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Endocrine Therapy in Early Breast Cancer

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Keywords
Tamoxifen · Aromatase inhibitor · Extended endocrine therapy · Late recurrence · Ovarian function suppression · Chemotherapy-induced ovarian failure · Neoadjuvant endocrine therapy

Abstract
Background: Endocrine therapy with a standard duration of 5 years is well known as an effective treatment for endocrine-sensitive breast cancer. ***Summary:*** In the adjuvant setting this treatment reduces the 15-year mortality rates by about 30 and 40% with tamoxifen and aromatase inhibitor, respectively. The well-known long-term recurrence risk of luminal cancers led to multiple trials examining the benefit of extended endocrine treatment for up to 15 years. Additional benefit with extended therapy was seen for patients with high recurrence risk. Also, additional ovarian suppression for premenopausal women exhibited a significant benefit for patients at higher risk. ***Key Messages:*** The data of the last years will be summarized and discussed, also considering the side effects of the different treatment options.

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Introduction

The risk of dying from breast cancer in the USA and Europe has declined by more than one third in the past 4 decades, owing to a combination of early detection and improved therapy [1]. Estrogen is known as a key regulator of breast tissue growth and differentiation. About 75% off all breast cancers are estrogen receptor (ER) positive. The cellular effect works through binding and activating the nuclear ER. Activated, the receptors exhibit transcriptional and membrane localized signaling activities. The majority of breast cancers express ERα (70%), while ERβ is less well characterized. The potential role of estrogen in breast tissue was first noted by George T. Beatson. In 1895 he performed an oophorectomy on a premenopausal patient with unresectable breast cancer. She had complete remission and survived another 4 years. Research over the next decades lead to the discovery of tamoxifen in 1967 by Harper and Walpole [2]. Tamoxifen is a nonsteroidal antiestrogen recommended for adjuvant treatment of patients with ER-positive tumors since 1985. In 2005 the Early Breast Cancer Trialists' Cooperative Group (EBCTCG) [3] described that 5 years of adjuvant tamoxifen in patients with ER-positive breast cancer resulted in a reduction in the breast cancer mortality rate by 31% and was more effective than 1 or 2 years of tamoxifen therapy. In 2011 the follow-up meta-analysis showed that 5 years of adjuvant tamoxifen in patients with ER-positive breast cancer significantly reduced disease recurrence throughout the first 10 years and reduced breast cancer mortality by approximately one-third throughout the first 15 years [4]. Till today tamoxifen is important in the treatment of endocrine-sensitive breast cancer. In postmenopausal women, estrogen is no longer produced by ovarian tissue and is predominantly synthesized from nonglandular sources via aromatase. This enzyme can be found in a number of tissues including subcutaneous fat, liver, and muscle and has also been isolated from breast cancer cells [5–7]. The aromatase inhibitors (AIs) used today are third-generation AIs that have increased specificity for aromatase and are either steroidal (irreversible inhibition of enzymatic activity, type I) or nonsteroidal (reversible competitive inhibitors, type II). The approval studies for

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treatment of postmenopausal women with comparison of AIs versus tamoxifen were the ATAC-Trial (anastrozole) and the BIG 1-98-Trial (letrozole). In the ATAC Trial (9,366 patients) after a median follow-up of 68 months, anastrozole significantly improved disease-free survival (DFS) (575 vs. 651 events), time to recurrence (402 vs. 498), distant recurrences (324 vs. 375), and contralateral breast cancers (35 vs. 59) [8, 9].

In the BIG 1-98 Trial (letrozole, 8,010 patients) the letrozole group had an improved 5-year DFS rate compared to the tamoxifen group (84.0 and 81.4%, respectively) [10–13]. In 2015 a third meta-analysis of the EBCTCG described the additional benefit of AIs in comparison to tamoxifen. For postmenopausal patients the choice remains between different treatment regimens: AI monotherapy for 5 years, sequenced treatment with tamoxifen and AIs for 5 years, extended tamoxifen monotherapy for 10 years, or tamoxifen followed by extended AIs for 10 years. Their meta-analysis showed that 5-year adjuvant endocrine treatment including AIs was more effective than tamoxifen monotherapy in preventing recurrence and breast cancer death in either continuous or sequential regimens [14]. There are no data to support the preference of one of the available AIs for NST carcinomas. There might be a small benefit of anastrozole compared to exemestane for lobular carcinomas [15].

