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Picking the optimal endocrine adjuvant treatment for pre-menopausal women

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ABSTRACT

Endocrine treatments are key component of the adjuvant strategy for pre-menopausal patients with luminal tumors. Treatment options should be based not only upon the risk of relapse and level of endocrine responsiveness, but also on co-morbidities, preferences of the patient and degree of side effects. Tamoxifen should still be considered as an appropriate endocrine therapy in a large group of premenopausal patients (e.g. lower risk patient, presence of co-morbidities, patient preference). However, the results of the SOFT and TEXT trials, evaluating the value of ovarian function suppression (OFS) as well as the role of adjuvant aromatase inhibitor (AI), raised questions about the use of tamoxifen alone in selected higher risk patient. In the SOFT study, premenopausal patients did not benefit from the addition of OFS, but for those women at sufficient risk of recurrence to deserve adjuvant chemotherapy and who maintained pre-menopausal estradiol, the addition of OFS to tamoxifen reduced the risk of recurrence. Moreover, in the TEXT trial, adjuvant treatment with exemestane plus OFS, as compared with tamoxifen plus OFS, significantly improved disease-free survival, breast cancer-free interval and distant disease-free survival, thus representing a new treatment option. Recent available information on endocrine options for younger patients with luminal tumors support the use of tailored endocrine treatments. Issues specific for younger patients related to pregnancies desire, family planning, safety, quality of life and subjective side effects should be a priority in the therapeutic algorithm.

Introduction

In the past decades little attention was dedicated to the investigation of tailored adjuvant therapies in premenopausal patients, including endocrine manipulation. Chemotherapy was commonly offered to the younger patients, considered per se at higher risk of relapse, due to the fact that adjuvant therapies were prescribed according to risk factors: the higher the risk, the more intensive the treatment. However, retrospective analyses suggest that the endocrine effects of chemotherapy alone are insufficient for this category of younger patients with breast cancer [1] supporting a role for endocrine therapies as an essential component of an effective adjuvant therapy program in endocrine-responsive pre-menopausal patients.

Selective interventions to minimize toxicity without compromising efficacy are required for up to date care in the adjuvant setting. In particular, for premenopausal patients, appropriate adjuvant systemic therapy includes treatments tailored to individual patients not only according to risk profile, but also according to comorbidities and patients' preference [2–4]. Important issues to be considered in the therapeutic algorithm contain acceptance of problems related with the terapies including menopausal symptoms, sexual functioning and fertility issues.

Adjuvant tamoxifen is currently considered standard of care for premenopausal women with endocrine-responsive disease. Five years of tamoxifen have been shown to be effective for reducing the risk of recurrent disease and death in patients with endocrine-responsive breast tumors [5]. In particular, adjuvant tamoxifen given for 5 years reduces the annual breast cancer death rate by 31% [5] in patients with ER-positive disease. The proportional recurrence risk reductions produced by tamoxifen are marginally influenced by age at study entry.

The profile of side effects for tamoxifen in monotherapy is well known. As reported in a meta analysis, tamoxifen was associated

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with a statistically significant endometrial cancer risk increase (RR 2.70), with a significantly increased risk of pulmonary emboli (RR 1.88) as well as an increased incidence of deep venous thrombosis (RR 1.87) [6]. Tamoxifen has also been related with increased bone mineral density (BMD) in postmenopausal women treated for breast cancer, but with decreased BMD in premenopausal women [7].

Recent data from the ATLAS and aTTom studies indicate a further reduction in recurrence and mortality for continuing tamoxifen to 10 years rather than stopping at 5 years [8,9]. A pooled analysis of the 17,477 patients enrolled in aTTom and ATLAS showed a 9% reduction in the risk of death for patients that received 10 vs. 5 years of tamoxifen for the follow-up period (RR 0.91, 95% CI [0.84, 0.97]; $p = 0.008$) with a relative risk reduction that increased to 16% starting at year 10 (RR 0.84, 95% CI [0.77, 0.93]; $p = 0.0007$).

ATLAS data mainly suggest favorable risk-benefits also for younger women although a limited number of young patients (19% aged < 45 years) were included in the study. Based upon these data, the recent ASCO clinical guidelines indicated that after 5 years, women who are pre- or perimenopausal should be candidate to receive tamoxifen for a total duration of 10 years [10].

It is also recommended that initial adjuvant endocrine therapy for premenopausal women with endocrine responsive disease should be tamoxifen for an initial duration of 5 years. However, the recently published results of the SOFT and TEXT trials questioned the use of tamoxifen alone in selected patient and introduced new treatment options in the therapeutic algorithm of premenopausal patents [11,12].

