Chemotherapy Induced Myelosuppression after First Cycle of Adjuvant Chemotherapy for Non- Metastatic Breast Cancer

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ABSTRACT:

BACKGROUND:

Breast cancer is the most common cancer in women. Chemotherapy makes cancer patients at risk of developing myelosuppression which may cause delay in treatment and dose reduction.

AIM OF THE STUDY:

To assess tendency for chemotherapy induced cytopenia after the first cycle of chemotherapy in non-metastatic breast cancer patients.

PATIENTS AND METHODS:

A prospective observational study included 152 patients diagnosed with breast cancer and planned to receive adjuvant chemotherapy in form of Adriamycin / cyclophosphamide (AC) based chemotherapy, all of them with normal complete blood count pre chemotherapy and were observed by recording their absolute neutrophil count, hemoglobin and platelet count for development of cytopenia after three weeks of the first cycle of chemotherapy.

RESULTS:

It is found that 32.2% of patients developed neutropenia with 7.2% of them reached to grade IV neutropenia , 5.9% patients had febrile neutropenia .There's 23% of patients developed anemia from those 19.1% developed grade I anemia while 3.9% had grade II anemia, and no one experienced thrombocytopenia. Anemia found to be significantly associated with immunohistochemistry status of patients.

CONCLUSION:

Chemotherapy induced neutropenia is a recognized complication on significant number of patients, Anemia is a reported complication but fortunately, it is of grade I or II , Neither patients included in this study developed thrombocytopenia .

KEYWORDS: Breast cancer, chemotherapy, myelosuppression

INTRODUCTION:

Cytotoxic chemotherapy places all cancer patients at risk of developing myelosuppression, which may cause significant morbidity and mortality increasing health care cost. [1]

Chemotherapy-induced myelosuppression can be mediated through multiple mechanisms; the most common shared mechanism is through direct DNA effects that can inhibit cell cycle progression at various phases or cause direct DNA damage. These can result in apoptosis or impaired growth and proliferation of progenitor cells. Radiation therapy can also cause direct bone marrow apoptosis and bone marrow failure [2].

Chemotherapy-related myelotoxicity is typically dose dependent, so the route and frequency of delivery (e.g., intravenous versus oral or twice versus once weekly) are also considerations in designing dosage schemas because these can affect drug distribution, peak drug concentrations, and consequently the degree of myelosuppressive toxicity[3]

Chemotherapy-induced cytopenias increase treatment-related morbidity and mortality, through infection, bleeding, or impaired quality of life. Unfortunately, the combination regimens that produce the greatest survival benefit are also often the most highly myelosuppressive [4]. Because of potential associated complications, neutropenia, thrombocytopenia, and anemia are the primary causes of unplanned delays or dose reductions in chemotherapy.

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The changes in dosage levels and interval frequency of administration that reduce relative dose intensity (RDI) may result in suboptimal levels that potentially compromise therapeutic efficacy[5]. Over time, repeated exposure to cytotoxic agents can also injure bone marrow function beyond recovery, resulting in a chronic hypo plastic state with permanently decreased cell counts, which further limits therapy options. When possible, chemotherapy regimens should be administered with the goal of avoiding unplanned delays or dose reductions so that relative dose intensity can be maintained. Cancer-related myelosuppression therefore represents a major clinical challenge in balancing optimal treatment dosage and schedules against their potential hematologic complications[5]

Neutropenia is defined as a decrease in the circulating subpopulation of white blood cells, called neutrophils, with the following designated thresholds for grade IV neutropenia: an absolute neutrophil count (ANC) of less than 500 neutrophils per cubic millimeter or a predicted decline to less than 500 neutrophils per cubic millimeter over the next 48-hour period[6]

Neutropenia significantly increases morbidity and mortality due to fever, infection, and sepsis. In cancer patients, neutropenia can result from myelosuppressive treatment or direct marrow replacement by tumor cells[2]

The time course for induction of neutropenia and the duration vary with the specific agents given, with more intensive regimens resulting in more profound and prolonged periods of neutropenia. In addition, individualized patient factors such as age and prior exposure to myelosuppressive drugs affect duration and depth of neutropenia, adding to variability of the myelotoxic effects of chemotherapy regimens.[7]

