HORIZONS

Iatrogenic Induction of Menopause as Adjuvant Therapy for Premenopausal Women With Early Breast Cancer

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Introduction

Breast cancer is the most common cancer diagnosed in women in North America and 25 % of them are pre-menopausal (1). The young pre-menopausal and peri-menopausal women constitute a significant group of patients with breast cancer and their specific treatment requires careful consideration. Approximately 60% of tumors in pre-menopausal women are hormone sensitive, and are potentially suitable for endocrine treatment (2,3). Systemic therapy which includes endocrine therapy and chemotherapy are used to reduce the likelihood of recurrence in early breast cancer (EBC) and to treat more advanced disease with or without distant metastases. Such therapy in the adjuvant setting in EBC will on average reduce the risk of recurrence by 20-35% and the odds of death by 15-30%. The adjuvant therapy decisions are guided by numerous factors like tumor size, lymph node status, hormone receptor status, HER2-neu over expression, grade of the tumor, DNA synthesis rate, gene profiling assay and host related factors like physiological age of the patient, menopausal status and presence of co morbid conditions.

Endocrine therapy: The presence of endogenous estradiol plays a significant role in the progression of disease and its impact is dependant on the hormone receptor status of the tumor. Thus, removal of the some of endogenous estrogen in pre-menopausal patients is likely to prevent growth of tumors that are sensitive to circulating estrogens. Hormonal manipulation has been used for more than 100 years to treat young women with advanced cancer, but there is still no complete consensus about how to translate this into the management of EBC. Tamoxifen, a selective estrogen receptor modulator (SERM), is an effective agent for pre-menopausal women with hormone receptor positive status and 5 years of tamoxifen is recognized as standard of care for these women based on individual trials and Early Breast Cancer Trialists Collaborative Group (EBCTCG) (4).

The definition of menopause in breast cancer patients presents a tricky situation because of the confounding factors like use of chemotherapy and hormonal therapy. However, menopause is generally synonymous with permanent cessation of menses and is accompanied by profound and permanent decrease in estrogen synthesis in ovaries. The universally accepted criteria for determining menopause in the context of breast cancer include any of those given in Table 1.

Table 1: Criteria for Defining Menopause in Breast Cancer patients

1. Prior bilateral oophorectomy
2. Age = 60 years
3. Age < 60 years and having amenorhoea for longer than 12 months in the absence of chemotherapy or use of SERMs or OA/OS and serum FSH and estradiol levels in the postmenopausal range
4. Serum FSH and estradiol levels in the postmenopausal range in a patient with age < 60 years and taking SERMs

Oophorectomy in EBC: Ovarian ablation/suppression (OA/OS) is acceptable adjuvant therapy in special circumstances. In reviewing data from adjuvant trials EBCTCG found that 2102 women under 50 years of age with node-negative or node-positive EBC, ablation of functioning ovaries by surgical oophorectomy or radiotherapy significantly improved 15-year disease free and overall survival compared with controls(5). This led the National Institute of Health Consensus Conference to endorse ovarian ablation or suppression as n alternative to tamoxifen in 2000. Also the 2003 St. Gallen Consensus Conference has suggested that OA/OS with tamoxifen represents reasonable adjuvant therapy for some intermediate risk premenopausal women. In direct and

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indirect comparisons, OA has been shown to have comparable efficacy to chemotherapy, but OA by surgery or RT induces permanent menopause with associated long term effects such as loss f bone mineral density and increased risk of cardiovascular problems (6).

Medical oophorectomy in EBC: Reversible ovarian suppression can be induced by the use of luteinizing hormone releasing hormone (LHRH) agonists alone or with tamoxifen has proven effective for the treatment of advanced breast cancer in pre-/perimenopausal women resulting in objective response rates similar to oophorectomy (7). LHRH agonists bind to the pituitary receptors, resulting in receptor downregulation, which leads to a profound suppression of LH and subsequently estradiol. The benefit of this approach lies in its reliable and reversible suppression of ovarian estrogen production

Recently the results of five comparative trials of adjuvant hormonal therapy using LHRH agonists alone (8,9) or in combination with tamoxifen (10,11), versus cytotoxic chemotherapy have shown at least equivalence of effect in premenopausal women with hormone receptor positive tumours. The Zoladex In Premenopausal Patients (ZIPP) trial determined the effect of adding goserelin to standard adjuvant treatment (surgery ± radiotherapy ± chemotherapy ± tamoxifen) compared with the effect of standard treatment alone in women under the age of 50 years (12). After a median follow up of 66 months, the event free survival was significantly longer for patients who received goserelin in addition to standard therapy compared with those who did not (HR=0.80, $p<0.001$). Overall survival was also significantly prolonged (HR=0.82, p=0.04). Another trial addressed the question of value of the addition of chemotherapy to goserelin therapy. The International Breast Cancer Study Group (IBCSG) Trial VIII was designed to compare six cycles of CMF with either 2 years goserelin, six cycles CMF followed by 18 months goserelin or no treatment in premenopausal women with node negative EBC. Interim analysis of 200 patients from the four original arms showed significantly longer 5 year DFS in the treated group (77% vs. 60%, p0.02) (13). Subsequent analysis showed that 5-year DFS were comparable in the three treatment arms (goserelin 81%; CMF 81%; CMF plus goserelin 88%) and there is no benefit of adding CMF chemotherapy to goserelin in node-negative, estrogen receptor-positive premenopausal breast cancer patients (14).

