REVIEW ARTICLE

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Premenopausal Breast Cancer
Chemotherapy and Endocrine Therapy

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Abstract

Modern treatment of premenopausal breast cancer is based on well-established prognostic and predictive factors for disease outcome such as nodal status, hormone receptor expression, tumour size, tumour grading and patient age. The development of strategies according to such individual risk profiles has resulted in significant improvements both in overall and disease-free survival. An abundant number of new prognostic and predictive factors in addition to those already mentioned may help to increase our understanding of the biology of breast cancer and to individualise therapy in premenopausal patients. Although less than 10% of patients directly benefit, it is estimated that approximately each year the life of more than 4000 women in Germany will be saved or prolonged by adjuvant treatment. Whether dose intensive modifications and new antineoplastic drugs can improve disease outcome will be clarified when ongoing studies have increased observation time.

At present, hormone ablation via surgical, radiotherapeutical or drug-induced castration in addition to selective estrogen response modifiers (SERM), such as tamoxifen, with or without chemotherapy remains the cornerstone of adjuvant treatment in premenopausal patients with breast cancer. In advanced disease, new highly effective hormonal and other target-oriented antineoplastic agents with few adverse effects have been recently introduced. However, overall survival in metastatic disease remains poor, even when intensive or high-dose chemotherapy

is used. Special attention must be given to longer follow up and potential toxic long-term adverse effects of therapy when new regimens are applied in clinical trials.

Breast cancer will remain the leading cancer among women in the Western world during the first decade of the new millennium. In most countries, it is the third most common cancer and the most common among women.[1] This is an even more striking challenge since the understanding of cellular and molecular biology of breast cancer has improved during the last years. The median age for diagnosis of breast cancer is between 60 and 65 years. It can be calculated that one in ten women will develop breast cancer in their lifetime. Approximately 5% of them will result from inherited susceptibility genes, such as the mutation of the tumour suppressor genes *BRCA-1* or *-2*,[2] or the ataxia telangiectasis gene causing several chromosomal instabilities.[3] The discussion on the potential of chemoprevention in breast cancer has just started with three large randomised trials producing conflicting results and only one showing that tamoxifen may prevent breast cancer.[4-6]

Prognostic factors such as patient age, tumour size, metastatic spread in lymph node(s), histological tumour type, pathological grading and the hormonal receptor status have the most important impact on survival in breast cancer. Thus, it is essential to consider the pathological data in every clinical trial. Novel prognostic and predictive factors are investigated in clinical trials but do not yet have an established role in patient management. In premenopausal patients, unfavourable clinical and pathological parameters have a more crucial impact on prognosis than in postmenopausal patients. In particular, younger patients under 35 years of age have a more aggressive disease than older patients. This overview focuses on premenopausal women with breast cancer and deals with systemic therapy in the adjuvant and palliative setting.

1. Treatment of Early Disease

Even with optimal local control by surgery and radiation therapy, systemic recurrences of breast cancer will develop in a significant proportion of women. It is thus obvious that micrometastases are commonly present at the time of diagnosis even in apparently localised breast cancer. This is the rationale for adjuvant therapies in patients with localised breast cancer. Systemic treatment should start as soon as possible after the diagnosis of breast cancer, usually after a surgical removal of the primary tumour and ideally within 4 to 6 weeks.

1.1 Preoperative (Neoadjuvant) Therapy

Studies with preoperative (neoadjuvant) hormone or chemotherapy in the treatment of locally advanced breast cancer have shown positive effects on long-term survival and time to progression of disease. However, most of these favourable results did not reach the level of significance.[7] In primary inflammatory breast cancer preoperative chemotherapy might have been beneficial for the patients,[8] with a strong correlation shown between initial response to chemotherapy and long-term outcome[9] (table I).

Early dose intensification with high-dose chemotherapy combined with stem cell transplantation (HDT) might be a promising option for primary inflammatory breast cancer. With a median follow up of 30 months, results with HDT compared with historical standard-dose chemotherapy were in favour of the HDT-option for disease-free and overall survival.[10] Only prospective, randomised trials will clarify the efficacy of HDT as neoadjuvant treatment for breast cancer.

