

Anemia Requiring Transfusion in Breast Cancer Patients on Dose-dense Chemotherapy: Prevalence, Risk Factors, Cost and Effect on Disease Outcome.

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Abstract

Purpose: Dose dense chemotherapy improves survival but also increases toxicity and treatment related cost. Here we report the prevalence of anemia, understand the risk factors of chemotherapy related anemia and determine the cost and time-delay associated with transfusion requirement in Indian non-metastatic breast cancer patients on dose dense preoperative chemotherapy.

Methods: In this study, 116 triple negative breast cancer (TNBC) patients were treated preoperatively with Docetaxel and Cyclophosphamide alternating with Epirubicin and Cisplatin every 2-weekly. Patients were evaluated for anemia pre- and post-chemotherapy. We examined trends in the cell counts, transfusion requirement, time to transfusion as well as risk factors associated with transfusion during treatment, along with delay in treatment due to anemia and the additional cost incurred.

Results: One hundred and sixteen women with high-risk non-metastatic TNBC were treated. Median age was 44.5 years. 56.1% had stage III disease. Delivery of 6/8 planned doses was achieved in 98.3% of patients, and all 8 doses in 86% patients. Anemia was detected at baseline in 54(46.5%) patients with mild(10-12g/dl) anemia in 42(36.2%) patients and moderate(8-10g/dl) in 12(10.3%) patients. Forty-four patients (37.9%) required transfusion during chemotherapy with 55(47.4%) patients having grade 1-2 anemia and 40(34.5%) patients having grade 3 anemia. The factors associated with transfusion were low grade of tumor (OR 2.48 (95% CI 1.08 - 5.68), $p = 0.025$), hemoglobin post 2 cycles of chemotherapy (OR 1.74 (95% CI 1.21- 2.51), $p = 0.003$), thrombocytopenia grade 3 or 4 (OR 4.35 (95% CI 1.062-17.827), $p = 0.034$) and drop in hemoglobin after 2 cycles (OR 1.65 (95% CI 1.09-2.48), $p = 0.017$). Nearly one fourth of the study population had a delay between two cycles of chemotherapy due to anemia. A median additional cost of Rs 7000 (IQR-Rs 7000 – Rs 14000) was incurred on transfusion.

Conclusion: Anemia is a common toxicity associated with dose dense chemotherapy during curative breast cancer treatment leading to delay in treatment and increased cost. Low grade tumor, grade 3 or 4 thrombocytopenia and Grade 2 or higher anemia after 2 cycles of chemotherapy are risk factors for blood transfusions during treatment.

Introduction

Anemia is the commonest complication encountered while treating cancer patients. It is present in 50-65% of cancer patients at the time of diagnosis [1–5] and rises to as high as 90% after completion of treatment.[6] Anemia has shown to not only affect quality of life in cancer patients but also is associated with reduced treatment effectiveness, increased mortality and increased transfusion requirement [5, 7–9].

Anemia in cancer patients is multifactorial and can be due to nutritional deficiencies, hemolysis, bleeding, anemia of chronic disease or due to the myelosuppressive chemotherapeutic agents.

Identifying factors which can predict development of anemia during the course of treatment will help in improving supportive care and individual management of patients at risk of developing severe anemia. [10] Baseline hemoglobin, body mass index (BMI), high haptoglobin, high ferritin and glomerular filtration rate (GFR) are considered important predictors for developing anemia. [6, 10–14]

In this study we looked at tumor characteristics and blood parameters (done prior to each cycle of chemotherapy) and the change in these parameters with each cycle of chemotherapy. We aimed to identify the cost of treating anemia, delay in cancer treatment and its impact on the outcome of disease.

Method

Study design and patients

This retrospective cohort study was done at a tertiary care referral teaching hospital in South India. We recruited 116 patients from January 2017 to January 2020, with triple negative breast cancer. All patients were treated with a regimen of dose dense chemotherapy. Patients were planned for a total of 8 cycles of chemotherapy every 2 weeks. Four cycles of Docetaxel(75mg/m²) and Cyclophosphamide(600mg/m²) were given alternating with four cycles of Epirubicin(90 mg/m²) and Cisplatin (60 mg/m²). The details of the clinical efficacy of this chemotherapy regimen have been reported previously [14].

