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Extended adjuvant endocrine therapy in hormone-receptor positive early breast cancer: Current and future evidence

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ABSTRACT

The optimal duration and regimen of adjuvant hormonal therapy for premenopausal and postmenopausal patients with hormone receptor positive early breast cancer has not yet been established. This review will give an overview of published and ongoing studies concerning extended endocrine treatment. Most of the currently published studies are based on the adjuvant treatment regime of 5 years tamoxifen, which has been proven to be inferior compared to aromatase inhibitor (AI)-containing regimes. Therefore, until today, there is no clear evidence for the extension of endocrine therapy after upfront AI-based adjuvant treatment regimes. Multiple clinical trials, which will be discussed in this review, are ongoing to elucidate on this matter. We emphasize the need for tailoring of extended adjuvant endocrine treatment. The quest for predictive biomarkers, which are currently being investigated in the context of decision-making whether or not to start adjuvant chemotherapy, should be expanded to include the feasibility of extended endocrine treatment based on these markers. By tailoring the extension of endocrine treatment, overtreatment, side effects and unnecessary costs will be prevented.

Introduction

Nowadays, endocrine treatment is one of the mainstays of breast cancer treatment, but the optimal duration is yet to be determined. It is estimated that 75% of all breast cancer patients are hormone receptor-positive (HR+) breast cancer, and therefore might benefit from endocrine treatment [1]. Endocrine therapy significantly reduced the risk of death among patients with HR-positive tumors compared to those with ER and PgR-negative tumors. Five years of adjuvant tamoxifen reduced the breast cancer mortality by about a third throughout the first 15 years [2]. However, estimations for the long term risk of recurrence show that HR-positive breast cancer patients remain at a significant risk of recurrence until at least 15 years post diagnosis, whereas the risk for recurrence for ER/PgR negative patients is highest shortly after diagnosis but decreases below that of ER/PgR positive patients later on [2,3]. There is scientific evidence that it is beneficial to use extended tamoxifen after 5 years of adjuvant tamoxifen [4,5] and to start using an aromatase inhibitor after having received tamoxifen for 5 years, even if tamoxifen was stopped a considerable time ago [6].

Adjuvant endocrine therapy

Ever since the first oophorectomy performed by Dr. Beatson in 1896 [7], endocrine therapy has been established as a treatment option for HR+ breast cancer. Currently, tamoxifen and aromatase inhibitors (AIs) are the two most important categories for endocrine treatment in postmenopausal patients. A third category of endocrine therapy, ovarian function suppression (OFS by GnRH agonists, ablation or radiotherapy) is used in premenopausal patients to diminish the ovarian function in combination with tamoxifen or AIs [8].

After its introduction in 1970, the selective estrogen receptor antagonist tamoxifen soon became standard therapy in the treatment of advanced hormone receptor-positive breast cancer [9]. Initially, treatment was based on 1–2 year strategies as this was the optimal duration in advanced disease [9,10]. However, it became clear that 5 year adjuvant treatment improved the clinical outcome, and for decades this has been the standard treatment for hormone receptor-positive breast cancer [11–13]. Five years of adjuvant treatment with tamoxifen versus no treatment showed a relative risk reduction in 15 year recurrence risk of 40%, with an absolute gain of 13.2% [2]. Furthermore, a decrease of 15 year breast cancer mortality has been observed with a relative risk of 0.7, and an absolute benefit of 9.2%.

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While tamoxifen was introduced, the first AIs were developed and proven to be efficient in metastatic breast cancer patients [14]. However, due to its inhibitory function on cytochrome P450, its effects on adrenal function and subsequent side effects, the first and second generation AIs did not become mainstream treatment for adjuvant treatment, and were only used in separate cases of metastatic disease [14,15]. AIs only became popular after the development of third generation compounds (anastrozole, letrozole and exemestane) which are less toxic. The first report of these third generation AIs in the setting of a large clinical trial was in the Anastrozole, Tamoxifen Alone or in Combination (ATAC) trial, in which anastrozole, tamoxifen and a combination of both were studied [16]. At initial 5 and 10 years follow-up, this study showed the superiority of AIs over tamoxifen as a first line adjuvant treatment for early breast cancer in postmenopausal patients, and comparable results for the combination treatment [16–18]. After these findings, multiple trials examined the effect of switching to an AI compared to continuing with tamoxifen. A meta-analysis by Dowsett et al. in 2010 showed a superiority of this switch scheme above continuing with tamoxifen [19]. This switch scheme consists of 2–3 years of tamoxifen, followed by 2–3 years of an AI. Two other major trials, BIG 1-98 and TEAM-trial, initially focused on the same research question whether AIs would be superior to tamoxifen. However, due to the results that AIs appeared superior to tamoxifen, they changed their design into a comparison of five years AI with the before-mentioned switch scheme. Both studies showed a borderline non-significant progressive decrease of disease free survival (DFS) or recurrence free survival (RFS) in the initial 2–3 years of tamoxifen. However, after the switch to an AI, the difference between both groups stabilized leading to a non-significant difference between both groups [20,21]. Therefore there is no evidence for superiority of either 5 years AIs or a switch scheme at long term follow-up.

