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Review

The choice of systemic adjuvant therapy in receptor-positive early breast cancer

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Abstract

Patients with endocrine-responsive breast cancer represent a distinct population for which tailored adjuvant treatments are needed. Endocrine therapy is mandatory for this population. For premenopausal patients, ovarian ablation or tamoxifen can be recommended; the combination of both, as well as the combination of ovarian ablation and aromatase inhibitors is under investigation. For postmenopausal patients, tamoxifen for 5 years is the 'standard of care'. Anastrozole can be recommended for patients with a contraindication to tamoxifen. The addition of 5 years of letrozole after 5 years of tamoxifen has yielded benefits in terms of disease-free survival. The sequential use of tamoxifen and exemestane was superior to tamoxifen for 5 years. However, in both studies, long-term toxicity is still not fully evaluated. The addition of chemotherapy to endocrine treatment can be recommended for patients at high risk of relapse and in young patients. Chemotherapy should consist of 3–6 cycles of cyclophosphamide, methotrexate, 5-fluorouracil or of an anthracycline-containing regimen. The addition of taxanes cannot be routinely recommended in this population. Endocrine treatment should start after completion of chemotherapy.

Keywords: Breast cancer; Endocrine-responsive; Endocrine therapy; Chemotherapy; Ovarian ablation; Tamoxifen; Aromatase inhibitors

1. Introduction

Breast cancer is the most frequently diagnosed cancer in the Western world, with a lifetime risk in the more developed countries of one in eight women [1]. The incidence of the disease is continuously increasing, both in industrialised and developing countries, and more than 1 000 000 cases are diagnosed each year worldwide [2]. During recent years, mortality due to breast cancer has started to decline and the reasons for this have been widely debated [3].

Several features have been used for determination of prognosis, but the most reliable factor remains the nodal status [4]. Hormone receptors [5–11] (oestrogen receptors – ER – and progesterone receptors – PgR) and HER-2/*neu* overexpression [12] are the most important predictors of response to therapy. The proportion of ER-positive tumours is higher with increasing age and reaches approximately 90% in elderly patients [13]. The percentage of ER- and PgR-expressing cells discriminating between endocrine-responsive and endocrine-non-responsive tumours is unknown. Even a low number of cells (1%) staining positive may identify a cohort of tumours with some responsiveness to endocrine therapies [14]. Conventionally, approximately 10% of cells staining positive for both ER and PgR are considered as a reasonable threshold for the definition of endocrine responsiveness [4]. Gene expression profiling studies support a distinct pattern for steroid hormone receptor-absent disease compared with disease showing some or high levels of receptors [15–18].

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Systemic adjuvant therapy has been shown to reduce relapses in treated women and to prolong their survival. Treatments consist of cytotoxic agents, hormonal manipulations or a combination of both modalities [19]. Ongoing clinical trials are currently investigating the role of additional agents (trastuzumab, bisphosphonates, Cox-2 inhibitors, etc.) [20–24].

Evidence from clinical trials has been used to draw guidelines for the choice of systemic adjuvant therapy after surgery for breast cancer (for example, the International Consensus Panel during the St. Gallen Conference, 2003). Four issues must be considered for treatment decisions outside of the framework of clinical trials: prognosis, prediction of treatment response, extrapolation of results on treatment effects obtained from randomised trials, and consideration of patient's preference concerning absolute and relative risks and benefits of effective therapies [4].

2. Endocrine therapies

Long before the discovery of hormone receptors by Jensen in 1968 [25], endocrine therapies have been used for the treatment of breast cancer.

2.1. Ovarian function suppression

Ovarian ablation was the first form of systemic treatment for breast cancer. Its efficacy in metastatic disease was described by Beatson in 1896 [26]. The first randomised trials investigating ovarian ablation in the adjuvant setting began in 1948. The combined analysis of these early trials conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [27] has unequivocally established that ovarian ablation as a single intervention, whether induced by surgery or radiotherapy, is associated with a significant improvement in recurrence-free and overall survival among women less than 50 years of age. Indirect comparisons show that the magnitude of the benefit derived from ovarian function suppression is similar to that observed with adjuvant chemotherapy [28] or tamoxifen [29]. During the last 20 years, luteinising-hormone-releasing-hormone (LHRH) analogues have frequently substituted surgical or radiotherapy-induced ablation because of their ease of administration and the reversibility of their effects. Cytotoxic chemotherapy represents a fourth form of ovarian function suppression because of its capacity to cause temporary or permanent ovarian dysfunction in premenopausal women. The risk of chemotherapy-related amenorrhoea is directly related to age at the time of treatment and varies with type, dose, and duration of chemotherapy. In general, less than 50% of women below 40 years of age will be rendered postmenopausal by standard adjuvant chemotherapy regimens, whereas most women aged 40 or more years of age will become permanently menopausal [30–32]. Therefore, the possibility of fertility loss after adjuvant treatment for breast cancer should always be discussed with young patients with favourable prognosis prior to planning adjuvant strategies.

