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Vaginal atrophy in breast cancer survivors: attitude and approaches among oncologists

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CONFLICT OF INTEREST PAGE

- N Biglia had financial relationship (member of advisory boards and/or consultant) with Gedeon Richter, Italfamarco S.p.A., MSD and Shionogi Ltd
- V Bounous had financial relationship with Italfarmaco S.p.A.
- T Perrone is an employee of Italfarmaco S.p.A.
- The other author (s) declare that they have no conflict of interest

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ABSTRACT

Background. Vulvo-vaginal atrophy (VVA) is a relevant problem for breast cancer survivors (BCSs), in particular for those receiving aromatase inhibitors (AIs). We conducted a survey, to assess the attitude of Oncologists towards the diagnosis and treatment of VVA in BCSs. **Materials and Methods.** In 2015, 120 computer-assisted-web-interviews (C.A.W.I.) have been performed among Breast Oncologists. **Results.** According to oncologists' perception, 60% of post-menopausal BCSs and 39.4% of pre-menopausal BCSs will suffer from VVA. Despite none of the physicians considers VVA as a transient event or a secondary problem in BCSs, only half of the oncologists (48%) directly illustrates VVA to the patients as a possible consequence. Forty-one percent of the Oncologists refers BCSs to gynaecologist to define VVA treatment, while 35.1% manages it alone. Non-hormonal treatments are preferred by most the 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. **Conclusions.** VVA is a relevant problem for BCSs. Great effort should be done in order to correctly inform health care providers about VVA problems and on the different possible available treatment.

Key Words: breast cancer, vulvovaginal atrophy, estrogen, genitourinary syndrome of menopause

INTRODUCTION

Every year, an increasing number of new cases of breast cancer is diagnosed among women in reproductive age. Many breast cancer survivors (BCSs), especially young women, undergo to 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 AIs¹⁻², refer to vulvovaginal atrophy (VVA) as one of the most unpleasant side effects³.

Published surveys on BCSs reveal that VVA has been reported by 42-70% of post-menopausal patients and those women rarely discuss the problem with health care providers⁴.

Furthermore, the problem of VVA, in BCSs, will increase because of practice of prolonged therapy with tamoxifen or AIs; to properly manage this side effect both oncologists and patient should be aware about the disease and therapeutic options⁵⁻⁶.

Symptoms of vulvovaginal atrophy (VVA) include dryness, burning, itching, dyspareunia and bleeding following sexual activity, with a high impact on quality of life (QoL), including relationship, sexual satisfaction and self-esteem⁷.

Recently, the term *genitourinary syndrome of menopause* (GSM) has been proposed instead of VVA, in order to include any genital, urinary and sexual signs and symptoms associated with menopause⁸.

GSM is usually reversible with hormone replacement therapy. Local estrogen treatment is the most used approach for symptom management and illness healing⁹⁻¹⁰. However, in BCSs, estrogen administration has safety concern, due to the hypothetical risk of cancer recurrence¹¹.

Therefore, in this setting of patients, the ACOG (American College of Obstetricians and Gynecologists) recommends local non-hormonal approach as first line treatment of GSM leaving estrogens to patients unresponsive to non-hormonal therapies¹².

It is not clear which health care provider (gynaecologist, 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 in order to investigate their attitude towards the VVA problem in BCSs.

MATERIALS AND METHODS

One-hundred-twenty C.A.W.I. (Computer assisted web interview) have been performed from May 18th 2015 and to June 8th 2015 to Italian breast oncologists, throughout the country (39.2% North, 20% Centre, 40.8 % South)

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

To describe the attitude of oncologists towards 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 about VVA with patients and 4) primary measure as soon as patient reveals VVA.

Furthermore, to evaluate oncologist experience in VVA treatment options, the following data have been collected 1) what kind of drugs they are used in the treatment of VVA and 2) their attitude towards hormonal or non-hormonal drugs. The attitude of the patient when hormonal drugs are prescribed was also reported.

RESULTS

One-hundred twenty oncologists (52.5% male and 47.5% female), belonging to several centers  have been interviewed using C.A.W.I.. A dedicated breast care unit was present in 64.2% of the hospitals, with a median of 240 new breast cancer diagnosis per year. Moreover, in 12% of the centers the median of new breast cancer diagnosis was more than 410 per year. Median number of BC naïve patients starting adjuvant hormonal therapy was 63 per year; in 13.3% of centres, this median value reached more than 100 cases per year.

