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ORIGINAL ARTICLE

IMPLICATION OF AGE AND GENDER ON CARDIO TOXICITY IN PATIENTS TREATED WITH TWO SCHEDULES OF 5FU/LV

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ABSTRACT:

Cardio toxicity induced by chemotherapeutic agents can interfere with the cumulative therapeutic benefit and debilitate the elderly with a comorbid burden. The cardio toxic potential of 5-FU based chemotherapy is known, however the specific risk in elderly patients is yet to be defined. The gender specific risk of toxicity induced by chemotherapeutic agents has been a wide area of debate. This prospective clinical study is designed to assess the cardio toxicity in patients treated with two schedules of 5-FU with high and low dose leucovorin. The cardiac markers, blood pressure, glucose levels and pulse rate of the patients were monitored to suggest any toxicity imparted by chemotherapy. The comparative assessment was made according to gender and age group of the patients. Significant risk of drug induced hypertension was seen in few patients of age below 60 years. The risk of cardio toxicity was not significant in either gender; however substantial risk of cardio toxicity in few elderly patients exacerbated as anginal pain was reported.

Keywords: Age, cardio toxicity, gender, 5FU.

INTRODUCTION

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. 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 (Shultz *et al.,* 2003). The intensity of cardiac adverse effects is modulated by factors such as the molecular site of action, the immediate and cumulative dose, the mode and method of administration, the presence of any underlying cardiac condition or disease, the demographic features of the patient and the choice of the antineoplastic agents (Yeh *et al.,* 2004). The different schedule (bolus or infusion) of administration may also alter the overall incidence of cardio toxicity. Several cases of cardiac toxicity due to 5-Fluorouracil (5-FU) chemotherapy is reported earlier (Collins *et al.,* 1987, Soukop *et al.,* 1978, Roth *et al.,* 1975). These adverse cardiac manifestations of 5FU are reported as angina, myocardial infarction (MI), congestive heart failure (CHF), ventricular tachycardia, Supraventricular tachycardia, reversible cardiomyopathy and sudden death (Gradishar et al 1990). The toxicity of antineoplastic chemotherapy is exacerbated in elderly patients due to altered pharmacokinetics associated with enhanced susceptibility of the

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tissues and organs to injury induced by cytotoxic agents (Balducci *et al.,* 1997). A decline in the glomerular filtration rate (GFR) is frequently associated with aging (Balducci *et al.,* 2000a), that may interfere with the elimination of 5-FU (Bernadou *et al.,* 1985) from the body and thus enhances its toxicity in elderly patients. Earlier studies reported the pharmacological changes due to old age, which increases the susceptibility of cardiotoxicity in patients subjected to chemotherapy (Balducci *et al.,* 2000b). Age may also have adverse effects on hepatic metabolism (Balducci *et al.,* 2000c), which in turn plays a role in augmented toxicity, since the hepatic metabolism serves as the main determinant of the pharmacokinetics of 5-FU (Tateishi *et al.,* 1999). The present study is designed to assess the comparative risk of cardio toxicity in elderly patients subjected to two schedules of 5-fluorouracil based chemotherapy with high and low dose Leucovorin. Similar to age, gender also implicates the toxicity of chemotherapeutic agents in certain ways and may serve as a predictive factor of non-hematological toxicity of 5-Fluorouracil based chemotherapy (Meta-Analysis Group in Cancer 1998).Sloan *et al.,* reported that women receiving 5-FU based chemotherapy experience more frequent and severe toxicity suggesting that this may be due to profound pharmacological differences in 5FU metabolism and clearance across sexes (Sloan *et al.,* 2002).