Table I. Response of inflammatory breast cancer to conventional-dose preoperative chemotherapy and disease free survival after 15 years[9]

Response	Number of patients	15 years disease free (% pts)
Total	178	24
Complete remission	21	40
Partial remission	106	29
Minimal remission	45	8

Table II. Ongoing trials with primary (neoadjuvant) chemotherapy in patients with operable breast cancer

Trial	Patient status	Protocol
National Surgical Adjuvant Breast and Bowel Project (NSABP)-B27	T >2cm, M0	4xAC + S versus
		4xAC → 4xD + S versus
		4xAC + S + 4xD
European Cooperative Trial in Operable Breast Cancer (ECTO)	T >2cm, M0	S + 4xA → 4xCMF versus
		S + 4xAT → 4xCMF versus
		4xAT → 4xCMF + S
German Preoperative Adriamycin Docetaxel (GEPARDO)	T2-3, No-2, M0	4xAD + S versus
		4xAC → 4xD + S
Arbeitsgemeinschaft Gynäkologische Onkologie [Germany] (AGO)	T >3cm, inflammatory	3xE → 3xT + S + 3xCMF versus
		4xET + S + 3xCMF

A = doxorubicin; **C** = cyclophosphamide; **CMF** = cyclophosphamide/methotrexate/fluorouracil; **D** = docetaxel; **E** = epirubicin; **S** = surgery; **T** = paclitaxel; → indicates followed by.

The largest trial of the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B-18 included more than 1500 patients with operable tumours (tumour sizes of ≥2cm) and has shown no survival difference between pre- or postoperative chemotherapy. Preoperative treatment in this randomised study permitted more breast conserving surgery in certain patients with stage I and II disease receiving preoperative chemotherapy with four cycles of doxorubicin and cyclophosphamide every 21 days.[11]

In comparing pre- versus postoperative chemotherapy, Fisher et al.[11] could show identical prognostic data after 5 years of follow-up. In the preoperative treatment group an analysis of the correlation of response and prognosis was performed, showing best prognostic data for those patients with pathological complete remission.

The role of new agents, such as paclitaxel or docetaxel, the most effective application regimen, and valid predictive factors for the efficacy of primary chemotherapy are still being evaluated in clinical trials (table II).

Primary endocrine treatment of breast cancer with tamoxifen was evaluated in postmenopausal elderly patients with hormone receptor-positive tumours.[12] The aim of this study was to show similar survival with pure endocrine therapy for primary breast cancer in elderly women to avoid postoperative mortality and morbidity. Results were comparable with primary neoadjuvant chemotherapy, indicating a new therapeutic modality without the adverse effects of cytotoxic drugs in this selected subgroup.

1.2 Endocrine Therapy

The rationale for the use of endocrine therapy is its reproduced efficacy for patients with receptor-positive breast cancer in a multitude of randomised trials, as summarised by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).[13] The presence of the estrogen (ER) and/or progesterone receptor (PgR) shows a high correlation with endocrine responsiveness, therefore, it is a good predictor for the effective use of endocrine therapy.

The goal of hormone therapy in breast cancer patients is the prevention of tumour recurrence (adjuvant therapy) or the reduction of tumour manifestations (palliative therapy). Protein synthesis and tumour cell cycle can be inhibited significantly by endocrine therapy as shown in *in vitro* studies and in clinical trials. Tamoxifen, the first generation drug of selective estrogen receptor modifiers (SERM), is the prototype of a nonsteroidal antiestrogen which binds to the estrogen receptor and shows part agonist activity. It is currently the only SERM approved for the use in adjuvant treatment of breast cancer. A treatment duration of 5 years with tamoxifen is now recommended,[14] which is superior to 1 to 2 years of treatment as shown in randomised trials and in a meta-analysis. However, more than 5 years of adjuvant treatment

with tamoxifen seem not to be superior to 5 years [15] but trials are still ongoing to address this question. In addition, tamoxifen may play a role in the setting of patients with ductal carcinoma-in-situ (DCIS). In the recently published NSABP-B-24 randomised trial the addition of tamoxifen to lumpectomy and radiation therapy reduced the incidence of ipsilateral and contralateral invasive breast cancer.[16]