Breast oncologists' attitude towards adjuvant treatment prescription is in accordance with the most recent guidelines on breast cancer treatment, preferring AIs to tamoxifen¹³. According to our survey, in Italy, the first choice (65.4% of cases), is tamoxifen with ovarian suppression as anti-hormone adjuvant treatment in pre-menopausal women; AIs with ovarian suppression are prescribed only in 15% of cases. In post-menopausal subjects, the oncologists prescribe AIs as first choice treatment (82.9% of cases) while tamoxifen is prescribed only in 17.2% of patients. In one fourth of the patients, in both groups, extended therapy is prescribed (26% and 21.7% respectively). Both for pre and post-menopausal patients, the compliance to the standard 5 years-adjuvant anti-hormone treatment is around 80% (83.2% and 79.1% respectively) as referred by the oncologist. According to oncologist opinion, in patients under adjuvant hormonal-treatment, 60% of post-menopausal and 39.4% of pre-menopausal women experienced VVA. In post-menopausal patients, VVA grade has been considered mild, moderate or severe in 43.1%, 39.9% and 17.1% of cases, respectively. Every participant is conscious that VVA strongly affects sexual health and increase probability of urinary tract infections.

Despite none of the physicians considers VVA as a transient event or a secondary problem in BCSs, only half of them (48%) straight 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 case of the patient complains about symptoms with the oncologists (56.9%) or with the nurse (14%). The oncologist address the problem of VVA only in the 26 % of cases, with no differences in relation to doctor's gender. Oncologists are aware of paying inadequate attention to the problem (85% of the answers) and they complain to not receive enough information on this topic (85% of the answers).

Forty-one percent of the oncologists indicates the patient to refer to the gynecologist

While another 35.1% directly illustrates treatment options to the subject.

Eleven-eight percent of patients do not require or refuse any kind of treatment; on the other hand, 11.9% of women manage the VVA with self-prescription.

As expected, non-hormonal treatments (lubricants or moisturizers, in the same proportion) are prescribed in most of the cases (71.1%). Vaginal estrogen therapy is prescribed by 21% of the oncologists and hormone replacement therapy (HRT) is considered only by a minority (4%). Refer to Fig.1.

Non-hormonal treatments are considered safe by 90% of the oncologists and effective only by 30% of them; conversely, hormonal treatment with vaginal estrogens is considered safe only by 15% and effective by 79.2% of oncologist. Refer to Fig.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%), also upon patient request (26.7%), and for recurrent vaginal or urinary infections (16.7%).

The 24.2% of the oncologist prescribes vaginal estrogen therapy for patients with non-hormone dependent breast cancer; only the 7.5% prescribes this therapy to patients with hormone dependent breast cancer, at the end of anti-hormone adjuvant treatment. In 15% of the cases, the oncologist does not prescribe hormonal drugs to treat breast cancer patients. Moreover, if a gynecologist prescribe vaginal estrogen therapy, only the 21.5% of the oncologists confirms the prescription; the 20.8% confirm the prescription only for a short period or just if the patient has non-hormone dependent breast cancer (18.9%) while the 20.4% of them does not agree at all.

The main reason to not prescribe vaginal estrogen therapy in BCSs is the probability of increase cancer recurrence, mentioned by 70.8% of the oncologists, followed by the interference with tamoxifen or AIs. Lastly, doctors may run into 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%), while 36.5% ask for reassurance before using it. However, 20.5% of women accepts vaginal estrogen prescription especially in the presence of severe symptoms.

Regarding oncologist knowledge about different available vaginal estrogen preparations, standard high dose formulation is mentioned by 70% of them, while the 52.5% prescribe low dose and gel formulation. Furthermore, only 1.7% of the oncologists know new treatment options such as vaginal laser.

DISCUSSION

VVA is one of the most frequent 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 impact on QoL^{1,3,15}. Younger women have higher rates of sexual dysfunction, even beyond the treatment period¹⁶⁻¹⁷. A QoL analysis including 1722 premenopausal patients, with hormone receptor-positive BC randomly assigned to receive adjuvant treatment (tamoxifen plus ovarian function suppression or tamoxifen alone for 5 years), shown loss of sexual interest at 6 months and vaginal dryness for up to 60 months, in patients on tamoxifen plus ovarian function suppression in respect to that in tamoxifen alone¹⁸.