METHODS

The prospective clinical study was designed at University of Karachi and conducted in a leading cancer hospital of Karachi, following institutional approval, on selected patients admitted during 2006-2011.Fifty patients clinically diagnosed with advanced colorectal carcinoma were recruited initially; however, forty five patients were evaluable by the end of the planned study. Three patients did not continue the therapy and two patients died during the treatment due to complications of advanced disease. Thirty evaluable patients (median age 64) were treated with High dose leucovorin regimen of 5-FU (Treatment Arm A-de Gramont regimen) and fifteen patients (median age 63) included in the study, were subjected to low dose leucovorin regimen of 5-FU chemotherapy (Treatment Arm B–Mayo clinic regimen). Informed consent was taken from each patient before the conduct of study. The patients were divided into two groups, 'patients of age above 60 years' and 'patients of age below 60 years' for comparative analysis. The chemotherapeutic protocol in each treatment arm was as follows:

Treatment Arm A:

5-Fluorouracil _ Leucovorin (de Gramont Regimen)

5-Fluorouracil: 400 mg/m^2 IV (5 min) and then

600 mg/m^2 IV for 22 hours on days 1 and 2 (Concentration 50 mg/ml, further diluted with 0.9% sodium chloride or D5W)

Leucovorin: 200 mg/m^2 IV on days 1 and 2 as a 2-hour infusion before 5-Fluorouracil (Powder/Solution reconstituted with sterile water, further diluted with NS or D5W.)

Day 3: Discontinue pump.

Chair time 3 hours on day's 1 and 2, and 15 minutes day 3. Repeat cycle every 2 weeks.1, 131

Treatment Arm B:

Fluorouracil (5 - FU)/leucovorin (External Radiotherapy as Adjuvant Therapy) (Low dose leucovorin)

5-FU..... 425 mg / m^2IV bolus days 1-5

Leucovorin..... 20 mg / m^2IV bolus days 1–5

above is given for 1 cycle postoperatively, followed by

5-FU..... 425 mg / m^2 IV bolus days 1-4, 38–40

Leucovorin..... 20 mg / m^2 IV bolus days 1-4, 38–40

Above is given concurrently with XRT to 4500 cGy in 180 cGy fractions

Chemotherapy is given on first 4 and last 3 days of radiotherapy

5-FU.....425 mg / m^2 IV bolus days 1–5

Leucovorin.....20 mg / m^2 IV bolus days 1–5

above portion of regimen is repeated every 28 days for 2 cycles post - concurrent therapy

After each alternate cycle of treatment, 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'(8 hours). Pulse rate was measured every 8'during the first and second infusion of each alternate cycle before and after each subsequent administration and the mean values were calculated from consolidated data of three cycles in each case. Anginal pain reported by the patient was assessed clinically, treatment was ceased upon suspected risk of cardio toxicity and the patient was relieved with nitroglycerines. False anginal pain was categorized as pain with indefinite characteristics.

STATISTICAL ANALYSIS

The data was analyzed by SPSS version19. The implications of different factors (Age/Gender) on the toxic parameters are compared between the two treatment arms (de Gramont and Mayo clinic regimens) by Pearson Chi Square tests, *p* value less than 0.05 is considered significant.

RESULTS AND DISCUSSION

The frequency of Anginal pain and the report of symptoms of anxiety, distress and palpitations according to the gender difference are shown in Figure 1 for Treatment Arm A and Figure 2 for Treatment Arm B.

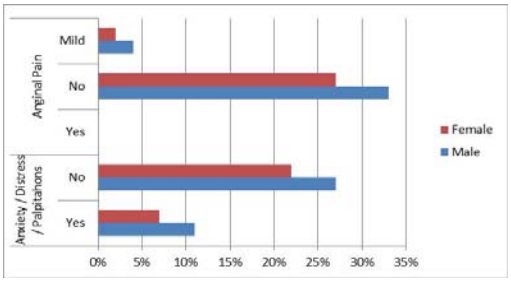

Fig. 1. Degree of Anginal pain & Discomfort-Gender, Treatment Arm A

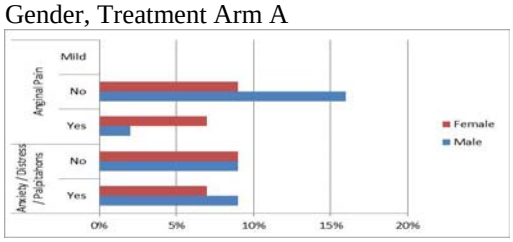

Fig. 2. Degree of Anginal pain & Discomfort - Gender, Treatment Arm B

The elevated levels of cardiac markers (CPK, GOT, LDL) and vital signs (Blood pressure/pulse rate) in the male and female patients of Treatment Arm A and Treatment Arm B is demonstrated in Figure 3 and Figure 4 respectively.

