An update on ovarian suppression/ablation

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Adjuvant ovarian function suppression is acknowledged today as effective therapy for premenopausal patients with early breast cancer. Various modalities have been applied to achieve this treatment option:

- First, early investigations comparing ovarian ablation with chemotherapy identified similar outcomes in terms of patients' rates of disease-free survival (DFS).
- Second, prospective randomized trials have more recently focused on luteinizing hormone-releasing hormone analogues (LHRHa) that induce medical ovarian suppression and avoid the morbidity and irreversibility associated with surgical ovariectomy or irradiation. These trials analyzed the value of treatment with goserelin or other LHRHa, with or without tamoxifen, as against chemotherapy. Goserelin was subsequently established as a valid alternative, and our own results demonstrated that goserelin + tamoxifen is more effective and better tolerated in hormone-responsive patients.
- Third, other multiple-arm studies have compared LHRHa + chemotherapy with chemotherapy alone. Addition of tamoxifen to goserelin + chemotherapy was shown to improve DFS, and significant benefits in goserelin-treated patients were seen irrespective of use of chemotherapy or tamoxifen.
- Finally, ongoing trials are addressing the appropriate duration of LHRHa therapy and other unresolved issues.

In summary, combined ovarian suppression with adjuvant goserelin and tamoxifen is considered to be at least as effective as chemotherapy in premenopausal breast cancer patients. Published reports have demonstrated that ovarian suppression is a safe means of reducing risk of recurrence in estrogen receptor-positive women and underlined its use as a competitive alternative to chemotherapy in this patient subset.

KEYWORDS: Ovarian ablation, ovarian suppression, goserelin, LHRHa, early breast cancer, tamoxifen, chemotherapy.

There is evidence today that adjuvant ovarian suppression/ablation—through surgical oophorectomy, ovarian irradiation, chemotherapy, or luteinizing hormone–releasing hormone analogue (LHRHa)—is an effective treatment for premenopausal patients with early breast cancer. In a meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group in 1998, women <50 years of age were shown to experience a significant survival advantage in terms of both disease-free survival (DFS) and overall survival (OS) with ovarian ablation compared with patients receiving no adjuvant treatment.

More recently, the 2005 St. Gallen Consensus Panel continued to view tamoxifen as a standard therapy for premenopausal women with hormone-responsive disease who have an indication for endocrine treatment alone; ovarian suppression is accepted as an alternative. At the same time, combined ovarian suppression with goserelin, the most extensively studied LHRHa, and tamoxifen is considered to be at least as effective as chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). Analyzed in controlled clinical trials, present-day modalities applied to achieve ovarian function suppression thus include the following: 1) ovarian ablation vs chemotherapy; 2) LHRHa +/+ tamoxifen vs chemotherapy; and 3) LHRHa + chemotherapy vs chemotherapy alone.

Ovarian ablation vs chemotherapy

The Scottish breast cancer trial investigators were the first to attempt a head-on comparison of ovarian...
ablation vs cytotoxic chemotherapy in early breast cancer in 332 node-positive patients. After a median follow-up of almost 6 years, the outcome for women allocated to receive ovarian ablation was similar to that for patients randomized to CMF. When patient outcome was analyzed according to tumor estrogen receptor (ER) status, patients with ER-positive tumors were found to fare better with ovarian ablation, while those with ER-negative tumors fared better with CMF. In another trial reported by Ejlertsen et al., 732 patients with hormone-sensitive, node-positive disease were administered the same treatment. Five-year DFS rates were not significantly different between the two treatment groups at a median follow-up of 68 months.

Overall, the major disadvantage of oophorectomy or ovarian irradiation for premenopausal women is the morbidity and rare mortality cases associated with these procedures and their irreversibility. Therefore, goserelin and other LHRHa, which produce medical ovarian ablation, have been developed for the treatment of breast cancer in premenopausal patients avoiding the complications associated with surgery and radiation. This therapy allows some to maintain their ovarian function after completion of LHRHa adjuvant therapy. Several phase III investigations with goserelin have been conducted and are described below.

**LHRHa +/- tamoxifen vs chemotherapy**

**Zoladex Early Breast Cancer Research Association trial**

The Zoladex Early Breast Cancer Research Association (ZEBRA) trial is a large adjuvant study exploring the effect of goserelin in pre/perimenopausal women with early breast cancer ($n = 1640$). In this equivalence-testing trial, patients were $\leq 50$ years of age, with node-positive, stage II breast cancer who had received no previous systemic treatment. After completion of local therapy (surgery and/or radiotherapy), they were randomized to receive either goserelin for 2 years or six cycles of CMF chemotherapy. Establishment of hormone receptor (HR) status was not required for entry into the study, but it was left to each center’s discretion to enter ER-positive patients. Primary end points were DFS and OS. At a median follow-up of 6 years, DFS was overall significantly better for CMF compared with goserelin ($P = 0.029$) unlike OS ($P = 0.067$). In ER-positive patients only, however, DFS was demonstrated to be similar between the CMF and the goserelin arms, while in ER-negative patients, goserelin was inferior to CMF ($P < 0.001$). OS was similar for both treatments in the ER-positive group; however, ER-negative patients did significantly better with CMF ($P = 0.004$). This trial established goserelin as an effective alternative for the treatment of early breast cancer in premenopausal, node-positive, and ER-positive patients.

