Adjuvant endocrine therapy options in hormone-dependent breast cancer

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Introduction

Approximately three quarters of all patients with invasive breast cancer are categorized as having hormone-responsive disease, i.e. the tumour cells express either estrogen receptors (ER) or progesterone receptors (PR) or both. Hormone-sensitive disease differs from hormone-unresponsive disease in terms of risk of recurrence, time to and site of recurrence, and growth rate of the disease. In addition to being a weak favourable prognostic factor, the expression of hormone receptors is a strong predictor of response to endocrine therapy in advanced breast cancer, and of the long-term efficacy of adjuvant endocrine interventions.

In this article, the present status of adjuvant endocrine treatment in both premenopausal and postmenopausal women will be summarized in light of ongoing clinical trials and emerging new data.

Premenopausal setting

The area of adjuvant endocrine therapy in premenopausal women is particularly complex because the use of adjuvant chemotherapy, leading to ovarian dysfunction in a large proportion of women, is an important confounding factor when analysing the effects of endocrine interventions. In addition, many trials studying premenopausal breast cancer patients have included women with both hormone-receptor positive and negative disease, and numerous studies have been small and underpowered.

When summarising the currently available data on adjuvant endocrine treatment in premenopausal women, several issues have to be considered.

First, in women treated with both chemotherapy and endocrine therapy, the specific effects of each of these treatments alone are uncertain. However, the majority of younger women with breast cancer are offered chemotherapy, making it difficult to estimate the contribution of each of the therapies on the treatment results.

Second, in women treated with ovarian function suppression (OFS), the best type and optimal duration of adjuvant therapy is still unclear, even more so when OFS is combined with other endocrine interventions, such as selective estrogen receptor modulators (SERMs), selective estrogen receptor downregulators (SERDs) or aromatase inhibitors (AIs).

Third, in premenopausal women there is an increased effectiveness of endocrine therapies with increasing concentrations of steroid receptors on the tumour cells [1–3]. However, in many studies, an arbitrary cut-off for ER and PR expression was used, which may have led to a dilution of the effect of endocrine treatments on highly hormone-sensitive disease. In future, the proper selection of patients with hormone-sensitive disease for treatment and for clinical trials will be important. It is recommended to use immunohistochemistry to determine ER and PR overexpression, and to report the results quantitatively instead of using a cut-off [4,5].

Ovarian function suppression

The use of ovarian ablation for the treatment of breast cancer goes back to the 19th century, when A. Schinzinger [6] and G. Beatson [7] produced remissions in premenopausal patients with advanced breast cancer. The first randomized trials of OFS in the adjuvant setting were started in 1948. Finally, in 1996, it was firmly established by the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), that OFS leads to a significant improvement in relapse-free and overall survival in women under 50 years of age [3].

Methods of ovarian function suppression

There are three known methods of OFS. The first form of OFS that was tested in clinical trials was surgical oophorectomy. The advantage of this method

is that it also reduces the risk of ovarian cancer in predisposed women. However, as every with form of surgery, surgical oophorectomy is associated with a certain, though small, perioperative morbidity and mortality. Radiation-induced OFS is a safe method, but it may be incomplete and OFS may be delayed in some women [8]. Both surgical and radiation-induced OFS have the disadvantage of being irreversible.

In contrast, suppressing ovarian hormone production by gonadotropin-releasing hormone (GnRH) agonists has the great advantage of being safe and reversible [8,9]. The response rates are similar to oophorectomy [9]. Currently, there is no systematic comparison among the three forms of OFS. Because of its obvious advantages, the use of GnRH agonists is the preferred method of OFS used today.

