Endocrine Manipulation in Advanced Breast Cancer: Recent Advances with SERM Therapies

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Abstract
Tamoxifen is one of the most effective treatments for breast cancer through its ability to antagonize estrogen-dependent growth by binding estrogen receptors (ERs) and inhibiting breast epithelial cell proliferation. However, tamoxifen has estrogenic agonist effects in other tissues such as bone and endometrium because of liganded ER-activating target genes in these different cell types. Several novel antiestrogen compounds have been developed that are also selective ER modulators (SERMs) but that have a reduced agonist profile on breast and gynecological tissues. These SERMs offer the potential for enhanced efficacy and reduced toxicity compared with tamoxifen. In advanced breast cancer clinical data exist for three first-generation SERMs (toremifene, droloxifene, idoxifene), which are related to the triphenylethylene structure of tamoxifen. In Phase II trials in a total of 263 patients resistant to tamoxifen, the median objective response rate to these SERMs was only 5% (range, 0–15%), with stable disease for ≥6 months in an additional 18% (range, 9–23%). As first-line therapy for advanced breast cancer, the median response rate was 31% (range, 20–68%) with a median time to progression of 7 months. Randomized Phase III trials for toremifene and idoxifene in more than 1500 patients showed no significant difference compared with tamoxifen. Fewer clinical data exist for the structurally distinct second- and third-generation SERMs (raloxifene, arzoxifene, EM-800, and ERA-923), although a similarly low median response rate of 6% (range, 0–14%) was seen in Phase II trials in tamoxifen-resistant patients. It remains unclear whether any clinical advantage exists for second- and third-generation SERMs over tamoxifen as first-line therapy. With the emergence of potent aromatase inhibitors (AIs) that are superior to tamoxifen, the clinical questions in advanced disease have shifted to which antiestrogen (including SERMs) may be effective following failure of AIs, and whether any merit exists for combined AI/SERM therapy. The main advantage for SERM therapy probably remains in early-stage disease (adjuvant therapy or prevention), in which the estrogenic effects on bone and reduced gynecological side effects may prove more beneficial than either tamoxifen or AI. The issue is whether the current clinical data for SERMs in advanced breast cancer are sufficiently strong to encourage that further development.

Introduction
Ever since evidence emerged that human breast carcinomas may be associated with estrogen, attempts have been made to block or inhibit estrogen’s biological effects as a therapeutic strategy for women with breast cancer. Estrogen has important physiological effects on the growth and functioning of hormone-dependent reproductive tissues, including normal breast epithelium, uterus, vagina, and ovaries, as well as on the preservation of bone mineral density and reducing the risk of osteoporosis, the protection the cardiovascular system by reducing cholesterol levels, and the modulation of cognitive function and behavior. Thus, a strategy to block or reduce estrogen function in an attempt to treat or prevent breast cancer could have a severe impact on a woman’s health by interfering with normal estrogen-regulated tissues.

For over 30 years, synthetic antiestrogens have been developed as treatment for ER+ve breast cancer, and the triphenylethylene tamoxifen was the first hormonal compound with efficacy in advanced breast cancer (1). Tamoxifen is the most widely used and tested drug in breast cancer and is now recognized to significantly improve survival as adjuvant therapy in early breast cancer (2), as well as to reduce the incidence of breast cancer in healthy women at risk of the disease (3). Despite concerns about unfavorable antiestrogenic effects on healthy tissues, paradoxically it was discovered that tamoxifen acted as an estrogen on bone, blood lipids, and the endometrium (4). More recently, the molecular structure and function of ER biology has been elucidated, revealing how tamoxifen and related drugs act as ligands to differentially switch on or off gene expression in specific tissues (5, 6). The ability of antiestrogens to have alternative effects on various estrogen-regulated targets led to the term “SERM” to describe this class of drugs. It is now possible to develop SERMs that range from full estrogen agonists to pure antagonists with different effects in separate target tissues. In this way, SERMs offer the potential to treat and prevent a number of conditions ranging from osteoporosis, menopausal symptoms, cardiovascular disease, and breast and endometrial cancer. This article will review the development of SERMs in breast cancer, addressing in particular the limitations of tamoxifen that SERMs have attempted to overcome and the clinical data available to date for each of the SERM compounds.

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3 The abbreviations used are: ER, estrogen receptor; ER+ve, ER positive; SERM, selective ER modulator; CI, confidence interval.
Tamoxifen: The Prototype SERM

