Endocrine Therapies in the Adjuvant and Advanced Disease Settings

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45.1 Introduction and Background

Hormone receptor-positive (HR+) breast cancer (BC) is the most common histological subtype across all age groups, but the proportion of HR+ BC is inversely correlated with age [1–4]. The therapeutic manipulation of endogenous estrogen levels and/or the estrogen receptor interaction is the milestone of adjuvant and palliative therapy in female patients with HR+ BC, i.e., estrogen receptor positive (ER+) and/or progesterone receptor positive (PR+). As a consequence, the accurate assessment of HR status is critical for the optimal use of endocrine therapy (ET). Over the years, HR determination has often been inaccurate and irreproducible, with variable thresholds for positivity (e.g., ≥1%, ≥10%, any) [5], significantly impacting interpretation of trial results. The 2010 joint American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of ER and PR established a cutoff of at least 1% of positive tumor cells for a specimen to be considered positive [6]. The degree of positivity provides valuable predictive and prognostic information to plan treatment strategies: several studies showed patients with higher HR levels have a higher probability of positive outcomes when treated with ET [7–11]. For the few patients reported as ER−/PR+, repeating testing on another tissue sample is recommended to rule out a false-negative or false-positive result which could influence treatment efficacy. Retesting is also recommended in case of ER- and PR-negative results in tumor subtypes (i.e., tubular, lobular, and mucinous) almost always associated with HR positivity [6]. The absence of benefit from ET for women with ER− BC has been confirmed in large overviews of randomized clinical trials.

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45.2 Early Breast Cancer

45.2.1 Indications

Precise assessment of menopausal status is important when deciding the optimal ET in the individual patient. The available biomarkers to determine the postmenopausal status [follicle-stimulating hormone (FSH), estradiol, inhibin B, and anti-Müllerian hormone (AMH)] are of limited availability, reliability, or reproducibility. Practical guidelines to properly discriminate pre- and postmenopausal patients have been developed [12]: in general, women >60 years, after bilateral oophorectomy, and <60 years not using oral contraceptives or hormone replacement therapy (HRT) with an intact uterus and amenorrhea for at least 1 year can be considered postmenopausal. On the contrary, women having regular periods without using oral contraceptives or HRT can be classified as premenopausal. The most difficult clinical situation is defining and managing the perimenopausal transition period [13]: cautious decisions and careful monitoring should be made in these patients.

45.2.2 Tamoxifen

Tamoxifen is a selective ER modulator (SERM) used for over 40 years to treat HR+ BC.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses repeatedly reported the benefits of adjuvant tamoxifen in pre- and postmenopausal women with HR+ BC regardless of age, the use of chemotherapy, and nodal status. In the 2011 overview [8], 5 years of tamoxifen compared to no ET were associated with a 15-year risk reduction of 39% in BC recurrence and of 30% in BC mortality. Efficacy is evident even at relatively low levels of ER positivity and independent of PR status: in ER+ disease, the absolute recurrence reduction at 15 years seems somewhat greater in ER+/PR poor disease than in ER+/PR+ disease,

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possibly because of the somewhat higher risk of recurrence without treatment in this tumor subtype [14]. The potential antagonism between tamoxifen and chemotherapy suggested by preclinical data [15] has not been definitively proven [16, 17]. The ongoing OPTIMA studies evaluate whether chemotherapy plus ET is better than ET alone in patients with positive nodes [18]: while waiting for new data, tamoxifen should be initiated at the end of chemotherapy, when given.

45.2.3 Premenopausal Women

The optimal adjuvant ET for premenopausal women is still a matter of debate. For over 30 years, tamoxifen for 5 years has been the gold standard in this setting. The sustained reduction in BC mortality well beyond year 10 is of particular interest in younger women. Several currently available additional therapeutic options [i.e., the combination of ovarian function suppression (OFS) to oral ET (either tamoxifen or aromatase inhibitors (AIs)] will be illustrated in the following paragraphs. The individual choice should consider the risk of recurrence, the latest scientific evidence, as well as toxicity profile, patient's comorbidities, and her personal preference.

45.3 Ovarian Function Suppression

OFS by surgical castration or ovarian irradiation was the first ET used in premenopausal patients [19]. In developed countries, this approach has been progressively replaced by gonadotropin-releasing hormone analogues (GnRHa) with comparable results [20]. Surgical castration remains a low-cost choice in developing countries. Bilateral salpingo-oophorectomy is also a valid alternative in BRCA1/2 mutation carriers who completed family planning.

The 2007 EBCTCG meta-analysis [21] looked at 11,906 HR+ premenopausal women (from 16 trials) who received GnRHa as OFS. As compared to the previous 2005 analysis [20], showing a benefit for OFS in terms of BC-related mortality and relapse rate in the absence of other systemic treatments, the updated results proved OFS to be beneficial whether used alone (recurrence risk reduction of 28%, $p = 0.08$), in addition to tamoxifen or chemotherapy (recurrence risk reduction of 13%, $p = 0.02$), or as an alternative to chemotherapy. The benefit was especially evident in young women (≤40 years of age) after adjuvant chemotherapy, either alone or in addition to tamoxifen. The latter effect is probably explained by the lack of permanent amenorrhea with chemotherapy alone in this subgroup of patients, treated with new chemotherapy regimens associated with less ovarian toxicity compared to CMF [22]. Few trials tested the addition of GnRHa to tamoxifen (±chemotherapy), and no trials compared a GnRHa against chemotherapy with tamoxifen in both arms.

