How Rapidly Do Oncologists Respond to Clinical Trial Data?

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ABSTRACT

In the era of evidence-based medicine, convincing clinical trial data should influence clinical practice if disseminated in an appropriate manner. Here we discuss the influence of clinical trial results from the Arimidex, Tamoxifen Alone or in Combination trial on the usage of tamoxifen and anastrozole in the treatment of postmenopausal women with hormone receptor-positive early breast cancer. Data were derived from structured interviews with practicing medical oncologists over a period of 28 months. The overall use of hormonal therapy was high and increasing over the period studied. Significant increases in the use of anastrozole as adjuvant hormonal therapy were accompanied by significant decreases in the use of tamoxifen. This culminated in the use of anastrozole surpassing tamoxifen use by the end of the study period, accounting for over 50% of hormonal therapy use for postmenopausal early breast cancer. This study suggests that the dissemination of key clinical data, accompanied by professional commentary and regulatory actions, can rapidly influence the clinical practice of medical oncologists.

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Learning Objectives

After completing this course, the reader will be able to:

1. Define the role of aromatase inhibitors in the treatment of early breast cancer.
2. Describe trends in the use of aromatase inhibitors to treat early-stage breast cancer.
3. Discuss U.S. trends over time in the use of aromatase inhibitors in the past 3 years.

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INTRODUCTION

There are many factors that may influence clinical practice. Scientific and clinical trial data, information awareness among community physicians and influential opinion leaders, marketing, public knowledge, and product features are among these factors [1].

In this era of evidence-based medicine, large clinical trials can and should have a profound impact upon clinical practice. The influence of positive data on the use of lipid-lowering agents was clearly seen in the 3.6-fold increase in monthly statin use after publication [2]. Conversely, the use of α-blockers in hypertension decreased by 54% between...

The weight given to specific published findings and guidelines may influence the speed at which practice patterns may change. There are relatively few studies assessing the influence of clinical trials on the practice of oncology, perhaps due to the complexity of trial designs and differing patient populations. One extensive analysis examined and modeled changes in adjuvant chemotherapy and tamoxifen therapy for early breast cancer (EBC) in relation to dissemination of trial data [5]. Although clinical trial data appeared to be disseminated fairly rapidly to both physicians and patients, the increase to approximately 70% in tamoxifen use in stage II/IIIA patients (aged 50–69 years) still took 10 years to occur (1981-1991) [5].

Evidence-based guidelines, such as the National Comprehensive Cancer Network (NCCN) guidelines for oncology [6], are generated following categorization of data from relevant clinical trials to assist physicians in translating trial data into practice. Clinical trial data are also commented on by professional societies, such as the American Society for Clinical Oncology (ASCO) [7], aiding the understanding of new waves of data. In specific medical specialties, there is, however, contradictory evidence as to the degree which guidelines are followed [8, 9].

Although breast cancer is the most common female cancer in the Western world [10], the mortality rate fell during the 1990s, largely due to improved diagnostics and therapies [11, 12]. There are now a range of endocrine therapies available for the treatment of breast cancer in hormone receptor-positive postmenopausal women that have contributed to these improvements. Tamoxifen has been an established treatment for patients with hormone receptor-positive breast cancer and has been the adjuvant endocrine treatment of choice for many years [13–15]. A new class of drugs for hormonal therapy, the aromatase inhibitors (AIs), was introduced in 1996, initially for metastatic breast cancer. The ATAC trial (Arimidex, Tamoxifen Alone or in Combination) was initiated to test the hypotheses that the AI anastrozole was non-inferior or superior to tamoxifen and that the combination of anastrozole and tamoxifen was superior to tamoxifen alone as adjuvant therapy over a 5-year period [16, 17].

The present study examines the impact of presentation and publication of the results from this very large EBC clinical trial on the practice of oncologists.

**Research Methods**

**Participants**

A nationally representative stratified quota sampling of 150 medical oncologists was recruited per study period (see below). All physicians were board certified and had been in practice for at least 2 years but not more than 30 years. The physicians had at least 50% office or private practice and had managed or treated at least 10 breast cancer patients within the past 30 days.

Using Intercontinental Marketing Services data, medical oncologists who wrote 100 or more hormonal therapy prescriptions for breast cancer in the past 6 months qualified for each time period. Oncologists were stratified by use of hormonal therapy for breast cancer in the 6 months preceding the interview as follows: group 1: 100–571 prescriptions, group 2: 572–870 prescriptions, and group 3: >870 prescriptions. The sample was randomly selected from each stratum to include: 75 group 1 (50%), 45 group 2 (30%), and 30 group 3 (20%) (except for July 2001, which contained 67%, 21%, and 12% of the three groups, respectively). To allow for a comparison of trend between the July 2001 sample and the other time points, the responses of the July 2001 sample were adjusted to reflect the mix at 50% group 1, 30% group 2, and 20% group 3.