To further improve the outcome for patients with ER-pos/HER2-neg breast cancer the additional benefit of adjuvant chemotherapy, extended endocrine therapy (ET), ovarian suppression for premenopausal women, bisphosphonate treatment for postmenopausal women, as well as life-style factors and new substances such as CDK4/6 inhibitors should be considered. To evaluate the absolute treatment benefit the risk of recurrence needs to be assessed. Today this is estimated by a combination of tumor extension, tumor biology, age, and patient conditions. Gene expression profiling is one helpful additional factor for defining risk [16]. There are different tests to define the prognosis in luminal breast carcinomas and to support the decision making in respect of additional chemotherapy [17]. Those tests might also be helpful to estimate the risk of late recurrence.

The Risk of Late Recurrence

Hormone receptor-positive breast cancers are characterized by a risk of late recurrence for years. Recurrences occur at a steady rate throughout the period from 5 to 20 years, strongly correlated with the original tumor and nodal status and the tumor grade. At least 50% of recurrences occur more than 5 years after diagnosis. The long-term risk of recurrence is about 1–2% per year. Estimating the risk of recurrence accurately is important because if the risk is low, even the most effective adjuvant therapy can only result in limited overall improvement. In an analysis by Pan et al. [18], after 5 years of ET for patients with stage T1 disease the risk of distant recurrence in the period from 5 to 20 years was 13% for N0, 20% with N1–3 status, and 34% with N4–9 status. Among T2 tumors, the risks were 19, 26, and 41%, respectively. Considering the impact of grade among patients with T1 N0 disease, the risk of distant recurrence was 10% for low-grade and 17% for high-grade disease. An EBCTCG analysis on this question presented by Pan et al. [19] showed an improved outcome for patients after only 5 years of ET diagnosed after the year 2000 in comparison with diagnosis of breast cancer before the year 2000. Possible explanations for the 25% reduction of distant recurrences in years 5–9 are the detection of lower-risk lesions by early detection and screening, an improved compliance to treatment and treatment guidelines, and real treatment improvements.

Extended Endocrine Treatment

Results of several randomized trials suggest that extending adjuvant endocrine treatment beyond 5 years can improve DFS. The ATLAS (Adjuvant Tamoxifen – Longer Against Shorter) trial (n = 6,846) demonstrated that extending tamoxifen to 10 years significantly reduced breast cancer recurrence (617 vs. 711 events), breast cancer mortality (331 vs. 397 deaths), and overall mortality (639 vs. 722 deaths) [20]. However, the absolute benefit was small and extended treatment was not without adverse effects. A total of 3,428 patients were treated for 10 years with tamoxifen to avoid 66 breast cancer deaths (so the number needed to treat was 52 to avoid one death), while 53 extra endometrial cancers and 20 extra pulmonary emboli were observed in the treatment group. Confirming these data, the aTTOM trial showed continuing tamoxifen to year 10 produced a reduction in recurrence (580/3,468 vs. 678/3,485; p = 0.003) from year 7 onward [21].

Trials investigating the use of AIs after 5 years of tamoxifen treatment – ABCSG-6a (anastrozol), MA.17 (letrozol), NSABP B33 (exemestane) – all showed a benefit of 5 years of AI treatment after an initial 5 years of tamoxifen in DFS [22–24]. For example, the early interim analysis MA.17 trial (n = 1,918) after a median of 2.5 years of follow-up showed that treatment with letrozole after 5 years of tamoxifen therapy improved DFS (95 vs. 91%; p = 0.01; HR 0.58). There was also an improvement in overall survival (OS), but this was not statistically significant because after unblinding 60% of placebo patients crossed over to letrozole [25] Goss et al. [26] presented an evaluation of the MA.17 study which showed that perimenopausal patients who entered the study after 5 years