Owing to its ability to suppress ovarian function in some women, chemotherapy can also be seen as a form of ovarian ablation. In premenopausal women, the effects of chemotherapy are due to two different effects: direct cytotoxicity on tumour cells, and ovarian failure [10]. However, the extent of the endocrine effect of chemotherapy is unknown. The risk of chemotherapy-induced ovarian failure is age related [11]. Overall, less than 50% of women under the age of 40 will become postmenopausal due to chemotherapy. In contrast, most women aged 40 years or older will be rendered postmenopausal by chemotherapy. The rate of chemotherapy-induced amenorrhea is also dependent on the kind of chemotherapy used, ranging from approximately 40% after four cycles of AC, to up to 70% after six cycles of oral cyclophosphamide, methotrexate and fluorouracil (CMF) [12].

Efficacy of ovarian function suppression as monotherapy

The efficacy of adjuvant OFS in women less than 50 years of age has been established by the EBCTCG meta-analysis of 1996 [3]. It was shown that OFS significantly improves recurrence-free and overall survival compared to controls. In this meta-analysis, 12 of the 13 trials of OFS by irradiation or surgery, but no study on OFS by drugs, was included. As menopausal status had not been consistently assessed in the trials included, the main analysis was confined to women of less than 50 years. Women of 50 years or older did not profit from OFS. In the trials including chemotherapy, the effect of OFS was smaller, most probably due to endocrine effects of chemotherapy. As for ER status, less than 60% of all women included in the analysis had tumours known to be ER positive.

In several studies, OFS was compared to chemotherapy in premenopausal women. In particular, the Zoladex Early Breast Cancer Research Association and the IBCSG VIII studies compared goserelin with six cycles of CMF in node-positive and node-negative breast cancer patients, irrespective of ER status [13–15]. In ER-negative patients, CMF was superior to endocrine therapy, whereas in the ER-positive cohort, goserelin and CMF gave equivalent results. The latter finding was confirmed by the Scandinavian and the Takeda Adjuvant Breast Cancer Study [16,17]. When patients were grouped according to the rate of ER expression in the Scottish trial, it was shown that patients with tumours having high values of ER did better on endocrine treatment, whereas those with tumours expressing ER only weakly benefited more from chemotherapy [18].

SERMs and SERDs

The efficacy of the SERM tamoxifen in premenopausal and postmenopausal breast cancer patients was established in the EBCTCG meta-analysis of 1998 including 37,000 women [2]. It was shown that adjuvant treatment with five years of tamoxifen resulted in a reduction of 47% in disease recurrence, and a mortality reduction of 26% [2]. The benefit of tamoxifen was restricted to the group of women with ER-positive tumours. The relative benefit from tamoxifen was independent of axillary lymph node involvement, age, tamoxifen dose, menopausal status, or use of chemotherapy. In particular, tamoxifen given after chemotherapy to premenopausal women with hormone-responsive disease led to a risk reduction of 40% for recurrence and of 39% for mortality [2]. Therefore, tamoxifen is usually also recommended in this setting. Based on the EBCTCG data, the 2000 US National Institutes of Health Consensus Development Conference recommended the use of adjuvant tamoxifen therapy for women "regardless of age, menopausal status, involvement of axillary nodes, or tumour size." [19]

Apart from tamoxifen, no other SERMs, and no SERD have been tested in the adjuvant setting in premenopausal women.

Combined endocrine treatment

OFS plus tamoxifen

Several adjuvant studies have compared the use of OFS plus tamoxifen with chemotherapy. In premenopausal patients with ER-positive disease, the combination is safe and at least as effective as chemotherapy [20]. The question as to whether

Table 1
The adjuvant SOFT, TEXT and PERCHE trials

Trial name	Main inclusion criteria	Treatment arms[a]
SOFT: Suppression of Ovarian Function	Premenopausal after adjuvant chemotherapy	TAM for 5 years OFS + TAM for 5 years OFS + EXE for 5 years
TEXT: Tamoxifen and Exemestane Trial	Premenopausal Receive GnRH analogue	OFS (± CT) + TAM for 5 years OFS (± CT) + EXE for 5 years
PERCHE: Premenopausal Endocrine Responsive Chemotherapy Trial	Premenopausal Receive GnRH analogue	OFS + TAM/EXE for 5 years OFS + CT + TAM/EXE for 5 years