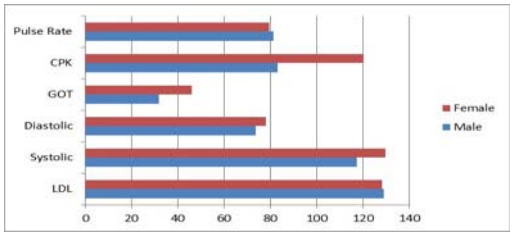

Fig. 3. Cardiac markers & Vital signs - Gender, Treatment arm A

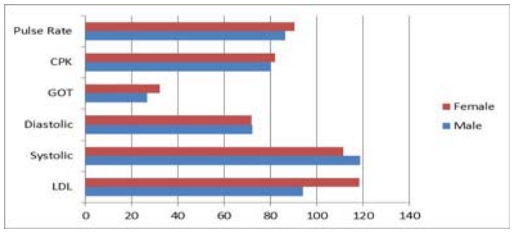

Fig. 4. Cardiac markers & Vital signs-Gender, Treatment Arm B

The frequency of Anginal pain and the report of symptoms of anxiety, distress and palpitations with respect to age difference (above and below 60) are shown in Figure 5 for Treatment Arm A and Figure 6 for Treatment Arm B.

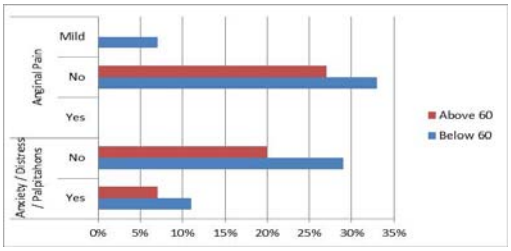

Fig. 5. Degree of Anginal pain & Discomfort-Age, Treatment Arm A

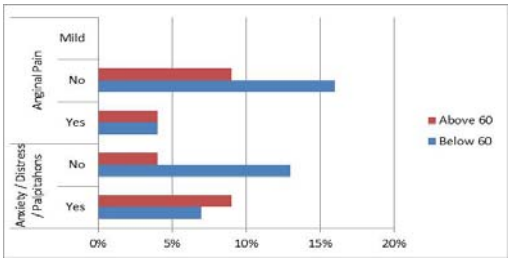

Fig. 6. Degree of Anginal pain & Discomfort-Age, Treatment Arm B

The elevated levels of cardiac markers (CPK, GOT, LDL) and vital signs (Blood pressure/pulse rate) in patients above and below 60 years of age in Treatment Arm A and Treatment Arm B is demonstrated in Figure 7 and Figure 8 respectively.

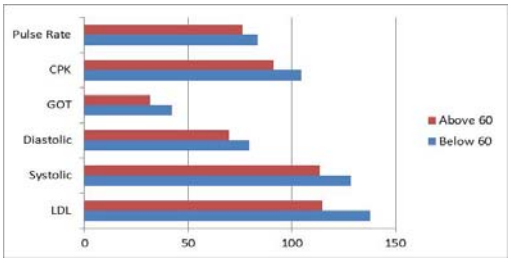

Fig. 7. Cardiac markers & Vital signs – Age, Treatment Arm A

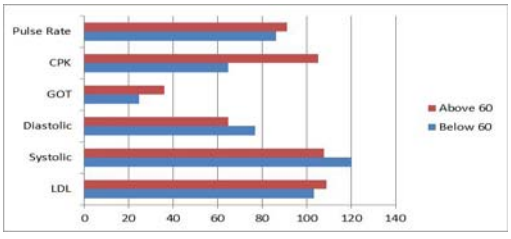

Fig. 8. Cardiac markers & Vital signs-Age, Treatment arm B

The frequency of symptoms indicative of cardiac deficiency in the patients of Treatment Arm A and B, categorized on gender bias is shown in Table 1.The frequency of symptoms of cardiac insufficiency evaluated in the same group of patients categorized with respect to age groups beyond and below 60 years is shown in Table 2.The effect of gender difference however, on the incidence rate of anxiety is not significant in either Treatment Arm A or Treatment Arm B. The onset of anginal pain, changes in glucose levels and blood pressure in patients of Treatment Arm A and Treatment Arm B is also not significantly related to gender or age difference. The LDL levels measured in the patients of Treatment Arm A between male and female patients is statistically significant (p=0.02). The difference in the LDL levels of male and female patients of Treatment Arm B is not significant.

