Comparative cardiac toxicity in two treatment schedules of 5-FU/LV for colorectal carcinoma

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Abstract: The purpose of the study is evaluation and assessment of parameters of cardiac toxicity in patients subjected to 5-FU based chemotherapy. Cardiac morbidity is a reported outcome in different 5FU/LV regimens; however none of them are definite or proximate. The bimonthly regimen of high dose leucovorin is reported to be less toxic and more effective as compared to the monthly regimen of low dose leucovorin. We report the detailed assessment of few cardiac parameter of toxicity in patients of advanced colorectal carcinoma subjected to two Schedules of high and low dose Folinic Acid, 5-Fluorouracil, bolus and continuous infusion. The correlation of elevated cardiac biomarkers, angina and hypertension is comparatively assessed in patients with normal general status, hyperglycemia and known cardiac disorders subjected to two different 5FU based chemotherapeutic regimen.

Keywords: Colorectal Carcinoma, Cardiac Toxicity, 5-FU, CPK, GOT.

INTRODUCTION

Cardiac toxicity of cancer chemotherapeutic agents 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 chemotherapy. Some may conclude that the risk of cardiac diseases can pose a greater threat than the recurrence of cancer itself (Schultz *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 and 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 cardiac toxicity. The present study focuses on the cardiac toxic profile of 5-FU and leucovorin (high dose) in de Gramont's regimen and compares with 5-FU and leucovorin (low dose) adjunct radiation therapy. Low cardiac toxicity with de Gramont's regimen (3.9%) is reported in a previous study (Meydan *et al.,* 2005); however, the risk of cardiac toxicity in diabetic patients or patients with a history of cardiac diseases is yet to be defined. The risk of cardiac toxicity is greater in those patients who are burdened by old age and diabetes, both of which are risk factors for cardiac diseases and subsequent mortality (Kronmal *et al.,* 2006). "The adverse influence of diabetes extends to all components of the cardiovascular system: The microvasculature, the larger arteries, and the heart, as well as the kidneys" (Joint Editorial Statement by American Diabetes Association 1999), posing a threat of augmented cardiotoxicity in diabetic patients especially women and the elderly subjected to 5-FU based chemotherapy. Cardiac toxicity with 5-FU chemotherapy is manifested as angina, supraventricular tachycardia, ventricular tachycardia, congestive heart failure, reversible cardiomyopathy, myocardial infarction and sudden death. The frequently reported ischemic syndrome may be reversible after cessation of 5-FU therapy and prompt cardiac treatment. Although the precise etiology remains to be unknown, 5-FU can impart direct toxicity on the heart or produce an indirect effect by perturbation of the coagulation system (Gradishar *et al.,* 1990). The patients with underlying CAD (coronary artery disease) are prone to a greater risk of ischemic toxicity after treatment with 5-FU and hence it has been suggested that 5-FU cardio toxicity which may even be rare, has to be taken into account in oncologic practice, chiefly in those patients already affected with cardiac diseases (Labianca *et al.,* 1982).Coronary vasospasm related to 5-FU is a rare clinical entity in oncological practice and may be seen during both bolus and protracted infusion administration. This toxicity is generally reversible and responds well to conventional treatment for angina following discontinuation of infusion. Cardiac toxicity is evaluated and reported after 5-FU infusions, by cardiac enzymes lab monitoring, ECG reports and symptoms of angina (Roben *et al.,* 1993).The cardiac effects on the myocardium are largely schedule dependent, which requires that the cardiac status of the patients should be carefully monitored during the therapy (Kosmas *et al.,* 2008). Angina induced by 5-FU has also been documented as a rare toxic phenomenon, but in direct effect of 5-FU administration suggesting a dose dependent correlation for 5-FU and angina (Yokoyama *et al.,* 2002). It was also postulated that combination of 5-FU and leucovorin does not differ from single-agent therapy in frequency or type of cardio toxicity (Schöber *et al.,* 1993).

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METHODOLOGY

The prospective clinical study designed at University of Karachi was 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. 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 (angina, hypertension, CAD), and the group of patients who were diagnosed with diabetes associated with CAD or cardiac risk factors. With the report of the symptoms of cardiac toxicity, the chemotherapy was interrupted for prompt cardiac monitoring and the patients received sublingual nitrates. 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.

