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A Case Report on A Unique Anti-Anginal Regimen for FOLFOX Therapy for Myocardial Infarction Prevention

Romil Patel, M.D, Charlie Robin, Jason Robin, M.D*

Department of Medicine, NorthShore University Health System Evanston Hospital, Evanston, Illinois, USA

***Corresponding Author:** Jason Robin, M.D, Department of Medicine, NorthShore University Health System Evanston Hospital, Evanston, Illinois,USA

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Abstract

Background

FOLFOX (folinic acid, 5-fluorouracil, and oxaliplatin) is an adjuvant chemotherapy used for colon cancer. 5-Fluorouracil (5-FU), a component of FOLFOX, is one of the most common chemotherapy drugs used for cancer treatment. Common side effects of the FOLFOX therapy include increased risk of infection, shortness of breath, bruising, bleeding, fatigue, diarrhea, neuropathy, and mouth sores. More rare side effects, however, do include heart problems that can cause chest pain, arrhythmias, myocardial infarction, or heart failure due to coronary vasospasm caused by 5-fluorouracil.

Case Presentation

Our case shows a 68-year-old Caucasian male actively being treated with FOLFOX therapy for colon cancer and developing a severe myocardial infarction with cardiogenic shock from chemotherapy. We demonstrate a unique presentation of therapy manipulation to allow patients to receive chemotherapy while reducing the risk of recurrent myocardial infarction.

Conclusion: With this therapy modification, our patient could continue with further treatment cycles of FOLFOX therapy for his cancer treatment.

Keywords: FOLFOX therapy, Myocardial Infarction, Anti-anginal pre-therapy treatment

Introduction

FOLFOX (folinic acid, 5-fluorouracil, and oxaliplatin) is an adjuvant chemotherapy used for colon cancer. 5-Fluorouracil (5-FU), a component of FOLFOX, is one of the most common chemotherapy drugs used for cancer treatment. Fluorouracil is a heterocyclic aromatic organic compound with a similar structure to pyrimidine molecules (specifically uracil) of DNA and RNA. Fluorouracil is converted to flurodexoyuridine monophosphate (FdUMP), whichthen forms a complex with thymidylate synthase (TS) and, therefore, inhibits deoxythymidine monophosphate (dTMP) production. dTMP is necessary for DNA replication and repair, and depletion will cause cytotoxicity and cell death **[1]**. FOLFOX treatment cycles are in two-week increments and can be up to twelve cycles, depending on the individual. Typically, with administration, 5-FU is administered over an extended duration between one to two days.

Common side effects of FOLFOX therapy include diarrhea, vomiting, nausea, dehydration, neutropenia, thrombocytopenia, and leukopenia **[1]**. However, in addition to that, 5-FU has multiple cardiotoxic effects, including coronary vasospasm, cardiomyopathy, and heart failure, with the leading hypothesis for cardiotoxicity being coronary vasospasm **[2]**. Based on different studies, the incidence of cardiotoxicity ranges between 1 % to 12 % of the patient population **[3-6]**. These cardiac side effects were typically seen within the first three doses, where more than 95 % of patients presented with chest pain and over 70 % had ST/T wave changes on EKG (electrocardiogram). But most importantly, the development of vasospasm negatively affected the cumulative dose of 5-fluorouracil dose administration **[7]**. With typical presentations of cardiotoxicity, current management includes stopping the therapy and not re-introducing therapy **[8]**.

With the hypothesis of coronary vasospasm, it is theorized that with the use of anti-anginal medication, the patient should be able to tolerate the therapy of FOLFOX. There is no standard treatment recommendation for fluoropyrimidine cardiotoxicity except for the discontinuation of therapy, as mentioned earlier. However, with the treatment of anti-anginal medications such as nitrates and non-dihydropyridine calcium channel blockers, it has been reported that these anginal symptoms are aborted in about 70 % of patients **[9]**. Our study shows a case where a patient developed a severe myocardial infarction with FOLFOX therapy, but with anti-anginal pre-treatment, they could tolerate further treatment.

