Special Feature

Predictors and Temporal Trends of Adjuvant Aromatase Inhibitor Use in Breast Cancer

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Key Words

Aromatase inhibitors, tamoxifen, breast neoplasms, adjuvant therapy

Abstract

After the first report of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial, adjuvant aromatase inhibitor use increased rapidly among National Comprehensive Cancer Network member institutions. Increased aromatase inhibitor use was associated with older age, vascular disease, overexpression of human epidermal growth factor receptor 2 (HER2), or more advanced stage, and substantial variation was seen among institutions. This article examines adjuvant endocrine therapy in postmenopausal women after the first report of the trial, identifies temporal relationships in aromatase inhibitor use, and examines characteristics associated with choice of endocrine therapy among 4044 postmenopausal patients with hormone receptor–positive nonmetastatic breast cancer presenting from July 1997 to December 2004. Multivariable logistic regression analysis examined temporal associations and characteristics associated with aromatase inhibitor use. Time-trend analysis showed increased aromatase inhibitor and decreased tamoxifen use after release of ATAC results ($P < .0001$). In multivariable regression analysis, institution ($P < .0001$), vascular disease ($P < .0001$), age ($P = .0002$), stage ($P = .0002$), and HER2 status ($P = .0009$) independently predicted aromatase inhibitor use. Institutional rates of use ranged from 15% to 66%. Adjuvant aromatase inhibitor use increased after the first report of ATAC, with this increase associated with older age, vascular disease, overexpression of HER2, or more advanced stage. Substantial variation was seen among institutions. (*JNCCN* 2009;7:115–121)

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Adjuvant endocrine therapy has been shown to decrease recurrences and deaths in women with hormone receptor [HR]–positive or unknown breast cancer. Until recently, tamoxifen was the only adjuvant endocrine therapy with proven efficacy in postmenopausal women. Treatment with this agent for 5 years confers relative risk reductions of 41% in the annual odds of recurrence and a 33% in the annual odds of death.[1]

In 1996, the FDA approved the selective aromatase inhibitor anastrozole for the treatment of metastatic HR-positive breast cancer. The effectiveness of the selective aromatase inhibitors for treating metastatic breast cancer led to the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, which compared the adjuvant use of anastrozole, tamoxifen, or anastrozole plus tamoxifen in postmenopausal women with early-stage breast cancer.[2,3] In December 2001, the initial results of the ATAC trial (median follow-up 33 months) were released, with anastrozole associated with improved disease-free survival (DFS; hazard ratio [HR], 0.78; $P = .005$), time to recurrence (HR, 0.73; $P = .003$), and risk for contralateral breast cancer (odds ratio, 0.42; $P = .007$). No difference was seen between tamoxifen alone versus tamoxifen plus anastrozole. Updated results (median follow-up, 68 months) confirmed the efficacy and tolerability of anastrozole over tamoxifen.[4]

Other large randomized trials subsequently supported adjuvant aromatase inhibitor use in postmenopausal women. Early results from Breast International Group 01-98 show improvement in DFS with 5 years of adjuvant letrozole compared with tamoxifen.[5] The MA-17 trial showed improvement in DFS with 5 years of extended letrozole versus placebo after approximately 5 years of initial adjuvant tamoxifen. Subset analysis in MA-17 found improved overall survival with letrozole in axillary lymph node–positive breast cancer.[6]

The Intergroup Exemestane Study showed improved DFS with sequential exemestane after 2 to 3 years of tamoxifen for a total 5 years of therapy.[7] The Italian Tamoxifen Study showed improvement in DFS with anastrozole after 2 to 3 years of tamoxifen for a total 5 years of therapy, compared with 5 years of tamoxifen.[8] The Austrian Breast and Colorectal Cancer Study Group Trial 8 and the Arimidex-Nolvadex 95 Trial reported superior event-free survival for switching to anastrozole after 2 years of tamoxifen compared with tamoxifen alone.[9] Although the results of these studies show the importance of aromatase inhibitors in treating early-stage breast cancer in postmenopausal women, only the initial results of the MA-17 trial were available during the late period of the current study.

