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GYNECOLOGICAL CANCER

Vaginal atrophy in breast cancer survivors: role of vaginal estrogen therapy

Luciano Mariani¹, Angiolo Gadducci², Enrico Vizza¹, Silverio Tomao³ & Patrizia Vici⁴

¹Department of Gynecologic Oncology, Regina Elena National Cancer Institute of Rome, Rome, Italy, ²Department of Procreative Medicine, Division of Gynecology and Obstetrics, University of Pisa, Pisa, Italy, ³Department of Medical-Surgical Sciences and Biotechnologies, “Sapienza”, University of Rome, Rome, Italy, and ⁴Medical Oncology; Regina Elena National Cancer Institute of Rome, Rome, Italy

Early menopause and related vaginal atrophy is a well known side-effect of hormone adjuvant treatment in breast cancer patients, particularly during aromatase-inhibitors therapy. Due to estrogens contra-indication, proper therapy for such symptom remains often an inadequately addressed clinical problem. After an accurate assessment of the risk/benefit ratio, vaginal low-dose estrogen treatment (better with estradiol) may have a role in controlling vaginal atrophy in selected and informed breast cancer women.

Keywords: Breast cancer survivors, menopause treatment-related, tamoxifen and aromatase inhibitors therapy, vaginal estrogen therapy

Introduction

Due to the improving in multidisciplinary oncological strategies, a great number of cancer survivors are increasingly expected in the near future. Thus, increasing cancer therapy efficacy, also treatment-related long-term side effects (such as early menopause after breast cancer therapy) are becoming worldwide an emerging issue and a common health priority.

Over 70% [1] of breast cancer (BC) patients show positive estrogen receptor (ER), thus after primary treatment require a hormonal adjuvant therapy to reduce the recurrence risk. Although representing a fundamental part of the strategy, adjuvant therapy is also one of the major concerns about treatment-related side effects. Since up to 35% of BC occur in premenopausal women [2], adjuvant strategy deeply affects gynecological health.

Indeed, the objective of such post-surgical therapy is to reduce the availability of estrogen to the cancer cell by means of: (i) blocking ER with tamoxifen (TAM), (ii) suppression of estrogen synthesis with gonadotropin-releasing hormone (Gn-RH) agonists, (iii) inhibition of aromatase pathway with specific agents (aromatase inhibitors, AIs) or (iv) bilateral ovariectomy. Such premature abrupt hormonal deprivation, particularly in younger patients, lead to a greater intensity and duration of menopausal symptoms compared to the healthy women in natural menopause. Therefore, during TAM-treatment vasomotor symptoms (such hot-flushes and night sweats) and vaginal atrophy are commonly experienced as intense symptoms [3], which negatively impair the quality of life (QoL) [4].

Furthermore, AIs-users usually report even more negative effects on sexual life (unsatisfactory sexuality, decreased libido, vaginal dryness with painful intercourse, dyspareunia) compared to the TAM-group [5,6]. Hence, such menopausal condition may reduce the compliance with BC therapy, in terms of early discontinuation and low adherence to treatment [7]. Not surprisingly, up to 20% of overall BC patients consider stopping any hormonal treatment because of worsened QoL [8,9]. Indeed, many cancer-patients, after being efficiently treated for the primary tumor, are lost to clinical surveillance when becoming cancer-survivors [10].

Since the mainstay of adjuvant treatment is a complete estrogen suppression, result a nonsense and formally contraindicated the use of systemic hormonal replacement therapy (HRT) in these women. Thus, management of most of BC patients suffering of treatment-related menopause is a challenge.

Actually, some menopause-related symptoms may be managed by alternative non-hormonal interventions. For instance, vasomotor symptoms, which may also spontaneously resolve over time [11], could be controlled by the use of selective reuptake inhibitors of serotonin (SSRIs) or norepinephrine (SNRIs) [12], or anticonvulsants such as Gabapentin [13]. Conversely the management of vaginal atrophy is more problematic. While in healthy menopausal women the optimal therapy of such condition is systemic HRT or vaginal estrogen administration, alternative therapies, such as water-based lubricants or polycarbophil moisturizers, are usually taken into account in BC survivors. However, these non-hormonal agents just partially and temporarily relieve local symptoms [14], leaving the patient in the need for a more appropriate therapy. Such topical treatment does not reverse the cytological effect of atrophy, and is not able to modify the maturation index [15] or vaginal pH.