HER2/*neu* overexpression has been associated with a reduced responsiveness to endocrine therapy, particularly to tamoxifen. In premenopausal patients with tumours expressing HER2/*neu* the addition of ovarian ablation to tamoxifen has been shown to reverse non-responsiveness [33].

The combination of ovarian function suppression and tamoxifen in premenopausal patients has been investigated in a meta-analysis of four trials including 506 women with advanced breast cancer randomised to either LHRH agonist alone or to the combination of LHRH agonist plus tamoxifen. A significant survival ($P = 0.02$) and progression-free survival (PFS) benefit ($P = 0.0003$) were observed in favour of the combined treatment [34].

In the adjuvant setting, over 700 premenopausal women with early-stage breast cancer recruited in China and Vietnam have been included in a trial comparing oophorectomy and 5 years of tamoxifen, either at the time of mastectomy or at relapse. Preliminary results suggest that immediate combined treatment significantly improves the 5-year disease-free survival (DFS) and overall survival (OS) in patients with receptor-positive tumours compared with no immediate adjuvant therapy [35].

No study has yet been performed in the adjuvant setting to compare tamoxifen plus ovarian function suppression with tamoxifen alone in premenopausal women with endocrine-responsive disease. An ongoing global trial conducted by the Breast International Group (BIG) and the North American Intergroup (Trial SOFT) investigates the role of the combination of oophorectomy with tamoxifen or with the aromatase inhibitor exemestane compared with tamoxifen alone in the adjuvant setting [36,37].

2.2. Tamoxifen

Tamoxifen for 5 years has been shown in women with ER-positive tumours to reduce recurrence and contralateral breast cancer by approximately 50% and mortality by 28%. These benefits appeared to be independent of age, menopausal status and additional use of chemotherapy. Benefits from treatment are larger for patients treated for 5 years than for those receiving tamoxifen for a shorter period. No benefit could be observed for continuing tamoxifen treatment longer than 5 years [29].

Tamoxifen is associated with several side-effects including increased risk for endometrial cancer and thromboembolic disorders [38]. Investigations of bone

mineral density in patients treated with prolonged tamoxifen have reported a possible decrease of density in premenopausal women and a protective effect of tamoxifen in the postmenopausal cohort [39]. The Scottish Trial has reported a decrease of death from myocardial infarction for patients treated with tamoxifen [40]. More recently, a report at the 2004 ESMO Congress from the Swedish tamoxifen trial of 5 years *versus* 2 has confirmed that the mortality from coronary heart disease was significantly reduced in the five year group [82].

2.3. Aromatase inhibitors

Inhibition of the enzyme aromatase is an important approach for reducing growth stimulatory effects of oestrogens in hormone-dependent breast cancer. The new generation of aromatase-inhibitors has shown an acceptable toxicity profile compared with the first compound (aminoglutethimide) and three molecules have been studied in the adjuvant setting [41].

In the Arimidex, Tamoxifen, Alone or in combination (ATAC) Trial, a randomised, double-blind trial, 9366 postmenopausal patients mostly with ER-positive tumours (84%) were randomised to receive tamoxifen alone ($n = 3116$), anastrozole alone ($n = 3125$) or the combination of anastrozole plus tamoxifen ($n = 3125$) for 5 years. After a median follow-up of 33.3 months, DFS at 3 years was significantly improved with anastrozole (89.4% for anastrozole and 87.4% for tamoxifen, hazard ratio (HR) = 0.83, $P = 0.013$). The combination did not add any benefit compared with both single drugs (87.2%, HR = 1.02, $P = 0.8$). Anastrozole was significantly better tolerated than tamoxifen with respect to endometrial cancer and cerebrovascular and venous thromboembolic events and hot flushes. Tamoxifen was significantly better tolerated than anastrozole with respect to musculoskeletal disorders and bone fractures in general. No increase in hip fractures was seen for anastrozole versus tamoxifen (11 versus 13, respectively) [42–44].

