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Current Perspective

Chemotherapy versus hormonal adjuvant treatment in premenopausal patients with breast cancer

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Abstract

Comparisons between the effects exerted by adjuvant cyclophosphamide, methotrexate and 5-fluorouracil (CMF)-based polychemotherapy and endocrine treatment in premenopausal breast cancer patients are validly drawn in the presence of steroid hormone receptor responsiveness. First, ovarian ablation still remains to show activity compared with chemotherapy in large patient groups. Second, tamoxifen is at least as active in this cohort and, by comparison, produces a significant effect in mortality reduction. Third, induction of reversible amenorrhoea by LHRH analogue administration has shown comparable effects in terms of recurrence-free survival. Finally, recent European investigations have indicated significant recurrence reductions with LHRH analogue-tamoxifen combination strategies. In conclusion, various endocrine treatment modalities have been substantiated as equiefficient to polychemotherapy. Tamoxifen added to a LHRH analogue further diminishes the recurrence rates and now appears to be a valid treatment alternative. We argue that selection of adjuvant systemic therapy for premenopausal breast cancer patients be increasingly guided by knowledge of the steroid hormone receptor levels.

Keywords: Adjuvant chemotherapy; Adjuvant hormonal treatment; Breast cancer; Premenopausal patients

1. Introduction

The key requirement for benefits to arise from hormonal manipulation in breast cancer patients is the presence of hormone-responsive tumour cells, be it in the primary tumour or advanced disease. With respect to tamoxifen therapy, this insight has been evidenced beyond doubt by results of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), indicating virtually no effect of 5 years of tamoxifen in patients with oestrogen receptor (ER)-poor tumours compared with 50 and 23% reductions in the annual odds of recurrence and death, respectively. This has been demonstrated both for pre- and postmenopausal patients [1]. By retrospective analysis, steroid hormone receptors have shown to be predictive for interaction with ovarian ablation and luteinising hormone-releasing hormone (LHRH) analogues alike [2,3].

Comparisons between the effects of adjuvant endocrine treatment and of adjuvant chemotherapy can thus only be drawn validly in patients with hormone-responsive breast cancer. Unfortunately, various trials investigating endocrine treatment—and nearly all investigating adjuvant chemotherapy—comprise a mixture of patients presenting with hormone-responsive and -unresponsive tumours. This circumstance may potentially either dilute the possible effect arising in one of these patient groups or, alternately, impede a valid answer to such an important research question.

This problem holds true not only for individual trials, but also for several EBCTCG analyses, as correctly indicated by Gelber and colleagues [4] and Henderson [5]. Chemotherapy administered to premenopausal women with ER-poor tumours induces a highly significant reduction in the odds of recurrence and death. In patients with ER-positive disease, a 30% reduction in recurrence and a 20% reduction in death have also been seen to reflect significance [6]. Testing for interaction showed no significance, but it should be taken into account that tamoxifen was given to trial participants

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presenting with ER-positive tumours. This could result in serious overestimations regarding the extent of benefit expected from chemotherapy in such patients with receptor-positive disease [7], and thus potentially lead to an overutilisation of chemotherapy in this cohort [5].

It would therefore seem very essential that future adjuvant chemotherapy trials not only be stratified, but also be guided by a knowledge of steroid hormone receptor status that is present in the primary tumour. This has been very well illustrated by an unplanned retrospective analysis focusing on the importance shown by ER status. The Cancer and Leukemia Group B (CALGB) 9344 Trial compared the effect of paclitaxel added to a combination chemotherapy regimen consisting of doxorubicin and cyclophosphamide. This analysis shows that the addition of paclitaxel is only beneficial in patients with ER-negative tumours [8]. Regrettably, however, none of the ongoing randomised trials containing either one of the two taxanes is based on tumour steroid hormone receptor status. Our future knowledge, and answers to this crucial question, will thus rely exclusively on retrospective analyses [9].

2. Materials and methods

Comparisons of adjuvant endocrine treatment and chemotherapy in premenopausal patients can be drawn along the lines of the following treatment strategies:

1. Chemotherapy versus ovarian ablation, induced either by surgery or radiotherapy;
2. Chemotherapy versus tamoxifen;
3. Chemotherapy versus LHRH analogues;
4. Chemotherapy versus LHRH analogues plus tamoxifen.