Dimension of the problem and pathogenesis of atrophy

Up to 40% of women experience [16,17] a vaginal atrophy 4–5 years after the natural menopause onset with intense subjective complaints, described as very bothersome in 20% of the cases [18]. Estrogen deprivation causes a thinning of vaginal epithelia, with loss of collagen tissue, dryness, burning, itching, and reduced elasticity associated to dyspareunia. Furthermore, the vaginal pH, usually in the range of 3.5–5 in fertile period, increases up to 6
in menopause due to reduction of lactobacillus, thus shifting normal flora toward coliform flora, and contributing to the higher risk of inflammation as well as traumatic bleeding. Maturation index obtained by cytological examination is also impaired, since estrogen stimulates the development of superficial squamous cells.

Low estrogens level may also decrease blood flow in vagina and surrounding tissues, with insufficient relaxation due to a loss of vaginal elasticity and decreased vaginal lubrication. This process is mediated by some estrogen-dependent neurotransmitters, such as nitric oxide [19]. Moreover, as shown by experimental studies in rats, a low-level milieu of estrogen appears to be associated with a hyperplasia of vaginal nerves that could explain a higher pain response to sexual intercourse [20].

Thus, all the above quoted clinical conditions provide evidence of negative impact of vaginal atrophy on QoL and sexual intercourse, increasing the rate of vulvo-vaginal infections and making it difficult also the routine gynecological examination. Furthermore, it should be noted that, unlike vasomotor symptoms, vaginal atrophy are often progressive.

Women with ER-positive BC women are usually submitted to adjuvant hormonal treatment, displaying complete estrogen suppression, corresponding to a higher prevalence of symptoms from estrogen-deprivation as above stated. The effects of TAM on vaginal tissues are complex, mainly depending on estrogen milieu. In postmenopause TAM acts as a weak pro-estrogen, while in premenopause it acts as an anti-estrogen. Therefore, TAM-users have threefold higher risk of hot-flushes and vaginal dryness [21], and AI-users experience an even higher incidence of these symptoms. Indeed, it should be emphasized that third generation of AIs (Anastrozole, Letrozole, Exemestane) obtain a rate of aromatase inhibition up to 98.9% [22], providing a quite complete estrogen deprivation. Indeed, in the ATAC trial (Arimidex, Tamoxifen, Alone or in Combination) vaginal dryness and dyspareunia were observed in 16.3% and 17.8% of anastrozole-treated patients, compared to only 8.4% and 7.5% of TAM-treated patients, respectively [6].

**Vaginal estrogen therapy**

In healthy women local estrogen therapy promotes vaginal cell growth and maturation, with further improvement of cytological index and vaginal thickness, enhances vaginal blood flow, improves recolonization with lactobacilli and improves sexual response. By means of topical creams, pessaries, tablets or rings, estrogen is efficacious in the treatment of vaginal atrophy at least as systemic HRT [23,24]. Some data [25] also suggest that local estrogen formulations may be able to provide even more complete relief of vaginal and urinary symptoms rather than oral/transdermic HRT.

Long et al. [26] randomly assigned 57 hysterectomized postmenopausal women to either oral (0.625 mg of conjugated equine estrogen [CEE] per table) or topical (0.625 mg of CEE per 1 g vaginal cream) estrogen once daily. Compared with oral therapy, vaginal preparations correlated with better symptom relief despite the lower serum estradiol (E2) levels. The same authors found that oral or vaginal estrogen therapy increased the blood flow around the bladder neck and mid-urethra and relieved the symptoms of hyperactive bladder and stress incontinence, with no difference in efficacy according to the route of estrogen administration.

Local treatment should be started as early as possible, namely before irrevocable atrophic changes have occurred [27]. A low-dose of 17 β-E2, delivered by vaginal ring or tablet, showed a great efficacy on vaginal symptoms and a good endometrial safety profile [28].

