Factors Determining Anthracycline Use in Hormone Receptor Positive, Early-Stage Breast Cancer

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Abstract

In this study we investigated factors associated with prescribing patterns for an anthracycline-based chemotherapy in hormone receptor-positive stage I to III breast cancer. We carried out a retrospective analysis of the Michigan Breast Oncology Quality Initiative data set of 17,788 women with stage I to III estrogen receptor/progesterone receptor-positive HER2/*neu*-negative invasive breast cancer. Patients with a high recurrence score and lymph node-positive status were just as likely to receive an anthracycline as a non-anthracycline-based regimen.

Background: Anthracyclines are associated with significant toxicities whereas nonanthracyclines have proven to be better tolerated. A 21-gene assay allows clinicians to predict who will not benefit from adjuvant chemotherapy and avoid systemic toxicities. Physicians are using the recurrence score to guide chemotherapy selection, despite the lack of evidence. In this study we examined factors associated with prescribing patterns for an anthracycline-based chemotherapy in hormone receptor-positive stage I to III breast cancer. **Materials and Methods:** This was a retrospective study using the Michigan Breast Oncology Quality Initiative data set (February 1, 2006 to December 31, 2015). Women with histologically confirmed stage I to III invasive breast cancer with estrogen receptor and/or progesterone receptor-positive, HER2/*neu*-negative receptor status were included. We used χ^2 analysis to determine associations of these characteristics with the 21-gene assay score and anthracycline use. **Results:** A total of 17,788 patients were evaluated. Most tumors were stage I (60%). Most procedures were lumpectomy with radiation (66%). Anthracyclines were used more often in stage III patients (69%), younger patients (40% for patients younger than 65 years), and those with higher 21-gene recurrence scores. Patients with low recurrence scores were more likely to receive anthracyclines if lymph node-positive (10%) than if lymph node-negative (1%; $P < .001$). Patients with high recurrence scores and lymph node-positive status were just as likely to receive an anthracycline-based as a nonanthracycline-based regimen (47.5% vs. 49.2%; $P = .89$). **Conclusion:** These data indicate that medical oncologists might be anticipating the results of Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer study (TAILORx) and the Clinical Outcomes in ER+HER2-node-positive Breast Cancer Patients Who Were Treated According to the Recurrence Score Results: Evidence From a Large Prospectively Designed Registry (RxPonder) trials and are avoiding the potential serious complications associated with anthracycline treatment in patients least likely to receive benefit.

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Introduction

Breast cancer remains the most common malignancy diagnosed in women and ranks number 2 among cancer-related deaths for women.[1] Most women carry a lifetime risk of 12% in developing breast cancer. In 2013, there were an estimated 232,340 new cases of female breast cancer.[1] The mainstay of treatment for localized disease remains surgery with or without radiation therapy.[2] Adjuvant chemotherapy was introduced to decrease the risk of relapse

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after mastectomy or lumpectomy with radiation.[3] Clinical trials began in the 1950s using systemic cytotoxic chemotherapy in the adjuvant setting. Several successful clinical trials of doxorubicin and epirubicin would make anthracyclines the backbone of breast cancer chemotherapy regimens starting in the 1980s and continuing for decades. In 1979, Buzdar et al compared 222 patients with stage II to III breast cancer treated with surgery and adjuvant doxorubicin with 151 corresponding patients from historical controls.[4] The treatment group had a significantly improved 3-year overall survival compared with the control group at 89% versus 58%, respectively.