The triphenylethylenne nonsteroidal antiestrogen tamoxifen was first synthesized in the 1960s and was found to have clinical activity in postmenopausal women with advanced breast cancer (1). Tamoxifen antagonizes the effects of estrogen in breast cancer cells by binding ER, inducing G1, cell cycle arrest, and inhibiting tumor growth. Although tamoxifen prevented growth of ER+ve breast tumor xenografts in vivo (7), at the same time it stimulated uterine growth (8) and supported the growth of endometrial xenografts in vivo (9). A similar spectrum of estrogenic and antiestrogenic effects emerged in patients, with vaginal dryness and hot flushes the most frequently reported antiestrogenic toxicities (10). Because of estrogenic activity of tamoxifen in the liver, total serum cholesterol levels were reduced by 10–15% (11). Likewise, bone mineral density was preserved in tamoxifen-treated postmenopausal women, although in premenopausal women, this effect was not apparent (12, 13). In patients, tamoxifen functioned as an estrogen on the endometrium, with endometrial thickening and hyperplasia together with an increased risk of endometrial cancer (14). Although some of these additional properties of tamoxifen are of potential benefit for women, SERMs were developed for breast cancer with the aim of reducing some of tamoxifen’s toxicities, in particular eliminating any agonist effects on the gynecological tract. In terms of breast cancer therapy, a meta-analysis of all clinical trials found that 5 years of tamoxifen in women with early stage ER+ve breast cancer significantly reduced the risk of recurrence (47% reduction in annual odds) and death (26% reduction in annual odds; Ref. 2). This benefit was greatest in women with ER-rich tumors and occurred across all age groups, irrespective of nodal involvement. In addition, tamoxifen’s antiestrogenic effects on normal breast epithelial cells resulted in a 50% reduction in new contralateral breast cancers, evidence that provided much of the impetus to developing a role for tamoxifen in chemoprevention. At the same time, the estrogenic effects of tamoxifen therapy on bone and cholesterol are of clinical benefit in reducing risk from osteoporosis and cardiovascular disease (11, 12). In the adjuvant setting, tamoxifen’s increased risk of endometrial cancer has been perceived as small in relation to the substantial benefit from reduction in breast cancer-related events (14). However, both in adjuvant and metastatic therapy with tamoxifen, breast epithelial cells and established tumors adapt to chronic antiestrogen exposure and develop resistance to tamoxifen, which may relate to the partial agonist effect of tamoxifen in stimulating tumor growth (reviewed in Refs. 15, 16). Experimental models have shown that novel antiestrogens that are devoid of agonist effects can antagonize tamoxifen-stimulated growth (9) and, as treatment of hormone-sensitive tumors, may delay the emergence of resistance (17). These observations generated hope that better SERMs with an improved antiestrogen/estrogen profile may overcome this form of resistance and improve further on the efficacy of tamoxifen in treating breast cancer.

ER Molecular Biology: Differential Effects of SERMs

Progress in our molecular understanding of ER function has provided insights into the differential effects of various ER ligands, including estrogen and tamoxifen, in different tissues (reviewed in Refs. 5, 6). Estrogen-regulated gene transcription is activated through two separate transactivation domains within ER, termed AF-1 in the NH2-terminal A/B region and AF-2 in the COOH-terminal E region (18). At its simplest level, tamoxifen functions as a competitive antiestrogen to inhibit estrogen action. Tamoxifen-bound ER still dimerizes and binds DNA, although the downstream effects differ because of the altered conformational shape of the tamoxifen-ER complex compared with estradiol, which induces a change in the receptor-bound balance of coactivators and corepressors, thus blocking gene transcription through the AF-2 domain while still allowing AF-1 mediated gene transcription to occur (19). This may explain the partial agonist activity of tamoxifen in addition to its ability to antagonize estrogen-regulated gene transcription (Fig. 1).

It has become clear that the molecular biology of ER is complex, and that other aspects of its function may mediate the differential ligand effects seen in response to estrogen or tamoxifen. In addition to classical ER (now called ERα), a second ER was cloned (ERβ), which shares sequence homology within the DNA-binding domain (20) but which differs in that AF-1 activity is considerably less than with ERα (21). Equally, ERβ lacks much of the COOH-terminal F domain of ERα, which may be an important region in determining an agonist response to tamoxifen (22). Recent evidence has implicated increased ERβ expression as a mechanism for tamoxifen resistance in breast cancer (23). Other response pathways may become acti-
activated indirectly by ER, including AP-1 response elements, which regulate genes involved in cell proliferation, motility, and apoptosis. Tamoxifen was shown to be an agonist on AP-1-regulated genes with either ERα or ERβ (24), whereas estrogen liganded with ERβ inhibited AP-1 gene transcription (25). Enhanced activation of AP-1 by tamoxifen may also be associated with tamoxifen resistance in models of breast cancer (26) and in tumors from breast cancer patients relapsing on tamoxifen (27). Finally, the relative balance in a given cell type of coactivator and corepressor proteins may also determine the response of ER to a particular ligand (28), and a reduction in the level of the corepressor N-CoR has been associated with the development of tamoxifen resistance in breast cancer xenografts (29).

The development of SERMs that are structurally different from tamoxifen has provided an additional insight into the biology of ER action (4). A crucial aspect of estrogen interaction with ER is the complete envelopment of the steroid in a hydrophobic pocket within the ligand-binding domain because of the critical positioning of a “lid” formed by helix 12 of the ER. The position of helix 12 is also critical for recruitment of coactivators to the AF-2 transactivation site, allowing subsequent initiation of RNA polymerase activity. SERMs or steroidal antiestrogens may result in a qualitatively different conformational shape of the liganded receptor, because of the alkylaminoethoxy side chain of the triphenylethlenes (e.g., tamoxifen), the different structure of the benzothiophenes (e.g., raloxifene), or the long side chain of steroidal antiestrogens (fulvestrant; Fig. 1). This imparts a different positioning of the helix 12 lid, the exact nature of which depends on the conformational shape each antiestrogen imparts to the ligand ER complex (30). As a result, the relative positioning of helix 12 may influence the likelihood of coactivator/corepressor binding and, thus, determine the transcriptional response to liganded ER for a given gene (31). This provides a new hypothesis based on the chemical structure of each of the different SERMs that may explain their differential antagonist/agonist profiles.

