Iran J Cancer Prev. 2017 January; 10(1):e4672. doi: 10.17795/ijcp-4672.

Published online 2016 September 27. **Research Article**

Frequency of Chemotherapy Induced Anemia in Breast Cancer Patients

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Received 2015 November 11; **Revised** 2016 April 23; **Accepted** 2016 September 24.

Abstract

Background: Breast cancer is the second most common malignancy in women, worldwide. Several etiologic factors may cause anemia in a patient with breast cancer. Anemia is a prevalent complication in patients with breast cancer who undergo chemotherapy which affects the health status and quality of life in these patients. The aim of this study was to evaluate the prevalence of anemia in patients with non-metastatic breast cancer who underwent adjuvant chemotherapy.
Methods: In this cross-sectional study, 144 women with non-metastatic breast cancer who referred to radiotherapy and oncology department of Imam Reza hospital and met inclusion criteria were included. Data were obtained from patients' archived documents and were analyzed by SPSS software (version16).
Results: In this study, 41% of patients were anemic before the chemotherapy and 43.1% of patients became anemic during and after treatment. The prevalence of post-chemotherapy anemia was significantly higher in advanced stages of cancer (P = 0.01). The chance of developing anemia were more in patients who underwent 8 cycles and AC + paclitaxel regimen, compared to the ones with 6 cycles and other regimens. There was no significant relationship between the prevalence of anemia and type of chemotherapy regimen, number of chemotherapy cycles, positive lymph nodes, co-morbidities, menstrual status, and body mass index (BMI).
Conclusions: Due to the high prevalence of chemotherapy-induced anemia and its effects on quality of life, even mild degrees of anemia should be detected and evaluated before treatment. Considering early interventions is of cardinal importance, especially in the elderly.

Keywords: Anemia, Breast Cancer, Chemotherapy, Adjuvant Chemotherapy

1. Background

Anemia, defined as a decrement in serum hemoglobin concentration to pathological levels (< 14 g/dL in men, < 12 g/dL in women), is usually resulted from chemotherapy in patients suffering from cancer. About 50% of cancer patients suffer from anemia and its common side effects, fatigue, at some point in the course of their disease (1). The severity of anemia and fatigue depends on chemotherapy regimen, disease type, patient's age, and other risk factors. For instance, patients who were in advanced stages of anemia during chemotherapy, reported more fatigue and worse quality of life (2).

Aside from chemotherapy, the process of disease in the cancer patients may lead to anemia, as in other chronic diseases. Multiple mechanisms can impair the normal production of erythrocyte in cancer patients, including cytokines and interleukins (IL). For instance, tumor necrosis factor (TNF-α), transforming growth factor (TGF-β), IL-1, IL-6, and interferon (IFN-γ) are involved as inhibitory mechanisms in the metabolism of Iron, causing anemia in cancer patients (3).

Anemia may develop either by impaired function in red blood cell (RBC) production or because of renal tubular damage following treatment with cytotoxic drugs as a consequence of chemotherapy in patients with breast cancer (4). Moreover, reduced levels of erythropoietin negatively affects RBC production in bone marrow, inducing anemia; accordingly, cancer patients with anemia have been shown to present abnormal erythropoietin levels (5).

The reported incidence of high-grade anemia associated with conventional combination of chemotherapeutic regimens used in the treatment of breast cancer has ranged from less than 1% with the combination of CMF (cyclophosphamide + methotrexate + 5-fluorouracil) to 80% with high-dose cyclophosphamide, mitoxantrone and etoposide. In addition, multi-agent chemotherapy has a

various range of side effects, including anemia and fatigue (6, 7). The commonly used CAF (cyclophosphamide + doxorubicin +5-fluorouracil) chemotherapy regimen is reported to induce grade I or II anemia in 55% of patients and grade III or IV anemia in 11% of previously treated patients with metastatic breast cancer (7).

The impact of anemia and its subsequent fatigue on the quality of life is concerning problem for cancer patients and it is often neglected in the management of these patients (8). The prevalence and severity of anemia in early-stage breast cancer patients undergoing adjuvant chemotherapy with many commonly used regimens are not well documented (2). The present study reports the frequency and severity of anemia that was developed during adjuvant chemotherapy in non-metastatic breast cancer in patients.

2. Methods

In this cross-sectional study, 144 female patients with non-metastatic breast cancer who were referred to the radiotherapy and oncology ward of Imam Reza hospital of Mashhad University of Medical Sciences, Iran, from January 2013 to December 2013 were included. All the patients were given the adjuvant chemotherapy. Exclusion criteria were: metastatic breast cancer, history of other cancer, history of previous chemotherapy or radiotherapy, anemia due to gastrointestinal bleeding, and patients below18 years.

