Non-adherence to endocrine therapy for breast cancer

Women with breast cancer often face a variety of decisions regarding their treatment at diagnosis and in follow-up. When considering endocrine therapy, whether for early or advanced breast cancer, there are several options available, with differing side-effects and routes of administration, from which a woman and her health care providers must choose. In this issue of *Annals of Oncology*, Professor Fallowfield and colleagues elucidate preferences of women with breast cancer regarding endocrine therapy, considering between tablet and injection formulations. Through interviews with 208 women with a history of early or stable advanced breast cancer, the investigators found that most women (63%) preferred tablet therapy to injections, although a substantial minority (24.5%) preferred injections [1]. This finding is consistent with previous reports of patient preferences for oral versus injectable cancer treatments [2]. Not surprisingly, the authors also found that when the estimated risk of hot flashes was decreased with injections or the estimated efficacy of injections was increased relative to tablets, a greater number of women preferred injections to tablet treatment. Disturbing, however, is the fact that approximately 50% of women surveyed admitted to sometimes forgetting or choosing not to take their current oral medications. And among 51 women who preferred injections to tablets, 43% cited a desire to ensure adherence as a reason for their preference. This finding of such a high rate of non-adherence is quite provocative and merits further attention.

Adherence to oral medication is a complex and multifaceted issue. Non-adherence can contribute greatly to the variability observed in a drug’s therapeutic effect, with the clinician possibly incorrectly attributing a patient’s worsening condition to an absence of drug activity [3]. Non-adherence has also been associated with an increase in physician visits, higher hospitalization rates, and longer hospital stays [4–7]. Suboptimal adherence can compromise the patient-provider relationship, as misconceptions about the effects of a therapy on the part of either the patient or the provider may lead to a breakdown in communication and negatively affect the patient’s views about care [8]. In the setting of a formal clinical trial, non-adherence can lead to misleading results, inconsistent response rates, and erroneous dosing recommendations [9–12].

The limited available evidence suggests that patient adherence to oral anti-cancer agents is quite variable, with reported adherence rates ranging from 20–100% [13]. With the rapid rise in availability and use of oral anticancer agents, adherence is becoming an increasingly important issue in oncology. There has been relatively little information previously published regarding adherence to oral agents for the treatment of breast cancer. In a study of 26 patients with breast cancer, Waterhouse et al. [8] found that patient self-report and pill counts statistically significantly overestimated the degree to which patients adhered to their tamoxifen regimen, as compared with data recorded by a microelectronic monitoring system (MEMS) device. In this study, patients were monitored for approximately 3 months and classified as adherent if the measure of adherence indicated that ≥80% of tamoxifen doses were taken as prescribed. When all dosing errors as measured by MEMS were considered, 18 of 24 patients were non-adherent, that is, they took less than 80% of their doses as prescribed (including dose omissions and/or schedule errors) during the monitoring period. Considering only dose omissions, adherence rates ranged between patients from 36.4% to 100%, with an overall average of 85.4% (SD±17.2%). Although patients were not informed before entry into this study that their adherence was to be monitored electronically via MEMS, they were asked to open the container only if they intended to take the drug. Furthermore, patients were informed that they would be asked to complete questionnaires concerning their pill-taking habits. They were also asked to bring their tamoxifen bottle to the clinic at each visit, so that their physician “could assure that they were receiving the proper medication in the correct dose” [8]. Thus, even in this setting, in which patients were most likely aware of some monitoring of drug adherence, patients were not fully adherent.

Partridge et al. [14] measured adherence to adjuvant tamoxifen therapy among 2378 women with early-stage breast cancer using a large insurance database. This study revealed that nearly one-quarter of patients missed taking tamoxifen on more than one-fifth of days studied during their first year of treatment. Furthermore, overall adherence decreased to 50% by year 4 of therapy. However, the methodology used in this study had significant limitations, and there has been little information available about why patients non-adhere to tamoxifen or other anti-cancer therapies. It is also important to note that few studies of cancer patients have evaluated the relationship between adherence levels and achievement of the treatment goal. In a retrospective analysis, Bonadonna and Valagussa [10] found that breast cancer patients who received 85% or less of their prescribed adjuvant chemotherapy had shorter relapse-free and total survival times than those who received more complete treatment. Patients who received less than 65% of planned therapy showed markedly inferior disease-free survival. Among women with early-stage breast cancer, the benefits of tamoxifen are greater with 5 years of therapy than with only 1 or 2 years [15, 16]. It is unclear, however, whether these data on tamoxifen, the adherence equivalent of total dropout after 1 or 2
years, can be extrapolated to other situations of non-adherence, including long breaks in therapy or frequent dosing omissions.

As Professor Fallowfield and colleagues note in their discussion, their finding of at least occasional non-adherence to oral medications by a substantial proportion of women surveyed is likely an underestimate [1]. In the adherence literature, including the limited studies of patients receiving anti-cancer therapy, self-reported adherence fairly consistently underestimates non-adherence as determined by more objective measures [13]. Further, the report by Professor Fallowfield and colleagues is limited by the fact that not all women surveyed were referring necessarily to oral anticancer therapy when describing omissions, as not all women were receiving oral anticancer treatments at the time. However, their finding highlights the increasingly important issue of adherence to oral anticancer treatment, and signals one potential way to improve adherence for some patients: to offer injectable treatment instead of tablet therapy when there is a choice to be made. Future studies should consider more precise prospective evaluation of non-adherence to oral medications compared with injectable therapy among women with early and advanced breast cancer.

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