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Comparative Tolerability of First-Generation Selective Estrogen Receptor Modulators in Breast Cancer Treatment and Prevention

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Contents

Abstract

In general, the selective estrogen receptor modulators (SERMs) currently indicated for the treatment and prevention of breast cancer, i.e. tamoxifen and toremifene, are fairly well tolerated. However, tamoxifen has been shown to induce hepatocellular carcinomas in rats, but not in humans, and can increase the risk of endometrial cancer in humans by two to three times. Other potentially serious adverse effects which have been associated with tamoxifen and toremifene therapy include vasomotor symptoms, an increased risk of venous thromboembolic events, and an increased incidence of cataracts and ocular toxicity,

fatty liver, and nonmalignant hepatic and uterine changes. In addition, long term tamoxifen use almost always results in resistance to the drug and, indeed, has actually been shown to promote tumour proliferation in human breast cancer cells. Both tamoxifen and toremifene display drug interactions with a variety of drug classes.

The adverse events associated with these compounds have raised significant concerns regarding their widespread use for the treatment and prevention of breast cancer. In addition, because of the weakness and scarcity of the data on toremifene, any conclusions about its tolerability remain tentative until outcomes of ongoing clinical trials in the adjuvant setting are known. A third SERM, raloxifene, is the focus of several large randomised trials examining its efficacy in the prevention of breast cancer. At present, each potential adverse event needs to be weighed against potential benefits in the decision to undergo SERM treatment. An array of therapies is currently available for patients with breast cancer and women at increased risk of disease; the risk-to-benefit ratio for each agent should be carefully examined in determining the most advantageous regimen.

Breast cancer is the most common nondermatological cancer in women and the second leading cause of cancer-related deaths among women in the US.[1] An association between ovarian hormones and breast cancer was first suggested in the 1890s when Beatson showed that oophorectomy could lead to tumour regression in women with metastatic breast cancer.[2] The link between hormones and neoplasia was substantiated in the mid-1960s by the description of the estrogen receptor (ER).[3] Estrogens are capable of promoting tumour growth via the stimulatory action of ligand-dependent nuclear ERs.[4] Consequently, endocrine therapies designed to block the effects of estrogen on mammary tumours have been developed and, at present, are the major treatment modalities for breast cancer management.

A class of synthetic nonsteroidal compounds that act through ERs has been developed for the treatment of estrogen-associated diseases. Originally called antiestrogens because of their ability to antagonise estrogen,[5,6] many of these compounds demonstrate tissue-specific estrogenic or antiestrogenic responses.[7] This class of compounds is now referred to as selective estrogen receptor modulators (SERMs).[8] Because of their unique pharmacologic properties, SERMs can achieve the beneficial effects of estrogens (i.e. demonstrate estrogen agonist activity) in nonmammary tissues such as bone, but have an estrogen antagonistic effect in breast tissue.

The subject of this paper is the tolerability of the SERMs tamoxifen and toremifene, which are currently indicated for the treatment and prevention of breast cancer. The paper discusses the carcinogenic and noncarcinogenic adverse effects which have been associated with tamoxifen and toremifene therapy, as well as potential drug interactions, and briefly reviews alternative therapies.

1. Selective Estrogen Receptor Modulators (SERMs) Used to Treat and Prevent Breast Cancer

1.1 Overview of the Mechanism of Action of SERMs

Elucidating the mechanisms for the site-specific action of SERMs remains a subject of ongoing research. Recent advances in the understanding of the ER, its subtypes ERα or ERβ,[9] and its structural characteristics[10] have provided deeper insight into the complex pharmacodynamics of SERM action.[11,12] It now appears that the biocharacter of a given SERM, which can range from acting as a full estrogen agonist to acting as a full estrogen antagonist, is determined by its chemical structure,

the ER isoform it binds to, and the set of coactivator or corepressor molecules that interacts with the ligand-ER complex and results in unique structural perturbations.[12,13] The final tertiary structure of the SERM-ER complex dictates whether transcription will occur at a particular promoter.

