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Factors Influencing the Occurrence of Anemia During Adjuvant and Neoadjuvant Chemotherapy in the Treatment of Breast Cancer

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ABSTRACT

Background: To determine the frequency and severity of anemia in non-metastatic breast cancer patients receiving neoadjuvant or adjuvant chemotherapy.
Methods: Cross-sectional study (2018–2023). Hemoglobin (Hb) was analyzed before, during, and after chemotherapy (~6 months). Regimens: dose-dense AC-T (q2 weeks) or standard AC-T (q3 weeks).
Main findings: Hb differed across time (Bonferroni all $p < 0.001$) and was lowest during therapy. During therapy, dose-dense AC-T had lower mean Hb than standard AC-T (118.2 ± 10.2 vs 123.1 ± 9.8 g/L; Δ = 4.9 g/L; ≈4.0%; $t = 2.620$; $p = 0.010$). No significant Hb differences by treatment setting (adjuvant vs neoadjuvant −2.1%; $p = 0.312$), trastuzumab (−2.6%; $p = 0.143$), pertuzumab (−2.5%; $p = 0.375$), surgery type (breast-conserving +1.7% vs mastectomy; $p = 0.432$), or comorbidities (−2.6%; $p = 0.105$). Menopausal status ($F(2,112)=0.635$; $p = 0.532$), histology ($F(3,111)=1.268$; $p = 0.289$), and stage ($F(2,112)=0.193$; $p = 0.825$) were not associated with Hb. Anemia prevalence was 46.1%. Cohort profile: 65.2% postmenopausal; 53.9% stage 2; 81.7% adjuvant therapy; 84.3% radical mastectomy; 25.2% trastuzumab; 8.7% pertuzumab. Age did not differ between anemic and non-anemic groups; anemic patients had significantly lower BMI.
Principal conclusion: Hb declines most during therapy; a dose-dense schedule is associated with an additional ≈4% reduction versus standard scheduling, while other evaluated clinical factors did not materially affect Hb. Lower BMI among anemic patients suggests nutritional status as a potential target for supportive care.

Key words: anemia; breast cancer; chemotherapy; adjuvant; neoadjuvant

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INTRODUCTION

Chemotherapy can cause various side effects such as anemia and fatigue, with severity depending on treatment type, dose, disease stage, age, and comorbidities (1). Anemia during treatment often increases fatigue and lowers quality of life (2). In breast cancer, acute toxicities like febrile neutropenia, mucositis, diarrhea, and neuropathy get clinical attention, but anemia and fatigue, though less visible, significantly affect patients (3, 4). Anemia is frequently underestimated, especially in adjuvant and neoadjuvant therapy, yet it influences treatment outcomes and quality of life (5, 6).

Research on anemia's frequency and severity during common adjuvant chemotherapy protocols for early breast cancer is scarce. Sharma et al. (2022) reported a high incidence of anemia with dose-dense chemotherapy, leading to treatment delays and increased costs. Key risk factors for transfusion included low tumor burden, grade 3–4 thrombocytopenia, and grade ≥2 anemia after two cycles (7). Pourali et al. (2017) also found more severe anemia in advanced stages. This study aims to evaluate anemia's frequency and severity during adjuvant and neoadjuvant chemotherapy, considering regimen type, comorbidities, stage, and surgery. Early recognition of chemotherapy-induced anemia, even mild cases, especially in older patients, is vital for timely intervention (8).

