REVIEW

Controversies Regarding Ovarian Suppression and Infertility in Early Stage Breast Cancer

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Abstract: A common side effect of chemotherapy in breast cancer is early menopause in premenopausal patients, which is mainly a result of an indirect form of ovarian ablation, and is associated with substantial impairment of quality of life. Suppressing the production of ovarian estrogen has been shown to reduce the recurrence of hormone receptor-positive early breast cancer in premenopausal women, but whether it has an added advantage over tamoxifen is being discussed. Types of permanent ablation of the ovarian function include surgical oophorectomy and radiation-induced ovarian failure. Both are associated with similar response rates in hormone receptor-positive metastatic breast cancer. Medical castration with luteinizing hormone-releasing hormone analogs (LHRHa) has the benefit of being a reversible approach. Another advantage that premenopausal patients who wish to reduce the risk of developing premature ovarian insufficiency induced by chemotherapy may be offered LHRHa irrespective of whether they desire pregnancy and their age at diagnosis. This also helps reduce the risk of menopausal signs and symptoms as well as the loss of bone density in the long-term, which are primary concerns for women. This is of utmost importance to premenopausal women who do not want to conceive after treatment or are not candidates for fertility preservation strategies because of age. It should be emphasized that for women who are interested in fertility preservation, gamete cryopreservation remains the first option, and LHRHa is not an alternative. During chemotherapy, however, temporary ovarian suppression with LHRHa may be given to women who either have no access to a fertility clinic or who have declined chemotherapy or have contraindications.

Keywords: ovarian suppression, ovarian fertility, chemotherapy, pregnancy, aromatase inhibitors

Introduction

Adjuvant chemotherapy has substantially reduced the risk of relapse and death following the diagnosis of breast cancer. For patients who are estrogen or progesterone receptor-positive, it is imperative to know if the ovaries are still functioning or not.[1] The choice of adjuvant hormonal treatment depends on the menopausal status of a patient. Both Ovarian ablation/suppression and hormones are reasonable adjuvant endocrine treatments.

Approximately 25% of breast cancer patients are premenopausal at the time of diagnosis.[2] The main concern following adjuvant chemotherapy is the risk of loss of fertility as adjuvant chemotherapy is known to induce early menopause in most premenopausal breast cancer patients. The incidence of chemotherapy-induced amenorrhea depends on the chemotherapy regimen used and the age of patients.

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Drugs like cyclophosphamide, ifosfamide predispose the patients to a high risk of gonadal dysfunction, while vincristine, methotrexate, 5 Fluorouracil, and bleomycin are considered low risk drugs. Platinum compounds, toxoids, and anthracyclines moderately affect gonadal dysfunction.[3]

Ovarian Function Suppression with Chemotherapy

Critical factors in evaluating the risk of infertility include age at diagnosis, drugs that are being administered, and age at pregnancy. LH-RH agonists work by decreasing ovarian estradiol production indirectly by impinging on the hypothalamic-pituitary-ovarian axis. LH-RH is released by the hypothalamus in a pulsatile manner, which causes the production of gonadotropins by the pituitary. This, in turn, stimulates the release of estradiol by the ovary. As a result, LH-RH analogs bind to the pituitary LH-RH receptors more avidly than LH-RH itself. Chronic administration of LH-RH analogs results in the down-regulation of pituitary LH-RH receptors, which causes a dramatic suppression of gonadotropin secretion, and leads to loss of ovarian steroid production.[4]

After completion of chemotherapy premenopausal levels of estradiol are detected in amenorrheic patients despite discontinuation of menstrual activity suggesting persisting ovarian function. Luteinizing hormone or gonadotropin hormone-releasing hormone analogs (LH-RH or GnRH) induce ovarian function suppression. This effect is considered temporal, and its reversibility depends on patient age. In 90% of patients who are younger than 40 years of age, menstruation returns following one year after the completion of therapy, compared with approximately 70% of patients older than 40 years of age.[5]

Various tests (i.e., FSH level, measurements of levels of inhibin B or antimullerian hormone, vaginal ultrasonography with an assessment of the number of antral follicles) can identify decreased ovarian reserve suggesting a reduced probability of pregnancy. However, no data is available on the use of these tests in breast cancer patients to assess ovarian reserve persisting after adjuvant chemotherapy and endocrine therapy.[6] Above 35 years of age, Anti-mullerian hormone in serum is especially promising as a marker of ovarian reserve in women.