Case Report

This is a 68-year-old Caucasian male with a history of colon cancer actively being treated with FOLFOX therapy. The patient started chemotherapy on January 4th with a home pump of 5-FU therapy and was scheduled to have the port disconnected on January 6th. However, on the morning of January 5th, the patient developed burning chest pain and came to the emergency room, where he was found to have ST elevation in multiple leads and ST depressions in V1 and lead aVR **(figure 1)** with an associated troponin rise from 107 to 430. The patient was also in atrial fibrillation with a rapid ventricular rate, so he was started on a Cardizem drip. The patient was found to have an ST-elevation myocardial infarction and was taken to the cardiac catheterization lab. The cardiac catheterization showed minimal coronary disease but left ventricular dysfunction with an ejection fraction of approximately 35% and apical akinesis. He was subsequently transferred to the cardiac intensive care unit for monitoring. During admission, an echocardiogram was completed and showed a reduced ejection fraction of 20-25 %, severely reduced global left ventricular systolic function, and severe diffuse hypokinesis. The patient was diagnosed with a massive ST elevated myocardial infarction and cardiogenic shock with reduced ejection fraction. After cardiology and oncology consults and evaluation, it was determined that the patient's myocardial infarction was due to coronary vasospasm secondary to 5-FU therapy. The patient was stabilized, discharged, and started on metoprolol, amiodarone, sacubitril/valsartan, and apixaban until follow-up.

