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E3. Menopausal symptoms and uterine changes in postmenopausal breast cancer patients receiving tamoxifen or third generation aromatase inhibitors

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1. Introduction

Menopause in breast cancer patients remains an issue of clinical concern. The discontinuation of hormone-replacement therapy (HRT) on diagnosis of breast cancer is at present more emphasised with recent publications confirming the detrimental effect of HRT on the breast [1,2]. Moreover, most non-hormonal interventions are of limited efficacy or questionable safety [3–8]. In the postmenopausal uterus, tamoxifen, the most widely used endocrine treatment in the management of breast cancer induces a wide range of uterine abnormalities from hyperplasia, polyps, growth of fibroids to cancer [9–11]. Although most of these changes are benign, many women undergo interventions to exclude malignant disease.

Nowadays, third generation non-steroidal aromatase inhibitors (NSAIs), such as anastrozole and letrozole, and the steroidal aromatase inhibitor (SAI), exemestane, are increasingly being used in the management of breast cancer. All three aromatase inhibitors (AIs) have been shown to be at least as effective or superior to tamoxifen in the metastatic setting [12–15], and are now challenging tamoxifen in the adjuvant setting [16]. Prospective studies primarily designed to compare the impact of different endocrine treatments on menopausal symptoms are limited. Similarly, although AIs are less likely to induce uterine abnormalities compared with tamoxifen, little data are available. Our aim was to compare the early effects of tamoxifen and steroidal and NSAIs on the occurence and severity of menopausal symptoms in postmenopausal breast cancer patients. We also aimed to compare early uterine sonographic changes induced by these treatments.

2. Evaluation of early changes in menopausal symptoms

In a prospective single-centre study in 181 consecutive postmenopausal breast cancer patients scheduled to start endocrine treatment, a validated menopause symptom questionnaire was completed by patients prior to the start of endocrine treatment, and after 1 and 3 months of therapy [17].

Both first-line treatments with either tamoxifen or NSAIs resulted in a significant increase in the occurrence and severity of hot flashes ($P < 0.0001$ and $P = 0.014$, respectively). Musculoskeletal pain significantly increased under NSAIs, ($P = 0.0039$), while no significant change occurred in patients receiving first-line tamoxifen ($P = 0.33$) and in those crossing-over from tamoxifen to a steroidal or NSAI ($P = 0.9225$).

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Treatment was interrupted in four cases due to intolerance; 2 on tamoxifen with intolerable hot flashes and 2 on letrozole with severe joint and muscle pain.

3. Evaluation of early uterine changes

In 77 consecutive postmenopausal breast cancer patients scheduled to start endocrine treatment and who provided written informed consent for uterine evaluation, transvaginal ultrasonography (TVUS) was performed before and after 3 months of therapy [18].

Tamoxifen significantly increased double endometrial thickness and uterine volume ($P < 0.0001$ and $P = 0.0062$, respectively). Additionally, tamoxifen induced internal cysts (40%), endometrial polyps (15%), and increased the size of pre-existing fibroids (25%). In contrast, AIs did not stimulate endometrial growth and were not associated with endometrial pathologies seen under tamoxifen. Furthermore, AIs showed a trend towards decreased endometrial thickness and uterine volume in patients previously exposed to tamoxifen ($P = 0.12$).

4. Differences in side-effects of tamoxifen and steroidal and non-steroidal aromatase inhibitors?

There are some significant differences between the early effects of tamoxifen and AIs on menopausal symptoms and uterine changes of breast cancer patients. Musculoskeletal pain occurring early in the treatment with first-line NSAIs may not only lead to possible treatment interruptions, but may have long-term consequences on the muscle and bone. In contrast, tamoxifen has the advantage of preventing normal bone loss associated with natural menopause [19]. In patients crossing-over from tamoxifen to a steroidal or NSAI, tamoxifen seems to blunt the effect of AIs on joint and muscle pain at least during the first 3 months of therapy. The absence of effect on musculoskeletal symptom changes in this subgroup may be due to either the short evaluation period, or the protective effect of tamoxifen treatment, or perhaps a possible bone-sparing effect of the SAI exemestane. Exemestane, being steroidal in structure, belongs to a different category of AI. It is devoid of total cross-resistance with NSAIs [20] and displays a different action (possibly androgen-mediated) on serum lipids [21–23] and on bone [24]. However, whether the SAI really has this advantage over NSAIs can only be determined with certainty in larger studies with longer follow-up or in adjuvant studies without the confounding effect of previous tamoxifen treatment.

In the postmenopausal uterus, tamoxifen and AIs have a distinct effect which can be documented as early as 3 months after start of therapy with a relatively non-invasive procedure such as TVUS. The atrophic effects of AIs on the uterus in contrast to the oestrogenic action of tamoxifen are reassuring from a gynaecological point of view. Furthermore, an important finding is that AIs, mostly exemestane in this series, may reverse tamoxifen-associated uterine changes. Although it is interesting to consider the possibility that a short treatment with AIs in patients with tamoxifen-induced uterine abnormalities could possibly reduce or obviate invasive procedures such as hysteroscopy or curettage, the validity and safety of such an approach warrants further evaluation. Nevertheless, on the assumption that tamoxifen-induced endometrial thickening by TVUS is often a precursor or surrogate marker of endometrial pathologies [10], the reversal of such suggests that tamoxifen therapy followed by an AI may not only be more effective as shown in the recent MA-17 trial [25], but may, in the end, lead to a reduction in the endometrial pathologies associated with tamoxifen.

Differences in tolerability profiles between tamoxifen and AIs and between the steroidal and non-steroidal types are important. Whether the difference exists in adverse side-effects or in non-life-threatening side-effects which may reduce quality-of-life or affect patient compliance, these differences may be taken into account in clinical decisions in the choice between different drugs. This is particularly true in cases where agents may have minimal differences in efficacy but exhibit marked differences in tolerance. Issues on acute and long-term side-effects will also become more important in the preventive setting, where otherwise healthy high-risk women will be taking these drugs.

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