In our study we analyzed the effect of gender differences on the parameters of cardiac toxicity in each treatment group. Varying degrees of anxiety, distress and palpitations is reported during our study in few patients receiving 5-FU based chemotherapy. The gender implications, however, in the report and severity of these symptoms is not significant in either treatment arm A (p=0.697) or Treatment Arm B (p=0.782).In case of Treatment arm A these symptoms were reported in 5 men and 3 women patients, whereas in Treatment arm B, the symptoms were experienced by 4 men and 3 women. Mild anginal pain is reported in 2 men and 1 women during chemotherapy in treatment arm A and the difference between the incidence of anginal pain in men and women is non-significant (p=0.713). In case of treatment arm B, anginal pain is reported in 8 men and 7 women patients during chemotherapy and again the difference of the gender on the rate of incidence of the symptom is non-significant (p=0.185). The LDL levels were measured at different stages of chemotherapy throughout the course. In patients subjected to Treatment arm A, the difference in the LDL levels of the male and female patients is significant(p=0.02)

Table 1
Implication of Gender on Cardiac Risk Parameters

Parameters		Treatment Arm A					Treatment Arm B				
		Male	Female	Total	Chi-Square	Sig Value	Male	Female	Total	Chi-Square	Sig Value
Anxiety	Yes	5	3	8	0.151	0.697	4	3	7	0.077	0.782
	No	12	10	22			4	4	8		
	Total	17	13	30			8	7	15		
Anginal Pain	Yes	-	-	-	0.136	0.713	1	3	4	1.759	0.185
	No	15	12	27			7	4	11		
	Mild	2	1	3			-	-	-		
	Total	17	13	30			8	7	15		
LDL Level	Optimal	4	5	9	11.448	0.022	5	2	7	3.367	0.186
	Near & above optimal	6	0	6			2	1	3		
	Borderline High	2	6	8			1	4	5		
	High	5	1	6			-	-	-		
	Very High	0	1	1			-	-	-		
	Total	17	13	30			8	7	15		
Glucose Level	Normal Fasting Glucose	6	7	13	1.038	0.595	6	2	8	4.152	0.125
	Impaired Fasting Glucose (Pre-Diabetes)	2	1	3			0	2	2		
	Occasion Diabetes	9	5	14			2	3	5		
	Total	17	13	30			8	7	15		
B.P.	Normal	7	2	9	5.970	0.201	4	3	7	2.755	0.252
	Prehyper tension	5	7	12			2	4	6		
	High Blood Pressure - Stage 1	5	2	7			2	0	2		
	High Blood Pressure - Stage 2	0	1	1			-	-	-		
	Hypertensive Crisis	0	1	1			-	-	-		
	Total	17	13	30			8	7	15		

Table 2
Implication of Age on Cardiac Risk Parameters

Parameters		Treatment Arm A					Treatment Arm B				
		<60	>60	Total	Chi-Square	Sig Value	<60	>60	Total	Chi-Square	Sig Value
Anxiety	Yes	5	3	8	0.028	0.866	3	4	7	1.607	0.205
	No	13	9	22			6	2	8		
	Total	18	12	30			9	6	15		
Anginal Pain	Yes				2.222	0.138	2	2	4	0.227	0.634
	No	15	12	27			7	4	11		
	Mild	3	0	3			-	-	-		
	Total	18	12	30			9	6	15		
LDL Level	Optimal	4	5	9	5.984	0.200	4	3	7	0.079	0.961
	Near & above optimal	2	4	6			2	1	3		
	Borderline High	7	1	8			3	2	5		
	High	4	2	6			-	-	-		
	Very High	1	0	1			-	-	-		
	Total	18	12	30			9	6	15		
Glucose Level	Normal Fasting Glucose	7	6	13	0.368	0.832	4	4	8	1.667	0.435
	Impaired Fasting Glucose (Pre-Diabetes)	2	1	3			2	0	2		
	Occasion Diabetes	9	5	14			3	2	5		
	Total	18	12	30			9	6	15		
B.P.	Normal	4	5	9	8.588	0.072	3	4	7	2.302	0.316
	Prehyper tension	5	7	12			4	2	6		
	High Blood Pressure - Stage 1	7	0	7			2	0	2		
	High Blood Pressure - Stage 2	1	0	1			-	-	-		
	Hypertensive Crisis	1	0	1			-	-	-		
	Total	18	12	30			9	6	15		

