Phase II and III Clinical Trials of Toremifene for Metastatic Breast Cancer

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Toremifene (Fareston) received FDA approval in 1997 for the first-line treatment of postmenopausal women with estrogen receptor (ER)-positive or -unknown metastatic breast cancer. Phase II and III trials have demonstrated that first-line therapy with toremifene, 60 mg/d, is as effective and as well tolerated as tamoxifen (Nolvadex), 20 or 40 mg/d, in such patients.

Toremifene (Fareston) is the first antiestrogen introduced into US clinical oncologic practice since tamoxifen (Nolvadex) was approved for use in postmenopausal breast cancer patients approximately 2 decades ago.

Phase I clinical trials of toremifene administered orally at doses ranging from 10 to 400 mg/d[1-4] established the drug's excellent tolerability in cancer patients at virtually all dose levels, with a subjective toxicity profile similar to that of tamoxifen. Nausea and vertigo were noted in two of five healthy postmenopausal volunteers who received a dose of 680 mg/d.[5] Three responses were seen in the phase I trial reported by Hamm et al. All three responders were treated with a dose of 200 mg/d, and two had previously responded to tamoxifen but had subsequently progressed.[1]

**Phase II Trials: First-Line Therapy**

**Postmenopausal Women With Positive or Unknown ER Status**

Six trials of toremifene were performed in postmenopausal women with metastatic breast cancer and positive or unknown estrogen-receptor (ER) status. In two trials, which tested a dose of 20 mg/d, response rates in a total of 104 patients were 21.4% and 22.2% in ER-positive and ER-unknown women.

Four trials administered 60 mg/d to a total of 195 women. Response rates in these women ranged from 32.6% to 54.3%, with median times to progression of 6.3 to 12.2 months. Only one published trial has used an intermediate dose of 40 mg/d. This trial reported a response rate of 33.4% in 81 patients and a median time to progression of 5.5 months. This latter result was similar to the 32.6% response rate and 6.3-month time to progression seen with the 60-mg/d dose in the same trial.[2]

In their recent update of a previously unpublished but reviewed trial,[2,6] Hietanen and co-workers[7] treated 73 women with 240 mg/d of toremifene and achieved a 59% objective response rate among the 56 patients evaluable for response (47% overall response rate). Although difficult to discern from the latter publication, the 15.2-month time to progression listed for this study by Hamm et al[2] is impressive. In addition, Hietanen et al reported that six patients responded for 2 to 4 years and four additional patients responded for 5 to 7 years.

**Commentary on These Data** Although inconclusive, these phase II data suggested that a toremifene dose of 20 mg/d may be suboptimal, and led to the recommendation of the 60-mg/d dose for the subsequent phase III trials. It remains unclear whether a dose of 40 mg/d is equivalent or inferior to 60 mg/d, but that issue is unlikely to be of major clinical import.

The time to progression of 15.2 months achieved with the high dose of toremifene in the study by Hietanen et al is tantalizing, especially given the number of responses lasting for 2 to 7 years. In contrast, however, pooled data from two phase III trials[8] involving 369 patients did not seem to show any significant benefit of high doses of toremifene compared with standard doses of tamoxifen and toremifene.

**Receptor-Negative Patients**

The use of high-dose toremifene in women with receptor-negative tumors is based on a report of the activity of high-dose toremifene in an estrogen-independent uterine sarcoma model[9] and on
speculations by Ebbs and co-workers[10] that antiestrogens may produce antitumor effects distinct from those mediated by estrogen receptors. No antitumor responses were seen in one study by Perry et al[11] of 400 mg/d of toremifene in 20 patients nor in a second study of 15 additional patients cited by Valavaara[12]. Valavaara noted that 4 of 15 patients in the latter unpublished study had minimal responses or disease stabilization for more than 6 months.

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**Phase II Trials: Second-Line Therapy**

**Patients [Refractory] to Tamoxifen**

All five published trials of toremifene conducted in patients who had been previously treated with tamoxifen used doses higher than the standard 60-mg/d dose recommended for first-line therapy (Table 1). The trials of Modig et al,[13] Ebbs et al,[10] and Vogel et al[14] used a dose of 200 mg/d, while Pyrhonen et al[15] used 240 mg/d and Asaishi et al[16] used 120 mg/d. In the European experience with toremifene as second-line therapy, as summarized by Kangas for publication in a review by Hamm, an additional 356 patients previously exposed to tamoxifen were treated with 240 mg/d of toremifene.[2]

**Commentary on These Data** While most of the response rates reported in these trials were consistent (and low), the interesting but, at first glance, puzzling observations of Kangas, warrant comment. Patients previously treated with tamoxifen alone had a low (8%) response rate to toremifene, consistent with other series. However, the response rate to toremifene in patients pretreated with both chemotherapy and tamoxifen was higher[16]. Although the lack of publication makes analysis of the actual data impossible at present, it could be that patients who did not respond to tamoxifen were subsequently treated with chemotherapy, and toremifene was administered after this intervening therapy. Responses to tamoxifen rechallenge after initial tamoxifen failure and then intervening therapies can occur, and have been seen by this author, although the reports are largely anecdotal. It is possible that the higher response rate of 16% in this subset of patients reported by Kangas could share the same mechanism of incomplete antiestrogen resistance encountered in some patients rechallenged with tamoxifen after intervening therapies.

