NON-ADHERENCE TO ADJUVANT HORMONAL TREATMENT IN EARLY BREAST CANCER

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NON-ADHERENCE TO ADJUVANT HORMONAL TREATMENT IN EARLY BREAST CANCER (Abstract): The benefit of hormonal adjuvant treatment is well established by clinical trials for the women with early breast cancer with hormonal receptors. Though, the information about adherence of the patients to this treatment are little known. We sought to estimate adherence and predictors of nonadherence in women starting hormonal adjuvant treatment in early breast cancer.

Methods: Subjects were age 18 years or older initiating hormonal therapy (tamoxifen, letrozole, exemestane, anastrozole) for primary breast cancer, treated in Center of Medical Oncology from Iasi, Romania, in the period 2001-2009. The patients have completed a questionnaire about predictors of non-adherence to treatment and about their level of adherence to hormonal treatment.

Results: Twenty-nine percent of patients missed taking hormonal therapy more than 2 months/year. Predictors of non-adherence are: adverse events (flushes, arthralgia), extreme ages (particularly after 70 years), psychological aspects. The percent of adherence during the treatment period (5 years), was find that the first 3 years was a period of 80% total adherence with a decreasing in the last years of treatment (50%).

Conclusion: More of one fourth of patients may be at risk for inadequate clinical response because of poor adherence. Because of the efficacy of hormonal therapy in preventing recurrence and death in women with early-stage breast cancer, further efforts are necessary to identify and prevent suboptimal adherence.

KEYWORDS: BREAST CANCER, NON-ADHERENCE, HORMONAL ADJUVANT TREATMENT

INTRODUCTION

The benefit of adjuvant treatment with tamoxifen or aromatase inhibition therapy using letrozole, anastrozole, or exemestane in early stage breast cancer for women with hormone-receptor–positive breast cancer was documented in many clinical trials, correlated with reducing of the risk of contralateral breast cancer and increasing overall survival [1-3].

Main side effects of tamoxifen and aromatase inhibitors include the worsening of menopausal symptoms and a small but significantly increased risk of thrombosis and endometrial cancer for tamoxifen and artralgia and osteoporosis for aromatase inhibitors. Clinical trials revealed that that the benefits of tamoxifen are greater with 5 years of therapy than with 1 or 2 years but that longer durations (beyond 5 years) provide no further advantage [2-4]. The advantages of 5 year treatment with aromatase inhibitors comparative with tamoxifen are on overall survival and time to progression. But for all the drugs, tamoxifen, anastrozole, letrozole and exemestane, the doses are

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well defined and there are not information about the survival and time to progression with lower doses.

Adherence rates for many chronic drug therapies have been shown to be low, often ranging between 40% and 50% [5-7]. Available data on adherence to tamoxifen are from limited study populations. Overall adherence to adjuvant tamoxifen has been reported to range from 25% to 96%, although the assessment methodology often has not been reported [1,4,8-10]. Waterhouse et al [11] found in a group of 26 women with breast cancer, that patient self-report and pill counts significantly overestimated the degree to which patients adhered to their tamoxifen regimen, compared with data recorded by a microelectronic monitoring device. In this study, 18 of 24 patients (75%) were less than 80% adherent with the tamoxifen regimen.

**METHODS**

The study population was from Center of Medical Oncology, Iasi county, Romania, in the period 2001-2009. We measured the adherence of 256 of women treated with tamoxifen, anastrozol, letrozol and exemestane as adjuvant breast cancer therapy and identified clinical and demographic factors associated with poor adherence in this population. These women were treated with tamoxifen, letrozole, anastrozole and exemestane. The information about the prescriptions (doses, time of prescription) were from the source documents from this center. In the same time, every patient treated was evaluated with a questionnaire at the beginning, during or at the end of 5 years of adjuvant treatment.

The questionnaire included 2 parts. The first part includes elements possible to modify the adherence to treatment: questions about psychologic aspects (depression, anxiety), about the consistency of patient – provider relationship (5 degrees from poor to excellent, including the trust of the patient in physician), associated diseases with concomitant medications (pills), difficulty obtaining prescriptions from their physicians, adverse effects of medication and the intensity.

The second part of the questionnaire was a self-report of the patient regarding the adherence to treatment; the report consisted of a questionnaire that asked patients whether their adherence was of 100% per year (were not consider the discontinuations of 1-5 days), if patients have interrupted the treatment for 2-5 months per year and if the patients have stopped the treatment for more than 6 months/year (Table 1).

<table>
<thead>
<tr>
<th>The elements of questionnaire completed by the patients</th>
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<tr>
<td>Factors influencing the adherence to treatment</td>
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<tr>
<td>Age</td>
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<tr>
<td>Psychological aspects (depression, anxiety)</td>
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<td>Patient - physician relationship</td>
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<td>Associated diseases with concomitant medication</td>
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<td>Accessibilty to treatment</td>
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<td>Adherence to treatment</td>
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<td>Discontinuation 2-5 months/ year</td>
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<td>Discontinuation more than 6 months/year</td>
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The questionnaires were completed by the patients in the period 2001 – 2009.
Adherence was defined as the proportion of eligible days during the 365 days following a patient’s first hormonal treatment prescription for which the patient had filled prescriptions [12-16]. Eligible days were considered those days before any evidence of recurrence or new breast cancer, or an adverse event possibly related to hormonal drug (tamoxifen, letrozole, exemestane, anastrozole). The hormonal adjuvant treatment swats stopped by the physician when exists an evidence for recurrent disease or new primary breast cancer included use of another hormone or hormonal manipulation, new chemotherapy or radiation therapy (if > 60 days after the initiation of tamoxifen), any biopsy, or new breast cancer surgery. The other reasons for stopping the treatment were the evidences for adverse events potentially related to tamoxifen included evidence of thrombosis, pulmonary embolism, pancreatitis, hepatitis, liver failure and other liver abnormalities, or any endometrial pathology or surgery.

