



Early-Onset 5-Fluorouracil Toxicity: Clinical Indicators of a Life-Threatening Emergency

A white paper and clinical action plan

Recognizing the Signs of Early-Onset 5-FU Toxicity Can Save Lives

Toxicity of 5-Fluorouracil

5-fluorouracil (5-FU) and capecitabine are potent chemotherapeutic agents commonly associated with mild to moderate side effects, such as grade 1-2 oral mucositis, nausea, vomiting, and diarrhea, which can manifest over a period of weeks and multiple cycles of 5-FU treatment.^{1,2} However, approximately 10% of patients receiving 5-FU or capecitabine suffer from potentially serious toxic reactions, and in nearly 1% of patients this toxicity can be fatal (Figure 1).³⁻⁷

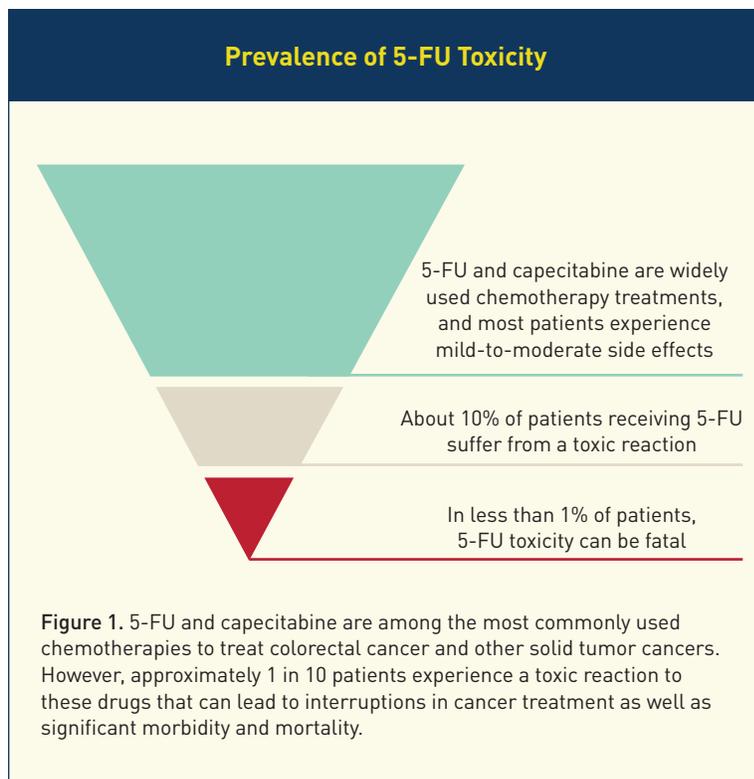
Emerging evidence suggests that an underrecognized subset of patients exhibits profound, often unexplained sensitivity to 5-FU or capecitabine which leads to the rapid onset of severe, potentially life-threatening toxicity within hours of the first or second treatment cycle of 5-FU.¹

Warning signs of this "early-onset" 5-FU toxicity may include grade 3-4 oral mucositis, intractable vomiting and/or diarrhea, and neutropenia (Table 1).⁵⁻⁹ Less commonly, patients may also exhibit signs of cardiotoxicity or central neurologic toxicity manifesting as dizziness, confusion, or changes in cognition (Table 1).¹⁰⁻¹²

In many cases, the signs of early-onset 5-FU toxicity may be qualitatively similar to common adverse reactions to 5-FU, resulting in diagnostic challenges for oncology teams. **However, the key differentiators that should alert healthcare professionals to the presence of early-onset 5-FU toxicity are the severity and timing of these symptoms.** For example, mouth sores that develop several weeks into a 5-FU treatment cycle are bothersome yet common adverse events, while those that develop within 96 hours may signal a potential oncologic emergency.¹³ In a prospective study of 243 patients with colorectal cancer treated with 5-FU and leucovorin, 57% of toxic episodes that required hospitalization and 80% of episodes that resulted in death occurred during the first treatment cycle.¹⁴ Although early-onset 5-FU toxicity is an unpredictable, rapidly progressing, and potentially life-threatening situation, mortality is often avoidable given proper education and awareness among both patients and healthcare professionals.

