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# Myelotoxicity of Cyclophosphamide, Methotrexate and 5-fluorouracil Regimen in the Early Stage Breast Cancer Patients with Diabetes Mellitus

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## ABSTRACT

CMF (cyclophosphamide, methotrexate and 5-fluorouracil) is one of the most commonly used chemotherapy (CT) regimens in breast cancer. To the best of our knowledge there are no published studies on the toxicity of this regimen in the existence of diabetes mellitus (DM), in the literature. We retrospectively analyzed the myelotoxicity of CMF CT after 40 adjuvant cycles of 18 diabetics, according to WHO toxicity scale. Leucopenia/granulocytopenia was the most prominent toxicity (observed in overall 30% of the cycles), but it was relatively mild (5% grade III and 2.5% grade IV granulocytopenia). Anemia was only grade I (10% of the cycles), and there was no thrombocytopenia. Two of the cases with grade III and IV granulocytopenia, had grade I and II urinary tract infections respectively, following the CT. The case with grade IV granulocytopenia and infection had received G-CSF. We conclude that CMF regimen is tolerable in DM as regard to its myelotoxicity. However, the patients should be closely monitored as infections may easily arise in parallel to deepening leucopenia in DM. Further extended studies would be appropriate on the toxicity of CMF as well as the other common CT regimens in DM.

**Key Words:** Breast cancer, Diabetes mellitus, CMF, Chemotherapy, Myelotoxicity, Infection.

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## INTRODUCTION

Breast cancer is the most common neoplasm in women and CMF (cyclophosphamide, methotrexate and 5-fluorouracil) is one of the most commonly used chemotherapy (CT) regimens in breast cancer<sup>[1,2]</sup>. Although the toxicity of this regimen has been well studied in the literature, to the best of our knowledge there are no published reports on its myelotoxicity in the existence of DM, yet<sup>[3]</sup>. Diabetes mellitus (DM) is a significant health problem with several potential immunological abnormalities and also a common comorbid disease in cancer patients<sup>[4]</sup>. So, we analyzed the myelotoxicity of adjuvant CMF CT in patients with breast cancer and DM.

## PATIENTS and METHODS

The registries of the diabetic, histopathologically confirmed early stage breast cancer cases who had received standard adjuvant CMF (cyclophosphamide 600 mg/m<sup>2</sup>, methotrexate 40 mg/m<sup>2</sup> and 5-fluorouracil 600 mg/m<sup>2</sup> intravenously on days 1 and 8 of every 28 days) CT regimen were analyzed retrospectively. The exclusion criterias were; age over 65 years, distant metastases, other comorbid diseases, concomitant radiothe-

rapy and medications to interfere with the myelotoxicity of the CMF regimen, and insufficient registries. The CMF CT cycles with modifications (such as dose reduction) in the regimen were also excluded during the analyzes. Forty CT cycles of 18 diabetic cases were identified as eligible for the study. All the cases had non-insulin dependent DM. Ten cases were under oral antidiabetic treatment while 8 were only under dietary control. The pretreatment and nadir (median 15<sup>th</sup> day of the CT) complete blood counts were analyzed by GENS Analyzer (S/WARE KIT N/A, Coulter GEN-S, Nokia Mikro Emission 447 L, Coulter corporation Hialeah, FL.), and the peripheric blood smears. The myelotoxicity of the regimen was graded according to WHO CT toxicity grading scala (Table I). Also the infection episodes and the usage of granulocyte colony stimulating factor (G-CSF) were examined.