The Future of Medical Oophorectomy in EBC: Despite these advances in the understanding of hormone therapy in breast cancer, a number of questions still remain unanswered viz. the value of combining or sequencing OA with chemotherapy; the value of combining OA with tamoxifen or aromatase inhibitors; and the utility of chemotherapy in premenopausal women with hormone responsive breast cancer who are already receiving endocrine therapy. Three prominent international trials are going on to address these issues. The Suppression of Ovarian Function Trial (SOFT) is randomizing premenopausal ER-positive or PR-positive tumors to 5 years of tamoxifen alone, 5 years of tamoxifen and GnRH agonist triptorelin, and 5 years of the exemestane with triptorelin. Tamoxifen and Exemestane Trial (TEXT) compares ovarian ablation (5 years of triptorelin) and tamoxifen with 5 years of triptorelin and exemestane. In the Premenopausal Endocrine Responsive Chemotherapy Trial (PERCHE), premenopausal women all receive OA with the triptorelin and then are randomly assigned to receive chemotherapy or no chemotherapy, followed by a subsequent random assignment to receive tamoxifen or exemestane.

Current treatment guidelines from St. Gallen and the European Society of Mastology (EUSOMA) now recommend the use of a LHRH agonist for 2 years with or without tamoxifen for 5 years, as an alternative to adjuvant cytotoxic chemotherapy for premenopausal women with hormone sensitive early breast cancer. Such treatment is also recommended for those women treated with chemotherapy whose menses return or who fail to achieve castrate levels of estrogens or follicle stimulating hormone after completing chemotherapy

Conclusion

The available data suggest that OA/OS provides a valuable treatment option in premenopausal patients with hormone receptor positive status and may be an attractive alternative to cytotoxic chemotherapy without the

associated distressing side effects. However, most of these trials did not use anthracyclines or taxanes, and used tamoxifen inconsistently. OA/OS itself is associated with adverse effects like weight gain, diabetes and hot flashes. As of now, OA should not be routinely used to replace adjuvant chemotherapy in premenopausal women with breast cancer. But it does offer a means of avoiding chemotherapy which may be a requirement in some patients. And it can also be used as a treatment combined with tamoxifen or aromatase inhibitors and/or chemotherapy in some selected patients with beneficial results.

References:

1 Theriault RL, Sellin RV. Estrogen replacement therapy in younger women with breast cancer. *J Natl Cancer Inst Monogr* 1994;16:149-152

2 Aebi, S., Gelber, S., Castiglione-Gertsh M, *et al*. Is chemotherapy alone adequate for young women with estrogen-receptor-positive breast cancer? *Lancet* 2000; 355:1869-74.

3 Kroman N, Jensen MB, Wohlfahrt J, *et al*. Factors influencing the effect of age on prognosis in breast cancer: population based study. *British Medical Journal* 2000; 320: 474-78

4 Early Breast Cancer Trialists' Collaborative group, Tamoxifen for early breast cancer: An overview of the randomized trials. *Lancet* 1998; 351: 1451-67.

5 Ovarian ablation in early breast cancer: Overview of the randomized trials. Early Breast cancer Trialists' Collaborative Group. *Lancet* 1996;348: 1189-96.

6 Goodwin PJ, Ennis M, Pritchard KI. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol* 1999,17:2365-70.

7 Taylor CW, Green S, Dalton WS, et al. Multicenter randomized clinic trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor positive metastatic breast cancer: an Intergroup Study . *J Clin Oncol* 1998;16:994-99.

8 Kaufmann M. Zoladex™ (goserelin) vs. CMF as adjuvant therapy in pre/peri-menopausal node-positive early breast cancer. Preliminary efficacy results from the ZEBRA study. *Breast* 2001, 10 (suppl 1), S30[abstr P53]

9 Wallwiener D, Possinger K, Bondar G et al. Leuprorelin acetate Vs. CMF in the adjuvant treatment of premenopausal women with ER/PR – positive, node-positive breast cancer: interim results of the TABLE study. *Proc ASCO* 2001, 20, 34a (abstr 132)

10 Jakesz R, Hausmaninger H, Samonigg H, et al. on behalf of the Austrian Breast and Colorectal Cancer Study Group (ABCSG). Complete endocrine blockade with tamoxifen and goserelin is superior to CMF in the adjuvant treatment of pre-menopausal, lymphnode-positive and lymphnode-negative patients with hormone responsive breast cancer. *Breast* 2001, 10 (Suppl. 1). S10 (abstr S26).

11 Boccardo F, Rubagotti A, Amoroso D, *et al*. Cyclophosphamide, methotrexate and fluorouracil versus tamoxifen plus ovarian suppression as adjuvant treatment of estrogen receptor-positive pre-/peri-menopausal breast cancer patients: results of the Italian Breast Cancer Adjuvant Study Group O2 randomized trial. *J Clin Oncol* 2000, 18: 2718-2727.

12 Baum M, Houghton J, Odling-Smee W, *et al*. On behalf of the ZIPP Group. Adjuvant Zoladex in premenopausal patients with early breast cancer results from the ZIPP trial. *Breast* 2001, 10(suppl 1), S23-S33 [abstr P64].

13 Castiglione-Gertsch M, Gelber RD, O Neill A, *et al*. Systemic adjuvant treatment for premenopausal node negative breast cancer. *Eur J Cancer* 2000;36:549-50.

14. Castiglione-Gertsch M, O Neill A, Gelber RD, *et al*. Is the addition of adjuvant chemotherapy always necessary in node negative (N-0 pre/perimenopausal breast cancer patients (pts.) who receive goserelin?: first results of the IBCSG trial VIII. *Proc ASCO* 2002,21,38a (abstr 49).