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Acute Myocardial Infarction Following 5-Fluorouracil Treatment

Jose Rivas Rios*, Melissa Oye, Yixin Zhang, Fabiana Rollini and Kadeja Esmail

Department of Medicine, University of Florida, Florida, USA

Abstract

A 62-year-old male with recently diagnosed stage IV pancreatic cancer was started on chenotherapy with 5-Fluourouracil. Shortly after initiation, he suffered cardiac arrest. We will review the proposed pathophysiology of 5-Fluourouracil cardiotoxicity, the reported incidence, treatment, and the antidote for 5-Fluorouracil overdose or toxicity. Myocardial infarction is an adverse cardiac reaction associated with 5-fluorouracil (5-FU). Data on the incidence, risk, and prognosis of 5-FU-related myocardial infarction are limited. Fluorouracil (5-FU) is the most commonly proposed chemotherapy drug for colorectal cancer. Cardiogenic side effects such as autopsy arterial vessels seizures, ventricular arrhythmias, and cardiac ischemia are also rare.

Keywords: Acute coronary syndrome • Chest pain • Cancer

Abbreviations: 5-Fluorouracil (5-FU); Food and Drug Administration (FDA); Electro Cardio Gram (ECG); Coronary Artery Disease (CAD); Myocardial Infarction (MI); Percutaneous Intervention (PCI); Left Anterior Descending Artery (LAD); Folinic Acid, 5-FU, Irinotecan, Oxaliplatin (FOLFIRINOX); Echocardiogram (ECHO); Ejection Fraction (EF); ST-Segment Elevation Myocardial Infarction (STEMI); Thrombolysis In Myocardial Infarction (TIMI)

Introduction

5-Fluorouracil (5-FU) is an antimetabolite chemotherapeutic agent that is US Food and Drug Administration (FDA) indicated for use in a variety of neoplasms and is a staple agent in many chemotherapeutic regimens. An important adverse effect of 5-FU is cardiotoxicity. There is a wide spectrum of clinical presentation of 5-FU cardiotoxicity from asymptomatic Electro Cardio Gram (ECG) changes to myocardial infarction that clinicians must be aware of when caring for patients receiving this agent.

Learning objectives

- Recognize the diverse clinical presentation of 5-FU related cardiotoxicity
- State the proposed mechanisms of 5-FU cardiotoxicity
- Recall the schedule of 5-FU administration that has the highest to lowest risk of 5-FU cardiotoxicity
- Name the antidote for 5-FU overdose or toxicity
- For your patients receiving 5-FU chemotherapy, counsel on potential cardiac related side effects.

Case Presentation

A 62-year-old man with a history of hypertension, hyperlipidemia, former heavy tobacco use, Coronary Artery Disease (CAD) with Myocardial Infarction (MI) resulting in Per Cutaneous Intervention (PCI) to the Left Anterior Descending artery (LAD) 10 years prior, and newly diagnosed stage IV pancreatic adenocarcinoma with recent initiation of Chemotherapy presented to the emergency room after suffering Ventricular Fibrillation arrest. He did not experience any symptoms prior to this event. Two days prior to presentation, he started palliative chemotherapy with folinic Acid, 5-FU, Irinotecan, and Oxaliplatin (FOLFIRINOX). 5-FU was given as a 400 mg/m^2 bolus followed by a 2400 mg/m^2 46-hour continuous infusion that finished shortly before his hospital arrival. Prior to starting chemotherapy, he underwent cardiac evaluation showing a normal Electro Cardio Gram (ECG), an Echocardiogram (ECHO) with mildly reduced Left Ventricle Ejection Fraction (LVEF) of 45%-50%, and a nuclear stress test due to mildly reduce LVEF and for risk stratification prior to chemotherapy. The test was negative for inducible ischemia.

