Comparative hematological profiles for dose-dense vs. regular anthracycline-based neoadjuvant chemotherapy in non-metastatic breast cancer

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Abstract. The aim of the present study was to examine both the feasibility and toxicity of neoadjuvant dose-dense chemotherapy in women with non-metastatic breast cancer. A search within the OncoHelp Association breast cancer database has been performed in order to identify all non-metastatic breast cancer patients who underwent an initial consultation with a medical oncologist between March 2016 and April 2020. The inclusion criteria used were: i) Age, ii) follow-up care obtained at OncoHelp Association, iii) the intent to treat with a neoadjuvant dose-dense anthracycline every two weeks for four cycles (C1-C4) followed by paclitaxel every two weeks for four cycles, with white blood cell growth factor support, and iv) regular anthracycline-based chemotherapy every three weeks for four cycles, followed by paclitaxel every three weeks for four cycles, v) weight, vi) height, vii) Eastern Cooperative Oncology Group (ECOG) performance status, viii) hemoglobin (Hb) level, ix) Platelet count and x) neutrophil count.

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Introduction

Breast cancer is the most frequently diagnosed malignancy among women in Romania and worldwide. According to GLOBOCAN data, in 2018, ~2.1 million women were diagnosed with breast cancer, which accounts for ~11.6% of all malignancies, meaning that 1 out of 4 women with a neoplasm currently has breast cancer and the incidence continues to be on the increase (1,2). The American Cancer Society reported that the breast cancer incidence rate increased by 0.3% per year between 2012 and 2016 (3). In addition, there is an estimation that in 2020, breast cancer will affect 276,480 women in USA alone (4). In Romania, there were 9,629 newly diagnosed breast cancer cases in 2018, i.e., 11.5% of all cancer cases among women. Furthermore, over the last three decades, the breast cancer incidence rate has more than doubled and the highest growth has been observed in women aged 50-69 years (2).

Regarding malignancy-related deaths worldwide, breast cancer is the second most common cause, just after lung cancer (626,679 cases, which accounts for 6.6%) (1). The same percentage was observed in Romania, in 2018 (2).

The proportion of women diagnosed with breast neoplasm in the premenopausal age is relatively small. In 2019, all ductal carcinoma *in situ* (DCIS) cases among women under 40 years of age accounted for only 2% of all cases, and invasive breast cancers account for 4% of all age groups (3). Nevertheless, American data have shown that breast cancer is, not only the most commonly diagnosed cancer among women aged 20-49 years, but it is also the leading cause of death in the same group (5). This situation is similar to that of Romania (2).

Although age is a significant risk factor for breast cancer, several studies have revealed an increase in the incidence of this type of cancer among premenopausal women (6-11).

Concerning the figures mentioned above, the increasing number of younger women who have breast cancer is becoming a public concern, including in our country. That is because younger women are not in the scope of breast cancer screening programs in Romania, which are primarily focused on women

aged 50-69 years. Breast cancer among young women is also a severe psychosocial problem. Cancer diagnosis and oncological treatment may impact quality of life, as it causes premature menopause and impaired fertility (12,13).

The rationale for dose-dense chemotherapy regimens is based on the hypothesis that maximal chemotherapy effectiveness can be achieved by scheduling the interval of chemotherapy to correspond to the period of most rapid tumor growth, as predicted by preclinical models. The granulocyte-colony stimulating factor (G-CSF) support has permitted the safe delivery of chemotherapy at shorter ('dose-dense') inter-treatment intervals. Randomized trials have been conducted to test the feasibility and effectiveness of anthracycline and/or taxane-based dose-dense strategies, being associated with a modest impact on disease recurrence and overall survival (OS) of patients with early-stage breast cancer (14).

The dose-dense neoadjuvant doxorubicin-cyclophosphamide (AC), followed by paclitaxel (T) regimen, significantly improves disease-free survival (DFS) and OS, but can also lead to hematological toxicity, resulting in a higher number of red blood cell (RBC) transfusions (CALGB C9741, AGO-ETC).

G-CSF support has permitted the safe delivery of dose-dense chemotherapy regimens, which, as predicted by preclinical models, have further improved survival. Recently, insights into tumor biology have led to the development of targeted therapies, such as trastuzumab for HER2-positive disease, and it has now been successfully incorporated into dose-dense therapy (15). Newer targeted agents may be similarly incorporated in order to improve patient outcomes further.