The Oxford Overview of more than 37 000 women with breast cancer receiving adjuvant tamoxifen showed a significant reduction in the risk of recurrence and death; however, this was limited primarily to women with hormone receptor-positive cancer including premenopausal patients. In women with receptor-negative cancer, almost no benefit could be detected. The positive impact was seen regardless of age, nodal status, menopausal status, dose of tamoxifen or addition of chemotherapy,[13] and was recently updated and confirmed at the National Institutes of Health Consensus Meeting on adjuvant therapy in breast cancer patients.[14]

New nonsteroidal antiestrogens, such as raloxifene or toremifene, with less estrogen agonist and more antagonist activity have been evaluated in clinical trials.[17] These new SERMs are proposed to have increased antitumour activity and reduced endometrial proliferation capacity and, thus, a reduced risk of endometrial cancer, which is the main adverse effect of tamoxifen. In contrast to other SERMs, the new steroidal antiestrogen fulvestrant, blocks estrogen receptor transactivation which results in a marked reduction in the cellular concentration of estrogen receptors.[18] Efficacy results on these new SERMs in adjuvant treatment of premenopausal breast cancer patients are still pending (figure 1).

Since two-thirds of premenopausal breast cancer tumours are hormone-receptor positive, suppression of estrogen production in the ovaries via decrease of gonadotrophin production is similar in efficacy to radiomenolysis or ovariectomy for suppressing estrogen levels, and seems a promising addition to 'standard therapies'. It is likely that

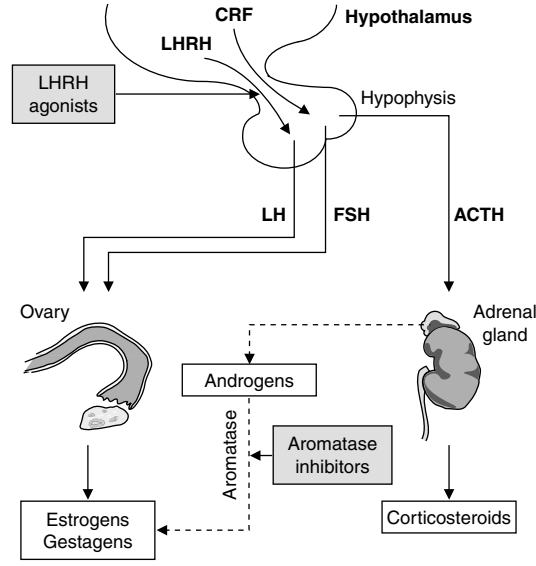

Fig. 1. Hormone dependent pathway in the biology of breast cancer. **ACTH** = adrenocorticotrophic hormone; **CRF** = corticotrophin releasing factor; **FSH** = follicle stimulating hormone; **LH** = luteinising hormone; **LHRH** = LH releasing factor.

beneficial clinical effects are achieved by suppressing the pituitary-ovarian axis since treatment with a luteinising hormone-releasing hormone (LHRH) agonist reduces circulating estrogen to castrate levels. Trials with ovarian ablation in the absence of chemotherapy resulted in a reduction in recurrence by an absolute value of 12.2% at 10 years and 13.3% at 15 years.[15]

The Eastern Cooperative Oncology Group (ECOG) 5188 study showed an increased 5-year relapse-free survival for premenopausal women with node-positive and receptor-positive disease, with a relapse-free survival rate of 78% in the group receiving the LHRH agonist goserelin and tamoxifen in addition to chemotherapy. The other two groups received either chemotherapy alone resulting in a relapse-free survival of 67% or chemotherapy and goserelin with 70%. In all three groups similar 5-year overall survival of 86% was noted.[19]

Recently, Jakesz et al.[20] showed in premenopausal patients with stage I/II receptor-positive

cancer that ovarian ablation with goserelin and the addition of tamoxifen offered better relapse-free survival than intravenous cyclophosphamide, methotrexate and fluorouracil (CMF). However, the overall survival was similar in both groups with a median follow up of 42 months.

In a randomised, parallel-group, multicentre Italian study,[21] which compared the efficacy and tolerability of standard chemotherapy (CMF) or the combination of tamoxifen plus ovarian suppression as adjuvant treatment of pre/perimenopausal patients with ER-positive early breast cancer, the treatments were comparable with respect to either relapse-free and overall survival. With a median follow up time of 76 months these results were similar for age, tumour size and nodal status with a trend favouring patients with poorly differentiated tumours treated with CMF.

