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Treatment of Premenopausal Women with Early Breast Cancer

Old Challenges and New Opportunities

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Abstract

Breast cancer occurring in women before the age of menopause continues to be a major medical and psychological challenge. Endocrine therapy has emerged as the mainstay of adjuvant treatment for women with estrogen receptor-positive tumours. Although the suppression of ovarian function (by oophorectomy, irradiation of the ovaries or gonadotropin releasing factor analogues) is effective as adjuvant therapy if used alone, its value has not been proven after chemotherapy. This is presumably because of the frequent occurrence of chemotherapy-induced amenorrhoea. Tamoxifen reduces the risk of recurrence by approximately 40%, irrespective of age and the ovarian production of estrogens. The worth of ovarian function suppression in combination with tamoxifen is unproven and is being investigated in an intergroup randomised clinical trial (SOFT [Suppression of Ovarian Function Trial]). Aromatase inhibitors are more effective than tamoxifen in postmenopausal women but are only being investigated in younger patients. The use of chemotherapies is identical in younger and older patients; however, at present the efficacy of chemotherapy in addition to ovarian function suppression plus tamoxifen is unknown in premenopausal patients with endocrine responsive disease. 'Targeted' therapies such as monoclonal antibodies to human epidermal growth factor receptor (HER)-2, HER1 and vascular endothelial growth factor, 'small molecule' inhibitors of tyrosine kinases and breast cancer vaccines are rapidly emerging. Their use depends on the function of the targeted pathways and is presently limited to clinical trials. Premenopausal patients are best treated in the framework of a clinical trial.

Breast cancer is not uncommon in young women. In Western countries, breast cancer is the most common cause of cancer deaths in women aged ≥30 years, and its incidence is much higher than those of Hodgkin's disease and other neoplasias commonly associated with young age (figure 1).[1] Breast cancer often affects women in the midst of developing a family or professional career, thus forcing young women to face profound personal and social challenges other than pure health issues. These issues, despite being of major importance, are not addressed in this review.

Breast cancers occurring in young patients have been found to be particularly aggressive and associated with a poor prognosis.[2-5] Age by itself does not explain the unfavourable outlook of young patients but it is a marker for several biological properties conferring an aggressive behaviour of breast cancers

in young women. Studies investigating known prognostic factors in young women at diagnosis describe higher proportions of poorly differentiated, rapidly proliferating, estrogen receptor (ER) and progesterone receptor (PgR)-negative tumours with vascular invasion, and diagnosis at more advanced stages in younger than in older women (figure 2).[4,6,7] Bone marrow micrometastases, an independent negative prognostic factor, are also more frequent in young patients.[8]

Retrospective studies are confounded by the use of adjuvant therapies modifying the natural course of the disease and by temporal changes in the selection of such therapies. For example, a recent analysis of Surveillance Epidemiology and End Results (SEER) data of patients aged <45 years with stage I breast cancer revealed a gradual reduction of the risk of breast cancer death between 1988 and 1997;[9] this could have resulted from a more widespread use of appropriate adjuvant systemic therapies in the same time period. This hypothesis is also supported by population-based data from Denmark: adjuvant chemotherapy substantially improved the outcome for very young patients, such that its omission in seemingly low-risk patients may have contributed to the poor prognosis associated with young age.[10]

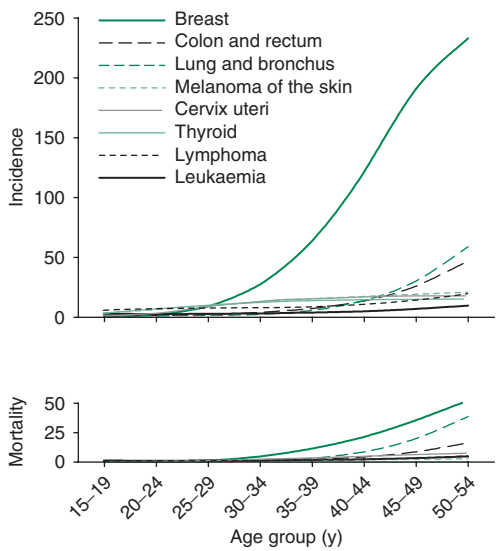


Fig. 1. Incidence and mortality of common malignant tumours.

The purpose of this synthetic review is to highlight the specific aspects and controversies of the adjuvant therapy of young women with breast cancer.

