Tamoxifen—What Next?

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ABSTRACT
Most patients with advanced breast cancer (ABC) ultimately die due to disease progression. Consequently, treatments for ABC are predominantly palliative in nature and, therefore, the tolerability profile of a given treatment is particularly relevant in these patients. While cytotoxic chemotherapy and endocrine therapy exhibit efficacy in hormone-sensitive, advanced disease, it is endocrine therapy that combines efficacy with minimal acute toxicity. Tamoxifen has been the chosen endocrine therapy for postmenopausal, hormone-sensitive, ABC for over 20 years. More recently, new endocrine agents with different mechanisms of action from tamoxifen have been introduced. Evidence indicates that the aromatase inhibitors anastrozole (Arimidex®; AstraZeneca; Wilmington, DE), letrozole (Femara®; Novartis Pharmaceuticals Corp.; East Hanover, NJ) and exemestane (Aromasin®; Pharmacia Corp.; Peapack, NJ) offer superior efficacy and tolerability to tamoxifen in the first-line treatment of postmenopausal, hormone-sensitive ABC. Similarly, after tamoxifen failure, fulvestrant (Faslodex®; AstraZeneca), a new estrogen receptor (ER) antagonist that downregulates the ER, is at least as effective as anastrozole, is well tolerated, and is not cross-resistant with tamoxifen. Unlike tamoxifen, fulvestrant has no known agonist effects. The sequential use of such agents may prolong the time during which endocrine therapies can be used, thereby avoiding the more acute toxicities associated with cytotoxic chemotherapy. Indeed, a series of studies has shown that this sequential use is a relevant, active, and well-tolerated option. Establishing the comparative efficacies and optimal sequences that incorporate the newer endocrine agents will be central in determining the future role of hormonal therapy in ABC; the results of this work will determine the relative place of tamoxifen in what is a rapidly changing therapeutic environment.

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

1. Understand the current treatment options available for postmenopausal women with breast cancer.
2. Explain the impact of new clinical trial data on the existing schedule of endocrine therapy.
3. Describe the future direction of endocrine therapy for advanced breast cancer.

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INTRODUCTION

In the U.S., from 1992-1998, the 5-year survival rate for patients with localized breast cancer was 96.8%, whereas the equivalent figure for patients with distant disease was 22.5% [1]. While the incidence of invasive breast cancer in women <40 years of age remained stable from 1973-1998, the rate in women 50 years of age and older increased considerably [1, 2]. As a result, there continues to exist a significant need for therapies that are effective in the treatment of advanced disease in postmenopausal women.

The fundamental treatment choice for the majority of advanced breast cancer (ABC) patients is between cytotoxic chemotherapy and endocrine therapy. For patients with hormone-receptor-positive breast cancer, endocrine therapy is the preferred treatment. However, if such a patient has rapidly progressing disease, chemotherapy may be a better initial treatment choice. Chemotherapy causes tumor regression more quickly than endocrine therapy [3]. The advantage of endocrine therapy, however, is that it offers antitumor activity without the detrimental adverse events associated with cytotoxic chemotherapy [4] that lead to a significantly reduced quality of life. These issues are particularly relevant to a patient population in which treatment is palliative in nature and the majority will ultimately die due to their disease [5]. Importantly, the availability of a variety of endocrine agents possessing different mechanisms of action means that cross-resistance between agents is not a significant problem. The choice of treatment can, therefore, be tailored to the endocrine status of the patient, irrespective of whether the patient is pre- or postmenopausal [6]. The lack of cross-resistance also offers the potential for the sequential use of these agents, which may prolong the time during which endocrine agents can be used and delay the need for initiating cytotoxic chemotherapy.

The most important indicator of response to endocrine therapy is the presence of estrogen receptors (ERs) and progesterone receptors (PgRs) in the tumor. While endocrine therapy produces responses in approximately 30% of unselected patients, in ER-positive and/or PgR-positive patients, response rates >80% have been observed [6, 7].

With the increasing number of new endocrine agents introduced in the last few years, one of the challenges is to identify the optimal use of these agents. This review examines how the introduction of these new agents is influencing the status of tamoxifen as the therapy of choice for hormone-sensitive ABC. In so doing, potential new options and changes to endocrine therapies that may be important in shaping the use of endocrine therapy in the near future are highlighted.