Another factor confounding the evaluation of the seemingly consistent negative results of these phase II trials of tamoxifen-pretreated patients is the assessment of prolonged stable disease. For some time, Robertson et al[17] and Howell et al[18] have suggested that prolonged stable disease for more than 6 months should be considered a surrogate for antitumor response. More recently, in a randomized trial of anastrozole (Arimidex) vs megestrol acetate, the 2-year survival rates of patients who had an objective antitumor response and those who had prolonged stable disease as their best response were virtually identical with either drug.[19] These data would appear to be supportive of therapeutic clinical benefit in at least some cases of prolonged stabilization, in contrast to the usual explanation of indolent progression without clinical benefit.

The only phase II trial of toremifene in tamoxifen-resistant patients that specifically reported on a population of patients with stable disease for more than 6 months was that by Asaishi et al[16] These researchers concluded that an overall objective response rate of 12% plus a 15% rate of stable disease for more than 6 months equated to a 27% rate of clinical benefit. These data were sufficient to permit the registration of toremifene (at a dose of 120 mg/d) in Japan for use in patients who do not respond to tamoxifen.

In the series by Vogel et al,[15] no reappraisal of the 23% of patients whose best response was stable disease has yet been performed to define the subset of patients with stable disease for more than 6 months. It remains possible that the overall clinical benefit rate in that previously reported [negative] trial could be similar to the rate seen in the trial from Japan.

With such conflicting data from phase II trials, it is impossible to determine whether or not doses of toremifene in excess of 60 mg/d could produce clinical benefit in patients who previously did not respond to tamoxifen therapy. The prolonged disease stabilization observed in some receptor-negative women cited by Valavaara[6] and in patients refractory to tamoxifen cited by Asaishi et al[16] raises questions about the possible clinical benefit of moderate- to high-dose toremifene in those patient subsets. If such an effect does exist, it is unlikely to be greater than 20% to 30%. Moreover, whether the same result could be achieved by tamoxifen rechallenge remains speculative.

Favoring the antiestrogen rechallenge hypothesis, as opposed to a toremifene dose-response effect, is a publication by Gershovanovich et al,[8] which summarizes the results of high-dose toremifene vs tamoxifen in two large-scale, randomized, phase III trials. In that analysis, standard-dose tamoxifen and high-dose toremifene appeared to be statistically equivalent with respect to disease.
progression and survival. Additional randomized clinical trials of toremifene may well be warranted in tamoxifen-refractory patients, especially in those who received several other therapeutic interventions after relapsing on tamoxifen. In such trials, toremifene could be compared to tamoxifen rechallenge.

**Phase III Trials**

Since the results of phase II clinical trials of 60 mg/d of toremifene suggested the possibility of antitumor activity at least comparable to that of tamoxifen, three phase III clinical trials were initiated—the so-called North American, Eastern European, and Nordic trials. These trials seemed to be of particular importance, since data were emerging at that time of a possible increased risk of uterine cancer[20] and other possible genotoxic effects with tamoxifen. Some of the latter issues were summarized recently by Williams and Jeffrey.[21]

The design of each of the three phase III trials is shown in Figure 1. Detailed analyses of each trial have been published,[22-24] and each has been the subject of other reviews.[8,25] To avoid redundancy with the other publications and reviews, this commentary will simply summarize the similarities among the trials and note the conclusions that led to the FDA approval of toremifene as first-line hormonal treatment for postmenopausal women with ER-positive or ER-unknown metastatic breast cancer.

All three trials accepted patients with measurable or evaluable metastatic disease; ER- or progesterone receptor (PR)-positive or -unknown status; good performance status with no serious, uncontrolled comorbid conditions, and no prior antiestrogen therapy for advanced disease. Adjuvant tamoxifen was allowed as long as the interval between discontinuation and relapse was more than 12 months. The North American trial permitted perimenopausal patients as well as postmenopausal patients to enter the trial, while the other two trials were limited to postmenopausal patients.

**Response Rates**

As shown in Table 2, the response rates in the North American and Eastern European trials for either high- or low-dose toremifene vs tamoxifen were virtually identical. In the Nordic trial, there was a slight trend toward a greater benefit with tamoxifen. In the Eastern European trial, the trend favored high-dose toremifene over tamoxifen, but neither of these trends was statistically significant.

