Expanding Role of Ovarian Suppression/ Ablation in Premenopausal ER-Positive Breast Cancer: Issues and Opportunities

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Luteinizing hormone-releasing hormone analogs (LHRHa) are often used alone or in combination with tamoxifen to suppress ovarian function in premenopausal women with endocrine-responsive breast cancer. However, aromatase inhibitors (AIs) are now the preferred first-line endocrine treatment for postmenopausal women with breast cancer. Their benefits over tamoxifen in postmenopausal patients and the availability of LHRHa to inhibit ovarian estrogen production in premenopausal women has resulted in much interest in their potential use in combination with AIs in premenopausal breast cancer patients. Preliminary data suggest that the LHRHa goserelin (Zoladex) is active in combination with anastrozole (Arimidex) in premenopausal women with advanced disease, but there are currently few data available in the early breast cancer setting.

There are concerns regarding the potential risk of ovarian stimulation in premenopausal women and also regarding potential effects of long-term LHRH/AI treatment on bone health. Nevertheless, preliminary data suggest that LHRHa may also have a role in protecting ovarian function in premenopausal women receiving chemotherapy.

Selection Factors

As Dr. Pritchard states in her outstanding remarks, due to the current lack of data, there are no patient subgroups for whom one could routinely recommend combination LHRH-plus-AI adjuvant therapy. Factors that have been suggested as possibly favoring the choice of an AI over tamoxifen (in combination with an LHRHa) include estrogen receptor (ER)-positive/progesterone receptor (PR)-negative status, HER2/neu overexpression, and high risk of relapse (younger patients with larger tumors of node-positive disease following chemotherapy, who did not achieve amenorrhea). However, given the longer-term data on hormone receptor and HER2 status from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) and Breast International Group (BIG) 1 98 trials, it appears that PR-negative status and HER2-positivity are no longer selection factors. Nevertheless, higher risk of relapse remains a potential reason for selecting an LHRHa combined with an AI rather than tamoxifen. Furthermore, current data from the Austrian Breast Cancer Study Group (ABCSG)-12 trial suggest that bone tolerability issues associated with the combination of an LHRHa plus AI in the adjuvant setting are manageable.

Unproven Assumptions

Several unproven assumptions regarding the management of premenopausal women with early breast cancer may prove obstacles to the acceptance of combined LHRHa plus AI adjuvant therapy. These assumptions include the belief that all premenopausal patients are at high risk of relapse and death and need adjuvant and more aggressive chemotherapy. Moreover, there is no proof that new treatment approaches must be combined with chemotherapy. The urgent need for clear data addressing these issues mandates the design of clinical trials investigating the activity of adjuvant combination LHRHa-plus-AI therapy.

LHRHa therapy is also currently being investigated as a means to protect ovarian function in premenopausal women receiving chemotherapy. Various trials have addressed this question. Ovarian protection might be very effective and desired, preserving quality of life after adjuvant treatment of these patients. But it also raises concerns of possible interference with combined

Page 1 of 2
chemotherapy by inhibiting chemotherapeutic effects on receptor-positive cancer cells, silenced by antihormone therapy.

**Adjuvant Trials**

Overall LHRHa may offer a valuable alternative for premenopausal women with ER-positive disease. In the advanced setting, it is acceptable to employ such a strategy in the event of progression on other endocrine therapies, as sequential relatively short-term treatment is the norm. However, in the adjuvant setting, more data regarding efficacy and safety are required before this combination can be recommended, due to the expected longer survival of patients. Nonetheless, initial data from the bone subprotocol of ABCSG-12 support the use of this combination by showing that concomitant bisphosphonate treatment prevents cancer treatment–induced bone loss, which can be a significant concern for both physicians and patients in this setting. Recruitment to ABCSG-12 is now complete, and these data should help to clarify the potential of combination adjuvant endocrine therapy in premenopausal women.

The slow recruitment to the remaining adjuvant trials is disappointing, and results from the ongoing studies (eg, Suppression of Ovarian Function Trial [SOFT], Tamoxifen/Exemestane Trial [TEXT], Premenopausal Endocrine-Responsive Chemotherapy [PERCHE]) are not expected for some time. Nonetheless, there are other interesting developments in the field, including the potential use of an LHRHa to protect ovarian function, which is directly related to quality of life.

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