Patients were transfused if their hemoglobin level dropped below 8g/dL or in case of heart failure due to anemia. Cost of transfusions and delay in treatment due to transfusion was also evaluated.

The study was approved by the Institutional Review Board and Ethics committee, Christian Medical College Vellore, Tamil Nadu, India (IRB number: 13960 [Retro] dated 28.04.21)

Data Collection

We collected baseline demographic details such as age, gender and place of origin along with tumor related characteristics such as tumor histology, tumor grade, TNM stage. Treatment details such as number of cycles given and the toxicity during chemotherapy was also documented. We measured the MCV, MCH, MCHC, RDW and Hemoglobin at baseline, in between chemotherapy cycles, and at the end of treatment. Anemia, neutropenia and thrombocytopenia were defined based on the WHO definition and graded based on CTCAE v5.0. Data was collected regarding the need of transfusion, time of transfusion and number of packed cells transfused. Dose delay was defined as a delay of > 2 days from the expected administration of a given cycle. Menopausal status was defined as amenorrhea for the last 12 months.

Statistical analysis

Continuous variables were summarized using the descriptive statistics. We used mean and standard deviation (SD) for variables with a gaussian distribution and median and inter quartile range (IQR) for variables with a skewed distribution. Univariate analyses were carried out using the chi-square test. Quantitative and qualitative variables were transformed, whenever possible, into ordinal variables, using predefined cutoff points. The results of univariate analyses are presented with adjusted odds-ratio, 95% confidence intervals (95% CI) and p-value. Significance levels were defined at 0.05. All analyses were performed using IBM SPSS Statistics 25 software and RStudio (Version 1.4.1717).

Results

Baseline characteristics and Prevalence of anemia

The mean age of the population was 43.3 ± 8.7 years. Stage II disease was seen in 41.1% of patients and 56.1% had stage III disease. Delivery of 6/8 planned doses was achieved in 98.3% of patients, and all 8 doses in 86%.

Nearly half (47.4%) of all patients were anemic at the time of diagnosis with 44(37.9%) patients having CTCAE v5.0 Grade 1 anemia, 10(8.6%) patients having Grade 2 anemia and 1(0.9%) patient having Grade 3 anemia. All of these patients developed anemia during the course of chemotherapy. Table II shows the hematological toxicities related to the chemotherapy. Only 1 out of 116 patients was evaluated for cause of anemia and only 24(20.6%) patients received any form of iron supplementation.

Transfusions

A total of 44(37.9%) patients required at least 1 unit of blood transfusion during chemotherapy. A total of 73 units of packed red cells were transfused in the study population with a maximum of 4 units being transfused per patient. There was a mean rise of 1.7 ± 0.5 g/dl in hemoglobin level following transfusion.

Risk factors

Patients in the transfusion group had comparable mean age, disease status and hematological characteristics as compared with the patients who did not require transfusion. Differences were noticed in both the groups with respect to number of cycles received, menopausal status and grade of tumor (Table I).

A greater percentage (54.5% vs 43%) of patients were anemic at the time of diagnosis in the transfusion group, however this difference was not statistically significant. Univariate analysis (Table III) shows that drop in hemoglobin after 2 cycles of chemotherapy (OR 1.649(1.094-2.485), $p = 0.017$), hemoglobin post 2 cycles of chemotherapy (OR 1.74 (95% CI 1.21- 2.51), $p = 0.003$), high grade thrombocytopenia (OR 4.351(1.062-17.827), $p = 0.034$) and low grade of tumor (OR 2.48 (95% CI 1.08 - 5.68), $p = 0.025$) were risk factors for developing anemia requiring transfusion. Graph A (Time to event analysis) shows patients with low grade tumors were more likely to be transfused. No other baseline factor was significantly associated with transfusion requirement.

Impact of anemia

Impact of anemia was assessed in terms of delay in treatment and cost associated with transfusion. Time to event analysis (Graph B) showed that patients who received 7 or less chemotherapy cycles were more likely to be transfused. This could be explained by the early termination of chemotherapy in patients who developed severe anemia requiring transfusion. A total of 27 patients (23.2%) had a delay between two cycles of chemotherapy due to anemia. Delay ranged from a minimum of 2 days to a maximum of 16 days with median delay of 6.5 (4.2 – 8.5) days. Treating triple negative breast cancer with the above-mentioned regimen costs approximately Rs 170,000 for 8 cycles (including drugs, hospital charges and investigations) if there are no adverse events. A median cost of Rs 7000(Rs 7000 – Rs 14000) was spent additionally on transfusion.

