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E16. Amenorrhoea, aromatase inhibitors, tamoxifen or a combination in premenopausal women

R. Jakesz *

Department of General Surgery, Vienna Medical School, Währinger Gürtel 18-20, Vienna 1090, Austria

The ovary is the major site of oestrogen production in premenopausal women. Removal of the ovaries in premenopausal patients with breast cancer has long been recognised to potentially alter the course of disease. This procedure leads to a marked reduction in the circulating levels of oestrogen. It has been shown that ovariectomy given as an adjuvant treatment reduces the odds of recurrence or death by approximately 25%.

Goserelin and other luteinising hormone-releasing hormone (LHRH) analogues produce reversible ovarian suppression by downregulating gonadotropin release via the LHRH receptors of the pituitary gland. Downregulated receptors lead to an inhibition of LH secretion, which causes a blockade in ovarian function.

Currently, there are at least five different kinds of adjuvant treatment in premenopausal patients presenting with hormone-responsive tumours:

1. Chemotherapy
2. Tamoxifen
3. Ovarian ablation
4. LHRH analogue
5. LHRH analogue combined with tamoxifen

1. Chemotherapy

From a pooled analysis of 1115 premenopausal patients with oestrogen-receptor (ER) positive tumours, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) obtained data showing adjuvant chemotherapy applied alone induced a significant 33%, and a non-significant 20%, risk reduction in the annual odds of recurrence and death [1]. However, we do not yet know whether anthracycline-containing regimens produce superior results in this setting.

There is currently little doubt that the effect of adjuvant chemotherapy is age-dependent. Thus, chemotherapy is much more effective in premenopausal than in postmenopausal women. The patient's age plays a key role for those experiencing amenorrhoea after chemotherapy, as younger women are less likely to become permanently amenorrhoeic upon such treatment [2]. Several relevant trials and retrospective analyses have specified that chemotherapy induces an outcome in patients undergoing amenorrhoea that is significantly superior to that shown by women who do not experience an interruption of menses [3,4]. In particular, overall prognosis is markedly increased in patients who experience chemotherapy-induced amenorrhoea. Cyclophosphamide, methotrexate and fluorouracil- (CMF) and fluorouracil, doxorubicin, and cyclophosphamide- (FAC) or taxane-containing regimens induce amenorrhoea in 60–70% and 30–50% of patients, respectively.

2. Tamoxifen

There is no direct comparison between tamoxifen and polychemotherapy in premenopausal patients with hormone-responsive breast cancer. The EBCTCG overview of randomised trials with tamoxifen has shown that the administration of 5 years of tamoxifen in patients younger than 50 years of age leads to a relative risk reduction in the annual odds of recurrence of approximately 45% and in the odds of death of approximately 32% [5]. Although the number of subjects randomised in these studies amounted to no more than 1327, tamoxifen can safely be stated to have at least an effect equal to polychemotherapy in inducing a reduction in recurrence. Furthermore, investigations have suggested tamoxifen is significantly active in reducing mortality, an effect which is lacking for polychemotherapy. However, final conclusions are still to be drawn as to whether

* Tel.: +43 1 40400 6916; fax: +43 1 40400 6918.
E-mail address: raimund.jakesz@meduniwien.ac.at.

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tamoxifen is indeed as effective as adjuvant polychemotherapy in the premenopausal setting.

3. Ovarian ablation

Among the currently available therapies for premenopausal early-stage breast cancer, ovarian ablation, together with aromatase inhibition, is applied to decrease oestrogen production.

The EBCTCG 1996 overview included a total of 2102 women under 50 years of age who had participated in a series of randomised trials investigating ovarian ablation applied alone in early breast cancer [6]. ER status was known in such studies – totalling 993 patients – investigating this treatment modality plus cytotoxic chemotherapy *versus* the same chemotherapy. The results of these trials clearly indicate that ovarian ablation significantly reduced the annual odds of death and recurrence regardless of patients' nodal status. However, ovarian ablation showed no activity in the presence of adjuvant chemotherapy.

Two trials have directly compared chemotherapy and ovarian ablation with patient numbers totalling over 1000 [7,8]. Neither investigation showed a significant difference between the two randomised groups. Amenorrhoea occurred in 68% of the patients receiving 3-weekly CMF. 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.

4. LHRH analogue

LHRH analogues have been shown to be effective treatment for advanced breast cancer, providing a similar clinical benefit to surgical oophorectomy in terms of progression-free survival (PFS) and overall survival (OS) [9,10]. Thus, they appear to be ideal tools to induce a hormone profile of – reversible – castration without surgical or radio-therapeutic interventions.

Two clinical trials of different maturity have compared CMF-based chemotherapy with LHRH analogues given for 2 years. The Zoladex Early Breast Cancer Research Association (ZEBRA) trial randomised more than 1600 patients to receive either 2 years of goserelin or 6 cycles of CMF [11]. OS rates were absolutely identical in the presence of ER-positive disease. However, in patients with receptor-negative tumours, CMF was shown to be significantly superior to goserelin in terms of survival. This leads to the conclusion that the efficacy of endocrine treatment is restricted to patients with hormone-responsive tumours. Second, the Takeda Adjuvant Breast cancer study with Leuprorelin Acetate (TABLE) compared an LHRH analogue with CMF in 600 premenopausal patients with hormone-responsive, node-positive breast cancer [12]. At 3 years follow-up, the TABLE trial evidenced no significant difference between the two arms under investigation, but there was a significantly lower amount of serious adverse events in the endocrine treatment group.

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

5. LHRH analogue combined with tamoxifen

In advanced breast cancer, combination endocrine treatment with an LHRH analogue plus tamoxifen has been shown to be superior to treatment with either LHRH or tamoxifen alone, as measured by the objective response rate, median PFS and OS [13].

In the adjuvant setting, the Austrian Breast & Colorectal Cancer Study Group (ABCSG) Trial 5 compared a combination of LHRH analogue and tamoxifen with CMF [14]. More than 1000 premenopausal patients with hormone-responsive tumours were randomised between 6 cycles of CMF intravenously (i.v.) and combination endocrine treatment consisting of 3 years goserelin and 5 years tamoxifen. After 6 years of follow-up, patients receiving combination endocrine treatment showed significantly better RFS rates than those treated with CMF. Conversely, other trials with similar designs have indicated no difference between patients given chemotherapy and those receiving a combination of LHRH analogue and tamoxifen [15,16].

Finally, another ongoing multicentre, randomised investigation in Austria, ABCSG Trial 12, is currently investigating whether the combination of goserelin and anastrozole is superior to goserelin plus tamoxifen. More than 1000 patients have been randomised so far.

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