The aim of the study was to evaluate the variation of the magnitude of the limiting dose parameters in dose-dense vs. regular chemotherapy, in order to choose the optimal chemotherapy frequency. In addition, it aims to outline the framework for the dose-dense chemotherapy concept within neoadjuvant breast cancer treatment and discusses its implications for clinical practice.

Materials and methods

General. Patients with non-metastatic breast cancer received doxorubicin (60 mg/m^2) + cyclophosphamide (600 mg/m^2) (AC), either four cycles every two weeks, followed by the same regimen of paclitaxel (175 mg/m^2) (T) (arm A) or four cycles every three weeks, followed by the same regimen of paclitaxel (175 mg/m^2) (arm B). All patients in arm A received prophylactic G-CSF support.

Criteria. A search within the OncoHelp Association breast cancer database was performed in order to identify all patients who underwent an initial consultation with non-metastatic breast cancer at a medical oncologist between March 2016 and April 2020. A retrospective chart review was performed and the following including criteria were analyzed: i) Sex, ii) follow-up care obtained at OncoHelp Association, iii) intent to treat with neoadjuvant dose-dense AC-T every two weeks for four cycles followed by paclitaxel every two weeks for four cycles, with white blood cell growth factor support, and iv) regular anthracycline-based AC-T every three weeks for four cycles followed by paclitaxel every three weeks for four cycles, iv) weight, v) height, vi) Eastern Cooperative Oncology Group (ECOG) performance status, vii) hemoglobin (Hb) level, viii) platelet count, ix) neutrophil count. In order to collect the data, the patient observation sheets were analyzed, and data were subsequently entered in electronic format using the Microsoft Excel 2016 program.

Regarding age, this study included two age groups, under 60 and over 60 years. In the latter group, 11 patients out of 60 received dose-dense chemotherapy, with the maximum age of 68 years, while 65 patients out of 133 received standard chemotherapy, with the maximum age of 78 years.

Statistical analysis. Non-parametric test (Mann-Whitney) was used for variables with non-normal distribution. $P<0.05$ was used as the threshold for statistical significance.

Results

Parameters. The evolution of clinical and biological parameters of 168 patients was followed in this retrospective study, 60 in arm A and 108 in arm B (Table I). Out of 739 chemotherapy settings, 254 were dose-dense regimens and 485 were regular schedules of neoadjuvant regimens.

Chemotherapy settings. One of the most exciting parameter dynamics was the evolution of average Hb values for each administration cycle, both in dose-dense or in regular chemotherapy settings. Relative Hb decrease was -15% after three cycles of chemotherapy. The Hb value starts from the same average, but the decrease in Hb in the case of dose-dense chemotherapy was faster and more profound (Fig. 1). Regarding dose-dense chemotherapy, individual variations of neutrophils and Hb cycle (C) 1 to C4, are presented in Fig. 2.

Dose-dense vs. standard chemotherapy. For individual variations of Hb from C1 to C4, the differences between dose-dense and standard chemotherapy were statistically significant. The z-score was 2.55645 and the P-value was 0.01046. In addition, for individual variations of Hb, the difference between dose-dense and standard chemotherapy in the over 60 years of age group was statistically significant (z-score=2.41663; P=0.01552). Similarly, the difference was statistically significant in the group under 60 years of age, also (z-score=2.43779; P=0.01468). The group over 60 years of age presented a variation of Hb at average -2.41 for dose-dense compared to -1.70 for standard chemotherapy, while the group under 60 years presented a variation of Hb at average -1.71 for dose-dense compared to -1.17 for standard chemotherapy.

Mean corpuscular volume. The mean corpuscular volume (MCV) started at higher values for dense doses and takes a steeper upward slope after an initial decrease lasting four weeks. In regular latent chemotherapy, the initiation of growth was shorter, but the growth was more sustained (Fig. 3). Unlike the MCV values, the number of erythrocytes shows a continuous decrease, with a steeper slope for dose-dense chemotherapy (Fig. 4).

Platelet count. Dose-dense chemotherapy leads to a 15% decrease in platelet count (possibly in the context

Table I. Average parameters depending on chemotherapy regimens.

Chemotherapy regimen	Average age	Average weight	Average height	Average ECOG	Average Hb	Average Plt	Average ANC	Cases
Dose-dense	48.1	69.1	160.9	0.1	13.3	296.5	4.8	60
Normal	58.4	74.9	150.7	0.3	13.3	275.4	4.5	108

ECOG PS, Eastern Cooperative Oncology Group performance score; Hb, hemoglobin; Plt, platelet; ANC, absolute neutrophil count.