Table 1. Endocrine treatment of early breast cancer

Menopausal status at time of diagnosis	Type of endocrine therapy	Reasons for therapy selection	Extended therapy: considerations	Type of extended therapy
Postmenopausal	AI (5 years)	High risk of early relapse History of thromboembolic disease Depression	No significant OS benefit Shared decision making if N2, N3, and AI well tolerated	AI (2 years)
	AI (2–3 years) -> Tam (2–3 years)	Higher risk Relevant cardiovascular disease	High risk, e.g., N2, N3, and treatment well tolerated	AI (2–5 years) or Tam (2–5 years)
	Tam (2–3 years) -> AI (2–3 years)	Intermediate risk Osteopenia/osteoporosis Relevant cardiovascular disease	High risk, e.g., N2, N3, and treatment well tolerated	AI (2–5 years) or Tam (2–5 years)
	Tam (5 years)	Low risk	Higher risk	AI (2–5 years) or Tam (5 years)
Peri- and Premenopausal	Tam (5 years)	Low and intermediate risk	Intermediate risk	Tam (5 years) or AI (2–5 years) if postmenopausal[a]
	Tam (5 years) + OFS (2–5 years)	<35 years or becoming premenopausal during the 2 years following chemotherapy	High risk	Tam (5 years) or AI (5 years) if postmenopausal[a]
	OFS (up to 5 years)	Tam contraindicated and low risk	–	–
	AI + OFS (5 years)	Tam contraindicated and intermediate or high risk	–	–

AI, aromatase inhibitor; Tam, tamoxifen; OFS, ovarian function suppression; COF, chemotherapy-induced ovarian failure. [a] Testing of E2/FSH after COF repeatedly before and during treatment. Treat osteopenia and osteoporosis according to guidelines; consider bisphosphonate oral or intravenous in osteoprotective dosage for patients (1) more than 5 years after menopause or (2) during therapy with AI or OFS.

of tamoxifen had the largest DFS benefit (HR 0.26; p = 0.0003).

The NSABP (National Surgical Adjuvant Breast and Bowel Project) B-42 trial (n = 3,923) compared 5 years of ET including an AI versus 5 additional years of letrozole and showed a 3% nonsignificant improvement in DFS (84 vs. 81%; HR 0.85) and a significant 28% reduction in distant recurrence (3.9 vs. 5.8%; HR 0.72) [27]. Thus, approximately 2,000 patients were treated to observe a 2% decrease in metastatic recurrence, while the risk of osteoporosis increased. The DATA trial (n = 1,912) compared 3 versus 6 years of anastrozole therapy after 2–3 years of tamoxifen therapy. Only in subgroup analysis of women with high-risk tumors was extended ET associated with an improved DFS. For instance, in women with node-positive disease, 5-year DFS was 84% in the 6-year group versus 76% in the 3-year group (HR 0.64); and 83 versus 69% if they also had a larger tumor size (≥T2; HR 0.53) [28]. The IDEAL trial investigated the use of 2.5 versus 5 years of letrozole after an initial 5 years of endocrine treatment. The initial treatment could either be tamoxifen monotherapy, AI monotherapy, or a sequential regimen. Regardless of the initial treatment regimen, no statistically significant benefit in DFS and OS was found for 5 years of extended letrozole treatment in comparison to an extended 2.5 years of AI treatment [29]. The AERAS trial (n = 1,697) compared 5 versus 10 years of anastrozole therapy and demonstrated improved DFS (91.9 vs. 84.4%; HR 0.548; $p < 0.001$) and distant metastasis-free survival (97.2 vs. 94.3%; HR, 0.514; p = 0.0077) with extended therapy in Asian women [30]. A different approach was tested in the SOLE trial. Here the hypothesis was tested that endocrine resistance to AI could be reversed by withdrawal and reintroduction. Postmenopausal women previously treated with 5 years of endocrine treatment were randomized to 5 years of intermittent letrozole or continuous letrozole. Intermittent letrozole use did not improve DFS compared with continuous letrozole use (HR 1.08). Adverse events were reported as expected and were similar between the 2 groups, including arthralgias [31]. An EBCTCG meta-analysis presented at SABCS 2018 by Gray showed a 33% risk reduction for any recurrence with extended AI therapy after approximately 5 years of tamoxifen, corresponding to a 5-year gain of 3.6% ($p <$ 0.00001); a 23% reduction in the risk of distant recurrence, with a 5-year gain of 1.5% (p = 0.008); and a 23% reduction in breast cancer mortality, with a 5-year gain of 0.8% (p = 0.05), respectively [32]. However, no reduction