Ovarian function suppression (OFS) added to endocrine therapy

OFS is an effective adjuvant therapy in the absence of chemotherapy for patients with early breast cancer. Suppressed ovarian function as achieved by surgical castration or by irradiation of the ovaries was in fact the first adjuvant treatment studied in clinical trials focusing on premenopausal women [13,14]. An earlier report from the The Early Breast Cancer Trialists Collaborative Group (EBCTCG) indicated that ovarian ablation was associated with significant improvements in recurrence-free survival and in overall survival whether or not the nodes were involved [13]. The subsequent EBCTCG meta analysis included almost 8000 women younger than 50 years of age with estrogen receptor (ER)-positive or ER-unknown disease [5]. Patients were randomized into trials of ovarian ablation by surgery or irradiation (4317 women) or of ovarian suppression by a GnRH analog (3408 women). Overall, there was a beneficial effect of ovarian ablation or suppression both on recurrence and on breast cancer mortality.

OFS may represent a crucial treatment modality in younger women with ER-positive disease, where the endocrine effect of chemotherapy alone was shown to be inadequate. In a retrospective analysis of 3700 premenopausal patients involved in IBCSG trials I, II, V and VI patients treated with adjuvant cyclophosphamide, methotrexate, and fluorouracil chemotherapy alone, the failure to achieve chemotherapy-induced amenorrhea was associated with an increased risk of relapse [15]. Moreover, a large analysis on 7631 patients treated with chemotherapy alone showed a markedly increased risks of relapse for young patients with ER−positive tumors compared with older patients [1].

The incidence and impact of amenorrhea was studied in IBCSG Trial 13−93 that evaluated adjuvant tamoxifen in premenopausal patients with node positive disease [16]. The achievement of amenorrhea was significantly correlated with improved DFS for patients with endocrine responsive disease, in agreement with other studies showing a beneficial effect for chemotherapy induced amenorrhea in premenopausal patients with endocrine responsive disease [17,18].

Retrospective analysis suggested that the combination of LH−RH analog and tamoxifen might be superior to tamoxifen alone in younger patients. In particular the combination of LH−RH analog with tamoxifen was correlated with significantly improved DFS for very young patients (aged < 35 years) with Luminal B-like subtype, if compared with either tamoxifen or LH−RH analog alone, thus supporting a role for complete endocrine therapy in the adjuvant treatment of young premenopausal patients with selected subtypes of breast cancer [19].

The question of whether additional benefit can be obtained from ovarian suppression in premenopausal patients receiving tamoxifen has been addressed by the global Suppression of Ovarian Function Trial (SOFT). The SOFT Trial compared tamoxifen alone vs. ovarian function suppression plus tamoxifen vs. ovarian function suppression plus exemestane for patients with steroid hormone receptor−positive tumors who remain premenopausal after adjuvant chemotherapy or for whom tamoxifen alone is considered a reasonable treatment option. After a median of 67 months of follow-up, premenopausal population did not benefit from the addition of OFS [11]. Nevertheless for women at sufficient risk of recurrence to deserve adjuvant chemotherapy and who maintained pre-menopausal estradiol, addition of OFS to tamoxifen reduced the risk of recurrence.

This effect can be related to the clinico-pathological features that required prior chemotherapy use as well as the younger age of the women who remained premenopausal after chemotherapy (median age, 40 years). In the higher risk cohort of patients who remained premenopausal after chemotherapy, tamoxifen plus ovarian suppression obtained an absolute improvement of 4.5%, as compared with tamoxifen alone. In the same study, the combination of exemestane plus ovarian suppression showed an improvement of 7.7% as compared with tamoxifen alone [11].

Although controversy exists about the definition of “very young age” or “very young patients” and different cut-off have been proposed, it has been shown that younger age is associated with a more unfavorable prognosis [19]. In the SOFT study, among the women younger than 35 years of age, the rate of freedom from breast cancer at 5 years was 67.7% in patients that received tamoxifen alone, 78.9% in those that received OFS and tamoxifen and 83.4% those that were candidate to receive exemestane plus ovarian suppression. Therefore, these results support the role of ovarian suppression as adjunct to adjuvant treatment in younger premenopausal patients.

On the other hand, acceptance of endocrine therapies by young women with endocrine-responsive tumors remains a substantial issue [1]. It has been demonstrated that GnRH analogs are associated with more side effects than tamoxifen alone, therefore this therapeutic choice should be weighed against the evidence of benefit in this population [1]. In particular, previous studies showed that treatment with GnRH agonists is associated with frustrating menopausal side-effects such as weight gain, hot flushes and vaginal dryness [20].

