Adherence to oral administration of endocrine treatment for the patient with breast cancer: a review

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Abstract

The adjuvant treatment with oral hormonal therapy improves clinical results of breast cancer, but women find difficulty in adhering to the 5-year-regime. The imperfect adherence to the therapeutic treatment has an impact on the clinical benefit; it can induce resistance to the treatment, disease progression and also death. The percentages of adherence to such treatments fluctuate between 15 and 50% and they are influenced by many factors (for example the appearance of side effects, elaborate dosage, the lack of confidence in the treatment, the price, the absence of relationship between doctor and patient). This article critically discusses the barriers to adherence to the endocrine oral therapy and the interventions able to improve it.

KEY WORDS: adherence, breast cancer, endocrine oral treatments.

Introduction

The adherence to treatments is extremely important for all chronic pathologies. In 1979, Haynes et al. defined adherence (which is still called “adhesion of the patient”), as “the level of the patient’s behavior – relating to taking medication, maintaining a diet and/or changing behavior in lifestyle – which agree with the specialist’s advice” (1). About 50% of patients who undergo treatment for a long progress disease, do not show adherence to oral therapy, with the result of a natural tendency towards the aggravation of the pathology and the increase of complications, admissions to hospitals, deaths and overall health cost (2, 3). The breast cancer is the main malignant tumor for women of the entire world; it affects one out of eight women, and it is also the main cause of deaths for cancer among women (4). Recently, phenotypes of breast cancer have been divided into 4 subgroups: luminal A, luminal B, HER-2 positive and basal like and triple-negative. Women with luminal A or B phenotype are positive to estrogen receptors (ER+), while those with HER-2 phenotype are rarely, and those with basal-like and triple-negative phenotype are never. About 2/3 of all breast cancers are ER+. The incidence of ER+ in breast cancer is major among Caucasian race (63%) than among the Afro-American one (52%), and the ER+ gives a prognosis better than ER negative. ER+ breast cancer requires the estrogenic stimulation for the growth. The ER+ breast cancer is treated with tamoxifen before and after menopause or with aromatase inhibitors (AI) only after menopause both in adjuvant and metastatic phase. Tamoxifen is a partial agonist of estrogen receptors and antagonizes the effect of endogenous estrogens that stimulate such receptors. Aromatase inhibitors (anastrozole, exemestane, letrozole) reduce the synthesis of estrogens, and this also reduces the stimulation of estrogen receptors. In order to obtain the greatest advantage from such endocrine oral treatments, women need to take medications for an extended period of at least 5 years to 10 years at the most (5). Recent considerations of adherence and persistence show that the adherence to tamoxifen fluctuates between 79% in 1 year and 65% in 5 years, and the adhesion to aromatase inhibitors (AI) fluctuates between 80% in 1 year and 72% in 5 years. The persistence decreases when the period of treatment increases: patients’ persistent adhesion to tamoxifen fluctuates between 86% in 1 year and 53% in 5 years, and the adhesion to aromatase inhibitors (AI) fluctuates between 80% in 1 year and 72% in 5 years. The persistence decreases when the period of treatment increases: patients’ persistent adhesion to tamoxifen fluctuates between 86% in 1 year and 53% in 5 years, and the adhesion to AI fluctuates between 88 and 69% (6). The low adhesion to tamoxifen is significantly associated with a risen risk of death for mammary carcinoma (7). Endocrine therapy per os is the adjuvant treatment of elections for this type of pathology. In order to obtain the greatest advantage from this kind of treatments, patients need to take medications for an extended period of time. The oral therapy is considered easy to use and it is generally well tolerated. Although patients prefer oral formulation because of a lower impact on the daily routine (suffice to think that women do not need to go to the hospital and stay there for several hours to receive treatment), percentage of adhesion to therapeutic regimes varies widely, from 53 (8) to 93% (7). In general, there is no adhesion to the therapy when its consumption is omitted, when the expected time is not
respected, but also when overdoses or wrong doses are taken (9). Whereas the persistence refers to take therapeutic treatment for all the time prescribed by the doctor (9).

This article summarizes problems related to the adhesion to the adjuvant endocrine therapy for breast cancer, and outlines strategies to reduce the lack of adhesion to clinical practice.

**Factors which influence the adherence to tamoxifen and aromatase inhibitors among women with breast cancer were recently and fully studied by Hadji (10). The Author divided such factors into 4 groups: 1. treatment-related; 2. patient-related; 3. correlated to health staff; and 4. predictors of low adhesion.**

1. Factors related to the therapy include opposing effects, the complexity of the treatment and the medication cost. Also Grunfeld et al. (3) identify reasons of no-adherence to the treatment such as the increase of side effects, in particular burst of heat, night sweats, difficulty of concentration and memory, sleep disorders, emotional problems (for example anxiety, panic, depression), putting on weight and the loss of libido.