Patients and drugs

Patients diagnosed with colorectal carcinoma were labeled as follows:

- Normal patients (normal cardiac status and no cardiac risk factors)
- Cardiac patients (abnormal cardiac status/cardiac diseases and cardiac risk factors)
- Diabetic patients (hyperglycemia associated with hypertension, nicotine intake, hyperlipemia, history of coronary or peripheral artery disease)

Patients treated with two regimens (Treatment arm A & Treatment arm B) of 5-FU and leucovorin were selected and labeled as treatment group A and treatment group B respectively.

Treatment arm A- de Gramont's regimen

(Initiate IV: 0.9% sodium chloride, premedication: oral phenothiazine /5-HT_3RA and 10–20 mg dexamethasone on indication)

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

Day 3: discontinue pump.

Chair time 3 hours on day 1 and 2, and 15 minutes day 3.

Cycle repeated every 2 weeks.

Treatment Arm B - Mayo clinic regimen

(Initiate IV: 0.9% sodium chloride, Premedication: Oral phenothiazine or 5-HT_3RA)

5-Fluorouracil: 425 mg/m^2 IV (50 mg/ml, further diluted with 0.9% sodium chloride or D5W.)

1 hour after start of leucovorin, on days 1–5

Leucovorin: 20 mg/m^2 IV on days 1–5, administered before 5-Fluorouracil.

Chair time 1 hour, days 1–5. Nadir at day 14.

Cycle repeated every 4–5 weeks for a total six cycles. (28 days for 6 cycles).

Cardiac assessment

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 version19. Analysis of the comparative data of the two treatment arms and different groups within the same treatment arm is made by Independent samples test. The implications of different factors on the toxic parameters are compared between the two treatment arms by Pearson Chi Square tests, p value less than 0.05 is considered significant. p value less than 0.001 is considered very highly significant.

RESULTS

Most of the patients in either treatment arm had optimal level of LDL whereas some patients in treatment arm A had high level of LDL. The percentage of patients falling into different categories of LDL levels is shown in table 1. The comparative differences in LDL, B.P, cardiac enzymes and pulse rate of the patients in both the treatment arms above and below 60 years of age is shown in table 2. The implication of gender, age of the patient and history of cardiac and diabetic disease on the cardiotoxicity parameters of the patients in treatment arm A is shown in table 3 and of patients in treatment arm B is shown in table 4 respectively. The comparative cardiac

Table 1: LDL levels in treatment arm A and treatment arm B

		Treatment					
		Treatment A			Treatment B		
		Normal Patients	Cardiac Patients	Diabetic Patients	Normal Patients	Cardiac Patients	Diabetic Patients
LDL Level mg/dl	Optimal	53%	0%	0%	41%	0%	0%
	Near Optimal, Above Optimal	6%	11%	21%	0%	6%	11%
	Borderline High	0%	33%	26%	0%	22%	16%
	High	0%	22%	26%	0%	0%	0%
	Very High	0%	6%	0%	0%	0%	0%

Table 2: Cardiac parameters in age group above and below 60 years

Treatment A (Below 60 Age Group)						
	LDL (mg/dl)	B.P(mm of Hg)		Biomarkers(U/L)		Pulse Rate
		Systolic	Diastolic	GOT	CPK	
Normal Patients	91.71	105.22	65.25	18.57	60.54	72.49
Cardiac Patients	160.15	145.78	89.35	60.65	140.9	89.26
Diabetic Patients	147.40	127.17	81.35	39.15	119.2	84.31
Treatment A (Above 60 Age Group)						
	LDL (mg/dl)	B.P(mm of Hg)		Biomarkers(U/L)		Pulse Rate
		Systolic	Diastolic	GOT	CPK	
Normal Patients	85.56	103.52	64.61	21.71	60.55	75.00
Cardiac Patients	129.71	128.07	77.22	50.98	146.49	69.41
Diabetic Patients	150.45	122.02	75.52	41.21	128.29	77.53
Treatment B (Below 60 Age Group)						
	LDL (mg/dl)	B.P(mm of Hg)		Biomarkers(U/L)		Pulse Rate
		Systolic	Diastolic	GOT	CPK	
Normal Patients	71.53	115.67	78.12	19.19	60.88	81.59
Cardiac Patients	138.11	108.18	64.55	28.55	54.69	94.28
Diabetic Patients	122.06	134.10	83.55	28.63	76.21	86.81
Treatment B (Above 60 Age Group)						
	LDL (mg/dl)	B.P(mm of Hg)		Biomarkers(U/L)		Pulse Rate
		Systolic	Diastolic	GOT	CPK	
Normal Patients	78.98	109.52	59.17	22.02	52.22	82.96
Cardiac Patients	138.84	106.38	69.93	50.06	158.33	99.68
Diabetic Patients	145.50	110.73	72.22	51.22	152.22	98.39

toxicity in patient with previous cardiac disease and no cardiac disease is shown in table 5. Table 6 shows the comparative analysis of cardiotoxicity of the patients with and without a history of diabetes. The cardiac parameters are compared between normal patients and patients with previous cardiac/metabolic disorders in table 7. The comparative toxicity between treatment arm A and treatment arm B is shown comprehensively in table 8.