1. Endocrine Therapy

Endocrine responsiveness has become the primary factor determining the choice of treatment in the 2005 St. Gallen algorithm for clinical decision making.[11]

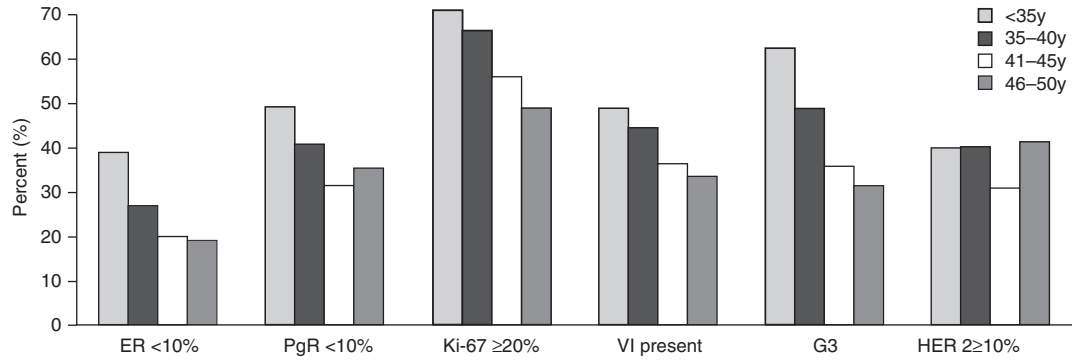
1.1 Ovarian Function Suppression

The suppression of ovarian function by oophorectomy, radiation therapy or gonadotropin releasing hormone (GnRH) agonists reduces the relative risk of recurrence on average by 17% and the risk of death by 13% in the recent Oxford meta-analysis; the protection is substantially larger if the suppression of ovarian function is not accompanied by adjuvant chemotherapy.[12,13] This observation is expected as chemotherapy commonly induces amenorrhoea, particularly in older premenopausal patients.[14,15] Therefore, it is not surprising that subgroup analyses of major randomised clinical trials showed that goserelin following chemotherapy was only effective if chemotherapy did not induce amenorrhoea and in patients aged <40 years.[16,17]

The suppression of ovarian function was at least as effective as cyclophosphamide, methotrexate plus fluorouracil (CMF)-based or low-dose, anthracycline-based chemotherapy in numerous randomised clinical trials of suppression alone[16,18-22] or in combination with tamoxifen.[23-26]

1.2 Tamoxifen

The most recent update of the Oxford meta-analysis revealed that 5 years of treatment with tamoxifen reduces the risk of recurrence by 40% and the risk of death by 32% in women with ER-positive breast cancer. This effect is very similar across all age groups and is not diminished by prior chemotherapy.[12,27] Indeed, tamoxifen was highly effective in reducing the risk of recurrence after ade-



	ER <10%	PgR <10%	Ki-67 ≥20%	VI present	G3	HER 2≥10%
<35y	38.8	49.1	71.4	48.6	61.9	39.6
35–40y	26.9	40.6	66.1	44.4	48.4	40.1
41–45y	20.0	31.2	20.0	36.1	35.6	30.7
46–50y	19.0	35.1	19.0	33.1	31.0	41.0

Fig. 2. Comparison of disease-free survival for tamoxifen versus no tamoxifen after adjuvant chemotherapy for premenopausal women with lymph node-positive breast cancer (reproduced from Colleoni et al.,[6] with permission from the European Society for Medical Oncology). **ER** = estrogen receptor; **G3** = grade 3; **HER** = human epidermal growth factor receptor; **Ki-67 ≥20%** = ≥20% expression of staining positive for Ki-67; **PgR** = progesterone receptor; **VI** = vascular invasion.

quately administered anthracycline-based chemotherapy.[17,28]

1.3 Open Questions and Emerging Therapies

1.3.1 Ovarian Function Suppression Plus Tamoxifen

Whereas it is clear that tamoxifen and the suppression of ovarian function are individually effective adjuvant therapies, it is not known whether the suppression of ovarian function adds to the efficacy of tamoxifen. In premenopausal patients with metastatic breast cancer, the combination of ovarian function suppression plus tamoxifen was superior to either therapy alone,[29] but very few trials have addressed this question in early breast cancer. The ZIPP (Zoladex® in Premenopausal Patients) trial was a highly pragmatic trial designed to determine whether adding goserelin and/or tamoxifen to adjuvant therapy (radiotherapy and/or chemotherapy) provided benefit to pre- or perimenopausal women with early breast cancer. Both goserelin and tamoxifen were similarly effective therapies by themselves but the combination of both agents was not more effective than either treatment alone.[30] The North American Intergroup trial 014 yielded similar results: 345 women with node-negative breast cancer were randomised to either tamoxifen or tamoxifen plus ovarian ablation. This study was closed early because of lower than expected accrual and therefore has limited statistical power. Nevertheless, the addition of ovarian ablation to tamoxifen did not result in an improved disease-free or overall survival but in higher toxicity (mainly in menopausal symptoms and sexual dysfunction).[31]