The results of the ATAC trial had the potential to significantly change the adjuvant endocrine therapy and outcomes in women with early-stage breast cancer. In December 2001, the NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org) were amended to include anastrozole as an alternative to tamoxifen in the initial adjuvant treatment of postmenopausal women.[10]

The current analysis was performed to examine the patterns and determinants of initial adjuvant endocrine therapy at NCCN institutions and identify temporal relationships between the release of ATAC data and aromatase inhibitor use as the first adjuvant endocrine treatment of postmenopausal women with HR-positive stages I to III invasive breast cancer.

Methods

Data Source

The NCCN Breast Cancer Outcomes Database Project has been collecting prospective data on patient and tumor characteristics, treatment, and outcomes on patients with newly diagnosed breast cancer at participating NCCN institutions since 1997.[11] Clinical and treatment information is gathered from tumor registries, chart review, and in- and outpatient records.

A patient-reported survey is conducted at first presentation to a participating institution to collect information on patient characteristics, such as menopausal, educational, employment, and performance status, and comorbidity. The data are subject to rigorous quality assurance and include onsite audits against source documentation. Each center is an academic cancer center, and the surgical and medical oncologists treating breast cancer at these institutions generally devote most or all of their clinical effort to breast cancer care. The Institutional Review Board (IRB) at each center approved the data collection process, transmission methods, and storage protocols. When the IRB required project-specific signed informed consent for data collection, only patients who provided consent were included in this analysis.

Cohort

The study cohort consisted of women with newly diagnosed stages I to III (according to the *American Joint Committee on Cancer* 5th and 6th editions) unilateral breast cancer presenting for care between July 1, 1997, and December 31, 2004, and receiving care for at least 365 days after their first visit at one of the NCCN institutions participating in the NCCN Breast Cancer Outcomes Database Project, including City of Hope, Dana-Farber Cancer Institute, Fox Chase Cancer Center, The University of Texas M. D. Anderson Cancer Center, Roswell Park Cancer Institute, University of Michigan Comprehensive Cancer Center, Arthur G. James Cancer Hospital & Richard J. Solove Research Institute at The Ohio State University, H. Lee Moffitt Cancer Center & Research Institute, UNMC Eppley Cancer Center at The Nebraska Medical Center, and Stanford Comprehensive Cancer Center.[11] Researchers identified patients who were postmenopausal at breast cancer diagnosis and had HR-positive disease.

This study included 5077 eligible postmenopausal patients with HR-positive or -unknown disease. Patients were excluded who transferred their care (n = 179), underwent bone marrow transplantation (n = 20), were diagnosed with a different cancer (n = 29), or died (n = 47) within a year of their first visit to the NCCN institution. Those with tubular,

colloid, or adenoid cystic histology only or with ductal carcinoma in situ and a positive axillary lymph node detected using immunohistochemistry were also excluded (n = 263). Finally, patients were excluded who did not undergo cancer-directed surgery (n = 32), underwent neoadjuvant endocrine or radiation therapy (n = 32), or were registered on a protocol that determined endocrine therapy use within their first year of care at the institution (n = 431). The final cohort consisted of 4044 postmenopausal women with HR-positive or -unknown stages I to III invasive breast cancer.

Variable Definitions

Women were classified as postmenopausal if they had no menses in the past 6 months because of natural menopause, removal of both ovaries, chemotherapy, radiation or endocrine therapy for a prior non–breast cancer, ovarian failure from a medical condition, or a menstrual period in the past 6 months while on hormone replacement. Patients with contradictory or missing data were classified as postmenopausal if they were aged 50 years or older. Hormone receptor status is defined as positive if estrogen receptor (ER)–positive and/or progesterone receptor (PR)–positive or if both ER- and PR-unknown. History of myocardial infarction or cerebrovascular disease was documented as a comorbidity at presentation to the NCCN center using the Charlson Index or the modified version of that index using a patient survey.[12,13] Human epidermal growth factor receptor 2 (HER2) overexpression is defined as a positive fluorescence in situ hybridization (FISH) result, or an immunohistochemical result of 3 or more, "high positive," or "positive nitric oxide synthase" (NOS) when a FISH result was not available.

