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Review

Ospemifene, vulvovaginal atrophy, and breast cancer

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ABSTRACT

The incidence and severity of vulvovaginal atrophy (VVA) in postmenopausal breast cancer patients has a significant impact on quality of life. While the etiology of VVA is primarily related to low estrogen levels seen in menopause, women with breast cancer have an added risk of VVA induced by a combination of chemotherapy, hormonal therapy, and menopause. Ospemifene is a new, non-hormonal selective estrogen receptor modulator (SERM) triphenylethylene derivative that is effective in treating VVA in postmenopausal women. Although other SERMs have antagonistic effects on the vagina, ospemifene exerts an estrogen-like effect on the vaginal epithelium. This review will focus on data demonstrating the antiestrogenic activity of ospemifene in several unique breast cancer animal models, and the implications for utilizing ospemifene in patients with breast cancer suffering from VVA. Additional research addressing the expanded use of ospemifene in breast cancer patients is also warranted.

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1. Introduction

Vulvovaginal atrophy (VVA) is a common problem among postmenopausal women with significant psychosocial impact [1]. Up to half of postmenopausal women can have VVA symptoms. In fact, postmenopausal women with breast cancer taking aromatase inhibitors such as letrozole experience symptoms of VVA at approximately twice the rate seen in the general population [2]. In premenopausal breast cancer patients treated with a combination of chemotherapy and hormonal therapy, over 80% develop early onset menopause as a result within a year of being diagnosed [3]. The only effective therapy currently available for VVA is estrogen

Abbreviations: VVA, vulvovaginal atrophy; SERM, selective estrogen receptor modulator; NDA, new drug application; FDA, Food and Drug Administration; NSABP, National Surgical Adjuvant Breast & Bowel Project; STAR, Study of Tamoxifen and Raloxifene; ER, estrogen receptor; RT-PCR, reverse-transcriptase polymerase chain reaction; DMBA, dimethylbenzanthracene; MIN-O, mammary intraepithelial neoplasia outgrowth; DCIS, ductal carcinoma in situ; PyV-mT, polyomavirus middle-T; MPA, medroxyprogesterone acetate; BSA, body surface area.

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delivered topically or systemically such as hormone replacement therapy. Due to the known breast cancer risks of hormone replacement therapy [4], this type of treatment is no longer recommended in breast cancer patients. Although lubricants applied topically can provide temporary relief, they do not treat the underlying condition. Thus, there is an unmet need for safe and effective VVA therapies in this patient population [2,5]. Ospemifene may represent the first safe and effective treatment for VVA in breast cancer patients. A number of preclinical animal models have shown that ospemifene, like the other triphenylethylenes tamoxifen and toremifene, acts as an antiestrogen in the breast and may in fact impart antitumor activity and may even be useful as a breast cancer chemopreventive agent.

Ospemifene (FC-1271a; deaminohydroxy-toremifene), chemical name Z-2-[4-(4-chloro-1,2-diphenyl-but-1-enyl)phenoxy]ethanol, is a new triphenylethylene SERM similar in structure to tamoxifen and toremifene that was originally developed as a treatment for postmenopausal osteoporosis. When the results of phase I and phase II clinical trials revealed that ospemifene was having a favorable estrogenic effect in the vaginal epithelium and clinically insignificant effects on the endometrium, the focus of phase III development became the treatment of postmenopausal VVA. Ospemifene completed phase III clinical trials in late 2009 [6], and a new drug application (NDA) was submitted to the U.S. Food and Drug Administration (FDA) in early 2012. A summary of ospemifene's development status is shown in Fig. 1.

Ospemifene is in a class of molecules known as triphenylethylenes, which also includes tamoxifen and toremifene, both of which are FDA-approved for the treatment of breast cancer. Following the completion of the National Surgical Adjuvant Breast and Bowel Project's (NSABP) Breast Cancer Prevention Trial, tamoxifen was approved for reducing the risk of breast cancer in women at high risk [7], an indication for which the benzothiophene SERM raloxifene has also been approved following the results of the NSABP's Study of Tamoxifen and Raloxifene (STAR) trial [8].