These findings beg the question of whether ovarian function suppression is needed for the optimal adjuvant therapy of young patients with ER-positive breast cancer. This important clinical question is being addressed in the SOFT (Suppression of Ovarian Function Trial) organised by the Breast International Group (BIG) and the North American Intergroup[32] (table I). In contrast to postmenopausal women, overexpression of human epidermal growth factor receptor (HER)-2 apparently does not affect and may even favourably influence the response to tamoxifen when given after surgical oophorectomy in premenopausal women with ER-positive breast cancer.[33]

1.3.2 Aromatase Inhibitors for Young Patients

Although the efficacy of aromatase inhibitors is firmly established in patients with breast cancer occurring after the menopause,[34,35] no similar data

Table I. Ongoing clinical trials testing the role of aromatase inhibitors for premenopausal patients with endocrine-responsive breast cancer

Study	Design
ABCSG 12 trial	Tamoxifen + GnRH ± bisphosphonate
	Anastrozole + GnRH ± bisphosphonate
BIG SOFT	Tamoxifen × 5 years
	OFS + tamoxifen × 5 years
	OFS + exemestane × 5 years
BIG TEXT	GnRH (± CT) + tamoxifen × 5 years
	GnRH (± CT) + exemestane × 5 years

ABCSG = Austrian Breast and Colorectal Cancer Study Group; **BIG TEXT** = Breast International Group Tamoxifen and EXemestane Trial; **CT** = chemotherapy; **IBCSG** = International Breast Cancer Study Group; **GnRH** = gonadotropin-releasing hormone; **OFS** = ovarian function suppression with oophorectomy or ovarian radiation or LHRH analogue; **BIG SOFT** = Suppression of Ovarian Function Trial.

are available for younger patients. Aromatase inhibitors do not sufficiently suppress the ovarian synthesis of estrogens and may even induce the recovery of ovarian function in some women with chemotherapy-induced amenorrhoea;[36] thus, their use in young patients is possible only in conjunction with measures to suppress the ovarian function. At least three clinical trials are investigating the role of aromatase inhibitors as adjuvant treatment in premenopausal women (table I). In the ABCSG (Austrian Breast and Colorectal Cancer Study Group)-12 trial, the concomitant therapy with zoledronic acid was also explored.[37] Information about treatment efficacy has not yet been published, but the combination of goserelin and anastrozole induced substantially more bone loss than the combination of goserelin and tamoxifen; zoledronic acid reduced the rate of bone loss to physiological levels.[38] The BIG and the North American Intergroup are conducting two trials (SOFT and TEXT [Tamoxifen and EXemestane Trial]) that compare the steroidal aromatase inhibitor exemestane with tamoxifen (both in conjunction with triptorelin)[32,39] [table I]. These trials are currently accruing patients and no data have been reported.

Although third-generation aromatase inhibitors in combination with ovarian function suppression may well turn out to be the emerging new therapy of choice, they should presently be used exclusively in the context of a clinical trial. A global collaboration between cooperative groups is the essential prerequisite to conduct tailored therapy trials of sufficient statistical power in this small group of patients.

The role of the latest addition to the endocrine armamentarium, fulvestrant, is being investigated in at least one phase II trial for premenopausal patients with advanced breast cancer.[40] At the time of writing, this selective ER downregulator cannot yet be recommended for use outside of a clinical trial in premenopausal women.

2. Chemotherapy

The proportion of patients with breast cancer that is not responsive to endocrine therapy is much higher in younger that in older patients. Up to 50% of patients aged <40 years present with ER- and PgR-negative disease.[4,6,7] Although this implies that chemotherapy will be indicated more frequently in younger than in older patients, very few studies have addressed the question of differential effects of chemotherapy by age, and most of them dichotomised the results using age 50 years or menopause as a cut-off point (reviewed by Aebi.[41]) Therefore, modern chemotherapies such as taxanes and dose-dense scheduling do not have indications that differ by age.

Patients with ER-negative tumours derive a higher benefit from more intensive chemotherapies than patients with ER-positive breast cancer.[42] Younger patients present with ER-negative tumours more frequently than older patients;[6] thus, it comes as no surprise that on average, chemotherapy is more effective in younger than in older patients.[12] Early initiation of chemotherapy might also be important for premenopausal patients with tumours that lack ER expression; this issue deserves further investigation.[43]

Although young women are only a small minority of patients with breast cancer, future studies should at least address the questions of age-related differences in toxicity and the quality of life in younger versus older patients.

