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Improving compliance and persistence to adjuvant tamoxifen and aromatase inhibitor therapy

Peyman Hadji *

Philipps-University of Marburg, Department of Endocrinology, Reproductive Medicine and Osteoporosis, Baldingerstrasse, 35033 Marburg, Germany

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Abstract

Better compliance and persistence with therapy are associated with improved patient outcomes. As more and more patients survive breast cancer, compliance with adjuvant therapy becomes increasingly important. In clinical trials, compliance with adjuvant endocrine therapy among women with breast cancer is usually high. Retrospective analyses of databases and medical records from clinical practice, insurance databases of prescription refills, and survey data show a significant decrease in persistence after 12 months of therapy. With ongoing therapy, a further decline in persistence of up to 50% has been reported. A consistent methodology is needed to measure patient behavior and identify patients who are not adhering to therapy. Promising strategies for enhancing adherence to treatment in clinical practice include improving access to health care, increasing patient satisfaction, managing side effects, patient education, and better communication between the patient and health care provider. Positive relationships between patients and their health care providers, and frequent monitoring and feedback, may be most effective. While the lack of conformity across studies in measuring makes cross-study comparisons difficult, this review evaluates the available data regarding compliance and persistence with adjuvant endocrine therapies for breast cancer (tamoxifen and aromatase inhibitors) and presents strategies for improving adherence.

Keywords: Adherence; Adjuvant therapy; Aromatase inhibitors; Compliance; Persistence; Tamoxifen

* Tel.: +49 6421 286 6486; fax: +49 6421 286 7070.
E-mail address: hadji@med.uni-marburg.de.

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1. Introduction

Breast cancer can be a chronic condition, with an early risk of relapse that peaks in the first 1–3 years postsurgery and continues even beyond 10 years postsurgery [1]. Early distant metastases (DM) constitute the majority of recurrences at 2 years postsurgery, even with tamoxifen therapy [2], and DM are the most life-threatening recurrence [3]. Breast cancer survival has increased as a result of improvements in early diagnosis and therapy, e.g. adjuvant endocrine therapy. The third-generation aromatase inhibitors (AIs) anastrozole (1 mg/d), letrozole (2.5 mg/d), and exemestane (25 mg/d) are more effective than 5 years of tamoxifen alone in terms of disease-free survival (DFS) and preventing DM in postmenopausal women with hormone-sensitive early breast cancer [4–6]. At 25.8 months of follow-up, improved outcomes were seen with initial adjuvant letrozole in terms of a significant improvement in DFS (19%) and reduction in the risk of DM (27%) [6]. Initial adjuvant letrozole has reduced the risk of both total recurrences and DM by 30% at 2 years, while initial adjuvant anastrozole has reduced the risk of total recurrences and DM by 17% and 7%, respectively, at 2.5 years [7,8].

Patients can only derive maximum benefit from their medications if they take them as instructed and adhere to dosing schedules [9]. However, patients often fail to take the correct dosage at the prescribed frequency and for the proper duration [10]. Awareness of poor patient compliance, persistence, and adherence has grown and has become the focus of an increasing amount of clinical research [11–14]. Compliance is generally defined as taking medication as directed (e.g. with or without food, at a certain time in the day); persistence, as continuing to take medications (correctly or incorrectly) for the recommended period; and adherence, as the patient's overall behavior, of which compliance and persistence are components [15,16].

Some studies may define these terms differently (e.g. compliance and adherence are sometimes used interchangeably), use different methods of reporting (self-report, pill counts, or electronic medication monitoring), and use different parameters (i.e. measure compliance by continuous medication gaps or medication possession ratio [MPR]; determine persistence by proportion of days covered, number of days to discontinuation, or number of refills) [12]. There are advantages and disadvantages associated with each reporting method and no currently accepted gold standard. Consistent methodology is needed to measure patient behavior and to identify individuals who are not adhering to therapy [16]. Yet, it may be difficult to measure adherence to treatment that has multiple components, for example, medication plus lifestyle and dietary changes [17].

Adherence studies often analyze databases retrospectively to gauge compliance and persistence patterns [18]. Guidelines from the International Society of Pharmacoeconomics and Outcomes Research recommend that such analyses include formal definitions of compliance, persistence, and adherence; commonly used measurements of compliance and persistence, such as MPR and proportion of days covered; and statistical analyses [18]. Persistence and compliance in a real-world setting are often measured using insurance databases of prescription refills, survey data, and medical records [19–21]. The adoption of a systematic approach would improve the quality and consistency of research in this growing field.

As more and more patients survive breast cancer, the issue of compliance with therapy becomes increasingly important [22]. To achieve the benefits of adjuvant endocrine therapy observed in the clinical trial setting, long-term adherence to medication regimens is required [23]. Rates of adherence in clinical trials are problematic and often suboptimal yet traditionally are much higher than those in clinical practice. Adherence tends to be worse in everyday practice, increasing the risk for treatment failure [21,24]. Because increased compliance and persistence with therapy are likely to improve patient outcomes, they have become an important area of research [12]. This review evaluates the data regarding compliance and persistence to adjuvant endocrine therapy and presents strategies for their improvement.

2. Search strategy and selection criteria

Data for this paper were identified by searches of MEDLINE, EMBASE, PubMed, and references from relevant articles using the search terms "tamoxifen," "aromatase inhibitors," "letrozole," "anastrozole," "exemestane," "breast cancer," "discontinuation," "adherence," and "compliance." Meeting abstracts from the American Society of Clinical Oncology, San Antonio Breast Cancer Symposium, and European Breast Cancer Conference were included only when they related directly to the discontinuation, adherence, compliance, or persistence of AIs or tamoxifen. Only papers published in English between 1996 and 2008 were included.

3. Endocrine therapy for postmenopausal women with breast cancer

3.1. Clinical trial data of tamoxifen versus placebo

Studies analyzing the efficacy and safety of tamoxifen in the prevention of breast cancer have found compliance and persistence rates to be suboptimal, lower even than those for placebo. In the International Breast Cancer Intervention Study-1 (IBIS-1) prevention trial (tamoxifen versus placebo; $N = 7152$), full compliance with 5 years of treatment was estimated (at a median follow-up of 50 months) to be 64% among those treated with tamoxifen, compared with 74% in the placebo group ($p < 0.001$) [25]. In the 5-year National Surgical Adjuvant Breast and Bowel Project (NSABP)-1 prevention trial (tamoxifen versus placebo; $N = 13{,}388$), 23.7% of those treated with tamoxifen and 19.7% of placebo-treated patients were determined (at a median follow-up of 4.5 years)