DISCUSSION

LDL levels

Our consolidated data shows that, LDL levels are low (less than 100 mg/dl) in patients of advanced carcinoma having no cardiac disease or diabetes (53% treatment arm A; 41% treatment arm B) (table 1). This may be in line with studies showing that the low LDL levels are associated with the risk of cancer although the relationship and the underlying mechanism remain controversial and elusive (Ding *et al.,* 2008). A prospective study by Yang and colleagues (2008) shows the lowest risk of cancer in patients with LDL cholesterol level (≥ 2.80 to < 3.80 mmol/L), whereas 50% greater risk of cancer was seen in patients with LDL cholesterol level above or below this range. A positive association was seen between high levels of LDL cholesterol and risk of cancer. On the other hand a large randomized Statin trial shows that the risk of cancer is significantly associated with lower achieved LDL-C levels and the cardiovascular benefits of low achieved levels of LDL-C may in part be offset by an increased risk of cancer (Al-Shiekh-Ali *et al.,* 2007).

About 33% of cardiac patients in treatment arm A and 22% of cardiac patients in treatment arm B have a borderline high level (130-159 mg/dl) of LDL cholesterol.

Table 3: Cardiac parameters within categorical distribution in treatment arm A

Treatment arm A									
		Gender		Age		Cardiac patients		Diabetic patients	
		Male	Female	Below 60	Above 60	Yes	No	Yes	No
LDL (mg/dl)		129.02	128.24	138.02	114.67	153.13	109.98	148.49	111.35
Systolic (mm of Hg)		117.2	129.57	128.71	113.33	141.69	107.93	125.33	120.14
Diastolic (mm of Hg)		73.66	78.01	79.37	69.81	86.55	67.14	79.27	72.3
GOT (U/L)		31.69	45.77	42.04	31.43	58.42	22.02	39.89	35.96
CPK (U/L)		82.98	120.29	104.4	91.28	142.25	66.19	122.45	78.76
Anxiety / Distress / Palpitations	Yes	11%	7%	11%	7%	13%	4%	13%	4%
	No	27%	22%	29%	20%	16%	33%	18%	31%
Anginal Pain	Yes	0%	0%	0%	0%	0%	0%	0%	0%
	No	33%	27%	33%	27%	22%	38%	24%	36%
	Mild	4%	2%	7%	0%	7%	0%	7%	0%

Table 4: Cardiac parameters within categorical distribution in treatment arm B

Treatment arm B									
		Gender		Age		Cardiac Patients		Diabetic Patients	
		Male	Female	Below 60	Above 60	Yes	No	Yes	No
LDL (mg/dl)		94.14	118.4	103.17	108.91	138.55	88.92	131.43	92.48
Systolic (mm of Hg)		118.66	111.39	120.14	107.95	107.1	119.35	124.75	110.52
Diastolic (mm of Hg)		72.12	71.79	76.91	64.55	67.78	74.06	79.02	68.45
GOT (U/L)		26.57	31.92	24.42	36.04	41.46	22.87	37.67	24.77
CPK (U/L)		80.01	81.87	64.61	105.28	116.87	62.88	106.61	68.01
Anxiety / distress / palpitations	Yes	9%	7%	7%	9%	7%	9%	4%	11%
	No	9%	9%	13%	4%	4%	13%	7%	11%
Anginal pain	Yes	2%	7%	4%	4%	7%	2%	7%	2%
	No	16%	9%	16%	9%	4%	20%	4%	20%
	Mild	0%	0%	0%	0%	0%	0%	0%	0%