in breast cancer mortality could be found for extended AI therapy after 5 years of an AI alone or after extended therapy with tamoxifen. Recent meta-analyses including these trials showed that extended adjuvant ET with AIs beyond 5 years in postmenopausal women with early breast cancer reduced the occurrence of secondary breast tumors, but had no or only a small impact on distant metastasis-free survival as well as OS [33–36]; and the benefit of extended therapy with an AI was restricted to patients at high risk (node positive and/or large tumors) or after initial treatment with 5 years of tamoxifen alone. The ASCO guidelines recommend an extended adjuvant therapy only for high-risk patients with ER-positive disease [37]. The AGO 2020 recommends assessing the baseline risk profile of the disease as well as the wish of the patient after 5 years of experience with endocrine treatment and its side effects [38]. Extended treatment should be considered for patients with higher risks and good tolerance of the treatment so far (Table 1).

Prognostic Tools to Assess the Risk of Late Recurrence

The Clinical Treatment Score post 5 Years (CTS5) is a late-recurrence predictor that includes tumor size, the number of positive nodes, histologic grade, and age. The score was developed from the ATAC data and validated with the BIG 1-98 data set. The model is freely available at www.cts5-calculator.com [39]. The score is probably less reliable for premenopausal patients [40].

The molecular features of the individual breast cancer are used by the commercially available gene signatures which derive their prognostic power from quantifying proliferation and ER-related genes. Proliferation- and ER-associated gene expression also shows a time-dependent interaction with risk of recurrence. In tamoxifen-treated patients, low proliferation and low-ER signaling, quantified through mRNA expression, define a group of patients with continuously increasing risk of relapse over time, whereas cancers with high- proliferation and high-ER signaling show a low risk of early relapse but a high risk of late relapse [41].

In 2018, Sestak et al. [17] presented the comparison the of 6 multigene signatures: Oncotype Dx® RS, the Breast Cancer Index (BCI), the PAM50 Prosigna Risk of Recurrence (ROR) score, EndoPredict (EPclin), Clinical Treatment Score, and 4-marker immunohistochemical score in women with early ER-positive breast cancer who were treated with ET for 5 years within the ATAC trial. Only ROR, BCI, and EPclin provided prognostic information for late recurrences between years 5 and 10. Patients with node-negative disease who were classified as low risk for late recurrence by the BCI, the ROR, and EpClin experienced a 3, 1, and 4% recurrence rate, respectively. Individuals classified as high risk experienced a 15, 23, and 15% recurrence rate, respectively, if they were node negative, and 36, 25, and 24% risk if they had 1–3 positive nodes.

However, having substantial risk for late recurrence does not automatically imply sensitivity to endocrine treatment and therefore a benefit from extended therapy. Currently, only the BCI assay reports predicted benefit to extended ET independent of risk of late recurrence. The BCI combines a 5-gene Molecular Grade Index that captures cell proliferation-related mRNA expression, and the *HOXB13* to *IL17BR* mRNA expression ratio (H:I) that informs about the likelihood of benefit from ET [42]. The prognostic value of the BCI was evaluated in several retrospective clinical studies including patients with none to 3 positive nodes [43–46]. The predictive value of the BCI was assessed on tissues from the MA.17 and the aTTom trial. High H:I ratio identified a subgroup of patients who benefitted significantly from extended therapy. The absolute risk reduction from extended ET for patients with high H:I was 16.5% (letrozole, MA.17 trial) and 10.2% (tamoxifen, aTTom trial) [47, 48].

