Optimizing Endocrine Therapy in Premenopausal ER-Positive Breast Cancer Patients

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The optimal endocrine therapy for premenopausal women with hormone receptor-positive early breast cancer remains elusive. Dr. Pritchard presents a thoughtful review of this important topic, including the historic context for the current controversy regarding the utility of ovarian suppression (either by medication or permanent ablation) in the adjuvant treatment of young women with breast cancer.

Role of Ovarian Suppression

In the metastatic setting, ovarian suppression in combination with tamoxifen has been shown to be more effective than either modality alone in treating hormone receptor-positive disease.[1] Small studies presented to date in abstract form also suggest that ovarian suppression in combination with aromatase inhibition is highly active in this setting.[2,3] In the treatment of premenopausal women with early-stage disease, endocrine therapy with ovarian suppression alone is also clearly an effective therapy for hormone receptor-positive disease.

In her review, Dr. Pritchard describes the array of studies that show equivalent risk reduction with chemotherapy compared to ovarian suppression. However, ovarian suppression has not yet been clearly demonstrated to add to the benefit of chemotherapy or tamoxifen. Many women included in trials to date (especially those who were older and already close to menopause) experienced ovarian suppression due to chemotherapy, potentially attenuating any evidence of an additional benefit from ovarian suppression in these studies. In contrast, several randomized trials and the Oxford Overview analyses have revealed additional risk reduction from tamoxifen in addition to chemotherapy for women in all age groups. Thus, initial adjuvant tamoxifen therapy has become the standard endocrine therapy recommendation for women with premenopausal hormone receptor-positive breast cancer.

Age, Menopause, and Risk

For young women, who generally have an increased risk of recurrence compared to older premenopausal women, optimizing hormonal therapy is particularly important. Therefore, many clinicians and patients consider the addition of ovarian function suppression for women who are at particularly high risk and do not become permanently amenorrheic with adjuvant chemotherapy, as well as for those who desire additional risk reduction beyond tamoxifen, but do not wish to receive chemotherapy. At present, however, it is not known whether outcomes with or without chemotherapy can be improved by prescribing ovarian suppression concurrently with tamoxifen rather than tamoxifen alone. And the potential impact of ovarian function suppression on menopausal side effects, quality of life, and future health risks may be significant in this young population.

Research has repeatedly demonstrated that experience of menopausal transition with breast cancer treatment is associated with menopausal symptoms, sexual dysfunction, and impaired quality of life.[4-6] As Dr. Pritchard discusses, it will be interesting to investigate whether the youngest women experience the worst side effects and also receive the most benefit from ovarian suppression because they possess greater ovarian function at baseline. The long-term impact of premature menopause on bones, cognition, and cardiovascular health is concerning for this population, and
further research will be imperative. Because an adjuvant hormonal regimen is given for a number of years and most women who receive it would not have recurred without the treatment, it is crucial not only that regimens be shown to clearly reduce risk, but also that side effects be tolerable in order to optimize adherence and quality of life in breast cancer survivors.

**SOFT Trial**

As Dr. Pritchard explains, the ongoing Suppression of Ovarian Function Trial (SOFT) has been designed to address many of these questions. The SOFT trial investigates whether adding ovarian suppression to tamoxifen or to aromatase inhibition provides superior reduction in risk of recurrence of early-stage premenopausal breast cancer compared with tamoxifen alone. Side-effect profiles, quality of life, and effects on bone health of the three different regimens will also be reported. Importantly, this trial will help to define the role of aromatase inhibition in the treatment of premenopausal women with breast cancer, recognizing that the incorporation of aromatase inhibitor therapy improves outcomes for postmenopausal women. Recent preliminary data suggest that 3 years of ovarian suppression combined with either tamoxifen or an aromatase inhibitor is similarly efficacious and tolerable in premenopausal women with hormone receptor-positive early breast cancer.[7] This trial also reveals that receipt of a bisphosphonate, zoledronic acid (Zometa), in combination with either of these therapies not only protected against bone loss, but also may reduce the risk of recurrence in this population.

Though we expect to be guided by the results of the SOFT trial and additional studies investigating the use of bisphosphonates as adjuvant therapy, many additional issues will need to be addressed in future research. The optimal duration and, potentially, sequence of hormonal therapy in young women, the role of cytochrome p450 (CYP) 2D6 genotype testing in those on tamoxifen, and how to maximize adherence and quality of life in young survivors are critical issues as we seek to improve outcomes in young women with early breast cancer.

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