High level of LDL cholesterol is shown only in the patients with cardiac disease/risk included in treatment arm A, (160-189 mg/dl) of LDL is measured in 22% of patients, whereas LDL levels more than 189 mg/dl are shown in 6% of patients (table 1). On the other hand, significantly low level of total cholesterol and LDL is reported in patients of colorectal carcinoma with coronary heart disease (Liang *et al.,* 2008). It is also reported earlier that the estimation of serum lipoproteins may have prognostic significance in colorectal adenomas as patients with colorectal adenomas have lower HDL cholesterol levels and higher LDL and VLDL cholesterol levels (Bayerdorffer *et al.,* 1993). Another study reports that the elevated serum lipid levels may facilitate the development of distant metastasis in colorectal carcinoma patients (Notarnicola *et al.,* 2005). The difference in the overall average percentage of LDL levels with age (above and below 60 years) for the normal, cardiac and diabetic patients is shown in table 2 for treatment arm A and treatment arm B. The LDL levels are raised slightly in diabetic patients of age above 60 years in both the treatment arms. The diabetic patients are prone to a greater risk of adverse reactions as the raised levels of LDL may pose a secondary threat, since it is understood that atherosclerosis causes most of the death and much of the disability in patients with diabetes (Beckman *et al.,* 2002). Table 3 shows that no significance difference in the LDL levels is seen in the male and female patients of treatment arm A. The results indicate that high LDL levels are more frequent in female patients of treatment arm B (table 4). Comparatively low LDL level is seen in patients above 60 years of age in both treatment arm A and treatment arm B. Statistical evaluation of the data by Independent samples test has shown that the difference in the LDL levels of the patients with and without cardiac disease is very highly significant ($p<0.001$) (table 5). Usually low level of serum lipoproteins such as LDL is seen in cancer patients as compared to non cancer patients (Alexopoulos *et al.,* 1987), hence the high level of LDL in cancer patients with cardiac disease may not be directly attributed to the cardiac toxicity imparted by chemotherapy, as the presence of cardiac disease as a clinical condition beforehand is significant.

Table 5: Comparative cardiac toxicity in patients with and without previous cardiac disease

Independent Samples Test - Cardiac Patients							
	Cardiac Patients	N	Mean	Std. Deviation	Mean Difference	t	Sig. (2-tailed)
Glucose (mg/dl)	Yes	18	117.357	41.286	12.699	1.148	0.257
	No	27	104.658	32.718			
LDL (mg/dl)	Yes	18	149.079	22.415	46.895	5.448	0.000
	No	27	102.184	31.544			
Systolic	Yes	18	132.080	25.067	19.917	3.050	0.004
	No	27	112.163	18.730			
Diastolic	Yes	18	81.335	14.243	11.634	2.836	0.007
	No	27	69.701	12.958			
GOT (U/L)	Yes	18	53.704	25.890	31.367	4.965	0.000
	No	27	22.337	8.507			
CPK (U/L)	Yes	18	135.200	72.251	70.236	3.815	0.000
	No	27	64.964	36.363			

Table 6: Comparative cardiac toxicity in patients with and without diabetes

Independent Samples Test - Diabetic Patients							
	Diabetic Patients	N	Mean	Std. Deviation	Mean Difference	t	Sig. (2-tailed)
Glucose (mg/dl)	Yes	19	148.064	16.209	66.334	14.237	0.000
	No	26	81.730	14.857			
LDL (U/L)	Yes	19	143.997	24.684	39.904	4.298	0.000
	No	26	104.093	34.476			
Systolic	Yes	19	125.177	24.348	8.736	1.245	0.220
	No	26	116.441	22.431			
Diastolic	Yes	19	79.199	13.054	8.385	1.975	0.055
	No	26	70.815	14.747			
GOT (U/L)	Yes	19	39.302	22.791	7.646	1.089	0.282
	No	26	31.656	23.589			
CPK (U/L)	Yes	19	118.282	76.782	43.656	2.221	0.035
	No	26	74.626	44.434			

Interesting is the statistical assessment of difference in LDL levels of diabetic and non diabetic patient (table 6) which is also very highly significant ($p<0.001$). The LDL level is raised in diabetic patients of colorectal carcinoma. The initial plot of data for treatment arms A & B show that, most of the diabetic patients had coexisting cardiac diseases, thus a clear picture is developed in table 7, the difference in LDL levels between normal (82.544 mg/dl) and diabetic/cardiac patients (144.255 mg/dl) of colorectal carcinoma ($p<0.001$). The difference in the LDL levels of patients in treatment arm A and treatment arm B is significant ($p=0.04$), as the risk of cardio toxicity seems higher in treatment arm A (table 8).