Hypo proliferation of red cells can be directly caused by bone marrow replacement of tumor cells. Commonly found in cancer patients, poor nutritional status and malabsorption can lead to depletion of nutrients necessary for generating the building blocks required for erythropoiesis: DNA, amino acids, and hemoglobin. Red cell production is additionally dependent on levels of erythropoietin (EPO), a key hormone whose signaling network is frequently altered in malignancy [8]

Anemia is a common complication of myelosuppressive chemotherapy but is often an over-looked problem in breast cancer patients[9]. Mild to moderate anemia in patients undergoing chemotherapy is often treated conservatively and is usually neglected. Several clinical data are suggesting that even mild to moderate anemia causes reduction in the patient's energy level and quality of life[10].

Thrombocytopenia is defined as a platelet count below 100 * 10^9 per liter, with National Cancer Institute grades defined as follows: grade 1 for 75 *10^9 to 100 *10^9 per liter, grade II for 50 *10^9 to 75*10^9 per liter, grade III for 25*10^9 to 50*10^9 per liter, and grade IV fewer than 25*10^9 platelets per liter. Significant thrombocytopenia necessitates delays or dose reductions in planned chemotherapy, which may also compromise therapeutic efficacy .The Mechanism for thrombocytopenia related to treatment with chemotherapy is not fully understood. In vitro and preclinical studies have suggested that chemotherapeutic agents may have direct cytotoxic effects with induction of apoptosis of erythroid and megakaryocytic progenitors at early differentiation stages[11]

PATIENTS AND METHODS:

This is an observational cohort prospective study carried out at Baghdad Oncology Teaching Center, Medical City Complex, Baghdad , Iraq during the period from 1st Feb 2019 till 8th of Oct 2019.

One hundred fifty-two female of different age groups are included in this study, all of them are known to have breast cancer proved by histopathological reports and underwent surgery and staged as (stage I, II, III) and referred by their oncologist to receive adjuvant chemotherapy Anthracycline/cyclophosphamide based protocol in schedule of Adriamycin 60mg/m2 intravascular infusion over half hour and cyclophosphamide 600mg/m2 intravascular infusion over one hour every 3 weeks for four cycles, all of them are with normal complete blood count before starting chemotherapy .

Exclusion criteria

Patients with metastatic breast cancer, Patients required neoadjuvant chemotherapy, Patients with history of other solid or hematological malignancies, Patients with history of infection, hematological conditions (preexisting anemias), Patients with initial abnormal CBC (complete blood count), Patients with history of renal

impairment, rheumatic diseases , Patients planned to receive adjuvant chemotherapy other than Adriamycin /cyclophosphamide (AC) based protocol, Patients planned to receive dose dense Adriamycin /cyclophosphamide (AC) when chemotherapy given every two weeks.

Data collection and sampling

A questionnaire consisted of age, menopausal state, past medical history including (Diabetes mellitus, hypertension, ischemic heart disease, renal impairment, history of anemia), weight and height with body mass index BMI calculated by equation (weight /height ^{2}) was taken directly from participants during their visits.

From histopathological reports tumor size, lymph node status are obtained to determine stage.

Immunohistochemistry including Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER2/ neu) status also obtained from histopathological reports.

Three ml of blood sample had been withdrawn from participant before the first cycle of chemotherapy (baseline sample) and second sample 21 day after the first cycle (before the second cycle), CBC done by automated hematology analyzer Celltac G (NIHON KOHDEN) and results of absolute neutrophil count (ANC), hemoglobin level, mean cell volume (MCV), mean cell hemoglobin (MCH), red cell distribution width (RDW) and platelet count were extracted and recorded. Only those with normal indices are included in this study and followed for next CBC sample 21 days after.

CBC after first cycle with the same indices was also recorded and development of neutropenia, anemia and thrombocytopenia were identified and severity of each parameter recorded according to common toxicity criteria of the national cancer institute version 2.0. [12]

Table 1: Common toxicity criteria of the national cancer institute version 2.0 [12].