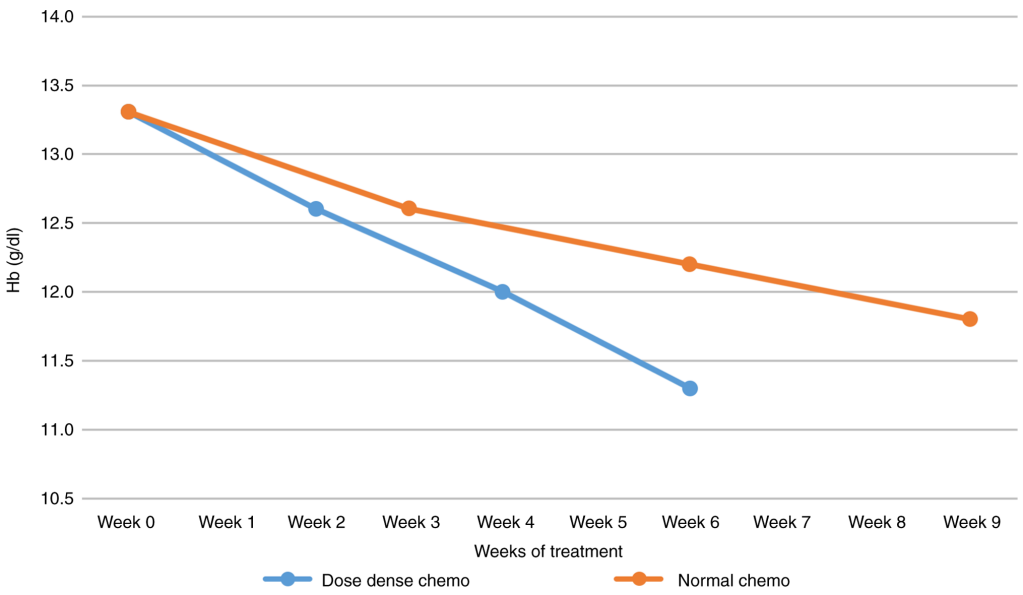

Figure 1. Average Hb evolution in dose-dense vs. normal AC chemo. Hb, hemoglobin.

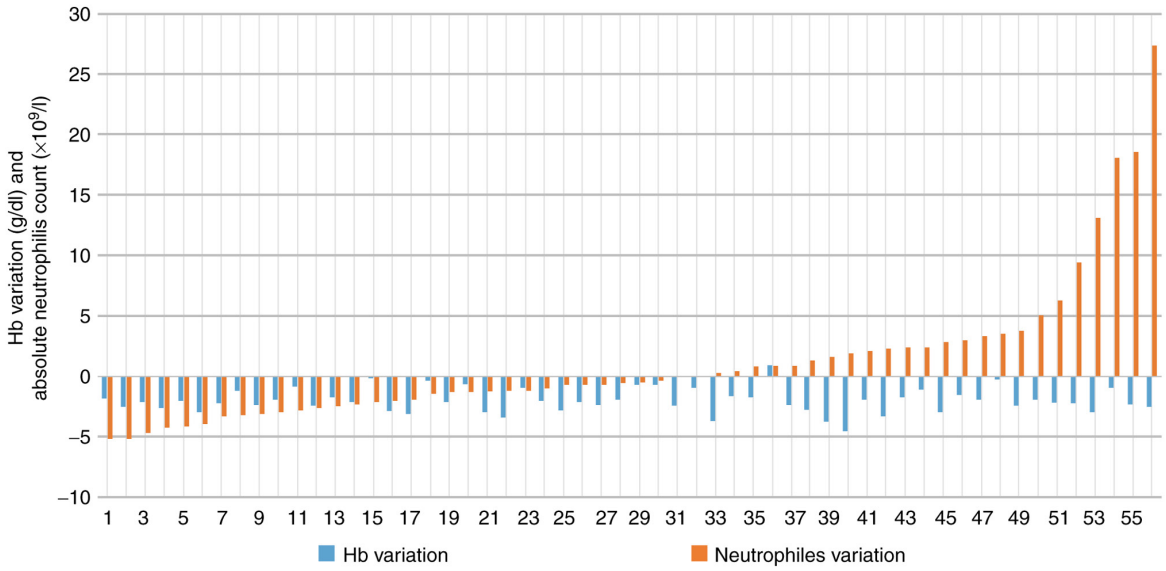

Figure 2. Dose-dense AC chemo, cycle 4-cycle 1, Hb (g/dl), neutrophils (1x10^9/l, individual variation (57 cases). Hb, hemoglobin.