**Data Collection**

Data were collected via structured computer-assisted telephone interviews of 45-60 minutes duration. Predefined questions were used (Table 1). Interviews were conducted over 3–4 weeks. Eight study periods were used for analysis: July 2001, March 2002, July 2002, November 2002, February 2003, June 2003, August 2003, and November 2003.

Oncologists were asked to report their first hormonal therapy choices for their last five postmenopausal patients with estrogen receptor (ER)-positive EBC (stage I and II).

**Statistical Analysis**

A t-test at the 95% confidence level ($p < 0.05$) was conducted to determine significant differences ($p < 0.05$) in

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<td>1. Thinking of the last five postmenopausal patients with ER-positive early- or adjuvant-stage breast cancer who you have treated in the past 3 months, what products, alone or in combination with other treatment modalities such as hormonal, chemotherapy, radiation, surgical, etc. did you use as first therapy?</td>
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<td>2. Please indicate the therapy you prescribed for your last five postmenopausal patients with early- or adjuvant-stage breast cancer.</td>
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<tr>
<td>3. If you used hormonal therapy, please specify the brand or product. Let’s start with patient #1... (Please use the number code[s] for each product used alone or in combination.) The total must equal five patients.</td>
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**Table 1. The predefined questions used to interview oncologists participating in the study**
hormonal therapy choices between and among different time periods.

**STUDY RESULTS**

**Physician Demographics**

At all time points, gender and geographic distributions of the participating medical oncologists were similar. The vast majority (81%–83%) of oncologists participating in the study were male. They were consistently divided across four geographic regions in the United States (northeast [26%–33%], north central [19%–25%], south [26%–33%], and west [17%–23%]).

Overall, there was minimal variation in the total number of breast cancer patients managed or treated across the time points. The mean number of breast cancer patients managed or treated per physician in the past 6 months ranged from 112–150 in group 1, 142-176 in group 2, and 192–284 in group 3. Across all time periods the medical oncologists consistently indicated that approximately 60% of their EBC patients were postmenopausal (59%–61%).

**Trends in Overall Use of Adjuvant Systemic Therapy**

The results obtained reflect the hormonal therapy choices of 150 oncologists for up to 750 total patients at each time period assessed. The overall reported use of hormonal therapy in postmenopausal ER-positive EBC patients was very high across all time periods, starting at 81% and rising to 98% of eligible patients receiving hormonal therapy (Fig. 1). A significant increase occurred from 81% in July 2001 to 91% in March 2002 ($p < 0.05$). Further significant increases occurred between March 2002 and July 2002 ($p < 0.05$) and again between July 2002 and November 2002 ($p < 0.05$). The use of hormonal therapy then remained stable at approximately 98% until the end of the study time period in November 2003.

The use of chemotherapy remained relatively stable over the time period studied, varying from 36% to 50% of breast cancer products and therapies prescribed (Fig. 1).

**Figure 2.** Impact of presentation and publication of ATAC results, professional discussions, and regulatory actions on use of adjuvant hormonal therapy for postmenopausal estrogen receptor-positive EBC. Abbreviation: SABC, San Antonio Breast Cancer Symposium.

*NCCN guidelines were first modified in December 2001 to allow consideration of anastrozole as an option.

**Figure 1.** Overall trends in use of adjuvant chemotherapy and hormonal therapy for postmenopausal patients with estrogen receptor-positive early breast cancer.

**Trends in the Use of Specific Adjuvant Hormonal Therapies**

The influence of the presentation and publication of the ATAC trial results and professional commentary and discussion, as well as the reported use of specific adjuvant hormonal therapies, are shown in Figure 2. Clinically relevant data publications and professional commentaries are presented along the time axis.

Over the time period assessed there were significant changes in the reported use of tamoxifen and anastrozole, but little change in the use of other hormonal agents. The significant increases in the trend in anastrozole prescribing was substantiated across the three strata of oncologists.

The first results of the ATAC trial were presented in December 2001 at the San Antonio Breast Cancer Symposium [18]. The trial data showed increased disease-free survival
Anastrozole use for adjuvant therapy rose from 27% of anastrozole over tamoxifen in efficacy endpoints and 2002 [24, 25]. These data continued to show the superiority at the San Antonio Breast Cancer Symposium in December with a median therapy duration of 36.9 months, were presented at the ASCO meeting in May 2002 [19-22]. The ASCO Health Services Research Committee assessment on the use of AIs was also presented at this ASCO meeting and published in August 2002 [23]. Although the committee found the ATAC results to be very promising, its opinion was that tamoxifen should remain the standard adjuvant therapy for EBC. The committee recommended that physicians discuss the available information with patients and, in making a decision, acknowledge that treatment approaches can change over time. As both efficacy and toxicity data for primary adjuvant use in EBC are only available for anastrozole, the committee recommended that anastrozole could be used if tamoxifen was contraindicated for a patient.