Early-Onset 5-FU Toxicity: A Clinical Case Study

Severe 5-FU toxicity can occur for a variety of reasons, including medication errors, dosage miscalculations, or impaired drug clearance due to renal failure or genetic influences.¹⁵ Conversely, early-onset 5-FU toxicity often presents unexpectedly in patients receiving standard therapeutic doses of 5-FU, as highlighted in a recent case study of a 73-year-old man treated for stage 1 squamous cancer of the anal verge (adapted from Vaudo et al, 2016).⁹



Medical history

- Patient had a history of hypertension, coronary artery disease, chronic thrombocytopenia, and anal fissure

Chemotherapy treatment regimen

- Day 1: Patient received radiation and concurrent chemotherapy, including mitomycin 10 mg/m² followed by 5-FU 4000 mg/m² administered over 4 days via continuous infusion
 - Baseline white blood cell count (WBC) was 4.49 K/μL, absolute neutrophil count (ANC) of 2.03 K/μL, and platelet count of 124 K/μL; liver and renal function were within normal range
- Day 4: Patient completed 5-FU infusion uneventfully

Course of toxicity

- Day 5: Patient returned to the oncology clinic complaining of fatigue and sporadic episodes of nausea, which was treated with prochlorperazine
- Day 6: Patient admitted to the emergency department after experiencing a brief syncopal episode at home, during which he was found to be cyanotic and unresponsive
 - On presentation, patient reported multiple painful ulcers in mouth and 2 episodes of diarrhea that resolved with loperamide
 - Electrocardiogram (ECG) indicated sinus rhythm, borderline interventricular conduction delay, QTc 443, and inferior Q waves with T-wave inversions comparable to a baseline ECG
- Day 7: Patient developed oral mucositis and a fever of 100.3°F. Overnight the patient suffered a second syncopal episode; repeat ECG showed no significant changes
- Day 8: Patient's oral mucositis worsened to grade 3 based upon Common Terminology Criteria for Adverse Events (CTCAE), resulting in difficulty swallowing
- Day 9: Fever and mouth ulcers worsened, patient continued to be neutropenic, with a WBC of 0.82 K/μL and ANC of 0.43 K/μL
 - 86 hours after completing 5-FU infusion, patient began treatment with VISTOGARD® (uridine triacetate) oral granules 10 grams every 6 hours for a total of 20 doses
- Days 13-15: Patient's oral mucositis showed marked improvement, and ANC normalized to 280 K/μL
 - Treatment with VISTOGARD® was completed after 5-day course of 20 doses

Follow-up

- Days 23-30: On follow-up visits to the oncology clinic, the patient presented in better health with no remaining indications of 5-FU toxicity
 - Patient resumed radiation treatment for anal cancer

Signs of 5-FU Toxicity		
Symptom	Expected reactions (Multiple weeks/ 5-FU cycles)	Red flags (< 4 days after treatment)
Oral mucositis	Mild-moderate pain, not interfering with oral intake	Severe mucositis, interfering with oral intake
Neutropenia	ANC ≥ 1500/mm ³	ANC < 1000/mm ³
Fatigue	Mild fatigue, does not alter daily activities	Rapid onset of severe fatigue, causing patient to be bed-bound
Skin reactions	Scattered redness or darkening, not debilitating	General rash or ulcerating dermatitis
Diarrhea	Increase of up to 6 stools over baseline	Severe diarrhea: ≥ 7 stools per day over baseline
Vomiting	1-5 episodes per day over pretreatment	≥ 6 episodes in 24 hours over pretreatment
Fever	None	> 101°F with neutropenia
Cardiotoxicity	None	Chest pain, myocardial ischemia, arrhythmia, left ventricular dysfunction, or cardiac arrest
Neurologic toxicity	None	Altered mental status, dizziness, confusion, cerebellar ataxia, or changes in cognition

Table 1. Common adverse events, such as nausea or vomiting, typically occur weeks after initiating 5-FU treatment, while severe reactions that occur within 96 hours of starting 5-FU may be indicative of early-onset toxicity.⁷

Treatment of Early-Onset 5-FU Toxicity

The case study by Vaudo and colleagues underscores the importance of treating early-onset 5-FU toxicity quickly and aggressively to prevent prolonged and potentially fatal overexposure to 5-FU. When early-onset 5-FU toxicity is suspected, the identification of an underlying genetic or physiologic cause of 5-FU overexposure is *not* a prerequisite to initiate immediate treatment.¹

