Adjuvant endocrine therapy in pre- and perimenopausal women with breast cancer: practice guidelines

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Oestrogen receptor positive early invasive breast cancer is a common disease in pre- and perimenopausal women. Adjuvant endocrine therapy is an essential part of its treatment. Until recently, premenopausal patients were uniformly treated with tamoxifen during five years. Given the recent publication of large clinical trials showing a benefit for other treatment regimens, the BSMO Breast Cancer Task Force met on the 6th of March, 2015, to propose common guidelines for adjuvant endocrine therapy for premenopausal patients. The members agreed that low-risk patients should be treated with five to ten years of tamoxifen, while the highest-risk patients should be treated with exemestane or tamoxifen plus ovarian function suppression. Special attention should be given to patients less than 35 years at diagnosis: in this subgroup, exemestane plus ovarian function suppression is preferred to tamoxifen plus ovarian function suppression.
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Introduction

Breast cancer is a common disease. In 2012 (latest available figures), 10,531 female breast cancer cases were diagnosed in Belgium. Among these, 2,079 were diagnosed before the age of 50 and 1,243 additional cases were diagnosed between the ages of 50 and 54. The exact number of premenopausal patients with oestrogen receptor positive early invasive breast cancer is unfortunately not known, but given these figures, we estimate that in Belgium, every year, between 2,000 and 3,000 women are diagnosed in this setting.

Endocrine therapy

Endocrine therapy has made significant progress in the last few years. Until recently, the standard adjuvant endocrine therapy for premenopausal breast cancer patients was limited to five years of tamoxifen.[1] The duration and the type of endocrine therapy have since then been refined.

Duration

Several recent studies, mainly in postmenopausal women, concluded that five extra years of endocrine therapy is superior to five years of adjuvant tamoxifen.

If premenopausal patients have become menopausal after the initial five years on tamoxifen, they benefit from extended adjuvant letrozole, which is reimbursed in Belgium for three years if lymph nodes are positive at diagnosis.[2]

If women remain premenopausal after five years on tamoxifen, two studies concluded that the new standard duration of tamoxifen should be ten instead of

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five years. ATLAS and aTTom included premenopausal women without breast cancer relapse five years after the diagnosis.

In the ATLAS study, 12,894 women with early breast cancer were randomised to stop taking tamoxifen after five years or to continue taking the drug for an additional five years.[3] Oestrogen receptor positive patients who took tamoxifen for ten years had an absolute mortality reduction of 2.8% during years five to fourteen, as compared to patients who had taken tamoxifen for only five years. Unfortunately, in the ATLAS study, less than 10% of the included patients were premenopausal at study entry. In this subgroup, while the ratio of annual breast cancer events was lower in the cohort of patients who took tamoxifen for ten years instead of five years (0.81), this risk reduction was not statistically significant due to the low number of premenopausal patients. The encouraging results of the ATLAS study were confirmed in the aTTom trial.[4] In both trials, the differences between the two treatment groups became apparent after year ten. The benefit of extended tamoxifen therapy should be balanced with the increased risk of a thromboembolic event and increased incidence of endometrial cancer; it should however be noted that the risk of these complications is lower in pre- than in postmenopausal patients.

Ovarian function suppression

The question of the usefulness of ovarian function suppression (OFS) was studied in the SOFT and E3193 trials. In the SOFT trial, 3,066 premenopausal breast cancer patients were randomly assigned to five years of tamoxifen, five years of tamoxifen plus OFS or five years of exemestane plus OFS.[5] The primary endpoint, disease-free survival (DFS), was not significantly improved with the addition of OFS to tamoxifen ($p=0.10$). However, the secondary endpoint 'five-years breast cancer free interval' (BCFI) showed a 4.5% absolute improvement in the patients who remained premenopausal after chemotherapy and an 11.2% absolute improvement in the patients who were younger than 35 years of age at diagnosis (out of which 94% had received chemotherapy). The data on overall survival is not yet mature and longer follow-up is warranted. The E3193 trial on the other hand did not confirm a benefit from the addition of OFS to a standard regimen of five years of tamoxifen in premenopausal breast cancer patients.[6] This was probably due to a different patient population, with lower-risk features than in the SOFT trial ($T < 3$ cm, N0, no chemotherapy). From these trials, we conclude that the biology and risk profile of the tumour drive the benefit of ovarian suppression; in other words, patients with low-risk features do not benefit from OFS, while patients who exhibit sufficient risk for recurrence probably do benefit.

