5-Fluorouracil and Capecitabine

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

Edith Brutcher, RN, MSN, APRN-BC, AOCNP®, Deb Christensen, MSN, APRN-BC, AOCNS®, HNB-BC, Melissa Hennessey Smith, MSN, AGPCNP-BC, Judy B. Koutlas, RN, MS, OCN®, Jean B. Sellers, RN, MSN, Tahitia Timmons, MSN, RN-BC, OCN®, and Joanna Thompson, RN, BSN

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

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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

Evaluation and Research, 2015). Uridine triacetate treatment is most effective within a 96-hour (or four-day) window; consequently, nurses must be aware of the uncommon side effects of 5-FU and capecitabine, educate patients about these toxicities, and know that life-saving treatment is available.

The incidence of toxicity with 5-FU and capecitabine has been reported to be as much as 40% (Meulendijks et al., 2016). In a cohort of 1,463 patients treated with capecitabine, 22% had a toxicity-related adverse outcome, 16% had severe toxicity, 9% had toxicity that resulted in hospitalization, and 10% had to stop treatment because of toxicity (Meulendijks et al., 2016). Patients experience severe adverse drug reactions at the standard dose of 5-FU about 20%–30% of the time (Hamzic et al., 2017). In a study of 243 patients, including 89% of patients prescribed capecitabine alone, capecitabine-related digestive, neurologic, and/or hematologic toxicities of grade 3 and 4 were documented in 10% and 2% of patients, respectively (Etienne-Grimaldi et al., 2017). In another study, 14% of 500 patients treated with 5-FU and capecitabine experienced early-onset severe toxicities (Froehlich, Amstutz, Aebi, Joerger, & Largiadèr, 2015). Regimens containing 5-FU typically have been associated with treatment-related fatality rates of 0.5%–3.1%, and even as high as 13% (Ma, 2017; Mikhail, Sun, & Marshall, 2010).

FIGURE 1.
RED FLAGS OF EARLY-ONSET SEVERE TOXICITY FROM 5-FU AND CAPECITABINE ADMINISTRATION

CLASSIC SIDE EFFECTS

Presentation occurs either while the patient is still undergoing therapy or is within 96 hours of the last dose of 5-FU. The severity is grade 3 or 4.

- Gastrointestinal: mucositis (mouth pain, pain on swallowing), anorexia, diarrhea
- Hematologic: leukopenia (white blood cell count of less than or equal to 2,000 or falling rapidly), neutropenia (absolute neutrophil count of less than 1,000 or falling rapidly), thrombocytopenia (platelet count of less than or equal to 50,000 or falling rapidly)

OTHER SIDE EFFECTS

The neurologic and skin side effects are known to be associated with 5-FU administration but are not normal or expected.

- Cardiac: acute cardiomyopathy, myocardial ischemia, arrhythmia, left ventricular dysfunction, cardiac arrest
- Neurologic or central nervous system: changes in consciousness, altered mental status, cerebellar ataxia, encephalopathy, coma
- Skin: erythema (other than hand-foot syndrome), desquamation

5-FU—5-fluorouracil
Note. Based on information from BTG International, 2017; Froehlich et al., 2015; Ison et al., 2016; Ma et al., 2017; Meulendijks et al., 2016.

"Traditional means of supportive care for these uncommon severe toxicities are insufficient."

Common Toxicities

Common 5-FU toxicities are gastrointestinal (GI) (e.g., mucositis, diarrhea, nausea, vomiting, anorexia), hematologic (e.g., neutropenia, thrombocytopenia, anemia), and dermal (e.g., hand-foot syndrome, erythema) in nature (see Figure 1 and Table 1) (Boisdron-Celle et al., 2017; Keiser, 2008). Expected toxicities do not typically begin until several days after the end of 5-FU administration (Fox & Howland, 2010; Schwartzberg, Vogel, & Campen, 2014); they are typically mild to moderate (grade 1 and 2) and appear in the third or later round of chemotherapy (Davis et al., 2014; Genentech, Inc., 2016; Meulendijks et al., 2016; Teva Parenteral Medicines, Inc., 2017; Treister & Sankar, 2017). These common toxicities can be managed with dose reduction and/or supportive care in an outpatient setting and usually by telephone triage (i.e., clinical management of symptom-based telephone calls by telephone only).