## RESULTS

The hematological toxicity of CMF regimen, in diabetic early stage breast cancer patients (median age, 44 years, range: 33-57 years) is shown in Table 2. Leucopenia/granulocytopenia was the most prominent toxi-

Table 1. WHO grading for myelotoxicity

Grade	0	I	II	III	IV
Hemoglobin*	≥ 11.0	9.5-10.9	8.0-9.4	6.5-7.9	< 6.5
Leucocyte**	≥ 4.0	3.0-3.9	2.0-2.9	1.0-1.9	< 1.0
Granulocyte**	≥ 2.0	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
Trombocyte**	≥ 100	75-99	50-74	25-49	< 25

\*g/dL, \*\*x 1000/mm<sup>3</sup>

Table 2. The myelotoxicity of CMF regimen in diabetic breast cancer patients\*

Grade	0	I	II	III	IV
Hemoglobin	36 (90%)	4 (10%)	0 (0%)	0 (0%)	0 (0%)
Leucocyte	28 (70%)	6 (15%)	3 (7.5%)	3 (7.5%)	0 (0%)
Granulocyte	28 (70%)	6 (15%)	3 (7.5%)	2 (5%)	1 (2.5%)
Trombocyte	40 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

\*The number (and the per centage) of the cycles resulted with the related toxicity grade.

city (observed in overall 30% of the cycles), but it was relatively mild (5% grade III and 2.5% grade IV granulocytopenia). Anemia was only grade I (10% of the cycles), and there was no trombocytopenia.

Two women with grade III and IV granulocytopenia had urinary tract infections following the CT. The severity of the infections were grade I (mild) and grade II (moderate) in these cases, respectively. Both infections were cured with antibiotics. The case with grade IV granulocytopenia and infection had received G-CSF.

## DISCUSSION

CMF is a widely used CT regimen in the treatment of breast cancer. Although the toxicity of this regimen has been well studied, to the best of our knowledge there are no published reports on its myelotoxicity in the existence of DM in the literature<sup>[3]</sup>. In this study we examined the myelotoxicity of CMF regimen in DM.

Leucopenia/granulocytopenia was the most frequent and highest graded toxicity in the studied diabetic patients. Leucopenia, has also been reported as the most common toxicity of this regimen in the literature<sup>[1,2,5]</sup> and cyclophosphamide had been mainly accused for leucopenia<sup>[6]</sup>. Anemia was mild and trombocytopenia was not observed in our cases. Fleming et al. had reported that the cancer patients with DM had more toxicity and higher plasma drug levels after 5-fluorouracil CT<sup>[7]</sup>. Overall the myelotoxicity was not so prominent in our study.

High grade myelotoxicities and/or infections after CT, sometimes necessitate modifications such as time delays, and/or dose reductions in the treatment of the patients<sup>[3]</sup>. This was so for the case with grade IV granulocytopenia and infection following the CT in our study. G-CSF was used routinely in the following CT cycles of this patient.

Immunodeficiency has been reported to accompany DM with various pathogenetic

mechanisms<sup>[4]</sup>. Delamaire et al. had reported alterations in the adherence chemotaxis, phagocytosis and the bactericidal activities of the polymorphonuclear leucocytes, while Jakelic et al. had revealed lower index of phagocytosis, and a significant correlation in-between the phagocytic activity of the leucocytes and the mean blood glucose levels in DM<sup>[8,9]</sup>. Rayfield et al. had reported more susceptibility to infections in DM than the normal controls<sup>[10]</sup>. Grade I (mild) and II (moderate) urinary tract infections were observed after 2 (5%) cycles in our study. Both cases had high graded leucopenia/granulocytopenia and G-CSF was used in the case with grade IV granulocytopenia. This high frequency of infections in leucopenia might be related to the immune abnormalities and the tendency to urinary tract infections in DM. We used to care more on the common sources of infections and especially the urinary system in the diabetic cases in the pre-CT evaluations, after this experience.

So we conclude that CMF is a tolerable regimen in DM as regard to its myelotoxicity. However the cases should be closely monitored as infections may easily arise in parallel to deepening leucopenia/granulocytopenia. This was the first study on the myelotoxicity of the CMF regimen in DM. Further extended studies would be appropriate on the toxicity of CMF as well as the other common CT regimens in DM.

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