Aromatase inhibitors

The role of aromatase inhibitors (AIs) in premenopausal early breast cancer patients treated with OFS was addressed in the ABCSG-12, SOFT and TEXT trials.

In the ABCSG-12 trial, 1,803 patients treated with goserelin after primary surgery for endocrine receptor positive breast cancer were randomly assigned to tamoxifen or anastrozole, both with or without zoledronic acid.[7] In this trial, the total duration of the adjuvant treatment was limited to three years. Patients' characteristics were very favourable, with a median age at diagnosis of 45 years, 75% of T1 tumours, 66% of N0 status, and 75% of grade 1 or 2 tumours. Only 5% of patients had received chemotherapy, all in the neoadjuvant setting. In this low-risk population, there was no difference in DFS between the tamoxifen and anastrozole groups, but there was actually a higher risk of death in the group of patients treated with an AI. In this population, the addition of zoledronic acid did not significantly reduce the risk of disease progression or death.

Conversely, in premenopausal patients treated with OFS, the combined analysis of the SOFT and TEXT trials showed a significant benefit for the use of an AI, as compared to tamoxifen. This analysis covered the outcomes of 4,690 patients randomly assigned to five years of adjuvant tamoxifen plus OFS versus exemestane plus OFS.[8] After a median follow-up of 68 months, although there was no statistically significant difference in overall survival between both groups, there was a clear advantage for the AI group in terms of DFS (91.1% versus 87.3%, HR 0.72, $p<0.001$), rate of freedom from breast cancer at five years (92.8% versus 88.8%, HR 0.66, $p<0.001$) and rate of freedom from recurrence of breast cancer at a distant site at five years (93.8% versus 92.0%, HR 0.78, $p=0.02$). In the SOFT trial, the most striking difference was observed in women younger than 35: among the 233 patients included in the primary analysis, the rate of freedom from breast cancer at five years was 67.7% for patients treated with tamoxifen alone, 78.9% for those treated with tamoxifen plus OFS and 83.4% for those treated with exemestane plus OFS. The positive results from the SOFT/TEXT studies compared to the negative ABCSG-12 trial can probably be explained by the lower number of events in the ABC-

SG-12 trial, the suboptimal three year duration of therapy in the ABCSG-12 trial and the different patient populations across these studies. Patients in the ABCSG-12 trial were at significantly lower risk of relapse than patients in the SOFT and TEXT trials, a difference that is mirrored by the lower number of patients requiring chemotherapy in the ABCSG-12 (5%) as compared to the SOFT/TEXT studies (57.4%). From these trials, we conclude that patients with low-risk features are less likely to benefit from aromatase inhibitors, while patients who exhibit sufficient risk for recurrence probably do benefit.

Quality of life and drug tolerance

Treatment-emergent adverse events are of major concern, as they negatively impact quality of life and may lead to early treatment discontinuation.

In the SOFT trial, patients receiving tamoxifen plus OFS experienced worse endocrine symptoms and sexual functioning than those receiving tamoxifen alone.[5] Most differences in symptoms between treatments were seen during the first two years of treatment and were no longer apparent at five years.

In the combined analysis of the SOFT and TEXT trials, grade 3 or 4 adverse events were seen in similar proportions in the group of patients treated with tamoxifen plus OFS and in the group of patients treated with exemestane plus OFS, at around 30%.[8] The most frequent were hot flushes, musculoskeletal symptoms, and hypertension. More than half of all patients reported symptoms of depression, with 4.1% of the patients reporting grade 3 or 4 depression. Patients treated in the exemestane plus OFS group were more frequently diagnosed with osteoporosis (13.2% versus 6.4%) and experienced more fractures, musculoskeletal symptoms, vaginal dryness, decreased libido, and dyspareunia, while thromboembolic events, hot flushes, sweating and urinary incontinence were reported more often in patients treated with tamoxifen plus OFS. Gynaecologic cancers were rare in both groups. In quality-of-life self-assessments, both groups reported similar changes in mood, physical well-being, and coping effort. There was more bone/joint pain, vaginal dryness and loss of sexual interest in the patients treated with exemestane plus OFS, whereas patients treated with tamoxifen plus OFS were more affected by hot flushes and vaginal discharge.