3. Results

3.1. Chemotherapy versus ovarian ablation

In an analysis of 1115 premenopausal patients presenting with ER-positive tumours, adjuvant chemotherapy applied alone has been shown to induce a significant 33%, and a non-significant 20%, risk reduction in the annual odds of recurrence and death, respectively [6]. It is currently not known whether anthracycline-containing regimens in fact produce superior results—and caution is called for on account of the tamoxifen administration, as discussed earlier.

Several relevant trials have indicated that chemotherapy induces an outcome in patients undergoing amenorrhoea that is significantly superior to that shown by women who do not experience interruption of menses [10,11]. Therefore, it is clear that adjuvant chemotherapy in premenopausal patients has a double-component effect—an indirect endocrine, as well as a direct cytotoxic one, which are probably difficult to discriminate from each other.

Patients' age plays a key role for experiencing amenorrhoea after chemotherapy, inasmuch as younger patients are less likely to become permanently amenorrhoeic upon such treatment [12]. A total of 2102 women under 50 years of age were included in a series of randomised trials investigating ovarian ablation applied alone in early breast cancer [13]. ER status was known exclusively in such studies comparing ovarian ablation plus cytotoxic chemotherapy versus the same chemotherapy (933 subjects). The results of these trials clearly specify that regardless of nodal status, ovarian ablation significantly reduced the annual odds of death and recurrence. Ovarian ablation showed no additional benefit in the presence of adjuvant chemotherapy—in general, however, the numbers of patients were limited [13].

A direct comparison of chemotherapy and ovarian ablation was performed in two trials with a participant number totalling 1064 (Table 1) [2,14]. Both investigations showed a non-significant difference between the two randomised groups. Amenorrhoea occurred in 68% of the patients receiving cyclophosphamide, methotrexate and 5-fluorouracil (CMF), despite the fact that chemotherapy was given 3-weekly, and thus perhaps suboptimally, although the data that support these results were based on a retrospective analysis [15]. These two trials unmistakably indicate that permanent surgery- or radiotherapy-induced ovarian ablation has significant activity—comparable to that produced with CMF-based chemotherapy—in patients with hormone-responsive tumours.

3.2. Chemotherapy versus tamoxifen

Tamoxifen was thought to be primarily active in postmenopausal patients, when circulating oestradiol levels are low, and tamoxifen and metabolites can thus more easily bind to the ER. In the 1998 Overview, tamoxifen given for 5 years was shown to induce highly significant reductions in the annual odds of recurrence

Table 1
Chemotherapy versus ovarian ablation in premenopausal breast cancer patients

Reference	Patients: number selection	Chemotherapy	Follow-up (years)	Result
Scottish (1993) [2]	332/ ER±	CMF×6 3-weekly	12	NS
Eijlertsen (1999) [14]	732/ ER +	CMF×6 3-weekly	5	NS

NS, non-significant; ER, oestrogen receptor; CMF, cyclophosphamide; methotrexate and 5-fluorouracil.

Table 2
Polychemotherapy versus tamoxifen (5 years) in premenopausal patients with oestrogen receptor-positive tumours (indirect comparison)

Overview (Ref.)	Patients *n*	Reduction in the annual odds of	
		Recurrence	Death
Tamoxifen [1]	1327	45% S.D. 8	32% S.D. 10
Polychemotherapy [6]	1115	33% S.D. 8	20% S.D. 10

S.D., standard deviation.

(45%) and death (32%) in patients younger than 50 years of age (92% ER-positive) [1]. However, the number of subjects randomised in these trials amounted to no more than 1327. Since the benefit of tamoxifen administration in this cohort was only reported recently, no trial has yet been launched to compare adjuvant polychemotherapy with tamoxifen in premenopausal ER-positive patients. Only indirect comparisons can thus be carried out, with all their well known drawbacks can thus be drawn.

Data shown in Table 2 are derived from the two EBCTCG Overviews of 1998 [1,6]. Although the numbers of patients are too small to arrive at final conclusions, tamoxifen can safely be stated to have at least an effect equal to polychemotherapy in inducing a reduction in recurrence. Yet moreover, tamoxifen does have a significant effect in the reduction of mortality which is lacking in polychemotherapy. These data can therefore be interpreted as tamoxifen being at least as active as CMF-based polychemotherapy in premenopausal patients with hormone-responsive tumours. Again, caution is warranted as to this indirect comparison, and it would seem to be a high-priority issue to reevaluate this question in large adjuvant clinical trials.

