

CLINICAL CASE CHALLENGES

Uridine Triacetate for Severe Fluoropyrimidine Cardiotoxicity in a Patient With Thymidylate Synthase Gene Variants



Inbar Raber, MD,^a Morgan B. Frazer, PHARM.D, BCOP,^b Jessica A. Zerillo, MD, MPH,^a Aarti Asnani, MD^c

A 56-year-old woman with history of hypertension, inadequately controlled on hydrochlorothiazide and nebivolol, presented with colorectal cancer with metastases to the liver in 2019. Genotypic testing revealed that her colorectal cancer was KRAS/NRAS wild-type and microsatellite stable. FOLFOX was initiated with palliative intent, to be administered at standard doses as follows: 5-FU bolus (400 mg/m²), 5-fluorouracil (5-FU) continuous infusion (2,400 mg/m² total over days 1 and 2), leucovorin (400 mg/m²), and oxaliplatin (85 mg/m² bolus on day 1), to be repeated every 14 days.

Hours after receiving her first bolus of 5-FU, she began to experience severe nausea, vomiting, and diarrhea. She presented to the emergency department, where she was found to have acute kidney injury with an increase in her creatinine from a baseline of 0.7 mg/dl, measured 1 week prior to chemotherapy, to 1.7 mg/dl in the emergency room. Electrolytes including potassium levels were within normal limits. An infectious work-up was performed, and blood, urine, and fecal cultures as well as testing for clostridium difficile and norovirus were all negative. She was thought to be hypovolemic and was treated with intravenous fluids and admitted to the oncology service.

On the first day of her hospitalization, she became tachycardic, and an electrocardiogram (ECG) showed atrial fibrillation with a ventricular rate of 161 beats/min. There were no ischemic ST- or T-wave changes, and she did not experience any chest pain. No recent ECGs were available for comparison. Her troponin was 0.02 µg/l (limit of detection 0.01 µg/l) which was stable on serial measurements. After receiving 5 mg intravenous metoprolol for rate control of atrial fibrillation, she became profoundly hypotensive and required transfer to the intensive care unit, where she was started on norepinephrine and phenylephrine for vasopressor support and amiodarone for rhythm control. She was additionally started on intravenous heparin for anticoagulation. Her lactate was elevated to 3.6 mmol/l, and she developed elevated liver enzymes consistent with ischemic hepatitis. A transthoracic echocardiogram demonstrated a reduced left ventricular (LV) ejection fraction of 20% as measured by the biplane method of disks, with global hypokinesis and no LV thrombus, left atrial enlargement (left atrial volume 48 ml/m², normal <35 ml/m²), mild LV hypertrophy, normal LV end-diastolic dimension, no significant valvular disease, and no pericardial effusion. There was no prior echocardiogram for comparison.

The patient's ventricular rates improved with amiodarone, although she remained in atrial fibrillation and continued to require norepinephrine for vasopressor support. The cardio-oncology and medical oncology

From the ^aDepartment of Internal Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA; ^bDepartment of Pharmacy, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; and the ^cCardioVascular Institute, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: CardioOncology* [author instructions page](#).

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**ABBREVIATIONS
AND ACRONYMS****5-FU** = 5-fluorouracil**DPD** = dihydropyrimidine
dehydrogenase**ECG** = electrocardiogram**TYMS** = thymidylate synthase

services were consulted and recommended treatment with uridine triacetate, as the timing of symptoms within 96 h of 5-FU administration were consistent with severe fluoropyrimidine cardiotoxicity. On day 2 of her hospitalization, she was initiated on standard dosing of uridine triacetate (10 g of uridine triacetate every 6 h for 20 doses) (**Figure 1A**).

On day 3 of her hospitalization, her blood pressures normalized and she no longer required vasopressors, although she remained in atrial fibrillation. A transesophageal echocardiogram excluded the presence of an atrial thrombus and demonstrated mildly depressed ejection fraction (not quantified), following which electrical cardioversion was performed with restoration of sinus rhythm. She was initiated on intravenous diuresis, resulting in improvement in her kidney function to her baseline creatinine of 0.7 mg/dl as well as normalization of her lactate and liver enzymes. Prior to discharge, metoprolol, lisinopril, and spironolactone were initiated as guideline-directed medical therapy for heart failure. FOLFOX was discontinued with a plan for reassessment of her cancer treatment options as an outpatient.