Blood pressure

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 (Jain *et al.,* 2002). It is observed that 5-FU treatment might cause transient, reversible diastolic dysfunction that develops with no symptoms even in patients without pre-existing heart diseases (Ceyhan *et al.,* 2004). The monitoring of blood pressure can indicate any risk or progression of any undesirable cardiac incidence. It is noted in our study that there are no reports of high blood pressure (stage 1 or 2) or hypertensive crisis in the patients without cardiac disease/diabetes (normal) subjected to treatment arm A and treatment arm B. In contrast to this, a prospective clinical study performed on 367 patients receiving high dose CIV infusional 5-FU reported cardiac events in 28 patients i.e. hypotension in (n=6) & hypertension (n=5) (Forni *et al.,* 2002).

It is noted in the patients with cardiac disease/risk, subjected to treatment arm A that blood pressure is raised beyond the normal limits in all of them. Blood pressure at pre-hypertensive stage was recorded in 28% of cardiac patients whereas 33% had stage 1 hypertension (systolic

Table 7: Comparative cardiac toxicity in patients with and without normal general status

Independent Samples Test - Normal Patients							
	Normal Patients	N	Mean	Std. Deviation	Mean Difference	T	Sig. (2-tailed)
Blood Sugar	Yes	17	81.899	14.713	-44.740	-5.895	0.000
	No	28	126.640	35.441			
LDL	Yes	17	82.544	11.707	-61.711	-11.497	0.000
	No	28	144.255	24.103			
Systolic	Yes	17	107.836	14.098	-19.757	-3.394	0.001
	No	28	127.593	24.928			
Diastolic	Yes	17	66.979	11.857	-11.853	-2.864	0.006
	No	28	78.833	14.325			
GOT	Yes	17	20.435	3.748	-23.222	-4.682	0.000
	No	28	43.657	25.801			
CPK	Yes	17	59.156	12.721	-54.485	-3.873	0.001
	No	28	113.641	72.626			

Table 8: Comparative cardiac toxicity in treatment arm A and treatment arm B

Treatment A Vs Treatment B							
Independent Samples Test							
	Treatment	N	Mean	Std. Deviation	Mean difference	t	Sig.(2-tailed)
Glucose (mg/dl)	Treatment A	30	112.310	38.748	7.718	0.665	0.510
	Treatment B	15	104.593	32.089			
LDL (mg/dl)	Treatment A	30	128.681	36.044	23.217	2.096	0.042
	Treatment B	15	105.464	32.839			
Systolic B.P	Treatment A	30	122.561	26.357	7.295	0.986	0.330
	Treatment B	15	115.266	15.605			
Diastolic B.P	Treatment A	30	75.548	15.051	3.579	0.776	0.442
	Treatment B	15	71.969	13.571			
GOT (U/L)	Treatment A	30	37.792	26.490	8.725	1.441	0.157
	Treatment B	15	29.067	14.122			
CPK (U/L)	Treatment A	30	99.148	66.747	18.269	0.911	0.368
	Treatment B	15	80.879	55.975			

140-159 / diastolic 90-99 mm of Hg). Stage 2 hypertension (systolic ≤160/ diastolic ≤100 mm of Hg) was seen in 6% of the patients with cardiac disease throughout the course of chemotherapy with high dose leucovorin and infusional 5-FU. A condition of hypertensive crises (systolic ≤180/diastolic ≤110 mm of Hg) developed in 6% of patients with history of cardiac disease which required the interruption of chemotherapy and provision of prompt emergency treatment. HTN can therefore be a significant risk factor in cardiac patients receiving high dose leucovorin and CIV 5-FU chemotherapy. It has been documented earlier that patients treated with 5-FU /LV for gastrointestinal cancer, with history of hypertension are prone to cardiac adverse effects such as heart failure and anginal pain with abnormal ECG changes (Tsibiribi *et al.,* 2006).

