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Correlation study between osteoporosis and hematopoiesis in the context of adjuvant chemotherapy for breast cancer

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ABSTRACT

It has been demonstrated that adipocytes in the bone marrow have an inhibitory activity on hematopoietic proliferation. This retrospective study attempts to establish if a correlation exists between osteoporosis and hematopoiesis before and after adjuvant chemotherapy in the context of breast cancer. Osteoporosis is interpreted both as a direct marker of osteoblastic decline and as an indirect marker of increased bone marrow adiposity.

Patients from the "Centre du Sein" at CHUV (Centre Hospitalier Universitaire Vaudois) undergoing adjuvant chemotherapy were included in this study. Evolution of blood counts was studied in correlation with osteoporosis status. Toxicity of chemotherapy was coded according to published probability of febrile neutropenia.

Results: 143 women were included; mean age 52.1 ± 12.5 years, mean BMI (body mass index) 24.4 ± 4.1. BMD (bone mineral density) scored osteoporotic in 32% and osteopenic in 45%. Prior to chemotherapy BMD was positively correlated with neutrophil ($p<0.001$) and thrombocyte ($p=0.01$) count; TBS (trabecular bone score) was not correlated with blood count. After the first cycle of chemotherapy, an increase of one point in TBS correlated with a decrease of 57% on the time to reach leucocyte nadir ($p=0.004$). There was a positive correlation between BMD and risk of infection ($p<0.001$).

Our data demonstrates an association between osteoporosis and lower blood counts in a younger cohort than previously published, extending it for the first time to neutrophil counts in females. Our results suggest that the healthier the bone, the earlier the lowest leucocyte count value, prompting further research on this area.

Key words: hematopoiesis, bone marrow, osteoporosis, adipocytes, breast cancer

INTRODUCTION

Hematopoietic stem cell niche

Hematopoiesis is the process by which precursor and mature blood cells are produced by hematopoietic stem cells (HSCs) within the adult bone marrow. In adults, the hematopoietic marrow resides within the axial skeleton and the proximal epiphysis of the femur and the humerus. In these areas the marrow consists of 10-90% fat depending on age. In fact, it is estimated that the bone marrow adipose tissue represents around 1 to 1.5 kg in a healthy adult. [1, 2]

The HSC niche, located within the bone marrow, is critical for the maintenance of the HSC. The niche is composed of different cells including osteoblasts, mesenchymal stromal cells, perivascular cells and adipocytes [3, 4].
Osteoblasts have a regulatory role in the HSC niche and support maintenance of the most primitive HSCs. Osteoblasts are a key element for the myeloid lineage as murine osteoblasts have been shown to produce G-CSF (Granulocyte colony-stimulating factor), M-CSF (macrophage colony-stimulating factor), GM-CSF (granulocyte-macrophage colony-stimulating factor), IL-1 (interleukin-1), IL-6 (interleukin-6) among other cytokines that support HSC proliferation[5]. At the same time osteoblasts also produce inhibitory molecules, such as osteopontin, that limit hematopoietic replication and have an overall supporting role in HSC long-term maintenance [5–10].
Adipocytes are important components of the hematopoietic microenvironment. Although long considered passive space fillers within the bone marrow, they also secret cytokines with mixed hematopoetic activity, such as neuropilin-1, adiponectin and leptin. In mice, adipocytes have been shown to have a negative regulatory effect on HSC proliferation in the context of stress-hematopoiesis and post-transplantation aplasia[11–13].