Another difference was the surprisingly low response rates to both drugs in both the North American and Eastern European trials. It has been estimated that 60% of postmenopausal women with estrogen receptor-positive tumors may have objective responses to first-line hormonal therapy, whereas women with ER-positive, PR-positive tumors may be expected to have even higher response rates.[26] Thus, the approximate 20% response rate in these two trials seems puzzling at first glance. However, the following facts should be noted:

- The 60% to 80% response rate in receptor-positive women comes largely from retrospective analyses of trials done during an era of clinical trials in which response evaluations were nowhere as meticulous and stringent as they are now.
- Many responses in the 1970s would probably be reinterpreted as stable disease in clinical trials performed in the current era.
- The North American and Eastern European phase III trials included ER-unknown patients, who are known to have lower response rates than receptor-positive patients.
- These phase III trials included patients with bone-only metastases and evaluable disease and did not mandate bidimensionally measurable disease. Objective response in the former populations is notoriously difficult to quantitate, leading to a larger population of patients with stable disease, many of whom derive clinical benefit from therapy.
- Adding patients with stable disease to the responders in the North American trial would bring the clinical benefit rates to 44% for tamoxifen (20 mg/d), 50% for toremifene (60 mg/d), and 47% for toremifene (200 mg/d). These values would seem to be quite consistent with a mixed population of receptor-positive and -unknown postmenopausal women. (The reader is rereferred to the commentary on stable disease as a surrogate for response on page 10.)
Time to Progression, Remission Duration, and Overall Survival

Just as with response rates, time to progression and response durations were virtually identical in the North American and Eastern European studies (Table 3). It is reassuring, and noteworthy, that response durations ranged from 1.3 years to over 2 years across the three trials, reaffirming the durability of clinical benefit with both of these antiestrogens.

Overall survival rates tended to be lower in the Eastern European trial than in the Nordic or North American trials. This may have resulted from later diagnoses in Eastern Europe and/or the unavailability, during the course of the trial, of some salvage regimens that were more readily available in the West. Regardless, overall survival rates with tamoxifen and toremifene were similar in the Eastern European trial.

Further comment regarding data on time to progression in the Nordic trial[24] is warranted. This trial noted a trend, which approached statistical significance, toward a longer time to progression in tamoxifen-treated patients than in toremifene-treated patients. Interestingly, there were more treatment discontinuations among patients taking tamoxifen in this trial. Thus, while the time to progression was 7.3 months for toremifene and 10.2 months for tamoxifen, the time to treatment failure (discontinuation of treatment for any cause) was 6.3 months for toremifene and 8.5 months for tamoxifen—a difference that is not statistically significant (P = .271).

In addition, further analysis revealed that there was an imbalance in the randomization of the Nordic trial, and that virtually all of the differences occurred in patients with ER-unknown tumors. When only ER-positive patients were analyzed, the time to progression was 9.1 months for toremifene vs 10.1 months for tamoxifen (95% confidence interval, 6.5 to 12.5 months; P = .578).

Toxicity

The comparative toxicity profiles of toremifene, at standard and higher doses, and tamoxifen have been extensively reported in the phase III publications[22-24] and have been summarized and reviewed by Gams[25] and Gershanovich et al [8] for standard- and high-dose comparisons, respectively. The most commonly noted adverse reactions to tamoxifen occurred with similar frequency in patients receiving 60-mg/d doses of toremifene. These events include: hot flashes, sweating, nausea and/or vomiting, vaginal discharge, dizziness, edema, vaginal bleeding, liver function abnormalities, ocular changes, and thromboembolic or cardiac events.

At high doses of toremifene,[8] there was a trend toward more nausea (13.6%, vs 9.1% with tamoxifen; P < .085), reversible corneal keratopathy (8 vs 2 patients; P < .061), clinically insignificant serum glutamic-oxaloacetic transaminase (SGOT) elevations (17.3% vs 7.1%; P < .0001), and hypercalcemia (13 vs 6 cases).

Despite these differences, the number of patients who discontinued therapy prematurely was similar for both high-dose toremifene and tamoxifen (17.3% vs 20.1%). The issue of endometrial cancer and other safety concerns are addressed in the paper by Dr. Lewis Smith in this issue (see pp 14-22).

Summary

It seems clear from both phase II and phase III clinical trials that, when used as the initial hormonal intervention in postmenopausal women with ER-positive (or -unknown) metastatic breast cancer, toremifene at 60 mg/d demonstrates similar efficacy and tolerability as does tamoxifen at 20 or 40 mg/d. To date, phase III trials have not demonstrated a statistically significant benefit for higher doses of toremifene compared with standard doses of tamoxifen in this same subset of women. High doses of toremifene would appear to have little efficacy in women with receptor-negative tumors, although patient numbers in these trials were small.

Although a number of trials of high-dose (200 to 240 mg/d) toremifene have been performed in tamoxifen-refractory patients, the data remain contradictory, depending on whether or not the trials included prolonged stable disease (≥ 6 months) as an indication of clinical benefit. Thus, while toremifene at 120 mg/d is approved in Japan for the treatment of tamoxifen-refractory patients based on a clinical benefit rate of 27% (responders plus patients with prolonged stable disease), a similar analysis of data from the other phase II trials has not been performed.

Toremifene is now available as an alternative to tamoxifen for the first-line treatment of postmenopausal women with ER-positive or -unknown metastatic breast cancer. Its overall role in breast cancer management, however, must await the maturation of ongoing adjuvant therapy trials.
References:


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