Adjuvant chemotherapy had been performed for all patients mostly with the following regimens:

- AC: doxorubicin + cyclophosphamide
- AC + Paclitaxel: AC followed by paclitaxel
- AC + Docetaxel: AC followed by docetaxel
- CAF: cyclophosphamide + doxorubicin + 5-fluorouracil
- CMF: cyclophosphamide + methotrexate + 5-fluorouracil

Demographic data were obtained from the files archived in the radiotherapy and chemotherapy department of Imam Reza hospital. Blood samples for detecting anemia were assessed in 3 periods: before the chemotherapy, during the chemotherapy, and afterwards. The hemoglobin level of blood samples was recorded. According to the common toxicity criteria of NCI (National Cancer Institute), the severity of anemia was classified as mild (grade I): Hb = 11.9 - 10 gr/dL, moderate (grade II): Hb = 9.9 - 8, and severe (grade III): Hb < 8 gr/dL (9). Other variables such as age, stage of the cancer, menstrual status, involvement of axillary nodes and accompanying diseases were obtained from the archived files.

Data were analyzed using statistical package for the social sciences (SPSS) software (version 16). Chi-Square test was used to compare the differences between the subgroups for each discrete variable. The Mann-Whitney test was used to compare median between the anemic and non-anemic patients, regarding positive lymph nodes. P values below 0.05 were considered as statistically significant.

3. Results

144 women with non-metastatic breast cancer met the inclusion criteria. Demographic and baseline characteristics of patients are summarized in Table 1. The age ranged from 26 to 75 years with the mean of 47.7 ± 10.4 years. The majority of women were premenopausal (n = 54, 37.5%) and overweight (n = 60, 41.7%). 42 (28.5%) patients had a history of concomitant disease, including hypertension (n = 18), diabetes (n = 12), and cardiovascular disease (n = 6). Tumors sized 2 - 5 cm (T2) had the most prevalence among the individuals (n = 89, 61.8%). 67.4% of patients had positive axillary lymph nodes. None of the patients received erythropoietin and only five patients (3.5%) had the history of blood transfusion.

We found a higher prevalence of anemia in patients who underwent more cycles of chemotherapy (38.2% and 50.9% in patients with 6 and 8 cycles, respectively).

Our results showed that anemia was most prevalent in patients who underwent the anthracycline (AC) + paclitaxel chemotherapy regimen (61.1%), which was followed by AC + docetaxel regimen (52.2%).

Before starting the chemotherapy, 59 patients (41.0 %; 95% confidence interval (CI)) already had anemia. In most cases, the anemia was mild, but seven patients (4.8%; 95% CI) had anemia of moderate or higher severity. During chemotherapy, 82 patients (56.9%; 95% CI) retained an Hb level of 12 gr/dL or above. Surprisingly, although the prevalence of anemia showed a slight increase after the chemotherapy, the severity of anemia decreased after the treatment as the number of patients with grade II anemia declined from 7 patients (4.8%) pre-chemotherapy to 5 patients (3.5%). Repeated measures analysis showed that the hemoglobin levels were not significantly different before, after and during the treatment (P = 0.69).

Table 2 compares the prevalence of anaemia in various subgroups. There were not any significant differences regarding the prevalence of anemia among various subgroups based on age, BMI, menstruation status, concomitant disease, number of chemotherapy cycles and the type of chemotherapy regimens.

Patients with post-chemotherapy anemia were at higher stages of breast cancer compared with non-anemic individuals and the difference was statistically significant

Table 1. Demographic Information and Baseline Characteristics

Variable/Subgroups	No. (%)
Age, y	
25 - 35	16 (11.1)
35 - 45	41 (28.5)
45 - 55	55 (38.2)
55 - 65	23 (16.0)
65 - 75	9 (6.2)
BMI, kg/m^2	
< 25	38 (26.4)
25- 30	60 (41.7)
> 30	46 (31.9)
Menstrual status	
Premenopausal	54 (37.5)
Perimenopausal	42 (29.2)
Postmenopausal	48 (33.3)
Stage of the tumor (T)	
T 1	2 (1.4)
T 2	46 (31.9)
T 3	51 (35.4)
T x	45 (31.2)
Chemotherapy	
CAF	47 (32.6)
CMF	41 (28.5)
AC+ Docetaxel	23 (16.0)
AC+ Paclitaxel	18 (12.5)
Other regimens	15 (10.4)
Cycles of chemotherapy	
6 cycles	89 (61.8)
8 cycles	55 (38.2)
Anemia, Hb < 12 mg/dL	
Before the chemotherapy	59 (41.0)
During chemotherapy	62 (43.1)
After the chemotherapy	62 (43.1)

Abbreviation: BMI, body mass index.