The comparison of clinical and molecular risk estimation (CTS5- and BCI-predicted risk) in 119 patients with stage I or II, ER-positive breast cancer (85% of low-to-intermediate histologic grade; 78% node negative) showed classification with the BCI assay in 54% of patients as low risk (0–5% risk of recurrence in years 5–10) and 46% as high risk (>5% risk). The CTS5 predictor, using the same thresholds, categorized 61 and 39% of patients as low and high risk, respectively [49, 50].

Because clinical and molecular variables provide independent prognostic value, the most accurate prognostic predictions require combined clinical and molecular variable-based models; and molecular models might provide additional predictive value.

The CYP2D6 Discussion

Tamoxifen is considered a prodrug, because it binds to ER with a much lower affinity than 2 of its metabolites, 4-hydroxy tamoxifen and endoxifen [51]. The metabolism depends on the activity of CYP2D6, a hepatic enzyme. The variable metabolism of drugs based on CYP2D6 genotypes separates patients into metabolic phenotypes: poor, intermediate, extensive, and ultra-rapid. Although endoxifen levels are much reduced in patients who are poor CYP2D6 metabolizers, this metabolite is still present, albeit at low concentrations [52]. It is very likely that tumor levels of ER are saturated regardless of whether the parent drug is rapidly or poorly converted to endoxifen. Recently, a report from Swedish breast cancer

cohort registries linked to the Swedish Prescribed Drug Registry evaluated more than 1,300 patients assigned to take adjuvant tamoxifen. They found that discontinuation rates, presumably because of toxicity, were 7.2, 7.6, 6.7, and 18.8% among poor, intermediate, normal, and ultra-rapid CYP2D6 metabolizers, respectively, confirming previously published reports [53–55]. In addition, they observed a breast cancer-specific mortality, with highest rates in the poor and ultra-rapid metabolizer groups, which is rather difficult to explain. There are further studies without an association between endoxifen concentrations or CYP2D6 genotype and relapse-free survival in 667 pre- and postmenopausal patients taking adjuvant tamoxifen [56–58]. However, this is an ongoing controversy [59]. The large multicenter Tamendox trial is focusing on this issue by supplementing endoxifen to a regular tamoxifen therapy based on genotypical or phenotypical features. According to guidelines today the CYP2D6 genotype should not be used to guide ET for women with ER-positive early or metastatic breast cancer [38, 60, 61].

Ovarian Function Suppression for Premenopausal Patients

To optimize the endocrine treatment for premenopausal patients, ovarian function suppression (OFS) was tested in the SOFT and TEXT trials [62–65]. Premenopausal women were randomly assigned to receive 5 years of tamoxifen, tamoxifen plus OFS, or exemestane plus OFS in SOFT and to receive tamoxifen plus OFS or exemestane plus OFS in TEXT after chemotherapy. In SOFT, the 8-year DFS rate was 78.9% with tamoxifen alone, 83.2% with tamoxifen plus OFS, and 85.9% with exemestane plus OFS ($p = 0.009$ for tamoxifen alone vs. tamoxifen plus OFS). The 8-year rate of OS was 91.5% with tamoxifen alone, 93.3% with tamoxifen plus OFS, and 92.1% with exemestane plus OFS ($p = 0.01$ for tamoxifen alone vs. tamoxifen plus OFS).