The second compound, letrozole, has been evaluated in a trial conducted by the National Cancer Institute of Canada (NCIC). Postmenopausal women completing 5 years of tamoxifen and free of recurrence were randomly assigned to 5 years of letrozole or placebo. A total of 5187 women were enrolled and, at a median follow-up of 2.4 years, patients receiving letrozole showed a significant increase of the estimated four-year DFS rates (93% for letrozole and 87% for placebo). Forty-two women in the placebo group and 31 women in the letrozole group have died ($P = 0.25$). Hot flashes and musculoskeletal disorders were more frequent in the letrozole-treated group, but vaginal bleeding was less frequent. New diagnoses of osteoporosis were more common in women receiving letrozole (5.8%) than in those receiving placebo (4.5%) ($P = 0.07$), but the rates of fracture were not significantly increased in the letrozole-treated group [45].

The Intergroup Exemestane Study has investigated the third compound in a trial comparing 5 years of tamoxifen to the sequential use of tamoxifen (for 2–3 years) and exemestane (for 2–3 years). More than 4700 patients have been enrolled and after a median follow-up of 30.6 months, the unadjusted HR for recurrence in the sequential tamoxifen–exemestane group compared with the tamoxifen group was 0.68 ($P < 0.001$), representing a 32% reduction of risk and corresponding to an absolute benefit in terms of DFS of 4.7% at three years after randomisation. OS was not significantly different in the two groups, with 93 deaths occurring in the exemestane group and 106 in the tamoxifen group. Severe toxic effects of exemestane were rare. Contralateral breast cancer occurred in 20 patients in the tamoxifen group and 9 in the exemestane group ($P = 0.04$) [46].

The aromatase inhibitor arm in each of the three studies was associated with improved DFS and fairly good tolerability. However, long-term follow-up and long-term toxicity data are missing for all of the compounds [47].

3. Chemotherapy

Polychemotherapy showed a proportional reduction of recurrence for patients with ER-positive disease and with both node-positive and -negative presentation of 33% in the age group below 50 years and of 18% for patients between 50 and 69 years of age. For mortality, the reduction was 20% among women aged under 50 years and 9% among those aged 50–69 years. Little data exist on the use of chemotherapy in patients and 70 years older [28].

In general, adjuvant chemotherapy regimens consist of 3–6 cycles of classical cyclophosphamide, methotrexate and 5-fluorouracil (CMF) [48–51] or 4 cycles of doxorubicin and cyclophosphamide (AC) [52]. More intensive combinations with the sequential use of taxanes after 4 cycles of AC have not yet proven superior to conventional regimens in patients with ER-positive disease [53,54], but docetaxel combined with AC (TAC) proved to be superior to FAC in patients with ER-positive and -negative primaries [55].

High-dose chemotherapy with stem cell support cannot routinely be recommended. However, the subgroup analysis of Trial 15 of the International Breast Cancer Study Group (IBCSG) showed a benefit using this procedure over standard chemotherapy for younger patients with ER-positive tumours. This benefit could be due to the higher prevalence and additional benefit of ovarian function suppression observed with the high-dose regimen (amenorrhoea in 61% *vs.* 24% for standard chemotherapy group) [56].

A recently published trial examining dose-dense chemotherapy including paclitaxel showed a significant benefit over standard chemotherapy, but the benefit in terms of overall reduction in hazard was smaller (19%) for patients with ER-positive disease compared with ER-negative (32%) [57].

Chemotherapy alone has been investigated in a trial of the American Intergroup, including 406 women with node-negative and either ER-positive tumours larger than 3 cm in diameter or ER-negative disease. Patients were randomly assigned to receive six four-weeks cycles of CMF with prednisone (CMFP) or no treatment. There was a statistically significant increase in the 10-year DFS in the chemotherapy group compared with the control group (73% *vs.* 58%, respectively, $P = 0.0006$) and in OS (81% *vs.* 71%, respectively, $P = 0.02$), both in the pre- and postmenopausal subgroups. Chemotherapy was beneficial for patients with large tumours, both ER+ and ER-, showing a 10-year DFS of 70% *vs.* 51% ($P = 0.0009$) and OS of 75% *vs.* 65% ($P = 0.06$) [58].

The use of chemotherapy in ER-positive patients has been challenged by the results of several trials comparing chemotherapy with different endocrine therapies, mostly ovarian function suppression or tamoxifen.