1.2 Tamoxifen

The most widely prescribed SERM is tamoxifen citrate, a derivative of triphenylethylene that demonstrates antiestrogenic properties in breast tissue and estrogenic properties in bone and uterus.[7,14] Although tamoxifen also has an estrogenic effect on lipids and lipoproteins,[7,14,15] tamoxifen did not reduce cardiovascular events in a recent clinical trial.[16] Tamoxifen binds to the ER with an affinity approximately 20 times lower than that of 17β-estradiol.[17] Due to its stimulatory effects on the uterus, tamoxifen is classified as a first-generation SERM.[18]

Tamoxifen has been used in the treatment of breast cancer for several decades and has proven efficacious for both early stage and advanced tumours.[19,20] The Early Breast Cancer Trialists' Collaborative Group analysed 55 separate randomised trials of tamoxifen prior to 1990, which included more than 37 000 women.[20] In their 1998 overview, the group found that tamoxifen treatment for up to 5 years significantly decreased cancer recurrence in women with ER-positive tumours. Health organisations currently recommend a 5-year regimen of oral tamoxifen at 20 mg/day for women with ER-positive tumours.[21]

Tamoxifen has also been shown to reduce the risk of breast cancer. In a large placebo-controlled trial conducted in the US, the National Surgical Adjuvant Breast and Bowel Project (NSABP)-P1 trial studied tamoxifen (20 mg/day) treatment in 13 388 women at high risk for developing breast cancer. Tamoxifen was found to reduce the risk of invasive and non-invasive breast cancers in all age groups by nearly 50% and to reduce the incidence of ER-positive breast cancer risk by 69%.[22] Based on the NSABP data, tamoxifen was approved by the US Food and Drug Administration (FDA) in October 1998 for use in breast cancer prevention.[23] In contrast, two European trials published the same year as the FDA approval did not observe a chemoprotective effect of tamoxifen in women with an increased risk for breast cancer.[24,25]

1.3 Toremifene

Toremifene citrate is a chlorinated analogue of tamoxifen and, like tamoxifen, a triphenylethylene derivative. Toremifene and its 4-hydroxylated metabolite bind tightly to ERs with affinities similar to that of tamoxifen,[26,27] and toremifene has antiestrogenic activity similar to that of tamoxifen. Since it can stimulate uterine proliferation[28] and acts as an estrogen agonist on bone and serum lipids,[15,29] toremifene is also classed as a first-generation SERM.

Three randomised phase III clinical studies conducted in North America, Eastern Europe, and Scandinavia served as the basis for the 1997 FDA approval of toremifene citrate for the treatment of metastatic breast cancer in postmenopausal women. In the North American trial, Hayes et al.[30] compared the efficacy of two different dosages of toremifene (60 and 200 mg/day) with that of tamoxifen (20 mg/day). Among the evaluable patients, the objective response rates for all three treatments were approximately 25%.[30] Response rates in the North American and Eastern European trials were virtually identical,[30,31] but the Nordic trial resulted in somewhat higher response rates for both tamoxifen and toremifene.[32] These three studies also showed equivalent efficacy between tamoxifen and toremifene in time-to-treatment failure and overall survival, supporting the conclusion that toremifene is as effective as tamoxifen for the treatment of metastatic breast cancer.[33]

The potential usefulness of adjuvant toremifene in the treatment of women with high risk or primary breast cancer is currently being examined by several large multi-institutional trials.[34] The Finnish Breast Cancer Group began a trial in 1992 to compare the efficacy and adverse effects of toremifene with tamoxifen as adjuvant therapies for postmenopausal node-positive breast cancer pa-

tients. Preliminary results from 899 patients demonstrated that after a mean follow-up of 3.4 years, the efficacy of adjuvant toremifene (40 mg/day) was not significantly different from that of tamoxifen (20 mg/day) in preventing breast cancer recurrence; there was a 23.1% recurrence rate among toremifene-treated patients and a 26.1% recurrence rate among tamoxifen-treated patients.[35] The authors note that the 3 years of toremifene use in this study may be too short to assess efficacy; the Early Breast Cancer Trialists' Collaborative Group overview of 55 tamoxifen trials found that 5 years of adjuvant tamoxifen therapy is superior to 2 years or less in preventing disease recurrence.[20]

As yet, the number of patients treated with toremifene is too small, and the number of follow-up years too few, to form strong conclusions about the efficacy and tolerability of toremifene. Results from ongoing adjuvant trials are awaited before making a determination as to whether toremifene should be used widely in breast cancer prevention.

1.4 Raloxifene

Raloxifene is classified as a second-generation SERM because it acts as an estrogen-receptor antagonist on both the breast and uterus but as an estrogen agonist on bone and blood lipid profiles.[36,37] Raloxifene binds to the ER with an affinity similar to 17β-estradiol.[38,39] In 1997, the FDA approved raloxifene hydrochloride for the prevention of osteoporosis in postmenopausal women.

