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EDITORIAL

Ovarian Suppression for Breast Cancer: An Effective Treatment in Search of a Home

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Adjuvant endocrine therapy is the most important systemic treatment for the majority of women with hormone receptor–positive breast cancer. Our understanding of the role of endocrine therapy in premenopausal women has lagged considerably in comparison with our knowledge of its role in postmenopausal women. Tamoxifen, for example, was initially shown to be beneficial in postmenopausal women; only after many years were similar benefits demonstrated in premenopausal women.[1] In the last few years, adjuvant endocrine therapy for postmenopausal women has taken another step forward with the incorporation of the aromatase inhibitors into the treatment armamentarium.[2] The benefits seen with aromatase inhibitors, which arise as a consequence of estrogen deprivation, have contributed to continued interest in the use of ovarian suppression in premenopausal women.

Why do we know so much less about endocrine therapy in premenopausal than in postmenopausal women? There are at least three reasons. First, breast cancer, and specifically hormone receptor–positive breast cancer, is much less common in premenopausal women than in postmenopausal women. However, receptor-positive breast cancer in premenopausal women is hardly a rare disease. There are approximately 47,000 cases of breast cancer in women younger than 50 years diagnosed in the United States each year; of these, 11,500 cases are in women younger than 40 years.[3] More than half of all premenopausal women with breast cancer have receptor-positive disease, resulting in more than 25,000 cases of receptor-positive disease among premenopausal women. Taking a more global perspective, there are hundreds of thousands of premenopausal women diagnosed each year with hormone receptor–positive disease. Second, there has been a long-standing conviction that chemotherapy was the more important treatment for younger women, and, consequently, trials of endocrine agents have been viewed as second-tier. There has been increasing reason to question this view, but translating hypotheses into practice-changing clinical trials can take many years. Finally, our understanding of endocrine therapy in premenopausal women has been clouded by the indirect endocrine effect of chemotherapy. At least some, if not most, of the benefit of chemotherapy in many premenopausal women with receptor-positive disease probably arises from suppression of ovarian function.

There are several reasons to investigate new and improved endocrine therapies for premenopausal women. There is evidence to suggest that estrogen receptor (ER) –positive breast cancer in young women, particularly women younger than 35 years old, is associated with a worse prognosis compared with ER-positive breast cancer in older women.[4,5] Women younger than 35 years old with ER-positive disease who are treated with adjuvant chemotherapy alone are more likely to develop a recurrence than women with ER-negative tumors, perhaps related to the limited impact of chemotherapy on ovarian function in this patient population.[6] Consistent with this hypothesis, several retrospective studies have suggested that women who develop amenorrhea after chemotherapy have better outcomes than women who do not develop amenorrhea.[7-9]

Although ovarian ablation (OA) was the earliest systemic therapy for breast cancer, progress in defining its role in the adjuvant setting has been slow. The initial trials of OA as adjuvant therapy failed to demonstrate a convincing benefit, though these trials were underpowered and included both patients with receptor-positive disease and those with receptor-negative disease. We now know that no benefit would be expected in women with receptor-negative disease. The Early Breast Cancer Trialists' Collaborative Group meta-analysis subsequently suggested, using indirect comparisons, that the benefit associated with OA seemed to be similar to the benefit of chemotherapy.[10] Importantly, the meta-analysis failed to demonstrate a

benefit for OA when given to women who received chemotherapy, many of whom would be expected to experience treatment-induced amenorrhea. A number of more recent trials have directly compared regimens such as cyclophosphamide, methotrexate, and fluorouracil (CMF) to ovarian suppression (OS) administered for 2 to 3 years.[11-15] These trials demonstrated that women with hormone receptor–positive tumors have a similar outcome whether treated with chemotherapy or OS. Some of these trials administered tamoxifen to women who were randomly assigned to OS; in general, tamoxifen was not included in the treatment of women who received chemotherapy. These trials answered some questions, but raised others: (1) Is OS equivalent to more "modern" chemotherapy? (2) Is OS plus tamoxifen equivalent to the standard treatment for many women, chemotherapy plus tamoxifen? (3) Does OS add to chemotherapy plus tamoxifen?

One of the most critical questions is how the results of studies with OS may vary across heterogeneous subgroups of patients with hormone receptor–positive tumors. Gene expression profiling identifies at least three distinct hormone receptor–positive subtypes of breast cancer. These groups include luminal A, luminal B, and a subset of the ER-positive cancers largely defined by HER2 amplification.[16] Limited data suggest that these subgroups are associated with distinct clinical outcomes, probably related to differences in natural history and response to treatment.[17,18] Recent findings from the Oncotype DX assay, another classifier based on gene expression, suggest that individual patients, based on tumor expression of 16 genes, derive very different levels of benefit from hormonal therapy and chemotherapy.[19,20] For women with ER-positive disease, there may be an inverse relationship between chemosensitivity and hormonal therapy sensitivity: chemotherapy probably provides the greatest benefit in those women who derive the least benefit from hormonal treatment and vice versa. The benefit from hormonal therapy may also be affected by an interaction between the tumor subtype and the specific endocrine intervention. Preliminary data indicate that those cancers in the HER2 subtype may be relatively insensitive to tamoxifen, but may respond well to aromatase inhibitors or the combination of tamoxifen and OS/OA.[21-23] Uniform treatment approaches for all women with receptor-positive disease are unlikely to be adequate in the years ahead; the treatment paradigm will need to allow for greater individualization.

