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ANALYSIS OF IMPLICATION OF AGE ON CARDIO TOXICITY IN PATIENTS TREATED WITH 5FU/LV IN BREAST CANCER PATIENTS

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Abstract:

Introduction: *Fluoropyrimidine chemotherapy [5-fluorouracil [5-FU] and the prodrug capecitabine] are the cornerstone drugs in the treatment of gastrointestinal [GI], breast, and other solid malignancies.*

Aims and objectives: *The basic aim of the study is to analyse the implication of demographic values on cardio toxicity in patients treated with 5FU/LV in breast cancer patients.*

Material and methods: *This clinical study was conducted in King Edward Medical University, Lahore during January 2018 to July 2019. This study was done with the permission of ethical committee of hospital. The data was collected from 50 patients of breast cancer. These evaluable patients [median age 55] were treated with high dose leucovorin regimen of 5-FU and fifteen patients included in the study, were subjected to low dose leucovorin regimen of 5-FU chemotherapy.*

Results: *The data was collected from 50 patients of breast cancer. Less well described is the chest pain associated with continuous infusion 5-FU. Chest pain associated with continuous infusion may also occur with the first or second chemotherapy cycle, typically between 24–72 hours after infusion initiation. The pain may be atypical compared to classical angina, i.e., occurring at rest, resolving spontaneously. Symptoms may also recur cyclically during the infusion and persist following infusion completion. Many patients find these symptoms tolerable and complete the planned infusion course.*

Conclusion: *It is concluded that cardio toxic potential is verified in both the treatment schedules of infusional and bolus 5-FU with high and low dose leucovorin implying varying attributes.*

Key words: *Cancer, Infusion, Symptoms, Leucovorin*

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INTRODUCTION:

Fluoropyrimidine chemotherapy [5-fluorouracil [5-FU] and the prodrug capecitabine] are the cornerstone drugs in the treatment of gastrointestinal [GI], breast, and other solid malignancies. Their use and effectiveness has been limited by hematologic and systemic toxicity [1]. Among the latter, a spectrum of cardiac toxicity occurs, ranging from coronary ischemia, systolic left ventricular dysfunction, arrhythmias and sudden death with an incidence ranging from 1–18%. Higher risk may be associated with longer duration infusions, pre-existing coronary artery disease [CAD], pre-treatment structural heart disease, chronic kidney disease [CKD], concurrent cisplatin chemotherapy and prior chest radiation [2]. In spite of these risk factors, most cardiac toxicity occurs in patients without concurrent chemotherapy or structural heart disease. Aside from the acute cardiovascular risk, fluoropyrimidine cardiac toxicity has resulted in early treatment termination with the potential for under treatment of the cancer and negative impact on survival [3].

Although fluoropyrimidine cardiotoxicity is a well-known phenomenon, there is still debate regarding mechanism of action of the drug, variations in clinical presentation of the cardiotoxicity, and the ability to identify the high-risk patient [4]. The most accepted mechanism for fluoropyrimidine-induced cardiac toxicity is coronary vasospasm leading to ischemia. Moreover, the most common cardiac symptom is chest pain with or without transient electrocardiogram [ECG] changes [5].

Silent ischemia has also been reported [ECG changes without chest pain] and continuous ECG monitoring studies suggest that up to 2/3 of patients may have silent ischemia during therapy. The risk of cardiac toxicity due to cancer chemotherapeutic drugs is an increasing area of concern; as such an adverse reaction may directly alter the morbidity rate and the quality of life of the patients subjected to it [6]. Cardiac toxicity is usually observed as a delayed effect in most of the patients whereas in many others it is reported as an acute reaction, also in few cases, the risk of cardiac diseases may pose a greater threat than the recurrence of cancer itself [7].

Aims and objectives:

The basic aim of the study is to analyse the implication of demographic values on cardio toxicity in patients treated with 5FU/LV in breast cancer patients.

MATERIAL AND METHODS:

This clinical study was conducted in King Edward Medical University, Lahore during January 2018 to July 2019. This study was done with the permission of ethical committee of hospital.

Data collection:

The data was collected from 50 patients of breast cancer. These evaluable patients [median age 55] were treated with high dose leucovorin regimen of 5-FU and fifteen patients included in the study, were subjected to low dose leucovorin regimen of 5-FU chemotherapy. Toxicological screenings of the cardiac profiles were attained for the patients diagnosed with advanced carcinoma subjected to chemotherapy with 5-FU and leucovorin. The changes in blood pressure, heart rate, LDL levels and cardiac enzymes were noted throughout the six cycles of chemotherapy in each patient. The data obtained from patients without any history of cardiac diseases was compared to the data of the group of patients with a history of previous cardiac diseases. The elevation in the levels of cardiac enzymes up to 2-fold, required monitoring of the patients in the coronary care unit for 36-72 hrs, whereas, in case of acute toxicities like MI and angina, the chemotherapy with 5- FU was terminated.