A strategy to reduce the risk of treatment-induced premature menopause includes suppressing the ovaries temporarily with a GnRH analog during chemotherapy as chemotherapy-induced menopause rises with increasing age.[7]

The risk of infertility is higher for women greater than 35 years of age while using different adjuvant/neoadjuvant chemotherapy regimens ranging from 60 to 100% while for women less than 35 years of age infertility ranges from 5–50%.[8]

Patients who received chemotherapy plus LH-RH analog have a rate of premature ovarian insufficiency more than twice as high in patients receiving chemotherapy. This was the outcome of five trials that include; PROMISE, POEMS/ SWOG S0230, Anglo Celtic Group OPTION, ZORO, and Moffitt.[9–13]

The randomized, open-label Phase III POEMS trial assessed premenopausal women younger than 50 years of age with hormone receptor-negative, stage I-IIIA breast cancer, adjuvant, or neoadjuvant cyclophosphamide-containing chemotherapy with or without the LH-RH analog goserelin.[14] Initial results confirmed that only 8% who received goserelin had ovarian failure, while 22% of patients on standard therapy experienced ovarian failure. Five years of follow-up suggested that, on average, 23% of women who took goserelin became pregnant compared with 12% who did not. Final results of the Prevention of Early Menopause Study (POEMS) show continued evidence that women who get goserelin along with standard breast cancer chemotherapy are more likely to become pregnant, with no impairment of quality of life, and worsening of overall survival. Women who took goserelin experienced even better or similar survival rates. Five years after treatment, 88% of women who took goserelin were alive and disease-free compared with 79% of women who received standard chemotherapy alone. While there were no statistically significant differences in survival, 92% of women who took goserelin were alive at 5 years compared with 83% of patients who did not receive it.

Goserelin + chemotherapy led to improved fertility and more successful pregnancies. Hence, it would be reasonable to say that premenopausal women starting radical or curative intent chemotherapy should consider this regimen to prevent premature ovarian failure.

In the PROMISE-GIM6 study, patients received concurrent administration of LH-RH analog and chemotherapy in hormone receptor-positive breast cancer patients, but results from this trial did not show any detrimental effect on prognosis either. In the Italian PROMISE (prevention of menopause induced by chemotherapy) trial, which included early breast cancer patients, both hormone

receptor-positive, and negative patients were either randomized to receive chemotherapy alone or chemotherapy plus LH-RH analogs.

Concern about the use of LH-RH analogs in hormone receptor-positive patients is that because of the protective effect of LH-RH analog, the benefit with chemotherapy-associated menopause might be lost as there is some evidence to suggest that chemotherapy-induced menopause is related with an improved prognosis in early breast cancer patients.[8] However, it cannot be ruled out with certainty that ovarian function resumption and as a result, estrogen production may adversely affect the survival of patients with hormone-sensitive tumors. PROMISE study addressed this by restarting LH-RH analog treatment in patients with ER and PgR positive tumors when ovarian function resumed. LH-RH analog treatment is continued for at least two years, thus assuring therapeutic ovarian function suppression. However, the mechanisms, by which LHRHa can protect ovarian function during chemotherapy are not fully known.[15,16]

Ovarian Function Suppression with Adjuvant Endocrine Therapy

Using tamoxifen therapy besides chemotherapy results in a small but statistically significant increase in the risk of menopause and depends on the age of the patient. The risk is like that of patients who have not had treatment in women younger than 45 years of age whereas in older menstruating women the additional increased risk of menopause from tamoxifen therapy is only about 10% greater than in those women who receive no therapy.[17]

Available guidelines until 2014 did not recommend the addition of ovarian function suppression to tamoxifen. In a meta-analysis which included five randomized trials (n= 1013 patients), there was no significant benefit in reducing the risk of recurrence [hazard ratio (HR), 0.85; 95% confidence intervals (CI), 0.67–1.09; P ¼ 0.20] or death after recurrence (HR, 0.84; 95% CI, 0.59–1.19; P ¼ 0.33) when LHRHa was added to tamoxifen alone.[18]

E-3193, INT-0142 trial randomly assigned patients to tamoxifen with or without ovarian suppression for 5 years. Three hundred forty-five premenopausal women with low risk node-negative breast cancer who had not received neoadjuvant chemotherapy were included. The study closed early without reaching the planned accrual of 1600 patients. Ovarian function suppression added to tamoxifen did not improve disease-free survival or overall

survival after a median follow-up of 9.9 years. Among women younger than 35 years at diagnosis, the combination of ovarian function suppression, and tamoxifen was also associated with increased side effects like menopausal symptoms and lower sexual activity.[19] Also notable was a higher level of nonadherence with medical ovarian function suppression.

In ASTRRA study, 1282 premenopausal patients with 45 or less were randomized to 5 years of endocrine therapy with tamoxifen alone or tamoxifen with ovarian function suppression for 2 years.[15] Patients who had received prior chemotherapy and were premenopausal up to 2 years after the end of chemotherapy (based on menstrual history or follicle-stimulating hormone levels) were included. After a median follow-up of 5.6 years, the extension of 2 years of ovarian function suppression to 5 years of tamoxifen showed significant improvement in DFS (HR, 0.69; 95% CI, 0.48–0.97; P ¼ 0.033), and OS (HR, 0.31; 95% CI, 0.10–0.94; P ¼ 0.029). The benefit was concordant among all patient subgroups.[15] Data from these three randomized trials suggest that premenopausal women with estrogen receptor-positive breast cancer at intermediate or high risk of disease recurrence enjoy the addition of ovarian function suppression to tamoxifen. The ABCSG 12 study and the joint analysis of the SOFT and TEXT are the trials addressing the role of combining ovarian function suppression and aromatase inhibitors as an adjuvant endocrine treatment in premenopausal women with estrogen receptor-positive early breast cancer.