**Novel SERMs: Potential Advantages for Breast Cancer**

An understanding of how the triphenylethylene antiestrogen tamoxifen interacts with ER has allowed novel SERMs to be synthesized that possess an improved antiestrogenic/estrogenic profile. These drugs have been developed with the aim of retaining both the antagonist activity of tamoxifen within the breast and the agonist profile in bone and the cardiovascular system, yet at the same time eliminating unwanted agonist effects on the gynecological tract, in particular the uterus. Non-steroidal SERMs fall into two broad categories: those that are structurally similar to the triphenylethylene structure of tamoxifen (first-generation SERMs; Fig. 2), and those that are structurally different and more related to the benzothiophene structure of raloxifene (second- and third-generation SERMs; Fig. 3). A third class of antiestrogen includes the steroidal antiestrogen ICI-182,780 (fulvestrant), which is a structural derivative of estradiol with a long hydrophobic side chain at the 7α position (Fig. 3; Ref. 32). Pharmacologically, these latter compounds are pure antiestrogens that not only impair ER dimerization but also induce ER degradation (33, 34) and, thus, act as potent antiestrogens in all tissues including the breast, uterus, and probably bone. Although some may argue that fulvestrant is not a true SERM because it lacks selective agonist/antagonist effects in different tissues and possesses a fundamentally different mechanism of action, others have suggested that it represents one
extreme (i.e., a pure antiestrogen) of the SERM spectrum, with estrogen as a pure agonist at the other end, and all other SERMs falling somewhere in between (5).

Each of the SERMs demonstrated pharmacological or pharmacodynamic benefit over tamoxifen in various preclinical studies, and as a consequence had a profile that supported clinical development in women with advanced breast cancer in the hope of producing a more effective and beneficial antiestrogen. The potential preclinical advantage for these SERMs included either greater potency attributable to enhanced affinity for ER, greater efficacy compared with tamoxifen against breast cancer in vitro or in vivo, or reduced risk of toxicity compared with tamoxifen on organs such as the liver and endometrium (Table 1). If resistance to tamoxifen occurs in part because of the agonist effects of the drug that stimulate tumor regrowth (15, 16), then SERMs would be expected either to be active against tamoxifen-resistant tumors or to delay the emergence of resistance. In the clinic, this profile would manifest as either a superior response rate or a delay in the emergence of resistance during long-term therapy. Thus, one might expect to see evidence of activity for SERMs in Phase II studies in tamoxifen-resistant breast cancer or, alternatively, an increased duration of clinical response or time-to-disease progression compared with tamoxifen in randomized Phase III trials as first-line therapy for ER+ve hormone-sensitive breast cancer (Table 1). The progress to date with each SERM compound is reviewed below, in particular recent data from clinical trials of SERMs in women with either tamoxifen-resistant or hormone-sensitive breast cancer.

Tamoxifen-like SERMs

Of the triphenylethylene derivatives, clinical data from Phase II/III clinical trials in women with advanced breast cancer have been published with three triphenylethylene tamoxifen-like compounds (toremifene, droloxifene, and idoxifene). For each one, preclinical data that had suggested an improved SERM profile compared with tamoxifen led to their clinical development with the hope that these agents might prove safer or more effective antiestrogens for the treatment of breast cancer.

Toremifene. Toremifene’s only structural difference compared with tamoxifen relates to a single chlorine atom at position 4 (Fig. 2), and the pharmacological profiles of both drugs are similar (35, 36). Unlike tamoxifen, toremifene was found not to be hepatocarcinogenic in preclinical models (37, 38), which in part may relate to an inability of toremifene compared with tamoxifen to induce DNA adducts in the rat liver (39). Toremifene had a similar relative binding affinity for ER compared with tamoxifen and inhibited the growth of ER+ve breast cancer cells in vitro (40) and hormone-dependent breast cancer xenograft growth in vivo (41). However, like tamoxifen,

Table 1  The ideal profile of a novel SERM in comparison with tamoxifen

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Greater binding affinity for ER</th>
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<tbody>
<tr>
<td>Ability to antagonize estrogen-dependent growth of breast cancer cells in vitro</td>
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<tr>
<td>Equal or greater inhibition of hormone-dependent xenograft growth in vivo</td>
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<tr>
<td>Activity against tamoxifen-stimulated (resistant) tumors</td>
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<tr>
<td>Delayed emergence of antiestrogen resistance in vivo</td>
<td></td>
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<tr>
<td>Reduced agonist effects in uterotrophic assays</td>
<td></td>
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<tr>
<td>Lack of stimulation of endometrial cancer cells in vitro/in vivo</td>
<td></td>
</tr>
<tr>
<td>Lack of DNA adduct formation</td>
<td></td>
</tr>
<tr>
<td>Prevention of bone loss in ovariectomized animals</td>
<td></td>
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<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Activity in hormone-sensitive breast cancer, at least equivalent to tamoxifen</td>
<td></td>
</tr>
<tr>
<td>Increase in time-to-disease progression compared with tamoxifen</td>
<td></td>
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<tr>
<td>Activity in tamoxifen-resistant breast cancer</td>
<td></td>
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<tr>
<td>Improved side effect profile (e.g., reduced hot flushes)</td>
<td></td>
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<tr>
<td>No endometrial thickening/hyperplasia/cancer risk</td>
<td></td>
</tr>
<tr>
<td>Preservation of bone mineral density</td>
<td></td>
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<tr>
<td>Reduction in serum cholesterol</td>
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</table>
Toremifene had estrogenic effects on both endometrial cells and the uterus in vivo (42, 43), although it had slightly reduced estrogenic effects on bone (44). Toremifene was developed, therefore, as a triphenylethylene derivative of tamoxifen that might have less genotoxic potential and, therefore, could be a safer antiestrogen for breast cancer treatment.