3.3. Chemotherapy versus LHRH analogues

LRHR analogues generate ovarian suppression by downregulating gonadotropin release via the LHRH receptors of the pituitary gland. These drugs have shown to be effective treatment for advanced breast cancer, providing a similar clinical benefit to surgical oophorectomy in terms of progression-free (PFS) and overall survival (OS) [16,17]. Therefore, it appears to be an ideal candidate for inducing a hormone profile of castration without surgical or radiotherapeutic intervention. Another advantage is the reversibility of medical castration by LHRH analogues.

Two clinical trials of different maturity have compared CMF-based chemotherapy with LHRH analogues given for 2 years (Table 3). The 'Zoladex' Early Breast Cancer Research Association (ZEBRA) trial included patients with both hormone-responsive and -unresponsive tumours [18]. However, the majority of this large patient series (1614) presented with ER-positive disease. For this cohort, no difference between goserelin and CMF was established in the final outcome after 5 years. In ER-negative patients, CMF induces significantly better disease-free survival (DFS) and OS rates. Significant, early quality-of-life benefits have nevertheless been observed in patients treated with goserelin in terms of improved scores on physical symptoms, activity levels and the ability to cope with illness [19]. Another trial reported by Wallwiener and collaborators presented data comparing leuprorelin acetate and CMF in 600 premenopausal patients with hormone-responsive, node-positive breast cancer [20]. At 2 years follow-up, the TABLE trial evidenced no significant difference between the two arms under investigation, yet a significantly lower amount of serious adverse events in the endocrine treatment group.

Taking these two trials together, the results clearly indicate that induction of amenorrhoea by the administration of LHRH analogues in approximately 2000 premenopausal patients with hormone-responsive tumours induces effects comparable to those of CMF-based chemotherapy in terms of recurrence-free survival (RFS).

3.4. Chemotherapy versus LHRH analogues plus tamoxifen

In advanced breast cancer, combination endocrine treatment with LHRH analogue plus tamoxifen has been shown to be superior to treatment with either LHRH or tamoxifen alone, as measured by objective response rate, median PFS and OS [21]. This randomised, European Organization for Research and Treatment of Cancer (EORTC) trial clearly indicates that tamoxifen exhibits higher activity in the presence of a

Table 3
Chemotherapy versus LHRH analogues in premenopausal breast cancer patients

Trial [Ref.]	Patients: number selection	Chemotherapy	Follow-up (years)	Result
ZEBRA (2000) [3]	1640/ ER±	CMF×6 days 1+8	5	NS for ER+
TABLE (2001) [20]	600/ ER+/PgR+	CMF×6 days 1+8	2	NS

LHRH, luteinising hormone-releasing hormone; NS, non-significant; ER, oestrogen receptor; PgR, progesterone receptor; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

Table 4
Combination endocrine treatment (LHRH analogues plus tamoxifen) versus chemotherapy

Trial [Ref.]	Patients: number selection	Treatment	Follow-up (years)	Results
ABCSG 5 [23]	1034/ ER + /PgR + stage I + II	i.v. CMF×6 days 1 + 8 goserelin 3 years amoxifen 5 years	4	Endocrine treatment superior to CMF RFS $P < 0.02$
GROCTA 2 [24]	244/ ER + /PgR ± stage I + II	(milan) CMF×6 days ovarian suppression tamoxifen 6 years	5	No difference
FASG 6 [25]	333/ ER + /PgR + stage II	FEC×6 triptorelin 3 years tamoxifen 3 years	4	No difference

ABCSG, Austrian Breast and Colorectal Cancer Study Group, trial 5; GROCTA 2; Italian Breast Cancer Adjuvant Chemo-hormone Therapy Cooperative Group, trial 2; FASG 6, French Adjuvant Study Group, trial 6; ER, oestrogen receptor; PgR, progesterone receptor; CMF, cyclophosphamide, methotrexate and 5-fluorouracil; RFS, relapse-free survival; i.v., intravenous; FEC, 5-fluorouracil, epirubicin and cyclophosphamide.

postmenopausal endocrine profile. In addition, an analysis of four clinical trials in 506 premenopausal women with advanced disease showed the addition of tamoxifen to a LHRH analogue induced a significant survival benefit compared with exclusive LHRH administration [22].