[a] TAM: tamoxifen; OFS: ovarian function suppression; CT: chemotherapy; EXE: exemestane.

chemotherapy is at all necessary in premenopausal patients with hormone-responsive disease is addressed in the ongoing PERCHE trial (Table 1). In this study, OFS plus chemotherapy, followed by tamoxifen or exemestane is compared to OFS plus tamoxifen or exemestane without chemotherapy. All patients in this trial must have hormone receptor positive tumours, and they must have premenopausal hormone levels confirmed within 12 weeks of primary surgery.

OFS plus aromatase inhibitors

AIs have recently brought about a significant change in the treatment of postmenopausal breast cancer patients. However, in premenopausal women, AIs are ineffective in suppressing ovarian hormone production, and in addition they may cause ovarian hyperstimulation [21]. Evidence that AIs are effective when combined with GnRH analogs in premenopausal women has been produced by a study using goserelin plus anastrozole following progression on goserelin plus tamoxifen in patients with advanced breast cancer [22]. The use of AIs combined with OFS with or without chemotherapy or tamoxifen will be investigated by the three ongoing SOFT, TEXT and PERCHE trials. The trial designs are shown in Table 1. SOFT addresses the question of whether OFS should be initiated in patients who remain premenopausal after completion of adjuvant chemotherapy and also additionally whether OFS plus exemestane is superior to OFS plus tamoxifen. TEXT will determine whether tamoxifen or exemestane is superior when combined with OFS prior to initiation of chemotherapy in premenopausal patients. Finally, PERCHE will help to tell whether the use of chemotherapy is necessary in premenopausal patients with hormone-sensitive disease who receive OFS plus tamoxifen or exemestane.

Endocrine treatment plus chemotherapy

It has been shown that chemotherapy, tamoxifen and OFS are all effective treatment modalities in premenopausal patients. However, little is known about their respective effects when the modalities are combined. In the IBCSG Trial VIII, pre- and perimenopausal breast cancer patients received either goserelin for two years, six cycles of CMF, or the chemotherapy followed by 18 months of goserelin [23]. Patients with ER-positive tumours had equivalent outcomes with goserelin and CMF. With the combined treatment, a non-significantly better outcome was achieved, presumably because OFS induced a more profound and longer duration of amenorrhea, particularly in younger women. As discussed above, the SOFT study is further investigating the question, whether it is necessary for patients who remain premenopausal after the completion of adjuvant chemotherapy to receive OFS, or whether tamoxifen alone is sufficient in this situation (Table 1).

Open issues

Duration of endocrine therapy

Based on the data from the EBCTCG overview from 1998, the currently recommended duration of tamoxifen use is five years in the adjuvant setting. In the overview, five years of tamoxifen therapy were better than one or two years of treatment, and the benefit from five years persisted through 10 years of follow-up. The question of whether even-longer tamoxifen treatment would be more beneficial was answered in part by the NSABP B-14 and the Scottish trials [24–26]. No trial was able to demonstrate a benefit from continuing tamoxifen beyond five years. The ongoing ATLAS (Adjuvant tamoxifen – longer against shorter) and aTTom (adjuvant Tamoxifen Treatment offer more?) studies, in which patients are randomized to five versus more than five years of adjuvant tamoxifen, will help to clarify the optimal duration of tamoxifen therapy but are not due to report for some time.

