Original Study

Vaginal Atrophy in Breast Cancer Survivors: Attitude and Approaches Among Oncologists

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Abstract

Oncologists are aware of the vulvovaginal atrophy (VVA) problem in breast cancer survivors (BCSs) but only half of them illustrate VVA as a possible consequence of treatment. Forty-one percent of the oncologists refer BCSs to gynaecologist to define VVA treatment, whereas 35.1% manages it alone. Nonhormonal treatments are preferred by most oncologists (71%). The main reason not to prescribe vaginal estrogen therapy in BCSs is the fear of increased cancer recurrence, the possible interference with tamoxifen, or aromatase inhibitors and the fear of medical litigation.

Background: Vulvovaginal atrophy (VVA) is a relevant problem for breast cancer survivors (BCSs), in particular for those who receive aromatase inhibitors (AIs). We conducted a survey, to assess the attitude of oncologists toward the diagnosis and treatment of VVA in BCSs. **Materials and Methods:** In 2015, 120 computer-assisted Web interviews were performed among breast oncologists. **Results:** According to oncologists' perceptions, 60% of postmenopausal BCSs and 39.4% of premenopausal BCSs will suffer from VVA. Despite that none of the physicians considered VVA as a transient event or a secondary problem in BCSs, only half of the oncologists (48%) directly illustrated VVA to the patients as a possible consequence. Forty-one percent of the oncologists refer BCSs to gynaecologist to define VVA treatment, whereas 35.1% manages it alone. Nonhormonal treatments are preferred by most oncologists (71%). The main reason not to prescribe vaginal estrogen therapy in BCSs is the fear of increased cancer recurrence, the possible interference with tamoxifen, or AIs and the fear of medical litigation. **Conclusion:** VVA is a relevant problem for BCSs. Great effort should be done to correctly inform health care providers about VVA problems and on the different possible available treatments.

Clinical Breast Cancer, Vol. ■, No. ■, ■-■

Keywords: Breast cancer survivors, Estrogen, Genitourinary syndrome of menopause, Treatment, Vulvovaginal atrophy

Introduction

Every year, an increasing number of new cases of breast cancer are diagnosed among women in reproductive age. Many breast cancer survivors (BCSs), especially young women, undergo menopausal symptoms, as direct consequences of cancer treatment chemotherapy, tamoxifen, aromatase inhibitors (AIs), and ovarian suppression. Breast cancer patients treated with hormonal adjuvant therapy, particularly those using AIs,[1,2] refer to vulvovaginal atrophy (VVA) as one of the most unpleasant side effects.[3]

Published surveys on BCSs reveal that VVA has been reported by 42% to 70% of postmenopausal patients and those women rarely discuss the problem with health care providers.[4]

Furthermore, the problem of VVA, in BCSs, will increase because of the practice of prolonged therapy with tamoxifen or AIs; to properly manage this side effect oncologists as well as patients should be aware about the disease and therapeutic options.[5,6]

Symptoms of VVA include dryness, burning, itching, dyspareunia, and bleeding after sexual activity, with a high effect on quality of life (QoL), including relationship, sexual satisfaction, and self-esteem.[7]

Recently, the term, genitourinary syndrome of menopause (GSM), has been proposed instead of VVA, to include any genital, urinary, and sexual signs and symptoms associated with menopause.[8]

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Submitted: Feb 14, 2017; Revised: Apr 29, 2017; Accepted: May 15, 2017

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http://dx.doi.org/10.1016/j.clbc.2017.05.008

Genitourinary syndrome of menopause is usually reversible with hormone replacement therapy (HRT). Local estrogen treatment is the most used approach for symptom management and illness healing.[9,10] However, in BCSs, estrogen administration has safety concerns, because of the hypothetical risk of cancer recurrence.[11]

Therefore, in this setting of patients, the American College of Obstetricians and Gynecologists (ACOG) recommends a local nonhormonal approach as first-line treatment for GSM leaving estrogens to patients unresponsive to nonhormonal therapies.[12]

It is not clear which health care provider (gynecologist, oncologist, or family doctor) might deal with the VVA. Moreover, no agreement is reached among the different specialists.

We performed this survey among oncologists in breast cancer to investigate their attitude toward the VVA problem in BCSs.

