

# 5-Fluorouracil and Capecitabine

## Assessment and treatment of uncommon early-onset severe toxicities associated with administration

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**BACKGROUND:** Uncommon early-onset severe toxicities from 5-fluorouracil (5-FU) and capecitabine can be fatal if early warning signs are not recognized and treated promptly.

**OBJECTIVES:** This article delineates the differences between expected side effects and uncommon early-onset severe toxicities from 5-FU and capecitabine. It also provides background for understanding the reasons patients may develop these toxicities and reviews the efficacy of standard supportive care against a novel therapy (uridine triacetate).

**METHODS:** A panel of nurses convened to review the literature about toxicities associated with 5-FU and capecitabine administration and determined methods to educate nurses about toxicities and treatment.

**FINDINGS:** Standard supportive care for 5-FU and capecitabine toxicities is associated with high fatality rates. Uridine triacetate treatment within 96 hours of administration is associated with survival.

### KEYWORDS

fluorouracil; capecitabine; uridine triacetate; overdose; side effects

### DIGITAL OBJECT IDENTIFIER

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**CHEMOTHERAPY WITH 5-FLUOROURACIL (5-FU) OR CAPECITABINE** (the oral prodrug of 5-FU) is an important cancer treatment. In the United States, about 275,000 patients with cancer receive 5-FU each year (Ma et al., 2017), and more than 1,300 patients die annually from 5-FU toxicity, which is the equivalent of three to four patients each day (Ma, 2017).

Commonly used to treat a range of solid tumors, 5-FU and capecitabine have well-established safety and efficacy profiles. Typically, 5-FU is administered via IV infusion during a period of one to four days or in the form of oral capecitabine; it is administered at or near the maximum tolerated doses and in combination with other anticancer agents (Boisdron-Celle et al., 2017). Although 5-FU and capecitabine are usually well tolerated, oncology nurses should be aware of important differences between common side effects and uncommon early-onset severe toxicities. Severe, or grade 3 and 4, according to the Common Terminology Criteria for Adverse Events (National Cancer Institute, 2010), toxicities occur when patients are overexposed to 5-FU or capecitabine through metabolic dysfunction or overdose.

Traditional means of supportive care for these uncommon severe toxicities are often insufficient. In 2016, the U.S. Food and Drug Administration (FDA) reviewed data from the Adverse Event Reporting System, specifically postmarketing voluntary reports of deaths in patients who had early-onset severe or life-threatening toxicities after 5-FU or capecitabine administration (Ison et al., 2016). This review examined 203 cases (58 for 5-FU and 145 for capecitabine); all patients were treated only with traditional supportive care (symptom management), and in all cases, the patients died.

Prior to December 2015, patients experiencing severe toxicity following 5-FU or capecitabine treatment could be treated only with traditional supportive care; no antidote to overexposure had been approved by the FDA. In 2014, the FDA granted uridine triacetate fast-track designation (expedited review to facilitate development of drugs that treat a life-threatening condition), and it was approved by the federal agency in December 2015 to treat patients experiencing either (a) an overdose of 5-FU or capecitabine or (b) early or unexpectedly severe toxic reactions to these drugs (Center for Drug