(P=0.01). In addition, the median of positive lymph nodes after the chemotherapy was higher in anemic patients, compared with non-anemic women (2.0 vs. 1.0, P = 0.056).

5. Discussion

Breast cancer is the second most common malignancy among women, worldwide and the most common among Iranian women (9, 10). Anemia is a frequent complication detected in patients with cancer (11). Adjuvant chemotherapy for the treatment of breast cancer, in turn, leads to an

Table 2. Post-Chemotherapy Prevalence of Anemia Categorized by Different Parameters[a,b]

Variable/Subgroups	Post-Chemotherapy Anemia	P Value
Age, y		0.656
25 - 35	6 (37.5)	
35 - 45	18 (43.9)	
45 - 55	23 (41.8)	
55 - 65	9 (39.1)	
65 - 75	6 (66.7)	
BMI, kg/m^2		0.108
< 25	18 (47.4)	
25- 30	30 (50.0)	
> 30	14 (30.4)	
Menstrual status		0.92
Premenopausal	24 (44.4)	
Perimenopausal	17 (40.5)	
Postmenopausal	21 (43.8)	
Stage of the tumor (T)		0.01
T 1	0	
T 2	16 (34.8)	
T 3	29 (56.9)	
Chemotherapy		0.095
CAF	22 (46.8)	
CMF	11 (26.8)	
AC+ Docetaxel	12 (52.2)	
AC+ Paclitaxel	11 (61.1)	
Other treatment	6 (40.0)	
Cycles of chemotherapy		0.135
6 cycles	34 (38.2)	
8 cycles	28 (50.9)	

Abbreviation: BMI, body mass index.
[a]Values are expressed as No. (%).
Chi-square test was used and P values under 0.05 were considered as statistically significant.

increase in both the incidence and the severity of anemia; especially in women of reproductive age (7, 11, 12). The subsequent anemia leads to complications, which affects the quality of life in these patients. Moreover, neglecting the chemotherapy-induced anemia might be a pitfall for the physicians by making the patient irresponsive to the treatments (13).

We found the general prevalence of anemia among the patients to be 41% before the chemotherapy, which reached to 43.1% after the treatment. This shows that the prevalence of anemia among our subjects increased by 2% after the chemotherapy. Our pre- and post-chemotherapy prevalence of anemia was almost equivalent to the pre- and post-radiotherapy prevalence of anemia, which was reported by Harrison et al. in a retrospective study on breast cancer patients (41% and 44%, respectively) (14). Our post-chemotherapy prevalence is concordant with the findings of Kirshner et al. who reported the rate of anemia to be 40% among their patients after the chemotherapy. However, the gap between pre- and post-chemotherapy prevalence of anemia was larger in their study with pre-chemotherapy anemia prevalence of 31% (15).

Coiffier et al. also conducted a retrospective study on the prevalence of anemia in a population of cancer patients who underwent non-platinum based chemotherapy, among whom approximately 50% had breast cancer. Their baseline hemoglobin results indicated that 37.1% of subjects were anemic (Hb $\leq$ 12 gr/dL) before the chemotherapy. Thus, their pre-chemotherapy prevalence of anemia was consistent with that of our study. However, after 3 cycles of chemotherapy, the rate increased to 54.1% and later remained over 50% after the fourth cycle, which is a bit higher than that of our study (16).

In the study done by Goldrick et al. pre-chemotherapy rate of anemia was 12% among the early breast cancer patients who underwent adjuvant chemotherapy. This rate is much lower than ours is, which might be due to the lower stage of their patients, compared to our study in which most patients were in late stages of breast cancer (2).

The results of present study showed the severity of anemia decreased after chemotherapy, compared with pre-chemotherapy. The results of the study done by Kitano et al. showed an increase in the severity and prevalence of anemia after chemotherapy. The different results may be due to more toxic chemotherapy regimen which were used for treatment of their patients (17).

We found a higher prevalence of anemia in the patients who underwent more cycles of chemotherapy (38.2% and 50.9% in patients with 6 and 8 cycles, respectively). This finding is consistent with the one from Hassan et al. who found that the prevalence of anemia among their solid tumor patients was increased after each chemotherapy cycle (onset of anemia was 0.5%, 18.4%, 37.5%, and 43.6% after the 1st, 2nd, 3rd, and 4th cycles, respectively) (18).

