Endocrine Therapy

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Abbreviations	
BC	Breast cancer
ET/ETs	Endocrine therapy/endocrine therapies
ER+	Oestrogen receptor-positive
PR+	Progesterone receptor-positive
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
RR	Relative risk
OFS	Ovarian function suppression
GnRHa	Gonadotropin-releasing hormone analogues
IBCSG	International Breast Cancer Study Group
SOFT	Suppression of Ovarian Function Trial
DSF	Disease-free survival
HR	Hazard ratio
CI	Confidence interval
AI/AIs	Aromatase inhibitor/aromatase inhibitors
TEXT	Tamoxifen and Exemestane Trial
OS	Overall survival
HR−	Hormone receptor-negative
DDFS	Distant DFS
ER−	Oestrogen receptor-negative
HER2+	Human epidermal growth factor receptor 2-positive
pCR	Pathologic complete response
NeoCENT	Neoadjuvant Chemotherapy versus ENdocrine Therapy
BCS	Breast conservative surgery
ORR	Overall response rate
PEPI	Preoperative endocrine prognostic index
RFS	Relapse-free survival
PROACT	Preoperative Arimidex Compared to Tamoxifen
LABC	Locally advanced breast cancer
ABC	Advanced breast cancer

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TTP	Time to progression
OA	Ovarian ablation
CBR	Clinical benefit rate
LD	Low-dose
HD	High-dose
HR+	Hormone receptor-positive
mTOR	PI3K/Akt/mammalian target of rapamycin
NSAI	Non-steroidal aromatase inhibitor
CDK4 and CDK6	Cyclin-dependent kinases 4 and 6

19.1 Introduction

Breast cancer (BC) is a heterogeneous disease with different immunohistochemical and molecular characteristics associated with different risk profiles and outcomes.

Endocrine responsive BC is the most represented subtype both in pre- and postmenopausal women, overall accounting for 65 % of cases [1]. This implies a wide use of endocrine therapy (ET) across ages in all disease phases.

We will summarize the indications and efficacy of ET in pre- and postmenopausal women in the neo/adjuvant and metastatic disease settings.

19.2 Adjuvant Therapy

In any case of endocrine responsiveness, defined as ≥1 % of oestrogen (ER+) and/or progesterone (PR+) receptor-positive tumour cells, there is indication for adjuvant ET, irrespective of the use of chemotherapy and/or targeted therapy.

The choice among different ETs depends on menopausal status, risk of recurrence, comorbidities, potential drug toxicity and patient's preferences, and should be discussed individually in a dedicated breast unit.

19.2.1 Premenopausal Patients

19.2.1.1 Tamoxifen

In the last decades, 5 years of tamoxifen have been the gold and unique standard.

Tamoxifen competes with oestrogens at the receptor site, inhibiting the growth of oestrogen-dependent BC. In addition, tamoxifen has a partial oestrogen-agonistic effect that is beneficial, for example, in preventing bone demineralization, but also detrimental in increasing the risk of uterine cancer and thromboembolic events. The updated Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview, conducted only in ER+ tumours, concluded that 5 years of adjuvant tamoxifen reduces the annual BC mortality rate by 31 % irrespective of age, the use of chemotherapy and nodal status [2]. The effect is maintained over time (years 0–4 and 5–14), confirming the previously reported carry-over data (years 0–9). The meta-analysis also reinforced that 5 years of tamoxifen were significantly more effective than 1–2 years in terms of BC recurrence and mortality.

The optimal duration of tamoxifen in the individual patient is still not completely clarified. In the ATLAS randomized trial, 12.894 pre- and postmenopausal women who had completed 5 years of adjuvant tamoxifen were randomized to continue for additional 5 years or to stop treatment. The analysis of the 6.846 women with ER+ disease showed a statistically significant reduction in the risk of BC recurrence (21.4 % vs. 25.1 %), BC mortality (12.2 % vs. 15 %) and overall mortality in the arm of longer assumption. Patients on extended therapy experienced more drug-related side effects with a relative risk (RR) of endometrial cancer of 1.74 and of pulmonary embolism of 1.87 [3]. The aTTom trial confirms, in 2.755 women with ER+ disease, a reduction in both BC recurrence and mortality [4]. Taken together with the results of 5 years of tamoxifen versus no therapy, these data indicate that 10 years of adjuvant tamoxifen, compared with no tamoxifen, can reduce BC mortality by about one-third in the first 10 years following diagnosis and by a half subsequently. This evidence can be of particular interest for patients at high risk of relapse and younger women, the largest population likely to consider 10 years of treatment, despite only 9 % of patients in the ATLAS study and an unspecified proportion in the aTTom study were premenopausal at enrolment.

19.2.1.2 Ovarian Function Suppression (OFS)

In premenopausal women, the main source of circulating oestrogens is by ovarian aromatization of exogenous and endogenous androgens: OFS by surgical castration or

irradiation has been the oldest ever ET, being progressively replaced by the administration of gonadotropin-releasing hormone analogues (GnRHa). Surgical castration represents still today a low-cost option in developing countries and a valid alternative in BC patients harbouring a BRCA 1/2 mutation who completed family planning. The chronic administration of a GnRHa, binding to the receptors in the pituitary gland, first induces a flare of FSH and LH secretion and subsequently a fall of gonadotropins and sex steroids to values similar to surgical castration.