Further data from the ATAC trial comparing efficacy, safety, tolerability, and quality of life of patients receiving anastrozole compared with tamoxifen were presented at the ASCO meeting in May 2002 [19-22]. The ASCO technology assessment committee published an update on the use of AIs in the adjuvant setting in July 2002 [24, 25]. These data continued to show the superiority of anastrozole over tamoxifen in efficacy endpoints and confirmed the safety and tolerability picture from the earlier report. Anastrozole use for adjuvant therapy rose from 27% in November 2002 to 41% in February 2003 (p < 0.05).

The peer-reviewed analysis of the ATAC trial appeared in the Lancet in June 2002 [16]. Between March 2002 and July 2002, the use of anastrozole rose from 14%-22% of primary adjuvant hormonal therapies (p < 0.05).

Further, the use of anastrozole as an adjuvant therapy increased significantly over the study period, while the use of tamoxifen decreased significantly. By September 2003, anastrozole use had overtaken that of tamoxifen, and in November 2003 anastrozole represented 53% of reported hormonal therapy choices for ER-positive EBC postmenopausal women (Fig. 2). The usage levels of other hormonal therapies remained relatively constant over the time period evaluated (accounting for approximately 4%-8% of therapy choices). Along with the increase in use of anastrozole, there was a clear decline in tamoxifen use for EBC in postmenopausal women (from 93% in July 2001 to 40% of adjuvant hormonal therapy use in November 2003, p < 0.05).

**DISCUSSION**

The practice of oncology is strongly evidence based, but the rates at which new data are weighed and incorporated into current practice are difficult to track. Direct data that link changes in practice to the influence of specific publications are more widely available in other specialties, particularly cardiovascular medicine. However, Mariotto et al. [5] used large SEER databases to analyze trends in chemotherapy and tamoxifen use in breast cancer over the period of 1975 to 1999. The large but slow increase in the use of tamoxifen for women aged 50–69 years with stage II/III A breast cancer (based on the American Joint Committee on Cancer staging system) [26] rose from almost zero in 1981 to about 70% in 1991, following the publication of data showing the benefit of tamoxifen in postmenopausal women with lymph node-positive disease [14, 27–29]. Similarly, the partial decline in tamoxifen use after 1991 in this group may be due to publication of data showing an increased risk of endometrial cancer [30]. The decline may also be due to data showing that tamoxifen is only effective in patients whose tumors are hormone responsive [31].

Against this background of the development of adjuvant systemic therapies, this paper describes a major change, which appears to be continuing, in the clinical practice of adjuvant hormonal therapy for postmenopausal women with ER-positive EBC that occurred between July 2001 and November 2003. Although the oncologists participating in the study were not asked direct follow-up questions to address their changes in clinical practice, the study did probe each physician’s sense of overall efficacy and safety measurements.

The observations presented here, based on structured interviews of samples of medical oncologists, appear robust. There are some limitations associated with the study methodology. A different sample of oncologists was interviewed at each time point and the data included in the study were self-reported; thus potential bias might be introduced and accuracy could be affected by personal recall. Despite these limitations, the consistency of answers between samples at each time period is supportive of the reliability of the
data. Sample size was chosen to allow reliable estimates of change at the ±5% confidence level.

This sampling methodology, in which a new sample was used at each study period instead of a static sample, ensured that a nationally representative stratified physician sample was recruited and that all medical oncologists had an equal chance of being selected each time. This design allowed the inclusion of oncologists who had just become eligible for the study, for example, based on the number of hormonal therapy prescriptions prescribed in the past 6 months prior to the conduct of the study. Furthermore, an analysis of the sample at each time period showed no significant differences between and among time periods in terms of gender and geographic regions. Sampling the same medical oncologists at each time period would not allow for measurements of real change in prescribing behavior if their patients were all doing well on a specific treatment modality. In addition, the change would only be reflective of the same sample, which would not take into consideration new oncologists in practice and/or newly eligible oncologists. Lastly, there would be a certain level of natural withdrawals of oncologists from the study, thereby necessitating the recruitment of new physicians to the study. Approximately 10% of oncologists surveyed did not agree to participate in this study. This outright refusal rate and/or nonavailability based on set study deadlines was lower compared with other therapeutic specialties, which may be as high as 20%–30%.

The use of tamoxifen as an adjuvant therapy in postmenopausal ER-positive EBC patients has declined, while the use of anastrozole has increased significantly, and now accounts for over 50% of hormonal therapy prescriptions (Fig. 2). The continuous increase in anastrozole usage may reflect an increasing confidence in the robust nature of the ATAC results, anastrozole became the dominant adjuvant hormonal therapy for postmenopausal women within 2 years. The observations in this paper suggest that clinical practice in oncology can change rapidly following the publication of robust, large-scale trial data that document clinically relevant improvements in efficacy and safety. Mariotto and colleagues [5] showed that it took nearly 5 years from the publication of the Nolvadex Adjuvant Tamoxifen Trial report in 1983 for adjuvant use of tamoxifen to reach a 50% level for postmenopausal women, and the adoption of adjuvant polychemotherapy took a similar time course. In contrast, following the initial presentation of the ATAC results, anastrozole became the dominant adjuvant hormonal therapy for postmenopausal women within 2 years.

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