The long-term results of the ZIPP trial [23] (median follow-up 12 years) were not included in the 2007 EBCTCG overview. The trial randomized 2710 patients into four arms: 476 patients (17.5%) did not receive any adjuvant ET, 469 (17.3%) received single-agent goserelin, 879 (32.4%) received tamoxifen alone, and 882 (32.5%) received the combination of goserelin + tamoxifen. ET was administered for 2 years. In all the three treatment arms, the disease-free survival (DFS) was higher than in the control arm, with no significant differences between treatments, in particular with no added benefit by the addition of GnRHa to tamoxifen. The 2009 Cochrane review [24], run in over 13,000 premenopausal women randomized in 14 trials, concluded that (1) there is no enough data to determine whether GnRHa alone is comparable to tamoxifen alone, (2) there is a trend of reduction in BC recurrence in favor of the combination of GnRHa + tamoxifen versus GnRHa alone, and (3) the association of GnRHa and chemotherapy shows no differences in recurrence or overall survival (OS) compared to GnRHa alone. The authors highlighted the need to assess the role for GnRHa when added to modern chemotherapy regimens and tamoxifen, to continue the follow-up in order to provide long-term outcomes, to compare different durations of GnRHa and the addition of aromatase inhibitors (AIs). The 2015 meta-analysis by Yan and colleagues [25] examined only trials comparing tamoxifen alone with tamoxifen plus OFS (6279 patients) and concluded that the addition of OFS to tamoxifen does not provide additional benefits in patients who did not received chemotherapy. Instead, in the subgroup with chemotherapy, the addition of OFS significantly improved OS with a mortality reduction of 24% ($p = 0.03$), possibly because these patients were considered at sufficient risk of relapse to candidate for adjuvant chemotherapy. This meta-analysis has some limitations, as stated by its authors: the results of the subgroup analyses were based on relatively small numbers of patients; the chemotherapy regimens varied across trials according to the period of enrollment as did the criteria for definition of menopausal status.

Since the abovementioned publications, the results of the International Breast Cancer Study Group (IBCSG)-led Suppression of Ovarian Function Trial (SOFT) became available [26]: 3066 premenopausal women were randomized to 5 years of tamoxifen, tamoxifen + OFS, or exemestane + OFS. Overall, at median follow-up of 5.6 years, adding OFS to tamoxifen did not provide a significant benefit in terms of DFS (84.7% in the tamoxifen group, 86.6% in the tamoxifen + OFS group; hazard ratio (HR) 0.83; 95% confidence interval [CI], 0.66–1.04; $p = 0.10$). The preplanned analysis according to the administration of chemotherapy allowed discriminating two different groups of patients and outcomes. In the low-risk patient subgroup

(mostly >40 years, with small, node-negative tumors of low-intermediate grade) who did not receive chemotherapy, >95% of patients remained free from BC at 5 years irrespective of treatment assignation. In contrast, in the cohort of patients at higher risk of relapse, who deserved chemotherapy according to the treating physician and remained premenopausal afterward, the rate of freedom from BC at 5 years was significantly higher among patients receiving tamoxifen + OFS than tamoxifen alone (82.5% and 78.0%, respectively, HR 0.78; 95% CI, 0.60–1.02). Of note, in the subset of very young patients (<35 years), BC recurred in approximately one third of the patients receiving tamoxifen alone and in one sixth of those treated with exemestane + OFS (67.7% and 83.4%, respectively), suggesting OFS plays a major role in younger premenopausal patients. SOFT data allow to better select premenopausal patients for whom tamoxifen alone is not indicated, as acknowledged in all the most recent consensus guidelines [27–30].

Data on the efficacy and safety of 3-monthly versus monthly GnRHa are scarce. In 170 Japanese women, 3-monthly goserelin was not inferior to monthly administration in terms of estradiol suppression, safety, and tolerability [31]. In clinical practice, the 3-monthly administration can be considered in older premenopausal women (>40 years): despite technical challenges, estradiol, LH, and FSH levels should be regularly checked and suppressed, as amenorrhea is not the only reliable indicator of OFS [27, 30].