Breasts are secondary sexual organs composed of mammary glands and connective tissue. In males, gland development ceases at puberty, while in females it continues hormonally, completing in pregnancy. Each breast has 12–15 lobes draining through ducts to the nipple; breast shape and pigmented nipple/areola help define quadrants (9). Breast cancer is the most common cancer in women worldwide. In developing countries, most deaths occur before age 70. WHO aims to reduce mortality by 2.5% annually through 2040. In Bosnia and Herzegovina, breast cancer accounted for 15–18.3% of female cancer deaths in 2020–2021 (10). Major risk factors include age, female sex, nulliparity, late childbirth, obesity, family history, radiation, and hormone therapy. Risk rises with age, reaching 200–300 per 100,000 by age 80. Family history increases risk eightfold; BRCA1/2 mutations are important, especially in younger women (9, 11). Most breast cancers arise from ductulo-lobular epithelial cells, mostly adenocarcinomas. Non-invasive types remain in ducts/lobules; invasive types breach the basement membrane. About 80% are ductal carcinoma NST, 10% lobular, and 10% special subtypes (12).

Breast cancer spreads locally to chest wall or via lymphatics to axillary, internal mammary, infraclavicular, and supraclavicular nodes. Distant node involvement indicates metastasis. Hematogenous spread affects lungs, bones, liver, brain, and skin. Invasive lobular carcinoma can metastasize to GI tract and ovaries (13). Presentation typically involves a firm, irregular, painless lump; less than 30% report pain. Skin changes, nipple retraction, discharge, or enlarged nodes may also appear. Metastases can be first symptoms depending on site (11, 13).

Diagnosis includes physical exam, imaging (mammography, ultrasound, MRI), biopsy, and blood tests. Further tests (CT, bone scan) are done if metastasis is suspected (13). Breast cancers are classified by genetics/immunohistochemistry into luminal A, luminal B, HER2-positive, and triple-negative groups; tumors are staged as in situ, microinvasive, or invasive. About 80% of invasive tumors are NST, with lobular carcinoma comprising 5–15% (14–16).

Treatment depends on stage, tumor biology, and patient health, guided by AJCC TNM staging. Options include surgery, radiotherapy, chemotherapy, hormone therapy, and immunotherapy, with decisions made by multidisciplinary teams (13). Non-invasive cancers (DCIS, LCIS, Paget's) have excellent

prognosis, treated mostly with local excision and adjuvant therapy. Early invasive cancers are treated with surgery plus adjuvant systemic and radiation therapies; neoadjuvant therapy is used in larger tumors or positive nodes (13,17). Locally advanced and inflammatory cancers often require neoadjuvant chemotherapy with anthracyclines and taxanes. HER2-positive tumors may receive dual anti-HER2 therapy. Adjuvant capecitabine is given after incomplete response in triple-negative and high-risk luminal B tumors (19).

Metastatic breast cancer treatment focuses on control, symptom relief, and quality of life, using hormone therapy for ER-positive tumors and bisphosphonates for bone metastases. Survival is limited (~23.4% five-year) (17). Prognosis worsens with lymph node involvement, larger tumors, and younger age. HER2 overexpression predicts poor prognosis but response to targeted therapy. Tumor proliferation and lymphovascular invasion also affect outcomes (13).

Chemotherapy uses cytotoxic drugs, given as adjuvant or neoadjuvant treatment (18). Adjuvant chemo targets micrometastases post-surgery (4–8 cycles), while neoadjuvant chemo shrinks tumors pre-surgery (2–4 cycles) (19–21). Regimens often combine anthracyclines and taxanes, with dose-dense scheduling and growth factor support for aggressive cases. Cardiac evaluation is important before anthracycline therapy (19–21). Treatment decisions consider tumor biology, stage, and patient factors including preferences (22–24).

Common chemotherapy side effects include nausea, vomiting, hair loss, fatigue, myelosuppression (neutropenia, anemia, thrombocytopenia), digestive issues, skin changes, neuropathy, and emotional symptoms (18,25). Myelosuppression lowers blood cell production, causing neutropenia (<0.5 × 10^9/L), increasing infection risk. Febrile neutropenia (>38.5°C fever with low neutrophils) is life-threatening and requires MASCC score-based management: hospitalization and antibiotics for high-risk, outpatient oral antibiotics for low-risk (19,26). Anemia results from reduced red blood cells, worsening fatigue; cisplatin and carboplatin have higher anemia risk. Treatment includes supplements or transfusions (27). Thrombocytopenia raises bleeding risk, sometimes necessitating hospitalization (28). Other toxicities include gastrointestinal symptoms, hair and skin changes, mucositis, and neuropathy (18).