The studies evaluating OFS used varying treatment durations ranging from two to five years. Therefore, the optimal duration of OFS remains unclear. For the individual patient, a decision about treatment duration should be made considering tolerability and other factors such as family planning in younger women. Additionally the use of five years of OFS is justifiable in view of that duration being selected by the international community for the SOFT and TEXT trials

Inclusion of novel agents

As can be seen in Table 1, several important open issues concerning the treatment of hormone-responsive breast cancer in premenopausal patients are being addressed by the three ongoing SOFT, TEXT and PERCHE trials. In addition, the question of whether to combine endocrine treatments with one of the novel anticancer agents, in particular antibodies targeting the human epidermal growth factor receptor family or small molecule inhibitors, has to be addressed. Studies including these novel agents should be tailored to groups with hormone-responsive, non-responsive and weakly hormone-responsive disease. Furthermore, the type of endocrine therapy has to be considered. For example, there are concerns that the effectiveness of tamoxifen is diminished by HER-2 overexpression [27]. However, when tamoxifen is combined with OFS, it seems that the magnitude of the beneficial effect is greater in women with Her-2 overexpressing tumours [28]. Very recently, data from two trials employing trastuzumab, an antibody targeting Her-2, in the adjuvant situation were stopped early because the antibody significantly improved recurrence-free (HR 0.48, $p < 5 \times 10^{-12}$) and overall survival (HR 0.67, $p = 0.015$). Importantly, this effect was independent of menopausal status and of hormone receptor expression.

Postmenopausal setting

Tamoxifen

As discussed in the premenopausal section, the available data on the use of tamoxifen in the adjuvant setting of ER-positive breast cancer have been extensively reviewed by the EBCTCG [2,29,30]. The recommendations by the National Institute of Health (NIH) and the St. Gallen panel to use tamoxifen in the adjuvant setting of patients with ER-positive breast cancer apply to postmenopausal patients as well. In addition, AIs are increasingly becoming an important part of the treatment strategy in postmenopausal patients with ER-positive tumours.

Aromatase inhibitors

In contrast to SERMs, aromatase inhibitors work by blocking the enzyme complex responsible for the final step in estrogen synthesis, aromatase, thus preventing the production of the substrate of the ER. In postmenopausal women all of the third generation AIs suppress circulating estrogen levels by approximately 98% [31–33]. At least ten adjuvant trials with AIs including over 40,000 women with primary breast cancer are currently ongoing or have just been completed. The results of four of them have shown that the outcome of postmenopausal breast cancer patients with hormone-sensitive tumours can be improved if AIs are included in the adjuvant treatment strategy. However, it is still unclear, whether the inhibitors should be given within the first five postoperative years, or whether they should follow five years of tamoxifen, thus extending the overall treatment duration.

Several large trials are evaluating the use of AIs instead of tamoxifen or in combination or in sequence with tamoxifen during the first five post-operative years. Results from the first and largest of these studies, the ATAC trial (anastrozole, tamoxifen, and combined, $n = 9366$), were published in 2002 and updated in 2003 and at San Antonio in 2004 [34–37]. When anastrozole was compared to tamoxifen for five years, the AI led to improved disease-free survival (HR 0.87, $p = 0.005$) and time to recurrence (HR 0.79, $p = 0.0005$) after a median follow-up of 68 months [35, 37]. To date, there is no difference in the rates of death from any cause or of breast-cancer related deaths.

Based on the published results from ATAC, the 2003 St. Gallen consensus panel included in their recommendations the option of giving anastrozole to postmenopausal women in the adjuvant breast cancer setting, "if tamoxifen is contraindicated" [38]. A similar recommendation was published by the American Society of Clinical Oncology Technology assessment in 2002 [39]. In the updated position statement in 2005, the panel recommends that adjuvant hormonal therapy for postmenopausal woman with hormone receptor positive breast cancer should "include an AI as initial therapy or after treatment with tamoxifen. Treatment options include five years of AIs treatment or sequential therapy consisting of tamoxifen (for either two-to-three years or five years) followed by AIs for two-to-three years or five years." [40]

Data from a trial employing exemestane within the first five years after breast cancer diagnosis have

also been published [41]. In the IES trial (Intergroup Exemestane Study) 4742 women completing 2–3 years of adjuvant tamoxifen, were assigned to either tamoxifen or exemestane for the remainder of the five years. After a median follow-up of 30.6 months, the hazard ratio for breast cancer recurrence was 0.68 ($p < 0.001$) in favour of exemestane. No difference in survival has been noted yet, but as 90% of patients had completed their five years of therapy at the time of unblinding, assessing survival should be possible with longer follow-up.

