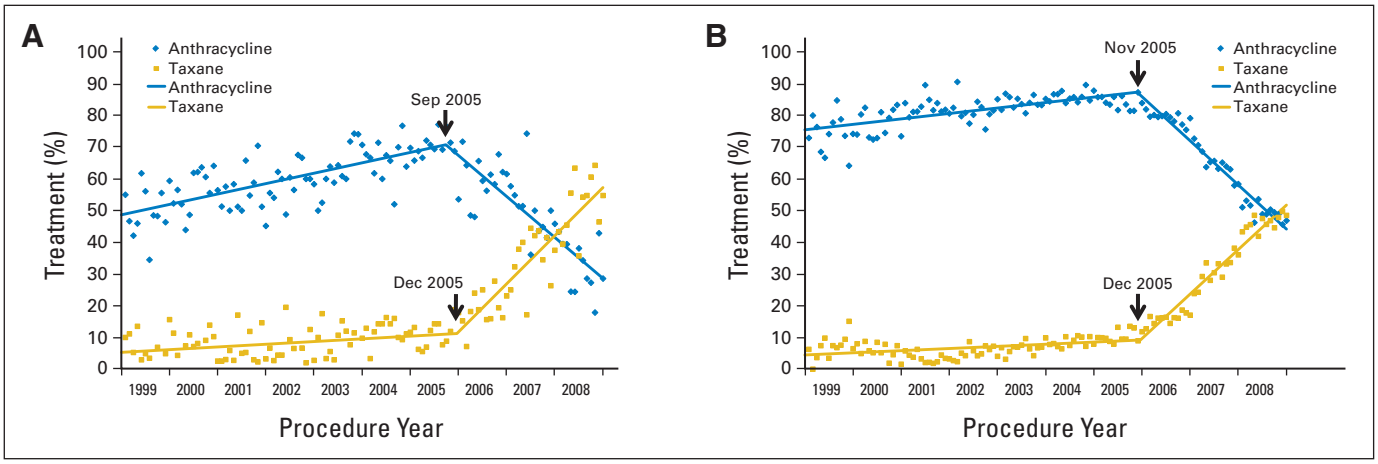
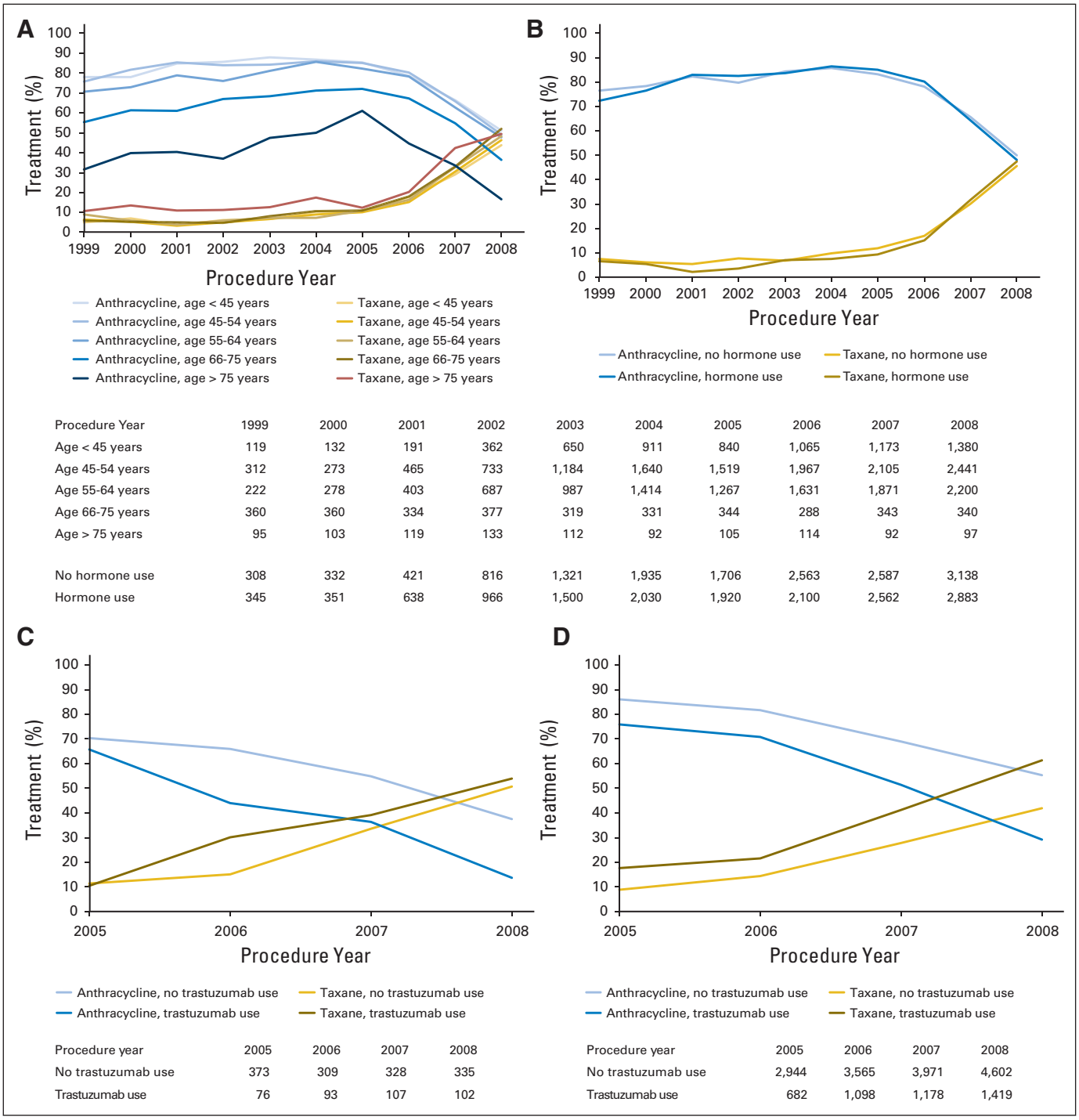