The role of OFS as part of ET in premenopausal women has been investigated with contrasting results. The 2007 EBCTCG meta-analysis of 16 randomized trials, including 11.906 women, studied the effects of GnRHa alone, GnRHa plus tamoxifen versus tamoxifen alone, GnRHa plus chemotherapy versus chemotherapy alone and GnRHa plus chemotherapy plus tamoxifen versus chemotherapy plus tamoxifen. The GnRHa duration ranged from 18 months up to 5 years. The analysis showed that GnRHa alone did not significantly reduce recurrence or death after recurrence but when added to tamoxifen, chemotherapy or both achieved a 12.7 % reduction in recurrence and a 15.1 % reduction in death after recurrence [5]. The benefit was especially evident in women ≤40 years after adjuvant chemotherapy, either alone or in addition to tamoxifen, possibly related to the lack of permanent amenorrhoea with chemotherapy alone in this subgroup of patients.

The recently available results of the International Breast Cancer Study Group (IBCSG)-led Suppression of Ovarian Function Trial (SOFT), a comparison between 5 years of tamoxifen plus OFS versus tamoxifen alone, after a median follow-up of 67 months, showed, overall, a disease-free survival (DFS) of 86.6 % in the tamoxifen plus OFS arm and of 84.7 % in the tamoxifen arm (hazard ratio [HR] 0.83; 95 % confidence interval [CI] 0.66–1.04; $p = 0.10$). However, in the pre-planned subgroup analysis of the cohort of patients receiving adjuvant chemotherapy, there was a significant benefit of tamoxifen plus OFS versus tamoxifen alone in terms of reduction in BC recurrences at 5 years (82.5 % vs. 78.0 %, HR 0.78; 95 % CI 0.60–1.02); these patients were at higher risk of relapse than the ones in the no chemotherapy cohort (younger with larger tumours of intermediate-high grade and more frequently node-positive). This result was confirmed in the subset of very young patients (<35 years) who achieved the highest benefit from the addition of OFS over tamoxifen alone (78.9 and 67.7 %, respectively), suggesting that in patients at higher risk of recurrence, the addition of OFS can improve outcomes [6], as acknowledged in all the most recent consensus guidelines [7–10].

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 comparison. On the basis of the available data, duration should not exceed 5 years and should also take into account side effects, patient preferences and family plans.

19.2.1.3 Aromatase Inhibitors (AIs)

AIs act inhibiting or inactivating aromatase, the enzyme responsible for the synthesis of oestrogens from androgenic substrates, thus almost completely suppressing plasma oestrogen levels in postmenopausal women. In premenopausal women, AIs cannot be used alone, because of the risk of indirect ovarian stimulation via the pituitary loop, with a paradoxical increase in circulating oestrogens.

In premenopausal women, the use of the AI Exemestane in combination with OFS, as compared to tamoxifen plus OFS, has been investigated in 4.690 patients in the combined analysis of TEXT (Tamoxifen and Exemestane Trial) and SOFT. After a median follow-up of 68 months, a DFS of 91.1 % was achieved in the Exemestane group compared with 87.3 % in the tamoxifen group (HR 0.72; 95 % CI 0.60–0.85; $p < 0.001$) with a 3.8 % absolute gain, comparable to the benefit of AIs in postmenopausal women. There was no difference in overall survival (OS) but a longer follow-up is needed in this population of patients who can develop late relapses. Overall, the incidence of adverse events of any grade was similar in the two treatment groups, with a different toxicity profile consistent with the specific class of drugs. Patients under tamoxifen reported more hot flushes, vaginal discharge and sweats, whereas patients who received Exemestane had more bone/joint pain, vaginal dryness and greater loss of sexual interest [11]. Nonetheless, during the treatment period, changes in global quality of life from baseline were similar between the two treatment groups [12].

Different results were reported in the ABCSG-12 trial in 1.803 women randomized to 3 years of OFS plus tamoxifen or plus the AI Anastrozole, with or without Zoledronic acid. 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; $p = 0.03$) [13].

These divergent results can be partly explained by some differences between ABCSG-12 and SOFT/TEXT: lower number of patients and smaller statistical power in the Austrian trial, low-risk population (only 5 % of patients receiving neo/adjuvant chemotherapy), shorter treatment duration (only 3 years) and the use of Zoledronic acid.

At present, the results of SOFT and TEXT support the use of the AI Exemestane plus OFS, as a new treatment option in

premenopausal women with early, ER + breast cancer for whom OFS is indicated.

19.2.2 GnRHa for Ovarian Protection

Different studies and meta-analyses tried to explore the role of GnRHa as prevention of ovarian failure during adjuvant chemotherapy with contrasting results, mainly due to non-homogeneous definition of ovarian failure and selection of patients.