TAMOXIFEN: CURRENT STATUS IN THE TREATMENT OF ABC

To appreciate the changing nature of endocrine therapy, it is necessary to first consider the current status of the antiestrogen tamoxifen. Since the 1970s, tamoxifen has been the most commonly used endocrine agent for the first-line treatment of postmenopausal metastatic breast cancer. Tamoxifen is a selective ER modulator (SERM) that competitively inhibits estradiol binding to the ER [8], and in so doing, disrupts a series of cellular mechanisms that regulate cellular replication. The disruption caused by tamoxifen changes the growth factor profile in responsive tissues and causes cells to be held at the G1 phase of the cell cycle [9, 10]. This produces changes in tumor cell proliferation and cell death, the balance of which results in the observed antitumor responses [11, 12] and improvement in overall survival [13].

The levels of expression of ER and PgR have been shown to correlate with overall response to tamoxifen. Postmenopausal patients have higher levels of ER and PgR expression than their premenopausal counterparts. For those patients with high ER and PgR expression levels, the overall response rate is as high as 70% [7, 14]. Tamoxifen has been shown to be better tolerated than—and to provide benefit equivalent to—hysterectomy and aminoglutethimide [15, 16], while being superior to standard-dose progestin therapy [17]. Eventually, disease relapse and resistance to tamoxifen treatment develop in many patients. This may be due to changes in interactions between tamoxifen and ERs. Target tissues recognize tamoxifen metabolites as estrogen agonists rather than estrogen antagonists. Another possible mechanism is increased intratumoral aromatase activity producing increased estrogen levels [18].

Despite being generally well tolerated, tamoxifen is associated with a number of adverse events due to its partial agonist action [19]. These include a higher rate of thromboembolic events [20] and a greater risk for developing endometrial cancers in women 50 years of age and older [21-23] that may exhibit a less favorable histology, a higher stage, and ultimately a worse survival [21]. These particular adverse events are perhaps most relevant to the adjuvant setting, where the duration of tamoxifen treatment is likely to exceed that in advanced disease. Ultimately, it is the risk-benefit ratio that determines the appropriate use of tamoxifen, with the risk of endometrial cancer being weighed against the risk of disease progression. Partly as a result of these tolerability issues and, more importantly, because of the development of resistance to tamoxifen, new endocrine agents have been developed. The increasing availability of new agents raises important questions regarding the positioning of tamoxifen in the sequential order of endocrine therapies [24].


**Tamoxifen: What Next?**

### As First-Line Therapy

Inevitably, the role of new endocrine agents in the first-line treatment of hormone-sensitive, ABC is being compared with that of tamoxifen. Two double-blind trials have compared the aromatase inhibitor (AI) anastrozole (Arimidex®; AstraZeneca; Wilmington, DE) with tamoxifen as first-line treatment for advanced disease in postmenopausal women [25, 26]. The aromatase enzyme is the major source of estrogen in postmenopausal women, converting adrenal hormones, such as androstenedione, into estrone or estradiol [27]. Inhibition of the aromatase enzyme, therefore, removes the main source of estradiol in postmenopausal women. In both trials, patients were permitted to have had prior adjuvant hormonal therapy or chemotherapy for early breast cancer, provided they had not received endocrine therapy within the 12 months before entry into the trial. A combined analysis demonstrated equivalent response rates, with objective responses (ORs) achieved by 29.0% and 27.1% of the anastrozole- and tamoxifen-treated patients, respectively. In a retrospective subgroup analysis of patients with ER-positive and/or PgR-positive tumors, the median time to progression (TTP) was significantly longer for anastrozole than for tamoxifen at 10.7 versus 6.4 months (two-tailed p = 0.022), respectively [28]. Importantly, anastrozole was better tolerated than tamoxifen, with significantly fewer venous thromboembolic events (p = 0.043) and less vaginal bleeding. Similarly, a recent study in postmenopausal women with ABC compared letrozole (Femara®; Novartis Pharmaceuticals Corp.; East Hanover, NJ) with tamoxifen. The results of that trial demonstrated that letrozole was superior to tamoxifen in measures of TTP (41 weeks versus 26 weeks), time to treatment failure (40 weeks versus 25 weeks; p = 0.001), and OR rate (30% versus 20%; p = 0.0006). As with other AIs, letrozole was well tolerated and produced a similar adverse event profile to that of tamoxifen [29]. The steroidal AI exemestane (Aromasin®; Pharmacia Corp.; Peapack, NJ) has also been compared to tamoxifen as first-line endocrine therapy in metastatic breast cancer. The recently presented results demonstrate that exemestane has excellent tolerability and better progression-free survival than with tamoxifen [30].