45.3.1 Aromatase Inhibitors

Third-generation AIs (the nonsteroidal letrozole and anastrozole, the steroidal exemestane) efficiently block the enzyme aromatase which synthesizes estrogens from androgens and achieve a nearly complete suppression of total-body aromatization and plasma estrogen levels in postmenopausal women [32]. Conflicting evidence has questioned the benefit of AIs in overweight/obese patients: the increased body aromatization in the fat tissue may in fact induce incomplete suppression of estrogen production by AIs. In overweight (BMI ≥25 kg/m^2) premenopausal patients treated with anastrozole in the ABCSG-12 trial, the risks of recurrence and death were significantly higher (HR, 1.49; 95% CI, 0.93–2.38; $p = 0.08$ and HR, 3.03; 95% CI, 1.35–6.82; $p = 0.004$, respectively) than in patients treated with tamoxifen [33]. In the ATAC study, menopausal women with a BMI >35 had a poor prognosis compared to lean women independent of treatment (tamoxifen or anastrozole) with a nonsignificant reduced benefit for anastrozole among obese individuals [34]. In contrast, in the BIG 1-98 study, the added benefit of letrozole over tamoxifen was irrespective of BMI [35]. No correlation was found between on-treatment aromatization levels or aromatase inhibition and BMI in 64 patients treated within six different clinical trials with a panel of aromatase inhibitors [36]. While waiting for the BMI data from TEXT-SOFT in premenopausal women, there is no sound data suggesting not prescribing AIs in overweight patients, if indicated [37].

45.3.2 Postmenopausal Women

Different AI treatment algorithms have been studied: (1) head-to-head comparison versus tamoxifen for a total of 5 years, (2) following 2–3 years of tamoxifen for a total of 5 years versus AI or tamoxifen for 5 years, and (3) following 5 years of tamoxifen for a total of 10 years of ET. In comparison 1 (9885 patients from the ATAC [38] and BIG 1-98 trials) [39], the 2015 EBCTCG overview [40] showed recurrence (local-contralateral-distant) was significantly reduced (by about 30%) by AIs as compared to tamoxifen during the treatment period but not afterward, suggesting that 5 years of an AI reduces recurrence by about one third during years 5–9, as does 5 years of tamoxifen. Little follow-up data are available beyond year 10. The 10-year BC mortality is also significantly but slightly reduced (by about 15%) by AI over tamoxifen even though about half the deaths were not due to BC. In the switching comparison (12,779 patients), recurrence was significantly reduced only during the first years when the treatments differed (RR 0.74; 95% CI, 0.62–0.89; $2p = 0.002$) and not afterward (RR 0.99), if both groups received an AI: no significant further effect was evident after year 5, but little follow-up data were available beyond year 7. These smaller reductions in recurrence, as compared to the head-to-head comparison, can possibly be attributed to the shorter duration in which treatment differed. BC mortality was not significantly reduced (RR 0.89; 95% CI, 0.78–1.03; $2p = 0.11$). The highest reduction in the recurrence rate during the treatment period was observed when the switching strategy was compared to tamoxifen for 5 years (11,798 patients) (RR 0.56; 95% CI, 0.46–0.67; $p < 0.0001$) with no significant further effect afterward but lack of sufficient follow-up beyond year 10. To accommodate for different randomization criteria in the different trials, only patients who completed 2 years of tamoxifen without recurrence were included. BC mortality was not statistically reduced (RR 0.84; 95% CI, 0.72–0.96; $2p = 0.015$). The BIG 1-98 trial [39] was the only study also to explore the reverse sequencing (tamoxifen following 2–3 years of letrozole for a total of 5 years versus AI for 5 years). Letrozole followed by tamoxifen provided similar DFS and OS to letrozole monotherapy in all patient groups: despite the study was not powered to test equivalence and these results are based on few patients and events they are of interest for women who do not tolerate AI. On the contrary, letrozole monotherapy tended to be better than tamoxifen followed by letrozole, especially for

control of distant recurrence in patients at higher risk of early relapse (e.g., patients with positive axillary nodes).

No apparent differences in efficacy emerge between different aromatase inhibitors: indirect and randomized comparisons [41] show little difference between AIs.

Overall, the reduction in 10-year BC mortality with AIs compared with tamoxifen is only slight but significant. As a consequence, as stated in the last San Gallen Consensus [28], tamoxifen alone may be suitable for patients at low risk of disease recurrence, while for patients at higher risk (i.e., ≥4 positive nodes, grade 3, high proliferation index), an AI should be considered and given up front. This attitude is supported by the STEPP analysis, performed in BIG 1-98 patients, of a composite measure of prognostic risk factors (i.e., number of involved lymph nodes, grade, tumor size, presence of peritumoral vascular invasion, age, and biological characteristics) which are commonly considered in clinical practice when deciding the best adjuvant ET for the individual patient. This analysis revealed patients at lowest risk did similarly well with letrozole monotherapy, a sequence of letrozole and tamoxifen, or tamoxifen monotherapy [42].

In a retrospective analysis of the BIG 1-98 trial, the magnitude of benefit of adjuvant letrozole seems greater for patients with lobular carcinoma (n = 324) versus ductal carcinoma (n = 2599) [43]. The small number of lobular cancers in the analysis and the unclear underlying biological mechanisms require further validation before AIs can be routinely recommended in this subset of patients. In the same analysis, no difference between letrozole and tamoxifen was reported in women with ductal carcinomas and luminal A-like subtype, defined as ER and/or PR+, HER2 negative, and with Ki-67 <14%. On the contrary, women with ductal carcinomas and luminal B-like subtype (i.e., Ki-67 ≥14%) experienced a significant reduction in the hazard of a DFS event with letrozole. This observation reinforces the role of tamoxifen in patients with favorable biological characteristics.