The patients subjected to low dose LV in treatment arm B with previous cardiac disease had no reports of hypertensive stage 1 & 2 or hypertensive crises, whereas only 11% of such patients had slightly elevated B.P. at pre-hypertensive stage, whereas 11% of patients with history of cardiac disease along with diabetes had reports of stage 1 hypertension, indicating therefore, the important aspect of 5-FU cardiotoxicity i.e. the role of preexisting risk factor. Therefore, diabetes and hypertension as comorbid factors in GI cancer patients treated with 5-FU can contribute to the incidence of cardiac adverse effects. It is shown in table 3 that the frequency of both systolic and diastolic blood pressure is slightly greater in female patients subjected to treatment arm A. Frequency of systolic and diastolic hypertension is more in patients below 60 years of age. Frequency of hypertension is more in patients with previous cardiac diseases as compared to diabetic patients in treatment arm A. Difference in the frequency of hypertension is minimal between male and female patients of treatment arm B, whereas the frequency of systolic blood pressure is slightly more in male patients. Frequency of both systolic and diastolic blood pressure is higher in patients below 60

years of age; frequency of hypertension in cardiac patients with diabetes is more than cardiac patient without diabetes. Statistical analysis of the data pertaining to record of blood pressure in patients with cardiac disease shows that the difference between blood pressure of cardiac and non cardiac patients is highly significant ($p<0.01$) (table 5). The difference in the blood pressure of diabetic and non diabetic cancer patients receiving chemotherapy is not significant (table 6), indicating that previous cardiac disease can lead mainly to raised blood pressure in patients when they are subjected to chemotherapy. The comparison of cardiac toxicity between treatments A & B in cardiac patient shows that the cardiac toxic profile is more pronounced in patients subjected to treatment arm A. Our data shows that the patients with previous cardiac diseases subjected to chemotherapy in treatment arm A are more prone to hypertension as compared to treatment arm B. The difference in the blood pressure of the diabetic and non diabetic patients in treatment arm A is not significant. The difference in the blood pressure in patients of treatment arm B is also not significant, which shows that the risk of hypertension in patients with or without cardiac diseases and diabetes is similar to normal patients subjected to treatment B. The overall difference in the blood pressure of the patients in patients of treatment arm A & B is not significant (table 8).

Cardiac enzymes

The serum levels of cardiac enzymes during chemotherapy can be an effective indicator of cardiac toxicity such as myocardial infarction (MI). Severe MI with 5-FU chemotherapy is reported in some studies but no factors predictive of the complication were identified (Villani *et al.,* 1979). Cardiac failure and toxic cardiogenic shock with cardiac enzyme elevation (CK) is reported by Coronel *et al.,* (1988), whereas severe hypotension as a manifestation of cardiac toxicity requiring cessation of therapy is reported with normal levels of cardiac enzymes is also reported (Jakubowski *et al.,* 1988). The elevation of CPK after the third injection of 1000 mg of 5-FU is reported in a case study indicating MI (Antonelli *et al.,* 1981), monitoring of serum levels of CPK in patients subjected to chemotherapy with previous cardiac diseases or risk factor therefore, may serve as an effective marker for early drug induced cardiotoxicity. In our study, we measured the serum CPK level in all the patients after each cycle throughout the course of therapy. The CPK levels measured in all the patients with and without previous cardiac diseases or risk factors are within the normal ranges in treatment arm A and arm B; indicating low risk of MI or myocarditis with 5-FU chemotherapy. High level of serum CPK (270 U /L) with mild anginal pain was measured in one of the elderly female patients with history of unstable angina. The chemotherapy was ceased in the patient and the condition was relieved by coronary vasodilators. The serum CPK values are elevated in female patients of both treatment arms A & B but within the normal ranges (tables 3 and 4). The CPK levels are relatively high but within normal range in patients below 60 years of age in treatment arm A and in patients above 60 years of age in treatment arm B. The CPK levels in the group of patients with history of cardiac disease are higher (but within normal reference range) as compared to the group of patients with history of diabetes with comorbid cardiac manifestations in both the treatment arms. Although it is observed that the CPK levels are within normal ranges and discussed before, but it is interesting to find that the mean difference between CPK levels of patients with cardiac diseases (135.20 ± 72.25 U/L) and without cardiac disease (64.964 ± 36.363 U/L) is very highly significant ($p<0.001$) (Table 5). The difference in CPK levels in the patients with and without diabetes and cardiac disease as comorbidity is also significant ($P=0.03$) (Table 6). The difference in the mean values of serum CPK in all the patients of treatment arm A compared to treatment arm B is not significant (Table 8). It is reported that estimation of GOT levels is an important prognostic factor in patients of metastatic colorectal disease treated with 5-FU and Leucovorin, whereas baseline albumin and GOT, and 5-FU/Folinic acid treatment are significant determinants of survival (Steinberg at.al 1992).Case reports of elevated levels of GOT due to cardiotoxicity induced by 5-FU based chemotherapy has been documented before (Singh *et al.,* 2004). In our study the average value of GOT levels measured after each chemotherapy cycle, are within the normal range in total of the male and female patients of age above and below sixty in both treatment arm A & B. The mean value of the GOT levels measured in the patients with previous cardiac diseases is higher (58.42>45 U/L) than the normal range in treatment Arm A, whereas the mean value of GOT levels of patients with cardiac disease history in treatment arm B is within the normal range (41.46> 45 U/L) (table 2).