Based on these findings the ASCO panel recommended that "higher-risk patients should receive ovarian function suppression in addition to adjuvant ET, whereas lower-risk patients should not" and that "ovarian function suppression may be administered with either tamoxifen or an aromatase inhibitor." Furthermore, the panel pointed out that "clinicians should be alert to the possibility of incomplete ovarian function suppression with gonadotropin-releasing hormone agonist therapy". The recommendations of the AGO-Mamma were more careful, also due to the results of the Austrian Breast Cancer Study Group-12 randomized trial (ABCSG-12) [66]. In this trial, premenopausal women with ER-positive, early-stage breast cancer were randomly assigned to anastrozole plus OFS or tamoxifen plus OFS with or without zoledronic acid for 3 years. After a median follow-up of 94.4 months, there was no difference in DFS between the anastrozole plus goserelin and tamoxifen plus goserelin groups (absolute DFS rate for anastrozole was 85.1 vs. 87.0% for tamoxifen (HR 1.13; $p = 0.335$). However, OS was worse with anastrozole plus goserelin compared with tamoxifen plus goserelin (absolute OS rate for anastrozole was 94.1% vs. 96.3% for tamoxifen; HR 1.63; $p = 0.03$) [66]. The discordant results for distant recurrence and OS are surprising, and the factors underlying this discordance are not clear but persistent [67]. The adequacy of estrogen suppression with gonadotropin-releasing hormone agonists in premenopausal women with early breast cancer has been questioned. If the combination is chosen, a frequent monitoring of adequate suppression of FSH and estradiol (E2) is mandatory. Due to different laboratory tests there is no absolute threshold for the E2 level. Taken together, these findings suggest that tamoxifen plus OFS represents a prudent approach for the management of premenopausal women with early-stage, ER-positive breast cancer at risk [67, 68]. A recent publication of an Asian trial ($n = 1,282$) confirms a DFS benefit of tamoxifen in combination with OFS for women aged <45 years who are premenopausal within 2 years after chemotherapy [69]. The estimated 5-year DFS rate was 91.1% in the tamoxifen + OFS group and 87.5% in the tamoxifen-only group (HR 0.69; 95% CI 0.48–0.97; $p = 0.033$). The estimated 5-year OS rate was 99.4% in the tamoxifen + OFS group and 97.8% in the tamoxifen-only group (HR, 0.31; 95% CI 0.10–0.94; $p = 0.029$).

OFS can be initiated concurrently with or after chemotherapy [65]. Starting before chemotherapy supports fertility preservation [70, 71].

Even if there are no data the AGO-Mamma recommends an extended treatment with another 5 years of tamoxifen after 5 years of tamoxifen plus OFS for premenopausal women at risk (Table 1).

AI in Women with Chemotherapy-Induced Ovarian Failure

Chemotherapy-induced ovarian failure (COF) must not guide a treatment decision in the direction of an AI even after 2–3 years of tamoxifen. van Hellemond et al. [72] reported an analysis of endocrine data of 329 DATA study participants with COF. In the DATA study all patients had taken tamoxifen prior to anastrozole for 2–3 years. These patients had a median age of 50 years (range 45–57 years). Thirty-nine patients (12.4%) developed ovarian function recovery (OFR) under treatment with AI. Of these, 11 (28.2%) were aged 50 years or older at AI initiation. The estradiol level decreased statistically sig-

nificantly for all women under AI treatment. However, the estradiol levels in the women who experienced OFR remained higher prior to OFR diagnosis compared with those who did not experience OFR. The 30-month OFR was 5.1% for patients aged 50 years or older vs. 25.2% for patients younger than 50 years. The results are in line with earlier smaller studies which described OFR rates of about 30% under treatment with AI in women with COF.

Side Effects of Endocrine Treatment

The main side effects of tamoxifen and AIs are partially different [73]. Menopausal symptoms such as sleeping disorders, vaginal dryness, and loss of sexual interest are characteristic for both treatments. The risk of venous thromboembolic events, endometrial cancer, depression, and hot flashes are dominant in patients treated with tamoxifen. With AI a decrease in bone mineral density, a higher risk of osteoporotic fractures, and musculoskeletal symptoms (arthralgia and myalgia) were observed more often. Assessments of side effects were also consistent with a higher risk of vascular diseases such as myocardial infarction and angina in AI users compared with tamoxifen users, but there was also a suggestion that this may be partly driven by a protective effect of tamoxifen on these outcomes [74]. In the SOFT trial thrombosis or embolism were reported in 2% of the patients with tamoxifen, and grade 3–4 musculoskeletal symptoms in about 6% of patients with tamoxifen and in 11.4% of the AI group. Osteoporosis (T-score <–2.5) was seen in 3.9, 7.2, and 14.8% of patients with treatment of tamoxifen, tamoxifen combined with ovarian suppression, and exemestane combined with OFS, respectively [75, 76].