The questionnaires were correlated with the period of treatment with medical indication for hormonal treatment.

The principal objective of the study was to evaluate the percent of women which have an adherence of 100% per year (were not consider the discontinuations of 1-5 days), how many patients have interrupted the treatment for 2-5 months per year and how many patients have stopped the treatment for more than 6 months/year.

The secondary objective was to evaluate the correlation of possible factors with the sub/non-adherence.

RESULTS

We indentified all women 18 years or older who were continuously enrolled at Center of Medical Oncology with hormone receptor – positive early breast cancer, with the indication of adjuvant hormonal therapy.

There were a number of 435 of patients. From these patients, 216 patients were premenopausal and 219 patients were postmenopausal. From premenopausal patients (receiving tamoxifen), 29 of patients were stage I of disease, 56 of patients were stage II of disease and 131 of patients were stage III of disease. From 219 postmenopausal patients, 12 patients were stage I of disease, 68 patients were stage II of disease and 139 of patients were stage III of disease.

Many of the patients have begun the treatment before 2001. For these patients, the completion of the questionnaire was at the end of the 5 years of adjuvant treatment. For the rest of the patients, the completion was in the period 2008 – 2009.

From the postmenopausal patients, 142 of patients have received letrozole, 29 of patients have received anastrozole and 48 of patients have received exemestane (Fig. 1).

The findings of questionnaires completed by 435 patients with adjuvant hormonal therapy for breast cancer indicated that 71% of the patients have a total adherence with the treatment and 16 % of these patients have stopped the treatment maximum 5 days/year. The 14% of the patients have an interruption of 2-5 monts/year (sub-adherence) and 15% of the patients have non-adherence to hormonal therapy.

The percent of adherence during the treatment period (5 years), was find that the first 3 years was a period of 80% total adherence with a decreasing in the last years of treatment (50%).

Predictors of non-adherence are: adverse events (flushes, arthralgia), extreme ages (particularly after 70 years), psychological aspects. Women with increased co-morbidity (concomitant medication with pills) have not correlated with non-adherence.
Patient - physician relationship and accessibility to treatment were not correlated with non-adherence too.

For the groups receiving different drugs, the main predictors for non-adherence in patients receiving tamoxifen remain side effects (flushes) and psychological aspects; for patients receiving aromatase inhibitors, the main predictor for non-adherence is arthralgia.

**DISCUSSION**

In this study of non-adherence of hormonal treatment of early breast cancer in adjuvant settings, we found that 71% of the patients have total adherence. Thus, more than one fourth of patients in this cohort had poor adherence and may have been at risk for inadequate clinical response as a result.

In an analysis of long-term follow-up, results caused particular concern: after four years of therapy, adherence rates among eligible women decreased from 85% to 50%.

Women with cancer are thought to be highly motivated by the gravity of their disease, with too much to lose by being nonadherent [11]. Yet, adherence is poor with other regimens well documented to reduce mortality or the risk of catastrophic outcomes (eg, statins after myocardial infarction, antihypertensive agents in patients with hypertension).[17-19] Adherence rates from studies of oncology patients range between 20% and 100%.

The International Society for Pharmacoeconomics and Outcome Research (ISPOR) recently defined adherence as synonymous with compliance, that is, "the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency [20]. Adherence is a term that is often preferred to compliance because it is generally believed to have a less pejorative and less judgmental connotation.

Adherence to oral medication is a complex and multifaceted issue. Non-adherence can generate the variability of a drug’s therapeutic effect, with the clinician possibly incorrectly attributing a patient’s worsening condition to an absence of drug activity [21]. Non-adherence can be also associated with an increase in physician visits and higher hospitalization rates. Suboptimal adherence can compromise the patient-
provider relationship and may lead to a breakdown in communication and negatively affect the patient’s views about treatment.

In this study, reliable predictors of nonadherence were few and included side effects of the drugs, extreme age and psychological aspects. These findings show that is very important for the patient the relationship with her doctor. In the same time, the detailed explanations about the results of treatment, explanation of side effects and the psychotherapy remain essentials in the treatment programme.

The number of subjects from this study made it possible to evaluate several possible predictors of non-adherence. In light of the efficacy of hormonal therapy in preventing recurrence and death in women with early-stage breast cancer, further efforts are necessary to detect and address suboptimal adherence, particularly in vulnerable populations such as the elderly and the poor. These results provide insight into potential nonadherence to oral antineoplastic agents in general. Future studies focusing on adherence to oral antineoplastic agents would likely reveal that adherence in typical care settings is dramatically worse than that seen in clinical trials.

CONCLUSIONS

More of one fourth of patients may be at risk for inadequate clinical response because of poor adherence. Because of the efficacy of hormonal therapy in preventing recurrence and death in women with early-stage breast cancer, further efforts are necessary to identify and prevent suboptimal adherence.

REFERENCES


