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A Case Report of Delayed-Onset Cardiotoxicity Following Long-Term Use of 5-Fluorouracil: Underlining the Importance of Long-Term Pharmacovigilance

Case Report

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ABSTRACT

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Pharmacovigilance is vital for the identification, evaluation, and mitigation of adverse drug reactions, especially those with delayed onset. 5-Fluorouracil (5-FU) is a widely used chemotherapeutic agent that has been a cornerstone in the management of various tumors. While generally well-tolerated, 5-FU is associated with a relatively rare side effect, cardiotoxicity, being clinically significant due to its potential for severe morbidity and mortality. A 40-year-old female patient with adenocarcinoma rectum treated with FOLFOX regimen presented in an unconscious state with lower GI bleed, low BP, and

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poor GCS to the emergency. Symptomatic treatment and multiple blood transfusions were given. Investigations revealed cardiomegaly, left-ventricular hypertrophy, mild mitral regurgitation, and a reduced ejection fraction (35%). Causality assessment was done, and patient was identified as a case of delayed-onset cardiotoxicity following long term use of 5-Fluorouracil. Patient was accordingly managed. The causality assessment of this case was possible as per the WHO-UMC causality assessment scale.

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INTRODUCTION

Pharmacovigilance is vital for the identification, evaluation, and mitigation of adverse drug reactions, especially those with delayed onset that may manifest weeks, months or even years after initiation of therapy. It ensures patient safety by enabling early intervention, reducing severe complications, and guiding clinicians in refining treatment protocols¹.

5-Fluorouracil (5-FU) is a widely used chemotherapeutic agent that has been a cornerstone in the management of various tumors, including colorectal, breast, and gastrointestinal cancers². A fluorinated pyrimidine analogue, its mechanism of action involves the inhibition of thymidylate

synthase, leading to disrupted DNA synthesis and repair in rapidly dividing cancer cells³. While generally well-tolerated, 5-FU is associated with several side effects, ranging from mild gastrointestinal disturbances to severe toxicities, including cardiotoxicity. Among these, cardiotoxicity, though relatively rare, is clinically significant due to its potential for severe morbidity and mortality⁴. The incidence of 5-FU-induced cardiotoxicity is estimated to range between 1% and 19%, with acute coronary vasospasm being the most commonly reported mechanism. Acute cardiac events, such as angina, myocardial infarction, and arrhythmias, have been extensively documented; however, delayed-onset cardiotoxicity is an underrecognized and underreported phenomenon⁵. The importance of long-term pharmacovigilance in oncology cannot be overstated, as the

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increasing survivorship rates highlight the need to monitor chronic adverse effects of cancer therapies.

The pathophysiology of 5-FU-induced cardiotoxicity is multifactorial and hypothesized to result from coronary vasospasm, oxidative stress-induced myocardial injury, and endothelial dysfunction. Recent studies also suggest the potential role of genetic predisposition and pharmacogenomics in determining susceptibility to 5-FU toxicity. Furthermore, risk factors such as advanced age, pre-existing cardiovascular disease, cumulative drug dose, and continuous infusion regimens are known to exacerbate the likelihood of cardiotoxic events. However, even in patients with no apparent risk factors, delayed-onset cardiotoxicity can occur, raising critical questions about the adequacy of current surveillance protocols^{5,6}.

A case of delayed onset cardiotoxicity following long term use of 5-Fluorouracil was reported to Pharmacovigilance Programme of India (PvPI)⁷, Indian Pharmacopoeia Commission (IPC), Ghaziabad by Adverse Drug Reaction Monitoring Centre (ADRMC) of Jawaharlal Nehru Medical College & Hospital, Aligarh Muslim University.

CASE STUDY

Patient in our case study is a 40-year-old female, diagnosed and registered case of adenocarcinoma rectum (post-surgical low anterior resection) in the Department of Radiotherapy, Jawaharlal Nehru Medical College & Hospital, Aligarh Muslim University. Patient was started on FOLFOX regimen (5-Fluorouracil, Leucovorin and Oxaliplatin) on 29/05/2017. Treatment started with Injection Oxaliplatin 100mg Day-1, Injection Leucovorin 250mg Day-1 and Day-2, Injection 5-FU 500mg bolus Day-1 and Day-2, Injection 5-FU 750mg infusion Day-1 and Day-2 and the patient was followed up at regular intervals during treatment. Treatment continued until 15/09/2018 during which patient received total 5 cycles of FOLFOX regimen after which the patient defaulted and presented again 5 years later (04/01/2024) in an unconscious state with poor GCS, low BP (80/46 mmHg), SpO₂ 92% and complaint of lower GI bleed. Patient was admitted and 8 units PRBC were transfused. Symptomatic treatment was given, and routine investigations were done.

The case was registered in Vigiflow software of WHO-UMC (World Health Organization-Uppsala Monitoring Centre) under the worldwide unique number IN-IPC-301010047, AMC Report Number JNMCH/Nov-2024/08. The causality assessment of this case was done as per the WHO-UMC Causality Assessment Scale.

After the patient gained consciousness, Informed Consent was obtained. Chest x-ray showed an increased cardiothoracic ratio with straightening of left heart border, suggestive of cardiomegaly. On echocardiography, global left-ventricular hypertrophy was evident and mild mitral regurgitation (MR) with left ventricular ejection fraction 35%, minimum pericardial effusion was noted.

DISCUSSION

Following a causality assessment, 5-Fluorouracil was identified as the probable causative agent. Patient was advised oral Angiotensin II Receptor Inhibitor (Aldactone) 25 mg (Captopril) once a day, oral LASIX 40 mg (Furosemide) once a day, oral Rosuvastatin 5 mg (Rosuvastatin 5mg) once a day and oral Carvedilol 6.25 mg (Carvedilol). The patient was subsequently monitored through comprehensive investigations, including ECG, chest x-ray, echocardiography, cardiac biomarkers, and CT-Scan, to assess and manage cardiotoxicity effectively. Patient had not completely recovered from signs and symptoms of cardiotoxicity at the time of this report.

VigiAccess status of cardiac disorders with use of 5-Fluorouracil is 3% (4855 ADRs), which means very less potential adverse drug reaction have been reported to the WHO Programme for International Drug Monitoring (WHO PIDM) till now.⁸

CONCLUSION

This was a rare case of delayed-onset cardiotoxicity associated with prolonged use of 5-fluorouracil. The causality assessment indicated a possible diagnosis. This case report underscores the necessity for ongoing monitoring and reporting of adverse drug reactions (ADRs) among healthcare professionals, highlighting the importance of increased vigilance regarding the use of 5-Fluorouracil in the future.

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