**Takeda Adjuvant Breast Cancer Study with Leuprolrelin Acetate trial**

Another trial, the Takeda Adjuvant Breast Cancer Study with Leuprolrelin Acetate (TABLE) reported by Wallwiener and collaborators, presented data comparing this LHRHa and CMF in 600 premenopausal patients with HR-responsive, node-positive breast cancer. At 2 years follow-up, the TABLE trial evidenced no significant difference between the two arms under investigation as to progression-free survival; yet, there was a significantly lower amount of serious adverse events in the endocrine treatment arm. Leuprolrelin also led to a more consistent suppression of menstruation. Taking these two trials together, the results clearly indicate that induction of amenorrhea by the administration of LHRHa in premenopausal patients with HR-responsive tumors induces effects comparable to those of CMF-based chemotherapy in terms of recurrence-free survival (RFS).

**Italian Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group 02 trial**

Italian Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group (GROCTA) trial 02 was a randomized, multicenter study comparing CMF with ovarian suppression—either goserelin for 2 years or ovarian irradiation—plus tamoxifen in premenopausal women. As reported by Boccardo, a total of 120 patients were randomized to CMF, and 124 patients were allocated to goserelin plus tamoxifen. After a median follow-up of 6.3 years, 37% of patients relapsed and 18% of patients died. There were no significant differences in DFS or OS comparing the chemotherapy and the endocrine groups. This trial demonstrated that the combination of hormonal therapy plus ovarian suppression was safe and effective in ER-positive patients with early breast cancer.

**Austrian Breast & Colorectal Cancer Study Group trial 5**

Our own investigation, Austrian Breast & Colorectal Cancer Study Group Trial 5 (ABCSG 5), was set up in 1990 to compare DFS and OS among premenopausal women with HR-positive, node-positive disease, or...
node-negative disease. Patients received six cycles of CMF every 28 days or goserelin for 3 years plus tamoxifen for 5 years. At a median follow-up of 5 years, only 9% of patients had died from breast cancer, and survival differences between the two treatments were not significant. Nineteen percent of women developed relapse; however, there were significant RFS differences in favor of the group receiving tamoxifen plus LHRHa compared with the chemotherapy arm ($P = 0.037$). In addition, local RFS also favored goserelin plus tamoxifen in this population ($P = 0.015$). OS was not significantly different between the endocrine arm and the chemotherapy group. Further follow-up is warranted due to the small number of events that had occurred. Hot flushes were the most common side effect reported in the goserelin plus tamoxifen group, but there were more reports of nausea and alopecia in the chemotherapy group compared with the combination arm. We concluded that goserelin plus tamoxifen is more effective and better tolerated than CMF as adjuvant therapy in premenopausal women with hormone-sensitive breast cancer.

**Vietnamese/Chinese trial**

In an Asian investigation coordinated by Love, 709 premenopausal patients were randomized to either receive adjuvant oophorectomy and tamoxifen for 5 years or observation and this combined hormonal treatment on recurrence. With a median follow-up of 3.6 years, significant differences in 5-year DFS rates were seen at 75% and 58% ($P = 0.0003$) and in OS at 78% and 70% ($P = 0.041$) for the adjuvant and observation groups, respectively. Only patients with receptor-positive tumors had an advantage with adjuvant treatment. In conclusion, the Vietnamese and Chinese patients with receptor-positive disease benefited from adjuvant treatment, with surgical oophorectomy and tamoxifen.

**LHRHa + chemotherapy vs chemotherapy alone**

**INT-0101**

The intergroup INT-0101 (INT-0101) study was based on the results of the early EBCTCG analysis and was designed to investigate the effect of adjuvant chemo-hormonal therapy in patients with HR-positive, node-positive breast tumors. Patients were randomized to chemotherapy with cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) for six cycles, chemotherapy plus goserelin for 5 years, or chemotherapy plus goserelin plus tamoxifen for the same period. Davidson et al. presented a 9.6-year updated analysis at the 2005 meeting of the American Society of Clinical Oncology. The combination arm of CAF + goserelin + tamoxifen continued to demonstrate significant reductions in recurrences ($P < 0.01$). The chemotherapy + goserelin arm, however, no longer illustrated such a benefit. OS differences were not significant. One limitation of the study was that a chemotherapy + tamoxifen alone arm was not included (which would be considered standard of care). In sum, this trial demonstrates that addition of tamoxifen to CAF-Z significantly improves time to relapse and DFS. The addition of goserelin after CAF chemotherapy did not improve overall outcome.