- The Italian Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group (GROCTA) reported data for patients with node-positive ER-positive tumours treated with either tamoxifen for 5 years, 6 courses of intravenous (i.v.) CMF followed by 4 courses of epirubicin, or a combination of both regimens. At a median follow-up of 5 years, the addition of chemotherapy to tamoxifen did not significantly improve the results achieved by tamoxifen alone, irrespective of menopausal status, but tamoxifen appeared to be significantly more effective than chemotherapy in postmenopausal women [59].
- The same observation was made in the trial presented by the Scottish Group and investigating in 332 premenopausal node-positive breast cancer patients either ovarian ablation or CMF, each with or without prednisolone 7.5 mg daily for 5 years. At 12 years follow-up, no significant differences were detected in the relapse rates, or in event-free (EFS) or total survival. However, ovarian ablation was associated with improved survival in patients with ER concentrations of 20 fmol/mg protein or more and CMF was significantly more beneficial for patients with values less than 20 fmol/mg protein [60].
- The Zoladex Early Breast Cancer Research Association (ZEBRA) trial showed for patients with ER-positive tumours the equivalence between goserelin and CMF in terms of DFS. Amenorrhoea occurred in more than 95% of goserelin patients by 6 months *vs.* 58.6% of CMF patients. Menses returned in most goserelin patients after therapy stopped, whereas amenorrhoea was generally permanent in CMF patients (22.6% *vs* 76.9% amenorrhoeic at 3 years) [61].
- The Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 5, comparing in 1045 premenopausal women with ER- or PgR-positive tumours i.v. CMF or 3 years of goserelin plus 5 years of tamoxifen showed that the endocrine therapy significantly improved recurrence-free survival compared with CMF [62].
- The Zoladex in Premenopausal Patients (ZIPP) Trial was set up with a pragmatic design to address the question of whether goserelin offered additional benefit to women managed according to the standard local therapy prescribed at the centre where they were treated. Patients could also be randomised to tamoxifen in a 2×2 factorial design. Of the 2710 patients enrolled (1356 control, 1354 goserelin), 1800 were also randomised to tamoxifen (899 control, 901 tamoxifen). For the rest, an elective decision was made. Patients randomised to goserelin had a prolonged EFS (Relative Risk = 0.80) [63].
- Boccardo and colleagues reported no difference in DFS and OS for either 6 cycles of CMF ($n = 120$), or 5 years of tamoxifen plus ovarian suppression with surgical oophorectomy, ovarian irradiation or monthly goserelin ($n = 124$) in pre/perimenopausal ER-positive patients [64].
- The observation of comparable efficacy for endocrine manipulations and chemotherapy in ER-positive patients was also confirmed with chemotherapy regimens containing anthracyclines [65,66].

4. Chemoendocrine therapy

The use of the combination of chemotherapy and endocrine manipulations has been stimulated by the hope of increased efficacy and non-cumulative toxicity.

The addition of ovarian ablation to chemotherapy failed to show an improvement in the results most probably because of the ovarian function suppression already resulting from the chemotherapy itself [67].

By contrast, it has been observed that the addition of chemotherapy to tamoxifen produced some additional benefits and, similarly, tamoxifen has been shown to add to the benefits of chemotherapy [28,29,68].

In the IBCSG trial VIII, in 1063 pre- and perimenopausal patients with lymph node-negative breast cancer, goserelin for 24 months ($n = 346$), six courses of "classical" CMF-chemotherapy ($n = 360$), or six courses of classical CMF followed by 18 months of goserelin ($n = 357$) were compared. Tumours were mostly

ER-positive (68%). After a median follow-up of 7 years, patients with ER-negative tumours achieved better DFS if they received CMF (5-year DFS for CMF = 84%; 5-year DFS for CMF → goserelin = 88%) than if they received goserelin alone (5-year DFS = 73%). By contrast, for patients with ER-positive disease, chemotherapy alone and goserelin alone provided similar outcomes (5-year DFS for both treatment groups = 81%), whereas sequential therapy (5-year DFS for CMF→goserelin = 86%) provided a statistically non-significant improvement compared with either modality alone, primarily in younger women that have been shown to carry a worse prognosis, in particular if ER-positive and treated by chemotherapy alone [69].