High-dose toremifene (120–240 mg) has been investigated in five Phase II studies as second-line therapy in a total of 260 patients with tamoxifen-resistant breast cancer (45–49). These patients had failed to respond to tamoxifen for advanced disease, had progressed after an initial response, or had relapsed on adjuvant tamoxifen. The objective response rate in these studies ranged between 0 and 14%, although a proportion of patients (17–23%) had stable disease for at least 6 months. Although occasional tamoxifen-refractory patients may have had an objective response to toremifene, especially if they had responded to tamoxifen previously, it was concluded that cross-resistance probably exists between the two drugs (50).

With toremifene as first-line therapy in hormone-sensitive advanced breast cancer, several Phase II studies in a total of 175 patients showed objective responses rates of 48–68% with doses of 60–240 mg daily, with a suggestion that higher response rates occurred with the 240-mg dose (reviewed in Ref. 50). Low-dose (20 mg) toremifene was associated with a response rate of only 21% in an additional small study and was not investigated further (51). Subsequently, there have been five large Phase III randomized controlled trials of toremifene (40–60 mg) versus tamoxifen (20–40 mg) as first-line endocrine therapy in advanced breast cancer (see Table 2; Refs. 52–56). The response rate to toremifene in these larger multicenter studies was lower than in the Phase II studies and ranged from 21 to 38%. In all of these studies, toremifene showed efficacy equivalent to tamoxifen for objective response rate, stable disease, time-to-disease progression, and overall survival (Table 2). In addition, two of these studies randomized patients between 60 mg and higher doses (200/240 mg) of toremifene and found no significant difference in efficacy (53, 55). There was no difference in drug-related toxicities, and both toremifene and tamoxifen were well tolerated. A recent meta-analysis of 1421 patients from these trials showed a similar response rate for toremifene compared with tamoxifen (24 versus 25.3%), with no significant difference in time-to-disease progression (hazard ratio, 0.98; 95% CI, 0.87–1.11) or overall survival (hazard ratio, 0.98; 95% CI, 0.83–1.15; Ref. 57).

Any potential difference in carcinogenicity identified in preclinical studies was not evaluated in any of these studies and is probably of relatively little clinical significance in advanced breast cancer. However, at least two adjuvant studies were subsequently initiated to compare efficacy and, in particular, long-term tolerability and safety in early breast cancer patients. Preliminary data from ~900 postmenopausal node-positive patients after a median follow-up of 3.4 years have been reported, and there were no significant differences in efficacy or tolerability compared with tamoxifen (58). In particular, the number of subsequent second cancers was similar, although longer follow-up will be needed to see if any differences emerge.

Droloxifene. Structurally droloxifene is 3-hydroxymyostamoxifen and, as such, has a 10-fold higher relative binding affinity for ER compared with tamoxifen (59). In preclinical studies, droloxifene had several potential advantages over tamoxifen, including a shorter half-life (60), greater growth inhibition of breast cancer cells and reduced estrogenicity in the rat uterus (61), and absence of DNA adduct formation or carcinogenicity (62). However, like tamoxifen, it also behaved as an estrogen in bone, preserving bone mineral density (63).

Early Phase I/II studies suggested some efficacy in patients who had received tamoxifen previously (64, 65). A Phase II study of droloxifene, 100 mg daily, in 26 patients who had received tamoxifen previously, found a response rate of 15%, with stable disease >6 months in an additional five (19%) patients (66). A large randomized dose-finding study of 20, 40, or 100 mg droloxifene as first-line therapy in 369 patients showed objective response rates of 30, 47, and 44%, respectively (67, 68). Better response duration and time-to-disease progression were seen with the two higher doses, and there were no significant drug-related toxicities. Other first-line Phase II studies were undertaken, including one study in 39 patients that showed a response rate of 51% (95% CI, 35–67%) and median time-to-progression of 8 months (69). These first-line data suggested a level of efficacy comparable with that expected with tamoxifen, and randomized Phase III studies comparing droloxifene versus tamoxifen were initiated. However, droloxifene was found to be less active than tamoxifen, and further development was stopped (70, 71).

Idoxifene. Idoxifene (Fig. 2) is a SERM that is metabolically more stable than tamoxifen as a result of a pyrrolidino side chain, with increased binding affinity for ER because of the substitution of an iodine atom at the 4 position (72). Idoxifene

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**Table 2**  Summary of clinical efficacy data from the randomized Phase III trials of toremifene (40–60 mg/day) versus tamoxifen (20–40 mg/day) as first-line endocrine treatment of advanced breast cancer in postmenopausal women (ER status positive or unknown)

<table>
<thead>
<tr>
<th>Study</th>
<th>Toremifene</th>
<th>Tamoxifen</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>ORR (%)</td>
</tr>
<tr>
<td>Hayes et al. (53)</td>
<td>221</td>
<td>21%</td>
</tr>
<tr>
<td>Pythönen et al. (54)</td>
<td>214</td>
<td>31%</td>
</tr>
<tr>
<td>Gershonovitch et al. (55)</td>
<td>157</td>
<td>21%</td>
</tr>
<tr>
<td>Nomura et al. (52)</td>
<td>62</td>
<td>24%</td>
</tr>
<tr>
<td>Milla-Santos et al. (56)</td>
<td>106</td>
<td>38%</td>
</tr>
<tr>
<td>Meta-analysis (57)</td>
<td>725</td>
<td>24.0%</td>
</tr>
</tbody>
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**Notes:**

