DIRECT EFFECTS OF PLATINUM-BASED CHEMOTHERAPY + BEVACIZUMAB ON THE BONE METABOLISM OF PATIENTS WITH PRIMARY AND PLATINUM-SENSITIVE RECURRENT TUBOOVARIAN CARCINOMA

Abstract #868P

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INTRODUCTION

Chemotherapy-induced bone loss (CTIBL) is among the most frequent sequelae of systemic anticancer treatment often leading to increased bone fragility and subsequent fractures [Hadji, 2015]. During the last two decades, CTIBL induced by endocrine therapy in both breast and prostate cancer has been investigated in depth. In females, it is very clear from these studies that CTIBL imitates normal postmenopausal osteoporosis but develops more rapidly [Hadji, 2015]. However, little is known about direct effects of antineoplastic chemotherapy (Ctx) on bone metabolism and turnover. Studies performed in the 1990ies gave evidence that premenopausal patients (pts) exposed to high doses of alkylating agents for either breast cancer or lymphoma are at high risk for developing premature osteoporosis [Hadji, 2015]. These effects have mainly been attributed to secondary hypoestrogenism following ovarian failure induced by Ctx [Hadji, 2009]. More recent investigations have revealed negative effects of modern Ctx protocols based on both anthracyclines and taxanes on bone metabolism of pts with primary breast cancer [Chen et al., 2015; Kurbacher et al. Proc ASCO 2015]. Since these effects occurred very early after the start of treatment and did not differ between pre- and postmenopausal women, it is likely that Ctx is directly toxic on bone metabolism and subsequent negative sequelae may well precede indirect endocrine mechanisms of further CTIBL. In contrast to breast cancer, almost nothing is known about the influence of Ctx on bone metabolism of pts with tuboovarian carcinoma (TOC) which may well be related to the relatively worse prognosis of this disease. However, the long-term survival has markedly improved in pts with potentially platinum-sensitive disease during the last decade. Therefore, late side effects of Ctx such as CTIBL should be certainly more recognized in TOC pts in future. There are various features that make TOC most suitable to study direct effects of Ctx on bone metabolism: (1) The vast majority of TOC pts is postmenopausal at time of diagnosis, many premenopausal pts are ovarectomized when undergoing their primary surgical treatment; (2) in contrast to breast cancer, TOC pts are normally not exposed to endocrine treatment; (3) for more than three decades, pts with primary TOC are exclusively subjected to platinum-based Ctx; (4) since 1996, chemotherapy with platinum and paclitaxel is the established standard of care in pts with advanced primary TOC; (5) in pts with late relapses (≥ 12 months after finishing primary Ctx), platinum-based re-induction (platinum monotherapy; platinum+taxane, platinum+gemcitabine, platinum+pegylated-liposomal doxorubicin) is the established standard of care. As a consequence, Ctx for primary and platinum-sensitive recurrent TOC is more standardized as compared to many other tumor types. In 2012 the European Medicines Agency (EMA) has approved the anti-angiogenic agent bevacizumab (Bev) for the treatment of advanced primary TOC in platinum-based Ctx, one year later it has also been approved for the treatment of platinum-sensitive recurrent TOC. Since then, the vast majority of TOC pts treated in the European Union (EU) are exposed to Bev alongside to their standard Ctx. This translational project to investigate the influence of platinum-based Ctx with or without Bev on the expression of bone turnover markers in pts with primary or platinum-sensitive TOC treated in the clinical routine.

METHODS

A total 84 pts with primary (n=47) or platinum-sensitive recurrent pts (n=37) who were subjected to platinum-based Ctx were included. 18 pts also received Bev. Patients must not have overt bone metastases. Any preceding Ctx for TOC or any other malignant condition must have been finished for at least 12 months. Pts must not receive bisphosphonates or other osteoprotective agents during their Ctx. Detailed pts characteristics are summerized in Tabel 1. The following serum markers of bone-turnover were analyzed by commercially available enzyme immunorobent assays (EIAs): C-terminal telopeptide of type I collagen (ICTP), as a marker of osteoclast function; N-terminal propeptide of type I collagen (P1NP), as a marker of osteoblast activitity, and alkaline phosphatase (AP) as a marker of general bone turnover. Bone markers were determined prior to every Ctx application for a maximum of six. The analyses prior to the first application was regarded as baseline (BL), whereas the determination prior to the subsequent Ctx administrations reflected the effet of the preceding Ctx cycle. In order to investigate the effect of the last Ctx cycle on bone marker expression, an additional blood draw was performed three weeks after cessation of Ctx. Baseline levels of ICTP, P1NP, and AP were compared by using student´s t-tests. Changes of bone marker expression over time were analyzed using one-way analyses of variance (ANOVA), differences between Ctx-Bev and Ctx+Ctx were analyzed by two-way ANOVA. For all statistical analyses, p<0.05 indicated significance.