Cardiac analysis:

After each cycle, the LDL, glucose, CK and GOT levels were estimated by blood tests. LDL and glucose levels were measured by blood drawn early in the morning to ensure 12 hrs fasting time. Blood pressure was measured every 8' and pulse rate was measured every 8'during the first and second infusion of each cycle and before and after each subsequent administration and the mean values were calculated.

Statistical analysis:

The data was analyzed by SPSS version 20.0. Analysis of the comparative data of the two treatment arms and different groups within the same treatment arm is made by Independent samples test.

RESULTS:

The data was collected from 50 patients of breast cancer. Less well described is the chest pain associated with continuous infusion 5-FU. Chest pain associated with continuous infusion may also occur with the first or second chemotherapy cycle, typically between 24–72 hours after infusion initiation. The pain may be atypical compared to classical angina, i.e., occurring at rest, resolving spontaneously. Symptoms may also recur cyclically during the infusion and persist following infusion completion. Many patients find these symptoms tolerable and complete the planned infusion course.

Table 1: Cardiotoxicity associated with intravenous 5-FU chemotherapy

Infusion type	Chest pain characteristic	Chest pain presentation	Time to symptoms	ECG at presentation
Bolus infusion	Classical angina	Acute coronary syndrome	First cycle	ST segment elevation
			During or Immediately After Administration	
Continuous infusion	Atypical chest pain	Intermittent and recurrent	24–72 hours after infusion initiation	Usually normal

The means of all markers were significantly higher in CP and cancer patients [p < 0.01] than the healthy controls. Moreover, the level of these markers in the cancer group was higher than CP patients except for Hs-CRP and P-selectin. Although healthy controls demonstrated the lowest level of the markers among the three groups, their LDH and NT pro-BNP levels did not fall in the normal range. In fact, the level of NT pro-BNP in all three groups was lower than the normal range.

Table 02: Expression level [Mean ± SE] of inflammatory and cardiac markers

Cardiac Markers	Groups	Mean values	Normal Range & Unit
	1	305[±4.644]	
LDH	2	485[±11.272]*	240-480 U/L
	3	678[±33.989]*	
	1	1.03[±0.041]	
Troponin T	2	10.47[±0.407]*	< 10 ng/ml
	3	18.10[±0.910]*	
	1	0.19[±0.007]	
Troponin I	2	1.88[±0.073]*	0-2.0 ng/ml
	3	3.44[±0.173]*	
	1	82.97[±1.040]	
NT pro-BNP	2	115.77[±1.002]*	140-320 pg/ml
	3	148.55[±1.650]*	
	1	0.39[±0.004]	
P-selectin	2	1.23[±0.051]*	0.6-10 ng/ml
	3	0.91[±0.008]*	
High sensitive	1	0.51[±0.030]	
C-reactive	2	2.82[±0.166]*	< 5 mg/L

DISCUSSION:

The relative incidence of toxic effects of 5-FU is directly related to the age of the patients which can serve as independent predictor of severe toxicity. It is hence difficult to adjust the dose in older patients, keeping in view the organ function status, comorbidities, overall physical status and goals of treatment [8]. Zalcberg et al. reported that "Grade 3/4 leucopenia and mucositis were significantly correlated with age. High blood pressure is a common comorbidity in cancer patients directly affecting the prognosis, which may lead to cardiac diseases in long term cancer survivors and hence the risk of cardiac disease in such patients is higher than the recurrence of cancer itself [9].

The fluoropyrimidines continue to be the cornerstone drug in the treatment of GI and other solid tumor malignancies. Treatment induced chest pain may lead to discontinuation of effective and potentially curable chemotherapy. There is no universally accepted approach to rechallenge once cardiac chest pain is suspected and/or documented [10].

Several alternative strategies have been reported that include chemotherapy without fluoropyrimidines, dose reduction, switching from infusional to bolus regimen and the addition of cardio-protective, anti-spasm medication. All prior reports have major limitations in size and approach [11]. Most are non-randomized retrospective, often single patient reports or small series with incomplete data. There has been no consistency to treatment with various combinations of medications and dosing. All have shown inconsistent and mixed results except for the largest successful case series reported by Ambrosy et al [12].

CONCLUSION:

It is concluded that cardio toxic potential is verified in both the treatment schedules of infusional and bolus 5-FU with high and low dose leucovorin implying varying attributes. Careful assessment and monitoring protocol for chemotherapy induced cardio toxicity e.g. angina, IHD, arrhythmias and pericardial diseases should be designed and specially tailored for each therapeutic regimen.

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