- ORR, objective response rate, including complete response and partial response; TTP, median time-to-disease progression.
- The meta-analysis (57) was published in 1999 and included data from the first four trials, together with a small German study (M. Kaufman, unpublished data), but did not include the Spanish study (56), which was published only in 2001.
inhibited hormone-dependent breast cancer growth and was more effective than tamoxifen at inhibiting both MCF-7 cell growth in vitro and rat mammary tumor growth in vivo (73). As a SERM, idoxifene had estrogenic agonist effects on bone (74). However, reduced agonist activity on breast cancer cells for idoxifene compared with tamoxifen in vivo was suggested by the greater inhibition of a MCF-7 xenograft growth in the absence of estradiol (75). Likewise, reduced stimulation of uterine weight was seen in various uterotrophic assays (73, 74). Thus, idoxifene was developed in the hope that the reduced agonist profile in breast and gynecological tissues would provide an advantage over tamoxifen for breast cancer patients.

In a Phase I study of idoxifene in 14 patients who had previously received tamoxifen, 2 patients had a partial response with idoxifene, and 3 patients had disease stabilization for >6 months (76). Results from a randomized Phase II study showed little evidence of significant clinical activity for idoxifene in 56 postmenopausal patients with tamoxifen-resistant breast cancer (77). Two partial responses (objective response rate, 9%) and two patients with stable disease were seen with idoxifene, whereas, in contrast, no objective responses were seen with a higher (40-mg) dose of tamoxifen. In a Phase III trial a total of 220 postmenopausal women with metastatic breast cancer were randomized to receive either idoxifene 40 mg/day or tamoxifen 20 mg/day as first-line endocrine therapy (78). The objective response rate [complete response plus partial response (CR+PR)] was 20% (95% CI, 12.7–28.2%) for idoxifene and 19% (95% CI, 12.5–28.2%) for tamoxifen, with a median duration of objective response of 8.1 months for idoxifene and 7.3 months for tamoxifen. There was no significant difference in time-to-disease-progression or overall survival. Although no differences were reported in gynecological adverse events between idoxifene and tamoxifen, in a parallel osteoporosis program an increased incidence of uterine prolapse and polyyps was reported in idoxifene-treated women. Thus, despite a reduced agonist profile for idoxifene seen in preclinical studies, there appeared to be no major differences in terms of clinical efficacy or safety profile between idoxifene and tamoxifen, and further development of the drug was stopped.

Other Tamoxifen-like Derivatives in Development. Other structural analogues of tamoxifen (Fig. 2) have been synthesized, including TAT-59, which has a 10-fold higher affinity for ER than tamoxifen and was more effective at inhibiting human breast cancer xenograft growth in vivo (79, 80). GW5638 is a carboxylic derivative in early clinical development that demonstrated significantly reduced agonist activity on the uterus in ovariectomized rats, yet remained a full agonist in reducing cholesterol and maintaining bone mineral density (81). CGP 336,156 (lasofoxifene) is a derivative of tetrahydronaphthalene that maintains bone mineral density in animal models (82) and, thus, may find an application for the prevention of osteoporosis (6). There are few (if any) published clinical data for any of these compounds in advanced breast cancer.

Clinical Efficacy of Tamoxifen-like SERMs. From the clinical data following failure of tamoxifen in advanced breast cancer, little significant activity has been observed overall with the first-generation tamoxifen-like SERMs (toremifene, droloxifene, and idoxifene) with a median response rate from all studies of only 5% (range, 0–15%; Table 3). The reduced agonist profile seen with droloxifene and idoxifene in preclinical studies may have been tissue- or cell-specific and did not appear to manifest itself as any improved efficacy in treating or preventing tamoxifen resistance in patients with breast cancer. If the agonist activity of tamoxifen were a major mechanism for the development of resistance, one might have hoped that SERMs with reduced agonist activity would offer a longer response duration or time to progression. The fact that they did not imply that, unlike the steroidal antiestrogen ICI 182,780 (fulvestrant), these drugs are probably completely cross-resistant with tamoxifen. Perhaps this is not surprising given the similar tamoxifen-like mechanism of action and structure-function interaction with ER for these triphenylethylene compounds. In contrast, fulvestrant acts by down-regulating ER expression (33, 34), and this may explain why the drug appears to have much better activity in tamoxifen-resistant breast cancer than toremifene or idoxifene (83, 84).

The combined Phase II/III clinical trial data for tamoxifen-like SERMs (toremifene, droloxifene, idoxifene) as first-line therapy suggest a median response rate of 31% (range, 20–68%), with a median time-to-disease progression of 6.9 months (Table 3). In the randomized first-line trials in hormone-sensitive advanced breast cancer, both toremifene and idoxifene were shown to be very similar to tamoxifen in terms of both clinical efficacy and toxicity (52–56, 78), whereas droloxifene appeared to be inferior (70). The toxicity profile was the same, including gynecological effects seen with idoxifene. On the basis of these present data, therefore, it is unlikely that the first-generation triphenylethylene SERMs will replace tamoxifen for advanced breast cancer, because they have failed to show superiority or any significant clinical advantage.