Recently, the randomized POEMS trial assigned 257 premenopausal women with hormone receptor-negative (HR−) BC to receive standard chemotherapy, with or without the GnRHa Goserelin. After 2 years, the ovarian failure rate was 8 % in the Goserelin group and 22 % in the chemotherapy-alone group. Among the 218 evaluable patients, pregnancy occurred in more women in the Goserelin group than in the chemotherapy-alone group (21 % vs. 11 %) [14].

Despite lack of universal consensus, we suggest to individually discuss this strategy with patients, balancing the adverse effects and benefits of this therapy.

19.2.3 Postmenopausal Women

AIs (both non-steroidal and steroidal) and tamoxifen represent valid adjuvant therapies for postmenopausal, endocrine responsive, early BC, with AIs showing overall a significant benefit in DFS and a slight improvement in OS across different trials.

The BIG 1-98, a randomized phase III double-blind trial, compared 5 years of tamoxifen or letrozole as monotherapy or their sequential administration (2 years of one drug followed by 3 years of the other). At median follow-up of 8.7 years, letrozole monotherapy was significantly better than tamoxifen monotherapy for both the primary DFS endpoint (HR 0.82) and the secondary OS (HR 0.79) distant recurrence-free interval (HR 0.79) and BC-free interval (HR 0.80) endpoints. On the contrary, at median follow-up of 8.0 years, there was no statistically significant difference in any endpoint between sequential therapies and letrozole monotherapy, sequential strategies being therefore a valid option in case of toxicity [15].

Likewise, the ATAC trial compared Anastrozole with tamoxifen, both for 5 years. At median follow-up of 120 months, both in the overall study population and particularly in ER+ patients, there were significant improvements in the Anastrozole group compared with the tamoxifen group, in terms of DFS (HR 0.86), time to recurrence (HR 0.79) and time to distant recurrence (HR 0.85). In ER+ patients, absolute differences in time to recurrence between Anastrozole and tamoxifen increased over time (2.7 % at 5 years, 4.3 % at 10 years) and recurrence rates remained significantly lower with Anastrozole as compared to tamoxifen after treatment completion (HR 0.81), although the carryover benefit decreased after 8 years. Fewer deaths after recurrence were reported with Anastrozole compared with tamoxifen in the ER+ subgroup (HR 0.87) but there was little difference in overall mortality (HR 0.95) [16].

Several other large randomized trials have compared one of the three third-generation AIs (Anastrozole, letrozole or Exemestane) with 5 years of tamoxifen, generally reporting reduced recurrence rates in the AIs treated groups but not a clear-cut reduction in BC mortality.

The latest EBCTCG meta-analysis included data on 31.920 women from randomized trials of different schedules as follows: 5 years of an AI versus 5 years of tamoxifen; 5 years of an AI versus 2–3 years of tamoxifen then the AI to year 5; 2–3 years of tamoxifen then an AI to year 5 versus 5 years of tamoxifen.

In the comparison of 5 years of an AI versus 5 years of tamoxifen, the recurrence rate ratios significantly favoured AIs during treatment (years 0–1 RR 0.64, years 2–4 RR 0.80) but non-significantly thereafter. The 10-year BC mortality was also lower with AIs than with tamoxifen (12.1 % vs. 14.2 %, RR 0.85). In the comparison of 5 years of an AI versus 2–3 years of tamoxifen then the AI to year 5, the recurrence rate ratios significantly favoured AIs when treatment differed (years 0–1 RR 0.74) but not when both groups received the AI (years 2–4), or thereafter; the BC mortality reduction was not significant (RR 0.89). In the comparison of 2–3 years of tamoxifen then an AI to year 5 versus 5 years of tamoxifen, the recurrence rate ratios significantly favoured AIs during years 2–4 when patients received the AI (RR 0.56) but not subsequently, and the 10-year BC mortality was lower when switching to the AI than when keeping on tamoxifen (8.7 % vs. 10.1 %). In summary, aggregating the three schedule comparisons, recurrence rate ratios favoured AIs when treatments differed (RR 0.70) but not significantly thereafter (RR 0.93). The BC mortality was also significantly reduced while treatments differed (RR 0.79), less subsequently (RR 0.89) and for all periods combined (RR 0.86).

The meta-analysis concluded that AIs reduce recurrence rates by about 30 % (proportionately) compared with tamoxifen while treatments differ, but not thereafter. Five years of an AI reduce the 10-year BC mortality rate by about 15 % compared with 5 years of tamoxifen, hence by about 40 % (proportionately) compared with no ET [17]. According to all most recent guidelines [7, 9], AIs should be therefore included at some point during adjuvant treatment.

Integration of AIs and tamoxifen, their upfront or sequential administration has therefore to be individually discussed and planned.

Also in postmenopausal women, the optimal duration of ET is still matter of debate.