BIGFEMTA is a large adjuvant study including the third inhibitor, letrozole, within the first five postoperative years. It is a four-arm trial comparing letrozole with tamoxifen for five years, but also including two additional arms with a cross-over design from tamoxifen to letrozole and vice versa. BIGFEMTA is still ongoing, but data on the comparison of tamoxifen versus letrozole have already been published [42]. After a median follow-up of 25.8 months, the HR for event-free survival was 0.81 ($p < 0.003$) in favour of letrozole translating into an absolute difference of 2.6%. Regarding breast cancer-free survival, the absolute difference was 3.4% in favour of letrozole ($p < 0.0002$). Unfortunately the other crucial question as to whether tamoxifen followed by letrozole is superior to letrozole alone is a secondary endpoint of the trial and the trial is not powered to answer this question specifically. It will also be some time before data from this analysis will be available. Among the other ongoing adjuvant AI studies evaluating a total of five years of adjuvant therapy, the ARNO (Arimidex versus Nolvadex) trial is of similar design to the exemestane study presented above. After two years of adjuvant tamoxifen, patients were randomized to either tamoxifen or anastrozole for the following three years. Two other ongoing exemestane studies are the TEAM study, comparing exemestane to tamoxifen for five years, and the EXEM 027 trial, in which exemestane or placebo were given for 2 years in very low-risk patients with ER-positive disease.

Results from the first, large study employing an AI after five years of tamoxifen, MA.17, have also been published [43]. The rationale for extending adjuvant therapy beyond five years is that approximately half of all breast cancer recurrences in women with ER-positive tumours taking five years of tamoxifen occur between 5 and 15 years after surgery, and that the risk of recurrence appears to continue indefinitely [2,29, 30]. In MA.17, after having completed 4.5–6 years of prior adjuvant tamoxifen, a total of 5187 women were randomized to five further years of letrozole 2.5 mg daily or placebo. After a median follow-up of 2.4 years, women on letrozole had a significantly superior disease-free survival (93% vs 87%, $p < 0.001$). Based on this interim analysis, the trial was terminated by the independent data and safety monitoring committee in order to offer women taking placebo an opportunity to take letrozole. There was a trend towards improved four-year overall survival for women on letrozole (96% vs 94%), but this was not statistically significant at the time of the first interim analysis.

In an Austrian trial with a similar design, ABCSG 6a, patients completing five years of adjuvant tamoxifen, either as monotherapy or combined with aminoglutethimide, were randomized to a further three years of anastrozole or placebo. Recently published data from this trial including 856 patients show that significantly fewer patients in the anastrozole group experienced disease recurrence compared with placebo (HR 0.64, $p < 0.05$).

The data from MA.17 and ABCSG 6a show that extending adjuvant endocrine therapy beyond five years with an AI offers significant benefit in disease-free survival. Currently, MA.17 patients who complete five years of letrozole are being re-randomized to a further five years or placebo. This will allow duration of efficacy and toxicity to be further evaluated. The second trial testing an AI after tamoxifen in the adjuvant setting was the NSABP B-33 study. This trial compared exemestane with placebo for five years after the standard five years of tamoxifen. Based on the results of MA.17, accrual to this trial was discontinued, the study medication unblinded and all participants taking placebo were offered exemestane.

In summary, a direct comparison of each of the three AIs for five years, versus tamoxifen for five years, is now available. In all three large trials, the AI was superior to tamoxifen. However, giving AI and tamoxifen sequentially might be even better. This strategy is being tested with all three inhibitors following two-to-three years of tamoxifen and data coming from the Intergroup Exemestane Study look promising. The inverse sequence, tamoxifen given after two-to-three years of an AI, will only be looked at in the BIGFEMTA trial with letrozole as mentioned above.

