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Editorial

EDITORIAL

Selection of Adjuvant Endocrine Therapy for Women With Breast Cancer in Menopausal Transition: Is It Simpler Than We Thought?

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Over the past decade, we have made notable strides in optimizing adjuvant endocrine therapy as the cornerstone of treatment for women with steroid receptor–positive subtypes of early-stage breast cancer. Aromatase inhibitors (AIs) are well established as standard of care for postmenopausal women, and extended durations for up to 10 years have been shown to improve outcomes (1,2). The pivotal SOFT and TEXT trials showed statistically significant improvement in disease-free survival (DFS) with the use of ovarian function suppression (OFS) with AIs, exemestane, or OFS plus tamoxifen compared with tamoxifen in high-risk premenopausal women (3). Thus, high levels of evidence supporting endocrine therapy recommendations based on large, prospective, randomized clinical trials exist for women whose menopausal status is clear (1-5). Considerable uncertainty remains, however, about how to select optimal endocrine therapy in the setting of chemotherapy-related amenorrhea, which is often observed in premenopausal women after chemotherapy. Might these women benefit from AI alone, or must they receive tamoxifen (perhaps followed by extended AI) or OFS plus AI because of the lingering concerns about the efficacy of AI alone if ovarian function returns?

In this issue of the Journal, Dackus et al. (6) used data from the prospective, population-based Netherlands Cancer Registry to try to address this important gap in our knowledge. The study population included 2295 women aged 45 to 50 years who were diagnosed with early-stage estrogen receptor–positive invasive breast cancer between 2004 and 2007 and who received both adjuvant chemotherapy and endocrine therapy. The authors devised an AI-to-endocrine treatment ratio ([AI treatment duration ÷ AI + tamoxifen treatment duration] × 100%) to compare outcomes among 3 endocrine therapy groups defined as mainly tamoxifen (AI < 25%, n = 624 [27.2%]), mainly AI (AI > 75%, n = 580 [25.3%]), or similar AI/tamoxifen (AI 25%-75%, n = 1091 [47.5%]). Primary endpoints were recurrence-free survival (RFS) and overall survival (OS). This was a high-risk study population, with 52.6% pathologic T2 stage, 72.1% with at least 1 lymph node involved, 86.4% with grade 2 to 3 tumors, and 7% HER2 positive. More than 95% of patients received an anthracycline-containing chemotherapy regimen, and 83% received tamoxifen initially. Overall, the average endocrine therapy duration was 5.5 years; for women who received therapy beyond 5 years, the average duration was 6.5 years. The majority of patients switched their endocrine agent during their treatment course, but about one-third stayed on the same agent (nonswitchers). Comparing the AI > 75% with AI < 25% subgroups, the authors concluded that both RFS (adjusted hazard ratio [HR] = 0.63, 95% confidence interval [CI] = 0.46 to 0.86) and OS (adjusted HR = 0.50, 95% CI = 0.34 to 0.74) were statistically significantly better for the AI > 75% subgroup during an average follow-up of 7.6 to 7.7 years to RFS and OS, respectively. The adjusted 5-year RFS rate was 94.5% vs 91.4%, and the adjusted 5-year OS rate was 97.3% vs 94.6% for the AI > 75% vs AI < 25% subgroups, respectively. A trend analysis showed that every 10% increase in the AI-to-endocrine treatment ratio reduced the risk of an RFS event by 5%.

The strengths of this study are its use of a well-curated population-based registry to evaluate a defined cohort of women aged 45 to 50 years who had received contemporary therapy to ask a pragmatic question about optimal endocrine therapy. Before this registry study, the only data on the effect of either tamoxifen or letrozole on DFS in women with chemotherapy-induced menopause were from BIG 1-98, a phase III double-blinded randomized trial (7-10). For this subset of patients (n = 105), a trend favoring letrozole compared with tamoxifen was observed for DFS (HR = 0.51, 95% CI = 0.19 to 1.39) (10). Notably, the breast cancer cohort included in the Dackus et al. (6) study predates the availability of results from the SOFT and TEXT trials as well as the large trials of extended adjuvant tamoxifen (4,5). Therefore, evaluation was limited to tamoxifen and AIs in this study; the combination of AI or tamoxifen with OFS was not included as a comparator, and extended adjuvant endocrine therapy was not always viewed as the norm. Nonetheless, this study showed that there is a clear advantage to starting with an AI or switching from tamoxifen to an AI

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when appropriate, with the goal of maximizing the duration of AI treatment.

The study authors acknowledged several limitations, foremost among them the use of chronological age as a surrogate for perimenopausal state and uncertainty about the precise menopausal status of these women because it was not reported either before or after chemotherapy. Other unaddressed issues in this study include information about any differences in the exact duration of and adherence to endocrine therapy by subgroups (AI < 25%, AI = 25%-75%, AI > 75%), which may further bias the reported results (6). Because AI adherence is generally lower than tamoxifen adherence, however, and the analysis favored AI, it seems unlikely that data about AI adherence would diminish the reported benefit. Also, with the trend toward longer duration of endocrine therapy up to 10 years, the 5.5-year average duration in this high-risk population is relatively short. Finally, longer follow-up is needed for RFS and OS given the risk of late recurrences in women with endocrine-sensitive breast cancers (11).

Despite these concerns, Dackus et al. (6) clearly demonstrated that longer AI duration (AI > 75% vs AI < 25%) was associated with the best RFS and OS (6). The narrow age criteria for inclusion in this study likely helped reduce the incidence of ovarian function recovery because the chances of recovery decrease with increasing age (12-14). It is estimated that only 10.9% of women aged 40 to 50 years recover ovarian function at 24 months after anthracycline- and cyclophosphamide-based chemotherapy (15). Also, it is important to acknowledge that a higher-risk group, as included in this study, is expected to derive more benefit from AI vs tamoxifen, as established previously (16). Therefore, these results may not be generalizable to a lower-risk population. Finally, other advances in clinical practice may affect the application of these results: 1) the use of the combination of OFS with tamoxifen or AI as endocrine therapy; 2) wider use of nonanthracycline-based chemotherapies, such as docetaxel-cyclophosphamide, in some countries, which may be less likely to cause chemotherapy-induced amenorrhea; and 3) use of tumor genomic testing (such as Oncotype DX [Exact Sciences Corp, Madison, WI] or MammaPrint [Agendia, The Netherlands]) to refine decisions about the use of adjuvant chemotherapy. Early data from the RxPonder study support the use of chemotherapy in premenopausal women with hormone receptor–positive breast cancer involving 1 to 3 axillary nodes regardless of Oncotype DX results, but longer follow-up is needed (17).

This study addresses a clinically relevant dilemma in endocrine therapy for women aged 45 to 50 years who have a high likelihood of developing chemotherapy-induced amenorrhea without ovarian function recovery. It provides evidence and reassurance that AIs should make up the majority of their adjuvant endocrine therapy for the best RFS and OS, and a switch from tamoxifen to AI can be considered early during endocrine therapy in this select group of women. Of course, these results should not be extrapolated to younger patients, because this group has a higher chance of ovarian function recovery after chemotherapy. As always, longer-term outcomes may further solidify these findings.

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