In some patients subjected to treatment arm A, comprising of age group below 60 years with history of cardiac diseases, GOT levels are higher than the normal range (average value 60.65U/L) indicating hepatic and cardiac toxicity whereas GOT levels in patients without previous cardiac diseases subjected to chemotherapy is within the normal reference range. GOT levels in patients above 60 years of age with history of cardiac disease in treatment arm A is also slightly raised above normal levels (average GOT 50.98>45U/L). Whereas the average value of measured GOT levels in patients without cardiac disease and cardiac risk factors is within the normal reference range. On the other hand the average value of GOT levels measured in patients below 60 years of age with previous cardiac diseases subjected to chemotherapy in treatment Arm B is within the normal reference range (28.55 U/L). The average values of GOT levels measured in patients without any previous cardiac diseases below

60 years of age, in treatment arm B, is also within the normal reference range. In contrast to this the average value of measured GOT levels in serum of patients above 60 years of age with history of cardiac diseases is slightly raised (50.06>45U/L). The GOT levels in patients with both diabetes and cardiac diseases in treatment arm B, comprising of age above 60 years of age is also slightly raised (51.22>45U/L), whereas the GOT levels in patients above 60 years of age subjected to treatment arm B without any diabetic or cardiac disease condition is well within normal reference range (22.02<45 U/L). This indicates that the risk of cardiac and hepatic toxicity is more in elderly patients with cardiac and metabolic disorder (diabetes) subjected to treatment arm B.

It is shown in (Tables 3 and 4) that the levels of GOT are relatively higher but within normal reference ranges in female patients subjected to treatment arm A and treatment arm B. Serum levels of GOT in patients below 60 years of age in treatment arm A is also relatively higher but within normal reference ranges. GOT levels in patients with cardiac diseases is higher as compared to the group of diabetic patients with and without cardiac diseases, in treatment arm A, signifying that the presence of previous cardiac disease is the elementary cause of raised GOT levels rather than metabolic disorder (diabetes). GOT levels of patients above and below 60 years of age subjected to treatment arm B is well within the normal ranges but relatively higher in patients above 60 years of age. GOT levels in patients of cardiac disease is higher than patients of diabetes with and without cardiac disease, but the levels in both the group of patients is within the normal reference ranges of GOT. Statistical analysis of overall data of patients by Independent samples tests show that the difference in the GOT levels of patients with or without cardiac diseases is very highly significant ($p<0.001$) (Table 5), whereas the difference in the GOT levels of patients with and without diabetes is not significant (0.282 >0.05) (Table 6), indicating that the history of previous cardiac diseases is a contributing factor for raised levels of GOT in patients subjected to different schedules of 5-FU/LV chemotherapy. The comparative analysis of both the treatment arms show that the difference in GOT levels of overall patients of treatment arm A and B is not significant (0.157>0.05), however the mean values of GOT levels in treatment arm A patients (37.792 ± 26.49 U/L) is higher than treatment arm B (29.067 ± 14.122 U/L) (Table 8). Although the estimation of serum enzymes in cancer patients subjected to treatment is an effective way to determine cardiotoxicity, however ECG changes are reported more frequently than changes in cardiac enzymes in case of cardiotoxicity. Bertolini *et al.,* (2001) reported the ischemic electrocardiogram (ECG) changes in 68% of patients, but only 43% have elevations in serum cardiac markers due to chemotherapy induced cardiotoxic event.