In future, it has to be clarified whether five or more years of an AI as an initial treatment are better than sequential treatment with tamoxifen followed by an AI, for five or more than five years. Important data pertaining to this issue will come from the still ongoing arms of BIGFEMTA, comparing the sequential use of tamoxifen and letrozole to letrozole only for five years. Very recently, Cuzick et al. published a model calculating recurrence rates up to 10 years for

a range of efficacy parameters [44]. It was shown that initial or early treatment with an AI dominates a strategy of using tamoxifen for five years initially for a wide range of parameters. It was concluded that using an AI as initial adjuvant treatment is thus a better option than switching patients to an inhibitor after two or more years of tamoxifen. In another mathematical model developed to predict the best adjuvant strategy, the opposite was concluded [45]. When patients were analyzed by receptor status of the primary tumour, sequential tamoxifen followed by an AI after two years appeared superior for ER and PR positive tumours, whereas upfront treatment with an AI yielded superior outcomes for ER-positive and PR-negative tumours.

Open issues

Comparison of aromatase inhibitors

Data on the comparison of different AIs are few. Letrozole was associated with a more profound suppression of aromatase than anastrozole in a small crossover study [46]. In a clinical trial in advanced disease after tamoxifen, letrozole was associated with a significantly better overall response rate (19.1% vs 12.3%, $p=0.014$), but was similar to anastrozole regarding the primary endpoint of time to progression and in several other response parameters [47]. Data comparing exemestane to any of the other inhibitors are not available. A large first-line international adjuvant trial is currently ongoing which compares anastrozole to exemestanes (MA.27).

Aromatase inhibitors used sequentially

Exemestane lead to clinical benefit in 24.3% of 241 patients with advanced breast cancer after failure of tamoxifen and a non-steroidal inhibitor [48]. This is the rationale for using the steroidal inhibitor after the non-steroidals anastrozole and letrozole in hormone-sensitive advanced disease. In a small study comparing various sequences of AIs no difference was seen in overall response and clinical benefit rates, implying that non-steroidal inhibitors can be used after exemestane as well [49]. A Spanish randomized cross-over study including 100 patients with metastatic breast cancer is currently evaluating the use of exemestane after anastrozole versus the opposite. There are no ongoing adjuvant studies exploring the sequence of two AIs.

Combination of agents

Tamoxifen plus aromatase inhibitors. The combination of tamoxifen and an AI in postmenopausal women has been evaluated in the adjuvant ATAC trial [34]. However, the combination arm was suspended when the combination was shown to be equivalent or worse than tamoxifen alone, and significantly worse than anastrozole. The reason for this finding might be that tamoxifen is more of an estrogen agonist in an estrogen-depleted environment. Thus, the use of a less agonistic SERM such as toremifene, or the use of a selective estrogen receptor downregulator such as fulvestrant, with an AI may achieve the intended "total estrogen blockade". Toremifene is currently being combined with an unregistered steroidal inhibitor, atamestane, in a trial comparing the combination to letrozole in women with locally advanced or metastatic breast cancer.

Conclusion

For endocrine-responsive and endocrine-uncertain breast cancer, endocrine therapy plays an important role as adjuvant therapy in pre- and postmenopausal women. The issue of the relative contribution of gain afforded to endocrine therapy is being addressed in the SOFT trial in premenopausal women. Furthermore, the question of whether aromatase inhibition in addition to OFS is superior to the addition of tamoxifen is also being explored in these trials. Their results are awaited with interest. Despite two mathematical models the relative benefit of AIs as initial therapy versus in-sequence with tamoxifen has not been answered for postmenopausal women. The BIG 1-98 trial will address that in part but may be inadequately powered to fully answer the question. Either way the implementation of AIs in both the pre- and postmenopausal setting is being established and is good news for women with early stage breast cancer.

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