45.3.3 Premenopausal Women

The combined analysis of SOFT and TEXT (Tamoxifen and Exemestane Trial), comparing 5 years of exemestane + OFS with tamoxifen + OFS (4690 patients), after a median follow-up of 68 months, showed an absolute 3.8% gain in the 5-year DFS in patients treated with exemestane + OFS compared to those receiving tamoxifen + OFS (91.1% versus 87.3%, HR 0.72; 95% CI, 0.60–0.85; $p < 0.001$) [44], comparable with the benefit of AIs in postmenopausal women. Overall, 57.4% of the patients did receive adjuvant chemotherapy. Timing of chemotherapy and ET initiation was different in SOFT and TEXT: in TEXT, patients received OFS at randomization concurrently with chemotherapy, at an average of 1.2 months after surgery; in SOFT, patients completed all chemotherapy before randomization and started OFS at an average of 8 months after surgery but were allowed to receive oral ET (typically tamoxifen) while waiting for menses to resume. In women who had received chemotherapy, the rate of freedom from BC at 5 years was higher with exemestane + OFS than with tamoxifen + OFS (5.5% in TEXT and 3.9% in SOFT): the shorter time before starting OFS might explain the different treatment benefits in TEXT compared with SOFT. Among patients who did not receive chemotherapy (20.7% and 8.3% node positive in TEXT and SOFT, respectively), >97% of those who received exemestane + OFS and approximately 95% of those receiving tamoxifen + OFS remained free from BC at 5 years: these data show effective combined ET alone is associated with excellent outcomes also in node-positive patients, arguing the routine administration of chemotherapy to all premenopausal patients with HR+ disease. Overall, the 5-year OS did not significantly differ between exemestane + OFS (95.9%; 95% CI, 94.9–96.7) and tamoxifen + OFS-treated patients (96.9%; 95% CI, 96.0–97.6): longer follow-up is however needed as HR+ patients can develop late relapses.

The Austrian Breast and Colorectal Cancer Study Group (ABCSG) 12 trial randomized 1803 premenopausal patients to 3 years of goserelin + tamoxifen or anastrozole [45]. After 94.4 months of median follow-up, no DFS difference between treatments was reported, but a higher risk of death for anastrozole-treated patients was observed (HR = 1.63; 95% CI, 1.05–1.45; p = 0.03). Overall, after disease recurrence, 61% of patients in the tamoxifen group received AIs as opposed to only 41% of patients in the anastrozole group. ABCSG-12 and SOFT-TEXT have several differences which can potentially explain the divergent results: in particular, in the Austrian trial, the statistical power was lower (half the number of events), and treatment duration was only 3 years, which is not the current standard of care for oral ET.

These data help clinicians in selecting premenopausal women with HR+ early BC who could benefit from the addition of AIs to OFS, according to their individual risk and the toxicity profile, as recommended in all the most recent consensus guidelines [27–30].

45.4 Treatment Duration

Women with HR+ tumors show no plateau for both recurrence and OS, with a low but continuous risk of relapse and death even after 10 years [46]: the annual rate for late recurrences exceeds 2% for at least 15 years, even after 5 years of tamoxifen therapy. The analysis of 111,993 patients, diagnosed between 1990 and 2003 and included in the SEER database, showed age differences in late relapses, younger age (<40 years) being associated with the higher hazard of BC-specific mortality throughout the period of 5–10 years, irrespective of nodal status [47]. Several clinicopathological parameters (e.g., nodal status and tumor size) are also associated with an increased risk

of late recurrence. Altogether, these results may help clinicians determine which patients are the best candidates for extended ET. Further research is therefore needed to detect individual biomarkers or multigene signatures for the identification of women at high risk of late recurrence, particularly in node-negative disease.

In contrast with earlier, smaller studies [48, 49], the ATLAS [50] and aTTom [51] trials show, in almost 20,000 pre- and postmenopausal women, that continuing tamoxifen to 10 years provides a further reduction in both disease recurrence and mortality. In the ATLAS trial, at median follow-up of 7.6 years, BC recurrence was reduced by 3% (RR 0.84; CI 95%, 0.76–0.94; $p = 0.002$), breast cancer mortality by 2% ($p = 0.01$), and overall mortality by 2.48% ($p = 0.01$). The protective effect extends well over the 10 years' treatment period (RR 0.90; 95% CI, 0.79–1.02 during years 5–9 and 0.70, 95% CI, 0.62–0.90 during subsequent years), regardless of age and nodal status. Premenopausal patients constituted only approximately 9% of the study population, and statistical significance was not reached in this subgroup, likely because of the much smaller number of events: nevertheless, these results provide the only available evidence of a beneficial effect of extended ET in premenopausal patients and should be discussed on an individual basis, especially for patients at high risk of recurrence. In the aTTom trial, despite HR status was not available in a consistent proportion of patients, the longer-treatment group had fewer BC recurrences (28% versus 32%; $p = 0.003$), and BC mortality was reduced (21% versus 24%; $p = 0.06$). Overall, these results can be considered practice changing, especially in case of a significant risk of recurrence.