The National Comprehensive Cancer Network (NCCN) guidelines currently include doxorubicin (Adriamycin; Lexi-com, Inc, Husdson, OH)—including regimens as an acceptable option in all but the lowest risk, early stage breast cancer.[3] The paradigm that allowed anthracyclines to come to the forefront of breast cancer treatment has come under scrutiny, however, and their use has been steadily declining over the past 15 to 20 years.[5] A population study at the University of California, San Francisco Breast Cancer Center reviewed the charts of 1116 patients treated for breast cancer between 2000 and 2010. The data gathered from this study showed anthracyclines being included in 95% of chemotherapy regimens from 2000 to 2005, whereas it was only included in 65% of regimens from 2005 to 2010. Prospective studies have shown that other chemotherapy options are available, specifically taxanes, that are noninferior to anthracyclines, particularly in early stage, hormone receptor-positive (HR$^+$) breast cancer. The US Oncology 9735 compared docetaxel (Taxotere; Sanofi-Aventis, Bridgewater, NJ)/cyclophosphamide with doxorubicin/cyclophosphamide in stage I to III breast cancer.[6] The 7-year overall survival was significantly better in the docetaxel group than in the doxorubicin group (87% vs. 82%). The nonanthracycline regimen was also better tolerated. This benefit was attributed to treatment effect, rather than increased mortality from the anthracycline. Despite this trend, anthracyclines are still widely prescribed, and considerable effort is being expended to determine who can safely avoid their use. Anthracyclines are associated with significant toxicities including cardiotoxicity in the form of dilated cardiomyopathy, which affects 1% to 5.5% of patients.[7] It also carries the risk of treatment-related acute myeloid leukemia and myelodysplastic syndrome, which affect approximately 0.5% to 1% of patients.[8]

Many patients with HR$^+$/HER2$^-$, lymph node-negative breast cancer can avoid adjuvant chemotherapy.[9] The 21-gene reverse transcriptase polymerase chain reaction (RT-PCR) assay is standard of care for HR$^+$, HER2/*neu*$^-$, lymph node-negative breast cancer that is >0.5 cm.[10] The RT-PCR assay scores patients on a scale of 0 to 100 as low (<18), intermediate (18-30), or high (>30) risk of recurrence. Paik et al showed a significant difference in 10-year rate of distant recurrence between low (6.8%), intermediate (14.3%), and high (30.5%) recurrence scores.[11] This study validated the RT-PCR assay as a predictor for rates of distant recurrence in this group of patients. This allows clinicians to accurately predict who will not benefit from adjuvant chemotherapy so as to avoid toxicities associated with systemic treatment. Controversy, however, exists as to the utility of the 21-gene assay in lymph node-positive disease.[12] There is currently no prospective data for lymph node-positive disease; however, retrospective analysis of the SWOG (Southwestern Oncology Group)-8814 suggests node-positive patients with a low recurrence score do not seem to benefit from adjuvant chemotherapy.[13] A descriptive study from the University of Michigan in 2016 reported that many physicians use the recurrence score to guide chemotherapy selection, despite the lack of evidence supporting its use in this manner.[14]

We conducted a study to determine factors associated with actual practice patterns when making prescription decisions for an anthracycline-based chemotherapy regimen in HR$^+$ stage I to III breast cancer. We also investigated the use of anthracyclines over time.

Materials and Methods

We performed a retrospective, descriptive study using the Michigan Breast Oncology Quality Initiative data. The study was approved by the Genesys Health System institutional review board in September 2016. We evaluated patient and disease characteristics

Figure 1 Anthracycline User According to Recurrence Group Among Patients With and Without 21-Gene Testing (n = 17,788)