The choice of the most appropriate first-line endocrine therapy must be given serious consideration in light of the evidence suggesting that a third-generation AI may be the more appropriate first-line therapy for advanced disease. The first analysis of the anastrozole, tamoxifen, alone or in combination (ATAC) trial provided encouraging support for the use of anastrozole in the adjuvant treatment of newly diagnosed, early breast cancer [31]. Importantly, the results of that trial may be indicative of the need for a more general reappraisal of the place of tamoxifen in the endocrine therapy of breast cancer.

### After Tamoxifen Failure

Until the use of AIs in the adjuvant setting is unequivocally established, many patients will continue to receive tamoxifen as their first endocrine therapy in early disease. As a result, endocrine options after progression on adjuvant tamoxifen or after first-line tamoxifen treatment for advanced disease are an important area of breast cancer therapy.

Obviously, given the evidence showing the efficacy of sequential endocrine therapies, disease progression on tamoxifen does not mean that endocrine therapy is no longer effective. Patients frequently benefit from further endocrine interventions, with approximately 40% of patients achieving useful tumor control with second-line therapy [32, 33]. Patients achieving ORs or disease stability on first-line endocrine therapy have a significantly better chance of achieving tumor remission on second-line endocrine therapy (Fig. 1) [34]. The subsequent use of a second agent after failure on initial hormonal treatment, therefore, offers the potential benefits of well-tolerated, effective, palliative treatment without recourse to cytotoxic chemotherapy. Commonly used second-line options have previously been the AI aminoglutethimide and the progestins megestrol acetate and medroxyprogesterone acetate. While effective, these agents exhibit significant tolerability problems that include weight gain, edema, and thromboembolic events, with the progestins [35], and rash, drowsiness, and lethargy, with aminoglutethimide [27]. As a result, approximately 35% of patients discontinue treatment with aminoglutethimide [36].

The efficacy and tolerability of AI treatment in postmenopausal women progressing on prior tamoxifen therapy have been clearly demonstrated. Compared with the progestin megestrol acetate, anastrozole offers a significant survival benefit. Figure 1. The relationship of response to first-line endocrine therapy to the proportion of patients in remission after second-line therapy [34].

![Figure 1. The relationship of response to first-line endocrine therapy to the proportion of patients in remission after second-line therapy [34].](image-url)
advantage (hazard ratio = 0.78) [14] and is well tolerated, with no evidence of increased weight gain. Letrozole has also been shown to offer superior efficacy and tolerability as second-line therapy compared with megestrol acetate [37, 38]. Similarly, the steroidal AI exemestane has been shown to produce a significantly longer median survival time and TTP than megestrol acetate [39]. It is worth noting that after progression on nonsteroidal AIs, such as anastrozole, letrozole, and aminogluthethimide, exemestane has shown efficacy, being well tolerated and producing a clinical benefit (CB) rate (complete response, partial response, or stable disease for ≥24 weeks) of 24.3% [40]. Similarly, preliminary results show that patients with ABC progressing on prior exemestane derive further benefit from treatment with anastrozole or letrozole [41]. These data suggest that the sequential use of nonsteroidal and steroidal AIs may be a relevant alternative option in the therapy of advanced, postmenopausal disease. However, further studies are required to substantiate observations such as these. A number of endocrine options are, therefore, becoming established as appropriate agents exhibiting efficacy after progression on tamoxifen. Along with newer agents for which data are emerging, these therapies will have a bearing on the position of tamoxifen in the endocrine therapy of postmenopausal breast cancer.

Fulvestrant and Endocrine Therapy

Fulvestrant (Faslodex®; AstraZeneca) is a new ER antagonist that downregulates the ER and has no known agonistic effects. Fulvestrant has recently been granted U.S. Food and Drug Administration approval for the treatment of hormone-receptor-positive, metastatic breast cancer in postmenopausal women progressing on prior antiestrogen therapy. Fulvestrant has a unique mechanism of action compared with other endocrine therapies. It binds to the ER, thereby inhibiting DNA binding, and promotes the rapid degradation of the ER, resulting in a dramatic loss of cellular levels [42, 43] that is associated with a significant reduction in PgR expression [44, 45]. This different mechanism of action of fulvestrant may ensure that resistance to prior endocrine therapies is not reflected in cross-resistance to fulvestrant.