Table 3 Overall efficacy of tamoxifen-like SERMs in advanced breast cancer: response rate ranges from Phase II studies of toremifene, droloxifene, and idoxifene in tamoxifen-resistant or hormone-sensitive patients, and Phase III trials in first-line versus tamoxifen

<table>
<thead>
<tr>
<th>Tamoxifen-resistant, Phase II</th>
<th>Hormone-sensitive</th>
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<tr>
<td>Tamoxifen</td>
<td>Response Rate %</td>
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<tr>
<td>Toremifene</td>
<td>ORR (%)</td>
</tr>
<tr>
<td>Droloxifene</td>
<td>ORR (%)</td>
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<tr>
<td>Idoxifene</td>
<td>ORR (%)</td>
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<tr>
<td>Median</td>
<td>5</td>
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ORR%, % patients with an objective response, including complete response and partial response; S.D., % patients with stable disease for ≥6 months; TTP, median time to disease progression (in months).
Novel Second- and Third-Generation SERMs

Greater optimism has surrounded the profile of second- and third-generation SERMs (Fig. 3), in particular, that this profile may translate into an improved clinical benefit for breast cancer patients. Much of the enthusiasm relates to the fact that these drugs appear devoid of any agonist activity in the endometrium, while at the same time appearing to be potent antiestrogens in the breast that retain agonist activity in bone. Structurally, most of these drugs resemble the benzothiophene raloxifene which is the most extensively studied SERM in this class.

Raloxifene. The binding affinity of raloxifene for ER is similar to that of tamoxifen (85), and most of the pharmacological data showed activity that was similar to tamoxifen in terms of inhibiting breast cancer cells in vitro and rat mammary tumor growth in vivo (86, 87). In preclinical models, the drug maintained bone mineral density (8) and reduced total cholesterol (88) but, compared with tamoxifen, had significantly less estrogenic activity on endometrial cells and could inhibit tamoxifen-stimulated endometrial cancer growth in vivo (9). Raloxifene was subsequently developed and is now indicated for osteoporosis based on clinical trials that showed prevention of bone loss in postmenopausal women (89).

Although raloxifene was not developed as an antiestrogen for breast cancer, some limited data exist on the activity of raloxifene in patients with advanced breast cancer. In a small study in 14 patients who had become resistant to tamoxifen after an initial response, only 1 patient had a minor response when treated with 200 mg of raloxifene (90). In 21 patients with ER+ve metastatic breast cancer treated with raloxifene 150 mg twice a day as first-line therapy, 14 (19%) had a partial response for a median duration of 22 months with an additional 3 (14%) patients showing stable disease (91). Raloxifene does not appear to relieve vasomotor symptoms such as hot flashes. However, during raloxifene’s development for osteoporosis, it was found to significantly reduce the incidence of breast cancer (in particular, ER+ve tumors) in postmenopausal women by 76% (95%, CI, 56–87%), without any increase in endometrial thickening or risk to the gynecological tract (92, 93). Because tamoxifen may also reduce breast cancer incidence, albeit with an increased risk of endometrial cancer and thrombotic events (3), the current Study of Tamoxifen and Raloxifene (STAR) chemoprevention trial is comparing the effects of raloxifene with tamoxifen. The potential exists that, as a SERM, raloxifene may reduce breast cancer incidence with a better safety profile compared with tamoxifen; it is hoped that this trial will clarify which patients (i.e., with what level of breast cancer risk) derive benefit from chemoprevention.

Arzoxifene. LY 353381 (arzoxifene) is a benzothiophene analogue, which is a more potent antiestrogen with an improved SERM profile compared with raloxifene (94). In particular, arzoxifene was a more potent inhibitor of breast cancer cells in vitro than either tamoxifen or raloxifene and inhibited the growth of mammary tumor xenografts in vivo (95, 96). As a SERM, in preclinical studies, arzoxifene was a more potent agonist on bone and cholesterol metabolism than raloxifene (97, 98), with no evidence of any estrogen-like agonist effects on uterine tissues (94). In view of these promising data, arzoxifene has entered clinical development for the treatment of breast cancer.

In a Phase I study, 32 patients who had received a median of two prior endocrine therapies were treated with arzoxifene in doses ranging from 10 to 100 mg daily (99). No significant toxicities were seen, and, in particular, transvaginal ultrasound showed no endometrial thickening after 3 months of therapy. Six patients had stable disease for a median of 7.7 months (range, 6–33 months). In a Phase II study with arzoxifene as first-line therapy, 92 patients were randomized to either 20 mg or 50 mg daily (100). Only 95 patients had received tamoxifen previously in the adjuvant setting. There was no difference in response rate (36 versus 34%), in clinical benefit rate that included stable disease (63 versus 64%), or in time-to-disease progression (10.4 versus 8.9 months). Likewise toxicities were minor, although 30% reported minor hot flashes. More recently, preliminary results were reported of a further Phase II trial that compared both doses (20 and 50 mg) in 63 tamoxifen-resistant patients, and separately in 49 patients with hormone-sensitive disease (i.e., first-line therapy; Ref. 101). Response rates were low in the tamoxifen-resistant patients (10% for 20 mg, 3% for 50 mg), all of whom either had relapsed on adjuvant tamoxifen after at least 1 year of therapy or had progressed on tamoxifen for advanced disease after an initial response. In contrast, a response rate of 30% was seen with 20-mg arzoxifene in the hormone-sensitive group, with an additional 17% having stable disease and an overall median time-to-progression of 8.3 months. The response rate for the 50-mg dose was somewhat lower (8%), although numbers were small (only 25 patients). On the basis of all of the Phase II data, 20-mg arzoxifene has now been taken forward into a large multicenter Phase III trial against tamoxifen as first-line therapy.