Definition of Receipt of Adjuvant Endocrine Therapy

Patients were considered to have undergone adjuvant endocrine therapy if a start date for endocrine therapy was scheduled after breast cancer was diagnosed, before any recurrence, and within 365 days of first presentation to an NCCN institution. Patients were considered to have undergone adjuvant systemic therapy if either chemotherapy or hormone therapy was prescribed within 365 days of first presentation to the institution, and before development of recurrent disease. For analysis of time trends, adjuvant endocrine therapy use was plotted according to the start date of endocrine therapy.

Statistical Analysis

Descriptive statistics of patient and tumor characteristics and initial endocrine therapy use were examined in the full cohort. Among the 3425 postmenopausal women who underwent adjuvant endocrine therapy, we first examined whether there was a statistically significant association between timing of receipt of initial endocrine therapy and type of therapy (adjuvant tamoxifen vs. aromatase inhibitor), controlling for various factors from July 1997 to December 2004. Next, to identify a specific temporal association between the release of clinical trial data and the adoption of aromatase inhibitor use in initial adjuvant treatment, we limited our cohort to those who received endocrine treatment from January 1, 2002 to December 31, 2004 (n = 1546).

Univariate and multivariable logistic regression analyses were performed examining potential relationships with candidate predictors that had a *P* value of .20 in the univariate model. These predictors included timing of endocrine therapy; NCCN institution; age at diagnosis; tumor stage; histologic grade; hormone receptor status; HER2 status; presence of comorbidities, including history of myocardial infarction or vascular disease; health insurance; prior hysterectomy; and history of chemotherapy. The multivariable models also explored potential interactions between preidentified predictor variables. Two-sided *P* values are derived from this model.

Because a small sample size (n = 67) made formal modeling unreliable, the authors also used descriptive statistics to examine initial aromatase inhibitor use before clinical trial data were released. All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Results

Patient Characteristics

The 4044 postmenopausal women with HR-positive or -unknown stages I to III breast cancer had a median age at diagnosis of 62 years (range, 31–94 years; Table 1). Preexisting vascular disease was present in 5% of patients, 3% had a history of myocardial infarction, and 21% had undergone a hysterectomy. Adjuvant chemotherapy was administered to 41%. Most women (86%) had either managed care or Medicare.

Table 1 Presenting Characteristics for 4044 Postmenopausal Women with Hormone Receptor–Positive/Unknown, Stages I, II, or III Breast Cancer*

Age at Diagnosis in Years (median [minimum–maximum])	61.7 [31.1–93.6]	
	n	%
Stage at Diagnosis		
Stage I	2276	56.3
Stage II	1507	37.3
Stage III	261	6.4
Age at Diagnosis		
< 50	231	5.7
50–59	1527	37.8
60–69	1284	31.7
70+	1001	24.8
Pathologic Tumor Size		
≤ 0.5 cm or microinvasive	464	11.5
0.6–1 cm	891	22.0
> 1–3 cm	2281	56.4
> 3 cm	341	8.4
Unknown	67	1.7
Nodal Status		
Node negative	2697	66.7
1–3	905	22.4
4–9	268	6.6
10+	152	3.8
Not applicable	22	0.5
Histologic Grade		
Low	644	15.9
Intermediate	1933	47.9
High	1138	28.1
Unknown	329	8.1
Hormone Receptor		
ER+/PR+	2962	73.2
ER+/PR-	836	20.7
ER-/PR+	86	2.1
ER+/PR unknown	36	0.9
ER unknown/PR unknown	124	3.1
HER2 Status†		
Overexpressed	377	9.3
Not overexpressed	2670	66.0
Unknown	246	6.1
Not performed	751	18.6
Hysterectomy		
Yes	846	20.9
No	3067	75.9
Unknown	131	3.2
Comorbidity		
0 - No comorbidity	2897	71.6
1+ - Comorbidity	1147	28.4
History of Myocardial Infarction		
No	3942	97.5
Yes	102	2.5
History of Cerebrovascular Disease		
No	3856	95.4
Yes	188	4.6
Health Insurance		
Managed	1950	48.2
Indemnity	338	8.4
Medicaid/indigent	117	2.9
Medicare	1520	37.6
Self-pay	79	1.9
Other	21	0.5
Unknown	19	0.5
Receipt of Chemotherapy		
Yes	1674	41.4
No	2379	58.6

*Excluding women enrolled in clinical trials specifying endocrine therapy.
†HER2 overexpressed: positive fluorescence in situ hybridization result or a 3+, "high positive," or "positive nitric oxide synthase" immunohistochemistry result if fluorescence in situ hybridization unavailable.