The EBCTCG meta-analysis excluded trials comparing an AI after 5 years of tamoxifen versus stopping ET. This sequence has been investigated in the MA.17 trial, a double-blind, placebo-controlled trial designed to determine the effectiveness of 5 years of letrozole after completing 5 years of tamoxifen. The primary endpoint was DFS; secondary endpoints included OS, distant DFS (DDFS) and incidence of contralateral tumours. The trial was stopped early after an interim analysis showed that letrozole improved outcomes: after a median follow-up of 30 months, women in the letrozole arm had statistically significantly better DFS, DDFS and contralateral BC incidence than women in the placebo arm. OS was the same in both arms except in women with node-positive disease who had an improved OS with letrozole. The conclusion from the MA.17 trial was that letrozole after tamoxifen improves both DFS and DDFS but not OS, except in node-positive patients [18, 19].

Considering also the results of the previously mentioned ATLAS trial [3], it is appropriate discussing with patients at sufficient risk of relapse the extension of adjuvant ET beyond 5 years, always bearing in mind drugs' toxicity and patients' preference. The recent results of the phase III, randomized, placebo-controlled MA.17R trial, showed a significantly higher 5-year DFS in patients receiving additional 5 years of letrozole after 4.5–6 years of adjuvant AI, preceded in most patients (79 %) by tamoxifen, than in those under placebo (95 % versus 91 %, HR 0.66; P = 0.01) with the greatest reduction achieved in contralateral BC. The rate of OS was not higher between treatments (HR 0.97; P = 0.83). The superiority of letrozole was observed in all subgroups, with no signs of treatment interaction and the incidence of most toxic effects similar in the two groups, with the exception of bone related toxic effects, more common in the letrozole group. While waiting for the results of ongoing trials, 10 years of adjuvant AIs can represent a reasonable option to discuss in high-risk patients.

19.2.4 Neoadjuvant Therapy

Neoadjuvant chemotherapy trials have consistently reported lower response rates in ER+ BC when compared with ER− or human epidermal growth factor receptor 2-positive (HER2+) patients [20]. The German Breast Group demonstrated pathologic complete response (pCR) rates of 6.2 and 22.8 % for ER+ and ER- tumours, respectively (p = 0.0001) [21]. In addition, in 6.377 patients enrolled in 7 randomized trials of anthracycline–taxane-based chemotherapy, pCR showed to be a good DFS surrogate endpoint for patients with luminal B/HER2-negative, HER2-positive (non-luminal) and triple-negative disease but not for those with luminal A tumours [22]. Direct comparisons of neoadjuvant chemotherapy against ET are rare. In the GEICAM/2006-03 phase II trial, 95 patients were randomized to 8 cycles of chemotherapy (EC-T) or ET (Exemestane 25 mg daily combined with Goserelin in premenopausal patients) for 24 weeks. Overall, the clinical response rate was higher with chemotherapy (66 % vs. 48 %; p = 0.075). In an unplanned exploratory subgroup analysis based on Ki-67 levels (10 % cut-off), similar clinical response was achieved in both treatment groups in patients with low Ki-67 (chemotherapy 63 %, ET 58 %; p = 0.74), while patients with high Ki-67 had a better response with chemotherapy (67 % vs. 42 %; p = 0.075). These results seem to suggest patients with low proliferation index could potentially avoid neoadjuvant chemotherapy [23]. The Neoadjuvant Chemotherapy versus ENdocrine Therapy (NeoCENT) feasibility trial, comparing letrozole for 18–23 weeks to 6 cycles of FEC100, met the recruitment and tissue collection primary endpoints, but despite both treatments showed to be equally effective, a larger phase III trial was deemed unfeasible due to slow accrual [24]. ET can therefore be an attractive alternative to chemotherapy as neoadjuvant therapy at least for some women with ER+ locally advanced primary BC. As neoadjuvant ET usually takes longer to achieve tumour response, treatment should continue for at least 4–8 months or until maximal response [7].

19.2.5 Premenopausal Patients

Little evidence is available in premenopausal patients with locally advanced ER+ BC, for whom the main goal of neoadjuvant therapy is to allow breast conservative surgery (BCS).

The STAGE trial is the only phase III, randomized, multicenter study, randomly assigning patients to receive monthly Goserelin plus either Anastrozole or tamoxifen for 24 weeks before surgery. The primary endpoint was best overall tumour response (complete or partial response). Among the 185 patients who completed the 24-week treatment period, more patients in the Anastrozole group had a complete or partial response than those in the tamoxifen group (70.4 % vs. 50.5 %, respectively). The authors concluded that given its favourable risk–benefit profile, the combination of Anastrozole plus Goserelin could represent an alternative neoadjuvant treatment option for premenopausal women [25]. Despite these encouraging results, data are insufficient to recommend this strategy outside of clinical trials [8].

19.2.6 Postmenopausal Patients

In postmenopausal patients, several randomized trials demonstrated the superiority of AIs over tamoxifen.

