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Adjuvant Endocrine Therapy in Premenopausal Patients

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Key Words

Breast cancer · Premenopausal patients · Endocrine treatment · Aromatase inhibitors · Bisphosphonates · Tamoxifen · LHRH agonists

Summary

Endocrine adjuvant therapy is the best-described molecular targeted treatment and should therefore be used for all patients with endocrine-responsive breast cancer. Tamoxifen for 5 years is standard of care and has proven efficacy in premenopausal patients. The combination of tamoxifen with ovarian function suppression and/or chemotherapy has been extensively tested, and some controversial approaches are used in clinical practice. Cessation or suppression of ovarian function appears to be beneficial for premenopausal patients. Particularly for premenopausal women with highly endocrine-responsive disease and/or low risk for relapse, the additional benefit of cytotoxic chemotherapy may be minor or nonexistent. While the use aromatase inhibitors is investigated in clinical trials, their application outside an academic trial setting cannot be recommended based on first available results. In contrast, the use of adjuvant bisphosphonates may offer another strategy of further improving clinical outcomes in this important patient subgroup.

Schlüsselwörter

Brustkrebs · Prämenopause · Endokrine Therapie · Aromatasehemmer · Bisphosphonate · Tamoxifen · LHRH-Agonisten

Zusammenfassung

Die endokrine Adjuvanstherapie bei hormonempfindlichem Brustkrebs ist die bestbeschriebene zielgerichtete Therapie im molekularen Zeitalter und sollte daher allen Patientinnen mit rezeptorpositivem Mammakarzinom angeboten werden. 5 Jahre Tamoxifen ist bewiesenermaßen bei prämenopausalem Brustkrebs effektiv und stellt den Stand der Kunst dar. Kombinationen von Tamoxifen mit ovarieller Suppression und/oder zytostatischer Chemotherapie wurden intensiv in Studien getestet und einige Strategien werden in der klinischen Praxis angewandt. Die Unterdrückung der Eierstockfunktion scheint jedenfalls für prämenopausale Brustkrebspatientinnen günstig; gerade bei hochrezeptorpositiven Patientinnen oder jenen mit geringem Risiko muss der zusätzliche Vorteil zytostatischer Therapie als gering oder nicht vorhanden gewertet werden. Aromataseinhibitoren werden auch in der Prämenopause in klinischen Studien getestet. Aufgrund der ersten vorliegenden Ergebnisse kann ihr Einsatz außerhalb dieses Settings derzeit nicht empfohlen werden. Im Gegensatz dazu könnte die adjuvante Anwendung von Bisphosphonaten eine weitere erfolgreiche Strategie zur Verbesserung der Ergebnisse bei dieser wichtigen Patientinnengruppe bedeuten.

Globally, the majority of breast cancers occur in patients before menopause; in the western world, this proportion is more like approximately 30%. About two out of three breast cancers in premenopausal women express steroid hormone receptors on the surface of at least part of their tumour cells [1] and are therefore called endocrine responsive. One of the most important – and less than trivial – determinations in recent Consensus Conferences [2] was to distinguish between endocrine-

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responsive and endocrine-non-responsive breast cancer – and to therefore finally get rid of the myth that endocrine therapy may be effective in endocrine-non-responsive or receptor-negative disease as well. Still, some of the older data about endocrine treatment in the scientific literature may be contaminated by receptor-negative (or receptor-unknown) patients in the dataset [3], which most likely has led to a diluting effect of the benefits of this treatment modality.

There are several specific issues to be discussed with respect to premenopausal patients – they differ in a variety of ways from postmenopausal breast cancer patients: Different age means different risk, but also different views on the disease. Both side effect tolerance and acceptance may considerably differ between all these age groups. For example – and of particular importance for the endocrine treatment of premenopausal patients – side effects on sexual function may be completely differently acceptable to a 30-year-old as compared to a 75-year-old patient.

Overtreatment is most likely a general phenomenon in the adjuvant therapy of premenopausal patients, because they are – in part rightfully so – perceived as being at high risk for relapse. In some parts of the world, this leads to a more or less general application of adjuvant chemotherapy in premenopausal breast cancer patients, irrespective of their tumours' endocrine responsiveness – particularly in the USA.

Generally speaking, one of the problems in modern adjuvant breast cancer treatment – beyond the subject of adjuvant endocrine therapy – is that most of us will have a tendency to increase treatment intensity with risk – which may be irrational since response prediction should guide us more than risk itself. Patients under the age of 35 are considered as high-risk just by their age – which will be triggering adjuvant chemotherapy in most specialised treatment units.

