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Research Paper

Goserelin, as an ovarian protector during (neo)adjuvant breast cancer chemotherapy, prevents long term altered bone turnover

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ABSTRACT

Background: The Ovarian Protection Trial In Premenopausal Breast Cancer Patients *"OPTION"* trial (NCT00427245) was a prospective, multicenter, randomised, open label study evaluating the frequency of primary ovarian insufficiency (POI) at 12 months in women randomised to 6–8 cycles of (neo)adjuvant chemotherapy (CT) +/− goserelin (G). Here we report the results of a secondary endpoint analysis of the effects of CT+/-G on markers of bone turnover.

Methods: Serum for bone alkaline phosphatase (BALP) and urine for N-terminal telopeptide (NTX) were collected at baseline, 6, 12, 18, 24 and 36 months. Changes in median levels of bone turnover markers were evaluated for the overall population, according to age stratification at randomisation (≤ 40 *vs* >40 years) and with exploratory analysis according to POI rates at 12 months.

Results: In the overall population, there was a significant increase in NTX at 6 months compared to baseline in patients treated with CT+G (40.81 *vs* 57.82 $p=0.0074$) with normalisation of levels thereafter. BALP was significantly increased compared to baseline at 6 months and 12 months in those receiving CT+G, but normalised thereafter. BALP remained significantly higher compared to baseline at 12, 24 and 36 months in patients receiving CT, resulting in a significant difference between treatment groups at 36 months (CT+G 5.845 *vs* CT 8.5 $p=0.0006$). These changes were predominantly seen in women >40 years. Women with POI at 12 months showed altered bone formation compared to baseline levels for a longer duration than women who maintained menses.

Conclusion: Addition of G to CT increases bone turnover during treatment with normalisation after cessation of treatment suggesting G may offer sufficient ovarian protection against CT induced POI to negate longstanding altered bone turnover associated with POI.

1. Introduction

Maintenance of bone health relies on a balance between bone formation by osteoblasts and bone resorption by osteoclasts. Under normal physiological circumstances, these two processes are tightly regulated to ensure preservation of the structural integrity of bone. However, cancer therapies can disrupt this delicate balance, leading to bone loss and subsequent increased fracture risk [1]. The pathophysiology of cancer treatment induced bone loss (CTIBL) is ascribed to either the direct effects of adjuvant treatments on bone turnover i.e. chemotherapy and endocrine therapy, or indirect effects via suppression of ovarian function with the subsequent low oestrogen environment causing clinically relevant bone loss [2].

Suppression of ovarian function in premenopausal women can be temporary or permanent dependent on the type of cancer treatment. The risk of POI is higher in women >40 years

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compared to 40 years or under [3] as loss of primordial follicles from direct chemotherapy toxicity depletes an already lowered ovarian reserve secondary to age [4]. Chemotherapy induces permanent primary ovarian insufficiency (POI) in 63–85% of patients receiving cyclophosphamide, methotrexate and fluorouracil (CMF) regimens and up to 50% with use of anthracycline containing regimens [5,6] with effects on bone metabolism and bone mineral density (BMD) as a consequence. For example, following induction of permanent ovarian suppression by six cycles of doxorubicin and cyclophosphamide chemotherapy, BMD fell at 6 months by 5.2% at the lumbar spine and by 2.8% at the femoral neck compared to baseline [7]. Bone loss associated with treatment induced ovarian failure appears to be more rapid and severe than the bone loss that occurs during a natural menopause, and therefore carries an increased risk of skeletal morbidity in long term survivors of premenopausal breast cancer [8]

Gonadotrophin-releasing hormone (GnRH) analogues, such as goserelin, induce a rapid but reversible suppression of ovarian function with serum levels of oestradiol and follicle stimulating hormone (FSH) reaching postmenopausal levels within 2 weeks of administration [9,10]. In addition to the adjuvant use of goserelin in endocrine sensitive breast cancer, GnRH analogues have been evaluated in prospective randomized trials as a possible protection against chemotherapy induced POI in premenopausal women receiving adjuvant chemotherapy. Conflicting results have been reported with some studies demonstrating a reduction in chemotherapy induced early menopause of between 17% and 56% with addition of goserelin [11,12], while others showed no statistical difference in resumption of menses post chemotherapy between those treated with or without goserelin [13,14]. The impact of combined GnRH and chemotherapy on acute bone loss during therapy, and the delayed effects on bone post treatment have not been reported to date. Herein we present the secondary endpoint of bone turnover marker changes (serum bone alkaline phosphatase [BALP] and urine N-terminal telopeptide [NTX]) in the *OPTION* trial. The preliminary primary endpoint data of amenorrhoea rates at 12 months post chemotherapy were not statistically different between those treated with or without goserelin [14], although final data have not been reported yet.