EM-800. This is an orally active so-called pure nonsteroidal antiestrogen that is a prodrug of the active benzopyrene derivative EM-652 (SC 57068; Ref. 102). The binding affinity of EM-652 for ER is significantly greater than estradiol, tamoxifen, raloxifene, or fulvestrant (103). The prodrug EM-800 is a potent antiestrogen and was more effective than 4-hydroxytamoxifen and fulvestrant at inhibiting estradiol (E2)-induced cell proliferation in breast cancer cells in vitro, and, in the absence of E2, had no agonist effects on growth (104). In ZR-75-1 xenografts, EM-800 was significantly more effective than tamoxifen at inducing tumor regressions in vivo and, in the absence of E2, antagonized tamoxifen-stimulated tumor growth (105). In intact mice, EM-800 was 30-fold more potent than tamoxifen at inhibiting uterine weight and reducing uterine/vaginal ER expression (106). Likewise, EM-800 was devoid of any stimulatory effect on alkaline phosphatase activity (a sensitive marker of estrogenic activity) in Ishikawa endometrial carcinoma cells (107), whereas EM-652 had no agonist activity in an immature rat uterotrophic assay (108). In addition, studies have shown that EM-800 prevented bone loss in the ovariectomized rat (109) and lowered serum cholesterol levels (102). Interestingly, EM-800 appears to significantly down-regulate ER levels both in tumors and normal estrogen-sensitive tissues in a similar fashion to the steroidal antiestrogen fulvestrant (106), but its specific agonist effects on bone differentiate it from fulvestrant, which has not been shown to prevent bone...
loss. As such, EM-800/EM-652 has a potentially promising SERM profile.

In terms of clinical development, a Phase II study of EM-800 (20 mg or 40 mg) was undertaken in 43 postmenopausal women for whom tamoxifen had failed either in the metastatic or adjuvant setting (102, 110). There was one complete response and five partial responses (response rate, 14%), with most of the responses occurring in those who had received at least 3 years adjuvant tamoxifen (110). An additional 10 (23%) patients had stable disease for >6 months. On the basis of these results, a randomized Phase III study in patients who had failed to respond to tamoxifen was undertaken, comparing the efficacy of EM-800 (20 mg or 40 mg) with the third-generation aromatase inhibitor anastrozole. At the defined interim review when over 300 patients had been entered, the efficacy was less than that of anastrozole, and the trial was terminated. There are no data at present on the activity of EM-800 in the first-line hormone-sensitive population.

**ERA-923.** ERA-923 is a novel SERM that appears to have an improved preclinical profile compared with tamoxifen and raloxifene (111). ERA-923 is now being evaluated in a randomized dose-finding Phase II trial (25 versus 100 mg) as second-line therapy in 100 ER+ve patients with tamoxifen-resistant metastatic breast cancer. A similar randomized Phase II trial has been proposed in receptor-positive hormone-sensitive metastatic breast cancer as first-line therapy.

**Clinical Efficacy of Second- and Third-Generation SERMs.** These new compounds in preclinical models appear to offer a greater increase in potency and tumor growth inhibition, together with an improved SERM profile on other tissues, in comparison with the tamoxifen-like SERMs. At the present time, there are too few clinical data to know whether these potential advantages will translate into beneficial effects for breast cancer patients. However, in tamoxifen-resistant patients, the reported level of activity is low for raloxifene (90), arzoxifene (101), and EM-800 (Ref. 102; Table 4), with a median response rate of 6.5%, which is very similar to that observed with the tamoxifen-like SERMs (Table 3). It is probable that activity in first-line therapy will be similar to that of tamoxifen, because the only Phase II data with raloxifene and arzoxifene give a median response rate of 30%, with a median time to progression of 9.4 months (Table 4). Results of ongoing Phase II/III trials with arzoxifene and ERA-923 are awaited, but to date, there is little clinical evidence to suggest that in advanced breast cancer, substantial improvements in efficacy will be made over tamoxifen.

**Conclusion: Future Role for SERMs in Breast Cancer**

It is unclear to what extent any preclinical advantages that have been observed for each of these SERMs over tamoxifen may be predictive of clinical outcome in the treatment of advanced breast cancer. Thus far, the clinical data in advanced breast cancer summarized above are somewhat disappointing for the first-generation tamoxifen-like SERMs. Instead, much greater potential may exist in either the adjuvant or chemopreventive setting in which an improved SERM profile on bone, lipid metabolism, and the endometrium will be of maximum benefit. It remains to be seen whether vasomotor symptoms associated with both tamoxifen and raloxifene are any less frequent with the new SERMs. The dilemma faced by those developing these therapies, however, is the need to demonstrate clinical activity against breast cancer that is at least equivalent to tamoxifen. The clinical data outlined above suggest that, although there is probably little role for these drugs after failure of tamoxifen, their efficacy and tolerability in hormone-sensitive advanced breast cancer is probably equivalent to that of tamoxifen. Are these sufficient data to justify expensive large-scale adjuvant programs?

To complicate matters further, the scenario in hormone-dependent advanced breast cancer has changed significantly within the last 6–12 months. It is now clear that third-generation aromatase inhibitors (e.g., letrozole, anastrozole) are probably superior and better tolerated than tamoxifen (112-114). As a consequence, it is now difficult to envisage whether SERMs will have any role as first-line therapy for postmenopausal women with advanced breast cancer. If aromatase inhibitors become the first-line postmenopausal endocrine therapy of choice in the adjuvant as well as the metastatic setting, the question will soon emerge if or when antiestrogens such as tamoxifen, SERMs, or the steroidal compound fulvestrant should be used in breast cancer treatment. *In vitro* it is known that breast cancer cells adapt when subjected to long-term estrogen deprivation, remaining ER+ve and becoming hypersensitive to very low concentrations of E2 (115). It is conceivable that potent antiestrogens including SERMs could be active in this setting, and clinical trials with fulvestrant after aromatase inhibitor failure are in progress.