Osteoporosis
Osteoporosis is a skeletal disorder characterized by compromised bone strength and microarchitectural deterioration. The bone mineral density (BMD) is evaluated by dual-energy X-ray absorptiometry (DXA). The result of the BMD is given as a T-score relative to normal values from a pool of a healthy 25-year-old population. Osteoporosis is defined by a T-score below -2.5 standard deviations (SD) [14]. The trabecular bone score (TBS) is a gray-level textural index, derived from lumbar spine DXA images, that is correlated with parameters reflecting bone microarchitecture[15]. TBS provides skeletal information that is not captured with standard BMD measurements. A low TBS is consistently associated with an increased risk of prevalent and incident fractures.
Osteoporosis, at the cellular level, can be explained by an imbalanced activity of the osteoblasts and the osteoclasts. This process results in an increase of the bone turnover and a trabecular bone loss which in turn results in increased adipocyte content [16–18]. In fact, bone composition can be partially deducted from T-score and TBS such that bone marrow fat tissue inversely correlates with bone marrow density. Bone mineral density and TBS thus also constitute an indirect marker of bone marrow adipogenesis [14, 19, 20].

We thus decided to test whether there is a correlation between osteoporosis and hematopoiesis upon stress hematopoiesis before and after adjuvant chemotherapy, in the context of a breast cancer cohort. Osteoporosis is interpreted here both as a direct marker of osteoblastic decline and as an indirect marker of increased bone marrow adiposity.

METHODS

Characteristics of the cohort:
All women treated for localized breast cancer at the Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland, between August 2008 and July 2015 were evaluated for this retrospective study. The women were included if they: 1) had a non metastatic breast cancer at the time of diagnosis; 2) belonged to the “Centre du Sein” database with no document attesting disagreement to share their data for research projects; and 3) received chemotherapy. BMD was evaluated by DXA before or at onset of adjuvant endocrine therapy.

The criteria for exclusion were: absence of available BMD measurement 3 years prior or following the diagnosis, absence of available laboratory values following chemotherapy, any prior chemotherapy, BMI >35, history of hematological disorders or of active hematological disease, active second malignancy concomitant to breast cancer, or moderate to severe renal impartment (Fig 1). Some patients received endocrine therapy after completion of the chemotherapy treatment. As blood counts are not influenced by endocrine therapy, this was not an exclusion criteria.

Bone parameters.
BMD was measured on the femoral neck, total femur and lumbar spine and TBS was measured at lumbar spine L1 to L4. According to the BMD values, osteoporosis was defined if any of the three locations obtained a T-score < -2.5 SD, osteopenia as a T-score between -1.0 SD and -2.5 SD, normal as a T-score $\geq$ -1.0 SD [14].
The following normal range for TBS values was used: TBS >1.310 was considered to be normal; TBS between 1.230 and 1.310 was considered to be consistent with partially degraded microarchitecture; and TBS < 1.230 defined degraded microarchitecture.

The baseline characteristics of the 143 included women are summarized in Table 1. No patient was excluded after analysis.

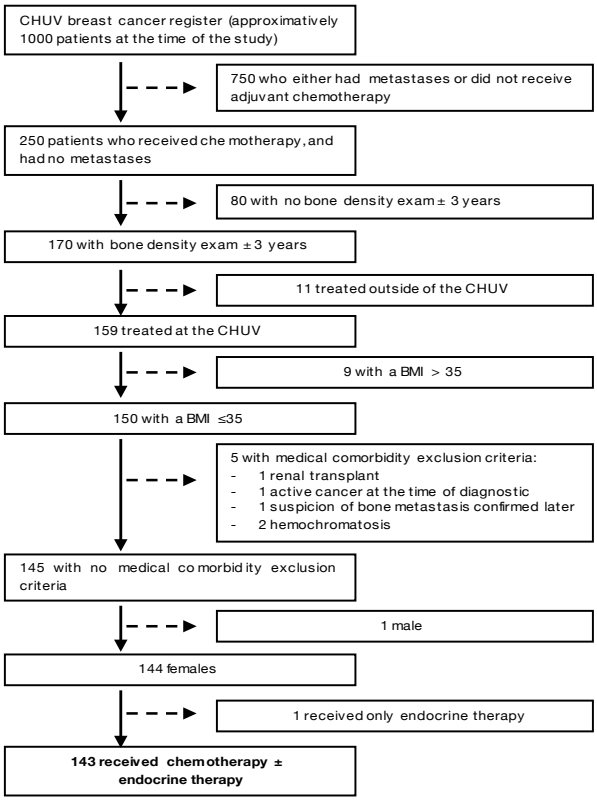

Figure 1 Exclusion process, CHUV: Centre Hospitalier Universitaire Vaudois, BMI: body mass index