Grade	neutropenia	anemia	thrombocytopenia
I	1500-2000 cells/mm^3	Less than normal limit to 10 g/dl	Less than normal limit to 75 *109per liter
II	1000-1500 cells/mm^3	Less than10g/dl – 8 g/dl	75 *10^9 – 50 *10^9 per liter
III	500-1000 cells/mm^3	less than 8 g/dl – 6.5 g/dl	50 *10^9- 25 *10^9 liter
IV	Below 500 cells/mm^3	Less than 6.5 g/dl	Less than 25 *10^{9}per liter

Data was analyzed using statistical package for the social sciences (SPSS version 23) computer software program.

Descriptive statistics presented as frequency tables, Continuous variables were expressed as mean and categorical variables as numbers and percentages. Analytic statistics as chi-square test to find association between two categorical variables. The P-value below or equal to 0.05was considered to be statistically significant.

RESULTS:

A total of 152 female patients with breast cancer were enrolled in this study, the mean age of patients was 50.8 years.

Table 2 :Characteristics of patients according to variables .

Variable		Number	Percentage
Age groups	<40 years	19	12.5%
	40-49 years	51	33.6%
	50-59 years	47	30.9%
	≥60 years	35	22.9%
BMI	Underweight(<18.5)	1	0.7%
	Normal (18.5-24.9)	30	19.7%
	Overweight (25-29.9))	47	30.3%
	Obese(30 and above)	75	49.3%
Menopausal history	Premenopausal	70	46.1%
	Postmenopausal	82	53.9%
Medical history	Negative	111	73%
	Hypertension	19	12.5%
	Diabetic mellitus	5	3.3%
	Both HT&DM	16	10.5%
	IHD	1	0.7%

The stage of cancer at time of diagnosis was 7.2% (11) of patients were in Stage I and 50% (76) of patients were in Stage II while 42.8% (65) of patients were in stage III.

All patients involved in this study had normal complete blood count prior to chemotherapy were started and after first cycle of chemotherapy. 117(77%) of patients had preserved hemoglobin level and 35(23%) of patients developed anemia from those 29(19.1%) of patients developed grade I anemia while only 6(3.9%) of patient developed grade II anemia, no one developed grade 3 or 4 anemia.

The percentage of patients that preserved absolute neutrophils count after the first cycle of chemotherapy were 103 (67.7%) and 49(32.2%) of patients developed neutropenia from those 16(10.5%) of patients developed grade I neutropenia, 10(6.5%) of patients developed grade II neutropenia, 12(7.8%) of patients developed grade III neutropenia and only 11(7.2%) developed grade IV neutropenia. Nine patients (5.9%) of those with grade IV had febrile neutropenia.

All patients had normal platelet count after first cycle of chemotherapy, all this were showed in table 3.

Table 3: Distribution of patients according to grade of anemia, neutropenia and thrombocytopenia.

Variable		Number	Percentage
Anemia grade	Normal Hb	117	77%
	I	29	19.1%
	II	6	3.9%
	III	0	0
	IV	0	0
Neutropenia grade	Normal ANC	103	67.3%
	I	16	10.5%
	II	10	6.5%
	III	12	7.8%
	IV	11	7.2%
Thrombocytopenia grade	Normal platelet	152	100%
	I	0	0
	II	0	0
	III	0	0
	IV	0	0

No significant association was observed between age, BMI, menopausal history, medical history, stage of cancer and hormonal status with development of neutropenia (p>0.05). There was a significant association between hormonal status and development of anemia (p= 0.01). where between the patients who developed anemia 51.4%(18) of patients had Hormonal +ve & HER2 –ve, 22.9%(8) of patients had triple negative, 2.9%(1) of patients had triple positive and 22.9%(8) of patients had Hormonal –ve & HER2 +ve

Table 4: Relation of patient's character with development of neutropenia and anemia.