The P024 study, a large multinational double-blind trial comparing letrozole versus tamoxifen, showed a significantly better overall response rate (ORR) (55 % vs. 36 %, respectively, $p < 0.001$) and BCS rate (45 % vs. 35 %) with letrozole than with tamoxifen. letrozole was also significantly more effective than tamoxifen in reducing tumour proliferation, measured by Ki-67 immunohistochemistry ($p = 0.0009$) [26]. In addition, at a median follow-up of 61.2 months, patients with pathological stage 1 or 0 and a low-risk biomarker profile in the surgical specimen (Preoperative Endocrine Prognostic Index [PEPI] score 0) had an extremely low risk of relapse (100 % relapse-free survival [RFS]) compared with higher stages ($p < 0.001$) therefore unlikely to benefit from additional adjuvant chemotherapy [27]. On the contrary, a non-statistically significant difference was found between Anastrozole and tamoxifen in the Preoperative Arimidex Compared to Tamoxifen (PROACT) randomized, multicenter trial in women with large, operable (T2-3, N0-2, M0), or potentially operable (T4b, N0-2, M0) BC. Patients received Anastrozole or tamoxifen, with or without chemotherapy for 12 weeks. Objective responses (by ultrasound) were achieved in 39.5 and 35.4 % of patients under Anastrozole and tamoxifen, respectively. In ET-only treated patients, surgery became feasible in 47.2 % of patients receiving Anastrozole and 38.3 % of those receiving tamoxifen ($p = 0.15$) [28].

The IMPACT trial randomized women with ER+ operable or locally advanced BC (LABC) to Anastrozole, tamoxifen, or a combination of tamoxifen and Anastrozole for 12 weeks. Objective response rates, measured either by clinical examination or ultrasound, were not statistically significantly different between treatment arms. A trend towards an improved rate of BCS was observed for patients receiving Anastrozole over tamoxifen (44 % vs. 31 %), which was also not statistically significant ($p = 0.23$). A meta-analysis of these trials supported the notion that an AI is more effective than tamoxifen for promoting breast conservation [29].

Another randomized, double-blind, multicenter study was conducted to compare the anti-tumour activity of letrozole versus tamoxifen. After 4 months of treatment, the overall objective response rate by palpation was significantly superior in the letrozole group compared with tamoxifen (55 % vs. 36 %, $p < 0.001$). The secondary endpoints of ultrasound and mammographic response and BCS rate confirmed letrozole to be significantly superior [30].

In the randomized phase II ACOSOG Z1031 trial, women with clinical stage II-III ER+ BC were randomly assigned to receive neoadjuvant Exemestane, letrozole or Anastrozole for 16 weeks. The primary endpoint was clinical response; secondary endpoints included BCS and Ki-67 changes. Although higher clinical response rates were reported with letrozole and Anastrozole compared with Exemestane, no differences in surgical outcome or Ki-67 changes were detected [31].

On the basis of all these data, it can be concluded that either AI is more effective than tamoxifen in decreasing tumour size and facilitating conservative surgery.

19.3 Metastatic Therapy

Approximately, 10 % of newly diagnosed BC patients have locally advanced and/or metastatic disease and 30 % of women with early BC develop advanced disease during their disease history. As reported in the ABC2 ESO-ESMO international consensus guidelines, ET should be the first-choice therapy in ER+/HER2− disease, also in presence of visceral metastases [32]. Several 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 [33]. Chemotherapy should be preferred only in case of high disease burden, life-threatening conditions requiring a rapid disease response or in presence of endocrine resistance. Endocrine resistance has been defined as follows: (1) primary endocrine resistance when a relapse occurs during the first two years of adjuvant ET, or a disease progression develops within the first six months of first-line ET for advanced breast cancer (ABC) and (2) secondary (or acquired) resistance when a relapse occurs after the first two years while on adjuvant ET, within 12 months of completing adjuvant ET, or progressive disease develops at least six months after initiating ET for ABC [32].

The selection of the most appropriate ET should take into account the menopausal status of the patient, the type of adjuvant ET received, any past medical history or comorbidities and patient's wishes. The concomitant use of chemotherapy and ET is not recommended, despite an increased ORR or time to progression (TTP) shown in some trials, as potentially antagonistic, but clinical trials in this area, with the newer classes of ETs and chemotherapy regimens/approaches, are lacking.

19.3.1 Premenopausal Patients

In premenopausal women, OFS/ablation combined with oral ET is the first-choice therapy; tamoxifen is the standard oral ET unless tamoxifen resistance is proven [8].

Ovarian ablation (OA) has long been established as an effective therapy for premenopausal women with ABC, with response rates ranging from 14 to 70 % in several studies. Both the presence and degree of HR expression are strongly predictive of response to endocrine manipulations, with responses seen in approximately 60 % of women having both ER+ and PR+ tumours, compared with 30 % in patients with either ER+ or PR+ disease alone [34].

After the introduction of GnRHa, several phase II trials investigated their efficacy in pre- and perimenopausal women with ABC. A meta-analysis of phase II trials with monthly Goserelin in 228 patients reported a median survival of 26.5 months, an ORR of 36 % (44 % in ER+ patients) and a median duration of response of 44 weeks, comparable to the outcomes historically obtained with oophorectomy in similar patient populations [35]. OA by laparoscopic bilateral oophorectomy ensures definitive oestrogen suppression and contraception, avoids potential initial tumour 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.