**International Breast Cancer Study Group trial VIII**

The International Breast Cancer Study Group (IBCSG) trial VIII randomized 1063 premenopausal women with node-negative, receptor-positive or receptor-negative breast cancer to one of four treatment arms. Following surgery, patients were randomized to 2 years' goserelin alone, to six cycles of CMF, or to CMF followed by goserelin for 18 months. Results have been published with a median follow-up of 7 years. Castiglione-Gertsch et al. found no significant DFS difference among the three treatment arms. In patients with ER-positive disease, CMF or goserelin were equivalent in terms of 5-year DFS. With the sequential administration of CMF followed by goserelin, DFS was 86%. Regrettably, none of the study arms included tamoxifen because at the time of trial conception, it was suggested that tamoxifen would not be beneficial in women less than 50 years of age. More detailed results and other studies need to be compared to better understand whether triplet therapy—chemotherapy + ovarian suppression + other endocrine agents—is better than chemotherapy alone or chemotherapy + tamoxifen.

**Zoladex in Premenopausal Patients trial**

The Zoladex in Premenopausal Patients analysis involved a combination of data from randomized trials initiated by four European collaborative groups, running concurrently with similar protocols. Each center could determine initial treatment (surgery/radiation/chemotherapy) and whether to randomize patients to tamoxifen therapy. Premenopausal patients received primary surgery and standard therapy, which could include chemotherapy (most commonly CMF).
and/or radiotherapy. This was followed by randomization to 2 years' treatment in one of four groups: goserelin, tamoxifen, goserelin plus tamoxifen, or no further endocrine therapy. A 5-year update was presented at the 2000 ASCO meeting that continued to demonstrate significant differences in DFS ($P < 0.001$), but the difference in OS was not significant with the goserelin-treated group ($P = 0.08$). The improvement with goserelin was observed irrespective of the use of chemotherapy or tamoxifen treatment. In this setting, ovarian ablation demonstrated added benefit compared with the other treatment arms; yet, the role of tamoxifen was not adequately addressed.

**French Adjuvant Study Group 06 trial**

Finally, the aim of the French Adjuvant Study Group (FASG) 06 trial was to compare the impact of complete hormonal blockade with tamoxifen and the LHRHa, triptorelin, on DFS and OS in 333 node-positive patients. Interestingly, only 41% of patients experienced amenorrhea, compared with over 65% in ABCSG 5 and GROCTA 02. After 54 months of follow-up, this investigation showed complete hormonal blockade with triptorelin and tamoxifen to be a competitive alternative to chemotherapy.

Several important issues regarding the role of ovarian ablation in the treatment of breast cancer remain unresolved. For example, areas of ongoing investigation include the appropriate duration of therapy with LHRHa in the adjuvant setting, the long-term sequelae of ovarian suppression among young breast cancer survivors, and refinement of the population most likely to benefit from ovarian suppression/ablation. To help answer these questions, three other complementary trials have been initiated to evaluate the use of chemotherapy, ovarian suppression, and other endocrine therapies (tamoxifen or aromatase inhibitors) as adjuvant therapy. The Suppression of Ovarian Function Trial is for women who remain premenopausal after surgery or after the completion of chemotherapy. Patients are randomized to either tamoxifen for 5 years, tamoxifen + ovarian suppression (with either triptorelin for 5 years or surgical oophorectomy) or exemestane for 5 years + ovarian suppression. The second study, the Tamoxifen and Exemestane Trial, accrues patients who plan to receive ovarian suppression (triptorelin) from the start of their adjuvant therapy and then are randomized to receive either tamoxifen or exemestane concurrently. Finally, the Premenopausal Endocrine-Responsive Chemotherapy trial randomizes women to ovarian suppression plus hormonal therapy (tamoxifen or exemestane) or to a triplet arm of chemotherapy, ovarian suppression plus hormonal therapy (tamoxifen or exemestane).

In summary, the published reports of prospective randomized trials demonstrate that ovarian suppression is an effective means of reducing risk of recurrence in ER-positive patients. Results of these investigations support the point that ovarian suppression could be utilized as an alternative to chemotherapy in this subset of patients. It should be emphasized that, unfortunately, some of the trials included ER-negative patients, and in some of them tamoxifen was not included. At any rate, it is important that we understand that we are passing through a time of considerable change concerning the role of ovarian suppression in the management of early-stage breast cancer.