The multinational Zoladex Early Breast Cancer Research Association (ZEBRA) trial, initiated in Germany, investigated premenopausal patients with lymph-node positive cancer receiving either six 28-day cycles of CMF chemotherapy or 2 years of goserelin 3.6mg every 4 weeks or once per month. Primary trial objectives were to compare relapse-free and overall survival, and adverse effects of the two treatments. Although final assessments and data analysis are still awaited, results of endocrine therapy appeared equal to cytotoxic treatment in patients with ER-positive cancer[22] but inferior to CMF in those with ER-negative tumours.

The data seem sufficient to presume that endocrine combination therapy is an alternative to chemotherapy alone, which is widely accepted as a treatment option. It is unclear whether chemo-endocrine combinations are superior to endocrine therapy alone and there is yet insufficient evidence for clear recommendations on this issue.

The impact of the new and better tolerated aromatase inhibitors and inactivators has been studied extensively in postmenopausal women with advanced disease, with improved results (see section 2.1). So far, new aromatase inhibitors of the triazole class are being investigated in the adjuvant setting because of their favourable toxicity profile when compared with aminoglutethimide and progestins. However, final results of these ongoing trials will not be available for several years.

The role of aromatase inhibitors for premenopausal breast cancer patients is difficult to define, mainly because very few studies (most of them with formestane or aminoglutethimide) in only a few patients are available to address this issue.[23]

With insufficient data in premenopausal patients, recommendations to use aromatase inhibitors for this indication are presently limited to postmenopausal patients.

Except for very good prognostic subgroups of patients, such as those with hormone-receptor positive pT1, N0, G1 tumours and age >35 years, nearly all women should receive adjuvant therapy adapted to the patient's 'risk of relapse'. Recent adjuvant trial data were presented at the 7th International Conference on Adjuvant Therapy in Primary Breast Cancer in St-Gallen, Switzerland in February 2001,[24] (table III and table IV) and the established consensus is comparable to other international meetings, such as the National Institutes of heath (NIH) Consensus Conference of November 2000[14] in the US.

1.3 Chemotherapy

The adjuvant chemotherapy regimen with six cycles of CMF has produced an improvement in long-term relapse-free and overall survival in patients with node-positive and intermediate or high-risk node-negative breast cancer. In the EBCTCG 1995 meta-analysis of trials of chemotherapy versus no treatment there was a 23.5% reduction in the annual odds of recurrence and a 15% reduction in the odds of death in favour of chemotherapy. In women <50 years of age the benefit was greater than in those >50 years of age.[25] Only the prognostic group of women with tumours <1cm, age ≥35 years, positive-receptor status and G1 pathology grading did not benefit significantly from adjuvant chemotherapy. Regarding the generally good prognosis of patients with G1 pathology and tumour size <1cm, the possible positive effect of

Table III. Adjuvant therapy in patients with node-negative (N-) premenopausal breast cancer[24]

Patient	Low risk[a]	Intermediate risk[b]/high risk[c]
Premenopausal receptor-negative		Chemotherapy (CMF, EC, studies)
Premenopausal receptor-positive	None	Ovarian ablation[d] + tamoxifen +/- chemotherapy
	or tamoxifen	or chemotherapy + tamoxifen +/- ovarian ablation
		or tamoxifen
		or ovarian ablation

a Low risk: tumour <1cm and receptor-positive and G1.

b Intermediate risk: tumour 1-2cm or G1-2 (receptor-positive/negative).

c High risk: tumour >2cm or age <35 years or G3 or lymphangiosis.

d Ovarian ablation or luteinising hormone-releasing hormone agonists.

CMF = cyclophosphamide/methotrexate/fluorouracil [600/40/600 intravenously d 1+8 or 100 orally d 1-14/40d 1+8/600 d 1+8] q4w x 6; **EC** = epirubicin/cyclophosphamide [90/600] q3w x 4; **G** = tumour grading (G1-G3); **qxw** = every x weeks.

adjuvant chemotherapy is not outweighed by the potential harm. Given the low risk of recurrence in node-negative breast cancer <1cm, only larger trials of chemotherapy versus no treatment would reach significance in these subgroups.[26]

Several variants of CMF in dosage and duration may explain inconsistent results of randomised trials.[27] Long-term follow up of CMF-regimens in node-positive disease when compared with melphalan, or observation in node-negative disease, could show better overall survival.[28,29] Subgroup analysis of patients with node-positive disease with more than four positive lymph nodes demonstrated no clear benefit leading to the question of whether CMF may be an inadequate treatment in this high-risk group.[30] This study from Milan triggered the discussion about the now widespread use of anthracycline containing regimens for patients with more than three involved lymph nodes.