The comparison between combined ET (tamoxifen plus GnRHa) and single agent ET has been summarized in a meta-analysis of 4 clinical trials randomizing a total of 506 women with ABC to GnRHa alone or GnRHa plus tamoxifen. With a median follow-up of 6.8 years, the combination was superior to monotherapy for all endpoints, with significant benefits in mortality (22 % relative reduction), disease progression (30 % relative reduction), objective clinical response (39 % vs. 30 %) rates as well as response duration (19 months vs. 11 months) [36].

Little data are available on the association of GnRHa and AIs as first- and second-line therapy.

Two small phase II trials evaluated the efficacy of Goserelin plus Anastrozole in women with advanced or recurrent BC. The JMTO BC08-01 trial enrolled 37 patients after failure to standard GnRHa plus tamoxifen; the primary endpoint was objective response rate; secondary endpoints included PFS, OS, clinical benefit rate (CBR, defined as disease response plus disease stabilization ≥6 months) and safety. The objective response rate was 18.9 %, the CBR was 62.2 % and the median PFS was 7.3 months. Eight patients had adverse drug reactions but none resulted in treatment discontinuation [37]. The second phase II study was a prospective, single-arm, multicenter trial in which 35 patients were treated with monthly Goserelin and Anastrozole, the latter starting 21 days after the first GnRHa injection. Patients continued on treatment until disease progression or unacceptable toxicity. One patient (3.1 %) experienced a complete response, 11 (34.4 %) a partial response and 11 (34.4 %) a stable disease lasting at least 6 months, translating in a CBR of 71.9 %. Median TTP was 8.3 months and median survival was not reached at time of publication. As expected, the most common adverse events were fatigue (50 %), arthralgia (53 %) and hot flashes (59 %); no grade 4–5 toxicities were reported [38].

Similar results derive from a single-institution, retrospective analysis of Goserelin plus letrozole in a total of 52 patients as first- (n = 36) or second-line (n = 16) ET. The median treatment duration was 11 months and the median follow-up 31 months. The objective response rate was 21.1 %, including two complete responses (3.8 %) and nine partial responses (17.3 %); the CBR was 50.0 % for an overall clinical benefit of 71.1 % and the PFS was 10 months. Therapy was well tolerated; no grade 3–4 toxicities were reported [39].

Little data are also available on the association of GnRHa and Fulvestrant in this setting. In a small study (n = 26), patients eligible for ET received low-dose (LD) Fulvestrant (250 mg/monthly) and monthly Goserelin as first- to fourth-line therapy. The primary endpoint was CBR. Eighty-one per cent of patients were pre-treated with tamoxifen and 69 % had received prior AIs in combination with Goserelin. The majority of patients (69 %) presented with visceral metastases. The CBR was 58 %, median TTP was 6 months and OS 32 months [40]. Although the drug does appear to be active in this setting, it would deserve further evaluation, made difficult by the forthcoming patent expiration.

19.3.2 Postmenopausal Patients

In postmenopausal patients, the main ET options include the following: AIs, tamoxifen, high-dose (HD) Fulvestrant (i.e. 500 mg monthly) and megestrol acetate. The choice is based mainly on previous ETs received either in the adjuvant and/or advanced disease settings.

In first line, the superiority of AIs over tamoxifen has been tested in several trials [41–44]. A meta-analysis of 6 eligible trials (2.560 patients) showed a significant difference favouring AIs over tamoxifen in ORR (HR 1.56; 95 % CI 1.17–2.07; p = 0.002) and clinical benefit (HR 1.70; 95 % CI 1.24–2.33; p = 0.0009) and a non-significant trend towards an improved OS (HR 1.95; 95 % CI 0.88–4.30; p = 0.10). Toxicities did not differ significantly except for increased vaginal bleeding and thromboembolic events associated with tamoxifen [45]. In the FIRST phase II study [46], HD Fulvestrant proved to be superior to Anastrozole in terms of OS (median OS 54.1 months vs. 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: confirmation is awaited in the larger phase III FALCON trial

(NCT01602380). The combination of a non-steroidal AI and LD Fulvestrant showed discordant results in 2 phase III trials with similar designs [47, 48]. Subset analysis in the successful SWOG study suggests a benefit in PFS and OS for the combination therapy only in patients without prior adjuvant tamoxifen 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 [49].

Beyond first line, the optimal sequence of endocrine agents is uncertain and depends on which drugs were used in the neo/adjuvant and first-line ABC settings.

All trials comparing Fulvestrant to AIs in this setting were conducted with LD Fulvestrant. Both treatments are effective and well tolerated with a different toxicity profile which can guide treatment choice in the individual patient; joint disorders (i.e. arthralgia, arthrosis and arthritis), occurring more frequently in patients receiving AIs, are the only significant difference [50–52]. A potential advantage of Fulvestrant over AIs is the monthly parenteral administration, which can enhance long-term adherence at least in selected patients [53].