The incidence of elevated Serum LDL levels and the ranges of the LDL levels in the male and female population is shown in the Table 1.The levels of LDL measured in males and female patients in treatment arm B is not significant (p=0.186). The changes in the serum glucose levels in the male and female patients of either treatment arm A (p=0.595) or treatment Arm B (p=0.125) is not significant. The male and female patients are categorized according to the blood pressure ranges in Table 1.The statistical interpretation of the data shows that the gender does not significantly affect the blood pressure changes due to chemotherapy in either treatment arm, (Treatment Arm A (p=0.201), Treatment Arm B(p=0.252)). Chansky *et al.* reported that the incidence and severity of 5-FU toxicity is different among men and women diagnosed with colorectal carcinoma, revealing that 5-FU toxicity is more severe in women than in men (Chansky *et al.,* 2005).John S. Macdonald stated that "Gender is a risk factor for 5-FU toxicity. Female patients have a statistically higher incidence of all 5-FU toxicities" (Macdonald *et al.,* 1999).It has been hypothesized that women are deficient in Dihydropyrimidine dehydrogenase, which play a major role in 5-FU catabolism (Milano *et al.,* 1999), whereas others report that Dihydropyrimidine dehydrogenase deficiency is a rare event (Etienne *et al.,* 1994).

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 (Stein *et al.,* 1995). Zalcberg *et al.* reported that "Grade 3/4 leucopenia and mucositis were significantly correlated with age (especially > 70 years) in patients receiving 5-FU+ LV" (Zalcberg et al 1998). The difference in the toxicity is attributed to the pharmacokinetic variability implicated by host factors such as age and gender affecting the clearance of 5-FU (Milano *et al.,* 1992). Mild degrees of anxiety, distress and palpitations was noted in eight out of thirty patients in Treatment Arm A. The difference in the rate of incidence of these symptoms in the patients in age group above 60 and below 60 is non-significant (p=0.866), implying that the frequency of these adverse effects is not affected by the age of the patients in Treatment Arm A. The symptoms of anxiety distress and palpitations were also reported in seven out of fifteen patients in Treatment Arm B, four patients of age group above 60 and three patients in age group below 60.The difference in the incidence of anxiety, distress and palpitations in the two age groups of patients in treatment arm B is not significant (p=0.205). Anginal pain has been reported many times in elderly patients subjected to 5-FU based chemotherapy (Lujan *et al.,* 2002, Cianci *et al.,* 2003). Mild anginal pain was reported in 3 patients of Treatment Arm A in age group less than 60 years, The difference in the relative incidence of these symptoms in patients above and below 60 years of age is not significant (p=0.138). In Treatment Arm B, Anginal pain was experienced by 2 patients above 60 years of age and 2 patients below 60 years of age. The difference in the rate of incidence of Angina in between the two age group of patients within treatment arm B is not significant (p=0.634). The distribution of the patients of age group above and below 60 years, according to the different LDL level is shown in Table 2. The difference in the LDL levels of the two age group of patients is non-significant in both the Treatment Arm A(p=0.200) and Treatment Arm B(p=0.961). Glucose levels were monitored in the patient throughout the course of chemotherapy. The difference in the glucose levels of the patients above and below 60 years of age is not significant in both the Treatment Arms A (p=0.832) & B (p=0.435). The patients of the two age groups are distributed according to the blood pressure ranges in different hypertensive groups in Table 2. Statistical analysis of the data shows that there is an positive relationship of hypertension with age and the difference in the blood pressure recorded in the patients above and below 60 years of age in Treatment Arm A is nearly significant (p=0.072), whereas the difference in the blood

pressure of the age groups in Treatment Arm B is not significant (p=0.316).

CONCLUSION

The cardio toxic potential is verified in both the treatment schedules of infusional and bolus 5-FU with high and low dose leucovorin affected variably by age and gender. Although the risk of cardio toxicity is similar in genders, 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 elderly patients.

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