To date, raloxifene has not been approved by the FDA for either the treatment or prevention of breast cancer. In studies examining efficacy in the prevention of osteoporosis, raloxifene has been shown to result in fewer breast cancers in women when compared with placebo.[40] Several large clinical trials are underway to examine the efficacy of raloxifene for the prevention of breast cancer. NSABP researchers are conducting the Study of Tamoxifen and Raloxifene (STAR) trial to compare raloxifene with tamoxifen treatment for reducing the incidence of breast cancer in women with an increased risk of developing the disease.[41] The Raloxifene Use for the Heart (RUTH) trial, initially designed to examine potential cardioprotective effects of raloxifene,[42] recently modified its main objectives to include an assessment of raloxifene's effect on breast cancer risk.[43]

1.5 Other SERMs

Two additional triphenylethylene derivatives, droloxifene (3-hydroxytamoxifen) and idoxifene (pyrollidino-4-idotamoxifene), have been evaluated clinically as breast cancer therapies, but information on these drugs is limited.[6,44] Phase I and phase II trials with droloxifene demonstrated efficacy for the treatment of breast cancer;[45,46] however, preliminary data from a large phase III trial indicate that the drug has no benefit beyond that of current therapies. As a result, the manufacturer has halted clinical development of droloxifene for breast cancer.[47] Idoxifene is currently in phase II trials for breast cancer treatment; data are not yet available to determine its benefit over currently recommended endocrine therapies.

2. Carcinogenic Effects Associated with Tamoxifen and Toremifene

Since tamoxifen and toremifene are the only SERMs currently indicated for the prevention or treatment of breast cancer, the following discussion is limited to these compounds. In general, tamoxifen and toremifene are fairly well tolerated, but both carcinogenic and noncarcinogenic adverse effects have been associated with their use. At this point, there is much more data on adverse effects of tamoxifen than toremifene; due to extensive clinical experience with tamoxifen. Thus, any conclusions about the tolerability of toremifene are highly speculative until outcomes of ongoing trials are known. Table I provides a summary of the tolerability profiles of tamoxifen and toremifene.

2.1 Breast Cancer

Animal studies evaluating long term tamoxifen treatment of athymic nude mice implanted with MCF-7 human breast cancer cells demonstrate that tamoxifen treatment eventually leads to tumour

growth.[58,59] The tumours remain ER-positive and will grow in response to either estradiol or tamoxifen.[59] The mechanism of tamoxifen-stimulated proliferation is unknown; one hypothesis is that a receptor mutation converts the antagonistic tamoxifen-ER complex into an agonistic complex, thus promoting tumour growth.[11]

These laboratory studies highlight the need to determine the appropriate duration of tamoxifen therapy: too short a treatment may not confer maximal anti-tumourigenic effects, whereas too long a treatment may result in drug resistance.[65] Investigators from the NSABP-B14 study examining the effects of tamoxifen on ER-positive, lymph-node negative breast cancer found that patients derived no additional benefit from tamoxifen treatment for periods of up to 7 years beyond the first 5 years.[66] Moreover, these investigators observed a slight advantage in patients who discontinued treatment after 5 years compared with those who continued tamoxifen therapy for up to 7 years. The NSABP results are consistent with recently updated results from the Scottish Adjuvant Tamoxifen Trial that found no additional benefit from tamoxifen therapy administered beyond 5 years.[67] Two large clinical trials are currently addressing the optimal duration of tamoxifen therapy for breast cancer: the 'adjuvant Tamoxifen Treatment offer more? (aTTom)' and 'Adjuvant Tamoxifen–Longer Against Shorter (ATLAS)' trials.[68] Until outcomes from these trials are known, 5 years appears to be the optimal time for tamoxifen treatment.

2.2 Hepatic Tumours

The estrogenic properties of tamoxifen have led to its implication in the pathogenesis of murine hepatic tumours.[48,49,51,59,69] At high doses, a reactive metabolite of tamoxifen is capable both of covalently binding to cytochrome P450 (CYP)[70,71] and of producing DNA adducts in rat liver microsomes.[72,73] As a result, tamoxifen is considered a strong hepatocarcinogen in rats.[49,50] In humans, however, examinations of liver biopsies from tamoxifen-treated patients have not found significant numbers of DNA adducts.[52,74] In a large Swedish trial, Fornander and colleagues[54] reported that out of approximately 5000 patients who had received tamoxifen treatment at 40 mg/day (twice the normal recommended dosage), two patients developed hepatocellular carcinoma as compared with no patients in the placebo group. In general, epidemiological evidence has refuted the hypothesis that