Characteristics	Values
Age (years), mean± SD	52.13 ± 12.47
T-score	
Osteoporotic, n (%)	33 (32)
Osteopenia, n (%)	64 (45)
Normal, n (%)	46 (23)
TBS, mean ± SD	1.33 ± 0.12
Degraded microarchitecture, n (%)	20 (15)
Partially degraded microarchitecture, n(%)	49 (35)
Normal, n(%)	70 (50)
Hormonal status	
Premenopausal, n (%)	78 (55)
Postmenopausal, n (%)	60 (42)
Undetermined, n (%)	5 (3)
BMI (kg/m^2), mean ±SD	24.47 ± 4.05
G-CSF, n (%)	96 (67)
Infections, n (%)	43 (30)

Table 1 Characteristics of the patients (n=143) from the data base, osteoporotic defined by a T-score <-2.5 or pathological fracture, osteopenia defined by a T-score between -2.5 and -1, normal defined by a T-score >-1. Degraded microarchitecture defined by a TBS score <1.2, a partially degraded microarchitecture is defined by a TBS score between 1.2 and 1.35, a normal microarchitecture is defined by a TBS score > 1.35

Collected data

We collected the identification code of the patients, date of birth, diagnosis, date of diagnosis, type of chemotherapy, starting date of chemotherapy, T-score and TBS values.

To study hematological recovery, all available blood counts between one week prior to the first cycle of chemotherapy and the first day of the second cycle of chemotherapy were collected. The incidence of infection between the first day of chemotherapy and the first day of the second cycle of chemotherapy was also recorded.

Confounding factors taken into account for the multivariate analysis were the age at the time of treatment, the use of G-CSF, and the type of chemotherapy, which was graded according to hematological toxicity.

To code the toxicity of the chemotherapy we took advantage of previous literature discussing the recommended use of G-CSF during chemotherapy for breast cancer[21]. Zielinski et al created a table with the associated risk of febrile neutropenia for each standard adjuvant breast cancer chemotherapy regime (Table 2). We used this reference to code the hematological toxicity of the different chemotherapy using the published risk of febrile neutropenia as a continuous variable to adjust for intensity of hematological toxicity.

Chemotherapy	**Number of patients (n=143), (%)**	**Risk of febrile neutropenia** (adapted from ref. 21)
Doc-Car	3 (2.1)	13
FEC-Doc	42 (29.4)	11
FEC	2 (1.4)	6

AC-Pac	1 (0.7)	5
Cap-Doc	1 (0.7)	5
EC	4 (2.8)	5
ECP	15 (10.5)	5
FEC-Pac	1 (0.7)	5
TC	66 (46.2)	5
AC	2 (1.4)	3
Paclitaxel	6 (4.2)	2

Table 2 Frequency of adjuvant chemotherapy regimes in our cohort. The corresponding risk of febrile neutropenia according to Zielinski et al. was used to code the toxicity of the chemotherapy regime as a continuous variable.
Doc-Car: Docetaxel – Carboplatine – Trastuzumab, FEC-Doc: 5-fluorouracil – Epirubicin – Cyclophosphamide – Docetaxel, FEC: 5-fluorouracil – Epirubicin – Cyclophosphamide, AC-Pac: Doxorubicin – Cyclophosphamide – Paclitaxel, Cap-Doc: Cyclophosphamide – Doxorubicin – Cisplatin – Docetaxel, EC: Epirubicin – Cyclophosphamide, ECP: Epirubicin – Cyclophosphamide – Paclitaxel, FEC-Pac: 5-fluorouracil – Epirubicin – Cyclophosphamide – Paclitaxel, TC: Docetaxel – Cyclophosphamide, AC: Doxorubicin – Cyclophosphamide

Response variables

To establish the response variables, we collected both the date and the absolute value for neutrophil, leucocyte and thrombocyte nadir. We calculated the difference between the starting count and the neutrophil, leucocyte and thrombocyte count at nadir, as well as the rate of infection.

