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Role of LHRH agonists in premenopausal women with oestrogen receptor-positive breast cancer: the ZEBRA experience

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Ovarian ablation has been used in the treatment of breast cancer for more than 100 years and its value as an adjuvant treatment for premenopausal women with early disease was clearly demonstrated by the recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Overviews. The data from the 1995 Overview showed that women under 50 years of age had a significant advantage in both disease-free survival (DFS) and overall survival (OS) when treated with ovarian ablation compared with no adjuvant treatment ($25 \pm 7\%$ reduction in the annual odds of recurrence and $24 \pm 7\%$ reduction in the annual odds of death) [1]. These results are comparable to those achieved by cytotoxic chemotherapy, which has traditionally been viewed as the optimal treatment approach for early breast cancer in premenopausal women.

Although ovarian ablation by oophorectomy or irradiation has been shown to improve survival, the resulting premature menopause is associated with long-term adverse effects, such as osteoporosis and increased risk of cardiovascular problems [2]. The luteinising hormone releasing hormone agonist (LHRHa), goserelin (Zoladex™ 3.6 mg), suppresses oestradiol concentrations to postmenopausal levels and can be used to provide a medical ovarian ablation which is reversible in the majority of patients on cessation of treatment.

1. Zoladex™ Early Breast Cancer Research Association (ZEBRA) trial

Goserelin was compared with cyclophosphamide/methotrexate/5-fluorouracil (CMF) in a large, randomised, multicentre trial. DFS, OS and side-effect profiles were compared in 1640 node-positive, pre-/perimenopausal patients (aged $\leqslant 50$ years) with early breast cancer [3,4].

After a median follow-up of 6 years, goserelin and CMF were found to be equivalent in terms of DFS (Hazard ratio (HR) = 1.01; 95% Confidence Interval CI 0.84–1.20) in Oestogen Receptor ER-positive patients (74% of the study population). A significant advantage in favour of CMF, however, was found for DFS (HR = 1.76; 95% CI 1.27–2.44) in ER-negative patients (19% of the study population) [4]. Side-effects for the two treatment groups were typical of chemotherapy and endocrine therapies. After 24 weeks of treatment, typical side-effects of chemotherapy, e.g. alopecia, nausea/vomiting (despite the use of antiemetics in over 97% of patients receiving CMF) and infection, were all substantially higher with CMF than with goserelin (43.4% versus 3.5%, 56.4% versus 5.3% and 12.9% versus 4.8%, respectively). Menopausal symptoms, e.g. vaginal dryness and hot flushes, were initially lower with CMF (13.9% versus 23.8% and 42.4% versus 72.4% at 24 weeks, respectively). However, at 1 year after cessation of goserelin therapy, the incidence of menopausal symptoms associated with goserelin decreased to below that seen with CMF.

Amenorrhoea was achieved more rapidly and more completely with goserelin than with CMF, with over 95% versus 60% of patients becoming amenorrhoeic by 6 months, respectively. Furthermore, amenorrhoea was found to be reversible in most goserelin-treated patients, but was generally permanent following CMF treatment [3].

Quality of life (QoL) and bone mineral density (BMD) sub-studies were included in the ZEBRA trial. During the first 3–6 months, the improvement in overall QoL from baseline was significantly ($P < 0.0001$) greater in the goserelin-treated group than in the CMF-treated group, and there were no significant differences thereafter [5]. In the BMD sub-study, data collected from 96 patients indicated BMD losses for both treatment groups during the first 2 years of the study, with mean losses being greater in the goserelin group. However, at 3 years (i.e. 1 year after cessation of goserelin therapy) partial recovery of BMD was seen with goserelin, whereas mean losses persisted in the CMF group throughout follow-up. As a result, by the 3-year assessment, no significant differences in BMD were observed between the treatment groups. In addition, the observed

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changes in BMD levels appeared to be related to menstrual status in both treatment groups [6].

In conclusion, goserelin (3.6 mg) provides equivalent efficacy without the distressing side-effects of cytotoxic treatment in pre-/perimenopausal patients with ER+, node-positive early breast cancer. Goserelin offers a real alternative to adjuvant chemotherapy in the management of this patient population.

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