Variable		Anemia		P value	Neutropenia		P value
		No	Yes		No	Yes	
Age groups	<40 years	13(11.1%)	6(17.1%)	0.2	15(14.6%)	4(8.2%)	0.7
	40-49 years	40(34.2%)	11(31.4%)		33(32%)	18(36.7%)	
	50-59 years	40(34.2%)	7(20%)		31(30.1%)	16(32.7%)	
	≥60 years	24(20.5%)	11(31.4%)		24(23.3%)	11(22,4%)	
BMI	Normal or underweight	27(23.1%)	4(11.4%)	0.3	23(22.3%)	8(16.3%)	0.4
	Overweight	34(29.1%)	12(34.3%)		33(32%)	13(26.5%)	
	Obese	56(47.9%)	19(54.3%)		47(45.6%)	28(57.1%)	
Menopausal history	Premenopausal	54(46.2%)	16(45.9%)	0.9	48(46.6%)	22(44.9%)	0.8
	Postmenopausal	63(53.8%)	19(54.3%)		55(53.4%)	27(55.1%)	
Medical history	Negative	84(71.8%)	27(77.1%)	0.5	76(73.8%)	35(71.4%)	0.7
	Positive	33(28.2%)	8(22.9%)		27(26.2%)	14(28.6%)	
Stage of cancer	Stage I	10(8.5%)	1(2.9%)	0.11	7(6.8%)	4(8.2%)	0.15
	Stage II	62(53%)	14(40%)		57(55.3%)	19(38.8%)	
	Stage III	45(38.5%)	20(57.1%)		39(37.9%)	29(53.1%)	
HC status	Hormonal +ve & HER2 –ve	77(65.8%)	18(51.4%)	0.01	63(61.2%)	32(65.3%)	0.8
	Triple negative	15(12.8%)	8(22.9%)		15(14.6%)	8(16.3%)	
	All positive	16(13.7%)	1(2.9%)		12(11.7%)	5(10.2%)	
	Hormonal –ve & HER2 +ve	9(7.7%)	8(22.9%)		13(12.6%)	4(8.2%)	
Total		117	35		103	49	

DISCUSSION:

Chemotherapy induced cytopenia is expected in any patient treated with chemotherapy regardless their diagnosis, and many studies were interested in the frequency of cytopenia in those patients because that development of anemia, neutropenia, thrombocytopenia and febrile neutropenia affects the course of treatment, quality of life and may resulted in comorbidity and mortality.

In this study, it is found that anemia is developed in 23% of patients after first cycle AC with severity Grade I&II which is comparable to the results of Goldrich et al[9].

There is a significant number of patients developed neutropenia 32% of them there is 5% with febrile neutropenia, comparable with Leonard, R. C. F., Miles, D., Thomas, R., & Nussey, F[13]showed that 28% of patients receiving anthracycline-based regimens experienced a neutropenic event, the development of anemia and neutropenia directed to myelosuppressive effect of combination of Adriamycin and cyclophosphamide as they are well-known to have self-limited bone marrow toxicity.

Tia L.J. , Lui A.G. et al[10] where 751 patients were included, reports that the incidence of cytopenia after the first cycle of chemotherapy is minimal in contrast to our study and that could be explained by larger number of patients included in their study and including chemotherapy lines other than Adriamycin cyclophosphamide.

Neither patients included in our study experience thrombocytopenia, few studies investigate about thrombocytopenia in breast cancer patients; A large study evaluated chemotherapy induced

thrombocytopenia in solid tumors (including breast cancer) revealed that the incidence of significant thrombocytopenia was about 10.1%[14].

Anemia is found to be significantly related to immunohistochemistry status of patients, while other studies such as Tia L.J. , Lui A.G. et al[10], Leonard, R. C. F., Miles, D., Thomas, R., & Nussey, F[13] showed there is no significant relation, this is a surprising finding, no study till now showed there is an association between developing anemia and immunohistochemistry status.

Age, stage of cancer, medical history and menopausal state) didn't reach a significant values in our study; studies such as Chan A. et al[15] and schwenkglenks M , Pettengell R[16] showed that there is a significant relation of neutropenia to body mass index, age, stage and number of chemotherapy cycles.

