Uridine triacetate provides antidote for 5-fluorouracil overdose and toxicity

Fluorouracil or 5-fluorouracil (5-FU) is an effective cytotoxic drug that is incorporated into various chemotherapeutic regimens for the treatment of numerous tumor types, but its clinical utility is limited by its narrow therapeutic index and the risk of overdose and serious toxic effects. Until recently, these outcomes were managed with supportive care, but the approval of uridine triacetate provides an antidote to reverse 5-FU-associated toxicity, to prevent death and potentially allow some patients to resume chemotherapy.

With its approval by the US Food and Drug Administration (FDA) in late 2015, uridine triacetate is indicated for the emergency treatment of adult and pediatric patients who experience overdose, regardless of symptoms, or early-onset of serious or life-threatening toxicity, following the administration of 5-FU or capecitabine.

Approval was based on the demonstration of the efficacy and safety of uridine triacetate in 2 single-arm, open-label, expanded access studies performed in 135 patients with 5-FU (n = 112) or capecitabine (n = 5) overdose or serious or life-threatening toxicities within 96 hours of receiving 5-FU (n = 18). The serious or life-threatening toxicities included those involving the central nervous system, such as encephalopathy and acute mental status change, the cardiovascular system, the gastrointestinal system, including mucositis, and the bone marrow.

The study drug was administered at a dose of 10 g orally every 6 hours for 20 doses in adult patients and of 6.2 g/m^2 of body surface area orally every 6 hours for 20 doses in the pediatric patients. The median age of patients enrolled in the study was 59 years, 56% were men, 72% were white, and there were 6 pediatric patients (aged between 1 and 7 years).

Overdose was defined as administration of 5-FU at a dose or infusion rate greater than intended or greater than the maximum tolerated dose. Among patients who experienced overdose, 94% was by infusion rate only, 4% by dose only, and 3% by both infusion rate and dose.

The primary endpoint of these trials was survival at 30 days or until chemotherapy could resume, if that was before 30 days. Among the patients treated for overdose, 97% were still alive at 30 days, and 89% of patients with early-onset severe or life-threatening toxicity were still alive at 30 days. Around one-third of patients were able to resume chemotherapy in less than 30 days following treatment with uridine triacetate.

The most common adverse events of any grade were vomiting (10%), nausea (5%), and diarrhea (3%). One patient experienced a serious adverse event – grade 3 nausea and vomiting. Treatment with uridine triacetate was discontinued in 2 patients, and 5 patients died within 30 days of their last dose, though none of those deaths were considered attributable to the study drug.

The prescribing information for uridine triacetate, which is marketed as Vistogard by Wellstat Therapeutics, details the recommended dosage as 10 g orally every 6 hours for 20 doses in adults and 6.2 g/m^2 of body surface area (not to exceed 10 g per dose) orally every 6 hours for 20 doses in pediatric patients. Uridine triacetate can be administered with or without a meal.

There are no warnings and precautions or contraindications associated with uridine triacetate. Very few case reports of its use during pregnancy have been described, and there

What's new, what's important

Uridine triacetate is a pyrimidine analog that was approved by the FDA in 2015 for the emergency treatment of 5-FU or capecitabine overdose regardless of symptoms in adult and pediatric patients, or those who have early-onset, severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (eg, gastrointestinal toxicity and/or neutropenia) within 96 hours of the end of fluorouracil or capecitabine administration. It is not indicated for the management of the expected side effects or non-emergent management of adverse reactions. Ideally, it should be given in the first 96 hours; the safety of this agent has not been not well studied beyond 96 hours.

The FDA-approved dose of this drug in adults is 10 g (or 1 packet) orally every 6 hours for 20 doses, without regard to meals. In pediatric patients, the dose is 6.2 g/m^2 of body surface area (not to exceed 10 g per dose) orally every 6 hours for 20 doses, without regard to meals.

Uridine triacetate is a well-tolerated drug, with minimal side effects such as vomiting, diarrhea, and nausea occurring in fewer than 2% of patients who receive it.