Materials and Methods

One hundred twenty computer-assisted Web interviews (CAWIs) were performed from May 18, 2015 to June 8, 2015 to Italian breast oncologists, throughout the country (39.2% [47/120] north, 20% [24/120] center, 40.8% [49/120] south).

The interview was planned in 3 different sections to determine the number of breast patients followed per year, the adjuvant treatment prescribed according to menopausal status, the attitude toward the assessment and diagnosis of VVA symptoms, and the knowledge concerning VVA treatment options.

To describe the attitude of oncologists toward VVA, they were asked about: (1) the perception of VVA grade among patients treated with hormonal depletion therapy; (2) clinical relevance granted to VVA; (3) first time discussing VVA with patients; and (4) primary measure as soon as the patient reveals VVA.

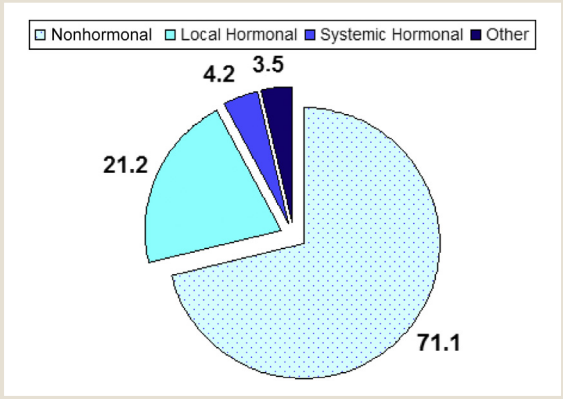
Furthermore, to evaluate oncologist experience in VVA treatment options, the following data were collected: (1) what kind of drugs they used in the treatment of VVA; and (2) their attitude toward hormonal or nonhormonal drugs. The attitude of the patient when hormonal drugs were prescribed was also reported.

Results

One hundred twenty oncologists (52.5% [63/120] male and 47.5% [57/120] female), belonging to several centers were interviewed using the CAWI. A dedicated breast care unit was present in 64.2% of the hospitals, with a median of 240 new breast cancer diagnoses per year. Moreover, in 12% of the centers the median of new breast cancer diagnoses was more than 410 per year. The median number of breast cancer-naive patients starting adjuvant hormonal therapy was 63 per year; in 13.3% of centers, this median value reached more than 100 cases per year.

Breast oncologists' attitude toward adjuvant treatment prescription is in accordance with the most recent guidelines on breast cancer treatment, preferring AIs to tamoxifen.[13] According to our survey, in Italy, the first choice (65% [29/44] of cases), is tamoxifen with ovarian suppression as antihormone adjuvant treatment in premenopausal women; AIs with ovarian suppression are prescribed only in 15% (7/44) of cases. In postmenopausal women, the oncologists prescribe AIs as first choice treatment (83% [63/76] of cases) whereas tamoxifen is prescribed only in 17% (13/76) of patients. In one-fourth of the patients, in both groups, extended therapy is prescribed (26% [11/44] and 22% [17/76], respectively).

Figure 1 Treatments Prescribed to Treat Vulvovaginal Atrophy. Nonhormonal, Local, or Systemic Hormonal Drugs, and Other (Mainly Alternative Medicine Products)



For pre- as well as postmenopausal patients, the compliance to the standard 5-year adjuvant antihormone treatment is approximately 80% (83% [36/44] and 79% [60/76], respectively) as referred by the oncologist.

According to oncologist opinion, in patients using adjuvant hormonal treatment, 60% (46/76) of postmenopausal and 39% (17/44) of premenopausal women experienced VVA. In postmenopausal patients, VVA grade has been considered mild, moderate, or severe in 43% (33/76), 40% (30/76), and 17% (13/76) of cases, respectively. Every participant is conscious that VVA strongly affects sexual health and increases probability of urinary tract infections.

Despite that none of the physicians considered VVA as a transient event or a secondary problem in BCSs, only half of them (48% [58/120]) explain to the patients that VVA could be a consequence of iatrogenic menopause or AIs treatment. In most of the cases, VVA is debated during the follow-up visit, in the cases for which the patient complains about symptoms with the oncologists (56.9% [68/120]) or with the nurse (14% [17/120]). The oncologist address the problem of VVA only in 26.5% (31/120) of cases, with no differences in relation to doctor's sex. Oncologists are aware of paying inadequate attention to the problem (85% [102/120] of the answers) and they complain to not receive enough information on this topic (85% [102/120] of the answers).