Two phase III trials have compared fulvestrant with anastrozole in the treatment of advanced postmenopausal breast cancer in women who had progressed on prior tamoxifen therapy [46, 47]. Those trials demonstrated that second-line fulvestrant was well tolerated and was at least as effective as anastrozole. A prospectively planned, combined analysis of data from those two trials showed that median TTP, the primary end point, was 5.5 months and 4.1 months and OR rates were 19.2% and 16.5% for fulvestrant and anastrozole, respectively. The median durations of response (DOR; from randomization to progression) were 16.7 and 13.7 months for fulvestrant and anastrozole, respectively. After an extended follow-up of 22.1 months, the mean DOR for all randomized patients (from onset of response to progression) was significantly greater for fulvestrant than for anastrozole: the ratio of average response durations was 1.30 (95% confidence interval = 1.13-1.50; \( p < 0.01 \)). Very few patients withdrew due to drug-related adverse events (0.9% and 1.2% of patients treated with fulvestrant and anastrozole, respectively), and fulvestrant was associated with significantly fewer joint disorders than anastrozole (\( p = 0.0036 \)) [46].

The analysis of responses to further endocrine therapy after progression on second-line fulvestrant indicates that patients retained sensitivity to agents such as AIs and progestins [48, 49]. Limited retrospective data from the two phase III studies, obtained by a follow-up questionnaire, showed that CB was achieved in 19/46 (41%) patients who derived CB on fulvestrant and were treated with an AI on progression (Table 1). Patients who do not respond to fulvestrant may also remain sensitive to further therapy, with CB from subsequent endocrine therapy reported for 18/51 (35%) patients [49] (Table 1). After progression on fulvestrant, patients have also been shown to retain sensitivity to tamoxifen. In a preliminary retrospective analysis of patients responding to fulvestrant as first-line treatment for advanced disease, second-line tamoxifen produced one partial response, seven cases of stable disease, and disease progression in two patients [50]. Patients

<table>
<thead>
<tr>
<th>Endocrine therapy total</th>
<th>PR</th>
<th>SD ≥24 weeks</th>
<th>PD</th>
<th>Total</th>
<th>PR</th>
<th>SD ≥24 weeks</th>
<th>PD</th>
<th>Total</th>
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<tr>
<td>4</td>
<td>21</td>
<td>29</td>
<td>54</td>
<td></td>
<td>1</td>
<td>17</td>
<td>33</td>
<td>51</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
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<td>16</td>
<td>27</td>
<td>46</td>
<td>1</td>
<td>15</td>
<td>26</td>
<td>42</td>
</tr>
<tr>
<td>Megestrol acetate</td>
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<td>5</td>
<td>2</td>
<td>8</td>
<td>0</td>
<td>1</td>
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<td>6</td>
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<tr>
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Abbreviations: PR = partial response; SD = stable disease; PD = progressing disease.
have also shown responses to fulvestrant as third-line therapy, after progression on tamoxifen and subsequent AI treatment [51].

Fulvestrant, therefore, provides an additional, flexible endocrine treatment option that prolongs disease control while maintaining quality of life. This may delay the requirement for cytotoxic chemotherapy and its associated side effects.

The positioning of fulvestrant in the sequence of endocrine therapies is currently under investigation, and the data in support of different sequencing regimens are limited. However, for hormone-sensitive ABC in postmenopausal women who have progressed on tamoxifen, the available data support the initial use of fulvestrant, which has been shown to offer similar efficacy to anastrozole [46, 47]. After progression, fulvestrant could be followed by AIs, which have been shown to be active after progression on fulvestrant [49]. Tentative sequences can, therefore, be proposed (Fig. 2) that incorporate fulvestrant and anastrozole in the sequential therapy of these patients. Of course, these sequences represent a starting point from which various postmenopausal endocrine-sequencing strategies may be considered and refined. It is, therefore, important that future studies assess the sequential use of endocrine therapies to provide data that can be used to ensure that patients gain maximum benefit with minimum toxicity.

**CONCLUSIONS**

The question “tamoxifen—what next?” covers a number of clinically important points, the answers to which will go a long way toward shaping the future profile of endocrine treatments for advanced, postmenopausal breast cancer. The first-line use of tamoxifen has been challenged by data indicating that other hormonal agents may be better options. In addition, the continuing development of new agents provides the opportunity and impetus to reassess and refine the preferred sequence of endocrine treatments. The development and incorporation of agents such as fulvestrant into the sequence of endocrine therapies may prolong the time during which hormonal treatments can be effectively used, before recourse to cytotoxic chemotherapy is necessary.

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