Selective estrogen receptor modulators are a diverse group of structurally unrelated compounds that can act as either estrogen receptor (ER) agonists or antagonists depending on the type of tissue. These agents were originally known strictly as antiestrogens, but it soon became evident that in addition to their well-known antiestrogenic effects in the breast, compounds such as tamoxifen were having estrogenic effects in other tissues. Tamoxifen was the first clinically useful SERM and has been in use for the treatment of breast cancer in the United States since 1978. The recognition of its mixed estrogen agonist/antagonist effects led to the research and development of new compounds such as raloxifene with ER agonist effects in tissue such as bone and ER antagonist effects in the breast and uterus. While the mechanism through which SERMs exert their unique pharmacological and biological effects remains to be fully elucidated, research has begun to reveal the molecular basis for modulation of the ER by these compounds [9–15]. The specific conformational change in ERα or ERβ following binding of the ligand is thought to determine whether a particular SERM acts as ER agonist or antagonist [14]. While bound to an agonist, the dimerized receptor is capable of interacting with the coactivators necessary for the expression of estrogen target genes. When bound to an antagonist such as tamoxifen, the receptor adopts an inhibitory conformation, resulting in the disruption of coactivator protein interactions and the promotion of co-repressor protein interactions [10,16]. In addition to the classical forms of ER that function as ligand-activated nuclear transcription factors, membrane-bound forms of the ER may also participate in the diverse effects of estrogen in normal and malignant tissues [17–20]. Whether non-genomic ER signaling pathways are involved in the complex biologic effects of SERMs remains unclear, although there is evidence to suggest that they may be contributing to the overall effects of these compounds [21–23].

One of the biggest concerns with SERM development has been endometrial safety. Tamoxifen, while effective as a breast cancer treatment, has been associated with an increased risk of endometrial cancer [24], and a number of investigational SERMs have been dropped from development due to uterine safety issues [25]. On the other hand, ospemifene given to human subjects with VVA for 12 weeks has been found to have clinically insignificant effects on endometrial thickness or histology in phases I–III clinical trials [6,26–28]. In the one-year phase III safety extension study, ospemifene given for 52 weeks had no clinically meaningful effects on the endometrium compared to placebo, and no cases of pelvic organ prolapse, endometrial hyperplasia or endometrial carcinoma were observed [6,29]. The proliferation marker Ki-67 was also studied and no significant increase was found, indicating no cellular proliferation effect of ospemifene on the endometrium [27]. Thus, ospemifene appears to have a favorable safety profile with respect to the uterus and endometrium, and it does not adversely affect vascular surrogate markers.

2. Ospemifene and breast cancer

2.1. In vitro studies

The effects of ospemifene and its major metabolite 4-hydroxyospemifene on the growth of MCF-7 and MDA-MB-231 human breast cancer cells have been evaluated in vitro. In a study by Qu et al., ospemifene was found to have no effect on the growth of ER+ MCF-7 cells at concentrations ranging from 0.1 nM to 10.0 μM [30]. In contrast, Taras et al. showed that ospemifene at concentrations ranging from 0.1 to 10.0 μM produced a moderate, dose-dependent growth inhibitory effect on MCF-7 cells, an effect that was less pronounced than that of either raloxifene or toremifene [31]. In this study, the metabolite 4-hydroxyospemifene actually had a somewhat stronger growth inhibitory effect on MCF-7 cells compared to ospemifene, which was apparently unrelated to dose. This inhibitory effect was not observed in ER-independent MDA-MB-231 breast cancer cells with either ospemifene or its metabolite at the same concentrations, suggesting that ospemifene's breast cancer inhibitory effect is dependent on ERα expression [31].

The modulation of the estrogen-regulated gene pS2 by ospemifene and 4-hydroxyospemifene has also been evaluated. Using RT-PCR, ospemifene and its major metabolite were found to inhibit the expression of pS2 in MCF-7 cells at concentrations of 0.1–10.0 μM [31]. Similar to their effects on cell growth, ospemifene's pS2 inhibition was dose-dependent, while the metabolite 4-hydroxyospemifene seemed to be equally inhibitory at all concentrations. These results were somewhat in agreement with Qu et al. who showed by Northern blot analysis that pS2 mRNA expression was barely detectable at the lowest concentrations tested (10 and 100 nM) [30].

2.2. Preclinical in vivo studies

2.2.1. MCF-7 xenograft mouse model

The effects of ospemifene on the growth of MCF-7 xenografts have been evaluated in two separate studies utilizing ovariectomized nude mice. In the study by Qu et al., MCF-7 xenografts were allowed to grow for eight weeks in the presence of estrogen delivered via subcutaneously implanted time-release pellets. The estrogen pellets were then removed from some of the mice, which were then treated with vehicle control ($n = 9$) or daily oral