of the use of granulocyte growth factors), while regular chemotherapy shows an exhaustible tendency to thrombocytosis (Fig. 5). For individual platelet variations from C1 to C4, the differences between dense and regular doses were statistically significant. The z-score was 7.48347 and the P-value <0.00001. At dense doses, the number of platelets slightly decreased, as long as the number of neutrophils usually increased from C1 to C4.

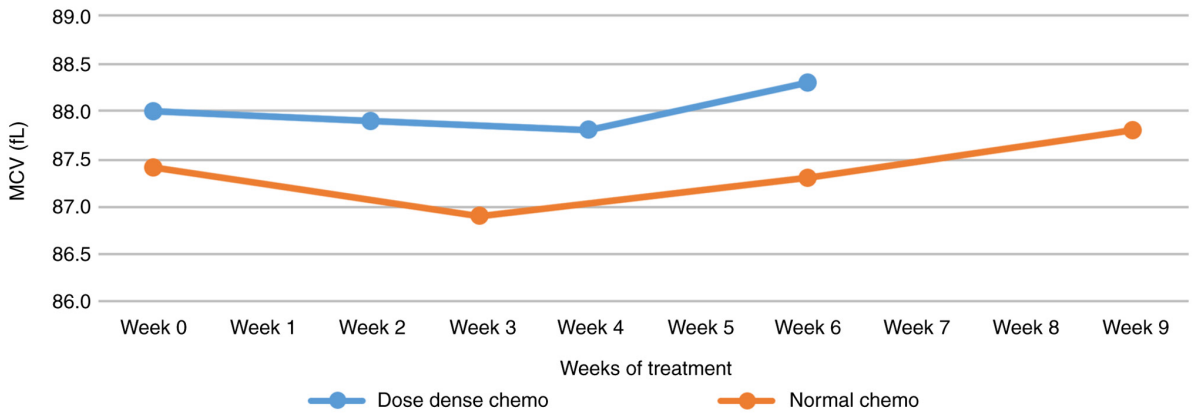

Figure 3. Average MCV evolution in dose-dense vs. normal AC chemo. MCV, mean corpuscular volume.

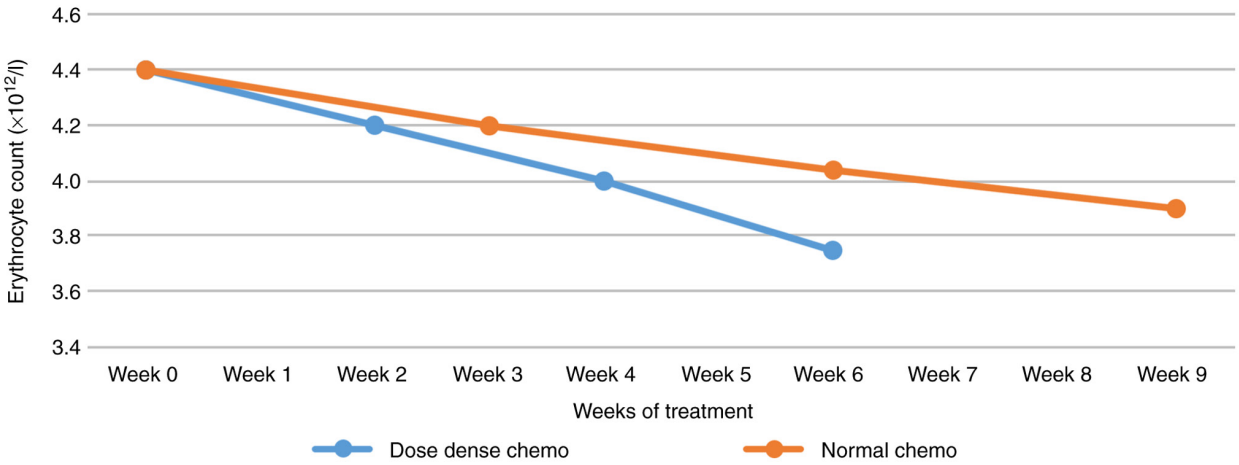

Figure 4. Average erythrocyte count evolution in dose-dense vs. normal AC chemo.