Fig 1. Monthly trends and fit curves of anthracycline and taxane use. (A) Medicare cohort; (B) Marketscan cohort.



Procedure Year	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Age < 45 years	119	132	191	362	650	911	840	1,065	1,173	1,380
Age 45-54 years	312	273	465	733	1,184	1,640	1,519	1,967	2,105	2,441
Age 55-64 years	222	278	403	687	987	1,414	1,267	1,631	1,871	2,200
Age 66-75 years	360	360	334	377	319	331	344	288	343	340
Age > 75 years	95	103	119	133	112	92	105	114	92	97
No hormone use	308	332	421	816	1,321	1,935	1,706	2,563	2,587	3,138
Hormone use	345	351	638	966	1,500	2,030	1,920	2,100	2,562	2,883

Procedure year	2005	2006	2007	2008
No trastuzumab use	373	309	328	335
Trastuzumab use	76	93	107	102

Procedure year	2005	2006	2007	2008
No trastuzumab use	2,944	3,565	3,971	4,602
Trastuzumab use	682	1,098	1,178	1,419

Fig 2. Yearly trends of anthracycline and taxane use. (A) Stratified by age group; (B) by hormone use, Marketscan cohort; (C) by trastuzumab use, Medicare cohort; (D) by trastuzumab use, Marketscan cohort. The tables below the figures show the patient number of each group at each year.

women in 2008. In patients who did not receive trastuzumab, the use of docetaxel changed from 42.6% in 2005 to 59.4% in 2008.

Figure 4 shows the regional variation in chemotherapy use, comparing Marketscan patients who had surgery in the most recent available years (2007 to 2008) with those treated in the several years immediately before the change in taxane use (2003 to 2005). There is marked state-by-state variation in the decline of anthracyclines and increase in taxane-based chemotherapy.

To evaluate which patients were being treated with taxane-based chemotherapy, we performed multivariable logistic regression models among those patients who underwent breast surgery from 2005 to 2008 (Table 2). Among the patients in both Medicare and Marketscan, the odds of receiving taxane-based chemotherapy increased by 6% per month and was greater among patients receiving trastuzumab and patients who had 21-gene recurrence score testing performed. Among the younger Marketscan patients, the