A repeat echocardiogram 3 weeks after her hospitalization showed normalization of LV function (LV ejection fraction >55%), suggesting either direct myocardial injury from 5-FU that resolved upon discontinuation of the offending agent, or potentially a stress cardiomyopathy in the setting of systemic fluoropyrimidine toxicity. Tachycardia-induced cardiomyopathy was also considered, but was felt to be less likely in the absence of any prior signs or symptoms of atrial fibrillation. Three weeks after discharge from the hospital, she underwent continuous-recording ambulatory ECG monitoring for 10 days, which demonstrated no further episodes of atrial fibrillation.

She underwent testing for gene mutations with the 5-FU Toxicity and Chemotherapeutic Response panel (ARUP Laboratories, Salt Lake City, Utah). Testing was performed to identify genetic variants in thymidylate synthase (TYMS), the target enzyme for 5-FU activity responsible for DNA synthesis, and dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme for 5-FU catabolism (**Figure 1B**). She was found to have 2 variants in the TYMS gene associated with fluoropyrimidine hypersensitivity, specifically a 6 base-pair deletion at the 3' untranslated region and a 28 base-pair tandem repeat in the 5'-promoter enhancer region with a G>C

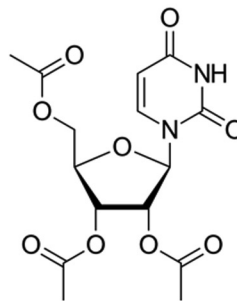
FIGURE 1 Treatment of Severe Fluoropyrimidine Toxicity and Evaluation for Genetic Risk**A**

FDA approval: for severe fluoropyrimidine toxicity in 2015

Population: adult and pediatric patients

Indications:

- 1) Severe cardiac or central nervous system toxicities
- 2) Severe gastrointestinal toxicity or neutropenia

Uridine Triacetate

Side effects: vomiting (10%), nausea (5%), diarrhea (3%)

Cost: \$10,000+ per course, depending on hospital and insurer

Dose: 10 grams orally every 6 hours for 20 doses

Timing: within 96 hours of fluoropyrimidine administration

B**Genetic Variants****Dihydropyrimidine Dehydrogenase (DPD)**

Genetic variants: rs55886062, rs3918290, rs67376798

Effect: Accumulation of 5-FU

Dosing Recommendation:

One nonfunctional allele: 50% dose reduction; titration based on toxicity

Two nonfunctional alleles: Alternative drug

Thymidylate Synthase (TYMS)

Genetic variants: 5' promotor tandem repeat, 3' untranslated region deletion

Effect: Increased response to 5-FU

Dosing Recommendation:

No guideline-based dosing recommendations

(A) Uridine triacetate indications and dosing. (B) Genetic variants associated with fluoropyrimidine hypersensitivity. 5-FU = 5-fluorouracil; DPD = dihydropyrimidine dehydrogenase; FDA = U.S. Food and Drug Administration; TYMS = thymidylate synthase.

single nucleotide polymorphism. These findings supported the diagnosis of severe fluoropyrimidine toxicity, and she was transitioned to palliative chemotherapy with irinotecan and cetuximab for continued treatment of her metastatic colorectal cancer.

DISCUSSION

The fluoropyrimidines are important chemotherapeutic agents used in the treatment of solid tumors, including colorectal cancers. Cardiotoxicity is a feared complication, and severe cardiotoxicity occurs in about 5% of patients treated with 5-FU and capecitabine (1). Although the most common cardiac manifestation of 5-FU or capecitabine toxicity is coronary vasospasm, life-threatening cases of cardiogenic shock and cardiomyopathy have been reported (2). Uridine triacetate is a pyrimidine analog that competitively inhibits 5-FU incorporation into RNA. It was approved by the U.S. Food and Drug Administration in 2015 as an antidote for severe fluoropyrimidine toxicity, including cardiotoxicity. The first dose of uridine triacetate should be given within 96 h of 5-FU toxicity, and administered orally at 10 g every 6 h for 20 doses in adults. At present, a potential limitation of uridine triacetate is its price, as a course of treatment can cost tens of thousands of dollars depending on hospital contracts and the patient's insurance coverage. Multidisciplinary discussion and a careful assessment of confounding diagnoses are therefore paramount when considering this agent in patients suspected to have fluoropyrimidine toxicity.

