CHANGES OF BONE METABOLISM INDUCED BY PERIOPERATIVE ANTHRACYCLINE- AND/OR TAXANE-BASED CHEMOTHERAPY FOR PRIMARY BREAST CANCER

Abstract # 1975

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INTRODUCTION

Loss of bone mineral density (BMD) is among the well known sequelae of pharmacological therapy of patients (pts) with primary breast cancer (PBC) [Hirbe et al., 2006]. Cancer therapy induced bone loss (CTIBL) progresses more rapidly as compared to normal age-related changes of BMD and is best known to be associated with the use of aromatase inhibitors (AI) in the adjuvant endocrine therapy of postmenopausal PBC pts [Body, 2010; Peppone et al., 2014]. Antineoplastic chemotherapy (Ctx) may also lead to a deterioration of BMD but in contast to AI therapy this phenomenon is by far less investigated so far [Hirbe et al., 2006; Bjarnson et al., 2008]. Most of these studies focused on the classical CMF protocol which is no longer in common use. A few studies also investigated the effects of anthracycline-based regimens (CAF/CEF) on BMD of pts with PBC and found effects comparable to CMF [Headley et al. 1998]. In premenopausal PBC pts, CTIBL following Ctx is commonly interpreted as an indirect endocrine effect since the BMD decline in women experiencing secondary amenorrhea is generally more severe than in those retaining their ovarian function [Bjarnason et al., 2008, Body, 2010]. However, Ctx may also have direct effects on the bone, since postmenopausal PBC pts show a BMD loss which is at least as high as in premenopausal pts with secondary amenorrhea. As a matter of concern, investigations on the effects of more recent Ctx protocols on bone metabolism or BMD of PBC pts including both anthracyclines and/or taxanes are still pending. This retrospective study was undertaken in order to gain more insights into direct effects of modern anthracycline- and/or taxane-based Ctx on the bone metabolism of both pre- and postmenopausal PBC pts.

METHODS

Data of 109 PBC pts (premenopausal, n=49; postmenopausal, n=60) receiving a total of 600 perioperative Ctx cycles were analyzed. All pts must have been treated with at least 2 cycles of either adjuvant or neoadjuvant Ctx based on anthracyclines, taxanes or both; 17 pts with HER2-positive disease also received concomitant trastuzumab. Characteristics of pts included are summarized in Table 1. Pts receiving trastuzumab without Ctx or a Ctx regimen not containing anthracyclines or taxanes (such as CMF) were excluded from this investigation as were those with overt bone metastases or a history of osteoporosis at the time of diagnosis. The following serum parameters were analyzed: C-terminal telopeptide of type I collagen (ICTP) as a marker of osteoclast function, N-terminal propeptide of type I collagen (P1NP) representing the osteoblast function, and alkaline phosphatase (BALP) as a sum marker of bone turnover. All three parameters were measured by commercial enzyme immunosorbent assays (EIAs) prior to start of Ctx and after each of the following cycles for a maximum of 6. Baseline bone marker levels of pre- and postmenopausal pts were compared by *student´s t*-tests. Absolute and relative changes of bone markers over time were evaluated by analyses of variance (ANOVA) for repeated measures. For all statistical analyses, p<0.05 indicted significance.

RESULTS

Figure 1 shows the baseline values for ICTP, P1NP, and BALP. For all three parameters, postmenopausal pts had significantly higher baseline levels as compared to premenopausal pts but within the normal range except for ICTP: ICTP, p=0.0027; P1NP, p=0.0063; BALP, p=0.0007. Figure 2 shows the absolute changes from baseline for ICTP, P1NP, and BALP during perioperative Ctx for PBC. With the exception of ICTP, all changes were within the normal range of the particular parameter and did not reach statistical significance for both ICTP, and BALP. In premenopausal pts, P1NP showed a significant decline until cycle #3 and then recovered completely until cycle #6 (p=0.0024). Postmenopausal pts, however, experienced a sustained P1NP decline from baseline until cycle #6 (p=0.0152). Figure 3 demonstrates the relative changes of all three bone markers versus baseline. Although starting from significantly different baseline values, relative changes were largely comparable between pre- and postmenopausal pts and particularly impressive for P1NP.

Table 1: Patients´ characteristics

Menopausal status	**n (%)**
Pre-/perimenopausal	49 (45)
postmenopausal	60 (55)
Tumor size	n (%)
T1-2	98 (90)
T3	7 (6)
T4	4 (4)
Nodal status	n (%)
negative	54 (49)
positive	55 (51)
Estrogen receptor status	**n (%)**
negative	27 (25)
positive	82 (75)
HER2 status	**n (%)**
negative	83 (83)
positive	18 (17)
Grading	**n (%)**
G1	4 (4)
G2	52 (48)
G3	53 (48)
Type of chemotherapy	**n (%)**
anthracycline-based	16 (15)
taxane-based	34 (31)
anthracycline- and taxane-based	59 (54)
concomitant trastuzumab (HER2+)	17 (16)