Statistical analysis

For the analysis of the blood count before chemotherapy, linear regressions were performed.
The univariate analysis was performed using GraphPad Prism version 7.0a for Mac OS X, GraphPad Software, San Diego California USA, www.graphpad.com. The multivariate analysis was performed using R (version 3.3.1).
For the three variables "date for neutrophil, leucocyte and thrombocyte nadir" both a Poisson regression and a linear regression were performed and both gave similar results. For the six variables "value of neutrophil, leucocyte and thrombocyte nadir" and "difference between the starting count and the neutrophil, leucocyte and thrombocyte count at nadir" a linear regression was performed. For the variable "infection" a logistic regression was performed. Each regression was performed four times changing the explicative variable: TBS score continuous, TBS score categorical, T-score continuous and T-score categorical. Each regression was adjusted for the variables age, G-CSF and toxicity of chemotherapy. Some variables showed missing values. Complete case analyses were performed.
The quality control of the regressions was done using residual versus fitted predicted values.

Ethical committee

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and in accordance with the 1975 Helsinki declaration as revised in 2008. The local ethical commission approved the study (CER-VD, Lausanne, Switzerland). For this type of study specific consent was not required. Patients having provided a document attesting disagreement to share their medical data for research projects were excluded.

RESULTS

Blood counts before chemotherapy

The blood counts before chemotherapy were analyzed according to T-score and TBS values. Our results indicate that an increase of one point in the T-score is associated with an increase of 13.51 G/l platelets and 0.644 G/l neutrophils within our cohort. (Fig 2).
No significant trends were found for the association of blood counts and TBS score before chemotherapy. Subgroup analysis using menopausal status (premenopausal and postmenopausal) did not attain a significant association between T-score and blood counts within our cohort.

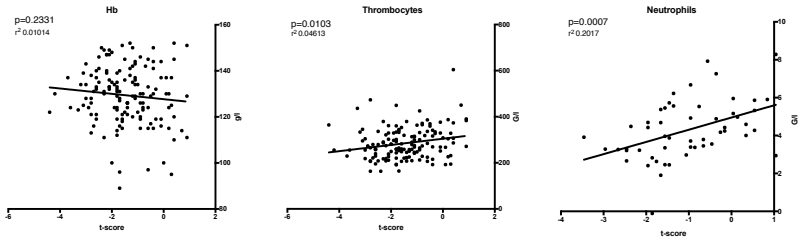

Figure 2 Blood cell counts according to T-score values. As BMD (bone marrow density) decreases neutrophils and thrombocytes also decrease (linear regression, $p<0.05$), Hb ns

Blood counts after 1st cycle of chemotherapy

The evolution of the blood counts during the first cycle of chemotherapy was analyzed.
The average day of leucocyte nadir was 9.9 ± 4.2 days.
An increase of one point in TBS correlates with a decrease of 57% of the mean day count on the time for leucocyte nadir with a p value of 0.004 (Table 3), such that average day of leucocyte nadir was 10 days for the degraded microarchitecture group and 9.82 days for the normal microarchitecture group.

A

TBS, multivariate (Poisson regression) n=139	**Day of leucocyte nadir**			
	risk ratio	**2.5 %**	**97.5 %**	**p value**
TBS	0.43	0.24	0.76	0.0039
Age	0.99	0.99	1.00	0.05
G-CSF	0.84	0.75	0.95	0.01
Toxicity of the chemotherapy	1.04	1.02	1.06	0.000046

B

T-score, multivariate (Poisson regression) n=143	**Day of leucocyte nadir**			
	risk ratio	**2.5 %**	**97.5 %**	**p value**
T-score	1.00	0.95	1.05	0.91
Age	1.00	0.99	1.00	0.45
G-CSF	0.84	0.74	0.95	0.0043
Toxicity of the chemotherapy	1.03	1.02	1.05	0.0002

Table 3, A Poisson regression multivariate, TBS, **B** Poisson regression multivariate, T-score

Rate of infection after 1st cycle of chemotherapy

From our analysis, rate of infection was also significantly correlated with the T-score with an odd ratio of 2.08 and a p value of 0.000989. TBS values did not significantly correlate with the rate of infection (Table 4).