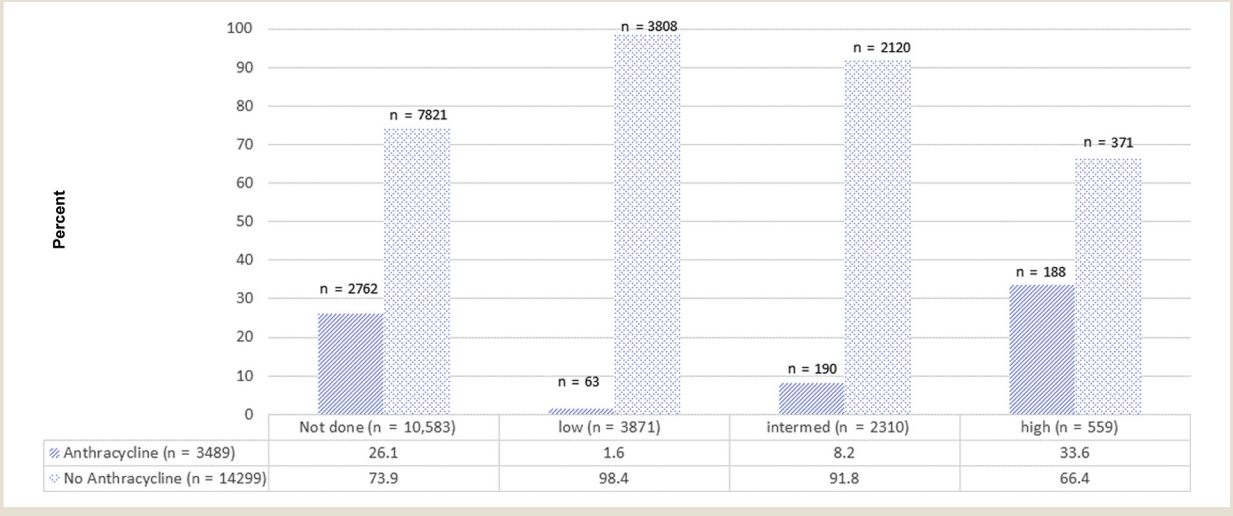
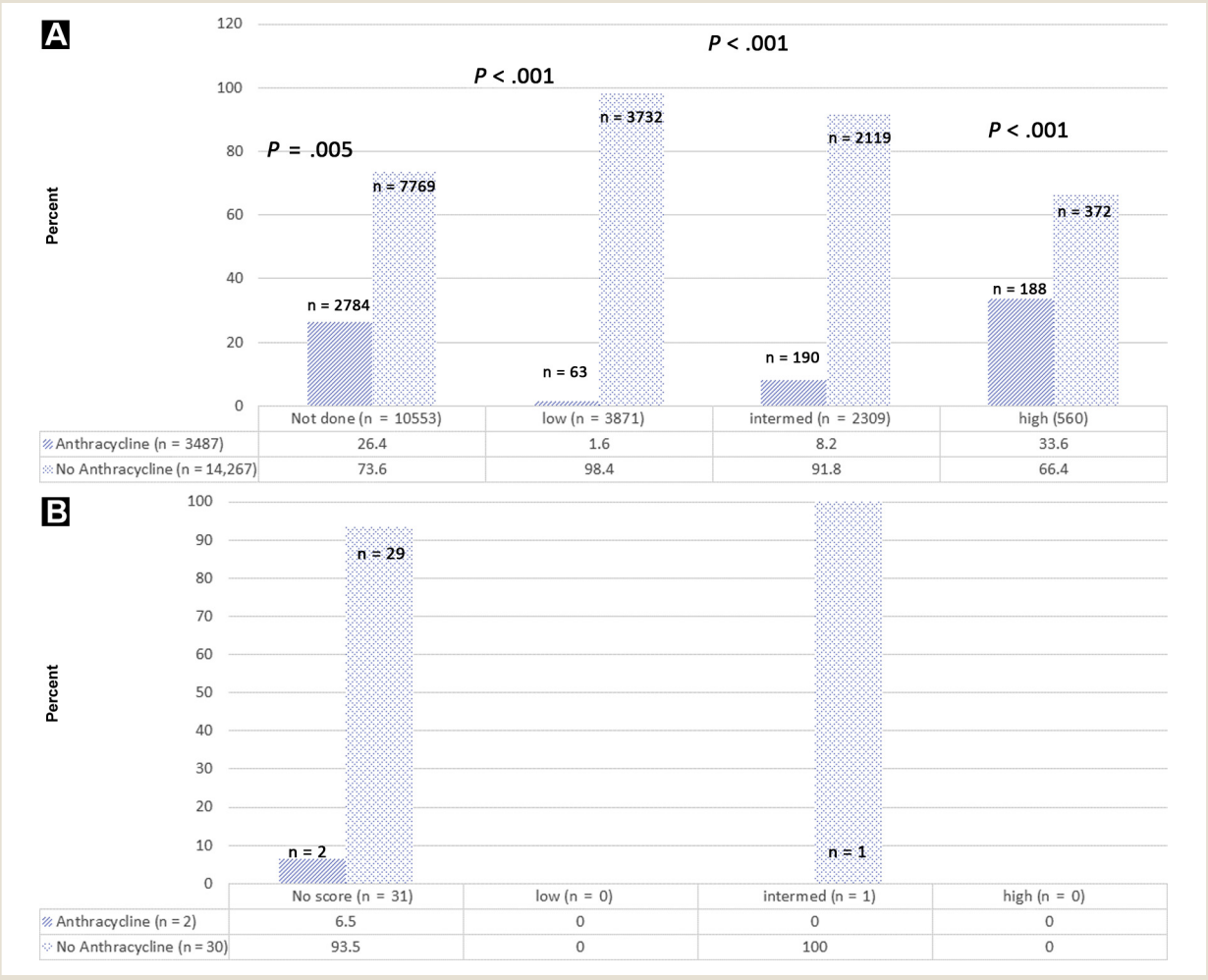