In the SOFT study a different degree of adverse events was observed for the three endocrine treatment options. The addition of ovarian suppression to tamoxifen increased the frequency of adverse events including depression, menopausal symptoms, hypertension, diabetes, and osteoporosis if compared with tamoxifen alone. Within this trial, the combination of exemestane and ovarian suppression, resulted in increased sexual, musculoskeletal, and bone-density effects than with tamoxifen plus ovarian suppression [11].

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Aromatase inhibitors plus ovarian function suppression vs. tamoxifen plus OFS

Selected randomized large trials conducted in the adjuvant setting showed an improved outcome among postmenopausal women that received aromatase inhibitors (AIs) than among those treated with tamoxifen. In particular, five years of adjuvant endocrine therapy with AIs (anastrozole or letrozole) was found to significantly reduce the risk of relapse among postmenopausal women with endocrine responsive disease [21,22].

The activity of AI in the premenopausal setting was explored in ABCSG 12 trial [23]. The study evaluated the effect of adding zoledronic acid to a combination of either goserelin and tamoxifen or goserelin and anastrozole in 1803 women with endocrine-responsive early breast cancer. According to the results observed, treatment with anastrozole and treatment with tamoxifen combined with OFS for 3 years is associated with similar rates of disease-free survival. However, when results were analyzed after a longer follow-up, patients treated with anastrozole showed similar DFS but worse OS than those treated with tamoxifen, results possibly associated to systemic therapies received after disease recurrence [24].

Whether adjuvant AI improves outcomes in pre-menopausal women with hormone receptors (HR)-positive breast cancer treated with OFS was evaluated in two phase III, randomized clinical trials, the SOFT and TEXT trials. A joint analysis was recently conducted on these studies that enrolled 2672 (TEXT) and 3066 (SOFT) premenopausal women with HR-positive early breast cancer [12]. Adjuvant endocrine therapy with exemestane plus OFS significantly improved DFS, BCFI and DRFI vs. tamoxifen plus OFS. Treatment with exemestane reduced both local-regional/contralateral events and distant recurrence. In women who received chemotherapy, the absolute reduction in distant recurrence was 2.6% in TEXT and 3.4% in SOFT trial. The magnitude of the effect was therefore clinically significant with risk reductions observed similar to those seen for AI vs. tamoxifen in postmenopausal women.

The adverse events profile observed was comparable with postmenopausal women.

Adverse events that were more frequent with exemestane included fractures, musculoskeletal symptoms, vaginal dryness, decreased libido, and dyspareunia. Those effects more frequently reported with tamoxifen included thromboembolic events, hot flushes and night sweats. Adherence was very good in both arms, with only 14% of patients interrupting both treatments before 5 years. The incidence of targeted grade 3–4 adverse events was similar (31% and 29%) and early cessation of all assigned treatments was more frequent with exemestane plus OFS (16% vs. 11%). It is noteworthy that patient's self-report indicated differential effects, but overall QOL did not favor one treatment. These results support Exemestane plus OFS as a new treatment option for young women with hormone-sensitive breast cancer at the cost of higher incidence of selected side-effects.

Conclusions

Breast cancer in premenopausal patients includes heterogeneous groups of diseases and patients. On one side, there are patients with tumors at very low risk of relapse for whom there is little evidence in favor of prolonged endocrine therapy (i.e. special types of breast cancer such as tubular and cribriform with node negative disease); on the other side there are those with higher risk disease where prolonged combined endocrine therapy appear clearly justified.

Based upon recently available literature data, exemestane plus ovarian function suppression, tamoxifen plus ovarian function suppression or tamoxifen alone can be considered as proper adjuvant endocrine therapies in premenopausal patients. It should be acknowledged that a large group of patients do very well with adjuvant tamoxifen alone, thus representing a reasonable alternative, as well as the only economically feasible option in many circumstances. The combination of exemestane plus ovarian function suppression might be preferred in patients with higher risk of relapse. The slight advantage for the combination of tamoxifen plus ovarian function suppression vs. tamoxifen alone, indicate the former as reasonable for premenopausal patients who presented some adverse risk factor and no contraindications to OFS, in particular if very young.

Women with breast cancer and their physicians must weigh the risks and benefits of all therapeutic options. It is crucial to allow for patient preferences, pregnancies desire, family planning, and quality of life issues in defining the therapeutic algorithm. Selecting the best-tolerated agent that can enhance adherence and reduces the impact on quality of life and health status is key to improve the adjuvant treatment of the individual premenopausal patient with endocrine responsive disease.

Conflict of interest statement

We wish to confirm that there are no conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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