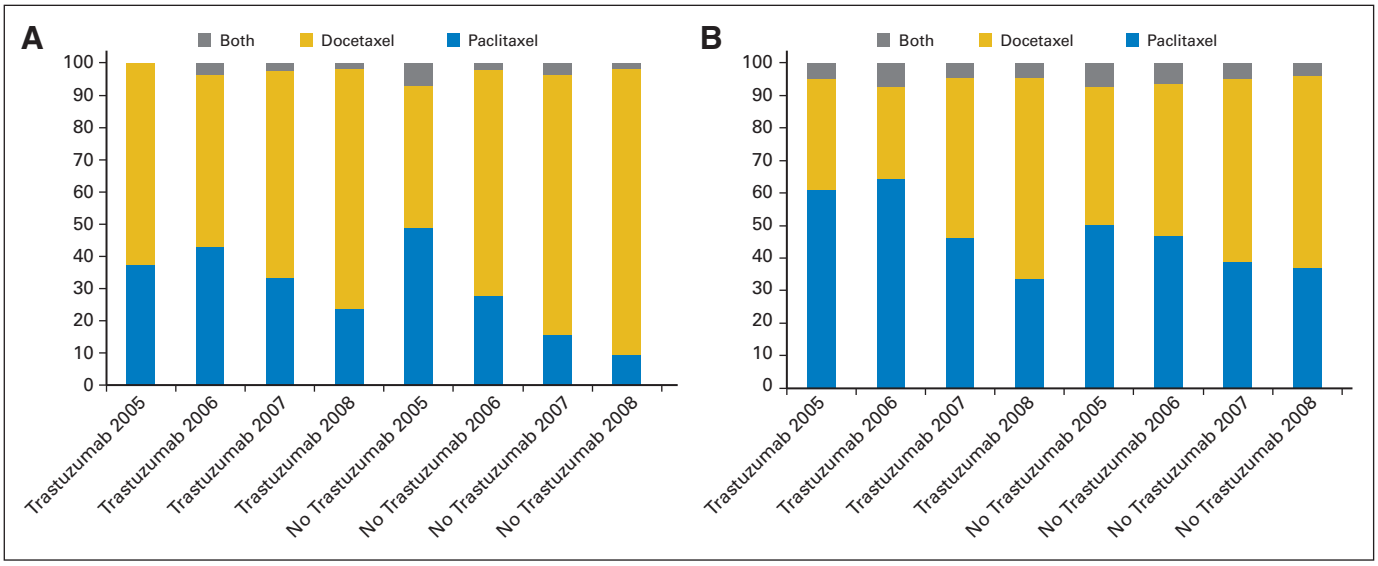


Fig 3. Rates of different types of taxane among trastuzumab users and nonusers who received taxane-based chemotherapy. (A) Medicare cohort; (B) Marketscan cohort.

use of taxane chemotherapy was also less common in patients age 35 years and younger (odds ratio, 0.79; 95% CI, 0.65 to 0.96). Regional differences were also seen; patients who resided in the West were more likely to receive a taxane-based regimen (odds ratio, 1.27; 95% CI, 1.10 to 1.47).

DISCUSSION

In this study, we have shown striking changes in the treatment patterns for breast cancer across the United States. The use of anthracycline-based