Figure 2 (A) Anthracycline User According to Recurrence Group: Node-Positive Patients (n = 17,756). (B) Anthracycline User According to Recurrence Group: Node-Negative Patients (n = 32)



such as stage, lymph node status, RNA-polymerase chain reaction assay score, and age. Eligibility criteria included women 18 years of age and older with histologically confirmed stage I to III invasive breast cancer with estrogen receptor and/or progesterone receptor (PR)-positive, HER2/*neu*-negative receptor status. There were no exclusion criteria. Data were gathered from the Michigan Breast Oncology Quality Initiative, a program launched in 2006 that abstracts data from 25 Michigan-based health systems regarding practice patterns in surgical, radiation, and medical oncology as it relates to early stage breast cancer. Key data collected included demographic characteristics, clinical care, medical history, and medical treatment. The study abstracted data between January 2006 and December 2015. Blue Cross/Blue Shield of Michigan supports this collaborative quality initiative. All centers adhered to the data collection procedures and definitions developed by the NCCN Breast Cancer Outcomes Database. Institutional review boards from participating centers approved all data collection, transmission, and storage protocols.

A χ^2 test of independence was performed to examine the association between anthracycline use and PR status, cancer stage, tumor grade, 21-gene assay recurrence score, age ($\leq$65 or >65 years), and diagnosis date. Bivariate analysis with Spearman ρ correlation was conducted to determine associations between receiving anthracycline and recurrence score. Multivariate regression analysis was conducted to predict anthracycline use per recurrence score with adjustment for confounding factors of age, race, stage, and Charlson Comorbidity Index. An α level of 0.05 was used as a significance criterion for all statistical tests.

Results

We evaluated data on 17,788 women who were treated between February 2006 and December 2015. The average age was 61.3 years (SD, 13.0). Most patients were Caucasian (83%), whereas 11% were African-American. Stage I tumors made up 60% of the cohort (n = 10,673), stage II was approximately 30% (n = 5336), and stage III was 10% (n = 1779) of patients. A large proportion

Table 1 Subgroup Rates Between Anthracycline and Nonanthracycline-Based and Chemotherapy and Nonchemotherapy Regimens