Other Studies [17,18] cleared that anemia is related to stage as more higher stage more risk of anemia, the previous studies also showed that previous history of anemia, presence of comorbid illnesses and age more than 65 were significantly associated with the development of anemia, as some factors were not taken in our study; 57% of cases who developed anemia were stage III with no statistically significant value . Most of our cases were < 60 years old and that might be the cause that age was not significantly related to development of anemia.

CONCLUSION:

1. Chemotherapy induced neutropenia is a recognized complication on a significant number of patients.
2. Anemia is a reported complication but fortunately, it is of grade I or II.
3. Anemia found to be significantly associated with immunohistochemistry status of the patients.
4. Neither patients included in this study developed thrombocytopenia

REFERENCES:

1. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: Incidence and treatment. J Natl Cancer Inst. 1999;91:1616–34.
2. Barreto JN, McCullough KB, Ice LL, Smith JA. Antineoplastic agents and the associated myelosuppressive effects: a review. J Pharm Pract. 2014 ;27:440–46.
3. Off PP, Here S. Abeloff's Clinical Oncology. Abeloff's Clinical Oncology. 2020.
4. Smith RE. Trends in recommendations for myelosuppressive chemotherapy for the treatment of solid tumors. JNCCN J Natl Compr Cancer Netw. 2006;4:649–58.
5. Dale DC, McCarter GC, Crawford J, Lyman GH. Myelotoxicity and dose intensity of chemotherapy: reporting practices from randomized clinical trials. *J Natl Compr Canc Netw*. 2003;1:440–54.
6. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52.
7. Davita VT, Lawrence TH , Rosenberg SA .cancer principles and practice of oncology .11th edition. United states: Lippincott-Raven Publisher ;2019: 2299-300.
8. Palis J. Primitive and definitive erythropoiesis in mammals. Front Physiol. 2014;5:1-9.
9. Goldrick A, Olivotto IA, Alexander CS, Speers CH, Barnett J, Allan SJ, et al. Anemia is a Common but Neglected Complication of Adjuvant Chemotherapy for Early Breast Cancer. Curr Oncol. 2007;14:227–33.
10. Tia LJP, Lui AGA, Chua NS, Strebel HMJS. Chemotherapy-induced neutropenia, anemia and thrombocytopenia among Filipino breast cancer patients on adjuvant chemotherapy. Acta Med Philipp. 2015;49:26–31.
11. Zeuner A, Signore M, Martinetti D, Bartucci M, Peschle C, De Maria R. Chemotherapy-induced thrombocytopenia derives from the selective death of megakaryocyte progenitors and can be rescued by stem cell factor. Cancer Res. 2007;67:4767–73.
12. NCI-CTC version 2 available from https://www.ncbi.nlm.nih.gov.
13. Leonard RCF, Miles D, Thomas R, Nussey F. Impact of neutropenia on delivering planned adjuvant chemotherapy: UK audit of primary breast cancer patients. Br J Cancer. 2003;89:2062–68.
14. Funakoshi T, Latif A GM. Risk of hematologic toxicities in cancer patients treated with sunitinib: a systematic review and meta-analysis. Cancer Treat Rev. 2013;39:818–30.

15. Chan A, Chen C, Chiang J, Tan SH, Ng R. Incidence of febrile neutropenia among early-stage breast cancer patients receiving anthracycline-based chemotherapy. Support Care Cancer [Internet]. 2012;20:1525–32. Available from: https://doi.org/10.1007/s00520-011-1241-6
16. Schwenkglenks M, Pettengell R, Jackisch C, Paridaens R, Constenla M, Bosly A, et al. Risk factors for chemotherapy-induced neutropenia occurrence in breast cancer patients: data from the INC-EU Prospective Observational European Neutropenia Study. Support Care Cancer [Internet]. 2011;19:483–90. Available from: https://doi.org/10.1007/s00520-010-0840-y.
17. V Caggiano, S Gupta RT. Chemotherapy-induced anemia in early-stage breast cancer. J Oncol Pharm Pr. 2001;7:1–6.
18. Pourali L, Taghizadeh A, Akhoundi MR, Varshoei F, Zarifian A, Andalibi MSS. Frequency of chemotherapy induced anemia in breast cancer patients. Int J Cancer Manag. 2017;10.