Indications for uridine triacetate include the following: emergent reversal of known life-threatening fluoropyrimidine overdose, presence of life-threatening cardiac or central nervous system toxicities, and the presence of early-onset severe gastrointestinal toxicity or myelosuppression. In 2 open-label clinical trials with 142 patients collectively, 96% of patients survived fluoropyrimidine overdose after receiving uridine triacetate, compared with 16% in a historical cohort who did not receive uridine triacetate (3).

Prospective identification of patients at risk for fluoropyrimidine cardiotoxicity remains a clinical challenge. Genetic variant testing is emerging as a potential strategy; however, it is not currently recommended for routine screening before treatment, given the variable penetrance and phenotypic variation that has been reported among gene carriers for chemotoxicity (4,5). Although there are insufficient data to recommend genetic testing in all patients with fluoropyrimidine cardiotoxicity, this strategy can be helpful in patients who present with cardiotoxicity early in the course of therapy (within the first 2 cycles) and also manifest other signs of systemic fluoropyrimidine toxicity, such as significant nausea and vomiting or early-onset cytopenias. Our patient presented with concurrent cardiotoxicity and gastrointestinal symptoms shortly after her first exposure to 5-FU. In light of her TYMS variants, the decision was made to forego additional fluoropyrimidine treatment in favor of an alternative regimen.

Several nonfunctional alleles of DPD (rs55886062, rs3918290, and rs67376798) have been associated with an increased risk of cardiotoxicity (6). In a study of 258 healthy volunteers, decreased DPD activity affected approximately 8% of African Americans and 2.8% of Caucasians (7). Patients with 1 nonfunctional DPD allele are recommended to have an initial fluoropyrimidine dose reduction of 50%, and those with 2 nonfunctional DPD alleles are recommended to receive an alternate therapy (8). Similarly, polymorphisms in untranslated regions of TYMS have been associated with predisposition to fluoropyrimidine toxicity, although their incidence in the general population is not well described and they are not typically associated with severe cardiotoxicity (9). While the incidence of severe fluoropyrimidine toxicity ranges from 50% to 88% among heterozygote carriers of a nonfunctional DPD allele (6), the incidence of severe toxicity is lower (18% to 43%) among heterozygote or homozygote carriers of TYMS variants (9). A 6-base pair deletion in the 3' untranslated region of TYMS has been shown to cause decreased mRNA stability and lower expression of TYMS (10). No specific guidelines exist for dose adjustments for patients with TYMS genetic variants.

In conclusion, the fluoropyrimidines 5-FU and capecitabine can be associated with a range of cardiotoxic phenotypes, including cardiomyopathy and arrhythmia. The present case demonstrates the use of uridine triacetate as an antidote for severe 5-FU cardiotoxicity. Rapid diagnosis of severe fluoropyrimidine toxicity is important to enable emergent administration of uridine triacetate within the 96-h time frame. The diagnosis of severe fluoropyrimidine toxicity is primarily based on clinical assessment. However, genetic variant testing for polymorphisms in the enzymes DPD and TYMS can support the diagnosis of severe fluoropyrimidine toxicity

and guide further oncologic treatment. A multidisciplinary approach incorporating oncology and cardiology can facilitate both inpatient and outpatient management of fluoropyrimidine-associated cardiovascular toxicity.

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ADDRESS FOR CORRESPONDENCE: Dr. Aarti Asnani, Center for Life Sciences, 3 Blackfan Circle, Room 911, Boston, Massachusetts 02115. E-mail: aasnani@bidmc.harvard.edu. Twitter: [@aartiasnani](https://twitter.com/aartiasnani).

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