Tumor Characteristics

All breast cancers in the cohort were HR-positive or -unknown. ERs and PRs were positive in 73% of patients; 21% were ER-positive but PR-negative; 2% were PR-positive and ER-negative; and 4% were both unknown. Tumor stage was 56% stage I, 37% stage II, and 7% stage III. Tumors were of low or intermediate grade in 64%, 67% of patients were lymph node-negative, and 9% overexpressed HER2 (Table 1).

Initial Endocrine Therapy Use

Adjuvant endocrine therapy was prescribed for 3448 (85%) of the 4044 women in the total cohort. Among these, 77% received tamoxifen, 21% anastrozole, and 2% letrozole or exemestane. Fewer than 1% (n = 23) of patients underwent another form of endocrine therapy (raloxifene, toremifene, megesterol acetate, or ovarian ablation) and were excluded from univariate and multivariable models.

Temporal Trends and Predictors of Initial Endocrine Therapy

The proportion of postmenopausal patients with HR-positive or -unknown breast cancer who received aromatase inhibitor as initial endocrine therapy increased dramatically after the release of ATAC results in December of 2001 (Figure 1). A concomitant decrease in tamoxifen use ($P < .0001$) was seen controlling for NCCN institution, age, stage, HER2 status, and history of vascular disease. Several factors were independently associated with aromatase inhibitor use, including age older than 50 years ($P = .0002$), history of vascular disease ($P < .0001$), higher disease stage ($P = .0002$),

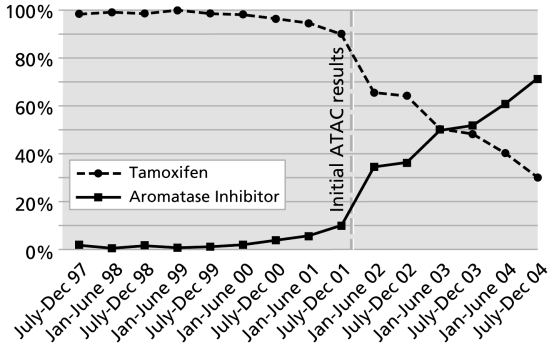

Figure 1 Time trend analysis: initial endocrine therapy among postmenopausal women with hormone receptor–positive/–unknown breast cancer receiving treatment from July 1997 to December 2004 (n = 3425). Time trend analysis showed an increase in aromatase inhibitor use after the release of Arimidex, Tamoxifen, Alone or in Combination trial (ATAC) results ($P < .0001$ controlling for NCCN institution, age, tumor size, lymph node status, histologic grade, HER2 status, and history of vascular disease).

HER2 overexpression ($P = .0009$), and NCCN institution ($P < .0001$; Table 2). Other variables that did not predict for aromatase inhibitor use were histologic grade, comorbidities other than vascular disease, prior hysterectomy, receipt of chemotherapy, and health insurance status. Hormone receptor and joint ER/PR status were also analyzed and did not predict for the use of aromatase inhibitor over tamoxifen.

The NCCN institution at which treatment was given was significantly associated with aromatase inhibitor use. From January 1, 2002, to December 31, 2004, institutional rates of aromatase inhibitor use across NCCN ranged from 15% to 66% (Figure 2).