— Jame Abraham, MD, FACP (abrahaj5@ccf.org)

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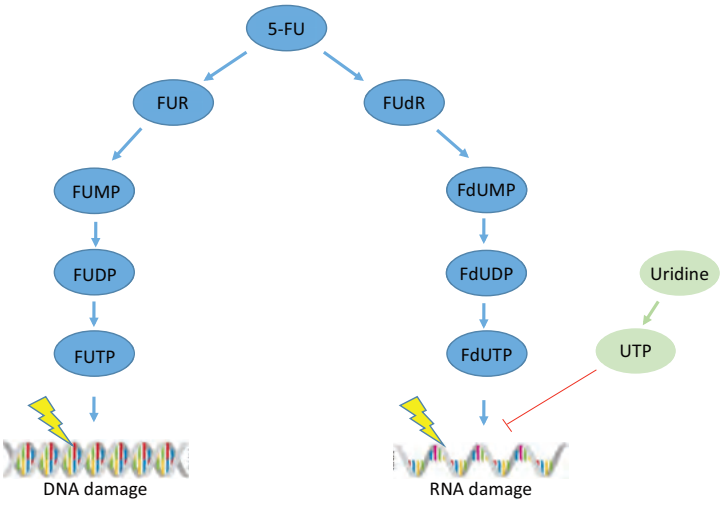
Mechanism of action: uridine triacetate

Antidote blocks RNA-based cytotoxic effects of 5-FU

5-FU is an antimetabolite with cytotoxic activity that is frequently exploited as a part of various chemotherapy regimens. The drug has a narrow therapeutic index and is often used close to its maximum tolerated dose. According to 2008 estimates from the National Institutes of Health, about 275,000 patients in the United States are treated with 5-FU each year and around 3% of them will experience a toxic reaction either due to unintentional overdose or factors that predispose patients to toxic side effects.

Currently, patients who overdose or experience serious toxicity are managed with supportive care, but it is estimated that there are more than 1,300 deaths annually associated with 5-FU treatment. The FDA approval of uridine triacetate offers an antidote to reverse the toxic effects of 5-FU when patients experience overdose or serious toxic effects.

5-FU exerts its cytotoxic activity predominantly through the activity of 2 of its metabolites, fluorodeoxyuridine monophosphate (FdUMP) and fluorouridine triphosphate (FUTP). FdUMP binds to thymidine synthase, an enzyme that is required for the production of thymidine, one of the building blocks of DNA, thus interfering in DNA synthesis. FUTP is incorporated into RNA, disrupting its processing and function.



5-FU exerts its cytotoxic activity by interfering with DNA synthesis and disrupting the processing and function of RNA and occasionally leads to serious toxicities when used as part of a chemotherapy regimen. The oral prodrug uridine triacetate is converted into uridine in the circulation and subsequently into uridine triphosphate, which competes with one of the metabolites of 5-FU for incorporation into RNA, thus acting as an antidote to 5-FU and limiting the cell death and damage it causes.

5-FU, 5-fluorouracil; FdUDP, fluorodeoxyuridine diphosphate; FdUMP, fluorodeoxyridine monophosphate; FdUTP, fluorodeoxyuridine triphosphate; FUDP, fluorouridine diphosphate; FUdR, fluorodeoxyuridine; FUMP, fluorouridine monophosphate; FUR, fluorouridine; FUTP, fluorouridine triphosphate; UTP, uridine triphosphate

Uridine triacetate is an oral acetylated prodrug of the nucleotide uridine, a building block of RNA. Acetylation of uridine allows for easier passage across the gastrointestinal mucosa, resulting in higher circulating levels of uridine than administering uridine itself. After administration, it is deacetylated and converted into uridine triphosphate, which competes with FUTP for incorporation into RNA, thus helping to block some of the cytotoxic effects of 5-FU.

are no data on its effects in lactating women. Although 30% of patients included in the pivotal clinical trials were 65 years or older, including 11% who were 75 or older, the numbers were insufficient to determine whether they respond differently from younger patients.

Uridine triacetate is not recommended for use in nonemergent treatment of toxicities associated with 5-FU or capecitabine, and its safety and efficacy has not been evaluated when treatment is initiated more than 96 hours after the end of 5-FU or capecitabine administration.

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