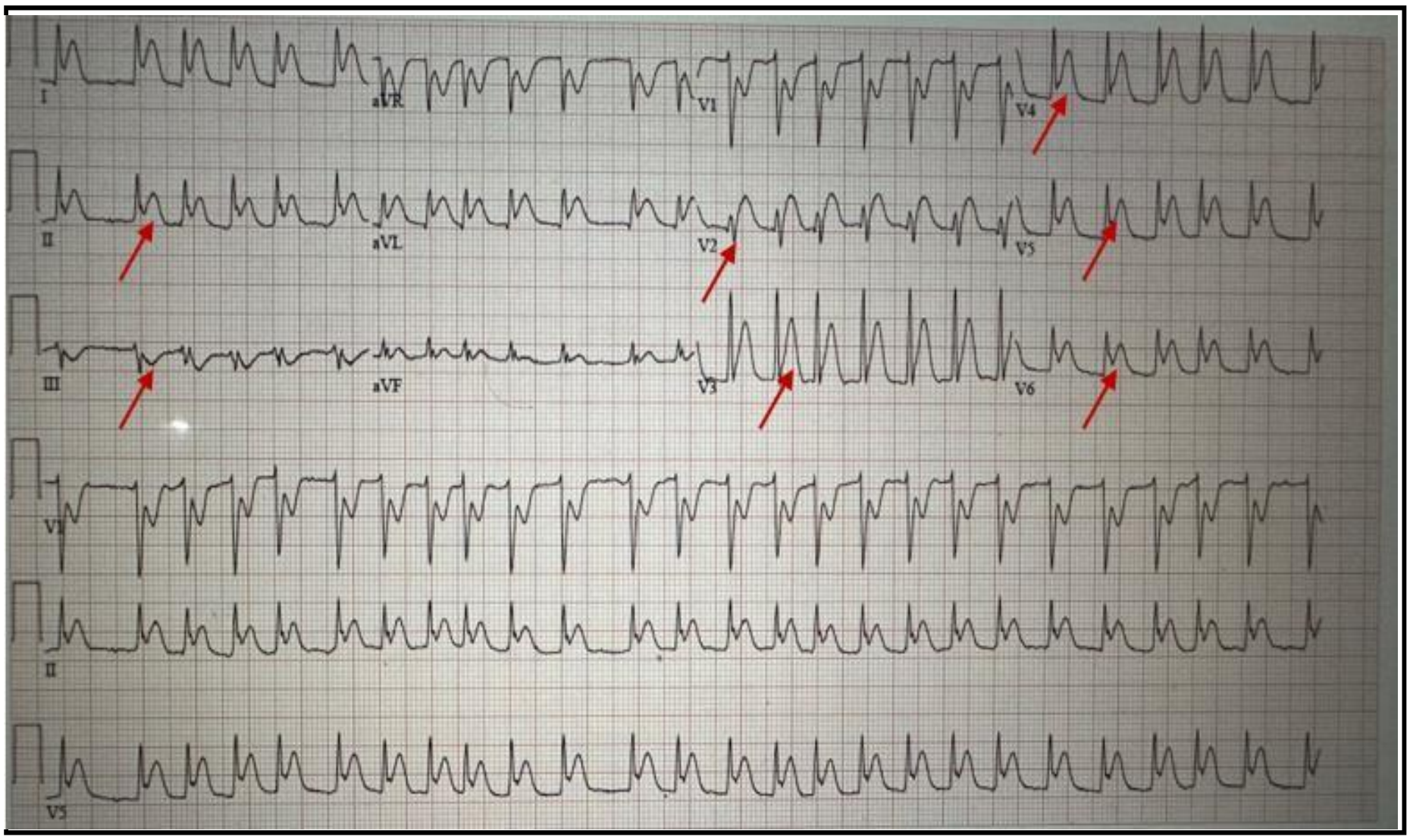

Figure 1: EKG on emergency room presentation showing multiple ST elevation in anterolateral and inferior leads.

Following discharge and follow-ups, the patient had a repeat ECHO that showed a recovery of an ejection fraction of 53%. After discussion with oncology, it was determined that the patient had a ~75-80 % chance of cure with chemotherapy. However, the patient had an increased risk of further side effects with a history of myocardial infarction with previous FOLFOX therapy. Therefore, a new protocol was developed as below to pursue additional treatment,and the patient was agreeable to treatment.

- Inpatient admission
- Changing 5-FU therapy to bolus dosing
  - Hold hypertension meds the day prior and the day of therapy to avoid hypotension with therapy below and can resume 2 days following infusion
  - 4 hours before 5-FU infusion, administer 60 mg of nifedipine ER and 60 mg of isosorbide mononitrate
  - 1 hour before 5-FU infusion, please administer diltiazem 30 mg short-acting
  - Monitor the patient closely for 90 minutes during the infusio
  - 12 hours after 5-FU bolus, repeat 60 mg of nifedipine ER and 60 mgof isosorbide mononitrate.
  - Take 60 mg of nifedipine 24 hours after infusion (half of the dose if SBP <100) and if the patient is feeling well, can discharge home.
  - Repeat regimen every 2 weeks for the remaining 3 months
  - If at any time SBP <100, should be discussed with cardiology and can give 1 L fluid bolus
  - Repeat EKG was done to monitor 24 hours administration of therapy

With the treatment above, the patient tolerated the 5-FU therapy without angina or myocardial infarction symptoms and could complete subsequent therapy sessions **(Figure 2).** Future treatments were conducted on an outpatient basis, with instructions provided to the patient to take nifedipine and isosorbide mononitrate four hours before coming to the cancer center for infusion. Once there, diltiazem was

administered, and then the information was done with close hours after information while checking blood pressure before each of those medication administrations. With this medication management, the patient could complete further treatment regimens of FOLFOX therapy without the complication of myocardial infarction.