RESULTS

As can be obtained from Table 1 the median age of the pts included was 59 years and thus roughly ten years younger as compared to other routine populations of TOC. The vast majority of pts had epithelial ovarian cancer with high grade serous adenocarcinoma being the predominant histologic subtype. 47 ps (56%) had primary disease) and 37 (44%) had platinum-sensitive relapses. A combination of paclitaxel + carboplatin with or without bevacizumab was the most frequently used Ctx regimen accounting for a total of 52 treatments (61.9%) in total. 80 pts (95.2%) were treated with platinum-based combinations, only 4 (4.8%) were subjected to carboplatin monotherapy. 18 pts (21.4%) received Bev as part of the systemic therapy. The baseline values of ICTP, P1NP and AP are demonstrated in Figure 1. It has to be noted that median values of both ICTP and P1NP were moderately elevated at baseline whereas AP narrowed the upper normal range. Differences between pts with and without Bev all lacked significance. For ICTP, a decrease was observed in both cohorts of pts which tended to recover particularly in the Ctx+Bev group (Figure 2). Changes over time for ICTP were significant only in the the Ctx-Bev group. In both groups, P1NP decreased rapidly and constantly in both groups of pts (Figure 2, 3). Changes over time were significant in both the Ctx-Bev and the Ctx+Bev cohort (Figure 2). These effects were more pronounced in the Ctx+Bev group with a final P1NP of only 43.1% of the baseline level. In contrast, P1NPdropped to only 70.2% of the baseline level in the Ctx-Bev group (Figure 3). Comparing the effects on therapy on the expression of P1NP, it could be shown that a significantly stronger depression was observed in the Ctx+Bev group (p=0.0037, Figure 3). In contrast to collagen cleavage products, AP did not change significantly in both groups of pts both over time and in the intergroup comparison (Figure 2, 3).

CONCLUSIONS

- This is one of the very rare systematic investigations on the effect of modern chemotherapy on the bone turnover in patients with platinum sensitive tuboovarian carcinoma and the first-in-human studying the effect of bevacizumab on bone metabolism in these patients.
- Bone turnover regarding both osteoblast and osteoclast markers were moderately increased at baseline with no difference in pts with and without bevacizumab.
- In both groups, a significant decline of P1NP over time was observed with was markedly stronger in patients exposed to bevacizumab.
- It can be concluded that platinum-based chemotherapy ± bevacizumab primarily produces a significant inhibition of osteoclast function in patients with tuboovarian carcinoma.
- This is the first report demonstrating that the effect of chemotherapy alone on osteoclast activity is significantly enhanced by adding an anti-angiogenic agent like bevacizumab.
- The effect of chemotherapy ± bevacizumab on the expression on osteoclast markers is less intensive and can be interpreted as reactive.
- As expected, these short-time effects did not translate into significant changes of AP levels.
- These results are in good agreement to our previous findings in pts with primary breast cancer exposed to anthracyline- and/or taxane-based chemotherapy.
- It is likely from these findings that platinum-based chemotherapy exhibits direct toxic effects on bone metabolism in patients with tuboovarian cancer which are even more prominent when adding bevacizumab.
- These effects should preferably interpreted as an inhibition of bone formation more likely than an enhancement of bone resorption.
- It remains a matter of debate whether the effects on bone metabolism in this study will further translate into an increased incidence of CTIBL and osteoporosis.

