More Options for Premenopausal Women With Early-Stage Hormone-Sensitive Breast Cancer

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With the presentation and publication of the Tamoxifen and Exemestane Trial (TEXT) and the Suppression of Ovarian Function Trial (SOFT) in 2014, along with the Adjuvant Tamoxifen—To Offer More (aTTom) and Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trials in the last few years, deciding among the standard adjuvant endocrine therapy options for premenopausal women with hormone-sensitive breast cancer has become increasingly complicated.[1-4] It is good news that there are a greater number of treatment options to reduce risk, particularly in very young women in whom risks are often higher.[5] The challenge now is incorporating these evolving data into the care of our patients, tailoring care optimally for the individual woman.

It is in this context that Jain et al present a fine review of available data on the use of ovarian suppression in premenopausal women with early breast cancer.[6] The authors focus on the modern evidence for the potential value of ovarian suppression as endocrine therapy in this population, noting that chemotherapy-induced amenorrhea has long been associated with improved survival in early breast cancer. The addition of ovarian suppression has also been associated with reduced risks. However, it had remained a question whether ovarian suppression in addition to tamoxifen, the long-standing standard endocrine therapy for premenopausal women, adds value and not just toxicity compared with tamoxifen alone.

As Jain et al describe, SOFT had an overall negative result: in the whole trial population, the addition of ovarian suppression did not improve outcomes. However, in higher-risk subgroups—women who remained premenopausal after chemotherapy, and thus were eligible for SOFT, and women who were under 35, the vast majority of whom received chemotherapy—there were demonstrable improvements in the breast cancer-free interval (BCFI) for those who received ovarian suppression. Thus, for these higher-risk subgroups, ovarian suppression can be considered. However, acknowledging the lack of a survival difference to date, Jain et al advise caution in using this additional treatment. Whether the addition of ovarian suppression will ultimately translate into an overall survival benefit is not known at this time.

The review also nicely describes the TEXT results in the context of prior research, including the apparently contradictory results of Austrian Breast and Colorectal Cancer Study Group Trial 12 (ABCSG-12).[7] In ABCSG-12, there was no improvement in outcomes with the use of an aromatase inhibitor (AI)—anastrozole—compared with tamoxifen in the setting of ovarian suppression. However in TEXT, the AI exemestane improved the BCFI compared with tamoxifen in the setting of ovarian suppression. Of note, neither study revealed any clear evidence for an improvement in overall survival, and given current data trends, it is not likely that they will in the future. Jain et al note, however, that the ABCSG-12 trial, which also included randomization to zoledronic acid, differed substantially from TEXT in size, patient population, drugs used, and other factors. At this time, as we await longer-term survival data, consideration of an AI with ovarian suppression is quite reasonable, if tolerated, in higher-risk women and women for whom avoidance of tamoxifen is preferred.

Another important concern highlighted in the review is the greater toxicity associated with escalating hormonal therapy, particularly when ovarian suppression is added to tamoxifen or is needed for AI therapy.[8] Adherence is a major issue with long-term endocrine therapy in general, and as toxicity is increased with the addition of ovarian suppression, it may emerge as a problem especially in very young women, who may need additional therapy the most but who may also be at particularly high risk for nonadherence.[9,10]

The issue of how long to treat women with hormonal therapy is also considered in the review. While...
ATLAS and aTTom provide data for 10 years of tamoxifen therapy, if a woman is going to receive an AI with ovarian suppression in the first 5 years of her therapy, the optimal endocrine therapy in the second 5 years in a higher-risk woman is currently unknown. For now, we will likely need to extrapolate from long-term studies in postmenopausal women to inform the care of these younger women.

Finally, as Jain et al discuss, in the current era, in which genomic testing is used to further risk-stratify women with hormone-sensitive early breast cancer, incorporation of the results of SOFT in particular can be challenging. Should we offer ovarian suppression to a woman who has higher-risk anatomic disease (eg, stage II) but a low-risk genomic profile, and who thus is not likely to benefit from chemotherapy? This area is complicated, and we can look forward to further data from correlative work from SOFT and TEXT, which may help inform such decisions. At the present time, however, as Jain et al note, these new data allow for more options that can be considered when tailoring treatment for premenopausal women with hormone-sensitive early breast cancer. In light of the recently reported pivotal trials, national and international guidelines are being updated to reflect the new choices available. Ultimately, with careful attention to disease risk as well as to patient concerns (including treatment tolerance, side effects, and psychosocial concerns), these advances should translate into both better disease outcomes and better quality of life for our premenopausal patients.

Financial Disclosure: The author has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

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