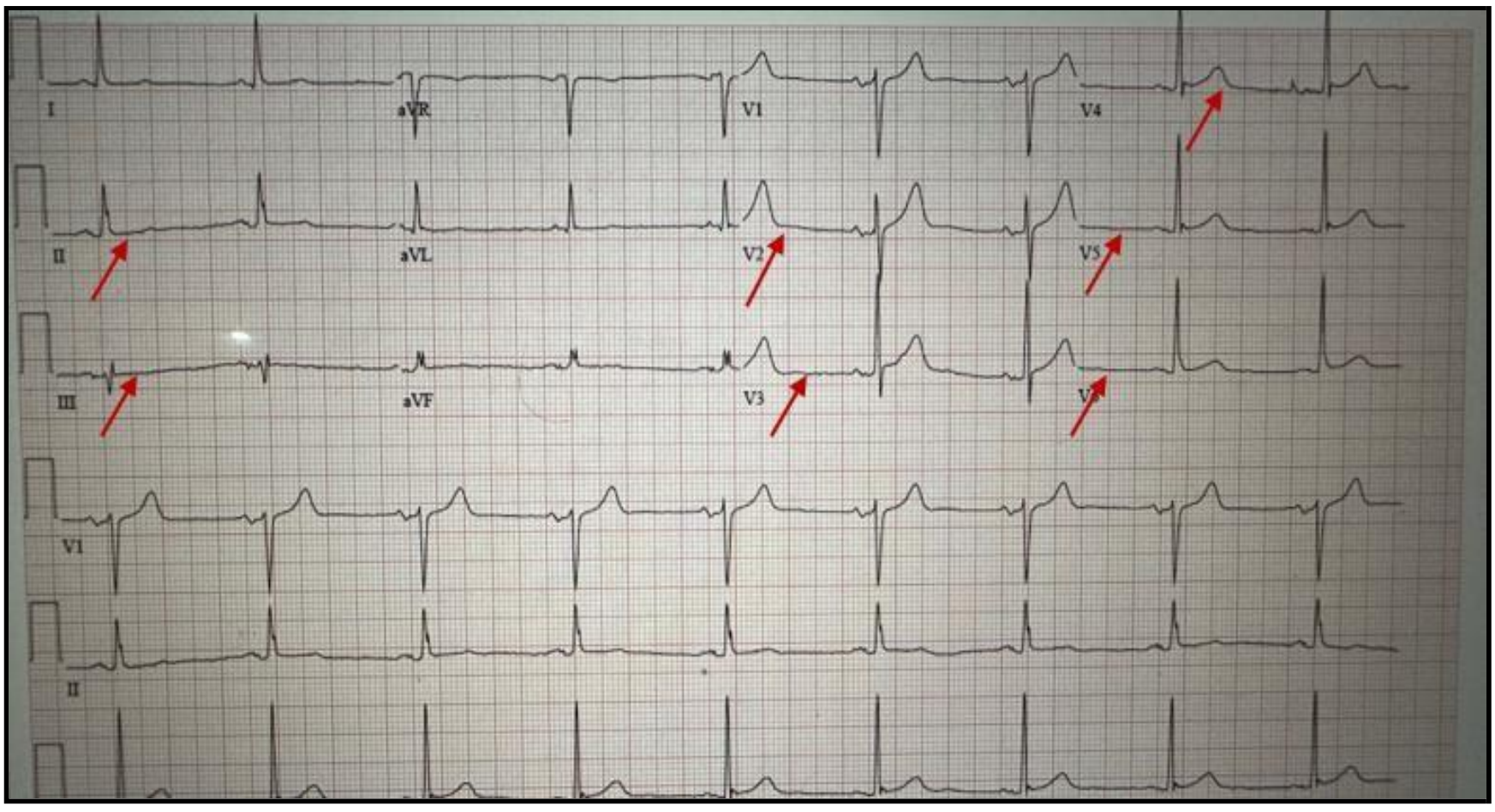

Figure 2: EKG following administration of FOLFOX therapy with the anti-anginal pre-medication treatment protocol.

Discussion

We present a unique case of a 68-year-old who, after a single dose of FOLFOX therapy, developed a severe myocardial infarction with cardiogenic shock but was able to continue FOLFOX therapy with bolus dosing and premedication with anti-hypertensive and anti-anginal medications.