PARTICIPANTS AND METHODS

Participants

The cross-sectional study included patients diagnosed with non-metastatic breast cancer who underwent neoadjuvant or adjuvant chemotherapy in the period from January 1, 2018 to December 31, 2023.

Methods

The study included female patients with non-metastatic breast cancer who received neoadjuvant or adjuvant chemotherapy at the Oncology Clinic of the University Clinical Hospital Mostar between January 1, 2018, and December 31, 2023. Patients varied by age, disease stage, chemotherapy regimen, comorbidities, BMI, type of surgery, and time from surgery to chemotherapy initiation.

Inclusion criteria: confirmed diagnosis of non-metastatic breast cancer, received neoadjuvant or adjuvant chemotherapy within the defined period, complete medical records, prescribed full course of chemotherapy.

Exclusion criteria: metastatic breast cancer, surgery or radiotherapy without chemotherapy, experimental therapies outside standard protocols, incomplete chemotherapy cycles or medical documentation.

Collected data included: age and menopausal status, chemotherapy type, dosage, and duration, tumor type and clinical stage, comorbidities and general medical history, pre-treatment BMI, type of surgery performed, time from surgery to chemotherapy, hematological

parameters (hemoglobin, hematocrit, RBC, WBC, platelets) before, during, and after treatment.

Statistical analysis

Numerical data are presented as mean ± standard deviation, and categorical data are presented as absolute and relative frequencies. The significance of differences was tested using the Student's t-test for independent samples and one-way ANOVA, while for categorical data the Chi-square test was used. Statistical analysis of the collected data was performed using IBM SPSS Statistics (version 25.0, SPSS Inc, Chicago, Illinois, USA) and Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA). Differences between groups were considered statistically significant at $p < 0.05$.

RESULTS

Table 1 shows distribution of patients included in the study according to selected parameters. A statistically significant difference was found in hemoglobin concentration before, during, and after therapy (Figure 1). Bonferroni post hoc test showed that hemoglobin levels were significantly higher before therapy compared to during ($p<0.001$) and after therapy ($p<0.001$), and significantly higher after therapy compared to during therapy ($p<0.001$).

Since the lowest hemoglobin concentration was recorded during therapy, that value was used in further analyses.

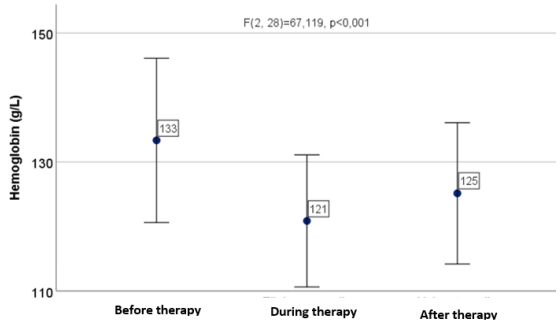

Figure 1. Hemoglobin levels in patients before, during, and after chemotherapy.

Table 2 shows the impact of selected factors on hemoglobin concentration during chemotherapy. During therapy, dose-dense AC-T had lower mean Hb than standard AC-T (118.2 ± 10.2 vs 123.1 ± 9.8 g/L; Δ = 4.9 g/L; ≈4.0%; t = 2.620; p = 0.010).

There was no statistically significant difference in age between patients with anemia and those without anemia during chemotherapy (Figure 2).

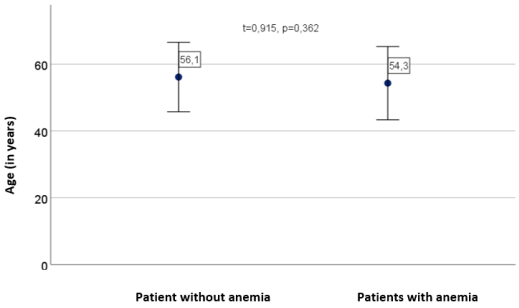

Figure 2. Comparison of age between patients with anemia and those without anemia during chemotherapy

Patients with anemia had a statistically significantly lower BMI compared to patients without anemia (Figure 3).