In a meta-analysis of 21 studies (13,177 participants) prevalence rates of musculoskeletal symptoms ranged from 20 to 70%. Another meta-analysis including 7 trials comprising 16,349 patients analyzed the reported toxicity of extended endocrine treatment with AIs [77]. Longer treatment with AIs was associated with increased odds of cardiovascular events (OR 1.18; $p = 0.05$, number needed to harm = 122), bone fractures (OR 1.34, $p = 0.001$, number needed to harm = 72). Extended use of AIs did not influence the odds of a second malignancy (OR 0.93), but a numerical excess of deaths without breast cancer recurrence was found with prolonged AI (OR 1.11; $p = 0.34$).

Compliance is an important issue in adjuvant ET in general because it influences the efficacy. An analysis of the BIG 1-98 trial looked at treatment adherence and its impact on DFS in patients on tamoxifen, letrozole, or a sequential regimen for 5 years [78]. Both early cessation and a low compliance score were associated with a reduced DFS. Sequential treatments were associated with higher rates of nonpersistence (tamoxifen-letrozole, 20.8%; letrozole-tamoxifen, 20.3%; tamoxifen 16.9%; letrozole 17.6%). In 82.7% of patients, adverse events were the reason for discontinuation. Other studies showed that younger age is a predictor of premature discontinuation of tamoxifen [79]. For both tamoxifen and AIs, the probability of early termination increases with a longer treatment duration: about 15% discontinuation during the first year of treatment, which increased to up to 45% at 5 years [80].

Definition of Endocrine-Sensitive Tumors

ER positivity and therefore endocrine responsiveness is assumed for tumors with >1% ER-positive tumor cells. However, the ER low-positive group is characterized molecularly by having features of triple-negative breast cancer in the majority of cases as basal-like phenotype, high incidence of germline BRCA mutation, and high-risk score by Oncotype DX®. Also, distant DFS is similar to triple-negative breast cancer in these cases. Therefore, a low threshold of 1% for ER positivity may include clinically insignificant ER expression and may lead to the false categorization of biologically ER-negative tumors as positive ones [81, 82]. In these patients, adjuvant chemotherapy is usually indicated. The exclusive use of IHC scores is discouraged [82].

CDK4/6 Inhibition in Early-Stage ER-Positive Breast Cancer

The exciting results observed with CDK4/6 inhibitors in the treatment of advanced ER-positive, HER2-negative breast cancer [83] have triggered the evaluation of these agents in the early-stage setting. For example, results of a neoadjuvant therapy setting were presented by Dowsett et al. [84] from the PALLET study. In this study, palbociclib was given in addition to 3 months of the AI letrozole. It was shown that the antiproliferative effect of the AI is substantially increased by palbociclib. The percentage of tumors which underwent a complete cell cycle arrest in the form of a Ki-67 value <2.7% during neoadjuvant therapy was able to be increased through the addition of palbociclib from 58.5 to 90.4%. In the (post-neo) adjuvant setting the PALLAS study has included 4,600 patients with stage II and III breast cancer and randomized between standard endocrine treatment +/– palbociclib. Comparable study concepts exist for abemaciclib (monarchE study) and ribociclib (EarLEE-1, NataLEE).

The ADAPTcycle study follows a different approach: the comparison of ET plus ribociclib versus standard chemotherapy in intermediate-risk ER+/HER2– early breast cancer.

Results are eagerly awaited to establish new treatment options for early luminal B breast cancers.

Neoadjuvant Endocrine Therapy

Neoadjuvant endocrine therapy (NET) has a well-established role in senior patients with ER-sensitive breast cancer for whom surgery is not indicated or should be delayed [85]. In the neoadjuvant setting of postmenopausal disease AIs are more effective than tamoxifen with response rates of about 60% and an improved breast conservation rate [86, 87]. For postmenopausal patients with low-risk ER-positive early breast cancer who want to avoid a neoadjuvant chemotherapy as well as a mastectomy, NET with an AI for up to 6 months is a reasonable option [88, 89].