Endocrine Therapy Use Prior to ATAC Results

Before the release of ATAC data in December of 2001, few women were prescribed an aromatase inhibitor in the adjuvant setting at NCCN institutions, with only 0.25% of women being treated with an endocrine agent were prescribed an aromatase inhibitor (n = 67). Although the sample size is not large enough to perform formal multivariable logistic regression modeling, descriptive analysis showed that subjects were more likely to receive an aromatase inhibitor if older, had a history of vascular disease, did not have a hysterectomy, or had HER2-negative disease. Tumor stage, histologic grade, and NCCN institution did not seem to influence the use of an aromatase inhibitor before January 1, 2002.

Discussion

The selective aromatase inhibitors have improved the long-term outcome for postmenopausal patients with HR-positive breast cancer. This study was designed to assess the temporal relationship between the emergence of high-impact clinical trial data, provided by the ATAC report in December 2001, and the adoption of these data at participating NCCN institutions, and to examine patient and tumor characteristics that may have predicted for the use of aromatase inhibitor. In December 2001, the NCCN Breast Cancer Guidelines Panel changed its guidelines to include anastrozole as an alternative to tamoxifen after the initial ATAC report.

In contrast, the ASCO Technology Assessment on the Use of Aromatase Inhibitors panel, which published its recommendations in May 2002, identified tamoxifen as the standard adjuvant endocrine therapy for women with HR-positive breast cancer. The ASCO panel stated that although the ATAC results were promising, they were insufficient to change standard practice at that time.[14] More recently, NCCN and ASCO recommendations became harmonious in recommending the incorporation of adjuvant aromatase inhibitors into the treatment of postmenopausal women with early-stage, HR-positive breast cancer.[15–17]

A recent analysis from structured interviews with 150 practicing medical oncologists from 4 different

Table 2 Predictors of Initial Endocrine Therapy*

	Odds Ratio	95% CI	P Value
Time			< .0001
NCCN Institution			< .0001
Age at Diagnosis (y)			.0002
< 50	1.0		
50–59	2.6	1.5–4.6	
60–69	2.9	1.6–5.1	
> 70	3.8	2.1–6.8	
History of Vascular Disease			< .0001
No	1.0		
Yes	4.4	2.2–8.7	
Stage			
I	1.0		.0002
II	1.6	1.3–2.1	
III	1.8	1.2–2.8	
HER2 Status			.0009
Not overexpressed	1.0		
Overexpressed	2.2	1.5–3.3	
Unknown	1.1	0.4–2.8	
Not performed	0.8	0.4–1.5	

*Therapy was aromatase inhibitor vs. tamoxifen among postmenopausal women with hormone receptor–positive/–unknown breast cancer undergoing treatment on or after January 1, 2002 (N = 1546).

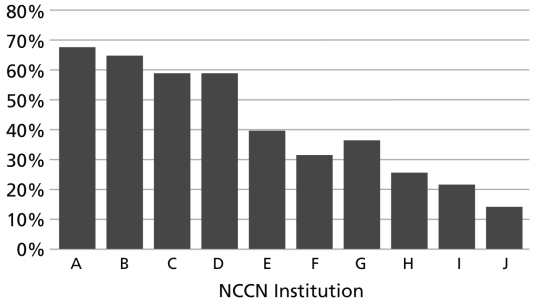

Figure 2 Variation in aromatase inhibitor use across NCCN institutions from January 2002 through September 2004. Each bar represents one NCCN institution.

geographic regions in the United States reported an increase in anastrozole use from 2% in July 2001 to 53% in November 2003 ($P < .05$), with a corresponding decline in tamoxifen use (93% in July 2001 to 40% in November 2003; $P < .05$).[18]

The authors' analysis is the first large retrospective study that uses an established database to address the practice patterns of use of adjuvant aromatase inhibitors in the United States. Among 4044 postmenopausal women with HR-positive or -unknown stages I to III breast cancer, 85% were prescribed adjuvant endocrine therapy, with 19% of the group receiving a third-generation aromatase inhibitor (anastrozole, letrozole, or exemestane). After the release of the ATAC data in December 2001, and subsequent modification of the NCCN Breast Cancer Guidelines to include anastrozole as an alternative to tamoxifen, a temporally related increase in the adjuvant use of aromatase inhibitors occurred at NCCN institutions.