Simon et al. [29] randomly allocated 3009 postmenopausal women to receive 10 µg E2 or placebo vaginal tablets. After 12 weeks of therapy, women treated with this ultra-low dose vaginal E2 showed a significant improvement in vaginal maturation index, maturation value, grading of vaginal health, vaginal pH and most bothersome urogenital symptoms compared to those who received placebo.

Vaginal estrogen therapy was never found to be associated with an increased risk for either ductal or lobular breast cancer, with the exception of one million study [30]. Moreover, it is noteworthy that vaginal estrogens were allowed in the placebo controlled MA.17 trial of letrozole [31], as extended adjuvant therapy after 5 years of TAM, without interfere with the observed efficacy.

In BC patients the safety issue of local estrogen is still debated, depending on the significance of systemic absorption and its possible negative impact on clinical outcome. In other words, there is reasonable concern that vaginal estrogen-therapy could affect endogenous suppression achieved with adjuvant therapy, particularly with aromatase inhibitors.

Although few studies have been conducted so far, all topical estrogens are absorbed depending on dose and formulation [32]. Indeed, atrophic vaginal walls tend to absorb estrogen, even at small doses, particularly if administered as a cream, rather than tablets or rings [33].

After used vaginal administration with 25 or even 10 µg, a quick higher E2 plasma level in healthy women has been detected, followed by a decrease concentration, which remained over the pretreatment levels [34]. E2 and estrone (E1) plasma maximum concentrations after vaginal CEE increased sixfold, for an overall steady-state estrogen concentration slightly above the normal postmenopausal reference range [25]. These studies confirm the capability of estrogen to be absorbed through the thinned, atrophic epithelia, until vaginal walls are restored. An indirect sign of systemic absorption is the improved serum lipid profile in elderly treated women. Conversely, the increased serum E2 after local therapy does not result in sufficient amount to relieve hot-flushes and does not appears to stimulate endometrial thickness [35].

The systemic absorption of vaginal E1 is lower than that of vaginal E2 [23] Moreover, E1 has a weaker and shorter estrogenic effect at endometrial level, because of lower affinity with plasma proteins and the faster metabolic clearance [36]. Dugal et al. [37] assessed 96 postmenopausal women with vaginal atrophy who were treated E2 vaginal tablets or E1 vagitories for 24 weeks. Endometrial thickness increased (1.1 mm with E2 and 0.5 mm with E1) in both groups during the first two weeks of daily treatment, but returned to basal level when the frequency of drug application was reduced to twice weekly.

Furthermore, as a safety issue, progesterone is not indicated when low dose estrogen is administered locally for vaginal atrophy [38].

Up-to-now, some clinical studies [32,39,40,42,43] have documented a systemic absorption after vaginal estrogen administration also in BC patients. How this absorption will affect (if any) breast cancer outcome still remains largely unknown. Unfortunately we have no large data, nor adequate follow-up on this matter. Nor, again, has still established a threshold of serum E2 level clearly associated to breast cancer risk.

After vaginal estrogen tablets Kendall et al. [44] reported a significant increase of serum E2 from baseline levels of <5 pmol/l to mean concentrations of 72 pmol/l at two weeks in

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postmenopausal women whilst AIs for BC. After 4 weeks, E2 levels had decreased to <35 pmol/l (median, 16 pmol/l) in the majority of patients.

For this reason the authors suggested, for selected women, to shift to TAM-therapy before vaginal therapy, after which AIs would be resumed again. No increased recurrence risk has been reported following local estrogen therapy in few small series.

Dew et al. [40] analysed 1472 BC patients, of whom 69 had vaginal symptoms as only bothersome menopausal problem and received topical E2 or E1 cream or tablets. Patients who took vaginal estrogen alone had a corrected hazard ratio [HR] of 0.57 (95% confidence Interval [CI] = 0.20–1.58, p = 0.28) for recurrence. It is noteworthy that 48% of these women received oral TAM together with vaginal estrogen. Although the small number of cases precluded definitive results, topic estrogen use did not appear to increase the risk of failure. Vasilopoul-Sellin et al. [41] found no recurrence among the 6 BC patients who received vaginal estrogen for a median duration of 49 months and who were followed for a median of 95 months from diagnosis.