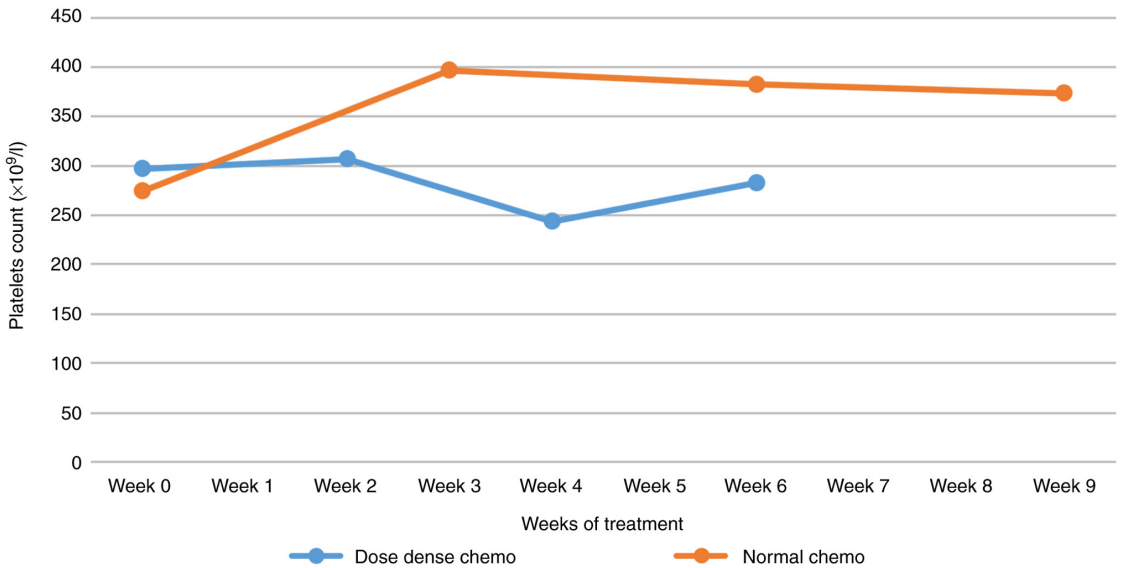

Figure 5. Average platelets count evolution in dose-dense vs. normal AC chemo.

Neutrophil count. Regarding the neutrophil count in dose-dense settings, there was a tendency towards neutrophilia, probably in the context of constant use of G-CSF. In regular chemotherapy, a plateau of absolute neutrophil count (ANC) was obtained, possibly in the context of the progressive use of G-CSF (Fig. 6).

