Toremifene for Breast Cancer: A Review of 20 Years of Data

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Abstract

Endocrine therapy is a cornerstone of medical treatment for estrogen receptor–positive breast cancer. The discovery of selective estrogen receptor modulators (SERMs) > 40 years ago represented a revolutionary advance in the treatment of breast cancer. As a therapeutic class, SERMs have either estrogenic or antiestrogenic activity, depending on the target tissue and the hormonal environment. In breast tissue, SERMs are antiestrogenic, making them a major treatment option for women with hormone-sensitive breast cancer. Toremifene citrate was developed > 20 years ago with the goal of achieving efficacy similar to that of tamoxifen and with an improved safety profile. Although studies to date have not confirmed a clear safety advantage or disadvantage for toremifene, clinical data support the efficacy and safety of toremifene for the treatment of breast cancer in postmenopausal patients. Toremifene also has a pharmacokinetic profile and metabolic pathway different from that of tamoxifen, which may provide a therapeutic advantage in certain patients. In addition, because of the selective estrogenic effects of SERMs in bone and on lipid levels along with a different side effect profile compared with the aromatase inhibitors (AIs), toremifene is a viable option to the AIs for some patients. Despite a number of clinical trials and over 500,000 patient years of use, many oncologists have limited familiarity with toremifene data. This article will examine the rationale for the use of toremifene in the treatment of women with breast cancer and review data from 20 years of clinical experience with this agent.

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Introduction

Breast cancer is the leading cause of cancer in women, accounting for an estimated 28% of new cancers.[1] The American Cancer Society estimates that 232,340 new cases of female breast cancer will be diagnosed and 39,620 women will die of breast cancer in 2013.[1] Early detection and more effective treatment regimens have improved 5-year survival rates, resulting in a population of approximately 2.5 million women in the United States living with breast cancer.[2]

Treatment of breast cancer is at the forefront of the trend toward personalized medicine. Examination of tumor samples for the presence of biomarkers provides information for clinicians in assessing the extent of disease and the risk of recurrence and in predicting response to treatment. Genetic information, such as the presence of the breast cancer genes 1 and 2 (*BRCA1* and *BRCA2*), is used to assess breast cancer risk and to guide surveillance and prevention strategies.[3,4] Additionally, the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) are considered critical diagnostic biomarkers for all newly diagnosed invasive breast cancers, according to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for breast cancer.[3] The tailoring of medical treatment to the individual characteristics of a patient has recently been extended to include assessment of multigene profiles that may influence a patient's response to a particular therapy, as exemplified by Oncotype DX, MammaPrint, and others.[5,6] This topic has been the subject of comprehensive review articles.[7-10]

Genetic testing is also increasingly used to assess an individual patient's ability to effectively metabolize medications.[4] Genetic polymorphisms in metabolism may result in increased toxicity or decreased efficacy of both parent drugs and their metabolites. Genetic tests are now widely available for patients who are taking certain prescription medications, such as clopidogrel and warfarin.[11]

Recognition of the impact of genetic differences in drug metabolism has motivated clinicians to take a new look at another

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Table 1 Baseline Characteristics in Toremifene Pivotal Trials in Postmenopausal Women With Metastatic Breast Cancer

Study	North American		Eastern European		Nordic	
	TOR60 n = 221	TAM20 n = 215	TOR60 n = 157	TAM40 n = 149	TOR60 n = 214	TAM40 n = 201
Median age, years ± SD (range)	61 ± 11 (35-85)	63 ± 10 (37-88)	61 ± 9.3 (31-90)	62 ± 8.3 (38-85)	66 ± 9.4 (45-90)	66 ± 10.4 (34-88)
White, %	84	86	10	100	100	100
ER^-, %	10	6	19	24	20	22
ER status unknown, %	30	27	66	66	42	43
Prior hormonal therapy, %	NR	NR	7.0	7.4	6.1	8.5
Dominant site						
Visceral, %	39	38	29	30	28	31
Bone, %	45	45	17	23	32	35
Soft tissue, %	16	16	53	46	39	32%

Data sources: Coezy E, et al.,[22] Wiebe VJ, et al.,[23] and Kelly CM, Pritchard KI.[24]
Abbreviations: ER = estrogen receptor; NR = not reported; TAM = tamoxifen; TAM20 = tamoxifen 20 mg; TAM40 = tamoxifen 40 mg; TOR = toremifene; TOR 60 = toremifene 60 mg.