Premature treatment discontinuation is a major issue in the adjuvant treatment of early breast cancer. In the combined analysis of the SOFT and TEXT trials, 16.1% of the patients in the exemestane plus OFS group and 11.2% of those in the tamoxifen plus OFS group stopped treatment prematurely. Outside the setting of a clinical trial, the rate of treatment discontinuation might even be higher, especially in younger women. In a cohort study of breast cancer patients treated with adjuvant endocrine therapy, women younger than 40 years had the highest risk of discontinuation with only 68% patients remaining on therapy after 4.5 years and 72% of those who continued being fully adherent.[9]

Endocrine therapy and pregnancy

The recent and growing trend in developed countries to delay childbearing is leading to an increase in the number of premenopausal women who still have a child-wish at the time of breast cancer diagnosis. Recent retrospective data suggest that pregnancy after breast cancer does not negatively affect disease-free and overall survival, even in ER positive premenopausal patients.[10,11] Completion of endocrine therapy remains a difficult challenge in this population with reproductive plans. Despite the amount of retrospective data, no prospective evidence regarding the impact of a temporary interruption of endocrine therapy is available. The phase II POSITIVE trial will investigate up to two years interruption of endocrine therapy interruption - after at least eighteen and maximum 30 months - to enable conception for young women. Breast cancer recurrence and offspring outcomes will be the primary and secondary trial endpoints.[12]

Proposed guidelines

The decision to prescribe endocrine therapy and the choice of treatment regimen has a major impact on the long-term outcome of oestrogen-receptor positive breast cancer patients. Although these drugs have arguably less toxic side effects than cytotoxic drugs, the difficulty resides in the fact that patients have to take these medications continuously for several years. In addition, the long-term side effects of the addition of OFS are not known yet. The added benefit on disease-specific outcomes must therefore be weighed in light of the toxicity profile of each treatment regimen.

The Breast Cancer Task Force of the Belgian Society of Medical Oncology met on the 6th of March, 2015, to propose common guidelines for adjuvant endocrine therapy for premenopausal patients. The recommendations are as follows:

Low-risk patients

The participants agreed that tamoxifen for duration of

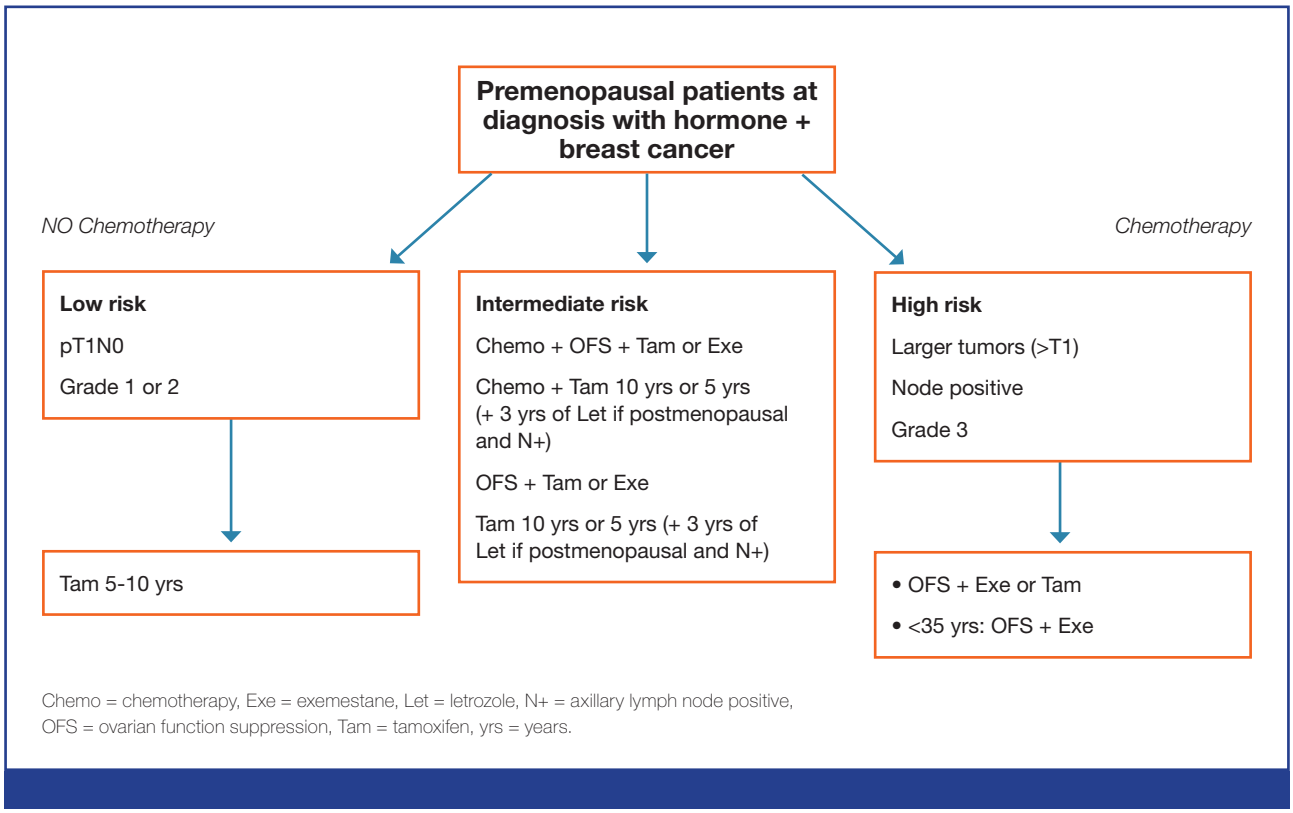

Figure 1. Algorithm for endocrine therapy in premenopausal women.

five to ten years remains the standard of care for patients with low-risk disease who do not require adjuvant chemotherapy.

High-risk patients

High-risk patients requiring adjuvant chemotherapy and who have persistent ovarian activity after chemotherapy should be treated with exemestane or tamoxifen plus OFS during the remaining period up to a total of five years. In patients younger than 35 years at diagnosis, exemestane plus OFS is the preferred combination. Unfortunately, in Belgium, the reimbursement of this regimen remains problematic, as goserelin is theoretically only reimbursed in patients as an alternative to chemotherapy (chapter IV § 470102) and exemestane is only reimbursed after two to three years of tamoxifen (chapter IV § 6570000). Tamoxifen is a reasonable option in case of intolerance to exemestane.

For patients younger than 35 years, exemestane plus OFS can be started immediately after the end of chemotherapy, independently from menses. OFS prior to the first chemotherapy course (as was done in the TEXT trial) can be discussed. This strategy has mainly been proven effective in protecting against ovarian failure in hormone receptor negative patients, but a recent meta-analysis suggests ovarian protection in all subtypes.[13,14]

In patients aged 36-44 years old who are amenorrheic after chemotherapy, and in whom chemotherapy-induced menopause is doubtful, tamoxifen monotherapy should be started, oestrogen levels should be checked regularly and treatment with exemestane or tamoxifen plus OFS should be started if oestrogen levels rise to premenopausal values. In the SOFT trial, this treatment could be started within eight months after the end of chemotherapy. In these patients, starting immediately with exemestane or tamoxifen + OFS is a reasonable option.

In patients aged 45 years and above who are amenorrheic after chemotherapy and who have low oestrogen and high FSH levels and thus a high chance of definitive chemotherapy-induced menopause, it is a reasonable option to start an aromatase inhibitor and to regularly follow oestrogen and FSH levels; contraception should be considered for these patients.

Intermediate-risk patients

In all other patients considered to have intermediate risk, various endocrine treatment options can be chosen: prolonged treatment with tamoxifen, exemestane plus OFS or tamoxifen plus OFS. In patients who become postmenopausal during the initial five years of tamoxifen and who had axillary lymph node involve-

Key messages for clinical practice

1. Adjuvant endocrine therapy is an essential part of the treatment of early stage oestrogen receptor positive breast cancer in premenopausal patients.
2. The type of endocrine therapy will depend on the risk features of the breast cancer and on age at diagnosis.
3. Low-risk patients will be treated with five to ten years of tamoxifen, while the highest-risk patients should be treated with exemestane or tamoxifen plus OFS.
4. Special attention should be given to patients less than 35 years at diagnosis: in this subgroup, exemestane plus OFS is preferred to tamoxifen plus OFS.

ment, treatment with letrozole during three years can be added after the initial five years of tamoxifen.

Additional points of discussion

Clinicians should take particular care in discussing endocrine treatment options with patients regarding potential benefits and different side effects. Endocrine treatment can be adjusted in case of intolerance.

The preferred method for OFS is a luteinizing hormone-releasing hormone (LHRH) agonist. Based on the data of SOFT and TEXT, the aim is five years of OFS. If the patient has a proven *BRCA1* or *BRCA2* mutation, a bilateral salpingo-oophorectomy can be considered unless the patient still wishes to get pregnant. In patients without a genetic predisposition, where definitive castration is desired, ovarian irradiation is also an option.

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