Original Article

A retrospective study of cardiotoxicities induced by 5-Fluouracil (5-FU) and 5-FU based chemotherapy regimens in Pakistani adult cancer patients at Shaukat Khanum Memorial Cancer Hospital & Research Center

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Abstract

Objective: To study cardiotoxicities, especially bradycardia in cancer patients treated with 5-Fluouracil and 5-Fluouracil based chemotherapy regimens in Pakistani population.

Methods: Data was extracted from the medical records of all diagnosed cancer patients at Shaukat Khanum Memorial Cancer Hospital and Research Center registered between January 2002 and December 2004 receiving 5- Fluouracil based chemotherapy regimens. The data was analysed retrospectively, including electrocardiogram and cardiac markers. Pearson's Correlation coefficient was calculated to see any possible correlation between 5-Fluouracil alone and 5-Fluouracil based regimens and cardiotoxicity, and other variables.

Results: Symptomatic cardiotoxicity was observed in 60 (19.93%) out of 301 patients whose cases were part of the study. Bradycardia was the most common cardiotoxicity and was observed in 36 (11.96%) patients. Nine (2.99%) mortalities were also observed. The incidence of cardiotoxicity was not significantly different between the patients with and without pre-existing cardiovascular disease ($p = 0.095$) and having negative correlation -0.305. Cardiotoxicities were more common with Continuous Infusion (CI) of 5-Fluouracil, radiotherapy concurrent with 5-Fluouracil and when 5-Fluouracil was used in combination with Cisplatinum (CDDP).

Conclusion: Cardiotoxicities were more prevalent when 5-Fluouracil was used along with concurrent radiotherapy and with Cisplatinum and when administered in continuous infusion pattern. Hence, 5-Fluouracil and 5-Fluouracil based chemotherapy regimens cause cardiotoxicities, especially bradycardia, in a significant number of cancer patients in Pakistani population.

Keywords: 5-Fluouracil, Bradycardia, Cardiotoxicity, Chemotherapy (JPMA 62: 430; 2012).

Introduction

A large number of patients with various cancers are treated with 5-Fluorouracil (5-FU) alone or in combination with other antineoplastics at Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH&RC). At our center, cardiovascular events with 5-FU have been found to be unusually high in comparison with reported toxicities. Moreover, the pattern of cardiotoxicity is different as compared to the established toxicity of the drug. Treatment with 5-FU usually causes myocardial ischaemia, unstable angina and tachycardia[1,2] but experience at SKMCH&RC is interestingly different as this drug has caused bradycardia in a large number of patients which is quite an unusual toxicity and was first reported from Srinagar, Indian Kashmir.[3] Transient asymptomatic bradycardia is also reported by Talapatra K et al 2007 from India.[4] Adding to that, bradyarrhythmias makes up the greater proportion of the total cardiac events with 5-FU at SKMCH&RC. Bradyarrhythmias with the drug were of too acute intensity to withhold or discontinue the drug in various patients. These patients having developed bradyarrhythmias had to be transferred to the intensive care unit for management, and some of them died.

It was hypothesised that 5-FU and 5-FU based chemotherapy regimens cause cardiotoxicities, especially bradycardia, in a number of Pakistani cancer patients Therefore, it had been planned to conduct a retrospective study in this regard to check the hypothesis. The study also aimed at identifying the pattern which may help in designing a more elaborative study with respect to pharmacokinetics, pharmacodynamics and possibly pharmacogenetics of 5-FU.

Patients and Method

The retrospective in vivo descriptive study was done at SKMCH & RC, Lahore, Pakistan and University College of Pharmacy, University of the Punjab, Lahore.

Data from medical records of all diagnosed cancer patients at SKMCH&RC registered between January 2002 and December 2004 receiving 5-FU as a part of chemotherapy was analysed retrospectively, including serial analysis of ECG. Heart Rate (HR) less than 60/min was considered bradycardia and was documented. 5-FU and 5-FU based chemotherapy regimens were only investigated for changes in the cardiac profile of the patients.