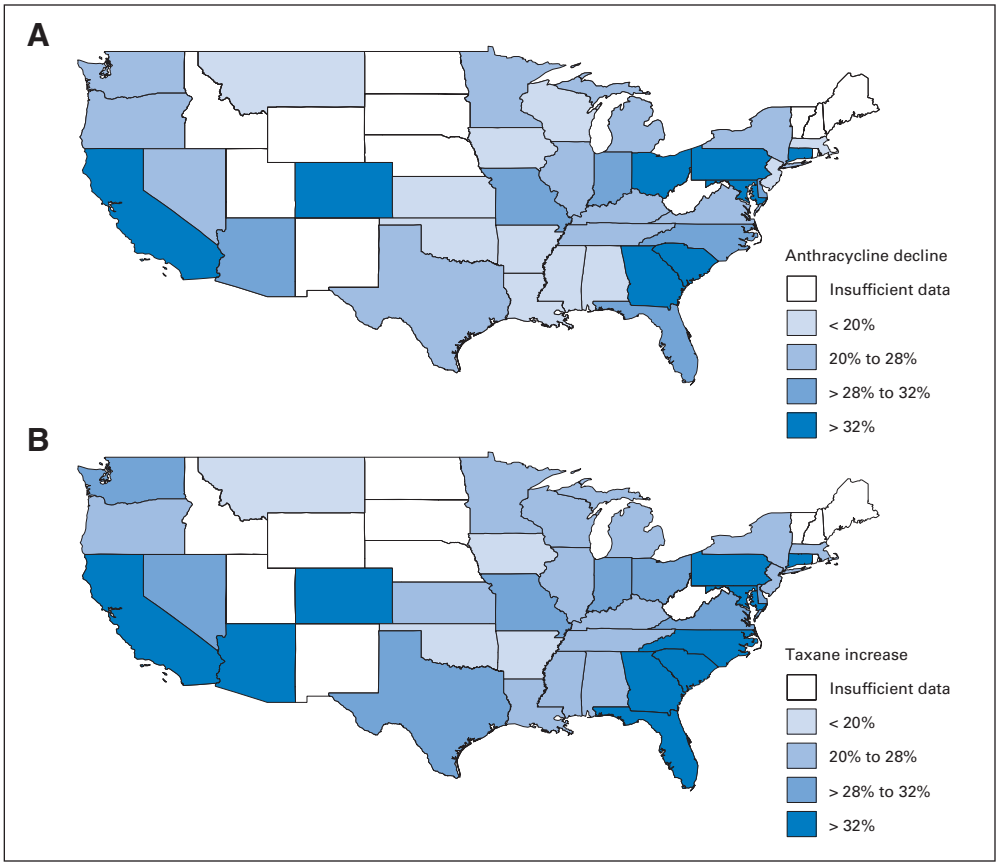


Fig 4. (A) Anthracycline decline and (B) taxane increase across states for the Marketscan cohort. The decline/increase results from the comparison between two time periods, 2003 to 2005 and 2007 to 2008. Rates for states with a denominator of fewer than 30 patients in either time period are not shown.

Table 2. Effect of Patient Characteristics on Receiving Taxane-Based Chemotherapy*

Characteristic	Medicare			Marketscan		
	OR	95% CI	*P*	OR	95% CI	*P*
Procedure time in months	1.06	1.05 to 1.07	< .001	1.06	1.05 to 1.06	< .001
Age group, years						
< 35				0.79	0.65 to 0.96	.019
35-44				0.91	0.82 to 1.00	.040
45-54				0.91	0.84 to 0.98	.014
55-64				Ref		
66-70	Ref					
71-75	1.06	0.82 to 1.38	.652			
76-80	1.10	0.80 to 1.51	.567			
> 80	1.49	0.92 to 2.41	.104			
Trastuzumab use						
No	Ref			Ref		
Yes	1.34	1.02 to 1.74	.032	2.07	1.92 to 2.24	< .001
Test for 21-gene recurrence score						
No	Ref			Ref		
Yes	2.18	1.42 to 3.35	< .001	2.86	2.52 to 3.25	< .001
Use of hormone therapy						
No				Ref		
Yes				0.99	0.93 to 1.06	.823
Cardiac condition						
No	Ref					
Yes	2.45	1.34 to 4.49	.004			
Other comorbidity						
No	Ref					
Yes	0.75	0.58 to 0.98	.033			
Race						
White	Ref					
Black	0.94	0.62 to 1.43	.783			
Other	1.16	0.59 to 2.27	.671			
Region†						
Northeast	Ref			Ref		
Midwest	1.12	0.79 to 1.60	.529	0.96	0.83 to 1.09	.514
South	1.06	0.76 to 1.46	.743	1.14	1.00 to 1.29	.051
West	1.38	0.93 to 2.05	.108	1.27	1.10 to 1.47	.001
Medicaid eligibility						
No	Ref					
Yes	1.00	0.69 to 1.43	.982			

Abbreviations: OR, odds ratio; Ref, reference.
*For patients who received the procedure between 2005 and 2008.
†Patients who resided in US territories were not included in the analysis (n = 9 for Medicare cohort and 89 for Marketscan cohort).

chemotherapy has decreased, so that by 2008, the majority of patients with breast cancer were not receiving an anthracycline as a component of their initial therapy. The use of taxane-based regimens has correspondingly increased, with the change in use correlating in time with the oral presentations of the US Oncology Research Trial 9735 (TC *v* AC) and the BCIRG 006 study in December 2005.[7,12] The US Oncology Study was published in 2006,[6] but the BCIRG 006 study was not published until 2011.[13] The change in practice for HER2-positive breast cancer was based largely on an oral presentation before the clinical trial results had gone through peer review, similar to the patterns of early adoption of adjuvant anthracycline and taxane combinations.[11] Also of note, the use of taxane-based chemotherapy in practice was not limited to docetaxel-based regimens as in clinical trials; a substantial minority of patients received nonanthracycline paclitaxel-based chemotherapy. However, the results of the comparison of paclitaxel with AC for women with early breast cancer in Cancer and Leukemia Group B 40101 have not yet been reported.