In the literature, it is reported that up to 20% of BCSs consider stopping antihormone therapy because of menopausal symptoms¹⁹⁻²⁰. In accordance with literature, in our survey investigating the attitude of breast oncologists towards the VVA problem in BCSs, 20% of pre and post-menopausal patients stop anti-hormone treatment, probably because of side effects such as VVA.

Oncologists are aware that VVA is a frequent problem among BCSs, complained by 60% of post-menopausal women and by 40% of younger women. 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 can increase probability of urinary tract infections.

The term GSM has been recently proposed instead of VVA, for better describes genital, urinary and sexual areas involved⁸.

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 untreated²¹: in our survey, no one considers VVA as a temporary problem.

Only half of the oncologists directly illustrates VVA to women as a possible consequence of adjuvant treatments, even if they do not considered 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 practice²¹.

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

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

According to the available current guidelines, non-hormonal vaginal moisturizers and lubricants are recommended as first-line treatment for BCSs^{9,11}. In our survey, oncologists prescribed, in most of the cases, non-hormonal treatments (lubricants or moisturizers in the same proportion), which are considered safe, even 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} following the results of the HABITS²²⁻²³ and Stockholm trials²⁴. In addition, a trial on tibolone, an alternative compound to conventional HRT, which displays estrogenic, progestogen and androgenic properties, was prematurely stopped because of a significant increase of recurrences in the group of BCSs treated with tibolone as compared to the placebo group²⁵.

Vaginal estrogen administration is the preferred way of delivery when vaginal symptoms are the only condition in post-menopausal 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 response¹⁰. Furthermore, vaginal estrogens also improve sensory urgency and reduce the frequency of urinary tract infections⁹.

Only few trials have been conducted to investigate vaginal estrogen therapy in BCSs suffering of VVA²⁶⁻³². 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 non-hormonal therapies may discuss the risks and benefits of low-dose vaginal estrogens with the oncologist¹¹. Systemic absorption can occur with conventional doses of vaginal estrogen therapy, particularly in case of atrophic vagina³³. 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 demonstrated that low-dose vaginal estrogens improve vaginal symptoms in the majority of treated subjects, with plasma estradiol levels in the range of postmenopausal value³⁴⁻³⁶. Ultra-low doses of vaginal estrogens have been recently investigated in postmenopausal healthy symptomatic women³⁷⁻³⁹ 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 from estrogens. Since 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 may exist⁴⁰. Standard doses of vaginal estrogens can determine an increase in plasma levels of serum estradiol, relevant for BCSs, especially for those under AIs, as shown in the study of Kendall et al²⁸. In this study, six postmenopausal BCSs treated with AIs received estradiol tablets at a standard dose (25 mg): serum estradiol levels increased from baseline levels < 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 BCS using low^{29, 32} and ultra-low doses³¹ of vaginal estrogens demonstrated that they can alleviate VVA symptoms without raising serum levels of estrogens. Previous published data from our department assessed the efficacy and safety of two low-dose vaginal estrogen treatments (estriol cream 0.25 mg or estradiol tablets 12.5 mg) and of a non-hormonal 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 tablets²⁹. In a prospective, randomized study on 10 postmenopausal BCSs using AIs it was found that the daily use of 0.5 mg estriol for two weeks did not result in increased serum levels of estriol or estradiol³². In a phase I clinical study with ultra-low dose 0.03 mg of estriol and lactobacillus combination vaginal tablets in 16 BCSs with VVA, after 3 months of treatment compared to 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 eight women³¹. Vaginal dryness and quality of sexual life continuously improved during the study period⁴¹. Only two studies assessed directly the risk of recurrence in BCSs using vaginal estrogens: in the study of Dew et al.³⁰ no increase in the recurrence rate in BCSs was observed while O'Meara et al. observed no increase in both recurrence rate and mortality, regardless of the total amount of vaginal estrogens employed²⁶.

Currently, it is not possible to determine the safety of vaginal estrogens in BCSs, because of the limitations due to the small sample size and design of the available studies and because they only report about the effect of these treatments on estrogens circulating levels. However, available data from literature do not show an increased risk of cancer recurrence among women with current or previous breast cancer who use vaginal estrogen to relieve GSM¹².

In the recent ACOG bulletin, even if non-hormonal 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 non-hormonal remedies¹². 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 estrogen¹². When vaginal estrogens are used, they should be prescribed at the lowest dose and for a limited period until symptoms improve¹². Treatment should be individualized based on each woman's risk-benefit ratio and clinical presentation¹².