2. Factors related to the patient concern: lack of faith in the treatment, psychologic disorders (in particular depression), omission, personal believes (11), low knowledge of the therapeutic advantage, the unease of the number of tablets to take (the potential no-adherence to the treatment by the patient is directly proportional to the number of tablets to take), and side effects of the therapy. Also Grunfeld et al., (3) identify reasons of no-adherence to the treatment such as the increase of side effects, in particular burst of heat, night sweats, difficulty of concentration and memory, sleep disorders, emotional problems (for example anxiety, panic, depression), putting on weight and the loss of libido.

3. Factors which affect the adherence and which are related to general practitioners are: a low relation-ship with the patient, the lack of comparison on side effects, the unsuitable follow-up and incomplete prescriptions.

4. According to Hadji (10) factors emphasized as predictors of no-adherence refer to the patient’s preferences, which are influenced by the perception of the pathology and by the expected outcome. The rise of the cost of medication and the timetable are other two deterrents to the adhesion to the treatment (12, 13).

5. Among predictors of no-adherence, the literature also quotes multiple concurrent therapies (polypharmacy), physical limitations, the stage of the disease, the age, the psychologic factors, the social-educational background and the high cost of medications. Treatments patterns, which require two or more daily doses, are related to a lower adhesion compared to those with mono daily administration (14). Patients with multiple therapeutic regime have to face further challenges concerning the dosage and the administration. There is a direct proportion at least to one prescription between the number of chronic comorbidity and the rate of no-adherence (15): The weakening of eyesight can limit the reading of labels for dosage instructions, the presence of peripheral neuropathy can affect the opening of a guarantee seal or a medicine bottle, the presence of dysphagia compromises the capacity to swallow, making adherence barriers further worse (16). The adherence differs in proportion to the stage of the disease; indeed, patients with mammary tumor at the initial stage do not feel as much ill as those with metastatic breast cancer; consequently they can become less adherent to the therapeutic regime. The adherence to the first endocrine therapy seems elevated, but it tends to decrease every year (17, 2). Several surveys show age as a factor determining the adhesion to orally endocrine medications in cases of breast cancer, but their results are not always coherent; indeed, very young women (<45 years old) and very old women (>85 years old) are less adherent to tamoxifen than those who are in the age interval. The adherence to aromatase inhibitors among very young subjects has not been reported (18), but old patients are always less adherent than the young (16, 19). Some surveys report that the lack of adherence among patients over 75 years old is the main reason of hospitalization (20). The lack of adherence among the old is often brought on by the presence of potential comorbidities which can cause cognitive disorders, such as memory diminishing, weakening of eyesight and hearing weakness, and specific generational perception with regard to taking medications (16, 19, 21). In addition, old patients have a low income, based on the National Health Service for pharmaceutical coverage, and economic difficulties facilitate the no-adherence (15, 16). Patients with psychological disorders (16), or with psychiatric disease that reduce the level of understanding or the memory loss, are less adherent to the therapeutic regime (15).
the educational level of the woman can affect the adherence to the treatment (22), as therapeutic instructions are often wordy and source of confusion for a generic public (19). The high cost of medicines, the limited access to health services, the lack of financial resources and hard working timetables are associated to the no-adherence to therapeutic regimes (23).

Interventions to reduce as much as possible side effects

The main problem noticed by health staff with the use of oral therapy is the potential no-adherence to the treatment by the patient, with the double issue of the wrong dosage meant both as low and high utilization. This is directly proportional to the number of tablets to take and the presence of potential side effects: self-administration of the medicine, outside the hospital/ambulatory context. A regime of treatment with significant side effects can reduce the patient’s quality of life (QOL) and consequently, compromises the adherence, whereas a regime that relieves the symptoms of the disease shows an improvement of QOL and promotes the adherence (24).

The need for the adherence to the treatment and a careful monitoring of eventual toxicity is necessary because, while possible toxicities of conventional chemotherapies can be anticipated, within terms limited by oncologist, those of biologic targeted therapies have not been known yet and they are much more variable chronologically. The toxicity control and the safety of oral therapy is also difficult: entered absorption, medicine interaction with other medicine or with food, have an important role in the effect of the treatment. It must be added the difficulty of the patient to correlate temporarily the consumption of medicine and the onset of side effects that can lead the patient to a low adhesion to the treatment.