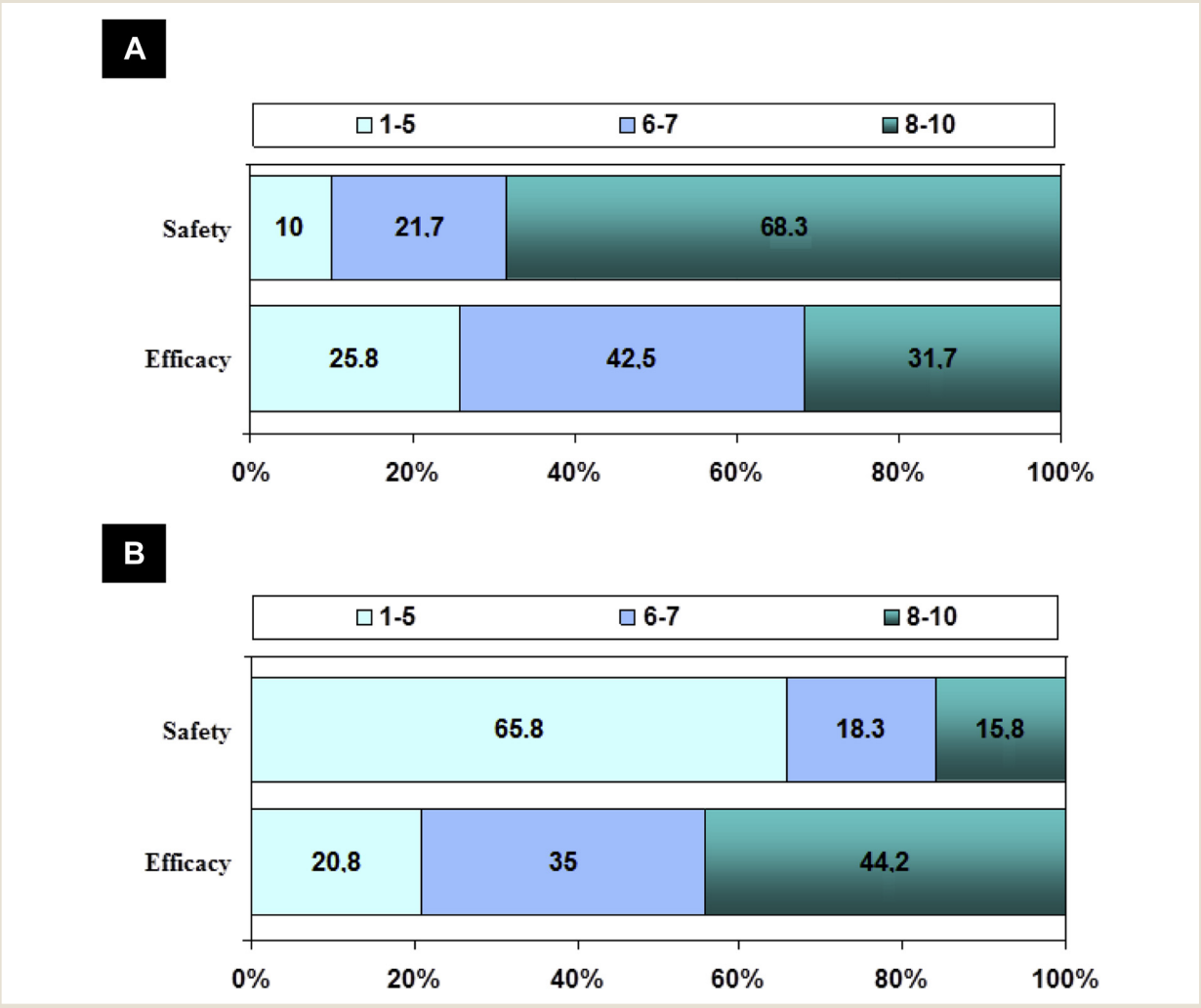
Forty-one percent (49/120) of the oncologists indicated they refer the patient to the gynecologist whereas another 35.1% (42/120) directly describe treatment options to the patient.

Eleven percent (13/120) of patients do not require or refuse any kind of treatment; in contrast, 12% (14/120) of women manage the VVA with self-prescription.