In this survey, vaginal estrogen therapy was prescribed by 21% of the oncologists, especially in case of severe dyspareunia after woman request or for recurrent vaginal or urinary infections, even if with limitations. About one fourth of the oncologists that prescribes vaginal estrogen therapy considers it only for women with non-hormone dependent cancer while the others prescribe it to patients with hormone dependent cancer only after the end of anti-hormone adjuvant treatment period. Moreover, when a gynecologist prescribe 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 non-hormone dependent cancer while the 20% of the oncologists refuses it. Hormonal treatment is considered safe only by 15% of the oncologists and effective by most of them. According to oncologists' opinion, also women are concerned about vaginal estrogens safety: many women refuse therapy, ask for reassurance or only accept it if complaining 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 may 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 receptor¹. For this reason, women on AIs who experience GSM refractory to non-hormonal approaches may benefit from the short-term use of estrogen with tamoxifen to improve symptoms, followed by a return to Ais¹²

When exploring the oncologists' knowledge on VVA treatments' options, in most of the cases only standard high dose formulation are mentioned and little is known about low and ultralow doses of vaginal estrogens. Only half of respondents know low doses 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

CO₂ laser has become an efficient and safe system that acts through a mechanism of a microablative action that stimulates tissue remodelling.⁴² Such 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 vasculo-genesis 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: CO₂ laser and Erbium laser. The efficacy and feasibility of fractional CO₂ 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 documented⁴⁶. The most recent study by Siliquini et al.⁴⁷ confirmed that CO₂ laser treatment induced significant improvement of VVA symptoms, in particular, after three treatments, objective and subjective parameters indicated no VVA and this improvement was long lasting until 15 months' FU. Also the time of FU 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, showing improvement in GSM, in particular of the symptoms of vaginal dryness, dyspareunia and mild to moderate stress urinary incontinence.

For these reasons, oncologists complain to not receive enough information on VVA treatment's option.

CONCLUSION

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

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

About 70% of the oncologists are against vaginal estrogenic therapy but although about one fourth of them do not, 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 frequent prescribed treatments are non-hormonal moistures or lubricants, they are considered safe but not very effective by the oncologists.

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

Since 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 that show the safety of vaginal estrogens. For this reason, it is important to inform the patients of the limits of the available studies, discussing risks and benefits in order to allow patients to choose according to their priorities.

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FIGURES: Fig. 1 Treatments prescribed to treat VVA. Non-Hormonal, local or systemic hormonal drugs and other (mainly alternative medicine products).