Another important issue of discussion is what exactly defines receptor positivity: In general, cut-off levels of 10 fmol/mg protein (LBA = ligand binding assay) or 10% positively staining cells by immunohistochemistry have been accepted for the discrimination between oestrogen receptor (ER)-positive and ER-negative tumours. It was, however, demonstrated that tumours with ≥ 1% ER-positive cells are already sensitive to endocrine therapy [4]. In trial IX of the International Breast Cancer Study Group (IBCSG) on adjuvant therapy with tamoxifen versus tamoxifen + CMF chemotherapy (CMF = cyclophosphamide, methotrexate and fluorouracil), tamoxifen already showed an increasing improvement of 5-year disease-free survival (DFS) in patients with tumour ER contents between 3 and 12 fmol/mg protein without any additional effect of CMF to tamoxifen alone above an ER value of 12 fmol/mg protein [5].

When aromatase inhibitors (AIs) are discussed as endocrine therapy, one has to bear in mind that they have been demonstrated to be particularly more effective than tamoxifen in patients with HER2/neu-positive tumours [6] but also in patients with lower ER tumour contents, and in patients with progesterone receptor (PR)-negative tumours [7].

With respect to the use of cytotoxic chemotherapy in premenopausal women with endocrine-responsive breast cancer, there are, in principle, two different approaches which can be distinguished by the decisional priority the patient and the counselling physician give to either relying on risk (basically defined by numerical age in such situation) or biology of the disease. The latter approach would weigh more the amount of endocrine responsiveness as for example determined by quantitative ER and PR measurements.

If one considers all young patients as being at high risk for relapse and/or death, probably everybody would be recommended chemotherapy – it is then a question of balancing additional benefits and side effects as to whether endocrine therapy is installed in addition or not. Since nowadays it is pretty obvious and substantiated by long-term data [8] that all endocrine-responsive patients derive at least some benefit from an adjuvant endocrine intervention, probably virtually everybody will receive chemotherapy plus endocrine therapy, suggesting that overtreatment and unnecessary side effects may be the consequence of such an approach.

We can, however, learn something about the 'hormonal' side of chemotherapy when we carefully review the available chemotherapy data: Polychemotherapy is more effective in premenopausal than in postmenopausal women [9]. As stated, the worst prognosis after adjuvant chemotherapy has been found in very young women (< 35 years) with ER-positive tumours and with continuing intact ovarian function [10]. This is probably because of the low incidence of ovarian function suppression (about 10%) in this young age group, resulting in tumour growth stimulation by high endogenous premenopausal oestrogen levels. The best results of adjuvant chemotherapy have been observed in women between 40 and 50 years of age, in whom chemotherapy-induced amenorrhoea occurs more often. Such differences in clinical outcome between premenopausal age groups due to ovarian suppression were not observed in premenopausal patients with ER-negative tumours, which clearly demonstrated that part of the chemotherapy successes in these patients come from indirect endocrine effects of chemotherapy.

When considering the biology as highest priority in deciding about adjuvant therapy, in patients with, e.g., significant ER and/or PR expression on her tumour cells, again virtually everybody will be a candidate for adjuvant endocrine treatment. With this approach, the secondary question then needs to be: Who will actually benefit the most from additional cytotoxic chemotherapy? What percentage in improved statistical relapse-free-survival and or overall survival will warrant the side effects of such therapy?

There is a remarkable lack of evidence in the investigation of the actual effects of either treatment on the patients' quality of life. Most likely, the side effect frequencies for both endocrine and cytotoxic treatments are underreported in the scientific literature, for a variety of reasons.

Interesting concepts trying to integrate objective survival ben-

efits and objective and subjective deteriorations of quality of life have been described (Q-TWiST = quality-adjusted time without symptoms of disease or toxicity of treatment), but are unfortunately not widely used [11]. It is therefore not too easy to actually counsel a patient in such a decision very accurately, and it is most likely that uncertainty both of patients and physicians is another source of overtreatment recommendations and treatment schedules. Putting 'safety first' will be an approach for a majority of patients in a breast cancer situation, and the expected reductions in relapse risk or risk of dying from the disease may both be overestimated by the patients and exaggerated by the physicians [12].

All of the above is background for a comprehensive review of the available data. Patients should be advised to take their time in deciding as to whether they want a given treatment or not. Such counselling strategy can also significantly improve the patient's compliance during treatment as well as during follow-up.