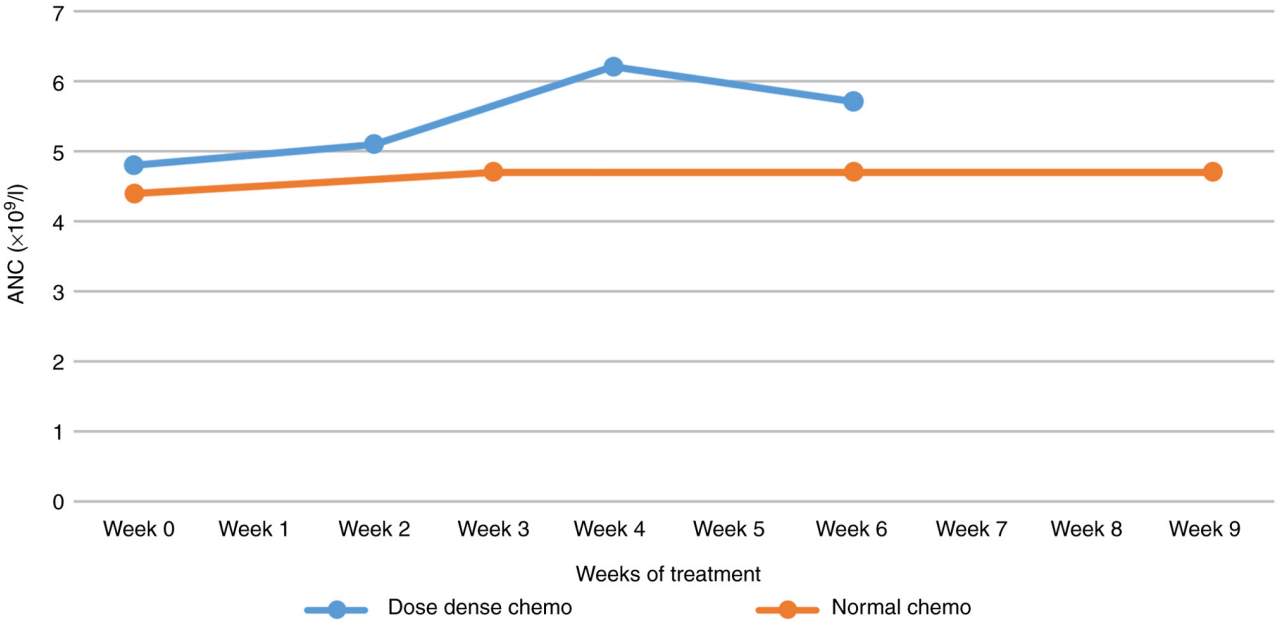

Figure 6. Average ANC variation in dose-dense vs. normal AC chemo.

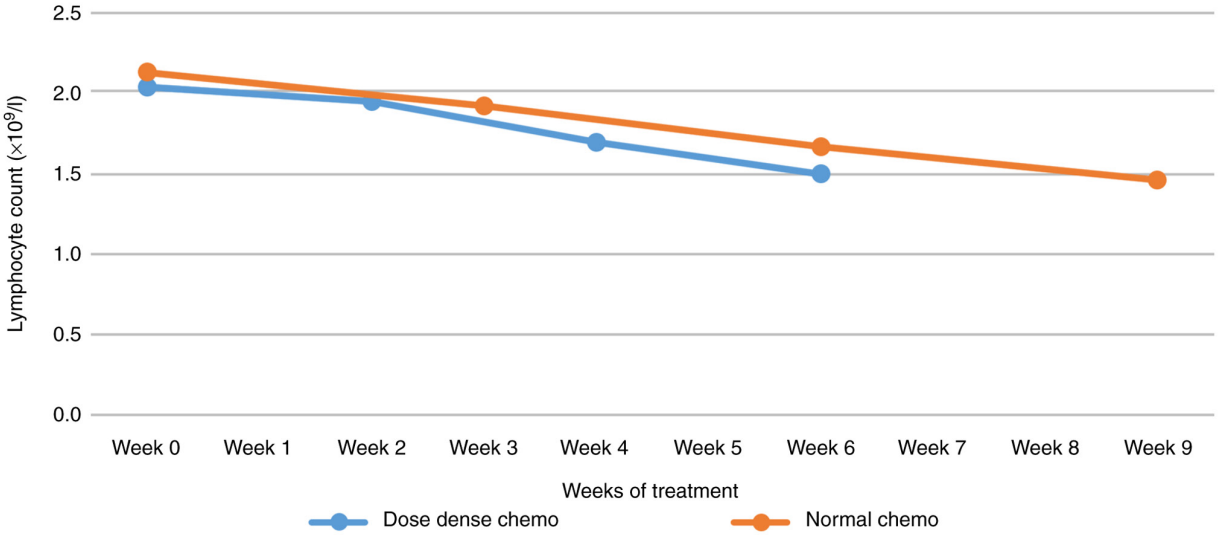

Figure 7. Average lymphocyte count variation in dose-dense vs. normal AC chemo.

For individual variations of neutrophils from C1 to C4, the difference between dense and regular doses was not statistically significant (Fig. 2). The z-score was 0.11739 and the P-value was 0.90448. In addition, for individual variations of neutrophils, the difference between dose-dense chemotherapy vs. routine chemotherapy in the group over 60 years of age was not statistically significant (z-score=1.71726; P=0.08544), the same being considered in the group under 60 years of age (z-score=1.40685; P=0.15854).

The over 60 years of age group presented a variation of neutrophils at average -1.20 for dose-dense compared to -0.20 for standard chemotherapy, while the under 60 years of age group presented a variation of neutrophils at average +1.65 for dose-dense compared to -0.55 for regular chemotherapy.

Lymphocyte count. Regarding the average lymphocyte count variation between dose-dense and regular regimens, the decrease in dose-dense was slightly steeper without necessarily being deeper (Fig. 7).

Average weight. Average weight variation in dose-dense vs. regular chemotherapy: patients with a dose-dense started from lower average weight and lost an average of 1.8 kg. Note the decreased cap after C2. For standard chemotherapy, the weight variation was insignificant (Fig. 8).