In the NCIC-CTG MA.17/BIG 1-97 study, patients receiving 5 years of letrozole after 5 years of tamoxifen experienced overall an improved DFS, but a significant OS benefit was evident only in patients with node-positive disease [52]. The best DFS benefit (HR 0.25; 95% CI, 0.12–0.51) was reported in premenopausal women at diagnosis who became definitively postmenopausal at the time of randomization, providing a new treatment option in this subgroup of patients, if clinically indicated.

Other two smaller trials (ABCSG 6a and NSABP-B33) confirmed the efficacy of 3-5 additional years of an AI beyond 5 years of standard tamoxifen.

Based on the available evidence, both extended adjuvant ETs with an AI after 5 years of tamoxifen in menopausal women and tamoxifen for 10 years in pre- and postmenopausal women reduce the risk of cancer recurrence. Tamoxifen for 2–3 years followed by an AI for additional 5 years, for a total duration of up to 7–8 years of therapy, is also a valuable treatment option [53]. It is not known which strategy is preferred; tamoxifen and AIs have different adverse effects which may influence treatment decisions.

In postmenopausal women who received adjuvant AIs in the first 5 years, several trials addressed different strategies of AI extension. Patients' populations are not homogeneous across trials (e.g. upfront therapy and total duration of AI), making the results difficult to interpret and translate into clinical practice. In the recently reported studies (MA.17R, NSABP-B42, DATA), a DFS benefit was shown only in the MA.17R trial, mainly driven by reduction in the incidence of contralateral disease. No survival benefit was reported so far [54]. Consequently, extended AIs should not be routinely proposed but possibly discussed in women at higher risk of relapse who did not experience significant toxicity under previous AIs.

Molecular signatures able to predict distant recurrence rates (BCI, EndoPredict, PAM50) need to be prospectively tested to define the cost-benefit ratio of extended ET.

The optimal duration of adjuvant GnRHa has not been established. In different trials, GnRHa were given for 2, 3, or 5 years, with no direct comparisons. The latest ESMO guidelines suggest at least 2 years of treatment [55]: the excellent outcome of patients treated for 3 years in the ABCSG-12 trial suggests this can be reasonable, especially in women reporting severe side effects. In the TEXT and SOFT trials, duration of both oral ET and OFS was 5 years: to date, there are no data on their extension beyond 5 years. A phase II single-arm trial evaluated, after at least 4.5 years of adjuvant tamoxifen, 2 years of OFS in combination with the AI letrozole [56]. The study was closed after only 16 patients enrolled over 3.5 years, suggesting young women may not be highly motivated to extended ET and challenging the feasibility of future studies.

45.5 Advanced Breast Cancer (ABC)

45.5.1 Indications

For patients with HR+ ABC, ET is the recommended initial treatment even in the presence of visceral metastases: chemotherapy should be reserved in case of rapidly progressive disease or proven endocrine resistance [57]. Confirmatory biopsy of metastases, where feasible, should be considered as it may confirm concordance (or discordance) of endocrine sensitivity allowing better identification of patients likely to benefit from ET [58]. Different sequential ETs can be given until disease progression, unacceptable toxicity, or development of symptomatic visceral disease. The sequential use of ETs with different mechanisms of action may prolong the duration of response, reduce the risk of resistance, and delay the need for chemotherapy [59]. Most studies addressing the combination of ET and chemotherapy showed an increased overall response rate (ORR) or an increased time to progression (TTP) but no improvement in OS with no age-related differences [60]. Trials examining concurrent versus sequential ET and chemotherapy need therefore to be conducted. The specific scenario of patients with both HR- and HER2-positive disease will be addressed in a separate chapter.

45.5.2 Available Options

The third ESO-ESMO ABC consensus conference confirmed the statement that for postmenopausal patients, the choice of first-line ET depends both on type and duration of adjuvant ET and disease-free interval (DFI) from the end of adjuvant ET. AIs, tamoxifen, or high-dose (HD) fulvestrant (i.e., 500 mg monthly) are acceptable alternatives. In the FIRST phase II study [61], HD fulvestrant proved to be superior to anastrozole in terms of OS (median OS 54.1 months versus 48.4 months; HR 0.70; 95% CI, 0.50–0.98; $p = 0.04$). These data need to be interpreted cautiously as the OS analysis was not originally planned and not all patients had OS follow-up: the preliminary results of the larger phase III FALCON trial (450 patients) showed a PFS benefit (16.6. vs 13.8 months, HR 0.797) with immature OS data. The combination of a nonsteroidal AI and LD fulvestrant (250 mg monthly) showed discordant results in two phase III trials with similar designs [62, 63]. Subset analysis in the successful SWOG study suggests a benefit in the PFS and OS for the combination therapy only in patients without prior adjuvant tamoxifen [63] to whom this strategy can be offered. In this study, the addition of fulvestrant to anastrozole significantly decreased anastrozole concentrations in a subset of patients treated with the combination, potentially affecting treatment efficacy [64].

The optimal sequence of endocrine agents after first-line ET is uncertain and depends on which drugs were used in the neoadjuvant/adjuvant and first-line ABC settings. Reasonable options include AIs, tamoxifen, fulvestrant, progestins, high-dose estrogens, and androgens [57].