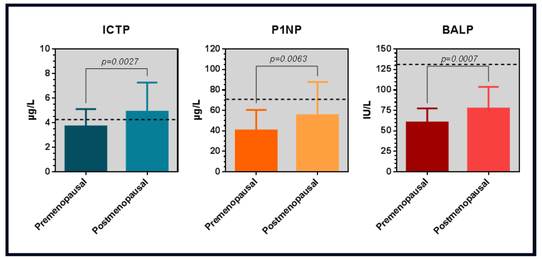

Figure 1: Baseline values (mean ± SD) for ICTP (left), P1NP (center), and BALP (right) in premenopausal and postmenopausal patients prior to receiving perioperative chemotherapy for primary breast cancer. The dashed lines represent the upper normal limits of the analyzed parameters. It should be noted that mean baseline values of all three bone markers were significantly higher in post- versus premenopausal women without exceeding the normal ranged except for ICTP.

CONCLUSIONS

- Our study represents one of the first systematic evaluations of short-term effects of modern anthracycline- and/or taxane-based Ctx regimens on the bone metabolism of PBC pts.
- Bone turnover at baseline was significantly higher in postmenopausal pts.
- Absolute and relative changes of all three bone markers over time were largely comparable between pre- and postmenopausal pts arguing in favor of direct cytotoxic rather than indirect endocrine effects of Ctx for PBC on bone metabolism.
- Absolute and relative changes of P1NP over time were particularly impressive indicating that the osteoblast function is the main target of suspected adverse effects of perioperative Ctx on bone integrity of PBC pts.
- The sustained P1NP decrease in postmenopausal pts may indicate a generally impaired ability to recover from negative pharmacological effects on bone metabolism in older pts or those having prematurely lost their ovarian function.
- Whether the observed short-term effects of modern perioperative Ctx for PBC will translate into a higher risk to further develop CTIBL must be clarified in subsequent analyses which should also focus on the individual importance of different agents and therapeutic antibodies such as trastuzumab.

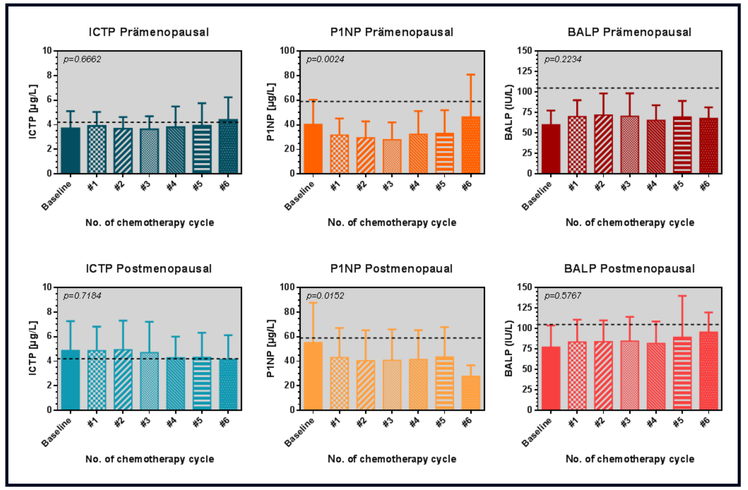

Figure 2: Absolute changes of ICTP (left), P1NP (center), and BALP (right) during perioperative chemotherapy for primary breast cancer. The upper row of charts represent the results for premenopausal patients, the lower row demonstrates results for postmenopausal patients. Bone markers were measured at baseline and after each of 6 subsequent chemotherapy cycles. Results are expressed as mean ± SD. The dashed lines represent the upper normal limits. It should be noted that changes over time for ICTP and BALP did not reach statistical significance. In contrast, P1NP declined significantly until cycle #3 in premenopausal patients before completely recovering until cycle #6. In postmenopausal patients, a sustained decline of P1NP could be observed throughout the whole observation period from baseline until cycle #6.

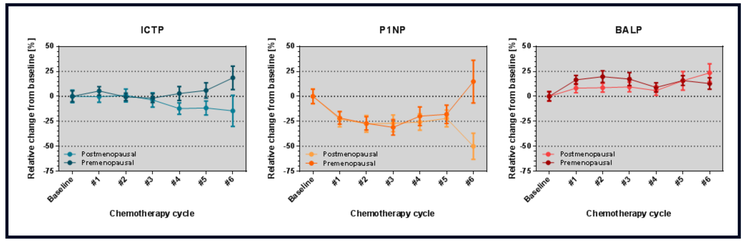

Figure 3: Relative changes of ICTP (left), P1NP (center), and BALP (right) from baseline during perioperative chemotherapy for primary breast cancer. Bone markers were measured at baseline and after each of 6 subsequent chemotherapy cycles. Results are expressed as mean + SEM. Although starting from different baseline values, the relative changes of bone markers over time are largely comparable between pre- and postmenopausal patients.

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