Anginal pain, anxiety, distress and palpitations

Cardiotoxicity by 5-FU was first identified by Dent and McColl in 1975 with the clinical manifestation of angina. The most commonly reported early sign of cardiac adverse effect of radiation and chemotherapy is chest pain due to coronary artery disease or acute coronary syndrome. It is also the most common symptom associated with cardiotoxicity due to 5-FU (Yeh *et al.,* 2009). Incidence of cardiotoxicity associated with 5-FU ranges between 1.5% to 18%; 48% as anginal symptoms and 2% as cardiogenic shock (Shaib *et al.,* 2009). Wang *et al.,* (1998) reported that the most common presenting symptom of drug induced cardiotoxicity, by a regimen, similar to treatment arm A in our study (high dose leucovorin and infusional 5-FU), is anginal pain with transient ECG changes. Klieman *et al.,* (1987) presented a case of prinzmetal's angina during IV 5-FU therapy in a patient with history of angina, documenting that "..drug-induced coronary artery spasm may be the cause of 5-fluorouracil-associated chest pain". Coronary vasospasm and free radical changes to the myocardium are understood to be the pathophysiological interpretation of cardiotoxicity that mimics ischemia (Ensley *et al.,* 1989), whereas, the exact mechanism of cardiotoxicity by 5-FU is not fully identified. Angina is an unreliable index of myocardial ischemia in diabetic patients with coronary artery disease (Nesto *et al.,* 1988), in our study however, there were reports of mild anginal pain (16%) in diabetic group of patients with a history of cardiac disease in treatment arm A. Table 3 shows that mild angina is reported in 4% of male and 2% of female patients of treatment arm A. The symptom of angina is reported only in patients below 60 years of age of treatment arm A. Anginal pain is reported in 7% of patients with history of cardiac disease with and without diabetes. Angina due to 5-FU induced cardiotoxicity in a patient with maturity onset diabetes with history of MI has been reported (McGlinchey *et al.,* 2001). Timour *et al.* (2002) reported 6 cases of cardiotoxicity of 5-FU manifested as angina and heart failure in patients with no previous cardiac disease but history of diabetes in 1 of the 6 patients. The history of previous cardiac disease or cardiac risk factor in patients appears to be directly related to the incidence of symptoms of cardiotoxicity e.g., anginal pain. Schöber *et al.* (1993) reported 15.1% of cardiac toxic symptoms in patients with history of cardiac disease and 1.5% of cardiac toxic symptoms in patients with no previous history of cardiac diseases, subjected to chemotherapy with 5-FU, whereas anginal pain mimicking MI was the leading symptom in 61% of the patients with cardiotoxicity.

Cases of unstable angina induced by a low dose Leucovorin and 5-FU regimen similar to treatment regimen B in our study are reported. Cases of treatment related cardiotoxicity (anginal pain, cardiac chest pain) with low dose IV 5FU/LV (Mayo clinic regimen) are also reported in a large phase III trial study (Van Custem *et*

al., 2001). In our study, varying degrees of anginal pain was reported in 17.5% of patients in treatment arm B. Table 4 shows that anginal pain in treatment arm B is 2% in male patients and 7% in female patients. Anginal pain is reported in 4% of patients above and below 60 years of age. There are 7% reports of anginal pain in patients of cardiac disease with and without diabetes. Mild anginal pain appears to be a frequent symptom in patients subjected to chemotherapy bearing a past history of cardiac diseases. It is also seen in the plot of initial data that cardiotoxicity exacerbated as anginal pain is more often seen in patients with reports of high blood pressure at some stage of chemotherapy. Chest pain and signs of ischemia resembling angina pectoris are suspected to be due to coronary spasms induced by 5-FU (Keefe *et al.,* 1993). These symptoms appeared during the CIV infusion, however they did not worsen in any patient and were promptly resolved after sublingual nitrates (prescribed earlier to patients with cardiac diseases e.g. CAD). The symptoms were also observed in hyperglycemic patients associated with cardiac risk factors in both the treatment arm A (32%) and treatment arm B (11%). Table 3 shows that the incidence of anxiety, distress or palpitations is more in male patients (11%) as compared to female patients (7%), subjected to treatment arm A. Incidence of anxiety, distress or palpitations is more in male patients (9%) as compared to female patients (7%) in treatment arm B. The symptoms are comparatively more frequent in patients below 60 years of age (11%) subjected to chemotherapy in treatment arm A. The reports of anxiety, distress and mild palpitations are more in patients above 60 years of age (9%) as compared to patients below 60 years of age (7%). Symptoms of anxiety, distress and palpitation in cardiac patients with and without hyperglycemia are 13% in treatment arm A, whereas the frequency of symptoms is more in patients without diabetes and history of cardiac diseases (7%) as compared to patients with diabetes and history of cardiac diseases (4%) in treatment arm B (Table 4).

CONCLUSION

The 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. Clinical assessment of cardio toxicity can be detailed by tests for ECG, rest and stress perfusion imaging and tropinin levels.

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