For premenopausal women, ovarian suppression/ablation combined with additional ET is the treatment of choice [65]. A meta-analysis of four studies ($n = 506$) comparing GnRHa ± tamoxifen showed the outcomes were significantly improved in patients who received the combination [66]. The limited evidence available [67] and indirect comparison of data from the adjuvant setting [44] and menopausal patients [68] suggest AIs can be a valuable alternative to tamoxifen: decisions should be made according to type and duration of prior adjuvant ET, DFI, toxicity profile, and patients' preferences. Fulvestrant is also a valuable option which mandates OFS [67]. Ovarian ablation (OA) by laparoscopic bilateral oophorectomy ensures definitive estrogen suppression and contraception, avoids potential initial tumor flare with GnRHa, and represents a cost-effective alternative particularly in middle-low-income countries. Patients should be informed on the options of OFS/OA, and decision should be made on a case-by-case basis.

45.5.3 Targeting Endocrine Resistance

Several potentially targetable mechanisms of intrinsic and acquired endocrine resistance have been identified, such as ER alterations (mutations, amplifications, or translocations) and upregulation of alternative growth pathways (i.e., the HER, the PI3K/Akt/mTOR, and the CDK4/CDK6 pathways). Tumors that are both ER and HER2+ are less responsive to tamoxifen treatment [69, 70]. At central review, 7% and 10.5% of patients in the BIG 1-98 and ATAC trials overexpressed HER2, respectively: in both trials, the benefit of AIs over tamoxifen was independent of HER2 status of the primary tumor. In SOFT and TEXT, 12% of premenopausal patients had HER2+ tumors and ~60% received HER2-targeted therapy, reflecting the accrual time period. In SOFT, the addition of OFS to tamoxifen appeared to be beneficial over tamoxifen alone (HR, 0.78; 95% CI, 0.62–0.98; $p = 0.03$) [26] as previously reported by others [71]. On the other hand, in the combined TEXT-SOFT analysis, in the presence of OFS, exemestane did not confer any advantage over tamoxifen (DFS HR = 1.25; 95% CI, 0.80–1.94) [44]. HER2 central assessment and further analysis are however needed before HER2 status is used for oral ET selection in premenopausal women.

45.5.4 mTOR Inhibitors

The mTOR inhibitor everolimus has proven to be effective in postmenopausal women relapsing/progressing under AIs both in combination with exemestane in the BOLERO-2 phase III trial [72] and with tamoxifen in the phase II TAMRAD study [73]. In the BOLERO-2 trial, a significantly longer median progression-free survival (PFS) with the combination versus exemestane alone was reported (central review: 11.0 months versus 4.1 months, respectively; HR 0.38; 95% CI, 0.31–0.48; log-rank $p < 0.0001$) [74]. Several predefined or exploratory subgroup analyses [75] demonstrated the PFS benefit was irrespective of age (i.e., <65, ≥65, and ≥70 years), the administration of prior chemotherapy for ABC (6.1 months versus 2.7 months; HR 0.38; 95% CI, 0.27–0.53), and the presence of visceral disease (6.8 months versus 2.8 months; HR 0.47; 95% CI, 0.37–0.60; $p < 0.05$). In addition, everolimus increased the median PFS in patients recurring after adjuvant therapy (11.5 months versus 4.1 months; HR 0.39; 95% CI, 0.25–0.62), suggesting to be potentially effective as first-line therapy. The overall PFS advantage did not translate into a survival benefit: the median OS in patients receiving the combination was 31.0 months compared with 26.6 months in patients receiving exemestane alone (HR 0.89; 95% CI, 0.73–1.10; log-rank $p = 0.14$) [76]; one possible explanation is that the trial was not powered to detect an OS advantage as the sample size was based on the primary end point of PFS. A network meta-analysis compared the PFS of everolimus + exemestane, as reported by the BOLERO-2 trial, with that of LD/HD fulvestrant after adjuvant or first-line ET from six studies [77]. Everolimus + exemestane was more efficacious than both

LD and HD fulvestrant (HR 0.47 and 0.59, respectively). Overall, these results contrast with those of the first-line HORIZON study, wherein adding the mTOR inhibitor temsirolimus to letrozole did not improve PFS in 1112 patients with AI-naïve ABC [78]. The single-arm BOLERO-4 phase II trial, assessing the safety and effectiveness of first-line therapy with everolimus + letrozole, has completed accrual and will also provide information on the efficacy of continuing everolimus after initial disease progression (PD); patients progressing under treatment will be allowed to maintain everolimus and add exemestane until further PD or unacceptable toxicity [79]. Everolimus is being studied also in the adjuvant setting [80, 81]. The decision to give everolimus must take into account the potential relevant toxicities associated with this combination and should be made on a case-by-case basis.

