EDITORIAL

New Insights Into Nonadherence With Adjuvant Endocrine Therapy Among Young Women With Breast Cancer

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Despite the well-established survival benefit associated with adjuvant endocrine treatment (ET), ensuring that breast cancer survivors adhere to the prescribed duration of therapy remains challenging. Studies have found young age to be a risk factor for nonadherence and nonpersistence to ET (1). However, little is known about the reasons why young women are less likely to take ET as prescribed, including noninitiation and early discontinuation. In this issue of the Journal, Llarena et al. focus on the potential predictors and reasons for nonadherence in this particularly high-risk population. Their findings not only shed new light on the role of side effects and concern about side effects on nonadherence in young women, but also draw attention to the impact of fertility concerns on adjuvant ET decision-making (2).

While patients of all ages may contend with myriad decisions surrounding their treatment, the youngest women with early-stage hormone receptor–positive breast cancer who are interested in having biological children after treatment face added complexity. Not only are these women at risk of premature menopause and infertility following chemotherapy, if needed, (3), but this issue is compounded by the time it takes to adhere to a regimen of adjuvant hormonal therapy. Because of the increased risk of infertility with age alone, even if a woman remains premenopausal, achieving pregnancy after completion of even five years of adjuvant ET may be particularly challenging for older premenopausal women with hormone receptor–positive breast cancer. Thus strategies to preserve fertility have been increasingly incorporated into the care of these young patients (4). According to the American Society for Clinical Oncology fertility preservation clinical practice guidelines, prior to beginning adjuvant treatment, premenopausal women should be informed of the potential risk of experiencing premature ovarian failure as well as counseled regarding fertility preservation options available to them (5). However, the literature suggests that issues related to impaired fertility and fertility preservation have been underaddressed historically in young breast cancer patients (6–8). It is therefore encouraging that among the women interviewed by Llarena et al. who did not take tamoxifen or who stopped treatment early, most indicated that they had been adequately informed about fertility preservation, with only 9% reporting that they had not (2). However, the generalizability of these findings is limited by the very nature of how this study was conducted, using the information provided after an electronic medical record prompt flagged providers to ask young patients about interest in future fertility.

Regarding the impact and safety of an interruption of ET in order to attempt a pregnancy, the Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine-Responsive Breast Cancer (POSITIVITY) Trial will prospectively address the important question of whether temporarily stopping ET for up to two years after 18 to 30 months of initial ET in young women who desire a pregnancy affects disease, fertility, and psychosocial outcomes. Findings from a recent survey that assessed potential patient willingness to participate in this study suggest that young breast cancer survivors would be receptive to enrolling in such a trial (9). Interest was particularly high among women who had been taking ET for 30 months or less, with 47% of women age 30 years and younger at diagnosis and 45% of women older than 30 years at diagnosis expressing interest (9). A feasibility study is currently underway to assess oncologists’ interest and ability to accrue patients to the POSITIVE trial, as well as to evaluate their fertility counseling practices, attitudes, and barriers to discussing fertility concerns and preservation strategies with young women with breast cancer.

There are many remaining questions about ET that can potentially impact decision-making, including the optimal duration of therapy. Results from the Attom and Atlas trials informed updated guidelines that recommend consideration of 10 years of ET treatment in women with hormone receptor–positive breast cancer (10). While there has been no indication that the effect of tamoxifen varies by age in women who have been on tamoxifen for five years, longer follow-up is needed to determine whether extended ET provides additional benefit for...
younger women (11,12). In their study, Llarena et al. reported that 15.5% of their sample stopped tamoxifen prior to completing five years (2). Future studies will need to evaluate how many women adhere to tamoxifen or other ET when recommended beyond five years. Further understanding of patterns of nonadherence and nonpersistence in young women, including the timing of discontinuation of ET and whether there are characteristics that differ in early vs late discontinuers, may ultimately lead to more targeted and timely interventions to improve adherence to therapy.

The use of both quantitative and qualitative methodology by Llarena and colleagues to delve into reasons for nonadherence has yielded provocative information pointing to a number of additional avenues for future evaluation (2). The finding that fear of side effects was commonly cited as a reason for both noninitiation as well as early discontinuation among a large subgroup of women provides a particularly compelling target for potential intervention. While the relationship between stage and noninitiation is intuitive, with similar associations between stage and nonadherence having been seen repeatedly in the literature (13), the association between declining radiation therapy and noninitiation and discontinuation merits further study. Further, while not reported directly in the current manuscript, it would be interesting to evaluate the relationship between receipt of bilateral mastectomy, a growing trend among young women in the United States with unilateral breast cancer (14), and adherence with endocrine therapy.

Because young women are at higher risk for recurrence and death from breast cancer, adherence to endocrine treatment is especially critical to ensure optimal survival outcomes in this population. In helping to answer the question as to why young women might be more likely to noninitiate or discontinue ET, the study conducted by Llarena et al. (2) highlights the importance of understanding how issues unique to young women with breast cancer affect treatment decisions. In turn, accounting for their concerns and identifying effective strategies to manage them may enhance quality of care, quality of life, and survival.

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References