In SOFT and TEXT trials, the questions asked whether tamoxifen plus ovarian suppression was superior to tamoxifen alone? SOFT and (combined with elements of SOFT): is exemestane plus ovarian suppression superior to tamoxifen plus ovarian suppression? (TEXT) and the eight-year follow-up was presentedASCO.[20]

The combined analysis of the SOFT and TEXT confirmed statistically significant improvements in disease outcomes with exemestane versus tamoxifen used in combination with ovarian suppression after a median follow-up of 9 years. Most benefits were seen in women with HER2-negative breast cancer and women who remained premenopausal after receiving chemotherapy before starting ovarian suppression, especially those who also received adjuvant chemotherapy for higher risk of recurrence. The benefit of OFS plus aromatase inhibitors (AI) over OFS plus tamoxifen was moderate in patients who received chemotherapy but had an intermediate risk of recurrence.[16] Across SOFT and TEXT, respectively,

absolute improvements in disease-free survival in these higher-risk groups were 7–9%, and freedom from distant recurrence was 5–7%. Women treated with ovarian suppression did not show a difference in overall survival after 9 years' median follow-up when the two groups of women were compared.

The above results are conflicting with the ABCSG-12 trial, where patients were randomized to receive LH-RH analog with goserelin plus tamoxifen or the AI anastrozole with or without zoledronic acid for three years.[21] With a median follow-up of approximately eight years, no difference was observed in DFS between the two arms, but OS was significantly worse in patients who received anastrozole. Potential reasons could be that the ABCSG study patient population included only patients that had a low risk of relapse, and only a 3-year duration of endocrine therapy was administered and that adjuvant bisphosphonates were given in half of the included patients.

The best timing for starting ovarian function suppression remains controversial in patients who receive neoadjuvant chemotherapy before starting adjuvant endocrine therapy. One way of dealing with this is to start ovarian function suppression together with chemotherapy and then to continue the treatment up to 5 years after diagnosis.[18] Mixed results were observed in trials testing oophorectomy as adjuvant therapy. Patients with stage II or III breast cancer (i.e., women who receive chemotherapy) should receive ovarian function suppression in addition to adjuvant endocrine therapy. Some patients with stage I or II breast cancer at higher risk of recurrence (i.e., women who might also consider receiving chemotherapy) may be offered ovarian function suppression beside adjuvant endocrine therapy. Ovarian function suppression can be administered with either tamoxifen or an aromatase inhibitor (with no clear preference between one option over the other).

In St. Gallen 2019 guidelines majority of panelists supported ovarian function suppression for patients with ER negative disease who wanted to be pregnant in the future. For patients with ERpositive disease, the proportion of the majority decreased but still, there was overwhelming support of overian suppression.

GnRH agonists appear to preserve ovarian function in women receiving chemotherapy irrespective of tumor subtype. It reduces the risk of early menopause, increasing the chances for future pregnancy, and is an option for patients with breast cancer who wants to preserve fertility and who are candidates for chemotherapy.[22]

Ovarian function suppression can be applied with either tamoxifen or an aromatase inhibitor with no clear preference between one option over the other in patients with uncertain "clinical risk" (node-negative)/"intermediate genomic risk". Ovarian function suppression can be administered, preferably with an aromatase inhibitor and in patients with intermediate/high clinical risk' (node-positive)/"intermediate/high genomic risk" and in those with high risk. Patients who are candidates for chemotherapy should have ovarian suppression during chemotherapy therapy as opposed to the end of treatment, this has been shown to be safe, and has the additional benefits of reducing the risk of treatment-induced premature ovarian insufficiency and infertility.[23–25]

According to ESMO 2018, guidelines regarding ovarian suppression as per the age group, for patients less than 35 years old and chemo naïve, ovarian suppression with tamoxifen is recommended. However, those who had previous chemotherapy are recommended to have ovarian suppression with AI. Patients in more than 35 years' age group are stratified according to the risk of recurrence. Chemo naïve patients with low risk are recommended tamoxifen, while intermediate, and high risk are advised ovarian suppression with AI.[26] It is also opined that those with previous chemotherapy (intermediate risk group) are recommended ovarian suppression with tamoxifen while those with previous chemotherapy but the high risk group is recommended to undergo ovarian suppression with AI.[27,28]

Conclusion

In the clinic, many breast cancers patients complain about fertility at the time of diagnosis. It is challenging to decide the best therapeutic adjuvant endocrine therapy option for a patient. In order for the patients to make an informed decision, patients should be well informed about the current evidence and different options should be discussed with the patient with pros and cons for each treatment. Proper counseling should be provided to women who desire future fertility and fertility-preserving options discussed with the patients before commencing chemotherapy. The choice of the optimal endocrine therapy in premenopausal women should be discussed with patients. Also, the pros and cons of ovarian suppression should be taken into account for each strategy.

Disclosure

The authors report no conflicts of interest in this work.

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