A

T-score, multivariate (logistical regression) n=143	**Infections**			
	odds ratio	**2.5 %**	**97.5 %**	**p value**
T-score	2.08	1.37	3.28	0.00099
Age	1.01	0.98	1.05	0.43
G-CSF	3.94	1.74	9.25	0.0012
Toxicity of the chemotherapy	0.83	0.71	0.96	0.02

B

TBS, multivariate (logistical regression) n=139	**Infections**			
	odds ratio	**2.5 %**	**97.5 %**	**p value**
TBS	10.08	0.18	654.67	0.27
Age	1.00	0.96	1.04	0.98
G-CSF	4.00	1.79	9.25	0.00089
Toxicity of the chemotherapy	0.86	0.73	0.98	0.04

Table 4 A logistical regression multivariate, T-score, **B** logisitical regression multivariate, TBS

DISCUSSION

The results of our retrospective study indicate that, before chemotherapy, a higher T-score is associated with a higher neutrophil and thrombocyte count. After the first cycle of chemotherapy, our results suggest that a higher TBS score significantly correlates with a faster drop of the leucocyte count, and that a higher T-score correlates with a higher risk of infection.

There are several published studies describing a link between osteoporosis and overall lower blood counts in postmenopausal women or the elderly [22–24]. Of note, a recent study has found a paradoxical increase in the neutrophil counts of osteoporotic elderly men while monocyte and lymphocyte counts were decreased.[25] We chose to analyze our data to see if the same pattern was found. It is important to note that our patients were younger (52 years in mean), leaner (no BMI >35), were not free of disease, as the breast cancer diagnosis was recently given, and they had recently recovered from lumpectomy/mastectomy. We thus consider that prior to chemotherapy our cohort was subject to the minor hematopoietic stress of surgery, which also added heterogeneity to hemoglobin values given differences in blood loss during the procedure. Congruent with the literature, our analysis found a positive association between T-score and both thrombocyte and neutrophil counts. Given their very short half life in circulation, neutrophils best reflect the ongoing function of the marrow upon stress hematopoiesis.

All previously published data refers to elderly or postmenopausal cohorts. Subgroup analysis within our cohort did not find a significant association within the postmenopausal subgroup,

probably due to the reduced number of postmenopausal patients (n=60). When comparing blood counts with TBS score instead of T-score, no significant association was observed. This difference may be explained by the fact that BMD evaluates the total bone mineral content, and TBS the organization of trabeculae. Thus our data demonstrates an association between osteoporosis and lower blood counts in a younger cohort than previously published, showing for the first time decreased thrombocyte and neutrophil counts in osteoporotic women subject to a minor hematopoietic stress. Specifically, we observed an average minimum difference of 20 G/l on the thrombocyte count and 1.0 G/l on the neutrophil count between patients with normal bone and osteoporotic bone. These differences may be clinically relevant and should thus prompt further studies on the pertinence of early osteoporotic treatment in oncological patients.