2.1 Combination of Chemotherapy and Hormonal Therapy

On the basis of both the 'Oxford' meta-analysis and the results of recently published clinical trials, there is no doubt that tamoxifen following adjuvant chemotherapy improves disease-free survival by at least one-third (figure 3).[12,28] Similarly, exploratory analyses of randomised controlled trials revealed that the suppression of ovarian function may be effective even after chemotherapy in patients who remain premenopausal, particularly in very young patients.[16,17]

Thus, adjuvant chemotherapy can be improved by adding hormonal therapy. However, the opposite postulate has never been proven conclusively in a randomised clinical trial. In young patients with ER-positive disease who receive maximum antiestrogenic therapy with GnRH analogues and tamoxifen, the value of chemotherapy is not known. Only one clinical trial has addressed this question so far. In trial 11 of the International Breast Cancer Study Group, 174 patients with node-positive, ER-positive breast cancer were randomly allocated to suppression of ovarian function and tamoxifen or to the same therapy preceded by four cycles of doxorubicin plus cyclophosphamide (AC). This trial was stopped prematurely because of lower than anticipated accrual. Although this obviously limits the power of the comparison, the addition of AC did not further reduce the short-term risk of recurrence or death after a median follow-up of 4.4 years (figure 4).[44]

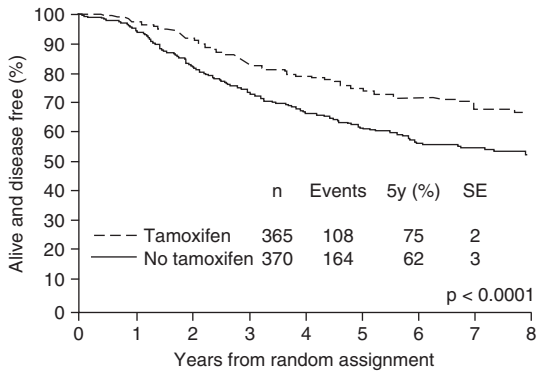


Fig. 3. Comparison of disease-free survival for tamoxifen versus no tamoxifen after adjuvant chemotherapy for premenopausal women with lymph node-positive breast cancer (reproduced from the International Breast Cancer Study Group,[28] with permission from the American Society of Clinical Oncology). **SE** = standard error.

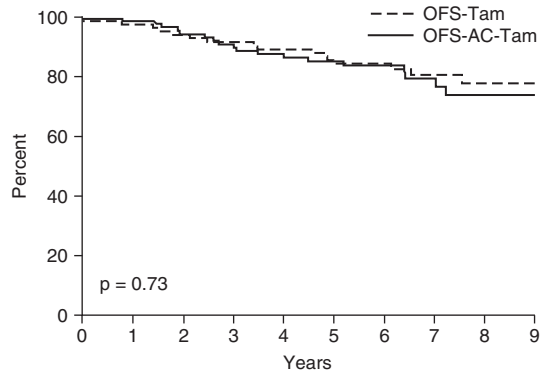


Fig. 4. IBCSG Trial 11-93. Disease-free survival in premenopausal women with estrogen receptor-positive, node-positive breast cancer randomised to ovarian function suppression (OFS) plus tamoxifen (Tam) ± adjuvant chemotherapy with doxorubicin plus cyclophosphamide (AC) [adapted from the International Breast Cancer Study Group,[44] with permission].

Whether or not adjuvant chemotherapy is useful in the presence of combined hormonal therapy is unknown and deserves to be addressed in a randomised clinical trial. This type of highly demanding trial (PERCHE [Premenopausal Endocrine Responsive CHEmotherapy], table I) was initiated by the BIG and the North American Intergroup,[45] but has recently been closed because of insufficient accrual of patients.

The new and rapidly commercially available microarray technologies still require testing and validation in rigorously designed prospective therapy trials, but they hold the promise of providing a novel test to predict the prognosis and response to therapies.

These tools will help not only in guiding who should be offered adjuvant systemic treatment but also in selecting the most appropriate, individualised regimen and approach.[46]

3. Targeted Therapies

Numerous agents are being developed that target cellular mechanisms involved in the pathogenesis of breast cancer in a more or less specific way. The rational use of such therapies should be based on a

molecular understanding of the targets and on appropriate clinical trials with relevant endpoints, and failure to do so may limit the medical and economic value of such agents.[47]

3.1 Monoclonal Antibodies

Trastuzumab has proven effective as a single drug and in combination with chemotherapies in the treatment of both advanced[48] and (particularly) early breast cancer. To date, five independent clinical trials have shown that trastuzumab is able to reduce the risk of recurrence by at least one-third, and all except one trial[49] also demonstrated a reduction of the risk of death.[49-53] Again, age does not predict the efficacy of adjuvant trastuzumab. Remarkably, subgroup analyses revealed opposing gradients of efficacy by age in two studies.[50,51] Several issues still need to be resolved (e.g. long-term cardiac toxicity, proper patient selection, sequential versus simultaneous administration with chemotherapy, radiation and endocrine therapy, optimal timing of initiation, and duration of therapy and drug resistance) to optimally and safely exploit the therapeutic activity of trastuzumab.