Table I. Tolerability profiles for tamoxifen and toremifene

Adverse effects	Tamoxifen	Toremifene	References
Carcinogenic effects			
Liver	Tumourogenic in rats	Nontumourogenic in rats	48, 49, 50
	Nontumourogenic in humans	Nontumourogenic in humans	22, 51-53
Endometrium	Uterotrophic	Unknown; may be less uterotrophic than tamoxifen	54, 55-57
MCF-7 human breast cancer cells	Resistance and stimulation of growth occurs with prolonged treatment	Inhibits growth	58, 59
Other effects			
Vasomotor	Hot flushes reported in ≈50% of patients	Hot flushes reported in ≈50% of patients	22, 35
Thromboembolism	3-fold increased risk of events	Risk of events appears similar to tamoxifen	22, 33, 35
Ocular	Low incidence of ocular toxicity. Increased risk for cataracts	Low incidence of ocular toxicity. Increased risk for cataracts	22, 33, 35
Hepatic	Abnormal enzyme values. Fatty liver in 30% of patients	Abnormal enzyme values. Fatty liver in 8% of patients	30, 33, 60, 61
Uterine	Endometrial hyperplasia, cysts, and fibroids	Endometrial hyperplasia, cysts, and fibroids	28, 35, 62-64

tamoxifen is a liver carcinogen in humans,[22,51,52,75,76] although the increase in prophylactic application of the drug has led some researchers to advise close monitoring of patients' hepatic status.[50,76-78]

In contrast to tamoxifen, toremifene does not produce hepatocellular carcinomas in rats,[48,49] possibly due to the fact that neither toremifene nor its metabolites result in DNA adducts in rat liver.[79] However, activated metabolic intermediates of toremifene are capable of inflicting DNA damage.[80] For example, in the presence of a promoter such as phenobarbital (phenobarbitone), toremifene is capable of inducing hepatic aneuploidy.[81] In general, very little data have been published regarding the carcinogenesis of toremifene, but to date no cases of hepatocellular carcinomas in humans have been reported during toremifene treatment.[33,35,53] Further long term studies are required.

2.3 Endometrial Cancer

Individual case reports of an association between tamoxifen and endometrial cancer have been published since the mid-1980s.[82] Results from the Swedish trial, published in 1989, were the first data from a large randomised study examining the association between endometrial cancer and adjuvant tamoxifen therapy. In this study, daily treatment with tamoxifen 40mg was associated with a relative risk (RR) of endometrial cancer of 6.4 [95% confidence interval (CI), 1.4 to 28] when compared with controls (who received no adjuvant endocrine therapy).[19,54] In the NSABP-B14 trial, where more than 2800 women with ER-positive tumours were randomised to tamoxifen 20 mg/day or placebo,[75] 23 of the tamoxifen-treated patients developed endometrial cancer after a mean follow-up of 8 years, as compared with two patients who received placebo (RR 7.5; 95% CI, 1.7 to 32.7). In analysing reported endometrial cancers from all placebo-controlled trials with tamoxifen up to 1996, Assikis and colleagues[55] found a 2- to 3-fold increase in the incidence rate of endometrial carcinoma in patients treated with tamoxifen. In the large NSABP-P1 prevention study, tamoxifen use at 20 mg/day for 5 years resulted in a similar 2.53 times greater risk of invasive endometrial cancer (95% CI, 1.35 to 4.97).[22] The increased risk was predominantly in participants 50 years or older (RR for women ≤49 years of age = 1.21, 95% CI, 0.41 to 3.60; RR for women ≥50 years of age = 4.01, 95% CI, 1.70 to 10.90).[22]

Total duration of tamoxifen treatment has also been examined with respect to endometrial cancer risk. Robinson et al.[83] reported that tamoxifen (20 mg/day) therapy for over 1 year results in a marked increase in the RR for endometrial cancer (RR 15.2; 95% CI, 2.8 to 84.4) over non-users. A case-controlled study in The Netherlands found that of women who had developed endometrial cancer following breast cancer, 36% had been treated with tamoxifen.[56] These authors demonstrated that the risk of endometrial cancer increased with duration of tamoxifen usage, with RRs of 2.0 (95% CI, 1.2 to 3.2) for 2 to 5 years of use and 6.9 (95% CI, 2.4 to 19.4) for at least 5 years of use. Endometrial cancer-specific survival 3 years after diagnosis was significantly worse for long term tamoxifen users: 76% survival for patients who had used tamoxifen for at least 5 years compared with 94% survival for non-users ($p = 0.02$). In 1996, tamoxifen was classified by the International Agency for Research on Cancer as a human endometrial carcinogen,[84] although some contend that further research is necessary before accepting this classification.[85-87]