Three different European studies have randomised patients to either a combination of a LHRH analogue and tamoxifen or adjuvant chemotherapy (Table 4) [23–25]. A total of 1611 trial participants were randomised to receive either intravenous (i.v.) CMF or 5-fluorouracil, epirubicin and cyclophosphamide (FEC) compared with combination LHRH analogue for 3 or 5 years plus tamoxifen for 3 or 5 years. All patients had hormone-responsive tumours, either with or without lymph node metastases. Conducted in Austria, the largest investigation demonstrated a statistically significant improvement in RFS in patients treated with combination endocrine therapy. The two other trials indicated no difference, despite the application of an anthracycline-containing regimen. It is interesting to note that with this regimen in the French study, only 41% of patients experienced amenorrhoea, compared with over 65% in the two other trials applying CMF. A combined analysis of these three investigations indicated an increase in RFS to reach a borderline level of statistical significance ($P < 0.06$), as presented at the St. Gallen Conference 2001 [30].

4. Discussion

It has been universally recognised that steroid hormone receptor levels should play an important role in selecting adjuvant systemic treatment strategies for patients with breast cancer. Unfortunately, this knowledge has not yet been sufficiently adopted in clinical trial designs. In the USA, chemotherapy was acknowledged as the gold standard in the majority of premenopausal breast cancer patients, regardless of hormone receptor levels. Only recently have reports from overseas emerged to question the predominant role of chemotherapy in this patient group [5,26], finalising in the statement that chemotherapy is underutilised in older patients with receptor-negative tumours, while it is being overutilised in those with receptor-positive disease [5]. This opinion prevailing in the USA, however, has stimulated comparative trials with endocrine treatment and chemotherapy in premenopausal patients being generally implemented in Europe. Overall, solid data now indicate that ovarian suppression, induced either by surgical castration, by radiotherapy or LHRH analogue administration, produces an effect that is similar to that displayed by CMF-based chemotherapy. The addition of tamoxifen to a LHRH analogue has shown a further improvement in RFS [23] and appears to be a valid alternative to CMF chemotherapy [27]. An identical conclusion was drawn by the panelists of the 2001 Consensus Meeting in St. Gallen.

A number of major questions remain to be addressed in future research. These include the importance of amenorrhoea induced in patients having received adjuvant chemotherapy. An analysis carried out by Aebi and coworkers has shown that breast cancer patients who are younger than 35 years of age and treated with adjuvant CMF experienced a higher risk of relapse and death than older premenopausal patients, especially if their tumours expressed ER [28]. Obviously, the endocrine effect of chemotherapy alone seems insufficient for the younger age group.

Two different sets of data have served to shed light on this problem. First, ovariectomy in the presence of chemotherapy fails to further improve results obtained with exclusively applied chemotherapy. As discussed, however, these findings are based on small amounts of patients without knowledge of the receptor status. Second, results of the INT-0101 Intergroup trial indicate that the addition of a LHRH analogue to an anthracycline-containing regimen in premenopausal patients with hormone-responsive tumours does not further improve chemotherapy results alone [29]. In turn, how-

ever, this trial was probably not powered to detect small differences. Retrospective analyses by the authors of this paper suggest that the addition of ovarian ablation is more important for younger than for older premenopausal patients.

In conclusion, we would generally argue that future adjuvant trials in premenopausal breast cancer patients be addressed on the basis of steroid hormone receptor levels. In particular, a direct comparison between tamoxifen and chemotherapy would be called for. Furthermore, the efficacy of combination endocrine treatment including LHRH analogues and tamoxifen, compared with anthracycline- and taxane-containing regimens, needs to be established. Finally, since it has been shown that aromatase inhibitors play an important role in postmenopausal patients with hormone-responsive advanced disease, future research should also focus on the combination of LHRH and aromatase inhibitors. In Austria, a trial comparing tamoxifen and anastrozole on the basis of primary treatment with LHRH analogue is presently ongoing in the adjuvant setting of premenopausal patients with hormone-responsive tumours.

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