Transfusion requirement, delay in chemotherapy, baseline anemia and pre-op hemoglobin did not have an impact on the outcome of the disease, assessed in terms of pathological complete response (T0/Tis N0). Data on the complete response rates and disease-free survival have been published separately [15].

Discussion

This paper describes the prevalence of anemia and transfusion practices in the routine treatment of early TNBC. Dose dense chemotherapy has been shown to improve clinical outcomes in breast cancer patients [16] but is associated with a higher incidence of anemia [17]. The incidence of anemia was found to be 47.4%, similar to other studies conducted in breast cancer patients. [1–5] Transfusion requirement in our population was higher than expected. At least 1 unit of Packed cells was transfused in 37.9% of the patients as compared to other studies conducted in breast cancer patients - 28.1% as seen in Moebus et al [17] and 11.4% as seen in Jones et al. [18] This could be due to the added toxicity of Cisplatin based regimen used in our study population. [19] A greater percentage of patients who were transfused were found to be anemic at the time of diagnosis. Baseline anemia and baseline hemoglobin have been identified to be independent risk factors for transfusion in multiple studies. [10–13] However, in our study the association was not found to be statistically significant.

Hemoglobin after cycle 2 was found to be a statistically significant risk factor associated with transfusion. As depicted in the Graph C, the patients who got transfused had a steady drop in hemoglobin as compared to the patients who did not get transfused. This can help us in identifying patients who might require transfusion based on the trend in their hemoglobin values at an early stage of treatment with chemotherapy.

Patients with grade 3 or 4 thrombocytopenia were more likely to be transfused. This could be explained by a greater extent of bone marrow suppression in patients requiring transfusion. We noticed that patients with low grade tumor were more likely to get transfused. We hypothesize that the slow growing nature of low-grade tumors could be responsible for anemia of chronic disease, thus requiring transfusion.

The burden of chemotherapy related anemia was assessed in terms of added cost of transfusion and delay in treatment. Time burden associated with out-patient transfusion in cancer patients has been studied previously. [20] We found that nearly one fourth of our patients had a delay of at least 2 days in their chemotherapy schedule. The direct cost of transfusion and the indirect cost due to delay in treatment lead to increase in the overall cost of treatment of breast cancer.

The main limitations of our study included the small number of patients and small number of events per variable. As another limitation, the study included only triple negative breast cancer patients. As the patients were given a Platinum based regimen, the transfusion requirement and degree of anemia might be exaggerated as compared to other pathological types of breast cancer for which usually non-platinum-based regimens are used. Baseline pretreatment evaluation of anemia was not uniform and therefore the underlying cause of anemia was not available for all our study population.

Conclusion

Anemia requiring transfusion is a common toxicity of dose dense chemotherapy. Patients experience substantial time burden due to delay along with additional cost of treatment of anemia due to chemotherapy. Early onset decline of hemoglobin within 2 cycles and low grade tumor were associated with subsequent transfusion requirement.

Declarations

Funding: Not applicable.

Conflicts of interest/Competing interests: The authors declare that there is no conflict of interests.

Availability of data and material: Patient data is being stored in a password protected computer which will can only be accessed by the first author and the corresponding author.

Code availability: Not applicable.

Authors' contributions: The authors had the following contributions:

Responsibilities									
Author(s) Name	Research and Study design	Data collection & Analysis	Laboratory analysis	Interpretation and conclusion	Preparation of Manuscript	Review of Manuscript	Guide and critical revision	Administration	Technical Support
Parth Sharma	✓	✓	✓	✓	✓	✓			
Josh T. Georgy	✓	✓	✓	✓	✓	✓			✓
Anand G. Andrews	✓	✓	✓	✓	✓	✓			
Ajoy O. John	✓			✓	✓	✓			✓
Anjana Joel	✓			✓		✓			✓
Raju T. Chacko	✓			✓		✓			✓
Ashish Singh	✓	✓		✓	✓	✓	✓	✓	✓

Ethics approval: The study was approved by the Institutional Review Board and Ethics committee, Christian Medical College Vellore, Tamil Nadu, India (IRB number: 13960 [Retro] dated 28.04.21)

Consent to participate: The patients consented for treatment and collection of data prior to initiation of treatment.