	Chemotherapy and Anthracycline (n = 3458)		P	Chemotherapy/No Anthracycline (n = 2166)		No Chemotherapy (n = 9773)		P
	n	%		n	%	n	%	
Age at Diagnosis, Years								
<65	3000	65.5	<.001[a]	1581	34.5	4949	51.9	<.001[b]
≥65	458	43.9		585	56.1	4824	82.2	
Diagnosis Date								
2006-2009	1349	69.5	<.001	593	30.5	2697	58.1	<.001
2010-2015	2109	57.3		1573	42.7	7076	65.8	
Stage								
I	446	32.9	<.001	910	67.1	7543	84.8	<.001
II	1836	63.9		1039	36.1	2002	41.0	
III	1176	84.4		217	15.6	228	14.1	
Grade[c]								
I	462	55.0	<.001	378	45.0	3962	82.5	<.001
II	1682	67.3		1083	32.7	4743	63.2	
III	1234	64.7		672	35.3	817	30.0	
Race								
Black	478	66.3	<.001	243	33.7	1173	61.9	<.001
White	2799	42.7		3750	57.3	8258	55.8	
Other	127	19.5		91	80.5	342	34.4	
Oncotype								
Low	2826	70.7	<.001	1169	29.3	8267	67.4	<.001
Intermediate	186	22.4		643	77.6	1340	61.8	
High	184	39.0		288	61.0	56	10.6	
Lymph Node								
Positive	3456	61.5	<.001	2165	38.5	9751	63.4	<.001
Negative	2	66.7		1	33.3	22	88.0	
Surgery[c]								
Mastectomy	24	57.1	.05	18	42.9	51	54.8	.33
Lumpectomy	1471	53.5		1280	46.5	7269	72.5	
No surgery	1927	69.3		855	30.7	2392	46.2	
ER$^-$	138	71.9	<.001	54	28.1	33	14.7	<.001
ER$^+$	3320	61.1		2112	38.9	9740	64.2	
PR$^-$	589	60.7	<.001	382	39.3	834	46.2	.001
PR$^+$	2869	61.7		1784	38.3	8939	65.8	

Abbreviations: ER = estrogen receptor; PR = progesterone receptor.
[a]Between anthracycline group significance.
[b]Between chemotherapy group significance.
[c]1% to 2% missing a score.

(79.7%; n = 14,175) had a Charlson Comorbidity Index of 0, 10.4% (n = 1843) had a score of 1, and 9.9% (n = 1770) had scores of ≥2. Most patients had lumpectomy with radiation as opposed to mastectomy (66% vs. 33%). Most patients were estrogen receptor-positive (n = 17,527; 98.5%) and progesterone receptor-positive (15,724; 88.4%). There were 5624 (31.6%) who received chemotherapy and 9773 (54.9%) who received no chemotherapy.

Among the total study population, the 21-gene assay was performed in 7205 patients (40.5%) and anthracyclines were used by 3489 (19.6%) patients. Among those with the assay performed, anthracyclines were used by 441 (6.5%) patients (see Table 1). There was a significant association between breast cancer stage and anthracycline use ($P < .001$). Anthracycline was used among 4.3% (n = 459) of patients with stage I breast cancer, 34% (n = 1814) of stage II patients, and 69% (n = 1227) of stage III patients.

The use of anthracyclines significantly declined over time. Of the 5356 patients who were eligible for evaluation from 2006 to 2010, 24.3% (n = 1301) received an anthracycline. Of the 12,432

patients eligible for evaluation from 2010 to 2015, 17.5% (n = 2175) received an anthracycline ($P < .001$).

Use of anthracyclines significantly declined with age. Anthracycline was used among 40% (n = 10,559) of patients younger than 65 years old and 6.4% (n = 7229) among patients aged 65 years and older ($P < .001$). The average age of patients who received an anthracycline was 52.6 years, whereas the average age of patients who did not receive an anthracycline was 63.4 years ($P < .001$).

Recurrence scores were available for 6741 of patients in the database and missing (or not done) in 10,583. Among those patients with testing, the recurrence score was significantly associated with anthracycline use ($P < .001$). Anthracycline use increased as scores increased (Figure 1): 1.6% of low score patients (n = 3871), 8.2% of intermediate score patients (n = 2310), and 33.6% of high score patients received anthracycline.

There was a substantial number among those without assay scores who received anthracycline (n = 2762; 26.1%). This group was more ill (Charlson Comorbidity Index 1 = 12%, >1 = 11.5%), higher stage (stage 3 = 14.1%), and older (older than 65 years = 47.1%) then the group who had testing ($P < .001$ for each).

We also evaluated patients stratified according to recurrence score and lymph node status (Figure 2).