Tamoxifen is an anti-oestrogen and one of the specific oestradiol receptor modulators (SERMs) with combined anti-oestrogenic and oestrogenic action [13]. Single treatment with tamoxifen has been shown to be an effective endocrine therapy in pre- and postmenopausal patients with metastatic or primary breast cancer [14, 15] and is even used for prevention in healthy women at high risk of breast cancer. The antitumour efficacy of the drug is somewhat higher in postmenopausal patients than in premenopausal patients [16]. The addition of a luteinising hormone-releasing hormone (LHRH) agonist to tamoxifen suppresses pituitary-ovarian function, resulting in postmenopausal plasma oestradiol levels and a near doubling of the antitumour efficacy of tamoxifen in premenopausal metastatic breast cancer, including an increase of the 5-year survival from 17 to 34% [14].

In the adjuvant setting in premenopausal patients with primary breast cancer, the relative risk reduction by tamoxifen for 5 years is at least as good as that by chemotherapy with respect to recurrence rate (45 ± 8% versus 33 ± 8%, respectively) and death rate (32 ± 10% versus 20 ± 10%, respectively). Furthermore tamoxifen reduces the risk of contralateral breast cancer with nearly 50%.

Tamoxifen is typically used for 5 years. According to the National Surgical Adjuvant Breast and Bowel Project (NSABP)-14, it is questionable whether increasing treatment duration with tamoxifen is leading to better results, mostly because of its side effects on the endometrium and an increase in thromboembolic events [17].

Ovarian ablation significantly increased recurrence-free survival with 13.4% in node-positive patients (from 24 to 37.4%, $2p < 0.0002$) and with 8.9% in node-negative patients (from 66.5 to 75.4%; $2p < 0.01$) after 15 years of follow-up in comparison with no ovarian ablation [18]. Overall, in comparison with no adjuvant therapy, ovarian ablation induced an improvement of the recurrence rate with 13.4% (from 45.6 to 59.0%) and of death rate with 10.4% (from 46.3 to 56.7%).

Table 1. Trials of chemotherapy versus ovarian function suppression in premenopausal breast cancer

Study	Treatments	Results
Scottish	CMF vs. surgery	no difference
Scandinavian	CMF vs. XRT	no difference
ZEBRA	CMF vs. OvS	no difference for ER+
IBCSG VIII	CMF vs. OvS	no difference for ER+
TABLE	CMF vs. OvS	no difference
GROCTA 02	CMF vs. OvS + TAM	no difference
ABCSG 5	CMF vs. OvS + TAM	better RFS for OvS + TAM
French	FAC vs. OvS + TAM	no difference
FASG 06	FEC vs. OvS + TAM	no difference

XRT: External beam radiation therapy; OvS: ovarian function suppression; TAM: tamoxifen; FAC: flourouracil, adriamycin, cyclophosphamide; FEC: flourouracil, epirubicin, cyclophosphamide; TABLE: Takeda adjuvant breast cancer study with leuprorelin acetate; GROCTA: Gruppo di Recerca in Oncologia Clinica e Terapie Associate; FASG: French Adjuvant Study Group; RFS: relapse free survival.

These results are similar to those of polychemotherapy alone. There was no effect of ovarian ablation in combination with chemotherapy versus the same chemotherapy, probably because chemotherapy by itself already induces ovarian insufficiency in the majority of patients. The most recent Consensus Conferences are viewing ovarian ablation as a reasonable adjuvant treatment option for premenopausal women with receptor-positive breast cancer.

In the adjuvant setting, ovariectomy plus tamoxifen was shown to yield an increase of 17% in 5-year DFS in favour of the combined endocrine treatment [19].

Goserelin is the most commonly used LHRH agonist [20]. Side effects are acceptable, and more than 75% of patients have a preference of goserelin over chemotherapy [21].

Several randomised trials (Zoladex Early Breast Cancer Research Association (ZEBRA), Austrian Breast and Colorectal Cancer Study Group (ABCSG)-05, INT101) showed that in the chemotherapy only arm patients with chemotherapy-induced amenorrhea had an absolute better relapse-free survival of 15–20% compared to women with ER-positive tumours who continued to menstruate [22–24]. An overview of trials containing information about chemotherapy-induced amenorrhea showed that amenorrhea is associated with a 44% relative reduction in the rate of relapse with a mean hazard ratio of 0.56 (range 0.39–0.86) [25]. Overall, these strong positive effects of drug-induced ovarian suppression are comparable with those of surgical castration, tamoxifen or polychemotherapy versus a control group without adjuvant systemic therapy. A summary of these trials is provided in table 1. Therefore, there is no doubt that in premenopausal women chemotherapy is an anti-hormonal therapy [26].