5-fluorouracil, a component of FOLFOX therapy, is one of the most common medications in solid tumor therapy. It primarily works by inhibiting the enzyme thymidylate synthase, blocking the thymidine formation required for DNA synthesis. In addition to that, 5-FU is a pyrimidine analog that can replace uracil or thymine in RNA and DNA. Combining these two factors will lead to cell death in rapidly proliferating cells **[1]**.

5- Fluorouracil, however, is the second most common chemotherapeutic agent associated with cardiotoxicity only after anthracyclines, and it can manifest as angina, atrial fibrillation, myocardial infarction, or death. Patients can present with chest pain with ST-segment elevation and troponin elevations while having a normal coronary angiogram, as seen in our patient **[9,10]**. Eventhough the mechanism is poorly defined, the incidence of cardiotoxicity is poorly defined, with the most reported symptom being chest pain due to coronary vasospasm **[11]**. A possible cause ofthe vasospasm can be related to endothelial dysfunction induced by 5-FU therapy. Typically, endothelial cells can induce vasodilation after administration of acetylcholine due to the release of nitric oxide, which diffuses to the smooth muscle lining, causing relaxation and vessel dilation through the cyclic-guanosine monophosphate (cGMP) pathway. Thus, this mechanism will not occur in endothelial dysfunction and can cause vasoconstriction instead. Though coronary vasospasm has not been consistently seen on coronary angiography, peripheral observed vasoconstriction that is related to 5-FU therapy is anticipated to correlate with coronary vasoconstriction **[10]**.

Our presentation shows a severe expression of coronary vasospasm that led to myocardial infarction with cardiogenic shock for our patient. Typically, with this side effect presentation, therapy would be discontinued. However, as FOLFOX therapy is one of the most beneficial chemotherapy options, we developed a medical premedication treatment to allow therapy to continue.

In a prior study by Eskilsson et al., prophylaxis treatment of verapamil 120mg three times daily did not reduce the incidence of ischemia with continued infusion of 5-FU therapy **[12]**. However, there is a theory that joint medical management of coronary vasospasm of nitrates and calcium channel blockers can prevent cardiotoxicity **[9]** with the change to bolus infusions and the use of a combination of nifedipine, diltiazem, and isosorbide mononitrate at scheduled intervals of four hours and one hour before as well as twelve hours and twenty-four hours after, our patient was able to tolerate treatments with 5-FU therapy without signs or symptoms of myocardial infarction through the mechanism of vasodilation and arterial dilation.

Conclusion

5-FU, a component of FOLFOX therapy, is the third most common chemotherapy agent for solid tumors. The cardiotoxicity related to 5-FU therapy, which can be as severe as myocardial infarction, will limit chemotherapy treatment. We hypothesize that the mechanism ofaction for the angina symptoms is due to coronary vasospasm.

Treatment with anti-anginal medications before chemotherapy that target coronary vasospasm like nitrites or calcium channel blockers to allow vasodilation and arterial dilation can prevent further episodesof chest pain and will enable the completion of therapy. Our case highlights unique medication management that helps patientscomplete their scheduled chemotherapy with FOLFOX therapy without symptoms of myocardial infarction.

The limitations of this study are that this is a unique case that pertainsto a single patient rather than a trial in a larger patient population. However, this study does show the benefits of this therapy for this individual patient, and therefore, it can be theorized to be a reasonable option for similar patients.

Abbreviations

FOLFOX - folinic acid, fluorouracil, and oxaliplatin

5- FU – 5-Fluorouracil

FdUMP – flurodexoyuridine monophosphateTS – thymidylate synthase

dTMP – deoxythymidine monophosphateEKG – Electrocardiogram

cGMP – cyclic-guanosine monophosphate

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Written informed consent was obtained from the patient to publish this case report and any accompanying images. A copy of the written permission is available for review bythe Editor-in-Chief of this journal.

Availability of data and materials: Not applicable

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions

RP researched the background information and wrote the manuscript.JR guided throughout the process. All writers read and approved the final manuscript.

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