In a pilot-study on 18 symptomatic BC patients, Biglia et al. [45] found that both E3 cream and E2 tablets were effective for relieving urogenital atrophy, with a minimal serum estrogen level, representing a safe clinical alternative in such women. Indeed, vaginal E3 is a weak estrogen that cannot be converted into E2 or E1 and can be more easily and safety used in BC survivors, providing good effect in the vagina, with limited systemic effect in spite of absorption [46].

Discussion

Management of vaginal atrophy with topical estrogen therapy in BC patients, particularly during AIs adjuvant treatment, remains controversial. Although, the small numbers of valued patients does not allow firm conclusions to be drawn, there is no evidence that systemic absorption after vaginal estrogen-therapy could increase the recurrence risk [40].

In ER-positive BC patients under AI-therapy affected by severe vaginal atrophy and non-responders to local alternatives (moisturized, lubricants), there could be a chance for a short-time vaginal administration of low, extra-low E2 doses or, preferably, estradiol formulations. Moreover, theoretically there is no contraindication at all for vaginal estrogen therapy in ER-negative women [47], but more clinical data are still needed.

Waiting to value the clinical significance of vaginal estrogen absorption, effective alternatives are advocated [48]. It has been suggested the use of intravaginal dehydroepiandrosterone (DHEA) in healthy menopausal women affected by vaginal atrophy [49]. DHEA is a steroid precursor converted, by aromatization in extra-gonadal tissues, into sex steroid having androgenic and/or estrogenic action, and thus exerting a maturation effect of the vaginal epithelium cells [50]. Nevertheless, by vaginal use there is no systemic steroid effect of DHEA therapy [32] because the active steroids are locally inactivated before being released as inactive metabolites into the general circulation [51]. In a randomized trial of postmenopausal women, vaginal atrophy reversed after DHEA intravaginally administered for 12 weeks with minimal changes in serum steroids, which remained within the normal postmenopausal range [52]. Moreover, in these cases endometrial thickness did not increase after therapy, thus confirming no systemic estrogenic effect. Nevertheless, safety trials are still warranted as some prospective studies showed association of DHEAS with breast cancer [53].

Trials with intravaginal testosterone have been conducted in early-stage BC patients with good clinical results [54,55]. The rationale is that testosterone induces proliferation of the vaginal epithelium, but the conversion to estrogen is blocked by AIs. Although both trials showed an improvement of vaginal symptoms, the elevation of testosterone levels in some women could represent a challenging issue [51]. Due to the conflicting observational data on BC risk and high testosterone serum level, any androgenic treatment should be valued with caution.

Conclusion

Proper and adequate therapy for vaginal atrophy remains often an inadequately addressed clinical problem for many BC survivors. Though “...there is no valuable study to recommend any evidence-based policy” [32], due to frequent discontinuation or non-adherence to adjuvant therapy, efficient interventions are needed.

The decision of how to treat requires a shared decision between the therapeutic team (gynecologist, oncologist) and the single patient, assessing the risk over the benefits. Thus, since any estrogen therapy in BC women has not been proven to be safe and may be associated with a recurrence risk (see NAMS position statement [56]), all women should be fully informed of the potential benefits and risks of such therapy. Moreover, it should also be kept in mind that estrogen local use would be classified as “off-label,” since these products are clearly contraindicated in women affected by estrogen-dependent neoplasias. Thus, from one hand the negative opinion of gynecologists may contribute to women’s reluctance towards estrogen local therapy, and from the other many BC patients may feel uncomfortable and unsafe using estrogen therapy.

Hence, individualization of therapy is the key to balancing the desired local positive effects of topical vaginal estrogens, with potential negative systemic effects.

Declaration of Interest: The authors report no conflicts of interest.

References

65. Labrie F, DHEA, important source of sex steroids in men and even more in women. Prog Brain Res 2010;182:97–148.
Notice of Correction

The version of this article published online ahead of print on 21 Sep 2012 contained an error within the abstract. (better with estradiol) was written instead of (better with estriol). The error has been corrected for this version.