In the CONFIRM multicenter phase III study, 736 patients were randomly assigned to either HD or LD monthly Fulvestrant based on the observation from preoperative trials that both clinical and biological effects (ER/PR receptor and Ki-67 downregulation) could be dose-dependent. The HD schedule resulted in a significantly longer PFS, corresponding to a 20 % reduction in risk of progression. Fulvestrant 500 mg was well tolerated with no dose-dependent adverse events [54]. Median OS was 26.4 months for HD and 22.3 months for LD Fulvestrant (HR ratio 0.81; 95 % CI 0.69–0.96; nominal $p = 0.02$), corresponding to a 19 % reduction in the risk of death. Type of first subsequent therapy and objective responses to first subsequent therapy were well balanced between the two treatment groups [55].

19.3.3 Hormone Receptor Positive/Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer (HR+/HER2+)

Approximately, 20 % of BC harbours an overexpression/amplification of HER2 and nearly 50 % of these tumours are also ER+ and/or PR+. The co-activation of both HR and HER2 pathways involves a different disease natural history and patients' outcome if compared with both HR−/HER2+ and HR+/HER2− tumours. In particular, prospective studies demonstrated different patterns of recurrence with more early relapses (instead of late) and brain metastases (instead of bone) as first site of relapse in HR−/HER2+ tumours compared with HR+/HER2+ tumours.

Moreover, the co-expression of HR and HER2 pathways seems to influence treatment efficacy: HER2 overexpression usually correlates with low HR expression and low response to ET, and it has been demonstrated that HER2 pathway activation may contribute to the development of endocrine resistance [56].

In the *adjuvant* setting, poorer outcomes have been shown in patients with HR+/HER2+ tumours compared with HR+/HER2− tumours.

Retrospective analysis of the ATAC and BIG1-98 trials reported worse clinical outcomes in postmenopausal HER2+ patients regardless of treatment type, confirmed the overall benefit of AIs over tamoxifen in this subgroup but failed to demonstrate a clear correlation between HER2 status, ET and long-term outcomes, in women frequently not exposed to HER2-targeted therapy due to enrolment periods [57, 58]. In premenopausal women enrolled in SOFT [11], the addition of OFS to tamoxifen appeared to be beneficial over tamoxifen alone (HR 0.78; 95 % CI, 0.62–0.98; $p = 0.03$) in HER2+ patients as previously reported by others [59]. On the other hand, in the combined TEXT–SOFT analysis [11], in the presence of OFS, Exemestane did not confer any advantage over tamoxifen (DFS HR 1.25; 95 % CI 0.80–1.94). HER2 central assessment and further analysis are, however, needed before HER2 status is used for oral ET selection in premenopausal women.

In the *advanced* setting, a retrospective analysis demonstrated better responses to chemotherapy plus anti-HER2 therapy in HR- tumours, whereas in HR+/HER2+ patients a significant benefit in PFS was achieved if maintenance ET was added to trastuzumab after chemotherapy [60]. On the contrary, in a retrospective observational study including patients with HER2+ disease treated with trastuzumab-based first-line therapy, a better long-term clinical benefit was observed in HR+ patients, probably because they received trastuzumab maintenance and/or ET after first-line treatment [61].

A prospective observational study in more than 1.000 HER2+ BC showed prolonged PSF and OS in HR+/HER2+ patients treated with dual targeting therapies (ET and anti-HER2 drugs, with or without chemotherapy), in comparison with patients treated with anti-HER2 therapy only [62].

All these data suggest the combination of ET with anti-HER2 therapies might represent a strategy to overcome both endocrine and anti-HER2 resistance in patients with advanced HR+/HER2+ BC. The TAnDEM trial was the first randomized phase III study to compare ET alone (Anastrozole) and ET plus HER2-targeted therapy (Anastrozole plus trastuzumab). The study showed an improved TTP for the combination over ET alone (2.4 months and 4.8 months

respectively, $p = 0.0016$), with a median PFS of 3.8 months versus 5.6 months, an ORR of 7 % versus 20 % and a CBR of 28 % versus 43 %, respectively [63].

The eLEcTRA trial investigated letrozole versus the combination letrozole-trastuzumab. The results were in favour of the combination with a PFS of 14.1 months versus 3.3 months, ORR of 27 % versus 13 % and CBR of 65 % versus 39 % [64]. An additional phase III trial randomized 1.286 postmenopausal women to letrozole plus placebo or Lapatinib (1500 mg once daily) as first-line therapy [65]. In the subgroup of women with HR+/HER2+ disease ($n = 219$), after a median follow-up of 1.8 years, the combination was superior to letrozole alone in terms of median PFS (8.2 and 3.0 months, respectively, HR 0.71; 95 % CI 0.53–0.96, $p = 0.019$) and CBR (48 % vs. 29 %). There was no significant improvement in OS; however, less than 50 % of OS events had occurred at time of reporting.

Even though none of these trials demonstrated a clear benefit in OS, the ABC guidelines recommend the combination of trastuzumab or Lapatinib with an AIs as first-line therapy in postmenopausal women with HR+/HER2+ BC if chemotherapy is not clearly indicated [32].

19.4 Overcoming Endocrine Resistance

The main studied mechanisms of endocrine resistance refer to ER alterations, such as mutations, amplifications or translocations, and/or to upregulation of alternative pathways, such as the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway.