Our data suggest that changes in patterns of care have occurred across all age groups of patients. However, patients younger than age 35 years were less likely to be treated with a taxane-based regimen, perhaps because of concerns over the higher risk of recurrence seen in younger patients. In contrast, women who received 21-gene recurrence score testing were more likely to receive a taxane-based regimen. Patients with HER2-positive breast cancer, as identified by the use of trastuzumab, were also more likely to receive a nonanthracycline, taxane-based chemotherapy regimen. By 2008, the only identified subset of patients who were still more likely to receive anthracycline-based chemotherapy rather than taxane-based chemotherapy were women younger than 65 years with HER2-negative breast cancer.

Which factors are driving the changes in adjuvant chemotherapy regimens? One possibility is concern regarding toxicity of treatment. However, in the US Oncology trial, the toxicities were fairly similar between the TC and the AC arms.[6] The patients treated with TC had more fever and neutropenia (5% *v* 2.5%), but congestive heart failure developed in one patient treated with AC (total N = 510) and none with TC (total N = 506). Two patients died while being treated with TC (one as a result of sepsis and one as a result of unrelated cardiac death), and none died while being treated with AC. It seems surprising that this small change in toxicity profile could drive such a large change in treatment. For patients with HER2-positive breast cancer treated on the BCIRG 006 trial, the differences in toxicity were larger: 21 patients developed congestive heart failure while being treated with doxorubicin, cyclophosphamide, and docetaxel (AC-T) plus trastuzumab (total N = 1074) compared with four patients treated with TCH (total N = 1075).[13] Although the outcome data must be interpreted cautiously because the trial was not designed to evaluate the noninferiority of TCH compared to AC-T-trastuzumab, 144 of the TCH patients developed distant recurrence as compared to 124 patients treated with AC-T-trastuzumab. From these data, we cannot tell whether the changes in chemotherapy are a result of some oncologists or oncology practices abandoning the use of anthracyclines or whether within each practice, physicians are selecting the patients they feel are most appropriate for each type of chemotherapy. It is also possible that due to concern about cardiac toxicity, patients are requesting more taxane-based chemotherapy regimens.

Whether or not these changes in treatment patterns will affect patient outcomes remains unknown. For women with HER-2 positive breast cancer, the results of BCIRG 006 were statistically similar between the anthracycline and taxane-based chemotherapy arms, which both included trastuzumab. While this is a single study, the taxane-based regimen was compared against a third-generation optimal chemotherapy regimen. In contrast, for women with HER-2 negative breast cancer, the data showing equivalence or superiority of taxane-based regimens are weaker. The US Oncology study was a single study of just over 1000 patients and the comparator arm was four cycles of doxorubicin cyclophosphamide (AC). Given that AC followed by paclitaxel given every 3 weeks is superior to four cycles of AC,[14,15] and multiple other adjuvant chemotherapy regimens have been shown to be superior to AC followed by every-3-weeks paclitaxel,[16-18] it remains uncertain how the TC regimen will compare with more contemporary third-generation breast cancer regimens. The trial comparing the TC regimen with a third-generation regimen of docetaxel, doxorubicin, and cyclophosphamide is still ongoing, and the relative outcome is unknown. It is also of concern, in view of the expected variability of clinical trial results, that physicians are willing to change practice on the basis of a single trial result, especially small trials such as the US Oncology trial, where the control arm is of historical interest only. This early adoption might place patients at risk of receiving inferior treatment.