Consent for publication: As this was a retrospective study consent for publication was waived by the Institutional Ethics Committee.

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Tables

Table I: Baseline characteristics

Characteristic	Not transfused (n= 72)	Transfused (n=44)
Age (years)*	42.2± 8.2	45.1±9.3
Stage (n =107)		
Early Stage (I and II)	28(26.0%)	19(17.9%)
Locally advanced (Stage III)	36(33.6%)	24(22.5%)
Grade of tumor (n = 112)		
Low Grade (Grade I and II)	16(13.7%)	19(16.3%)
High Grade (Grade III)	53(45.6%)	24(20.6%)
Cycles completed (n=114)		
7 or less	7(10%)	9(20.5%)
Completed all 8 cycles	63(90%)	35(79.5%)
Baseline Hemoglobin (mg/dl)*	11.8±1 .3	11.6±1.1
Baseline MCV (fL)*	83.6±7.5	84.6±7.8
Baseline MCH (pg)*	27.0±3.1	27.3±3.1
Baseline MCHC (g/dL)*	32.2±1.3	32.2±1.3
Baseline RDW *	15.1±3.8	14.4±1.8
Menopausal status		
Premenopausal	52(72.2%)	25(56.8%)
Post-menopausal	20(27.3%)	19(43.2%)
ECOG score		
0 score	50(69.4%)	32(72.7%)
1-2 score	22(30.6%)	12(27.3%)
Anemia at diagnosis		
Grade I (10 – 12 g/dl)	24(33.3%)	20(45.4%)
Grade II (8 – 9.9 g/dl) and Grade III (6.5 – 7.9 g/dl)	7(9.6%)	4(9.1%)

* Mean and standard deviation

Table II: Hematological Toxicity of chemotherapy

Characteristic	Not transfused (n= 72)	Transfused (n=44)
Anemia* (n= 113) **		
Grade I	27(37.5%)	4(9.1%)
Grade II	40(55.6%)	27(61.4%)
Grade III		13(29.5%)
Drop in hemoglobin after 2 cycles*** (mg/dl)	1.25 (0.42-1.97)	1.75 (1.00 - 2.40)
Thrombocytopenia*		
Low Grade (Grade I and II)	40(55.5%)	24(54.5%)
High Grade (Grade III and IV)	3(4.2%)	7(15.9%)
Neutropenia*		
Low grade(Grade I and II)	13(18.0%)	9(20.4%)
High grade(Grade III and IV)	8(11.1%)	11(25.0%)

*CTCAE v5.0 grading

** 2 patients were not anemic at the end of chemotherapy. Data missing for 3 patients in the Not transfused group.

***Median and IQR

Table III: Univariate analysis

Characteristic	Odds ratio (95% CI)	Unadjusted p-Value
Age	1.04(0.99-1.09)	0.09
Drop in Hemoglobin after 2 cycles	1.65(1.09-2.48)	0.017
Baseline Hemoglobin	0.89(0.67-1.21)	0.474
Baseline MCV	1.02(0.99-1.07)	0.533
Baseline MCH	1.02(0.91-1.16)	0.691
Baseline MCHC	0.98(0.74-1.29)	0.868
Baseline RDW	0.90(0.76-1.07)	0.235
Hemoglobin post cycle 2	1.74 (1.21- 2.51)	0.003
Stage (n =107) (Locally advanced vs. Early stage)	0.98(0.45-2.14)	0.561
Grade of tumor (n = 112) (Low grade vs. High Grade)	2.48 (1.08 - 5.68)	0.025
Cycles completed (n=114) (8 cycles vs. 7 or less)	0.43(0.15-1.26)	0.100
Menopausal status (Postmenopausal vs. premenopausal)	1.98(0.89-4.35)	0.067
ECOG PS (1-2 vs. 0)	0.85(0.37-1.96)	0.437
Neutropenia Grade 3/4	2.67(0.98-7.27)	0.070
Thrombocytopenia Grade 3/4	4.35(1.06-17.83)	0.034