We found that post-chemotherapy anemia was most prevalent among 65-75 years age group (66.7%), which is rather unusual due to their postmenopausal status. The patients 35-45 years old were the second prevalent anemic group. Kirshner et al. observed that the majority (52.4%) of patients who did not develop anemia during the course of chemotherapy were aged 50 - 64, which means that postmenopausal women tend to maintain a higher concentration of hemoglobin possibly since they lose less blood (15).

This finding might be related to the fact that we had only nine (6.2%) subjects in this age group, which is a rather small sample compared with the 45 - 55 years age group with 55 (38.2%) patients. The other reason for this unusual finding might be other underlying disorders that can affect the hemoglobin concentration and subsequently lead to anemia in the older ages (e.g. malnutrition, or chronic disease) (3).

Chaumard et al. who studied the incidence and risk factors of anemia in patients with early breast cancer, reported that the rate of anemia was 73.8% in patients aged 40 or less, and 62.5% in patients aged more than 40. The rates became very close when they compared patients aged $\leq$ 50 (65.8% anemic) with the ones aged > 50 (62.3% anemic) (19).

Considering BMI, we found that the highest rate of anemia was among patients who were overweight ($25 < BMI \leq 30$). This might be due to the high frequency of subjects in this group (41.7%). Contrary to our results, Chaumard et al. found a significant difference regarding the prevalence of anemia between the patients with BMI $\leq$ 25 and those with BMI > 25 (P = 0.02). Anemia was less frequent among their overweight and obese subjects (57.6%), compared with subjects with BMI $\leq$ 25 (69.6%) (19).

The results of our study showed a statistically significant increase in the rate of anemia, as the stage of breast cancer got higher (P = 0.01). The highest rate of anemia was in the patients with stage 3 (56.9%). This might be due to the fact that most of our patients were diagnosed at higher stages (35.4% in stage3 and 31.9% in stage 2), which affects our sampling in a way that we have very few patients with low-stage breast tumors (1.4% in stage 1).

The results of Goldrick and colleagues were inconsistent with this finding. They found that only 6% of their subjects were in stage 3, whereas most of their patients were in early stages (36.9% in stage 1 and 47.2% in stage 2). This might be due to their bigger sample size compared with that of ours (702 versus 144) (2).

Our results showed that anemia was most prevalent in patients who underwent the anthracycline (AC) + paclitaxel chemotherapy regimen (61.1%), which was followed by AC + docetaxel regimen (52.2%). In contrast, Goldrick et al. found the highest rate of anemia in patients taking "cyclophosphamide + epirubicin + 5-fluorouracil" regimen (98.2%) while anemia rate in patients taking "doxorubicin + cyclophosphamide followed by paclitaxel or docetaxel" regimen was third highest (81.8%) (2). In addition, Chaumard et al. found the highest prevalence of anemia (92.3%) among patients taking concomitant taxanes regimen (19).

We had some limitations in the present study. First, we had a small sample size. Another limitation of our study was our lack of advanced diagnostic imaging tools, which resulted in several patients being categorized as unknown stage of tumor, so they were excluded from the study. In addition, our retrospective design along with missing data limited the availability of patients for a follow-up and led to exclusion of many patients and subsequently a smaller sample size.

In conclusion, the present study showed significant proportion of patients with breast cancer are anemic (41%), before chemotherapy. In addition, the incidence rate of anemia increases during adjuvant chemotherapy, especially among the elderly, so special attention is recom-

mended for correction of nutritional habits and controlling of comorbidities among this group.

With regard to the increased rate of anemia in patients who underwent more than 6 courses of chemotherapy especially taxane based regimen, we recommend early screening and monitoring for iron storage and rational prescription of iron supplements if needed. Moreover, nutritional consultation for optimal iron absorption and valuable iron supplementation is recommended.

Acknowledgments

The authors would like to appreciate the research faculty of Mashhad University of Medical Sciences which supported this paper financially. Also, Amir Nik is thankful for his cooperation in writing this article.

Footnotes

Authors' Contribution: Leila Pourali designed the study, analyzed the data and wrote the paper. Ali Taghizadeh contributed to the data entry, literature review and writing-up process. Mohammad Reza Akhoundi and Fatemeh Varshoei contributed to the study design and analysis. Ahmadreza Zarifian and Mohammad Sobhan Sheikh Andalibi contributed to the study editing. All authors read and approved the final manuscript.

Conflict of Interests: There is none to declare.

Financial Disclosure: There is none to declare.

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