Currently, aggressive supportive care measures—including colony-stimulating factors, antibiotics, antiemetics, and hydration—are the mainstay of treatment.^{2,15} However, a recent study suggests that supportive care alone may have limited success in preventing 5-FU-related deaths.¹⁶ Among 58 cases of early-onset 5-FU toxicity and 145 cases of early-onset capecitabine toxicity over the last 50 years, all 203 cases had fatal outcomes despite the use of supportive care measures.¹⁶ In a separate analysis of 5-FU overdose cases, only 16% of patients survived when treated with supportive care alone.¹⁷

Alternatively, a recently approved antidote for 5-FU toxicity, VISTOGARD®, has demonstrated significantly higher survival rates in clinical trials.¹⁷ Across 135 cases of 5-FU/capecitabine overdose or early-onset toxicity, the overall survival rate was 96% when VISTOGARD® was administered within 96 hours of 5-FU infusion.¹⁷ In addition, 33% of study participants were able to resume chemotherapy within 1 month after treatment with VISTOGARD®.¹⁷ Thus, where supportive care has been unable to successfully resolve severe or early-onset 5-FU toxicity, prompt application of novel treatment options, such as VISTOGARD®, could potentially prevent fatal outcomes.

Implications for Oncology Nurses

In an effort to improve clinical care and management of 5-FU toxicity, the Institute for Safe Medication Practices (ISMP) recommends proper education of nurses and staff to facilitate prompt recognition of 5-FU toxicity, defining treatment protocols for 5-FU toxicity, and administering uridine triacetate as soon as possible.¹⁸

In addition to following recommendations from ISMP, oncology nurses are encouraged to implement the following 5-FU Toxicity Clinical Preparedness Action Plan to optimize patient outcomes when 5-FU overdose or early-onset 5-FU toxicity is suspected.

5-FU Toxicity Clinical Preparedness Action Plan

Phase 1: Educate Patients & Caregivers	Phase 2: Evaluate Your Patients	Phase 3: Treat Early-Onset 5-FU Toxicity	Phase 4: Educate Your Peers
<ul style="list-style-type: none"> • Provide education on 5-FU therapy: expected side effects vs signs of severe or early-onset toxicity • Instruct patients and caregivers to stay alert for and immediately report any unusual or unexpected side effects, regardless of severity • Assure patients that reporting side effects is an important part of ensuring their health and safety during chemotherapy 	<ul style="list-style-type: none"> • For patients who report 5-FU toxicity that is unusual in timing or severity, perform a prompt, thorough examination • Determine if the patient's symptoms are typical at their stage of 5-FU treatment • Grade 5-FU toxicity using an objective system, such as the Common Terminology Criteria for Adverse Events⁸ 	<ul style="list-style-type: none"> • Develop a clear triage protocol for patients with a known overdose of 5-FU or who exhibit signs of early-onset 5-FU toxicity¹⁷ • Administer VISTOGARD® 10 mg orally every 6 hours for 20 doses at the first sign of overdose or early-onset toxicity¹⁷ • Avoid medications that might interfere with absorption of VISTOGARD® or reduce clearance of 5-FU¹⁸ 	<ul style="list-style-type: none"> • Promote awareness and recognition of early-onset 5-FU toxicity among oncologists, nursing staff, physician assistants, and other healthcare professionals to improve preparedness and clinical care

5-FU toxicity is a potentially life-threatening medical emergency that requires a comprehensive and cooperative treatment approach by the entire oncology team. Timely recognition and prompt medical treatment with appropriate therapies may help prevent unnecessary morbidity and mortality related to 5-FU.

Indication

VISTOGARD® is indicated for the emergency treatment of adult and pediatric patients:

- following a fluorouracil or capecitabine overdose regardless of the presence of symptoms, or
- who exhibit early-onset, severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity and/or neutropenia) within 96 hours following the end of fluorouracil or capecitabine administration

Limitations of use

VISTOGARD® is not recommended for the non-emergent treatment of adverse reactions associated with fluorouracil or capecitabine because it may diminish the efficacy of these drugs.

Important Safety Information

- In clinical studies, adverse reactions occurring in >2% of patients receiving VISTOGARD® included vomiting (10%), nausea (5%), and diarrhea (3%).
- One person receiving uridine triacetate experienced grade 3 nausea and vomiting.
- VISTOGARD® was discontinued for adverse reactions in 2 (1.4%) patients.

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