Table 1: Patients´ characteristics

Age (years)	
median	59
range	39-86
Menopausal status	**n (%)**
pre-/perimenopausal	16 (19.0)
postmenopausal	68 (81.0)
Tumor type	**n (%)**
ovarian carcinoma	78 (92.9)
fallopian tube carcinoma	2 (2.4)
primary peritoneal carcinoma	4 (4.8)
Histologic subtype	**n (%)**
Type I carcinoma	***19 (22.6)***
serous, non-high grade	6 (7.1)
mucinous	2 (2.4)
endometrioid	3 (3.6)
clear cell	4 (4.8)
small cell	1 (1.2)
other	3 (3.6)
Type II carcinoma	***65 (77.4)***
serous, high grade	60 (71.4)
Mullerian mixed tumor	5 (6.0)
Disease status	**n (%)**
Primary	47 (56.0)
Recurrent	37 (44.0)
Type of chemotherapy	**n (%)**
Regimens without bevacizumab	***66 (78.6)***
carboplatin monotherapy	2 (2.4)
paclitaxel + carboplatin	38 (45.2)
carboplatin + gemcitabine	19 (22.6)
carboplatin + pegylated liposomal doxorubicin	6 (7.1)
paclitaxel+carboplatin+gemcitabine	1 (1.2)
Regimens with bevacizumab	***18 (21.4%)***
carboplatin monotherapy	
paclitaxel + carboplatin	3 (3.6)
carboplatin + gemcitabine	14 (16.7)
	1 (1.2)

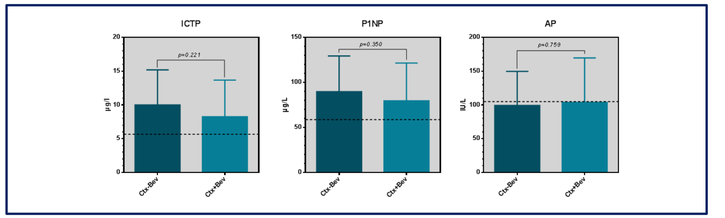

Figure 1: : Baseline values (mean ± SD) for ICTP (left), P1NP (center), and AP (right) in tuboovarian cancer patients exposed to platinum-based chemotherapy without (dark blue) or with (light blue) bevacizumabcancer. The dashed lines represent the upper normal limits of the analyzed parameters. It should be noted, that both osteoclast and osteoblast activity in both groups of patients

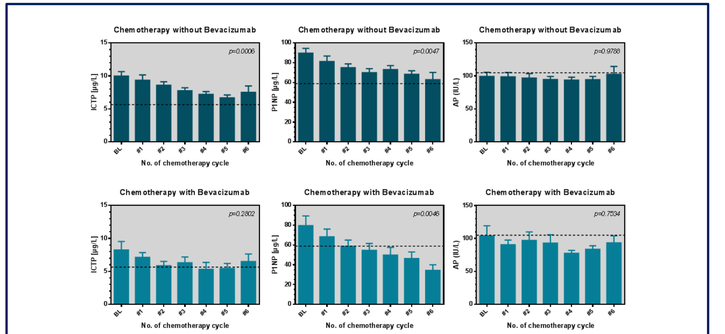

Figure 2: Absolute changes of ICTP (left), P1NP (center), and AP (right) during chemotherapy for tuboovarian cancer. The upper row of charts represent the results for chemotherapy without bevacizumab, the lower row demonstrates results for chemotherapy with bevacizumab. Bone markers were measured at baseline and after each of 6 subsequent chemotherapy cycles. Results are expressed as mean ± SEM. The dashed lines represent the upper normal limits. It should be noted that changes over time for AP did not reach statistical significance. In contrast, P1NP declined significantly over time in both groups of patients. This effect was significantly more pronounced in patients exposed to chemotherapy with bevacizumab.

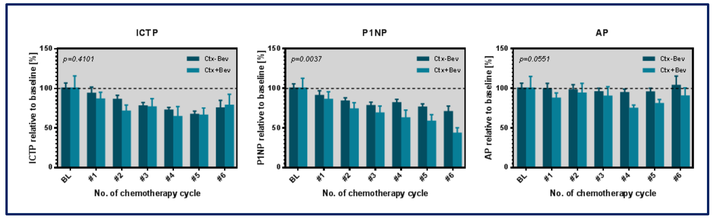

Figure 3: Relative changes of ICTP (left), P1NP (center), and BALP (right) from baseline during platinum-based chemotherapy with and without bevacizumab for tuboovarian cancer. Bone markers were measured at baseline and after each of 6 subsequent chemotherapy cycles. Results are expressed as mean ± SEM. The constant decline of P1NP was sgnificant in both groups of patients and significantly more pronounced in patients receiving chemotherapy with bevacizumab.

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