The inclusion criteria related to adult Pakistani patients with a definitive diagnosis of cancer and having received 5-FU and 5-FU based chemotherapy regimens during January 2002 and December 2004. This resulted in a study population of 301 patients.

Pearson's Correlation coefficient was calculated to see any possible correlation between 5-FU alone and 5-FU based regimens and cardiotoxicity, and other variables. Correlation is significant at the $p = 0.01$ level (2-tailed). The Kruskal-Wallis H test was used to define the cardiotoxicity differences among the various administration patterns. A p-value < 0.05 was considered statistically significant. The statistical analyses were performed by SPSS version 10.0.

Results

We evaluated 301 patients of mean age 47 (ranges 18-81) years and a female/male ratio of 226/75. Symptomatic cardiotoxicity was determined in 60 (19.93%) patients (Table-1). The overall frequency of cardiotoxicity among patients receiving 5-FU alone and 5-FU based regimens was significant and the correlation between patients receiving 5-FU alone and 5-FU based regimens and cardiotoxicities was 0.546 ($p = 0.001$).

Table-1: Total Number of Patients Observed with Cardiotoxicities.

Regimen Administered	Number of Patients. Received Chemo	Number of Patients Observed with Cardiotoxicity	
	n	n	Percentage
5-FU Alone			
5-FU	2	0	0.00%
5-FU Based Regimen			
5-FU/CDDP	50	30	60.00%
5-FU/CDDP, AC	1	1	100.00%
5-FU/CDDP/Epi	4	0	0.00%
5-FU/CDDP/MTX	1	1	100.00%
5-FU/CDDP/XRT (ECOG)	13	3	23.08%
5-FU/CDDP/XRT (ECOG), 5-FU/LV	1	0	0.00%
5-FU/CDDP/XRT (ECOG), CEF	1	0	0.00%
5-FU/CDDP/XRT (RTOG)	1	1	100.00%
5-FU/DTIC/Epi	1	0	0.00%
5-FU/LV	16	3	18.75%
5-FU/LV, CPT 11	2	0	0.00%
5-FU/LV, FOLFIRI	1	0	0.00%
5-FU/LV, CAPE	1	1	100.00%
5-FU/LV, FOLFOX,	1	0	0.00%
5-FU/LV, FOLFOX, FOLFIRI	1	0	0.00%
5-FU/LV, FOLIRI, CPT 11	1	0	0.00%
5-FU/Mitomycin	2	0	0.00%
5-FU/Paclitaxel/LV	1	0	0.00%
AC, CAF	3	0	0.00%
AC, CAF, CMF	3	0	0.00%
AC, CMF	7	1	14.29%
CAF	131	8	6.11%
CAF, CAPE	3	0	0.00%
CAF, CMF	16	4	25.00%
CAF, DOX, CMF	2	0	0.00%
CMF	26	3	11.54%
Doxo, CMF	3	0	0.00%
FOLFIRI	3	2	66.67%
FOLFIRI, FOLFOX	1	0	0.00%
FOLFOX-6	2	2	100.00%
	301	60	19.93%

AC: Adriamycin + Cyclophosphamide. CAF: Cyclophosphamide + Adriamycin + 5Fluorouracil. CAPE: Capecitabine. CEF: Cyclophosphamide + Epirubicin +5-Fluorouracil. CDDP: Cisplatin. CMF: Cyclophosphamide + Methotrexate + 5-Fluorouracil. CPT11: Irinotecan. DOXO: Doxorubicin. DTIC: Dacarbazine. ECOG: Eastern Cooperative Oncology Group. Epi: Epirubicin. FOLFIRI: 5-Fluorouracil + Leucovorin + Irinotecan. 5-FU: 5-Fluorouracil. FOLFOX: 5-Fluorouracil + Leucovorin + Oxaliplatin. FOLFOX-6: 5Fluorouracil + Leucovorin + Oxaliplatin. LV: Leucovorin. MTX: Methotrexate. RTOG: Radiation Therapy Oncology Group. XRT: Radiotherapy.