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF) that inhibits multiple functions of VEGF. It is active in the initial treatment of metastatic breast cancer in combination with paclitaxel[54] but not at a later stage with capecitabine.[55] Whether or not this drug is active in the adjuvant setting and which tumour or patient characteristics predict its efficacy remain to be investigated. Overall, drugs targeting angiogenesis could result particularly effective in high-risk, endocrine-unresponsive tumours (e.g. the so-called 'triple negatives').[56]

Pertuzumab is a monoclonal inhibitor of the dimerisation of the HER2 protein with epidermal growth factor receptor (EGFR; HER1) and other partners.[57] Its mode of action differs from trastuzumab and small molecule kinase inhibitors such as gefitinib. To date, the observed activity in patients with breast cancer that does not express HER2 has been modest.[58]

3.2 Tyrosine Kinase Inhibitors

Lapatinib is an orally active dual kinase inhibitor that reversibly inhibits the HER1 and HER2 kinase activities; its activity seems to be limited to breast cancers that have a strong expression of HER2.[59] Preliminary results indicate that lapatinib is effective in the therapy of advanced HER2-positive breast cancer after the failure of anthracycline-, taxane- and trastuzumab-based therapy.[60] The use of lapatinib in the adjuvant therapy of patients with HER2-positive breast cancer will be investigated in a global trial conducted by BIG that will compare lapatinib with trastuzumab, as well as sequential- and combined-treatment lapatinib and trastuzumab.

Temsirolimus (CCI-779) in an inhibitor of mammalian target of rapamyin (mTOR) kinase and has moderate activity as a single drug in heavily pretreated breast cancer.[61] It has been investigated in combination with letrozole in postmenopausal women with advanced breast cancer; however, the development of this combination has been discontinued despite promising early results.[62]

Numerous other tyrosine kinase inhibitors, such as pazopanib (GW786034), a VEGF receptor-1, -2, and -3 kinase inhibitor, and erlotinib, an EGFR kinase inhibitor, are being investigated in advanced breast cancer. Neither gefitinib nor erlotinib have so far demonstrated significant single-agent activity against breast cancers refractory to chemotherapy or hormonal therapy. The molecular crosstalk between several receptor kinases and steroid hormone receptors is likely to be involved in the resistance to antiestrogens; thus, modifiers of these mechanisms will potentially improve the management of hormone-sensitive breast cancer.[63] At present, the future impact of such agents in the management of breast cancer is difficult to predict and their use should be limited to clinical trials.

3.3 Vaccines

Active immunisation by tumour antigens that are able to induce specific long-term antitumour immune responses is still an investigational approach in early and advanced breast cancer. Early data from clinical trials show some antitumour activity and

low toxicity. Promising results have been reported from a small randomised clinical trial of active immunisation with a vaccine targeting HER2 protein in patients with early breast cancer: the vaccine significantly reduced the risk or recurrence without causing serious toxic effects.[64] The next generation of clinical studies will integrate breast cancer vaccines with standard therapies. The adjuvant setting is considered most promising as the immunosuppressive effect of bulky disease does not interfere with effective immune responses.[65]

4. Conclusions

Breast cancer in young women is associated with adverse prognostic factors. It appears clear that young age by itself is not the cause but is a surrogate marker of an aggressive phenotype of the disease. 'Targeted' therapies are meant to exploit the cellular functions that initiate and drive the development of breast cancer. Therefore, it is impossible that a drug could be developed that will be used based on age criteria; it seems more likely that such future therapies will be chosen based on the molecular characteristics of the tumour and, possibly, on host factors such as drug-metabolising enzymes. Several areas of controversy and uncertainty exist on the best way to combine targeted and conventional therapies (i.e. endocrine treatments). The best way to exploit the crosstalk between different biological pathways in the different subsets of breast cancer patients should be the topic of future clinical trials. Clinical trials of primary (neoadjuvant) systemic treatment in patients with operable breast cancer could represent the optimal disease setting to test new drugs and strategies, and to verify predictive markers.

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