Grunfeld et al. (3) noticed that 46% of women interrupt the treatment with tamoxifen after the onset of side effects, in particular because of burst of heat and night sweats. In regard to the adherence and persistence related to side effects of AI (aromatase inhibitors), the ATAC survey by Baum et al. (25), observed that women who take off the treatment with anastrozole are very few than those who are on medication with tamoxifen; however, higher level of no-persistence to AI have been noticed in comparison studies of exemestane and letrozole with tamoxifen (26).

Side effects, such as diarrhea and stomatitis, can interfere with the oral pharmacological therapy (27), in particular because of burst of heat, night sweats, difficulty of concentration and memory, sleep disorders, emotional disorders (for example anxiety, panic, depression), putting on weight and the loss of libido (3). Adverse effects to tamoxifen include gynecological disorders (high incidence of vaginal bleeding, endometrial polyps, endometrial thickening, ovarian cysts), an increased risk of endometrial cancer, and an increased risk of deep venous thrombosis (28). Concerning aromatase inhibitors, negative effects include the loss of bone tissue, skeletal muscle pain, arthralgia (28), bursts of heat, fatigue, sleep and memory disorders (29). Reducing to the minimum such side effects the adherence to endocrine oral medicines may improve. An approach used to reduce adverse effects is the change of the endocrine treatment. So, if a woman who takes tamoxifen has to stop the therapy because of bad effects, she can change the treatment and assume aromatase inhibitors and vice versa. For example, endometrial thickening associated to the use of tamoxifen has determined a change of therapy towards exemestane in IES (30). However, there is no evidence that such change can make the adherence to the endocrine oral therapy better.

With tamoxifen and aromatase inhibitors (anastrozole, letrozole and exemestane), 35/40% of women have bursts of heat, the incidence is a little lower with anastrozole and letrozole compared to tamoxifen (28). The treatment for side effects such as bursts of heat/night sweat, is purely pharmacological; however, alternative approaches have been used in order to reduce such effects among women who are menopausal (31), but with a limited scientific evidence. Among alternative approaches, Yoga Awareness program (kind yoga, meditation and breathing exercises) seems it can reduce the frequency of bursts of heat and articular pains (32). Acupuncture can reduce bursts of heat in women who have mammary carcinoma and are treated with tamoxifen (33). Bone loss is more heavy with aromatase inhibitors than with tamoxifen, and fractures occur in more than 11% of subjects with anastrozole (28). Bone losses and associated fractures can be managed with bisphosphonates (28), but it is not clear if this will bring up more adherence than aromatase inhibitors. Bisphosphonates provoke light adverse gastrointestinal effects (6-16%) among women, but it is not known how much the presence of such effects affect the adherence; what it is known by studies is that they make the adherence better among women with osteoporosis (34, 35).

The interruption and the change of the treatment can help to control side effects and prevent the symptomatology aggravation (27, 36). Indeed, a bad control of side effects contributes to patients’ no-adherence, thus, all of them should know what to expect since the beginning of the therapy and what measure will be taken in order to relieve their side effects.

Intervention of the health professionals

A great number of interventions is suggested by the literature review in order to improve adherence to the endocrine therapy for women with breast cancer, but few studies have estimated the possible efficacy of these methods. Even if according to a widespread belief, communication between doctor/oncologist and the patient with breast cancer will be a key factor in establishing adherence to the oral endocrine therapy (37), there are not studies establishing if a continuous communication with the doctor effectively improves adher-
ference. Also for nurses, there are numerous suggestions to improve adherence to the oral endocrine treatments for women with breast cancer, but also these ones have not been confirmed. For example, it is believed that nurses working in oncology, during intravenous chemotherapy administration, have few difficulties in instructing women who begin oral adjuvant therapy, as it has been demonstrated that women are very perceptive during the administration of chemotherapy medicine (38). An analysis of different studies on costs and benefits of patient education has led to the following conclusions: on the average, each American dollar invested in patient education has allowed to save three or four dollars. None of these studies has concluded that patient education costs more of what it allows to save (39). Educational path can be associated to nursing path, because both include phases of identification, diagnosis, intervention and evaluation (40). This education can include verbal communication, written information, web sites on organizations for breast cancer (38, 41). Instruction must include the name of the medicine, schedule for administration, how the medicine must be taken, safety, side effects and treatment of the symptoms (38). For administration and planning, a reminder can be recommended (42). People learn in different ways, and repeating can help to reinforce important messages (43). Nurses of the oncology departments can improve communication with women by using individual plans of communication or learning strategies with brainstorming between nurse and patient. According to the basic practical skills of the patient, communicative strategy can include calls, e-mail, contacts with family members or close friends or other ways by which patient and nurse can keep in contact.