ECOG performance. Regarding the average ECOG performance status variation in dose-dense vs. regular AC chemotherapy, it should be noted that the average ECOG performance status decreased during dose-dense regimens (subjective assessment, also related to the observer's

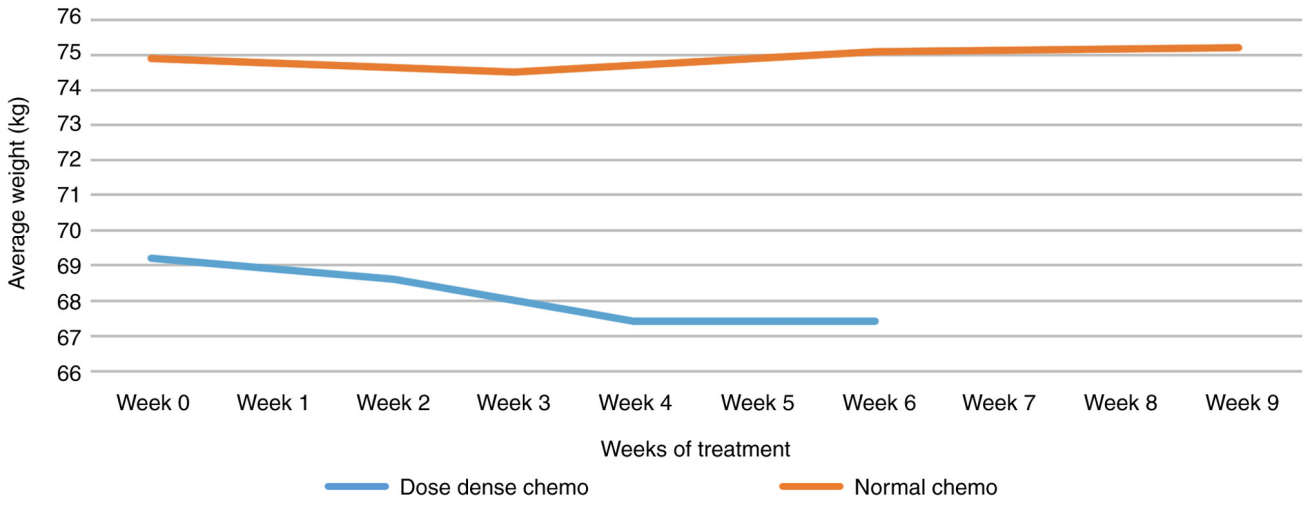

Figure 8. Average weight variation in dose-dense vs. normal AC chemo.

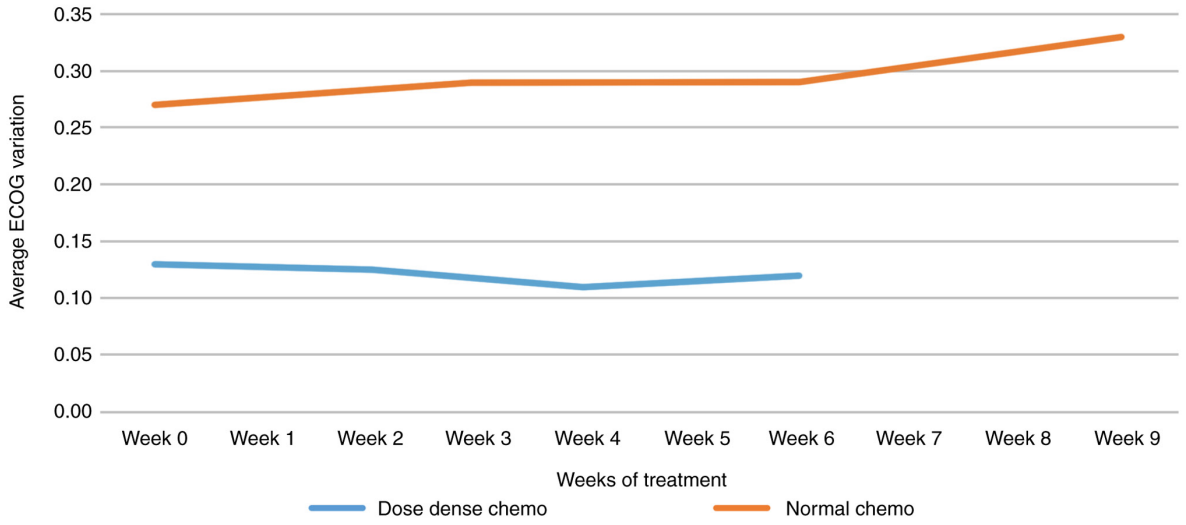

Figure 9. Average ECOG variation in dose-dense vs. normal AC chemo. ECOG, Eastern Cooperative Oncology Group.

expectations). In regular chemotherapy, there was a degradation of ECOG performance status (Fig. 9).