45.5.5 CDK4/CDK6 Inhibitors

The randomized phase I/II PALOMA-1 study showed an impressive PFS improvement in patients treated with the combination of the CDK4/CDK6 inhibitor palbociclib and letrozole compared to letrozole alone as first-line treatment (20.2 months versus 10.2 months; HR 0.488; $p = 0.0004$). The presence of CCND1 amplification and/or p16 loss was not predictive for efficacy. No significant difference in OS has been shown so far: a preliminary analysis suggested a trend toward increased OS (37.5 months versus 33.3 months; HR 0.813; $p = 0.2105$) in the combination arm [82]. Combination therapy was very well tolerated, and common grade 3/4 toxicities seen in the palbociclib-containing arm versus the letrozole alone arm were neutropenia (54% versus 1%), leucopenia (19% versus 0%), fatigue (4% versus 1%), and anemia (6% versus 1%). On the basis of these favorable results, the FDA granted palbociclib accelerated approval as first-line treatment for postmenopausal women with HR+ and HER2− ABC pending confirmatory results from the phase III PALOMA-2 trial (NCT01740427). The double-blind phase III PALOMA-3 trial evaluated the efficacy of palbociclib + HD fulvestrant versus HD fulvestrant alone in pre- and postmenopausal women with HR+/HER2− ABC who had relapsed/progressed on prior ET [83]. Pre and perimenopausal women received also the GnRHa goserelin. At the first interim analysis, the primary end point was reached; the median PFS was 9.2 months in the combination arm and 3.8 months in the fulvestrant arm (HR 0.422; 95% CI, 0.318–0.560; $p < 0.000001$). Of note, the relative difference in PFS was independent of menopausal status, providing a new treatment option also for young patients with HR+ ABC. At the time of the interim analysis, data on OS were immature, with a total of only 28 deaths. Several trials evaluating palbociclib plus ET are in progress in the adjuvant and neoadjuvant settings, as well as in combination with chemotherapy and HER2-targeted agents. A significant PFS improvement was also reported with Ribociclib, another selective CDK4/6 inhibitor, in combination with letrozole as first-line treatment in menopausal women, myelosuppression being the only relevant associated toxicity of the compound [84]. A third agent (LY2835219, abemaciclib) is under evaluation in different disease settings.

45.5.6 Other Compounds

The encouraging results in terms of efficacy and tolerability of a small phase II placebo-controlled trial ($n = 43$) of anastrozole combined with gefitinib, an orally active EGFR tyrosine kinase inhibitor, compared to anastrozole alone [85] were not replicated in a larger phase II study ($n = 71$) with similar design [86]. Overall, both the RR, not clearly superior to ET alone, and the toxicity profile do not support further evaluation of this combination. Efficacy of VEGF inhibitors has been disappointing to date: the pan-VEGF inhibitor pazopanib is being evaluated as an add-on therapy in a phase II trial of patients with HR+, locally advanced or metastatic BC progressing on nonsteroidal AIs in the adjuvant or metastatic setting (NCT01466972). Several additional targeted agents are under evaluation in combination with ET, e.g., PI3K, SRC, FGFR, and histone deacetylase inhibitors [87].

It is currently unknown how the different combinations of ET + biological agents compare with each other and with single-agent chemotherapy and whether a targeted agent should only be combined with ET to restore endocrine sensitivity or whether it may also prevent or delay the development of resistance [88]. Appropriate patient selection based on prior treatment history and disease characteristics will become increasingly important in maximizing the potential incremental benefit from these new agents combined with standard ET.

45.5.7 Side Effects and Adherence

ET is associated with potential physical and psychosocial long-term and late effects, specific of the drugs used and their duration. Accurate evaluation of potential contraindications to specific compounds and strategies to manage the most common toxicities [29, 54, 89, 90] should be part of routine clinical care.

ET adherence and persistence are relevant and may affect disease outcomes [91, 92]. A systematic review of 29 studies in the adjuvant setting showed that at the end of 5 years of treatment, adherence ranged from 41% to 72% (59% nonadherence for tamoxifen and 50% for AIs) and nonpersistence from 31% to 73%. Age (older or younger), increasing out-of-pocket costs, follow-up care with a general practitioner instead of an oncologist, and treatment side effects were all

negatively associated with adherence and/or persistence [93]. Health professionals should routinely assess and encourage adherence to ET [54, 94] and specifically address side effects to reduce symptom burden and potentially improve adherence [90].

The most commonly reported side effects of tamoxifen mimic menopausal symptoms including hot flashes, weight gain, sleep disturbance, sexual dysfunction, and gynecologic complications which may negatively impact QoL: rare but serious toxicities include increased risks of endometrial cancer and thromboembolism. In premenopausal women, there is little uterine cancer risk or excess risk of fatal pulmonary embolism [8]. The incidence of endometrial cancer and thromboembolism is very low even with longer therapy duration (3.1% versus 1.6% endometrial cancers for tamoxifen-treated versus placebo-treated women and relative risk of pulmonary embolism of 1.87 in the ATLAS trial) [51]. As opposed to menopausal women, tamoxifen may decrease bone mineral density (BMD) in premenopausal women, although the exact mechanism remains unclear [95].