The introduction of anthracyclines in adjuvant trials with cyclophosphamide, doxorubicin and fluorouracil (CAF) or cyclophosphamide, epirubicin and fluorouracil (CEF) has produced circumstantial results, although a small but significant advantage for anthracycline containing regimens against the CMF regimens is obvious. The results of the Intergroup trial INT 0102, comparing six cycles CMF with six cycles of CAF with or without tamoxifen in patients with node-negative disease, showed a small absolute benefit in the CAF-subgroup.[31] In premenopausal patients, two randomised trials from Sweden and Canada showed a survival advantage for CEF compared with CMF (table V). Findings from the NSABP B-16 trial supported the efficacy of doxorubicin and cyclophosphamide (AC) versus CMF therapy in patients with node-positive disease with ER-positive tumours.[32] In addition, when considered relative to quality of life and toxicity, AC was preferable. Thus, there is justification for the use of AC therapy in either premenopausal or postmenopausal patients with breast cancer who have either negative or positive axillary nodes, as well as in breast cancer patients with ER-negative or ER-positive tumours. Anthracycline containing regimens seem to be appropriate at least in patients with more than four metastatic lymph nodes.

However, the best dosage and duration of the anthracyclines (either doxorubicin or epirubicin) are still not clear. Moreover, long-term cardiotoxicity data showed a higher incidence of cardiac dysfunction without clinical cardiac events in women after CAF compared with CMF.[35] Six cy-

Table IV. Adjuvant therapy in premenopausal patients with lymph node-positive (N = 1-3 or N >4) breast cancer[24]

Patient	Therapy
Receptor-negative	Chemotherapy (EC, EC → CMF, CMF)
Receptor-positive	Chemotherapy + tamoxifen +/- ovarian ablation[a]
	or
	Ovarian ablation[a] + tamoxifen +/- chemotherapy

a Ovarian ablation or LHRH agonist.

CMF = cyclophosphamide/methotrexate/fluorouracil; **EC** = epirubicin/cyclophosphamide; **LHRH** = luteinising hormone-releasing hormone; → indicates followed by.

cles of CAF seem to be better than three cycles when analysing 8-year, disease-free survival and overall survival data. When high and moderate doses of CAF where compared with low-dose CAF, better results were shown with what should be considered 'full dose' (moderate and high dose) CAF.[36] In an 8-year follow up of premenopausal women with node-positive disease, six cycles of FEC with epirubicin 50 mg/m^2 was superior to three cycles of FEC with epirubicin 75 mg/m^2 or 50 mg/m^2.[37] Therefore, the potential survival benefits should be weighed against the potential toxicity when women with localised breast cancer and pre-existing heart disease receive adjuvant chemotherapy.

The addition of taxanes (docetaxel or paclitaxel) in chemotherapy regimens after anthracycline and cyclophosphamide, such as in the CALGB 9344 study,[38] or a dose-dense chemotherapy with sequential doxorubicin, paclitaxel and cyclophosphamide,[39] may reduce the risk of relapse. However, a higher hospitalisation rate and the need for haematopoetic growth factor support should be noted. In addition, a recently reported insignificant reduction of the mortality risk[13] should caution the deliberate incorporation of taxanes in adjuvant chemotherapy protocols. Thus, the value of the addition of taxanes to standard adjuvant chemotherapy must be confirmed by a longer follow up and by further trials.