As expected, nonhormonal treatments (lubricants or moisturizers, in the same proportion) are prescribed in most of the cases (71.1% [85/120]). Vaginal estrogen therapy is prescribed by 21% (25/120) of the oncologists and HRT is considered only by a minority (4% [5/120]; Figure 1).

Nonhormonal treatments are considered safe by 90% (108/120) of the oncologists and effective only by 30% (36/120) of them;

Figure 2 Oncologist's Perspective of Safety and Efficacy for (A) Nonhormonal and (B) Hormonal Therapy to Treat Vulvovaginal Atrophy in Breast Cancer Patients, According to a Visual Analogue Scale (Numbers Indicate 1 for Minimum and 10 for Maximum)



conversely, hormonal treatment with vaginal estrogens is considered safe only by 15% (18/120) and effective by 79.2% (95/120) of oncologists (Figure 2).

Prescription of local hormonal therapy is driven by different reasons, mainly in the presence of severe dyspareunia symptoms, interfering with sexual life (51.7% [62/120]), also upon patient request (26.7% [32/120]), and for recurrent vaginal or urinary infections (16.7% [20/120]).

Of the oncologists, only 24.2% (29/120) prescribe vaginal estrogen therapy for patients with nonhormone-dependent breast cancer; only 7.5% (9/120) prescribe this therapy to patients with hormone-dependent breast cancer, at the end of antihormone adjuvant treatment. In 15% (18/120) of the cases, the oncologist does not prescribe hormonal drugs to treat breast cancer patients. Moreover, if a gynecologist prescribes vaginal estrogen therapy, only 21.5% (26/120) of the oncologists confirm the prescription, and 20.8% (25/120) confirm the prescription only for a short period or just if the patient has nonhormone-dependent breast cancer (18.9% [23/120]), and 20.4% (25/120) of them do not agree at all.

The main reason to not prescribe vaginal estrogen therapy in BCSs is the probability of increased cancer recurrence, mentioned by 70.8% (85/120) of the oncologists, followed by interference with tamoxifen or AIs. Last, doctors might encounter a lawsuit by the patient if a relapse due to estrogen therapy occurs.

When the oncologist prescribes hormonal therapy, a significant percentage of women refuse to take it (43% [52/120]), whereas 36.5% (43/120) ask for reassurance before using it. However, 20.5% (25/120) of women accept vaginal estrogen prescription especially in the presence of severe symptoms.

Regarding oncologists' knowledge about different available vaginal estrogen preparations, standard high-dose formulation was mentioned by 70% (84/120) of them, whereas 52.5% [63/120] prescribe low-dose and gel formulations. Furthermore, only 1.7% (2/120) of the oncologists knew of new treatment options, such as vaginal laser.

Discussion

Vulvovaginal atrophy is one of the most frequently reported side effects by BCSs, recurrent among young women forced to premature menopause and for those using AIs,[2,14] affecting sexual health and with negative effect on QoL.[1,3,15] Younger women have higher rates of sexual dysfunction, even beyond the treatment period.[16,17] A QoL analysis including 1722 premenopausal patients, with hormone receptor-positive breast cancer randomly assigned to receive adjuvant treatment (tamoxifen with ovarian function suppression or tamoxifen alone for 5 years), showed loss of sexual interest at 6 months and vaginal dryness for up to 60 months, in patients who received tamoxifen with ovarian function suppression with respect to that in patients who received tamoxifen alone.[18]

In the literature, it is reported that up to 20% of BCSs consider stopping antihormone therapy because of menopausal symptoms.[19,20] In accordance with literature, in our survey to investigate the attitude of breast oncologists toward the VVA problem in BCSs, 20% of pre- and postmenopausal patients stop antihormone treatment, probably because of side effects such as VVA.

Oncologists are aware that VVA is a frequent problem among BCSs, with 60% of postmenopausal women and 40% of younger BCSs with the complaint of VVA. Furthermore, oncologists know that VVA is an important issue for BCSs, being of moderate or severe grade in most of the cases.

The oncologists are conscious that VVA strongly affects women's sexual health and that it can increase probability of urinary tract infections.

The term GSM has been recently proposed instead of VVA, because it better describes genital, urinary, and sexual areas involved.[8]

In contrast to vasomotor symptoms that usually improve over time even without treatment, GSM is a chronic condition, unlikely to resolve spontaneously, and often progressive if left untreated[21]: in our survey, no one considered VVA as a temporary problem.