In contrast to data from the NSABP-P1 trial mentioned above,[22] several smaller studies investigating tamoxifen use at the dosage of 20 mg/day have found no association with endometrial cancer,[88,89] although trends toward a duration- and dosage-dependent relationship have been seen.[90,91] Importantly, it is not known whether tamoxifen actually causes the endometrial cancer or whether tamoxifen use facilitates detection through more frequent check-ups. In the laboratory, tamoxifen has been found to directly stimulate growth of ER-positive endometrial tumours in athymic mice,[59,92,93] suggesting a causative clinical relationship. Further, since the NSABP-P1 trial[22] was placebo-controlled, the observed 2.5-fold increase in endo-

metrial cancer risk observed with tamoxifen treatment cannot be attributed to diagnosis bias.

Studies have typically not found an increased risk of endometrial cancer with toremifene, although toremifene produces histological effects on the uterus similar to tamoxifen.[29,57] In summarising published data, Mäenpää et al.[57] noted that after a total cumulative clinical exposure to toremifene of 140 000 patient years, only 9 cases of endometrial cancer have been reported to date. These authors calculated an annual hazard rate (per 1000 patient years) of 1.14 for endometrial carcinoma in postmenopausal breast cancer patients receiving adjuvant toremifene;[57] this rate falls within the hazard rates for adjuvant tamoxifen and placebo (2.0 and 0.4, respectively).[94]

The extremely limited clinical experience with long term use of toremifene warrants caution in interpreting these figures. The power to detect increased endometrial cancers with toremifene as compared with tamoxifen is further limited by the fact that, prior to 1992, toremifene trials took place in the metastatic breast cancer setting, where the development of endometrial cancer is unlikely to be detected. In addition, toremifene may unmask pre-existing endometrial tumours rather than playing a causative role.[57] Further clinical evidence is therefore required to determine whether there is a relationship between toremifene and endometrial tumours.

2.4 Colorectal and Stomach Cancers

Rutqvist et al.[95] combined data from three major Scandinavian studies (the Stockholm Trial, the Danish Breast Cancer Group Trial, and the South-Swedish Trial) that evaluated adjuvant tamoxifen therapy in approximately 5000 postmenopausal women. In these studies, tamoxifen-treated patients exhibited a 2-fold greater risk of colorectal cancer (RR 1.9; 95% CI, 1.1 to 3.3) and a 3-fold greater risk of stomach cancer (RR 3.2; 95% CI, 0.9 to 11.7) compared with non-users. However, other large studies have not found any increased incidence of colon[20,22] or stomach cancer in patients treated with tamoxifen.[22] This disparity may result from dosage differences; in the Scandinavian studies, women were administered tamoxifen at higher doses than in the larger studies. To date there have been no reports of increased incidence of colon or stomach cancer with toremifene treatment.[33,35]

3. Noncarcinogenic Effects Associated with Tamoxifen and Toremifene

3.1 Vasomotor

Because of its antiestrogenic properties, vasomotor instability (e.g. hot flushes and sweating), similar to that encountered with menopause, is a common adverse effect of tamoxifen. In the NSABP-P1 study, 46% of patients treated with tamoxifen reported hot flushes as quite bothersome to extremely bothersome, compared with 29% of patients in the placebo group.[22] Numerous studies confirm an increased incidence of hot flushes and sweating with tamoxifen,[33,35,78,96-98] which can cause discontinuation of treatment.[96]

An increased incidence of vasomotor adverse effects with toremifene has been demonstrated, both in comparison with placebo[99] and in comparison with tamoxifen-treated patients. In a meta-analysis of the 5 phase III trials completed as of 1999, Pyrhönen et al.[33] reported that the incidences of hot flushes (18%) and sweating (14%) in patients receiving toremifene were similar to those observed in tamoxifen-treated patients. Similarly, the Finnish Breast Cancer Group trial that compared adjuvant toremifene with tamoxifen found that the incidences of sweating and hot flushes were comparable between the two treatment groups; approximately 50% of patients in both treatment groups reported vasomotor adverse effects.[35]

3.2 Venous Thromboembolism

As with other estrogen therapies, there is clinical evidence of an increased risk of thromboembolic events such as deep vein thromboses and pulmonary emboli in patients treated with tamoxifen.[78,100] The NSABP-P1 researchers observed pulmonary emboli in almost 3 times as many women in the tamoxifen-treated group as in the placebo group

(RR 3.01; 95% CI, 1.15 to 9.27).[22] Of tamoxifen-related pulmonary embolic events, 89% occurred in women 50 years of age or older. The NSABP data further showed that more women who had received tamoxifen developed deep vein thromboses than women who had received placebo (RR 1.60; 95% CI, 0.91 to 2.86); the majority of these events also occurred in women 50 years of age or older. In addition, there was an increase in the incidence of stroke among women over 50 who had received tamoxifen (35 events in the tamoxifen group compared with 20 events in the placebo group).[22]

The rate of thromboembolic events associated with toremifene treatment appears similar[33] to that found with tamoxifen. Holli and colleagues[35] observed slightly more vascular complications with the tamoxifen-treated patients than with the toremifene-treated patients, but the small difference was not statistically significant (5.9% and 3.5% respectively, p = 0.11).