A total of 17,756 (99.8%) of patients were node-positive and 32 (0.2%) were node-negative. The rate of anthracycline use among node-positive patients overall was 19.6% (n = 3487). Anthracycline use according to recurrence group for these patients increased significantly as scores increased (Figure 2A). Also, among node-positive patients, anthracycline was significantly more likely for those without a score (26.2%) than among patients with a recurrence score at 6.6% ($P < .001$). Among node-negative patients, only 2 had received anthracycline (Figure 2B) and both did not have genetic test scores reported. Only 1 patient had a score (intermediate) although that patient did not receive anthracycline.

Furthermore, patients with low recurrence scores were significantly more likely to receive chemotherapy (anthracycline- or nonanthracycline-based regimens) if they were lymph node-positive (10% anthracycline-based chemotherapy/23% nonanthracycline-based chemotherapy) compared with lymph node-negative patients or those with micrometastasis (1% anthracycline-based chemotherapy/2.5% nonanthracycline-based chemotherapy; $P < .001$). Patients with intermediate recurrence scores were significantly more likely to receive anthracycline-based chemotherapy if they were lymph node-positive (16.4%) compared with lymph node-negative patients or those with micrometastasis (7%; $P < .001$). However, there was no significant difference according to node status in the use of nonanthracycline-based chemotherapy (30% vs. 27.6%, respectively; $P = .45$). Patients with high recurrence scores were significantly more likely to receive anthracycline-based chemotherapy if they were lymph node-positive (47.5%) compared with lymph node-negative patients or those with micrometastasis (32%; $P = .02$). There was no significant difference according to node status in the use of nonanthracycline-based chemotherapy (49.2% vs. 51.6%, respectively; $P = .72$). Patients who had a high recurrence score and were lymph node-positive were just as likely to receive an anthracycline-based regimen as a nonanthracycline based one (47.5% vs. 49.2%; $P = .89$).

Bivariate analysis among patients who were node-negative showed no association between recurrence score and anthracycline use ($r = -0.05$; $P = .78$). Bivariate analysis among all node-positive patients showed a highly significant positive association between the recurrence score and having anthracycline treatment ($r = 0.35$; $P < .001$). Higher scores were associated with higher rates of anthracycline use. The multivariate regression analysis showed that the recurrence score was a highly significant independent predictor of anthracycline use before and after adjustment for nodal status, stage, age, Charlson Comorbidity Index, and race ($\beta = 0.33$; $P < .001$). Higher scores (0-100) predicted higher rates of anthracycline use. Cancer stage, age, and the Charlson Comorbidity Index were also independent predictors of anthracycline use in the adjusted model ($P < .001$, $P < .001$, and $P = .02$, respectively). Higher stage (1-3), lower Charlson Comorbidity Index (0-21), and younger age (<65 years) were more likely to receive anthracycline.

Discussion

Anthracyclines have been the backbone of breast cancer chemotherapy regimens for the past 3 decades. However, despite its potent activity against breast carcinoma, it is not without significant toxicities. Dilated cardiomyopathy is one of the more serious side effects of doxorubicin, which can lead to congestive heart failure. Studies have shown up to a 5.5% incidence of cardiac toxicity with doxorubicin.[7] Anthracyclines also lead to late-onset acute leukemia or myelodysplastic syndrome.[8] These serious adverse events have prompted investigation into nonanthracycline-containing regimens that might be just as effective. Physician awareness of these severe toxicities along with development of equally efficacious regimens has caused the use of anthracyclines to decrease in recent years.[14]

An ongoing study by US Oncology Research is comparing a taxane used with cyclophosphamide with a taxane used with doxorubicin/cyclophosphamide in the hopes of definitively determining whether anthracyclines are necessary in early stage breast cancer.[15] Preliminary results reveal a 3-year invasive disease-free survival of 94.1% with docetaxel and cyclophosphamide regimen (TC) and 93.7% with anthracycline and taxane regimen for HR^+ disease. This study also looks at the presence of the topoisomerase 2-α inhibitor gene, present in approximately 5% to 10% of $HER2^-$ breast cancers, which might be a marker to predict which patients will benefit from an anthracycline. The National Surgical Adjuvant Breast and Bowel Project is also evaluating an anthracycline-based regimen versus a nonanthracycline-based regimen.[9] Three different arms will be used in the adjuvant setting, doxorubicin with docetaxel/cyclophosphamide compared with docetaxel/cyclophosphamide and docetaxel/cyclophosphamide/bevacizumab. It is the first study to evaluate the role of doxorubicin in taxane-based adjuvant therapy of $HER2^-$ breast cancer. A joint efficacy analysis was published in April, 2017. Results showed a statistically significant improvement in the invasive disease-free survival for anthracyclines (hazard ratio, 1.23; 95% confidence interval, 1.01-1.5; $P = .04$). The benefits were more evident in the studies with longer follow-up, however, the absolute benefits were small (study with 4-year rates: 88.2% TC6 vs. 90.7% doxorubicin and cyclophosphamide regimen with a taxane (TaxAC); absolute difference:

2.5%) and the combined median follow-up was only 2.2 years. The studies continue in follow-up. This study, along with the Eastern Cooperative Oncology Group 5103 will not only ascertain the effectiveness of bevacizumab in the adjuvant setting, but whether doxorubicin is needed in combination.[16]

Further effort is being put forth to determine the role of the RT-PCR recurrence score in HR$^+$, lymph node-positive breast cancer. SWOG S1007 is a randomized phase III clinical trial comparing hormone receptor therapy with or without chemotherapy in patients with 1 to 3 positive lymph nodes and recurrence score of 0 to 25.[17] Validating the RT-PCR recurrence score for lymph node-positive patients has the potential to affect a significant group of patients who otherwise might receive very little benefit from chemotherapy, whether anthracycline- or nonanthracycline-based.

In our analysis, anthracyclines were used significantly less often in patients who were older, lower stage, and lymph node-negative. Despite no randomized data supporting the use of the 21-gene assay recurrence score to influence the selection of chemotherapy we observe that patients were significantly more likely to avoid anthracyclines with a low recurrence score. Additionally, the use of anthracyclines showed a significant decrease from 2006 to 2010 compared with 2010 to 2015. Lymph node status did not influence the choice to give nonanthracycline-based chemotherapy in patients with intermediate/high recurrence scores, but it did influence whether or not they received anthracycline-based chemotherapy. Patients in the high recurrence score/lymph node-positive group were just as likely to receive nonanthracycline-based chemotherapy as they were to receive an anthracycline-based regimen.

Strengths of this study include a large sample size with reliable data gathered from a prospective registry specifically designed to evaluate demographic characteristics, pathology, and treatment choices across the state of Michigan. Weaknesses include the retrospective design, which makes it difficult to control for all potential confounders, and the inability to evaluate patient outcomes on the basis of their treatment.

Studies are currently under way which will refine our understanding of who benefits from chemotherapy in the setting of early, HR$^+$ breast cancer, including the Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer study (TAILORx) and the Clinical Outcomes in ER+HER2-node-positive Breast Cancer Patients Who Were Treated According to the Recurrence Score Results: Evidence From a Large Prospectively Designed Registry (RxPonder).

Conclusion

Our data demonstrated that rates of anthracycline use are significantly less common for patients who were older, and had lower stage, and lymph node-negative cancer. Despite the lack of randomized trial data supporting the use of the 21-gene assay recurrence score to influence the selection of chemotherapy, these data indicate that medical oncologists might have been anticipating the results of TAILORx and RxPONDER trials and are using the oncotype recurrence score to aid selection of chemotherapy in an effort to avoid the potential serious complications associated with anthracyclines in patients least likely to receive benefit.

Clinical Practice Points

- Anthracyclines pose significant toxicities and their additional use with chemotherapy has decreased but continue to be widely prescribed.
- Nonanthracycline regimens are better tolerated and efforts to determine who can safely avoid anthracyclines has been ongoing.
- Among patients who had 21-gene assay scoring, rates of anthracycline use were less common in patients who were older, had lower stage cancer, and had lymph node-negative cancer.
- The use of the oncotype recurrence score to aid selection of chemotherapy might continue to increase with a potential corresponding decrease in serious complications associated with anthracycline use in patients least likely to benefit.

Disclosure

The authors have stated that they have no conflicts of interest.

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