Only half of the oncologists directly describe VVA to women as a possible consequence of adjuvant treatments, even if they do not consider VVA a minor problem. In most of the cases, the VVA is discussed during the follow-up visit, only if the patient complain about symptoms.

It is well described in the literature that, despite the prevalence and associated burden of GSM, the condition is often inadequately addressed in medical practice.[21]

For the choice of the more appropriate treatment for VVA in BCSs, most of the oncologists refer patients to the gynecologist, whereas 35% of them discuss treatment options with the patients, directly.

In our survey, approximately 10% of women did not require or refused treatment and another 10% managed the problem with self-prescription.

According to the available current guidelines, nonhormonal vaginal moisturizers and lubricants are recommended as first-line treatment for BCSs.[9,11] In our survey, oncologists prescribed, in most of the cases, nonhormonal treatments (lubricants or moisturizers in the same proportion), which are considered safe, even if not completely effective.

In our survey, HRT is considered only by 4% of the oncologists and only for women with important vasomotor symptoms associated with VVA. Available guidelines consider HRT contraindicated in BCSs[9,11] after the results of the HABITS[22,23] and Stockholm trials.[24] In addition, a trial on tibolone, a compound alternative to conventional HRT, which shows estrogenic, progestogen, and androgenic properties, was prematurely stopped because of a significant increase of recurrences in the group of BCSs treated with tibolone compared with the placebo group.[25]

Vaginal estrogen administration is the preferred way of delivery when vaginal symptoms are the only condition in postmenopausal women. It is more effective than systemic estrogen administration in the relief of symptomatic VVA, with 80% to 90% of women who report a favorable response.[10] Furthermore, vaginal estrogens also improve sensory urgency and reduce the frequency of urinary tract infections.[9]

Only a few trials have been conducted to investigate vaginal estrogen therapy in BCSs suffering from VVA.[26-32] The North American Menopausal Society states that there are few reports regarding the safety of local estrogens in BCSs: patients who do not respond to nonhormonal therapies might discuss the risks and benefits of low-dose vaginal estrogens with the oncologist.[11] Systemic absorption can occur with conventional doses of vaginal estrogen therapy, particularly in the case of atrophic vagina.[33] Low-dose local estrogen therapy is considered to have a lower risk profile compared with standard doses because it produces very low serum levels when administered intravaginally. Several studies in healthy postmenopausal women showed that low-dose vaginal estrogens improve vaginal symptoms in most treated subjects, with plasma estradiol levels in the range of postmenopausal value.[34-36] Ultra-low doses of vaginal estrogens have been recently investigated in postmenopausal healthy symptomatic women,[37-39] showing good efficacy and a very favorable safety profile on breast and endometrium, with negligible plasma levels. Systemic absorption of vaginal estrogens can be relevant for BCSs, in particular for those receiving AIs, which completely deprive the female body of estrogens. Because results of many in vitro studies suggest that long-term estradiol deprivation causes an upregulation of estrogen receptors alpha as well as upregulation of growth factor pathways with consequent hypersensitivity of cancer cells to low concentrations of estrogens, serious concern might exist.[40] Standard doses of vaginal estrogens can determine an increase in plasma levels of serum estradiol, relevant for BCSs, especially for those receiving AIs, as shown in the study of Kendall et al.[28] In this study, 6 postmenopausal BCSs treated with AIs received estradiol tablets at a standard dose (25 mg); serum estradiol levels increased from baseline levels of < 5 pmol/L to a mean of 72 pmol/L at week 2; however, a decrease to a mean of 16 pmol/L was observed after 1 month.

On the contrary, studies among BCSs using low[29,32] and ultra-low doses[31] of vaginal estrogens showed that they can alleviate VVA symptoms without raising serum levels of estrogens. Previous published data from our department showed the efficacy and safety of 2 low-dose vaginal estrogen treatments (estriol cream 0.25 mg or estradiol tablets 12.5 mg) and of a nonhormonal polycarbophil-based vaginal moisturizer (2.5 g) administered twice a week for 12 weeks in postmenopausal BCSs with urogenital atrophy. Estradiol levels increased by a mean of 3.5 pg/mL in women who received vaginal estriol cream and by a mean of 2.7 pg/mL in the