3.3 Ocular

Reports of a low incidence of ocular toxicity with tamoxifen, including retinopathy, corneal keratopathy, and optic neuritis, have appeared in the literature for several decades.[78,98,101] Small prospective studies in women who were administered long term, low dose tamoxifen have found decreased visual acuity,[102,103] bilateral macular oedema,[102] and retinal deposits.[102] In these studies, ocular symptoms appeared in approximately 6% of the patients after 1 year of treatment with tamoxifen and were generally reversible upon cessation of treatment.[102] Larger clinical trials have not corroborated a high incidence of vision-threatening ocular toxicity,[22,101,104,105] although intraretinal crystals and posterior subcapsular opacities have been shown to occur among tamoxifen-treated patients.[101,105]

More recently, attention has focused on an association between cataracts and tamoxifen therapy. Data from the NSABP-P1 trial demonstrate an increase in the rate of cataracts for tamoxifen-treated women versus placebo.[22] The rate of cataract development among participants was 21.72 per 1000 women in the placebo group and 24.82 per 1000 women in the tamoxifen group (RR 1.14; 95% CI, 1.01 to 1.29). Paganini-Hill and Clarke[104] investigated cataract frequency in 1297 patients with breast cancer and calculated that long term users of tamoxifen (6 years or greater) had an increased risk of cataract development of 1.70 (95% CI, 1.11 to 2.59) when compared with non-users.

Available data suggest that toremifene results in ocular effects similar to those seen with tamoxifen.[29,33] In the three large comparative studies published to date, there was no significant difference between toremifene and tamoxifen in the observation rates for ocular events, although a slight trend toward more ocular events with toremifene was observed. For example, twice as many patients experienced corneal keratopathy with toremifene (0.7% of toremifene patients *vs* 0.3% of tamoxifen patients). Cataracts are associated with toremifene treatment at rates similar to tamoxifen.[33,35]

3.4 Hepatic

In addition to the potential association with hepatocellular carcinoma described in section 2.2, non-malignant hepatic effects of tamoxifen have been reported. These effects include abnormal hepatic enzyme values,[35] hepatic steatosis,[60,106,107] and non-alcoholic steatohepatitis.[60] Researchers in Japan have used abdominal computed tomography scanning to diagnose fatty liver in more than 30% of patients treated with adjuvant tamoxifen.[60] In contrast, larger studies using serum markers to assess hepatic status did not find liver damage with tamoxifen;[108] one study suggests that the difference in diagnostic method accounts for the discrepancy in the detection of fatty liver.[61]

The distribution incidence of hepatic toxicity is similar for toremifene, with reported incidences of abnormal enzyme levels,[30,35] hepatic steatosis, and non-alcoholic steatohepatitis.[61] In general, no differences between toremifene and tamoxifen have been seen in the incidence of abnormal enzyme values;[35] however, laboratory results have suggested a difference in the incidence of fatty liver. A study of 52 breast cancer patients in Japan found that the incidence of toremifene-induced

fatty liver was significantly lower than that induced by tamoxifen, with toremifene resulting in roughly 8% of patients with fatty liver[61] as compared with 36% for tamoxifen.[107] The absence of clinical manifestations of non-alcoholic steatohepatitis often precludes early diagnosis, and it has been suggested that patients undergoing SERM treatment should have liver function tests prior to initiating, and periodically throughout, treatment.[61,106,107] However, the small number of patients in the studies examining toremifene and hepatic effects cautions against drawing firm conclusions.

3.5 Uterine

Nonmalignant effects of tamoxifen on the uterus have been reported. The effect of tamoxifen on uterine morphology has been studied by ultrasonography and hysteroscopic imaging, both prior to initiation, and at regular intervals during, therapy. In a prospective, hysteroscopic follow-up study, Neven and colleagues[109] found endometrial changes in 9 out of 16 tamoxifen-treated patients. The majority of these changes were benign, including endometrial polyps and hyperplasia. Other investigators have identified similar uterine effects of tamoxifen, including endometrial thickening, cysts, and fibroids,[28,51,62-64] as well as ovarian cysts.[62,110] To date, a large clinical trial assessing nonmalignant effects of tamoxifen on the uterus has not been conducted.