selective ER modulator (SERM), toremifene (Fareston, Prostrakan Inc, Bridgewater, NJ), as an option for the treatment of breast cancer in certain patient groups. Toremifene citrate differs in structure from tamoxifen by only 1 chlorine atom. Toremifene has been marketed in Finland since 1988 and was approved for use in the United States in 1997 for the treatment of metastatic breast cancer in postmenopausal women with ER positive (ER^+) or tumors of unknown ER status.[12] Toremifene's in vitro efficacy, as measured by binding of toremifene to ERs and growth inhibitory effects on Michigan Cancer Foundation (MCF) human cancer cells, is similar to that of tamoxifen.[13,14] However, 2 metabolites of tamoxifen, 4-hydroxyl-tamoxifen and 4-hydroxyl-*N*-desmethyl-tamoxifen (endoxifen), are more potent in binding the ER and inhibiting MCF cell growth than the parent compound.[15] Tamoxifen is thus frequently referred to as a prodrug and plasma concentrations of tamoxifen and its metabolites have been shown to be significantly altered in patients with different *CYP2D6* genotypes.[15-18] Additionally, concomitant use of potent CYP2D6 inhibitors and tamoxifen result in alterations in serum plasma concentrations of both tamoxifen and its active metabolites.[15,19] In contrast, toremifene is not a prodrug and does not require enzymatic conversion by cytochrome P450 enzymes, such as CYP2D6, for activity.[20] There has been considerable discussion and debate regarding the clinical sequelae of these alterations.[16,21-24] Two recent subset analyses, from the Breast International Group (BIG) 1-98 and Arimidex, Tamoxifen, Alone or in Combination (ATAC) studies, cast significant questions on the clinical applicability of testing for *CYP2D6* polymorphisms in patients treated with tamoxifen.[25,26] Subsequent challenges to the BIG 1-98 and ATAC conclusions have centered on concerns regarding the retrospective nature of the pharmacogenomics analyses and on large deviations from Hardy-Weinberg equilibrium in their results.[27] In contrast, a third recent study, The Austrian Breast and Colorectal Cancer Study Group Trial 8 (ABCSG-8), found an association between *CYP2D6* polymorphisms and cancer recurrence during the first 5 years of tamoxifen therapy but no association when women had been switched to anastrozole after 2 years of tamoxifen therapy.[28] These conflicting results in 3 recently reported studies highlight the controversy surrounding *CYP2D6* polymorphisms and outcome with tamoxifen. A detailed analysis of the *CYP2D6* controversy goes beyond the scope of our review but has been discussed in depth by others.[27,29,30] Because of the controversial but potential issues of impaired metabolism and drug interactions, tamoxifen may be a less appealing SERM than toremifene in certain patients with breast cancer.

Toremifene Efficacy in Breast Cancer

Postmenopausal Women With Metastatic Breast Cancer

Toremifene is indicated for the treatment of metastatic breast cancer in postmenopausal women with ER^+ or ER^- unknown tumors.[12] Three prospective, randomized, controlled clinical studies were conducted to evaluate the efficacy and safety of toremifene for the treatment of metastatic breast cancer in postmenopausal women who had ER^+ or ER^- unknown tumors.[31-33] The North American trial randomized patients to parallel groups receiving toremifene 60 mg or tamoxifen 20 mg.[32] Both the Eastern European and the Nordic studies randomized patients to toremifene 60 mg or tamoxifen 40 mg (a dose commonly used outside of the United States).[31,33] In addition to these randomizations, there were high-dose toremifene groups in 2 trials (toremifene 200 mg in the North American study and 240 mg in the Easter European study). Because these doses provided no additional benefit over the 60 mg dose, no further details will be provided here but are available in the original publications.[31,33] The North American study included both perimenopausal and postmenopausal patients with metastatic breast cancer, whereas the Eastern European and Nordic studies included only postmenopausal women. In all 3 studies, patients had at least 1 measurable or evaluable lesion, the majority of which were in the liver, lungs, or bone. Baseline characteristics are listed in Table 1. Primary efficacy variables were response rate (RR) and time to progression (TTP). Survival was also evaluated. Additionally, 95% confidence intervals (95% CIs) were calculated for the difference in RR between groups and the hazard ratio (relative risk was calculated for an unfavorable event, such as disease progression or death) between groups for TTP and survival. Of the 3 studies, 2 demonstrated similar results for all efficacy endpoints.[31,32] The Nordic study showed a longer TTP for tamoxifen (Table 2).[33]