Bothersome toxicities of AIs include musculoskeletal symptoms (i.e., arthralgias, myalgias, tendonitis, and carpal tunnel syndrome), menopausal symptoms, decreased BMD and consequent increased risk of fracture, and dyslipidemia [40]. Interestingly, although all AIs have the same mechanism of action and side effect profile, some patients who are treated with more than one of the individual AIs experience a different constellation of side effects from the different drugs. A meta-analysis of seven randomized controlled trials that compared AIs and tamoxifen as adjuvant ET in postmenopausal women (30,023 patients) showed AIs were associated with increased cardiovascular disease (OR = 1.26; 95% CI = 1.10–1.43; $p < 0.001$) and bone fractures (OR = 1.47; 95% CI = 1.34–1.61; $p < 0.001$) but a decreased odds of venous thrombosis (OR = 0.55; 95% CI = 0.46–0.64; $p < 0.001$) and endometrial cancer (OR = 0.34; 95% CI = 0.22–0.53; $p < 0.001$) [96]. Switching from one class of drug to the other can be a valuable strategy for balancing serious adverse events of individual drugs. ET may also adversely affect cognition [97]: objective but not subjective cognitive function improved approximately 1 year after cessation of either adjuvant letrozole, tamoxifen, or their sequence in a subset of patients treated within the BIG 1-89 study [98].

The addition of OFS to oral ET is associated with greater menopausal symptoms, anxiety, and depression [27]: in women who develop severe side effects, the risk-benefit ratio should be discussed according to the individual risk of relapse and OFS interruption proposed. Side effects and quality of life (QoL) have been extensively analyzed in SOFT and TEXT. Overall, 16.1% of the patients in the exemestane + OFS group and 11.2% of those in the tamoxifen + OFS group completely stopped ET. Global QoL and symptom indicators were assessed every 6 months for 24 months and then every year between years 3 and 6 in 4096 patients of both trials. Patients under tamoxifen + OFS reported more hot flushes, vaginal discharge, and sweats than those under exemestane + OFS, whereas patients who received exemestane + OFS had more bone/joint pain, vaginal dryness, and greater loss of sexual interest compared with patients on tamoxifen + OFS. Nonetheless, during the treatment period, changes in global QoL from baseline were similar between the two treatment groups [99].

Genetic polymorphisms may classify low or extensive drug metabolizers of either tamoxifen, via CYP2D6, or AIS, via CYP19A1. Many attempts have been undertaken to explore the impact of ET metabolism on toxicity and outcome with discordant results, preventing the utilization of pharmacogenomic data to select the best oral ET in the individual patient [100–102].

As ET side effects are related to suppression of estrogen production or ER blockade, it has been questioned whether the development of side effects is related to ET benefit. A number of unplanned retrospective analyses evaluated the association between symptoms of ET in general, rather than specifically for tamoxifen or AIs, and BC outcome. Most but not all analyses identified a positive association between musculoskeletal toxicity and improved DFS and OS. A subset also identified associations between vasomotor symptoms and improved outcomes. Major limitations of these data include: physician-graded adverse events instead of patient-reported outcomes, with the related underreporting of symptoms and no consistent definition for musculoskeletal symptoms across studies; exclusion of symptomatic patients at baseline, not capturing baseline symptoms and global severity, which makes it difficult to interpret these findings and to possibly apply this information to drive treatment decisions in individual patients [89].

45.6 Fertility Considerations and Pregnancy

Fertility and safety of pregnancy after the disease are major concerns for many young women with early BC [103, 104]. Fertility preservation should be addressed early after diagnosis according to all the most recent guidelines [30, 105, 106]: ideally patients should be referred to a fertility specialist before starting therapy to discuss all the available options [107]. Pregnancy following BC does not seem to negatively influence DFS or OS in HR+ premenopausal patients [108, 109]. A global IBCSG-led trial (POSITIVE-IBCSG 48-14 NCT02308085) is assessing patients' safety and pregnancy outcomes of interrupting ET after at least 18 months but no longer than 30 months to attempt conception.

45.7 Future Directions and Conclusions

The current therapeutic armamentarium in early BC requires a careful evaluation of both tumor's and patient's characteristics to select the optimal class of drugs, their sequence, and duration, carefully monitoring side effects and adherence. Patient's preference, requiring adequate and complete information, is therefore a key point to ensure the excellent outcomes reported by clinical trials translate in the overall population.

Cross talks between ER and growth factor pathways and discovery of new molecular aberrations in breast tumors will allow to develop new strategies for the cure of HR+ BC, moving from the advanced disease setting to earlier disease stages. Future treatments will likely include combination of several targeted therapies with cumulative side effects and extra personal and social costs which need to be anticipated and managed. A marker-driven selection of targeted agents for each patient and the reproducible and biologically significant detection of key molecular alterations responsible for both intrinsic and acquired resistance are therefore mandatory if we want to move to precision medicine and optimal resource allocation. As a consequence, sensitive, early, and reproducible predictors and markers of response/resistance are urgently needed in ABC to avoid unnecessary and toxic therapies. This is particularly relevant as improvements in PFS not always translate into OS benefit. Different disease end points, e.g., the post-progression survival (SPP) and/or composite end points including measurements of efficacy and toxicity and patients reported outcomes, such as the ESMO Magnitude of Clinical Benefit Scale [110], need therefore to be systematically implemented and tested.

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