In order to help patient education, nurses may identify the personal learning style preferred by the patient. For example they can ask: the patient prefers lectures? Face-to-face talks? Talking to other patients? (41). In order to have a positive consultation, oral communication may be linked to a written documentation. In fact, while oral communication is the best form when simple information are given, written documents can help to underline information orally given (44). Moreover, according to Doak and Root (45) the efficacy of the written material is increased if it is customized for each patient. For this reason, the question-answer format and a bulleted list clarify the text (46). Photos and images simplify the text, but they must be chosen with care and attention. Practically, for nurses, it has been suggested that in order to improve adherence to adjuvant endocrine therapy for women with breast cancer, it is necessary to develop a collaboration with the patient, establishing common targets and a plan to realizing them (31, 47).

Availability and capacity of the women to take part to the schedule should be evaluated, the targets and the schedule must be regularly evaluated, without accusation if these targets have not been reached (47). A brief questionnaire on the medicine that woman fills out in the waiting room before the therapy can help in identifying possible problems with adherence and understanding why there are these problems (47). As part of the effects of the endocrine therapy can interfere with adherence, it is important to talk about them and clarify that are not to be intended as a relapse of the cancer (31, 47). Moreover, if women are aware of possible negative effects, they can already inform doctors and nurses, their treatment can begin before, and consequently adherence is improved (31, 47, 48). Nurses can have an important role in managing negative events talking to patients and notifying the problem to the doctors. Moreover, patients must be unequivocally instructed to contact healthcare and medical assistants to the first signal of a negative event. Changes of administration, if possible, can prevent the interruption of the treatment for a lot of patients. Moreover, nurses have an important role in the telephone triage. When patients call for negative events, nurses are often able to give advices to help solving simple problems or take detailed information for more urgent problems (41).

Using reminder systems can improve adherence to anticancer oral medicines in breast carcinoma (43). Reminders included systems of memo on calendars, alert, post-it, diaries or papers, boxes, blisters of pills, packages, telephone reminders, micro electric control of the systems and pager with alarms and text messages (43). Anyway, at the moment no one of these systems of alert has been tested in a specific way on women using oral medicines against cancer. According to the opinion of the experts, the type of the developed activity during the day-hospital in the present structures is not sufficient to control the above-mentioned problems, for the high turnover of the patients and for the distribution of the work among the assistants. So, it is necessary to plan specific structures for oral chemotherapy, in which the patient is well informed on the therapy to follow, how and when he has to take medicines and their possible side effects. Management of these structures must consider the involvement of the oncologist, the pharmacist (to control the negative effects according to AIFA – Italian Medicines Agency) and the nurse. The patient must be constantly supported during the treatment period, through creation of specific call-centers or, even better, through oncological tele-consulting for any doubt concerning the therapy. After an admission, routine follow-up are recommended, as for example a telephone contact (49). Patients need time to process new information. Information not still clear at the end of the consult can easily seem senseless at home. Soon, problems no one had predicted can arise. Telephone follow-up programs not only increase patient satisfaction, but they are also efficient means to increase the educational continuity (40).

Conclusions

The non-optimal adherence to the treatment can have an impact on clinical benefit, sometimes causing resistance to the treatment and a further development of the disease. Consequently, oral therapy in the cancer treatment will be efficient only if an optimal adherence will be reached. Adherence reasons change according...
to type of treatment, side effects, lack of confidence in the prescribed medicines.

Identifying possible obstacles and using interventional strategies can contribute to improve adherence and, consequently, also clinical results.

First of all, nurses must inform patients of the proved benefits of adjuvant endocrine therapy of the breast cancer in the premature phase (less recidivism and less mortality) and then connect best clinical results with the best levels of adherence. Communication improves adherence to the prescribed regimen. Although at the end patients decide to follow or not the prescribed regimen, nurses and other healthcare professionals can play an important role on their final decisions. Endocrine therapies are associated to adherence widely demonstrated by studies respect to other anti-cancer therapies. Nurses can take advantage in knowing information for searching what they need, when monitoring and reinforcing adherence to the treatment. Nurses have skills for an important role in identifying non adherence, motivating patients, and fighting to obtain clinical benefits of the endocrine therapy (50). Nurses must continue to supply and improve qualities as well as their competence, their know-how, their behaviors and their skills for the good of their patients (51).

In addition, it might be coherent to validate the realization of a project of information, formation and communication for the patient, managed by the oncologist, the pharmacist and the nurse in order to solve adherence problems. Moreover, this project should be appraised and quantified by refund ways. On the basis of this premise, it could be necessary to start experiments among different organizational models that represent logistic and communication dynamics related to the assistance-therapeutic path of the cancer patient treated with oral therapy, also considering the economic consequences.

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