The relative importance of ovarian suppression, when used together with other adjuvant therapies, is summarised and dis-

Table 2. Percentage of change in hazard ratios for DFS in hormone receptor-positive patients, according to the LHRH overview group [45]

No systemic therapy ± LHRH	–25.2 (–40.6; –5.8), p = 0.01
No systemic therapy ± (LHRH + tamoxifen)	–60.0 (–73.5; –39.6), p < 0.01
Tamoxifen ± LHRH	–13.9 (–31.8; +8.7), p = 0.21
Chemotherapy ± LHRH	–11.0 (–22.0; +1.5), p = 0.08
Chemotherapy + tamoxifen ± LHRH	–12.8 (–39.7; +25.9), p = 0.46
(Chemotherapy ± tamoxifen) ± LHRH	–11.2 (–21.6; +0.5), p = 0.06
Any therapy ± LHRH	–11.8 (–21.0; –1.6), p = 0.02
Chemotherapy ± (LHRH + tamoxifen)	–23.8 (–35.9; –9.4), p < 0.01
Chemotherapy vs. LHRH	+3.0 (–8.5; +16.0), p = 0.063
Chemotherapy vs. LHRH + tamoxifen	–11.3 (–25.6; +5.8), p = 0.18

cussed in a recent overview of gonadotropin-releasing hormone (GnRH) analogue-using trials [27]. In general, GnRH-based treatments offer an advantage over the respective control groups; table 2 summarises the findings of that overview.

AIs have recently superseded tamoxifen in the treatment of postmenopausal endocrine-responsive breast cancer. These agents act by blocking the aromatisation of androgenic precursors to oestrogen in postmenopausal women and reduce plasma and intra-tumoural oestrogen concentrations. Third-generation AIs comprise reversible non-steroidal (anastrozole, letrozole, vorozole) or irreversible steroidal (exemestane) inhibitors.

AIs have shown superiority to tamoxifen when given upfront (5 years of AI versus 5 years of tamoxifen), or in early sequence (after 2–3 years of tamoxifen) and late sequence (after 5 years of adjuvant therapy (usually with tamoxifen): The Arimidex, Tamoxifen Alone or in Combination (ATAC) trial compared anastrozole with tamoxifen and the combination of the two drugs. This is the largest adjuvant therapy trial ever completed, with 9366 patients recruited, i.e. more than 3000 patients per treatment arm [28]. Anastrozole induced undetectable or scarcely detectable plasma oestradiol levels in contrast to the SERM tamoxifen with its mixed oestrogen-antagonistic and -agonistic actions. In the hormone receptor-positive subgroup, the absolute difference in DFS was nearly 3% (89.0 versus 86.1%) in favour of anastrozole. The combination therapy did not appear to be better than anastrozole alone, probably due to the fact that the oestrogen-agonistic properties of tamoxifen were more pronounced than its oestrogen-antagonistic effects in the presence of the anastrozole-induced very low oestrogen levels. In addition, anastrozole was significantly better tolerated than tamoxifen with respect to endometrial cancer (p = 0.02), vaginal bleeding and discharge (p < 0.0006), venous thromboembolic events (p = 0.0006), and hot flushes (p < 0.0001), whereas tamoxifen was significantly better tolerated than anastrozole with respect to musculoskeletal disorders and bone fractures (p < 0.0001 for both).

Comparable results were obtained with letrozole in the Breast International Group (BIG) 1–98 study [29].

Furthermore, in patients on adjuvant therapy with tamoxifen for 2.5 years, a switch to treatment with anastrozole [30, 31] or

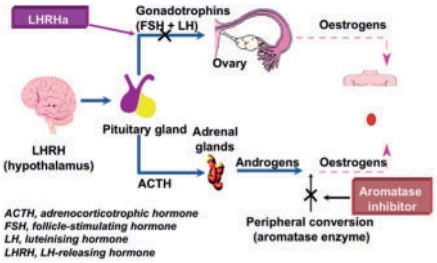

Fig. 1. Endocrinological rationale for combining GnRH analogues and AIs.

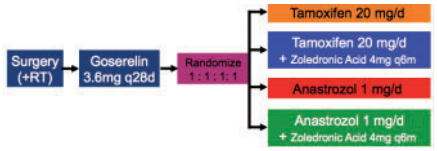

Fig. 2. Design of the ABCSG-12 trial.

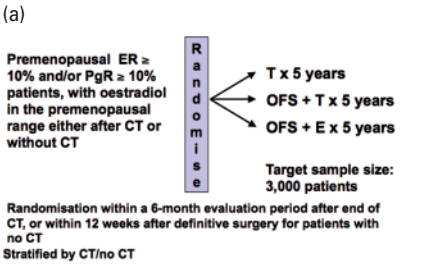

Fig. 3. (**a**) SOFT and (**b**) TEXT, current IBCSG trials for premenopausal breast cancer open for accrual. T = Tamoxifen, E = exemestande, OFS = ovarian function suppression, CT = chemotherapy.