Table-2: Differential cardiotoxicities observed during or after 5-FU alone and 5-FU based regimen.

Cardiotoxicities	n	Percentage
Total Number of Patients	301	
Angina		
ICP	10	3.32%
Myocardial Ischaemia	2	0.66%
Anginal Attack	10	3.32%
Variant Angina	0	0.00%
CS		
Cardiogenic Shock	0	0.00%
Reversible CS	0	0.00%
Cardiomyopathy		
ADC	0	0.00%
ECG		
CD	1	0.33%
ST depression	3	1.00%
ST elevation	5	1.66%
Inverted T waves	11	3.65%
Non-Sep ST	1	0.33%
P-W Changes	1	0.33%
IVR	1	0.33%
QRS Changes	1	0.33%
Cardiac Enzymes		
CK	7	2.33%
CK-MB	11	3.65%
Troponin	2	0.66%
AST	10	3.32%
MI		
MI	0	0.00%
Cardiac Arrest	1	0.33%
Acute CV Effects		
Ischemic ECG changes	10	3.32%
Chest Pain	10	3.32%
Dysrythmia	0	0.00%
CAS	0	0.00%
Hypotension	18	5.98%
Heart Failure	0	0.00%
AV Block	2	0.66%
Hypertension	7	2.33%
Ventricular tachycardia	11	3.65%
Bradycardia	36	11.96%

ICP: Ischaemic Chest pain. CS: Cardiogenic Shock. ADC: Acute dilated cardiomyopathy. CD: Conduction disorders. P-W Changes: P-wave changes. IVR: Idioventricular Rhythm. CAS: Coronary Artery spasm. CK: Creatinine Phosphokinase. CK-MB: An iso form of CK. ECG: Electrocardiogram. AV: Atrio-ventrical block.

Differential cardiotoxicities observed during and after 5-FU alone and 5-FU based regimen were noted (Table-2). Bradycardia was the most common cardiotoxicity observed in 36 (11.96%) patients. The overall frequency of cardiotoxicity was not significantly different between the patients with and without cardiovascular disease ($p = 0.095$) and having negative correlation -0.305. Cardiotoxicities were most commonly seen in those patients who received 5-FU along with CDDP, as 72 patients received 5-FU/CDDP and, of them, 36 (50%) patients developed cardiotoxicities.

Results indicated that statistically there was significant difference among the three types of administration pattern ($p = 0.038$); the Bolus, the CI, and both, with their mean rank being 8.83, 8.67, and 3.0 respectively (Table-3).

Table-3: Correlation of the administration pattern of 5-FU with its cardiotoxicities.

	Administration Pattern	Cardiotoxicity Observed	
	n	n	%age
Bolus	228	22	9.67%
CI	61	34	56%
Both	12	4	33.33%

CI: Continuous infusion.

The incidence of cardiotoxicity with concurrent 5-FU/CDDP and XRT was 25 out of 54 patients (46.3%) while remaining 35 patients who received 5-FU/CDDP without radiotherapy (XRT) developed cardiotoxicities. The correlation between 5-FU induced cardiotoxicity and patients those who received concurrent chemo (5-FU based regimen) XRT is 0.905 ($p = 0.001$).