Regarding blood counts after the first cycle of chemotherapy, our analysis suggests that a healthier bone is associated with a more rapid drop in the total leucocyte count, or in other words, that osteoporosis slows down the leucocyte drop immediately after chemotherapy. This result is unexpected. The osteoblasts and the perivascular cells have been shown to have a supportive effect on hematopoiesis. Adipocytes have been shown to decrease the support of hematopoietic progenitors in the bone marrow[11]. In the osteoporotic bone, both the osteoblast count and microvasculature are reduced and the adipocyte load increased. Therefore, we had expected to see a negative effect of osteoporosis on blood counts post chemotherapy, as it has been described in homeostatic conditions prior to chemotherapy. Our results could have different interpretations.
The osteoporotic microenvironment may indeed be actively protective to the hematopoietic progenitors immediately after chemotherapy. Alternative explanations include that the adipocytes within the bone marrow might mediate a non-specific protective effect by facilitating delayed drug release. In fact, obesity is associated with lower toxicity during chemotherapy for gynecological cancers in part due to the delayed drug release for drugs with high distribution volumes [26, 27]. Within the bone marrow, increased adipocytic mass would thus possibly translate into a lower bolus dose but a longer exposition time upon chemotherapy, especially for chemotherapy agents with a high volume of distribution. Additionally, we cannot exclude a sampling bias. Since the depth of the leucocyte drop was not significantly different between osteoporotic and non-osteoporotic patients, even though non-osteoporotic patients had significantly higher blood counts before chemotherapy, the earlier nadir of non-osteoporotic patients may just reflect a faster rate of hematological recovery in patients with healthier bone. Our results should prompt further studies in a cohort with more abundant data points for the blood count recovery.

Finally, we observed a positive association between T-score and the rate of infection. This result is also unexpected, but it is congruent with the slower drop of leucocytes in osteoporotic women, which could indicate a protective role of the osteoporotic microenvironment for infection. We could not however measure the duration of neutropenia and therefore could not test if a slower fall is associated with a shorter period of neutropenia.
Several sources of bias could also explain the observed outcome for infection. The quality of the data was lower for the qualitative analysis of infection than for the quantitative analysis of blood counts. First, the G-CSF treatment was only coded yes/no, as information was not always available to know whether it was given as primary or secondary prophylaxis of severe neutropenia. Second, the infections were recorded but no distinction was made on the

severity. To further support our hypothesis of confounding bias, it is interesting to note that age is not a significant explicative variable anymore in the multivariate analysis for rate of infection. It is thus likely that other variables influence the infection rate in our cohort.

Other limitations of our cohort should be addressed. From the included patients of the "Centre du Sein", a significant number (n=80) did not have BMD and were therefore excluded. Also, a low number of postmenopausal women (n=60) were part of the cohort, which limited subgroup analysis. Unfortunately, we did not have differential blood count for all patients, which most likely explains why some results including neutrophil counts post-chemotherapy did not reach statistically significance.
Nevertheless, our overall observations underline that, as predicted by recent research on the bone marrow hematopoietic stem cell niche, differences in the osteoporotic bone microenvironment translate into altered dynamics upon hematopoietic stress. As other authors, we observed a positive correlation between T-score and blood counts in homeostasis or minor hematopoietic stress. After the first cycle of chemotherapy, a strong stressor for the bone marrow, we observed a slower fall of the leucocyte count in osteoporotic patients. Further studies are needed to clarify how bone physiopathology affects human hematopoiesis in different contexts both during homeostasis and stress hematopoiesis.

CONCLUSION

The results of our retrospective monocentric study indicate that, before chemotherapy, a higher T-score is associated with a higher count in neutrophils and thrombocytes. This correlation was specific for T-score; no trend was observed when TBS was considered. No significant association was observed for the hemoglobin in our post surgery cohort.
After the first cycle of chemotherapy, our results suggest that a higher TBS significantly correlates with a faster drop on the leucocyte count, and that a higher T-score correlates with a higher risk of infection. The rate of hematological recovery was not measurable due to insufficient data points. Blood counts following chemotherapy suggest that the healthier the bone, the earlier the lowest leucocyte count value.
Further studies are needed to better understand the kinetics of blood cell count recovery after chemotherapy as related to bone health.

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Author Contributions F.S, A.W. and O.N. conceived the original idea. F.S. and A-L.N. collected the data. F.S and J.P performed the statistical analysis. F.S., A.W., O.L., and O.N. analyzed results and interpreted the data. F.S, O.L. and O.N. wrote the manuscript. All authors edited and reviewed the final manuscript.