Table 3 shows the impact of selected factors on hemoglobin concetration during chemotherapy. Menopausal status, histology and stage were not associated with Hb.

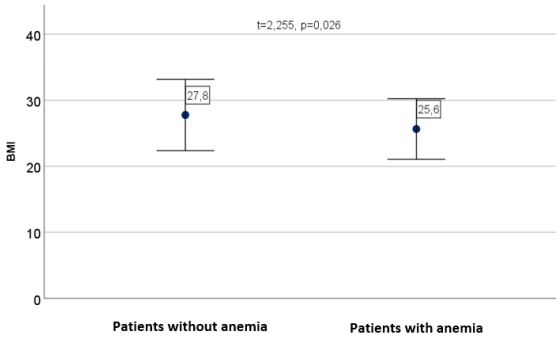

Figure 3. Comparison of Body Mass Index (BMI) between patients with anemia and those without anemia during chemotherapy. BMI – Body Mass Index

DISCUSION

After conducting the statistical analysis, the results showed a statistically significant difference in hemoglobin concentration in

Table 1. Distribution of patients included in the study according to selected parameters

Parameter	n	%	χ^2	p
Anemia			0.704	0.401
Yes	53	46.1		
No	62	53.9		
Menopausal status			58.922	<0.001
Premenopausal	31	27.0		
Perimenopausal	9	7.8		
Postmenopausal	75	65.2		
Histological type of carcinoma			63.887	<0.001
Ductal	47	40.9		
Lobular	10	8.7		
NST (No Special Type)	53	46.1		
Other	5	4.3		
Stage			36.122	<0.001
1	10	8.7		
2	62	53.9		
3	43	37.4		
Adjuvant or neoadjuvant chemotherapy			46.339	<0.001
Neoadjuvant	21	18.3		
Adjuvant	94	81.7		
Chemotherapy protocol			1.052	0.305
AC-T dose-dense (2-week intervals)	52	45.2		
AC-T (3-week intervals)	63	54.8		
Trastuzumab			28.252	<0.001
Yes	29	25.2		
No	86	74.8		
Pertuzumab			78.478	<0.001
Yes	10	8.7		
No	105	91.3		
Type of surgery			54.270	<0.001
Breast-conserving	18	15.7		
Radical mastectomy	97	84.3		
Comorbidities			4.600	0.032
Yes	46	40.0		
No	69	60.0		

patients before, during, and after chemotherapy. Specifically, hemoglobin concentration before chemotherapy was significantly higher compared to during and after chemotherapy, which aligns with the initially stated hypothesis. Regarding the decrease in hemoglobin levels during chemotherapy treatment of breast cancer patients, studies reporting similar results are quite common (1-8). Furthermore, this study found a statistically significant difference in hemoglobin concentration depending on the chemotherapy protocol to which the patients were subjected. Patients treated with the two-week AC-T DD protocol showed a statistically significantly lower hemoglobin concentration compared to those treated with the three-week AC-T protocol. We found several studies with results consistent with ours. In the study conducted by Sharma et al. (7), the occurrence of anemia was analyzed in breast cancer patients who received two-week dose-dense platinum-based chemotherapy. The results showed that all patients developed anemia during therapy. It is important to note that half of the patients were already anemic before the start of chemotherapy, which likely influenced the final outcome of the study (7). On the other hand, the study by Chaumard et al. monitored the frequency of anemia in patients treated

Table 2. The impact of selected factors on hemoglobin concentration during chemotherapy. *Hemoglobin concentration is reported in grams per liter of blood.*