The established endometrial effects of tamoxifen have resulted in a tendency for clinicians to recommend routine endometrial surveillance for postmenopausal tamoxifen users[111] despite a lack of uniform consensus on its effectiveness. Conflicting opinions exist regarding the method, usefulness, and/or cost effectiveness of endometrial screening in patients receiving tamoxifen.[112-114] A few recent studies indicate that endometrial screening in asymptomatic patients is not warranted because of high false-positive rates of endometrial sonographic screenings[112] and the low frequency of significant findings with hysteroscopy.[63,115,116] Others recommend that only patients who present with abnormal vaginal discharge or bleeding should have a hysteroscopy with endometrial sampling.[113,114,116,117]

Uterine effects of toremifene have not been extensively studied. In comparing the endometrial effects of tamoxifen (20 mg/day) with those of toremifene (60 mg/day), Tomás and colleagues[28] found a greater percentage of patients with endometrial changes in the tamoxifen group than in the toremifene group (57 *vs* 30%). Holli et al.[35] reported an equal number of endometrial events between adjuvant tamoxifen- and toremifene-treated patients, including uterine polyps, haemorrhage, endometrial hyperplasia, uterine fibroids, and ovarian cysts. In this latter study, the number of endometrial polyps in toremifene-treated patients was similar to that in tamoxifen recipients (8 *vs* 7, respectively), leading the authors to suggest that in the uterus, toremifene may have carcinogenic potential similar to tamoxifen. Outcomes of ongoing trials are awaited to determine if this is the case.

3.6 Other Adverse Effects

Additional adverse effects reported for both tamoxifen and toremifene include vaginitis (bleeding and discharge), itching, dizziness, nausea, headache, diarrhoea, rash, depression, and insomnia.[22,30,35,77,97] While these events are not generally considered life threatening, their impact on patients quality of life can be profound.[22,77,97] Typically, profiles for these quality-of-life effects are similar for tamoxifen and toremifene.[33,35] In one study, the incidence of nausea was significantly higher in patients treated with a high dosage of toremifene (200 mg/day) than in patients treated with a lower dosage of the drug (60 mg/day) or tamoxifen (20 mg/day; 20 *vs* 14%, $p < 0.05$).[30]

There have been no adequate and well-controlled trials of tamoxifen or toremifene in pregnant women, but studies with neonatal animal models suggest that tamoxifen may be teratogenic.[77] Pregnancy in premenopausal women taking tamoxifen or toremifene is strongly discouraged, and the manufacturers recommend careful monitoring and assessment of the risks to the fetus.[118,119] Tamoxi-

fen and toremifene are classified as FDA Category D for pregnancy risk.

4. Drug Interactions with SERMs

Drug interactions with SERMs have been reported in animal studies; however, clinical data are limited.[44] Interactions have been reported with anticoagulants, drugs metabolised by CYP3A4 and certain antineoplastic agents.

First, triphenylethylenes such as tamoxifen and toremifene are known to interact with coumarin-type anticoagulants (e.g. warfarin).[120,121] This interaction is considered life threatening because it can lead to a 1.5- to 2-fold increase in prothrombin time.[120,121] In clinical situations in which concurrent therapy is justified, the patient's prothrombin time needs to be closely monitored.[119]

Second, tamoxifen, toremifene, and some of their metabolites are potent inhibitors of CYP3A4. In the process, they inhibit their own metabolism as well as that of an array of xenobiotics.[44] In addition, the metabolism of tamoxifen and toremifene is altered by drugs known to inhibit CYP3A4 enzymes; for example, ketoconazole and other antimycotics.[118,119]

Third, the risk of thromboembolic events with tamoxifen increases when coadministered with the antineoplastic agents cyclophosphamide, methotrexate, and fluorouracil (CMF).[122] In a multicentre, randomised trial involving 705 postmenopausal women undergoing treatment for breast cancer, the incidence of serious thromboembolism while undergoing tamoxifen-only therapy for 2 years was 2.6%; the incidence of thromboembolic events was 13.6% in patients who had undergone a 6-month regimen of CMF in addition to the 2 years of tamoxifen.[122] Interaction between toremifene and CMF has not been evaluated.