The role of adjuvant HDT in high-risk patients, predominately in patients with more than nine positive nodes, is not yet defined. The ongoing randomised trials need longer follow-ups before a reliable judgement can be made. Recently, a Dutch study[40] randomising between HDT and intensive conventional treatment reported a significant benefit for patients after HDT. This is in contrast to the reported data by most of the other study groups from the US[41,42] or Scandinavia.[43]

1.4 Antibody Therapy

Positive results with the humanised anti-HER2 antibody trastuzumab in studies in patients with metastatic breast cancer either as monotherapy or in combination with chemotherapy have led to the inclusion of trastuzumab in adjuvant studies. *HER-2* is a protooncogene that encodes for a tyrosin-kinase cell membrane receptor, which is overexpressed on tumour cells in 10 to 30% of women with intraductal breast cancer. In general, these women tend to have a more aggressive disease and an overall poorer survival.[44] HER-2 overexpression may identify women with node-positive disease who benefit from chemotherapy.[45] However, these were retrospective data from the CALGB 8541 trial where dose and dose intensity in the adjuvant treatment of breast cancer patients were studied. Ongoing trials are evaluating taxane (paclitaxel) weekly and trastuzumab as a component of adjuvant therapy for patients with node-positive and HER-2–positive breast cancer. In these patients, retrospective studies have demonstrated a poor response to adjuvant tamoxifen. These observations have triggered discussion about the predictive value of HER-2 for the use of different chemotherapy regimens.

In addition, this has led to the speculation that HER-2 overexpression may be a marker of breast cancer resistance to endocrine therapy,[46] thus, becoming a predictive factor for endocrine adjuvant therapy. The predictive value of HER-2 on endo-

Table V. Adjuvant cyclophosphamide/epirubicin/fluorouracil (CEF) versus cyclophosphamide/methotrexate/fluorouracil (CMF) in premenopausal women with node-positive or -negative breast cancer

Reference	Patient	Regimen	5-year RFS (%)	5-year OS (%)
Levine et al.[33]	node +ve	CEF	63	77
		CMF	53	70
Mouridsen et al.[34]	node +ve	CEF	NR	76
	or -ve	CMF	NR	69

NR = not reported; **OS** = overall survival; **RFS** = relapse-free survival.

crine therapy can not be answered at this time. Neither the consensus panel of the NIH[14] nor the consensus conference of St Gallen 2001[24] regarded the presented evidence as sufficient enough to discourage the use of tamoxifen for patients overexpressing HER-2.

2. Treatment of Advanced Disease

2.1 Endocrine Therapy

By blocking the binding of estrogen to its receptors, tamoxifen when used as first line treatment can induce response rates up to 35% in patients with ER- or PgR-positive metastatic breast cancer. Another 20% of these patients have stable disease lasting for approximately half a year.[47] Other clinical criteria predicting a greater likelihood of response to endocrine therapy are soft-tissue metastases, a longer disease-free survival and increasing age. Response to first-line endocrine therapy is predictive of response to second- and third-line treatment.

Adverse effects, such as an increase in thrombotic events, general antiestrogenic effects and an increase in endometrial cancer risk have to be considered with tamoxifen treatment. In contrast, the endogenous estrogen effects of tamoxifen on bone mineral density and a reduction of serum cholesterol levels are beneficial.

Classical endocrine treatment options for premenopausal women with breast cancer who have advanced disease are tamoxifen, ovarian ablation or LHRH agonists. Small, randomised trials reported similar efficacy for either tamoxifen or LHRH agonists compared with the older gold standard of ovarian ablation.

A meta-analysis from eight phase II and two phase III trials in 348 premenopausal patients treated with tamoxifen reported an objective response rate of 30%.[48] A further meta-analysis of small studies showed an objective response of 38% with single LHRH agonist treatment in premenopausal patients with metastatic breast cancer.[49] In premenopausal women, the addition of antiestrogen treatment to surgical or medical castration seems to be appropriate in suppressing estrogen and blocking the estradiol receptor.

A randomised EORTC trial in premenopausal patients with hormone receptor-positive metastatic breast cancer showed a significant improvement in objective responses and overall survival for the combined treatment compared with medical castration with the LHRH agonist buserelin alone or tamoxifen alone.[50] It should be noted that estrogenic stimulation could be observed with tamoxifen as monotherapy in premenopausal women. Recently, a meta-analysis combining four randomised trials further favoured the combined chemohormonal treatment with a significant survival benefit.[51]

Aromatase inhibition is an established means to suppress estrogen production in postmenopausal women. Estrogen is produced in breast cancer tissue itself and in peripheral tissues. Therefore, effective inhibition of tumour aromatase is likely to be an important issue.