This study has some limitations. First, these data were derived from medical claims from Medicare and from private insurance and therefore lack detailed clinical information. No data were available on cancer stage, so a small percentage of the patients were likely being treated for metastatic disease. Only 5% of patients with breast cancer present with stage IV disease, and fewer than half of those with stage IV disease undergo surgery, so we would expect only 2% to 3% of patients to have had metastases and the vast majority to be undergoing adjuvant therapy.[19,20] We also had no information regarding hormone receptor status, but we were able to use prescriptions for hormonal therapy as a surrogate for hormone receptor positivity in the Marketscan data. It is possible that some patients who had hormone receptor–positive disease were not identified correctly if they did not take hormonal therapy, used only samples from doctor's offices, or had additional prescription drug plans. Similarly, data are not available on HER2 status, but we used administration of trastuzumab to identify an HER2-positive patient subset.

In conclusion, anthracycline-based chemotherapy is no longer the most commonly used initial chemotherapy regimen for the treatment of breast cancer. The use of anthracyclines has been quite rapidly replaced by taxane-based regimens. The non–anthracycline-based regimens are likely to benefit patients in that the rates of cardiac toxicity should be lower. However, particularly for women with HER2-negative breast cancer, we will need to await the results of the definitive phase III trials to determine whether this change will have a negative, neutral, or positive effect on survival.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Sharon H. Giordano, Yong Fang Kuo, James S. Goodwin
Financial support: Sharon H. Giordano, James S. Goodwin
Administrative support: Sharon H. Giordano, James S. Goodwin
Provision of study materials or patients: James S. Goodwin
Collection and assembly of data: James S. Goodwin
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687-1717, 2005

2. Harlan LC, Clegg LX, Abrams J, et al: Community-based use of chemotherapy and hormonal therapy for early-stage breast cancer: 1987-2000. J Clin Oncol 24:872-877, 2006

3. 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

4. Pinder MC, Duan Z, Goodwin JS, et al: Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. J Clin Oncol 25:3808-3815, 2007

5. Piccart-Gebhart MJ, Burzykowski T, Buyse M, et al: Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. J Clin Oncol 26:1980-1986, 2008

6. Jones SE, Savin MA, Holmes FA, et al: Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol 24:5381-5387, 2006

7. Slamon DJ, Eiermann W, Robert N, et al: Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab in HER2 positive early breast cancer patients: BCIRG006 Study. Breast Cancer Res Treat 94:s5, 2005 (suppl)

8. Freeman JL, Zhang D, Freeman DH, et al: An approach to identifying incident breast cancer cases using Medicare claims data. J Clin Epidemiol 53: 605-614, 2000

9. Nattinger AB, Laud PW, Bajorunaite R, et al: An algorithm for the use of Medicare claims data to identify women with incident breast cancer. Health Serv Res 39:1733-1749, 2004

10. Gold HT, Do HT: Evaluation of three algorithms to identify incident breast cancer in Medicare claims data. Health Serv Res 42:2056-2069, 2007

11. Giordano SH, Duan Z, Kuo YF, et al: Impact of a scientific presentation on community treatment patterns for primary breast cancer. J Natl Cancer Inst 98:382-388, 2006

12. Jones SE, Savin MA, Holmes FA, et al: Final analysis: TC (docetaxel/cyclophosphamide, 4 cycles) has a superior disease-free survival compared to standard AC (doxorubicin/cyclophosphamide) in 1016 women with early stage breast cancer. Breast Cancer Res Treat 94:S20, 2005 (suppl)

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

14. Henderson IC, Berry DA, Demetri GD, et al: Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 21:976-983, 2003

15. Mamounas EP, Bryant J, Lembersky B, et al: Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28. J Clin Oncol 23:3686-3696, 2005

16. Burnell M, Levine MN, Chapman JA, et al: Cyclophosphamide, epirubicin, and fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by paclitaxel versus doxorubicin and cyclophosphamide followed by paclitaxel in node-positive or high-risk node-negative breast cancer. J Clin Oncol 28:77-82, 2010

17. Citron ML, Berry DA, Cirrincione C, et al: Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 21:1431-1439, 2003

18. Sparano JA, Wang M, Martino S, et al: Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 358:1663-1671, 2008

19. Siegel R, Ward E, Brawley O, et al: Cancer statistics: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 61:212-236, 2011

20. Gnerlich J, Jeffe DB, Deshpande AD, et al: Surgical removal of the primary tumor increases overall survival in patients with metastatic breast cancer: Analysis of the 1988-2003 SEER data. Ann Surg Oncol 14:2187-2194, 2007