Finally, pharmacodynamic interactions between tamoxifen and etoposide result in an increase in haematologic toxicity, as manifested by leucopenia or neutropenia.[123] Corona et al.[123] studied this phenomenon by coadministering etoposide (100 mg/day) and oral tamoxifen (40 mg/day) to a study group (n = 14). The control group (n = 17) received the same regimen of etoposide without tamoxifen. A significantly larger percentage of patients who had received both tamoxifen and etoposide experienced haematologic toxicity when compared with the control group (43 *vs* 26%, respectively).

5. Alternatives to SERMs

Due to the potential adverse effects, proposed limited benefits,[124] and conferred resistance[65] with tamoxifen and toremifene use, therapeutic alternatives are being developed and introduced for the treatment and prevention of breast cancer. For example, novel chemotherapies are currently under investigation for use in combination with known breast cancer agents to improve response rates and tolerabilities. Luteinising hormone-releasing hormone analogues, i.e. goserelin acetate, reduce plasma estrogen levels and are currently used to treat breast cancer in pre- and perimenopausal patients.

Inhibitors of the enzyme aromatase, which produces estradiol from testosterone and androstenedione, can be useful in limiting endogenous estradiol levels. Historically, these compounds were not very selective and inhibited the biosynthesis of several hormones.[125] More recently, however, compounds have been developed that selectively target and irreversibly bind to aromatase. Three such aromatase inhibitors are currently approved by the FDA for use in the second-line treatment of postmenopausal women with breast cancer (letrozole, anastrozole and exemestane). Results from recent clinical studies have demonstrated that letrozole[126] demonstrates superior efficacy in the treatment of breast tumours when compared with tamoxifen, and that exemestane improves survival among patients with breast cancer who failed on tamoxifen.[127] The results from the phase III letrozole trial served as the basis for the FDA to recommend (on December 13, 2000) that letrozole be approved as a first-line therapy for postmenopausal women with advanced breast cancer.[128] The efficacy of aromatase inhibitors as preventive treatment of breast cancer is also being examined, but accelerated bone loss or cardiovascular disease from lowered estrogens, or both together, remains

a legitimate concern and needs to be carefully monitored in these patients.[129]

A different endocrine approach proposed for the prevention and/or inhibition of hormone-dependent tumours involves the suppression of ovarian function using gonadotropin-releasing hormone analogues with concomitant supplementation of low dose estrogen and progesterone to maintain cardiovascular and bone health.[130] This regimen is still experimental and is currently being evaluated in high-risk younger women.[131]

Combining SERMS with hormone replacement therapy (HRT; estrogen combined with a progestin) has been proposed to ameliorate postmenopausal symptoms in patients with a history of breast cancer.[132,133] Despite a lack of definitive evidence of a causal relationship,[133] commonly prescribed doses of HRT have been associated with a potential increase in breast cancer risk.[134] Lower dose HRT formulations in combination with tamoxifen may improve adverse effect profiles to the extent that patients with breast cancer can benefit from HRT.[133] In addition, lower mortality rates have recently been reported in women with breast cancer who used HRT after diagnosis compared with patients with breast cancer who did not use HRT, challenging the notion that HRT should not be given to women with a history of breast cancer.[135]

All of these therapies have their own set of potential adverse effects, and each requires further definition of target population and optimal duration of treatment. Given a patient's hormonal status, age, family history, and quality of life considerations, these options should be considered along with SERMs in designing a suitable treatment regimen.

6. Conclusion

In general, tamoxifen and toremifene have similar tolerability profiles. Few data are as yet available, however, for comparison between these compounds. The very slight differences observed between tamoxifen and toremifene[33,35,57,61] may result from differences in their relative estrogenic versus antiestrogenic properties since tamoxifen has been shown to have a greater estrogenic-to-antiestrogenic ratio than toremifene.[136,137]

During the last 2 decades, tamoxifen has been the major first-line treatment in advanced breast cancer and has recently been approved for long term preventive therapy. Evidence that prolonged administration of tamoxifen can result in an increased incidence of endometrial cancer[54-56] and that tamoxifen can induce tumour promotion in human breast cancer cells *in vitro*[58,59] suggests that the clinical use of long term prophylactic tamoxifen warrants careful examination.[56] For many women at high risk for breast cancer, the benefit of tamoxifen treatment may outweigh the associated risks.[20,98,138,139] However, the data reviewed here have led some to suggest that there is a significant symptom 'cost' of tamoxifen therapy in women,[97] which could become intolerable with extended treatment.[77] For breast cancer patients or healthy women at increased risk of breast cancer, the potential for these adverse effects with SERMs must be carefully weighed against other therapeutic agents or combination regimens.[65,139] The development of future generations of SERMS that improve upon the current therapies is eagerly anticipated.

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