Lately, the NET setting has developed as a platform for scientific issues as the validation of biomarkers of prognostic and predictive information, drug resistance, and the evaluation of targeted therapy combinations. Pathological complete response, an approved surrogate marker for long-term outcome of neoadjuvant chemotherapy, is not feasible for evaluating NET. However, for example, therapy-induced changes in the proliferation marker Ki-67 and the Preoperative Endocrine Prognostic Index (PEPI), a score of posttreatment ER, Ki-67, tumor size, and nodal status are used as markers for evaluation of response in NET trials [90, 91]. After ET with an AI for 2–4 weeks, about 70% of patients showed levels of Ki-67 positive cells ≤10% (nuclear staining) and this correlated with excellent long-term outcome [92]. And recently, in the POETIC trial patients with low baseline Ki-67 (<10%) had an excellent 5-year DFS compared to that in patients with high Ki-67 (Ki-67 ≥20%) and no drop of Ki-67 after ET (5-year DFS 95.5 and 80.4%, respectively). Patients with luminal-B-like tumors and good response to ET (Ki-67 <10% after short ET) had a better outcome than those with poor ET response, yet it was still somewhat worse than that in "baseline luminal-A-like" tumors (5-year DFS of 91.1%) [93]. In the ADAPT trial, about 70–80% of patients with genomically low-to-intermediate risk and about 40% of those with genomically high-risk disease responded to preoperative ET by decrease of the proliferation marker Ki-67 ≤10% [94].

The effect of decreased proliferation after neoadjuvant treatment can be increased by adding a CDK4/6 inhibitor to ET. In the neoMONARCH study, more patients in the abemaciclib-containing arms versus anastrozole alone achieved complete cell cycle arrest (Ki-67 ≤2.7%) after 2 weeks of ET (68/58 vs. 14%; $p < 0.001$). At the end of treatment, following 2 weeks lead-in and 14 weeks of combination therapy, 46% of intent-to-treat patients achieved a radiologic response, with pathologic complete response observed in 4% [95]. As another example, the results of the CORALLEEN trial were presented at SABCS 2019; 106 postmenopausal patients with early luminal B breast cancer (PAM 50) were randomized between standard multiagent chemotherapy and ribociclib plus letrozole. The endpoint was the achievement of ROR-low disease after 6 months of treatment evaluated at the time of surgery. In both treatment arms almost 50% of the patients reached this endpoint [96]. These trial settings will help to gain knowledge about breast cancer in short-time intervals and will help us to optimize personalized treatment.

Conclusions

- The standard endocrine treatment for pre- and perimenopausal patients is 5 years of tamoxifen, and for postmenopausal patients 5 years of an AI or a sequence of AI and tamoxifen.
- Extended ET with an AI should be discussed with postmenopausal patients at risk, considering the side effects.
- Risk can be assessed by clinical features as tumor size, nodal status, grading, and age (CTS5 score) as well as by gene expression profiling.
- The need for osteoprotective therapy should be assessed early on.
- Ten years of tamoxifen should be recommended for premenopausal patients at risk.
- Additional OFS for 2–5 years should be discussed with patients younger than 35 years or if menstruation starts again within 2 years after chemotherapy.
- There are discordant results for distant recurrence (better) and OS (worse) with the combination of exemestane with OFS in premenopausal women.
- Control of adequate OFS when giving AI to premenopausal women is mandatory.
- CYP2D6 genotypes should not be used to guide the selection of ET.
- Careful consideration of treatment recommendation in the low ER-positive situation is needed.
- Trial results with integration of CDK4/6 inhibitors in the treatment of early luminal B carcinomas are awaited.

NET and preoperative short-term ET are promising tools for the treatment and understanding of luminal carcinomas.

Conflict of Interest Statement

The authors have no conflict of interest to declare for this specific work.

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K.K. and E.S. both contributed to the review of the literature and writing.

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