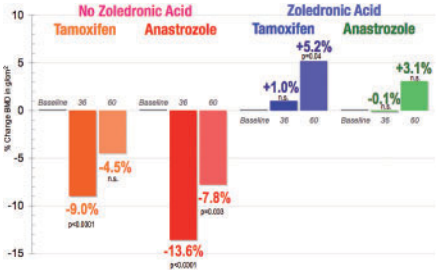

Fig. 4. Bone mineral density measurements after 3 and 5 years in the ABCSG-12 Bone Substudy [39].

exemestane [32] improved relapse-free survival in comparison with continuation of tamoxifen. In addition, continuation of endocrine therapy with letrozole after 5 years of adjuvant tamoxifen therapy improved relapse-free survival in comparison with placebo [33], and similar results were shown for anastrozole by ABCSG-06A [34].

Thus, it is obvious to ask whether these moderate but significant improvements by AIs can also be exploited in the pre-

menopause. However, AIs must not be used alone in premenopausal patients, since an intact ovarian function would lead to interference with the negative feedback mechanism between the ovaries and the pituitary gland (fig. 1). Specifically, reducing the peripheral oestradiol levels with unbalanced AIs would stimulate the release of GnRH, and eventually increase ovarian oestradiol release. Together with – nowadays usually medical – ovarian suppression by GnRH analogues, however, the combination can be used safely.

The combination of GnRH analogues and AIs has been demonstrated to work in principle, leading to even further decreased peripheral serum oestradiol levels as compared to goserelin and tamoxifen [35]. Clinical experience of this combination is, however, limited to only few reports, generally from late-line breast cancer patients [36]. While in all these studies follicle-stimulating hormone (FSH) and luteinising hormone (LH) were effectively suppressed by GnRH analogues, the effects of AIs on their levels varied [37].

Whether these endocrinological advantages of the GnRH analogue/AI combination translate into clinical benefit is investigated in several large clinical trials: Among others, ABCSG-12 (fig. 2), Tamoxifen and EXemestane Trial (TEXT), and Suppression of Ovarian Function Trial (SOFT) are investigating this combination, both in combination with chemotherapy and without, usually versus tamoxifen.

In recent results from ABCSG-12 there was no difference between goserelin plus anastrozole as compared to the goserelin/tamoxifen combination [38]. This was somewhat unexpected given the superiority of AIs over tamoxifen in the postmenopausal setting. One possible explanation is the dominant effect of ovarian suppression on oestrogen levels in premenopausal women. Moreover, long-term administration of goserelin can lead to androgen reduction, thereby limiting the available substrate for aromatase activity. Therefore, the off-study use of AIs in this patient population is currently not recommended. Results from ongoing trials, such as SOFT and TEXT (fig. 3a, b), will be needed for definite guidance regarding the use of AIs in premenopausal women.

What has already been shown is that the combination of ovarian suppression and AIs will lead to increased bone loss in premenopausal patients. This known side effect of AIs is particularly dramatic in younger patients (fig. 4), and can be completely abrogated with the use of the intravenous bisphosphonate zoledronic acid [39], as it has been shown in the postmenopause [40, 41].

More strikingly, the adjuvant use of zoledronic acid prevented recurrences in ABCSG-12 by more than one third as compared to endocrine therapy alone [38]. There are several possible antitumour mechanisms that may explain the significant DFS benefit from just seven infusions of the bisphosphonate in this setting: Preclinical antitumour activities of zoledronic acid include inhibition of tumour cell adhesion, invasion, and proliferation, and induction of apoptosis in a variety of human tumour cell lines; delayed disease progression in animal models of human cancers; and antitumour synergy with many chemotherapy agents. Furthermore, early clinical data suggest that zoledronic acid may stimulate antitumour immune reactions and have anti-angiogenic effects. In any case, this result rejuvenates Stephen Paget's 'Seed and Soil' hypothesis [42], and may lead to a paradigm shift in our thinking about our ability to influence not only tumour cells but also the microenvironment in our patients.

In summary, endocrine treatment of premenopausal breast cancer patients with endocrine-responsive breast cancer can be considered the standard of care. While not all available options are satisfyingly applied in daily clinical practice [43], there are a variety of treatment options available with sufficient standardisation to be eventually offered to virtually every premenopausal breast cancer patient with hormone receptor-positive breast cancer [44]. In fact, endocrine adjuvant therapy is the best-described molecular targeted treatment and should not be neglected in general clinical practice.

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