group treated with micronized estradiol tablets.[29] In a prospective, randomized study on 10 postmenopausal BCSs using AIs it was reported that the daily use of 0.5 mg estriol for 2 weeks did not result in increased serum levels of estriol or estradiol.[32] In a phase I clinical study with an ultra-low dose of 0.03 mg estriol and lactobacillus combination vaginal tablets in 16 BCSs with VVA, after 3 months of treatment compared with baseline, serum estrone and estradiol did not increase in any of the women at any time. Serum estriol transiently increased after the first application in 15 of 16 women, with a maximum of 168 pg/mL 2 to 3 hours after insertion; after 4 weeks serum estriol was slightly increased in 8 women.[31] Vaginal dryness and quality of sexual life continuously improved during the study period.[41] Only 2 studies directly assessed the risk of recurrence in BCSs using vaginal estrogens: in the study from Dew et al[27] no increase in the recurrence rate in BCSs was observed whereas O'Meara et al observed no increase in recurrence rate or mortality, regardless of the total amount of vaginal estrogens used.[26]

Currently, it is not possible to determine the safety of vaginal estrogens in BCSs, because of the limitations of small sample size and design of the available studies and because they only report about the effect of these treatments on estrogen circulating levels. However, available data from the literature do not show an increased risk of cancer recurrence among women with current or previous breast cancer who use vaginal estrogen to relieve GSM.[12]

In the recent ACOG bulletin, even if a nonhormonal approach is considered the first-line treatment for GSM in BCSs during and after treatment, low-dose vaginal estrogens are indicated as an option for BCSs unresponsive to nonhormonal remedies.[12] The decision to use vaginal estrogen must be taken in accordance with the oncologist and must be preceded by an informed consent process considering benefits and potential risks of low-dose vaginal estrogen.[12] When vaginal estrogens are used, they should be prescribed at the lowest dose and for a limited period until symptoms improve.[12] Treatment should be individualized on the basis of each woman's risk-benefit ratio and clinical presentation.[12]

In this survey, vaginal estrogen therapy was prescribed by 21% of the oncologists, especially in cases of severe dyspareunia after the woman's request or for recurrent vaginal or urinary infections, even if with limitations. Approximately one-fourth of the oncologists who prescribe vaginal estrogen therapy consider it only for women with nonhormone-dependent cancer whereas the others prescribe it to patients with hormone-dependent cancer only after the end of the antihormone adjuvant treatment period. Moreover, when a gynecologist prescribes vaginal estrogen therapy to a patient, only few oncologists confirm the prescription without limitations, others confirm the prescription only for a short period or if the patient has nonhormone-dependent cancer, whereas 20% of the oncologists refuse it. Hormonal treatment is considered safe only by 15% of the oncologists and effective by most of them. According to oncologists' opinion, women are also concerned about safety of vaginal estrogen: many women refuse therapy, ask for reassurance, or only accept it if they have severe symptoms.

The main obstacles for the oncologists in prescribing vaginal estrogens are the probability of increased cancer recurrence risk and the possible interference with antihormone adjuvant treatments. In particular, the use of vaginal estrogens might be appropriate for women with GSM using tamoxifen, because low and temporary increases of plasma estrogen do not appear to increase recurrence risk because of a competitive interaction with the estrogen receptor.[1] For this reason, women receiving AIs who experience GSM refractory to nonhormonal approaches might benefit from the short-term use of estrogen with tamoxifen to improve symptoms, followed by a return to AIs.[12]

When exploring the oncologists' knowledge on VVA treatment options, in most of the cases only standard high-dose formulations are mentioned and little is known about low and ultra-low doses of vaginal estrogens. Only half of respondents knew of low-dose and gel formulations.

Furthermore, only few oncologists were informed about the most innovative therapies for VVA in BCSs, such as vaginal laser or other physical therapies.[14] In recent years, microablative fractional CO_2 laser has become an efficient and safe system that acts through a mechanism of a microablative action that stimulates tissue remodeling.[42] Such a process involves interaction with heat shock proteins 43, 47, and 70,[43] which induce a local increase in different cytokines, specifically transforming growth factor-A (stimulating matrix proteins such as collagen), basic fibroblast growth factor (stimulating angiogenic activity with endothelial cell migration and proliferation), epidermal growth factor (stimulating re-epithelization), platelet-derived growth factor (stimulating fibroblasts to produce extracellular matrix components), and vascular endothelial growth factor (regulating vasculogenesis and angiogenesis) activating fibroblasts to produce new collagen, other components of the extracellular matrix (proteoglycans, glycosaminoglycans, and other molecules), and new vessels, with specific effects on epithelial tissue.[42-44]