Figures

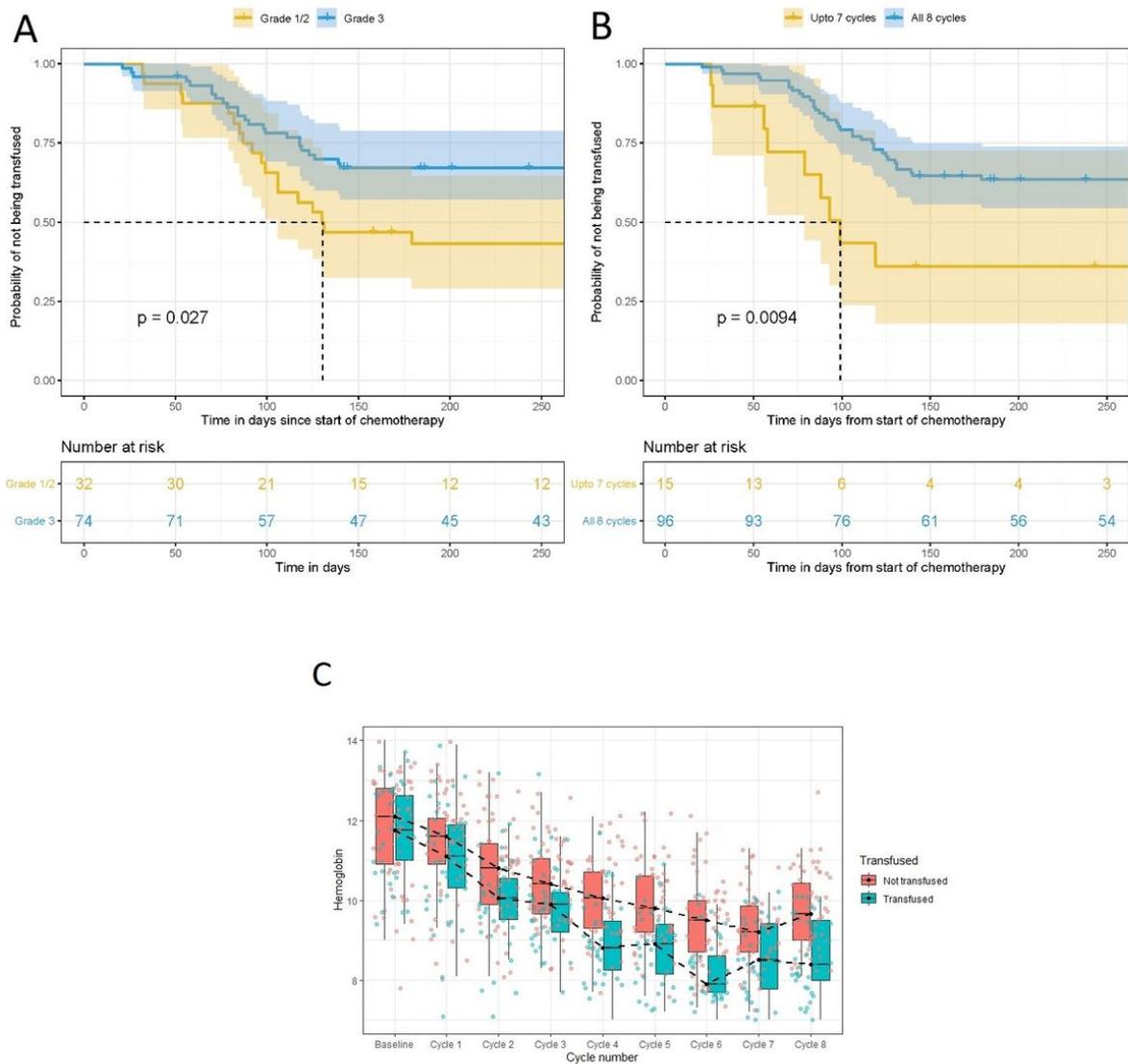


Figure 1

Time to event analysis of Grade of tumor (Graph A) and Number of cycles (Graph B) and day of transfusion from start of chemotherapy. (Graph C) Drop in hemoglobin with chemotherapy in Transfused group and Not-transfused group.