In this issue of the *Journal of Clinical Oncology*, Davidson et al[24] report the mature results of a large trial conducted in premenopausal women with node-positive, receptor-positive disease. The study compared cyclophosphamide, doxorubicin, and fluorouracil (CAF) chemotherapy alone; CAF followed by goserelin for 5 years (CAF-Z); and CAF followed by goserelin plus tamoxifen for 5 years. At a median follow-up of 9.6 years, the authors found substantial improvements in time to recurrence (TTR) and disease-free survival (DFS) with the addition of tamoxifen to CAF-Z (hazard ratio [HR] for DFS = 0.73; $P < .01$). No significant effect was seen in terms of overall survival, though given the long natural history of receptor-positive disease, a modest survival advantage could still emerge. The addition of goserelin to CAF demonstrated no benefit in TTR, DFS, or overall survival in the study population as a whole.

In an unplanned retrospective analysis among patients younger than 40 years, there was a trend toward benefit from goserelin when added to CAF (HR for DFS = 0.78; 95% CI, 0.56 to 1.08), whereas no benefit was observed for patients 40 years or older (HR, 1.0). We do not know what proportion of these younger women retained ovarian function after chemotherapy. Nor do we know how this analysis would have been altered if all women had received tamoxifen, the standard today.

The investigators succeeded in conducting one of the largest trials of its kind. Why did the addition of goserelin fail to improve a woman's risk of developing recurrent disease? One possible explanation is that despite the trial's relatively large size, it was still underpowered. OS is unlikely to have any additive benefit in the subset of patients who have experienced permanent menopause as a result of chemotherapy. Six cycles of CMF-type chemotherapy lead to chemotherapy-induced amenorrhea in approximately 80% to 95% of patients older than 40 years, with a much lower incidence in younger patients.[25] There is evidence that rates of chemotherapy-induced amenorrhea with six cycles of anthracycline-based regimens may be even higher.[26] As over 70% of the patients in this trial were 40 years or older, the relevant patient population (those women who remain premenopausal or have only temporary ovarian dysfunction after chemotherapy) would be less than 40% of the actual sample size. Additional data concerning hormone levels of women participating in the trial will be of great interest. The trend toward a benefit from goserelin in patients less than 40 years supports the hypothesis that OS may be of benefit in women who do not undergo chemotherapy-induced menopause. Of note, a similar result (risk ratio 0.34; 95% CI, 0.14 to 0.87 in ER-positive, age $<$ 40 years; risk ratio 1.0; 95% CI, 0.64 to 1.57 in ER-positive, age $\geq$ 40 years) was observed in a second trial of chemotherapy followed by goserelin compared with chemotherapy alone.[11] These data, together with the association between chemotherapy-induced amenorrhea and outcome, suggest that chemotherapy-induced OS is responsible for a substantial portion of the benefits of chemotherapy in hormone receptor–positive breast cancer. As noted above, however, hormone receptor–positive breast cancer is heterogeneous; in some patients the indirect hormonal effect of chemotherapy is probably responsible for the benefits, while in others the direct cytotoxic effect almost certainly is more important.

While clinicians and patients await results of current and future trials, they must weigh the available evidence. Based on the results of this trial, the addition of OS to CAF-type chemotherapy and tamoxifen should not be considered a standard treatment approach for the large majority of premenopausal women with hormone receptor–positive breast cancer. Not only is the benefit of OS in this setting uncertain, but there is clear evidence of toxicity. This trial and others demonstrate that the toxicities associated with OS, which include hypertension, diabetes, and weight gain, as well as long-term risks, should not be ignored. In our view, women with functioning ovaries who have completed chemotherapy and are taking tamoxifen should not be placed on OS as a routine practice. In a young woman with breast cancer, it is always tempting for the clinician to add further treatment in the hope of minimizing the risk of disease recurrence. It is worth remembering, however, that the toxicity of therapy is borne equally by women at high and low risk of disease recurrence. Given the available data, the use of OS in addition to chemotherapy and tamoxifen should be reserved for patients on clinical trials and those with a high risk of disease recurrence who are willing to endure the side effects of OS, for what remains an uncertain benefit.

In an attempt to determine the role of OS in the adjuvant treatment of breast cancer, the International Breast Cancer Study Group has initiated a number of randomized clinical trials. The Suppression of Ovarian Function Trial (SOFT) will address the question of whether OS adds to adjuvant therapy with tamoxifen. Women enrolled in the trial may or may not have received chemotherapy. To avoid the potential loss of power related to chemotherapy-induced menopause, SOFT will only include women who remain premenopausal after chemotherapy. SOFT, as well as the Tamoxifen and Exemestane Trial (TEXT), will also compare the effect of OS plus tamoxifen to OS and exemestane. At this time, the use of OS plus an aromatase inhibitor remains an unproven approach in premenopausal women and should be administered only within the context of clinical trials. The final trial, the Premenopausal Endocrine Responsive Chemotherapy Trial (PERCHE), will address the question of whether chemotherapy adds to combined endocrine therapy. These trials ask critical questions about adjuvant endocrine therapy in young women and represent the key to further improvements in the adjuvant endocrine therapy for premenopausal women. OS is clearly an effective treatment for premenopausal women with hormone receptor–positive breast cancer, but in 2005, its optimal use and ultimate home in the adjuvant setting remain unclear.

Authors' Disclosures of Potential Conflicts of Interest

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