Several smaller studies were performed with the older aromatase inhibitors aminoglutethimide and formestane in premenopausal patients and confirmed that the combination of LHRH agonist and aromatase inhibitor is more efficient in suppressing peripheral serum estrogen levels than LHRH agonists alone.[52,53] Further trials report insufficient ovarian suppression by using aromatase inhibitors alone.[54] These observations should warn against the use of aromatase inhibitors as monotherapy in premenopausal women until sufficient data are available. By using LHRH agonists, premenopausal patients are at least theoretically turned into postmenopausal women, so there is an endocrinological rationale for using aromatase inhibition in combination.

It is still unclear whether premenopausal women may respond to aromatase inhibitors in the same way as postmenopausal women.[55] Potent nonsteroidal aromatase inhibitors of the triazole class, such as anastrozole, letrozole or vorozole, were clinically better tolerated than the formerly used aminoglutethimide. Significantly improved efficacy and tolerability was shown with the oral

aromatase inhibitors letrozole and anastrozole compared with megestrol in postmenopausal women.[56,57] Recently, letrozole was superior in terms of time to progression when compared with tamoxifen in first-line hormone treatment in postmenopausal women with metastatic breast cancer.[58] This was also true for the North American study on anastrozole but not for the European study.[59,60]

In contrast to non-steroidal aromatase inhibitors, new steroidal aromatase drugs bind irreversibly to the substrate binding sites. Exemestane has been studied in phase III clinical trials versus megestrol after tamoxifen failure in postmenopausal women with advanced breast cancer[61] after showing activity in phase II trials.[62] These so-called steroidal aromatase-inactivators may have some additional antitumour effects, partly explaining the response seen with one aromatase inhibitor after failure with another. In comparison to these new options, megestrol has lost its role as second or third line treatment, mainly because of its adverse effects.

Exposure to endocrine therapy does not decrease later response to chemotherapy which is important to note when designing therapeutic strategies for metastatic disease in premenopausal women, it cannot even be definitely excluded that prior endocrine therapy induces resistance to chemotherapy. Unless patients have rapidly progressive disease, the sequential use of now available hormone therapies (table VI) can minimise toxicity while maintaining high quality of life.

2.2 Chemotherapy

Advanced breast cancer is characterised by variable clinical courses. This heterogeneity of tumour progression depends on the age of the patient, disease-free interval after primary diagnosis, hormone-receptor status, and site of metastases (liver and lung versus other). The goal of treatment in advanced stages of breast cancer is to obtain maximal control of disease symptoms, prevent serious complications, and thereby improve quality of life and increase length of life.

The assessment of the menopausal status is mandatory for the sequence of hormonal therapy options, whereas it has no influence on the approach for chemotherapy in metastatic disease. The disease should have become refractory to hormonal treatment or should rapidly progress before cytotoxic treatment for metastatic breast cancer is started. In addition, limited surgery and radiotherapy may used to provide substantial palliation. Whether to use combined chemo-endocrine therapy or chemotherapy alone in these patients re-

Table VI. Hormone therapies for breast cancer in clinical and preclinical use

Substance-group	Drug	Usual dosage
Antiestrogen	Tamoxifen	20mg PO daily, for 5y in adjuvant trials
	Toremifene	60 mg/day PO
	Raloxifene	NA
Steroidal antiestrogen	Fulvestrant	250mg IM, every 4wk
LHRH agonist[a]	Goserelin	3.6mg SC implantation, every 4 weeks
Aromatase inhibitors	Aminoglutethimide	2 x 250mg PO per day
	Letrozole	2.5 mg/day PO
	Anastrozole	1 mg/day PO
	Vorozole	2.5 mg/day PO
Aromatase inactivators	Formestane	250mg IM every 2 wk
	Exemestane	25 mg/day PO
Progestins	Medroxyprogesterone	500 mg/day PO
	Megestrol	160 mg/day PO

a Buserelin is approved in The Netherlands; leuprorelin is approved in Germany.