Two laser technologies have been testing in VVA: CO_2 laser and Erbium laser. The efficacy and feasibility of fractional CO_2 laser in the treatment of VVA symptoms in postmenopausal women was evaluated in the pilot study of Salvatore et al.[45] Vaginal dryness, burning, itching, dyspareunia, and dysuria were significantly improved at the 12-week follow-up with minimal discomfort experienced after 3 applications of laser treatment; a significant improvement of sexual function and satisfaction in sexual life in postmenopausal women with VVA symptoms was also documented.[46] The most recent study by Siliquini et al[47] confirmed that CO_2 laser treatment induced significant improvement of VVA symptoms, in particular, after 3 treatments; objective and subjective parameters indicated no VVA and this improvement was long-lasting to a 15-month follow-up. Also the time of follow-up was correlated with better objective and subjective scores.

The efficacy of another type of vaginal laser, the Erbium laser, was evaluated in the pilot study of Gambacciani et al,[48] which showed improvement in GSM, in particular of the symptoms of vaginal dryness, dyspareunia, and mild to moderate stress urinary incontinence.

For these reasons, oncologists complain they do not receive enough information on VVA treatment options.

Conclusion

In conclusion, GSM is a relevant problem for BCSs because it has a negative influence on QoL and because it can affect patients' compliance to adjuvant treatment.

However, breast oncologists tend to not deal directly with the problem and wait for a specific request from the patient.

Approximately 70% of the oncologists are against vaginal estrogenic therapy. The remaining 30% prescribe it, in particular in case of patients with non hormone-dependent cancer.

Oncologists do not receive enough information on the topic, in particular little is known about the different types of vaginal estrogenic therapy and on the other possible treatments for VVA in BCSs, such as vaginal laser. They mentioned mainly high doses vaginal estrogens and they were not well informed regarding new formulations, like low-dose vaginal estrogen gel.

The most frequently prescribed treatments are nonhormonal moisturizers or lubricants; they are considered safe but not very effective by the oncologists.

Great effort must be done to correctly inform health care providers about the VVA problem and on the available treatments.

Because the number of patients required to perform a randomized clinical trial on this topic is huge, it seems difficult to have a study with enough statistical meaning to show the safety of vaginal estrogens. For this reason, it is important to inform patients of the limits of the available studies, and discuss risks and benefits to allow patients to choose according to their priorities.

Clinical Practice Points

- VVA is an important problem for BCSs; in particular for those under AIs
- Vaginal non-hormonal treatment is the first line approach to VVA; however for patients unresponsive to non-hormonal therapies, vaginal low dose estrogens can be proposed, after discussion of risks and benefits
- Among health care providers there is reluctance in the use of vaginal estrogens
- In this survey we assessed the attitude of Breast Oncologists towards VVA:
    - Only half of the Oncologists directly illustrates VVA to the patients as a possible consequence of premature menopause induced by adjuvant treatments
    - Only around one third of the Oncologists self-manages VVA treatment, while forty percent refers BCSs to a gynaecologist to define VVA treatment
    - Non-hormonal treatments such as lubricants or moisturizers are preferred by most the oncologists
    - The main reason not to prescribe vaginal oestrogen therapy in BCSs is the fear of increased cancer recurrence, the possible interference with tamoxifen or AIs and the fear of medical litigation
    - In selected cases (for non-hormone dependent breast cancer or for hormone dependent tumors, after the completion of anti-hormone adjuvant treatment), one-forth of the Oncologists considers using vaginal oestrogens
    - Only half of the respondents know low-dose and gel formulation of vaginal estrogens
- Because of the relevance of the problem, great effort should be done in order to correctly inform health care providers about VVA problems and on the different available treatments

Acknowledgments

Italfarmaco SpA sponsored the survey.

Disclosure

N. Biglia has had financial relationships (member of advisory boards and/or consultant) with Gedeon Richter, Italfamarco SpA, MSD, and Shionogi Ltd. V.E. Bounous has had a financial relationship with Italfarmaco SpA. T. Perrone is an employee of Italfarmaco SpA. The remaining authors have stated that they have no conflicts of interest.

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