Factor	n	Mean (x̄)	SD	t	p
Adjuvant vs. neoadjuvant chemotherapy				1.015	0.312
Adjuvant	21	118.8	9.3		
Neoadjuvant	94	121.3	10.4		
Chemotherapy protocol				2.620	0.010
AC-T dose-dense (2-week)	52	118.2	10.2		
AC-T (3-week)	63	123.1	9.8		
Trastuzumab				1.474	0.143
Yes	29	118.5	11.4		
No	86	121.7	9.8		
Pertuzumab				0.891	0.375
Yes	10	118.1	5.7		
No	105	121.1	10.6		
Type of surgery				0.788	0.432
Breast-conserving	18	122.6	10.0		
Radical mastectomy	97	120.5	10.3		
Comorbidities				1.635	0.105
Yes	69	119.6	9.4		
No	46	122.8	11.3		

Table 3. The impact of selected factors on hemoglobin concentration during chemotherapy. *Hemoglobin concentration is reported in grams per liter of blood.*

Factor	n	Mean (x̄)	SD	F (df)	p
Menopausal status				0.635 (2, 112)	0.532
Premenopausal	31	131.3	7.9		
Perimenopausal	9	135.6	10.5		
Postmenopausal	75	134.0	14.5		
Histological type of carcinoma				1.268 (3, 111)	0.289
Ductal	47	132.5	14.5		
Lobular	10	132.9	6.5		
NST (No Special Type)	53	135.1	11.9		
Other	5	124.2	10.0		
Stage				0.193 (2, 112)	0.825
1	10	133.9	8.0		
2	62	133.9	11.3		
3	43	132.4	15.5		

with the three-week protocol, with anemia occurring in 64% of cases (29). Comparing the results of these studies, it can be concluded that the frequency of anemia in breast cancer patients depends on the type of therapy applied, which was also confirmed in our study (3, 29).

One of the aims of this research was to investigate the possible association between body mass index (BMI) and the occurrence of anemia in patients. The analysis showed that anemic patients had a statistically significantly lower BMI compared to patients without anemia (Figure 5). Our results support the findings of Chaumard et al. (29), who also observed a higher frequency of anemia in patients with a BMI ≤ 25 kg/m². The influence of this parameter can be explained by the standard calculation of chemotherapy dosage, which takes into account the body surface area (BSA), considered less precise for patients with low BMI (29).

The limitations of this study include its unicentric design, limited sample size, and the potential influence of these factors on the final results. Therefore, further research on a larger sample is needed to adequately recognize such issues and to enable appropriate responses to complications related to reduced hemoglobin concentration.

Overall, the results of this study are consistent with expectations and largely correspond to findings presented in earlier studies.

CONCLUSION

Based on the results of this study there is a statistically significant difference in hemoglobin concentration in patients before, during, and after chemotherapy. Specifically, hemoglobin concentration before chemotherapy was significantly higher compared to during and after chemotherapy.

A statistically significant difference in hemoglobin concentration was found depending on the chemotherapy protocol the patients underwent. Patients treated with the two-week AC-T DD protocol showed a statistically significantly lower hemoglobin concentration compared to those treated with the three-week AC-T protocol.

Anemic patients had a statistically significantly lower BMI compared to patients without anemia.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

M.K. and I.M. conceived and designed the study, provided critical revisions and supervised the research. A.S., M.Ko. and D.M. collected and curated the data. N.P.M. contributed to data analysis and interpretation. All authors participated in drafting and revising the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

ETHICAL BACKGROUND

Institutional Review Board Statement: The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine, University of Mostar.

Informed Consent Statement: Due to the retrospective nature of the study and the use of existing data from the hospital information system, individual informed consent was not required. The study was conducted with the approval of the Ethics Committee of the Faculty of Medicine, University of Mostar.

Data Availability Statement: The data supporting the findings of this study are not publicly available due to privacy and confidentiality considerations but may be available from the corresponding author upon reasonable request and subject to applicable ethical and institutional restrictions.

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