Department of Oncology and Pathology

ADJUVANT TAMOXIFEN AND LUTEINIZING HORMONE-RELEASING HORMONE AGONISTS IN PREMENOPAUSAL BREAST CANCER

On long-term benefits and side effects in a randomised study

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ABSTRACT

Adjuvant tamoxifen and luteinizing hormone-releasing hormone agonists in premenopausal breast cancer
On long-term benefits and side effects in a randomised study
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Adjuvant endocrine therapy improves breast cancer survival, unconditional of other treatment. In premenopausal breast cancer, tamoxifen for 5 years is the standard treatment, with or without the addition of ovarian ablative therapy. The optimal timing and duration of ovarian ablative treatment is not yet defined, and it is not clear if there is additional benefit from ovarian suppression in combination with cytotoxic chemotherapy. With improving survival and excellent prognosis, there is increasing need for prevention of long-term adverse effects, monitoring and treatment when appropriate. Premature ovarian failure is frequent from adjuvant treatment of young breast cancer patients with a following risk of accelerated bone loss and infertility. The possible ovarian protective effect of ovarian ablation from luteinizing hormone-releasing hormone (LHRH) agonists is debated.

Aims: The purpose of our study is to examine the efficacy of the LHRH agonist goserelin for adjuvant therapy of premenopausal breast cancer, the role of interaction between goserelin and tamoxifen and the impact of estrogen receptor (ER) content. We also examine long-term side effects in regard to ovarian function and bone health.

Patients and methods: The study was designed to determine whether the addition of the LHRH agonist goserelin and/or tamoxifen to adjuvant therapy provided benefit for premenopausal women with breast cancer. Patients were entered into a 2 x 2 factorial randomisation to tamoxifen 40 mg daily with or without concomitant goserelin, 3.6 mg every 28 days or goserelin alone for 2 years. Efficacy was analysed as well as the effects on ovarian function, bone mineral density and bone markers.

A total of 927 women were recruited to the Stockholm part of the ZIPP trial. At a median follow-up of 12.3 years, goserelin reduced the risk of first event by 32% (P = 0.005) in the absence of tamoxifen, and tamoxifen reduced the risk by 27% (P = 0.018) in the absence of goserelin. The combined goserelin and tamoxifen treatment reduced the risk by 24% (P = 0.021) compared with no endocrine treatment. In highly ER-positive tumours, there were 29% fewer events among goserelin-treated patients (P = 0.044) and a trend towards greater risk reduction, depending on the level of ER content. The greatest risk reduction from goserelin treatment was observed among those not receiving tamoxifen (HR: 0.52, P = 0.007). In the study of ovarian function, 36% of the women in the goserelin group reported menses one year after completed CMF- and endocrine therapy, compared to 7% in the goserelin plus tamoxifen group, 13% in the tamoxifen group and 10% of the controls. Among women treated with goserelin, there was a statistically significant increase in the proportion of menstruating women one year after completed treatment, compared to at 24 months of treatment (P = 0.006), in contrast to all other treatment groups, who were unchanged or more often amenorrheic. The bone mineral study showed that after 2 years of treatment, there was a significant decline in bone mineral density (mean change, -5%: P < 0.001) in the women receiving goserelin. The combined goserelin and tamoxifen treatment, as well as tamoxifen alone, resulted in a lesser, but statistically significant, decrease in bone mineral density (mean change, -1.4%; P = 0.02; and -1.5%; P < 0.001). One year after cessation of treatment, the goserelin group alone showed partial recovery from bone loss (mean change, 1.5%; P = 0.02). In the study of bone turnover markers (BTM), there was a significant rise in Osteocalcin (RR: 1.57, p < 0.001), PINP (RR 1.65, p < 0.001) and CTX (RR 1.98, p < 0.001) among goserelin-treated patients. There were no significant changes in BTM among those treated with either goserelin and tamoxifen or tamoxifen alone. Among patients where bone mineral density measurements were available, change in BMD was inversely associated with change in BTM (r = -0.40 to -0.51).

Conclusions: Adjuvant tamoxifen in combination with the LHRH agonist goserelin is not superior to either tamoxifen alone or goserelin alone in regard to recurrence-free survival in premenopausal endocrine responsive breast cancer. A significant interaction indicates that the effect of goserelin depends on whether tamoxifen is given or not, and the effect of tamoxifen depends on whether goserelin is given or not. In this study there is a trend towards greater efficacy of goserelin with increasing ER levels. A subgroup of women with strongly ER-positive tumours benefits more from goserelin treatment, whereas the benefit of tamoxifen does not seem to be dependent on ER content. This study shows some evidence of a protective effect of goserelin on ovarian function in CMF treated women. This effect was not observed where tamoxifen was given in addition to goserelin treatment. Further studies are needed to confirm this. Two years of ovarian ablation from goserelin treatment induces a significant reduction in bone mineral density, but there is partial recovery from the bone loss one year after stopped treatment. After six months of goserelin treatment, markers of both bone resorption and bone formation increase, whereas there is no change in bone turnover from tamoxifen alone or in combination with goserelin. Furthermore, there was an inverse correlation of changes in BMD and bone markers. The addition of tamoxifen seems to counteract the effects of goserelin on BMD and BTM. In addition to BMD measurements, biochemical examinations of bone turnover markers may be useful for monitoring bone health, identifying women at risk for bone loss and making early interventions possible.