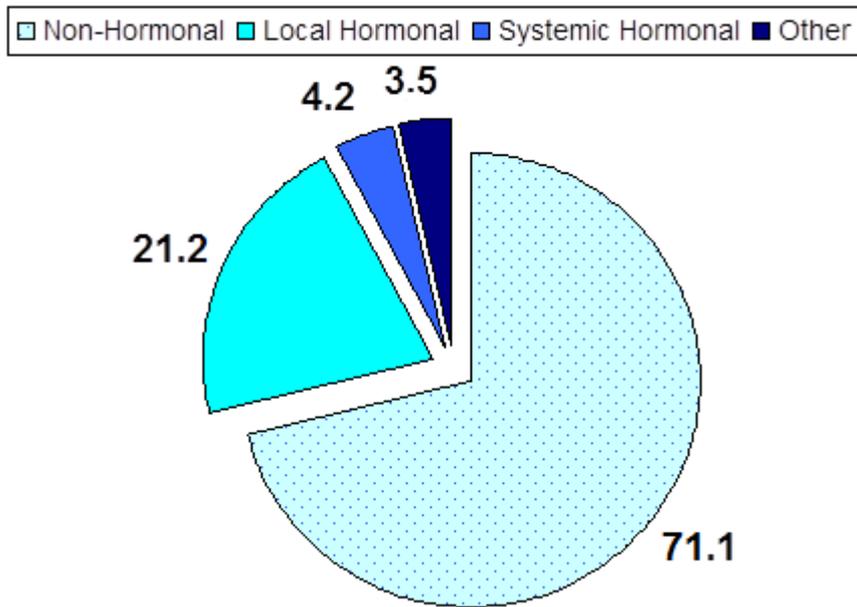
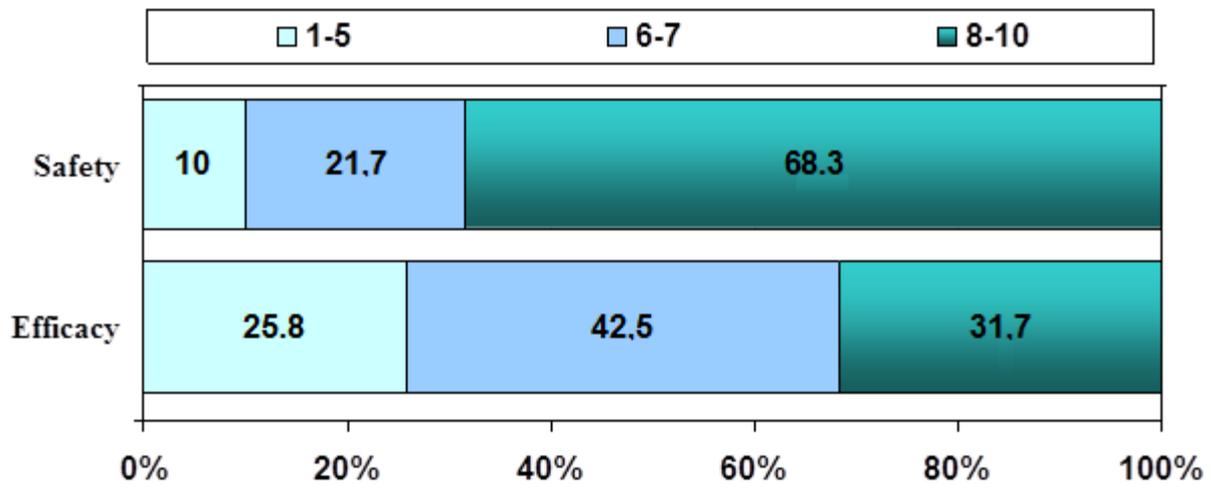
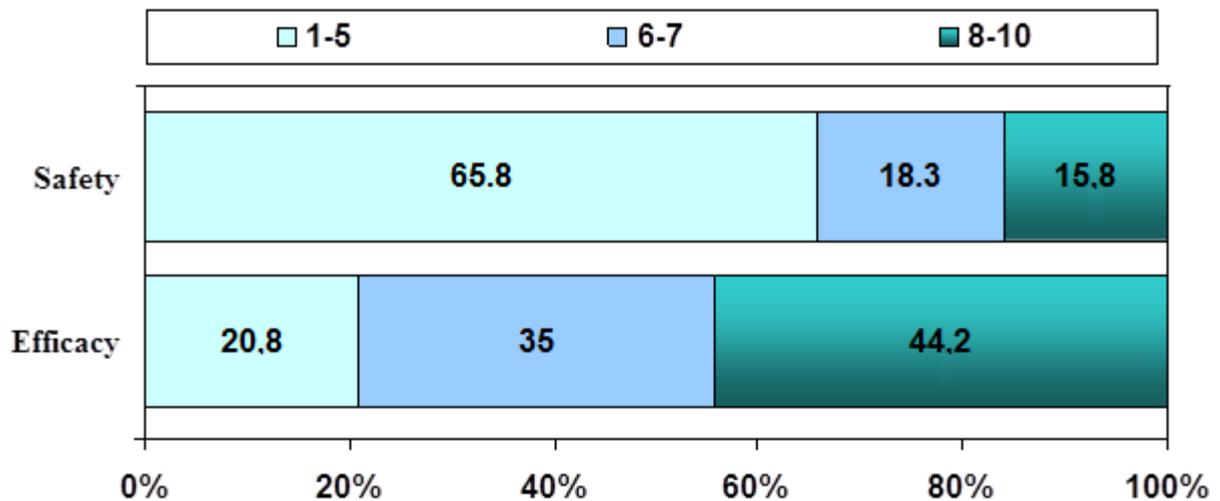


Fig. 2 Oncologist's perspective of safety and efficacy of NON-HORMONAL (a) and HORMONAL (b) therapy to treat VVA in breast cancer patients, according to visual analogical scale (VAS) (VAS numbers indicate 1 for minimum and 10 for maximum)

a) perspective for NON-HORMONAL THERAPY



b) perspective for HORMONAL THERAPY



LEGENDS

Fig. 1 Treatments prescribed to treat VVA. Non-Hormonal, local or systemic hormonal drugs and other (mainly alternative medicine products).

Fig. 2 Oncologist's perspective of safety and efficacy of NON-HORMONAL (a) and HORMONAL (b) therapy to treat VVA in breast cancer patients, according to visual analogical scale (VAS) (*VAS numbers indicate 1 for minimum and 10 for maximum*)

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