In the field, return of spontaneous circulation was achieved after one round of resuscitation. Post-resuscitation ECG showed ST segment elevations in leads V1-V3 suggestive of an acute anterior ST-Segment Elevation Myocardial Infarction (STEMI) (Figure 1). High-sensitivity Troponin T was 102 ng/L at zero hour and rose to 1450 ng/L at 1 hour with delta of 1348 ng/L. He was pre-treated with Aspirin and Nitroglycerin. Emergent left heart catheterization showed a 100% acute thrombotic lesion of the mid LAD with Thrombolysis In Myocardial Infarction (TIMI) 0 flow. A PCI with a 3.5 × 28 mm drug-eluting stent post dilated with 3.0 × 12 mm non-compliant emerge balloon was performed with subsequent TIMI-3 flow (Figure 2). Dual-antiplatelet therapy was started, and his home beta blocker, cholesterol-lowering medication, and angiotensin receptor inhibitor were continued. He was transferred to the cardiac care unit with an uneventful recovery. While inpatient, chemotherapy was held and his regimen was subsequently changed to Abraxane/Gemzar after obtaining Cardiology clearance to resume chemotherapy.

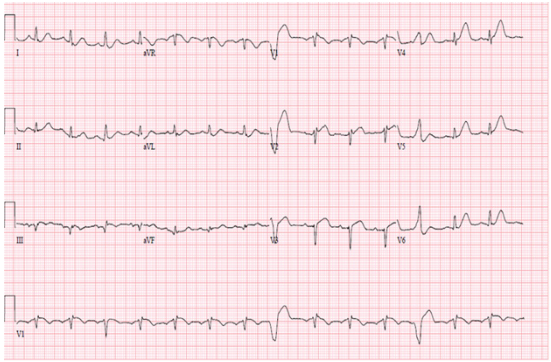

Figure 1. Serum protein liver function biomarkers discriminates between the study groups.

***Address for Correspondence:** Jose Rivas Rios, Department of Medicine, University of Florida, Florida, USA; E-mail: jose.rivas@jax.ufl.edu*

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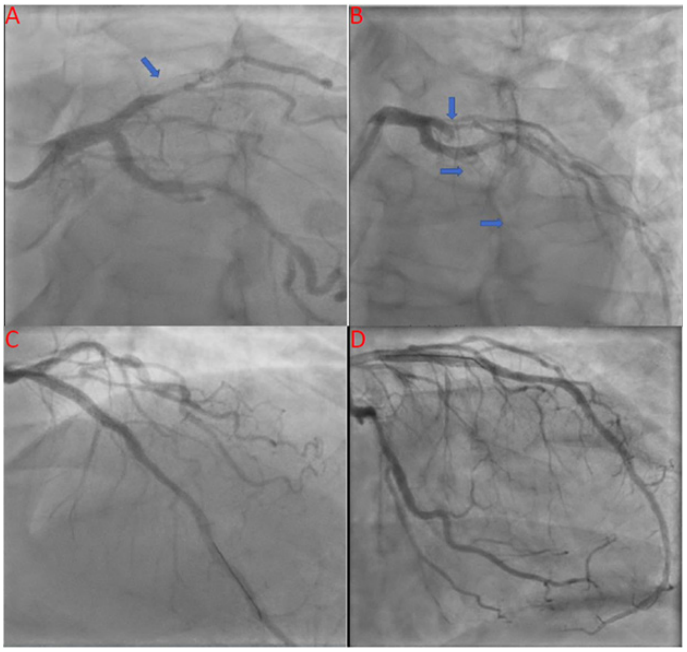

Figure 2. (A) LAO Caudal view with mid-LAD 100% thrombotic occlusion (B) LAO Cranial view with mid-LAD 100 % occlusion. (C) LAO Cranial view of revascularized LAD lesion. (D) RAO Caudal view of revascularized LAD lesion.

Results and Discussion

5-FU belongs to the fluoropyrimidine family, which is a class of antimetabolite drugs. 5-FU is a common agent used in the treatment of solid malignances. Despite its wide use, 5-FU is associated with undesired cardiotoxicity. The most common 5-FU related cardiac events are ECG changes associated with typical or atypical chest pain; however, acute coronary syndrome including MI, heart failure, arrhythmias, and sudden cardiac death have also been related to 5-FU use [1,2]. The pathophysiology of 5-FU induced cardiotoxicity is not fully delineated, but the most widely proposed mechanisms include ischemia from coronary vasospasm, vascular endothelial damage, and direct myocardial toxicity.