Discussion

The 5-FU therapy is occasionally complicated by cardiac toxicity characterised by chest pain, arrhythmia and changes in electrocardiograms (ECGs). Retrospective studies suggest a frequency under 10%. This complication has been noted with both bolus and infusional schedules.[5,6] It has been suggested that high-dose infusional regimens may predispose to cardiac toxicity.[7] In some patients, chest pain recurred with subsequent administration of the drug. The chest discomfort often was accompanied by ECG and serum enzyme changes, indicative of myocardial ischaemia. Some, but not all, of these episodes have occurred in patients with a prior history of chest irradiation or cardiac disease. In selected cases, however, coronary angiography subsequent to the acute ischaemic event demonstrated no evidence of atherosclerotic disease, suggesting that coronary vasospasm might be involved.[8]

There is limited information concerning possible mechanism and underlying pathophysiology of cardiac toxicity. There have been suggestions that 5-FU metabolites contribute to cardiotoxicity. FBAL (Fluoro Beta-Alanine) accumulated in cardiac tissue of rats for up to 8 days following a single dose.[9] Using a fluorine-19 magnetic resonance imaging, Lemaire et al[10] detected fluoroacetic acid in perfusates of isolated rabbit's hearts and also observed cardiotoxicity and accumulation of citrate (presumably reflecting the inhibition of citrate metabolism). Interestingly, these abnormalities were seen only with the commercial formulations of 5-FU (available as an aqueous solution of 50 mg/ml buffered with either Tris, pH 8.5, or sodium hydroxide), but not with 5-FU freshly prepared from reagent-grade powder.[10] The study found impurities in

the commercial formulation, which were thought to be the result of degradation of 5-FU formed in the basic medium employed to dissolve the drug. One of these impurities was fluoroacetaldehyde, which is metabolised into fluoroacetate by the isolated perfused rabbit heart.

Sinus bradycardia occurred in a young female after prolonged use of 5-FU in the department of medical oncology, Institute of Medical Sciences, Srinagar 19001 (Kashmir). Vagolytic test (atropine test) was done, and sinus bradycardia attributed to a hypervagotonic state induced by 5-FU.[3] Transient asymptomatic bradycardia associated with infusional 5-FU in 6 patients has also been reported by Talapatra K et al 2007 again from India.[4] It may have certain pharmacogenomic basis and possibly have a typical ethnic distribution in the subcontinent and/or South Asia

The overall incidence of cardiotoxicity among patients receiving 5-FU alone and 5-FU based regimens was significant and correlation between patients receiving 5-FU alone and 5-FU based regimens and cardiotoxicities was 0.546 ($p = 0.001$). By squaring the correlation and then multiplying by 100, we calculated the percentage of the variability that is shared by 5-FU cardiotoxicity. Hence, 5-FU cardiotoxicity shares about 29.81% of its variability with patients who received chemo (5-FU alone or 5-FU based regimen). Cardiotoxicities observed in Pakistani cancer patients after receiving 5-FU and 5-FU based regimens are found to be higher (19.93%) than the reported cardiotoxicities (Less than 10%).[5,6]

It was identified that the pattern of cardiotoxicity was different from that of established one; as 5-FU usually causes CAD and Ventricular tachycardia,[1,2] but at SKMCH&RC, bradycardia was the main cardiac toxicity and occurred in 36 (11.96%) patients out of 301. Bradycardia is quite an unusual toxicity of the drug.

Our data suggests that cardiotoxicities were very commonly observed with 5-FU/CDDP (36 out 72 patients) as compared to other 5-FU based chemotherapy regimens which can be explained in the light of the fact that cardiotoxicity is a well-known toxicity of CDDP and has been observed in 15% patients receiving 5-FU and CDDP combination[11] but bradycardia is not associated with CDDP. Besides, CI pattern of 5-FU is used in 5-FU/CDDP chemotherapy protocols and incidence of cardiotoxicities was very high with CI pattern of 5-FU which is inconsistent with the reported pattern of cardiotoxicity of 5-FU.[7,12,13]