IM = intramuscular; **LHRH** = luteinising hormone-releasing hormone; **NA** = not available; **PO** = orally; **SC** = subcutaneously.

mains a contentious issue. In patients with receptor-positive metastatic breast cancer, chemohormonal therapy as front line therapy prolongs the time to treatment failure without improving overall survival compared with chemotherapy alone.[63]

In first-line chemotherapy for metastatic disease, 40 to 70% of the patients show an objective response to conventional chemotherapy with the common CMF or CAF/CEF regimens. An increase in overall survival after anthracycline containing combinations versus other combinations has become evident.[64] While phase II trials of the taxanes[65] used as single-agent therapy in the first-line treatment of metastatic breast cancer, have suggested response rates of up to 60 %, other phase II trials have indicated a lower level of response. Some of the agents for salvage chemotherapy today, commercially available or in phase II or III trials, are shown in table VII.[66,67]

Retransfusion of haematopoietic stem cells has allowed the administration of alkylating agents in doses of up to 20-times those previously used in an attempt to overcome tumour resistance. Remission rate and disease-free survival increased by approximately 20% during a follow up of 3 to 5 years.[68] Our own data evaluating double chemotherapy intensification with stem cell retransfusion including paclitaxel in patients with metastatic disease has shown initially high response rates.[69] However, the clinical studies so far lack the evidence that HDT is superior to modern standard-dose chemotherapy regimens in metastatic disease. Maintenance treatment with chemotherapy and tamoxifen versus observation after induction of complete response in an ECOG trial for patients with metastatic breast cancer resulted in increased toxicity and longer time to relapse, but did not improve overall survival.[70]

Studies have found a significant association between symptom improvement and objective tumour regression,[71] thus providing a good argument for including chemotherapy options in the overall treatment strategy.

Table VII. Recently introduced or new cytotoxic agents for systemic therapy in women with advanced breast cancer

Class	Agent
Anthracyclines	Liposomal doxorubicin
Purine analogues	Gemcitabine
Thymidylate synthase inhibitors	Capecitabine
Vinca alkaloid	Vinorelbine

2.3 Antibody Therapy

Monotherapy with trastuzumab in previously treated patients with metastatic breast cancer has produced an objective response rate of 18% for those patients with a 3+ HER-2 overexpression, which seem to correlate with the degree of overexpressing the HER-2 receptor protein.[72] In patients with a low 2+ overexpression, there was only an overall response rate of 6%.

Chemotherapy (paclitaxel or doxorubicin/cyclophosphamide) in combination with trastuzumab increased overall survival in metastatic disease up to 4 months compared with chemotherapy alone.[73] Present trials include only women overexpressing HER-2/neu receptor in the tumour tissue, which accounts for 25% of premenopausal women with breast cancer.

2.4 Role of Additional Therapy

The most common site of metastases is the bone, and bone lesions are the cause of substantial morbidity and complications in patients with breast cancer. Additive bisphosphonate infusion can reduce bone skeleton related events in patients with advanced breast cancer in addition to palliative chemotherapy.[74] This is less clear in the adjuvant setting. One study demonstrated that the bisphosphonate clodronate (clodronic acid), when administered for 2 years in an adjuvant randomised trial, could reduce the incidence of bone and visceral metastases compared with observation.[75] In a double-blind study with more than 1000 women receiving adjuvant clodronate or placebo, the incidence of bone metastases were not statistically different at 2.5 years of follow up, neither in the total patient population nor in the subset of premenopausal women.[76] Recent guidelines stress the sup-

portive but not life-prolonging benefit of bisphosphonates in patients with advanced disease.[77]

3. Conclusion

The usefulness of adjuvant endocrine and chemotherapy for premenopausal patients with breast cancer is firmly established. The optimal chemotherapy regimen and applications regarding toxicity, rather than efficacy, are still to be properly defined. Combined endocrine therapy resulting in complete estrogen blockade is an alternative to chemotherapy alone, an option which is obsolete nowadays. The combination of chemotherapy and endocrine therapy might be superior even at the expense of additional toxicity. The adverse effect profiles and incidences of adverse effects of the aromatase inhibitors are comparable with tamoxifen. New prognostic and predictive factors such as HER-2 might change our treatment decisions especially in the adjuvant situation with younger women. All approaches lacking significant clinical superiority should be limited to controlled clinical trials.

Sequencing of hormonal therapies and chemotherapy with defined toxicity in premenopausal patients with advanced breast cancer should still be the state of art approach. So far, there does not seem to be a significant overall survival benefit with endocrine combination strategies, cytotoxic dose intensification or trastuzumab in this patient population. However, several concepts with the new endocrine drugs, combination modalities with or without chemotherapy in adjuvant and advanced disease status are ready to be investigated over the next few years, and can be expected to improve quality of life and, hopefully, survival in premenopausal patients with breast cancer.

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