The theory of coronary artery vasospasm causing myocardial ischemia has been supported by numerous studies showing that many patients with suspected 5-FU cardiotoxicity lack significant coronary artery stenosis on angiography [3]. Direct visualization of coronary artery vasospasm on angiography has been observed in some cohorts, albeit inconsistently, suggesting the potential role of vasospasm in 5-FU cardiotoxicity. In our case, the etiology of ischemia was from a fixed stenotic lesion insinuating a multi-factorial mechanism of cardiotoxicity. An experimental study on rabbits exposed to 5-FU showed severe cell damage with accompanying thrombus formation supporting the potential direct cytotoxic effect of 5-FU [4]. An *in-vitro* study on human cardiomyocytes and endothelial cells demonstrated increased reactive oxygen species in cardiomyocytes exposed to 5-FU [5]. These findings support the potential thrombogenic effect of 5-FU secondary to its effect on the endothelium.

The true incidence of 5-FU cardiotoxicity is unknown as there are many confounding variables, such as a standard definition of cardiotoxicity, route and schedule of administration, presence of underlying CAD, concurrent use of other potentially cardiotoxic agents, and the methods and intensity of monitoring patients for signs and symptoms of cardiotoxicity. The majority of literature is based on retrospective studies with varying definitions of cardiotoxicity, which limits widespread inferences. Reported incidences range from 1-19. 5-FU cardiotoxicity tends to be more common during the first cycle of administration [6]. Continuous infusion regimens of ≥ 5 days carries the highest risk of toxicity followed by short-term infusion chemotherapy than bolus regimens [7,8].

Despite a preceding history of Cardio Vascular (CV) disease being a suggested risk factor for 5-FU cardiotoxicity, there is limited data on this population. An analysis of 16 clinical trials performed on 5-FU and its prodrug Capecitabine showed that 81% of studies excluded patients with preexisting CV disease [9]. As the exact interplay between CV disease and the risk for 5-FU cardiotoxicity is not well defined, there is insufficient evidence to withhold treatment in patients with underlying cardiac disease. Perhaps these patients should undergo closer cardiac monitoring as deemed suitable by their provider, as there are no established guidelines. At minimum, there should be adequate education of potential cardiac symptoms and adverse effects. Despite our patient having an unremarkable pre-chemotherapy cardiac workup, he still suffered a near life ending consequence.

If 5-FU related cardiotoxicity is suspected, the first step is immediate drug discontinuation followed by empiric treatment with antianginal therapy such as calcium channel blockers and/or nitrates, which was shown to abort anginal symptoms in~70% of patients. Rechallenging patients with suspected 5-FU cardiotoxicity is controversial. Two important factors that may influence the decision to perform a 5-FU re-challenge is the availability of effective alternative regimens and the intent of therapy (palliative versus curative). In general, re-challenge is not advised due to small studies showing a high risk of cardiotoxicity recurrence associated with severe morbidity and mortality, up to 13% in one review paper.

Perhaps underrecognized by clinicians due to the lack of widespread availability, Uridine Triacetate is an FDA approved antidote for fluoropyrimidine toxicity. To date, the largest clinical trial utilizing Uridine Triacetate was in 135 patients with fluoropyrimidine overdose or early onset of severe toxicities [10]. Complete 30-day recovery was achieved in 96% of patients with 0% mortality in any patient who received the antidote within 96 hours after drug cessation. These findings are promising for Uridine Triacetate as a safe, effective lifesaving antidote against a drug class with potentially fatal toxicities.

Conclusion

5-FU is a staple chemotherapeutic agent that is widely used in the treatment of solid malignancies. Despite its efficacy, cardiotoxicity is a major potential adverse effect that may limit its use. Unfortunately, the exact mechanisms of cardiotoxicity are not well defined. We currently do not have a reliable method to risk stratify patients who may have a higher probability of developing cardiotoxicity, such as those with pre-existing heart disease. Larger scale studies are required to develop evidence-based protocols on monitoring for cardiotoxicity and cardioprotective strategies in patients receiving 5-FU.

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The authors have nothing to disclose

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