We found that most of the patients received Bolus injection of 5-FU. As many as 228 out of 301 patients received Bolus injection of 5-FU and 61 patients received CI of 5-FU and only 12 patients received both Bolus injection of 5-FU and CI of 5-FU. Results indicated that statistically there was significant difference among the three types of administration pattern ($p = 0.038$) the bolus, CI and both, with their mean rank 8.83, 8.67, 3.0 respectively. Out of 228 patients who received Bolus injection of 5-FU, 22 (9.64%) developed cardiotoxicities; whereas 34 (56%) patients out of 61, who received CI of 5-FU, developed cardiotoxicities, and, lastly, out of the 12 patients who received both Bolus injection of 5-FU and CI of 5-FU, 4 (33.33%) developed cardiotoxicities. In the case of those patients who received both Bolus injection of 5-FU and CI of 5-FU, cardiotoxicities were probably due to CI pattern of 5-FU administration because of higher incidence of cardiotoxicities observed with CI pattern of 5-FU administration in our retrospective analysis.

Hence, the data suggests that cardiotoxicities were more common with CI of 5-FU (56%) and among those who received both Bolus injection of 5-FU and CI of 5-FU (33.33%) as compared to those with Bolus injection of 5-FU alone (9.64%).

The study observed that out of the 72 patients who received 5-FU/CDDP, 39 received 5-FU/CDDP plus radiotherapy (XRT) (Concurrent Chemo-Rads) and 33 patients received 5-FU/CDDP without XRT. A total of 36 patients out of the 72 developed cardiotoxicities.

The correlation between 5-FU induced cardiotoxicity and patients who received concurrent chemo (5-FU based regimen), XRT was 0.905 ($p = 0.000$). By squaring the correlation and then multiplying by 100, we calculated the percentage of the variability that is shared. Hence, 5-FU induced cardiotoxicity shard about 81.9% of its variability with patients who received concurrent chemo (5-FU based regimen) XRT.

Patients ($n = 39$) who received 5-FU/CDDP with concurrent XRT, 22 (56.41%) developed cardiotoxicities; whereas, out of the remaining 33 patients who received 5-FU/CDDP without XRT, 14 (42.42%) developed cardiotoxicities.

The data suggests that the incidence of cardiotoxicities was significantly high (25 out of 54, 46.30%) when 5-FU and 5-FU based chemotherapy regimens were used concurrently with radiotherapy. Besides, the incidence of cardiotoxicities was very high (36 out of 72, 50%) when 5-FU was used along with CDDP. When radiotherapy was also given concurrently with 5-FU/CDDP, the incidence of cardiotoxicities became greatly increased (22 out of 39, 56.41%). Out of the remaining 33 who received 5-FU/CDDP without XRT, 14 (42.42%) patients developed cardiotoxicities. Besides, CI pattern of 5-FU is used in 5-FU/CDDP chemotherapy protocols, and the incidence of cardiotoxicities was very high with CI

pattern of 5-FU which is in line with earlier studies.[7,12,13]

Conclusion

Cardiovascular events with 5-FU were found to be unusually high (n = 60, 19.93%) in comparison to the reported toxicities (Less than 10%),[5,6] with a high mortality rate (n = 9, 2.99%). Moreover, the pattern of cardiotoxicity was different compared to the established toxicity of the drug. Treatment with 5-FU usually causes myocardial ischaemia, unstable angina and tachycardia,[1,2] but at SKMCH&RC, it was different as this drug has caused bradycardia in a significant number of patients. The study supported the toxic effects of 5-FU on myocardium. Cardiotoxicities were more prevalent when 5-FU was used along with concurrent radiotherapy with Cisplatinum and when administered in CI pattern. Considerable vigilance is required when using this drug, and its toxic effects on coronary endothelium and myocardium need to be further investigated. Hence, 5-FU and 5-FU based chemotherapy regimens cause cardiotoxicities, especially bradycardia, in a significant number of cancer patients among Pakistani population.

Limitation of the study:

Delayed submission. Data was extracted in 2005 and submitted for publication in 2010. But there had been no development on this unique subject although lot of work was expected to be done during these 5 years. This study still provides the largest series of the patients experiencing cardiotoxicities especially bradycardia associated with 5-FU and 5-FU based chemotherapy regimens

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