The authors' results confirm and extend the results from the Cancer Research Network, which has a common database, including members of 13 integrated health care delivery systems that are part of the HMO Research Network. The Cancer Research Network investigators documented an increase in the use of aromatase inhibitors from 2002 through 2003, similar to those observed in the NCCN institutions. However, in the Cancer Research Network study, it was not possible to unequivocally distinguish between the use of aromatase inhibitors in adjuvant treatment from use in the metastatic setting.[19]

Significant variability in the use of adjuvant aromatase inhibitors occurred among NCCN institutions. The differences seen among NCCN centers may be from different interpretations of the maturity of the ATAC data by the expert oncologists at these centers, a difference in interpretation also reflected in the NCCN guidelines and ASCO Technology Assessment at the time. Alternatively, the change in practice pattern may not relate to guidelines per se, but to other undefined factors, such as selection of the alternate strategy of tamoxifen followed by sequential or extended aromatase inhibitor. The authors believe this is unlikely, however, because the first reports of sequential or extended aromatase inhibitor therapy after tamoxifen occurred either very late during or after the study period. This analysis of the NCCN database did not include data on sequential endocrine therapies, because women were not yet followed up long enough to become eligible for extended adjuvant aromatase inhibitor therapy.

Certain patient and tumor characteristics significantly predicted for the more frequent use of aromatase inhibitors. Older patients were more likely to be prescribed aromatase inhibitor rather than tamoxifen, possibly because of differences in reported side-effect profiles. Patients with a more advanced stage of disease or whose tumors overexpressed HER2 were more likely to be prescribed aromatase inhibitor. Although the ATAC trial did not show a greater benefit from anastrozole with more advanced disease or HER2-positive tumors, clinicians may be more apt to adopt a new therapy when disease seems to be more aggressive.

Patients with a history of cerebrovascular, peripheral vascular, or thromboembolic disease were more likely to be prescribed an aromatase inhibitor, probably because of the more favorable side-effect profile for vascular events.[4] An intact uterus did not predict for aromatase inhibitor use over tamoxifen, although one might expect increased aromatase inhibitor use because of the increased risk for endometrial cancer associated with tamoxifen use in these women.[20] The effect of bone health on prescribing patterns could not be examined because the NCCN database does not collect this information.

Subset analysis of the ATAC trial showed a greater risk reduction from anastrozole use in patients whose tumors were ER-positive and PR-negative ($P = .05$).[21] However, analysis did not determine that the combination of ER and PR status had a significant influence on endocrine therapy choice within the cohort that was HR-positive or -unknown.

The receipt of adjuvant chemotherapy or health insurance status and type did not seem to influence the endocrine therapy prescribed, despite issues concerning treatment cost.

Interestingly, before December 2001, a small number of women received adjuvant aromatase inhibitors (0.25% of the final cohort). These women were more likely to be older, have a history of vascular disease, have no history of hysterectomy, and have HER2-negative disease. However, the NCCN institution at which they were treated and the stage and histologic grade of their disease did not significantly influence their prescribed treatment. These women were being treated with adjuvant aromatase inhibitors before data supporting the use of aromatase inhibitors were available.

The authors did not collect information from individual clinicians on the choice of therapy, but possible reasons may be an extrapolation of data from the preclinical or metastatic setting to the adjuvant setting, especially for patients who had a contraindication to tamoxifen, or because the patients declined tamoxifen as an adjuvant therapy. Clinicians were also likely aware of the large ATAC trial underway and may have been anticipating favorable results.

Initial aromatase inhibitor therapy is now the most commonly administered adjuvant endocrine therapy for early-stage breast cancer in postmenopausal women treated at NCCN institutions. After the initial release of ATAC data, some NCCN practitioners were early and rapid adopters of anastrozole as adjuvant therapy, using specific patient and tumor characteristics to guide them, whereas others waited for more mature data and the results of more studies before adopting the aromatase inhibitors. This study suggests that the release of preliminary high-impact clinical trial data rapidly influenced oncologic practice at some NCCN institutions, whereas others were slower to adopt the use of adjuvant anastrozole. This study could not identify the origin of this heterogeneity in rates of adopting new technology.

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