The phase III BOLERO-2 trial investigated the role of everolimus in postmenopausal ER+ patients. Patients previously treated with a non-steroidal AI (NSAI) in the adjuvant setting or progressing under a NSAI in the metastatic setting were randomized to everolimus (10 mg daily) plus Exemestane (25 mg daily) versus placebo plus Exemestane. Previous therapy also included tamoxifen (48 %), LD Fulvestrant (16 %) and chemotherapy (68 %). At the first interim analysis, based on central disease evaluation, the median PFS favoured the combination versus placebo (10.6 vs. 4.1 months, respectively, HR 0.36, $p < 0.001$). At final analysis, with a median 18-month follow-up, the median PFS remained significantly longer with everolimus plus Exemestane versus placebo plus Exemestane (central review: 11.0 vs. 4.1 months, respectively, HR 0.38, $p < 0.0001$) in the overall population and in all prospectively defined subgroups, including patients with visceral metastases. The most common grade 3–4 adverse events in the everolimus arm were stomatitis, anaemia, dyspnea, hyperglycaemia, fatigue and pneumonitis. The OS analysis (secondary endpoint) did not confirm a statistically significant improvement in the everolimus arm (median OS of 31.0 months compared with 26.6 months in the placebo arm, HR 0.89, $p = 0.14$) [66–68].

Everolimus has been also investigated in combination with tamoxifen in a small randomized phase II trial in postmenopausal patients with metastatic BC resistant to AIs. Patients were randomized to tamoxifen 20 mg daily plus everolimus 10 mg daily or tamoxifen alone. The primary endpoint was CBR: the 6-month CBR was 61 % with tamoxifen plus everolimus and 42 % with tamoxifen alone. TTP also increased from 4.5 months to 8.6 months with tamoxifen plus everolimus, corresponding to a 46 % reduction in the risk of progression (HR 0.54). The risk of death was reduced by 55 % with the combination (HR 0.81). The main toxicities associated with tamoxifen plus everolimus were fatigue, stomatitis, rash, anorexia and diarrhoea [69].

Recently, evidence has been collected on the role of cyclin-dependent kinases 4 and 6 (CDK4-6) in the growth of ER + BC, based on their role in promoting progression from the G1 to the S phase of the cell cycle. The randomized phase I/II PALOMA-1 study showed a significant PFS improvement in patients treated with the combination of the CDK4/6 inhibitor Palbociclib and letrozole compared with letrozole alone as first-line treatment (20.2 months vs. 10.2 months, HR 0.488, $p = 0.0004$). The preliminary OS analysis suggested a non-statistically significant trend towards increased OS (37.5 months vs. 33.3 months, HR 0.813, $p = 0.2105$) in the combination arm. Based on these results, the FDA granted Palbociclib-accelerated approval as first-line treatment for postmenopausal women with HR+/HER2− ABC and the drug is going to become commercially available also in European countries [70]. The double-blind phase III PALOMA3 trial randomized 521 patients, regardless of menopausal status, who relapsed or progressed during prior ET, to receive Palbociclib plus HD Fulvestrant or HD Fulvestrant plus placebo. Premenopausal or perimenopausal women also received Goserelin. The primary endpoint was investigator-assessed PFS. Secondary endpoints included OS, objective response, CBR, patient-reported outcomes and safety. The median PFS was 9.2 months with Palbociclib-Fulvestrant and 3.8 months with placebo-Fulvestrant (HR 0.42). Of note, the relative difference in PFS was independent of menopausal status, providing a new treatment option also for young patients with ER+ ABC. Overall objective response was 10.4 % with Palbociclib-Fulvestrant and 6.3 % with placebo-Fulvestrant ($p = 0.16$). CBR at the interim analysis was 34.0 % with Palbociclib-Fulvestrant and 19.0 % with placebo-Fulvestrant ($p < 0.001$). At the time of the interim analysis, OS data were immature, with a total of 28 deaths: 19 patients (5.5 %) in the Palbociclib-Fulvestrant group and 9 (5.2 %) in the

placebo-Fulvestrant group. The most common grade 3–4 adverse events in the Palbociclib-Fulvestrant group were neutropenia, leukopenia, anaemia, thrombocytopenia and fatigue [71].

19.5 New Perspectives

Additional mechanisms of ET resistance are under active investigation. An increased genetic heterogeneity has been demonstrated in metastatic tumour cells in comparison with the primary. Many hypotheses could explain this finding: the selection pressure favouring a resistant subclone, altered gene expression profile secondary to treatment exposure and stochastic mutations owing to genetic instability. While studying the most common pathways involved in these mechanisms of resistance, efforts are also directed to the identification of biomarkers predictive of response.

Phase II and III studies are ongoing further exploring the cost-effectiveness of mTOR inhibitors (also in the neoadjuvant setting), and the role of different CDK4-6 inhibitors (ribociclib, Abemaciclib), histone deacetylase inhibitors (entinostat), PI3K inhibitors (pictilisib, buparlisib). Such efforts could hopefully lead to an improvement in understanding and overcoming the mechanisms of resistance to ET. 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 such a resistance [72]. 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.

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