For premenopausal patients monotherapy with tamoxifen was the standard therapy for a long time with a possible benefit from ovarian suppression for patients of 40 year and younger [22,23]. Recently, the results of the TEXT and SOFT trial revealed that for premenopausal patients addition of ovarian function suppression should be considered for patients younger than 35 years (5 year breast cancer free interval of 67.7% for tamoxifen vs 78.9% for tamoxifen plus OFS and 83.4% for exemestane plus OFS) or who received chemotherapy (5 year breast cancer free interval 78% for tamoxifen vs 82.5% for tamoxifen plus OFS vs 85.7% for exemestane plus OFS [8].

Side effects of aromatase inhibitors are different from those of tamoxifen. Generally, tamoxifen is well tolerated, with most reported events to be hot flushes, osteoporosis, arthralgia and gynaecologic symptoms like vaginal bleeding and discharge [17]. More severe toxicities which have been described with the use of tamoxifen are venous thromboembolisms and a hazard ratio of approximately 2 for endometrial carcinomas and mood change or depression [24–28]. For aromatase inhibitors, hypertension, dyslipidaemia, arthralgia and osteoporosis are more frequently described. Gynaecological symptoms and hot flushes are less common [16,17,29–31]. Arthralgia is usually reported by patients as the most relevant side effect [29,32]. Generally, just as tamoxifen, aromatase inhibitors are relatively well tolerated. In designated trials comparing the switch scheme with aromatase inhibitors only, no important differences in side effects or quality of life were shown [33]. The TEAM trial showed that in general, there are more gynaecological and vascular side effects with the tamoxifen-containing switch scheme, while in the aromatase inhibitor group hypertension, dyslipidaemia and musculoskeletal complaints were more pronounced [20]. Similar results were observed in the BIG 1-98 study [21]. Therefore, regarding side effects and toxicity, therapy choices should be tailored on the individual patient taking co-morbidity and patients preference in consideration.

These findings have led to the conclusion that AIs should be included in the adjuvant treatment of early HR+ breast cancer in postmenopausal patients, and also in combination with ovarian suppression for premenopausal patients. However, there is no evidence for superiority of either 5 years aromatase inhibitors or a switch scheme of tamoxifen followed by an AI. This review will comment on the current evidence for therapy extension, ongoing studies and possible predictive markers suitable for decision-making concerning extended endocrine treatment.

Extended therapy

The current period of 5 or 10 years of adjuvant endocrine treatment for early breast cancer is based on early results of adjuvant tamoxifen [2,5,34]. However, it was shown that approximately 50% of recurrences happened after the initial 5 years of adjuvant treatment [2,35]. These findings initiated a debate on the optimal duration of therapy, and a number of studies was set up to elucidate on this matter.

The NCIC CTG MA.17 trial in 5187 patients showed that 10 years of treatment (5 years of tamoxifen followed by 5 years of letrozole) was superior to five years of tamoxifen [6]. After a median follow-up of 30 months, a hazard ratio of disease free survival of 0.58 was found, with a non-significant HR of 0.76 for overall survival. Upon these interim results the study was unblinded, and cross-over was allowed. However, with a 66% cross-over from the placebo to treatment arm, there was a significant loss of power for further follow-up. At 60 months of follow up, this has led to a HR for disease free survival of 0.68 (0.55–0.83), but no difference in overall survival (HR = 0.98). With a statistical test called the inverse probability of censoring weighted analysis (IPCW-analysis), they estimated that the HR for overall survival would have been 0.61 (0.52–0.71) without cross-over [6,36,37]. Although this was the first proof of principle for extended endocrine therapy, the interpretation of these findings is difficult. Starting five years of letrozole after 5 years of tamoxifen is basically the same strategy as the switch scheme described above, only with longer treatment intervals. It could be stated that this study confirms the benefits of a (late) switch scheme, rather than a general benefit for extended therapy. In 2006, Ingle et al. showed that the hazard ratios for disease free survival when using letrozole decreased over time, which was attributed to an increasing risk of recurrence in the placebo-controlled group [38]. These findings indicate a possible benefit for extending the treatment even further beyond the studied term of 5 years. Whether this also implies for patients who received up-front AI treatment is only supported by circumstantial evidence, and has not been studied yet.

Three other, smaller studies have confirmed the results of the MA.17 study (Table 1). The Austrian Breast and Colorectal Cancer Study Group (ABCSG)-6a study, had a similar setup in which 856 patients after 5 years of tamoxifen were randomized between 3 years of anastrozole or regular follow-up [39]. A reduction of 38% in the risk of breast cancer recurrence was observed (HR 0.62, 95% CI 0.4–0.96), which is in concordance with the MA.17 results. This study failed to show any benefit on overall survival, most likely due to the relative short follow-up of 5 years. Two other studies, both evaluating exemestane as extended therapy after 5 years of tamoxifen, were closed prematurely due to the results of the MA.17 trial [40,41]. One of them however published their underpowered results, already showing a borderline significant decrease in DFS at 30 months of follow-up [41]. A meta-analysis conducted with the four trials mentioned above, has led to an overall decrease in breast cancer recurrence of 43%