An alternative role for SERMs could be as adjuvant therapy, either alone or in combination with aromatase inhibitors, thus providing protection to the bone and cardiovascular system while enhancing antitumor efficacy. However, it is not clear whether any potential negative interaction on tumor cell growth could occur because of agonist activity of SERMs in an environment of complete estrogen deprivation. It has always been thought that endocrine therapies are better given in sequence rather than in combination, a view that has been challenged recently by data in premenopausal ER+ve advanced breast cancer in which combined estrogen deprivation with an antiestrogen was superior to either therapy alone, including a benefit.
in overall survival (116). To develop SERMs as adjuvant therapy, including as combined therapy with aromatase inhibitors, there seems to be no shortcut to performing some form of clinical efficacy/safety study in advanced breast cancer. Additional evidence of a SERM's biological activity and clinical efficacy could be ascertained from short-term randomized neo-adjuvant studies, as undertaken for idoxifene (117), raloxifene (118), and fulvestrant (119). The next 5 years will be crucial to see whether the latest generation of SERMs have a significant role in breast cancer therapy, and more importantly, what that role might be.

Open Discussion

Dr. Stephen Johnston: Droloxifene went into randomized studies against tamoxifen, but its development was stopped. I don’t know if anyone has any information on that.

Dr. Aman Buzdar: There were more than 1100 patients randomized to tamoxifen versus droloxifene, and there was no time-to-progression advantage in favor of the new compound. So the study was stopped, and the manuscript was submitted. The first journal thought it was a very good study, but because it’s a negative study, they didn’t want to publish it.

Dr. Kathleen Pritchard: Here’s an example of perfectly good data that should come out not getting published anywhere. I wondered, when I looked at the data from that study, whether it was another example of choosing a dose that may not have been high enough. Because what else is the explanation? You have a very big study with a lot of patients, and you see this phenomenon where the drug worked poorly in the younger group of patients where maybe there was competing estrogen, whereas in the patients over 60, the drugs were essentially equivalent. We had a small dose-finding study, and the two higher doses looked the same. One wasn’t more toxic than the other, and we decided to go with the lower dose because it looked just as good.

Dr. Per Lonning: It raises the question, how do we actually do a dose selection for the SERMs? All of the surrogate parameters we know are related to the estrogen agonistic, not the antagonistic effects.

Dr. Johnston: The other way to do that is to do the short-term preoperative study. You can look at proliferative or apoptotic changes in the primary tumor. You can do it in far fewer patients, and you can probably get a cleaner study. But then it’s an issue of whether you can take a brand new SERM and put it into earlier stage patients, because you need safety or toxicity data prior to that.

Dr. Kent Osborne: Are you looking at the very minimal data on raloxifene and breast cancer? If anything, it would seem to be a worse drug than tamoxifen, and certainly cross-resistant. How do you explain the fact that the same dose seems to be so effective in breast cancer prevention, or is it?

Dr. Johnston: The first question is: is it? The second is whether or not we’re looking at something completely different in terms of the effect on primed or unprimed breast epithelium that may or may not be malignant or premalignant versus an established tumor that may be heterogeneous in terms of its responsiveness. Having said that, tamoxifen is pretty effective in both scenarios, so we just have to wait and see what the STAR study shows.

Dr. Anthony Howell: That’s right. But the women treated in the MORE study were all old, whereas in the PI study they ranged in age, and it may be that these agents are better in older people, and the difference is a serious difference.

Dr. Victor Vogel: Just a comment on the MORE study. Not only were those patients old, but they were old with osteoporosis. There’s a summary of osteoporosis data in the current issue of the Journal of the National Cancer Institute showing that with demonstrable osteoporosis, the breast cancer risk is about 3-fold lower [J. M. Zmuda et al., J. Natl. Cancer Inst. (Bethesda), 93: 930–936, 2001]. Now, whether or not that would translate into an inability of raloxifene to reduce risk is exactly the question in the STAR trial.

Dr. Paul Goss: It’s true osteoporosis is a reduced risk factor, but when you actually look at the incidence of breast cancer risk in the placebo arm of the MORE trial, it’s higher than the SEER population-based age-matched incidence. The trial still attracted women with an increased risk of breast cancer, despite early osteoporosis.

Dr. Matthew Ellis: Dr. Brodie has a very nice aromatase inhibitor model of the transfected MCF-7 cells. What about in the tamoxifen-resistant tumor models in nude mice? That model also is not quite as robust, although at least it predicted fulvestrant worked in tamoxifen-resistant breast cancer.

Dr. Osborne: I think tamoxifen-stimulated growth is a common source of resistance, and I think it predicts what happens with different endocrine therapies.

Dr. Johnston: You have to be careful with that model; we did some studies with idoxifene in that scenario as well. We were able to show partial non-cross-resistance. Some of the tumors that grew with tamoxifen were more likely to respond to idoxifene. But it wasn’t dramatic by any means—not as convincing as the fulvestrant data. It’s a model. But when we’ve gone to look in patients, we just don’t see the response.

References


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