Discussion

The present study is retrospective and is based on a group of 168 patients diagnosed with non-metastatic breast cancer. The aim was to examine the feasibility and toxicity of dose-dense neoadjuvant chemotherapy.

The hematological profiles of the patients were analyzed. Both patients receiving dense-dose chemotherapy and those receiving standard chemotherapy had similar hematologic profiles when initiating chemotherapy. Following the analysis performed on Hb values during the 9 weeks of treatment, we found that although it started from an average Hb value equal for both types of chemotherapy, there was a faster and more pronounced decrease in the case of dense-dose chemotherapy. The average erythrocyte volume also changed, signaling a decrease until the 4th week after which the slopes of both types of chemotherapy become ascending, in the case of dose-dense chemotherapy, the slope is steep, and so the increase is more sustained. Unlike the MCV values, the number of erythrocytes shows a continuous decrease, with a steeper slope for dose-dense chemotherapy. RDW-SD is a size that describes the width of the red blood cell volume distribution curve (measured at 20% of its height). It indicates how much these cells differ in size and volume, quantifying the difference between a small blood cell and a large one. The average value ranges between 46 and 47. Values >47 observed during standard chemotherapy reflect anisocytosis caused by the production of macrocytes in the hematogenous bone marrow as an effect of chemotherapy. During the use of dose-dense regimens, there is a tendency towards neutrophilia, probably in the context of constant use of G-CSF. In standard chemotherapy, a plateau of the ANC is obtained, possibly in the context of the progressive use of G-CSF. Dose-dense chemotherapy leads to a 15% decrease in platelet count (possibly in the context of using granulocyte growth factors), while regular chemotherapy shows an exhaustible tendency to thrombocytosis. Regarding the

number of leucocytes, progressive leucopenia was observed, more accentuated in dose-dense chemotherapy. Overall, as seen in other studies, dose-dense regimen associated hematologic toxicity has been more pronounced. However, hematologic toxicity did not affect the treatment protocol, further confirming the safety of dose-dense administration, with prophylactic measures (14-17).

The weight loss aspect was also taken into account, so that the average weight of patients treated with the dose-dense regimen is lower than the average weight of regular chemotherapy. The medium-weight loss was ~1.8 kg over 9 weeks. Note the constant maintenance of weight after C3. During regular chemotherapy, weight variations were insignificant.

It should be noted that the average of ECOG performance status decreases during dose-dense (subjective assessment, also related to the observer's expectations). ECOG performance status degradation is noted in standard chemotherapy.

As a conclusion, a retrospective study of 168 patients with non-metastatic breast cancer showed a good safety profile when administering dose-dense chemotherapy regimens in neoadjuvant settings. It should be noted that the mean age of patients on dose-dense chemotherapy regimens was lower than in the group of patients on normal-dose chemotherapy regimens. ECOG performance status was similar in the two groups of patients at the initiation of chemotherapy. The evolution of the monitored parameters recommends that the dose-dense and regular AC followed by T can be given with manageable toxicity. It was shown that the group under 60 years of age, despite the hematological toxicity, is suitable for dose-dense chemotherapy and the toxicity is manageable. Further studies are needed in order to define the optimal regimen and the patient population that will receive the most significant benefit from the dose-dense strategy.

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Availability of data and materials

The data generated or analyzed during this study are included in this published article or are available from the corresponding author on reasonable request.

Authors' contributions

DP, CO and SS organized the study, analyzed and interpreted the study data and wrote the manuscript. AN, MM, HTS, AT and SS analyzed the data and helped draft the output and critically reviewed the manuscript; SN interpreted the data and critically reviewed the manuscript for intellectual content. All the authors have read and approved the final version of the manuscript for publication.

Ethics approval and consent to participate

All patients gave their informed consent for the procedure. The study protocol was conducted according to the principles of the Declaration of Helsinki after the approval of our institution's Ethical Committee. All patients provided written informed consent for the study participation and data collection.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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