The report of National Surgical Adjuvant Breast and Bowel Project (NSABP) B-20 trial shows a survival benefit for the combination of chemo-endocrine therapy (tamoxifen plus either MF or CMF) over tamoxifen alone. The risk of treatment failure was reduced after both types of chemotherapy, regardless of tumour size, tumour ER or PgR receptor level, or patient age; however, the reduction was greatest in patients aged 49 years or less [70].

The value of the addition of anthracycline-containing chemotherapy in ER-positive disease has recently been questioned by the results of a small trial conducted by the IBCSG and showing no difference between AC combined with ovarian function suppression plus tamoxifen compared with the same endocrine combination alone [71].

The role of combined chemo-endocrine therapy is even more controversial in postmenopausal women.

IBCSG trial IX, in postmenopausal patients with node-negative disease did not show any additional benefit for patients with ER-positive disease by adding 3 cycles of CMF chemotherapy prior to tamoxifen up to 5 years [72].

The NCIC trial [73] (706 postmenopausal patients; tamoxifen for 2 years or tamoxifen for 2 years plus CMF for 8 cycles, given concurrently) and the Ludwig Trial III [74,75] (463 postmenopausal patients; CMF for 12 cycles plus prednisone plus tamoxifen for one year, prednisone and tamoxifen for one year or no adjuvant therapy) also failed to demonstrate a benefit for the addition of chemotherapy to tamoxifen in patients with ER-positive tumours.

In contrast, the IBCSG trial VII [76] showed that for patients with ER-positive tumours, the addition of CMF, either early or delayed or both, to tamoxifen reduced the relative risk of relapse by 22–36%. The same observation was done with an anthracycline-containing regimen in the NSABP B-16 trial [77,78], in which DFS was 62% in the AC plus tamoxifen group compared with 49% in the tamoxifen alone group, and OS rates were 74% and 65%, respectively, and in a European trial [79] in which a statistically significant improvement in recurrence-free survival was obtained with the addition of epirubicin to tamoxifen.

Today, virtually all premenopausal women with lymph node-positive, steroid hormone receptor-positive disease receive chemotherapy, despite the absence of evidence showing that it is necessary for all. Endocrine therapy alone with ovarian function suppression and tamoxifen or an aromatase inhibitor may be sufficient to achieve excellent outcomes without chemotherapy, especially for patients at low risk of recurrent disease. This question is being investigated in the Premenopausal Endocrine Responsive Chemotherapy (PERCHE) trial, which compares ovarian function suppression plus chemotherapy followed by tamoxifen or exemestane versus ovarian function suppression and tamoxifen or exemestane without chemotherapy for patients with steroid hormone receptor-positive tumours [36,37].

5. Conclusions

Patients with ER-expressing tumours represent a distinct population for which tailored treatment is needed.

Endocrine therapy is mandatory in this population. However, several issues still need further research:

- Role of combination endocrine therapies in premenopausal women (ovarian function suppression plus tamoxifen or aromatase-inhibitors).
- Duration of ovarian function suppression by LHRH analogues.
- Definitive role and best use of aromatase-inhibitors in postmenopausal patients.
- Definitive role of chemo-endocrine therapies in defined patient subpopulations.

6. Recommendations

For patients with ER-positive tumours, the following recommendations can be drawn today:

Endocrine therapy is mandatory for both pre- and postmenopausal patients [27,29].

The choice of the endocrine manipulation depends on the menopausal status:

For premenopausal patients, ovarian ablation or tamoxifen can be recommended [27,29].

The combination of both is under investigation, as well as the combination of ovarian ablation and aromatase inhibitors [36,37].

For young patients, especially if at low risk of recurrence, preservation of fertility may be warranted.

For postmenopausal patients, tamoxifen for 5 years is the standard of care [29].

Anastrozole upfront can be recommended for patients with a contraindication to tamoxifen [80,4].

The addition of 5 years of letrozole after 5 years of tamoxifen has proven to yield benefits in terms of DFS. However, the long-term toxicity of this approach is still poorly evaluated [45].

The use of a sequence including 2–3 years of tamoxifen and 2–3 years of exemestane proved to be superior to tamoxifen for 5 years. However, long-term toxicity is still not fully evaluated [46].

The addition of chemotherapy to endocrine treatment can be recommended in particular for patients at high risk of relapse and in young patients [28].

Chemotherapy should consist of 3–6 cycles of CMF or of an anthracycline-containing regime. The addition of taxanes cannot be routinely recommended for patients with ER-positive tumours

Endocrine treatment (tamoxifen) should start after completion of chemotherapy [81].

Conflict of interest statement

None declared.

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