2. Patients and methods

2.1. Study population

The *OPTION* trial was an open, randomised multicenter study registered on the ClinialTrials.gov website, number NCT00427245. The trial was approved by South West Research Ethics Committee and performed in accordance with ICH GCP and the EU Directive. The primary objective was to evaluate the effect of goserelin on the incidence of POI at 12 months following chemotherapy in early breast cancer. All premenopausal ER negative women (or ER positive women for whom ovarian suppression was not considered necessary as part of the adjuvant therapy programme) recommended to receive (neo)adjuvant chemotherapy were eligible for inclusion. The average age of patients was 40. Women were stratified by age at randomisation (≤ 40 or >40 years) and by centre. Chemotherapy (CT) regimens comprised 6–8 cycles of cyclophosphamide and/or anthracycline and/or taxane. Goserelin (G) 3.6 mg by depot subcutaneous injection was randomly allocated to start before or at first chemotherapy cycle and continued 3–4 weekly until the final cycle of chemotherapy. At trial closure 227 patients had been randomised and all had given written informed consent for serum and urine analysis.

2.2. Patient evaluation

Secondary objectives of the *OPTION* trial included measurement of changes in bone turnover markers. Baseline serum and urine samples were available from 89 and 94 patients respectively. The serum and urine was stored at -80 °C pending batch analysis at Sheffield University's Academic Unit of Bone Metabolism. Patients were excluded from this analysis if they did not have a follow up time point sample. Follow up time points were 6, 12, 18, 24 and 36 months post baseline. BALP was measured using the AcessÕ automated immunoassay, Beckman Coulter Inc (High Wycombe, United Kingdom). The inter assay coefficient of variation (CV)=5.2%. NTX and creatinine were measured using the Ortho Clinical Diagnostics automated immunoassay (High Wycombe, United Kingdom). The inter assay CV=4.4%. NTX was expressed as a ratio to creatinine and the inter assay CV for creatinine=1.8%.

2.3. Statistical analysis

Changes in median levels of bone turnover markers from baseline and between treatment groups were evaluated using the Mann Whitney *u* test. All analyses were performed using GraphPad PRISM v 6.0d. Significance was assigned at $p \leq 0.05$.

3. Results

Of the 89 and 94 patients who provided serum and urine, 58 (serum) and 65 (urine) patients had at least one follow up sample and were included in the analyses (Fig. 1). The bone marker population had an average age of 38 years and predominantly ER positive tumours. The percentage of patients receiving anthracycline only (23%), anthracycline+cyclophosphamide (72%) or taxane (4%) chemotherapy was identical to the overall study population. Within this sub group treatment groups were well matched for age with a median (range) age of 41.5 years (30–51) in the CT alone group ($n=54$) and 41.0 years (26–49) in the CT+G group ($n=54$). Baseline BALP and NTX were similar between CT and CT+G groups with a median [IQR] BALP (μg/l) of 6.1 [4.9–7.9] and 6.3 [4.7–7.5] respectively and a median [IQR] NTX (nmol/mmol creatinine) of 33.9 [23.3–43.2] and 34.9 [28.8–47.2] respectively. Adjuvant tamoxifen use was similar between both groups (CT $n=20$, CT+G $n=22$).

3.1. Bone resorption

Acute/on treatment median [IQR] NTX was significantly increased at 6 months (6/12) in patients treated with CT+G (6/12=57.8 [39.4–72.9] $p=0.0030$). This acute effect on bone resorption was not seen in patients treated with CT (37.07 [27.5–59.1]), resulting in a significantly higher NTX level at 6 months in the CT+G group compared with the CT group ($p=0.0032$) (Fig. 2a).

Subsequently, following completion of G treatment at around 12–18 months, NTX returned to near baseline levels in the CT+G group with no significant differences from baseline at any further time point, indicating the acute G-induced increase in bone resorption resolved upon cessation of the drug. CT did not significantly change bone resorption compared to baseline at any time points.

3.2. Bone formation

Acute/on treatment median [IQR] BALP was significantly increased at 6/12 compared to baseline in patients treated with