Uncommon Toxicities

Although GI, hematologic, and dermal toxicities are expected, the rapid onset of these toxicities at a severity level of grade 3 or 4 is considered an unexpected red flag that requires immediate in-person nursing assessment and, if needed, appropriate escalation of care and evaluation. Similarly, it is unexpected for symptoms at a severity level of grade 3 or 4 to appear early, such as while the patient is still undergoing therapy, is within the first 96 hours of administration of planned doses of 5-FU, or is within three to nine days of beginning capecitabine (Ma et al., 2017).

Cardiac and central nervous system (CNS) toxicities are also uncommon (Cordier et al., 2011; Polk et al., 2016; Polk, Vaage-Nilsen, Vistisen, & Nielsen, 2013). Cardiac involvement includes acute cardiomyopathy, myocardial ischemia, arrhythmia, chest pain, left ventricular dysfunction, acute pulmonary edema, congestive heart failure, Takotsubo cardiomyopathy, and cardiac arrest. Neurologic or CNS toxicities include changes in consciousness, altered mental status, cerebellar syndrome, encephalopathy, seizures, and coma.

Sequelae of unmanaged early-onset toxicities range from acute respiratory distress syndrome, to multisystem organ failure

secondary to sepsis, to septic shock (Ma et al., 2017). For patients with severe toxicities, traditional supportive care is insufficient.

Early-onset capecitabine toxicity has been described as occurring within the first cycle of treatment with the oral medication (Sahu, Ramaswamy, & Ostwal, 2016). Of 506 patients treated with capecitabine, 31 developed grade 3 and 4 toxicities in the first treatment cycle (Ison et al., 2016). The majority of these patients had mucositis (77%) and diarrhea (94%). A substantial percentage also had hand-foot syndrome (42%) and myelosuppression (16%). Early-onset severe toxicities may lead to chemotherapy delays, dose reductions, or discontinuation of treatment. Severe toxicities can result in hospitalizations, need for intensive care unit stays, and death (Ison et al., 2016; Keiser, 2008).

Mechanisms of Action

A synthetic analog of naturally occurring uracil, 5-FU is metabolized by cancer cells more than by healthy cells. Capecitabine is an orally bioavailable 5-FU prodrug that is converted to 5-FU in three metabolic steps (Ma et al., 2017). In normal cells and in cancer cells, 5-FU interferes with DNA and RNA synthesis. About 80% of 5-FU is catabolized and eliminated by the enzyme dihydropyrimidine dehydrogenase (DPD) (Mir, 2016), with the remaining percentage anabolized to the cytotoxic metabolites fluorodeoxyuridine monophosphate (FdUMP) and fluorouridine triphosphate (FUTP). FdUMP inhibits synthesis of thymidine, which is required for DNA replication and repair. This is the primary antitumor mechanism of 5-FU. FUTP is the primary cause of 5-FU toxicity and is the dose-limiting factor in 5-FU treatment.

Causes of Overexposure

Toxicity from 5-FU is a product of exposure (area under the curve, or the actual body exposure to the drug after administration of a dose of the drug) and can result from accidental overdose or from metabolic and clearance issues. Only 1%–3% of the administered dose of 5-FU or capecitabine is converted into cytotoxic metabolites, whereas more than 80% of the drug is rapidly catabolized by DPD and eliminated from the body (Ma et al., 2017). Overdose results from oversaturation of DPD, leading to toxic levels of cytotoxic metabolites. Metabolic defects involve a lack of DPD to catabolize 5-FU and, subsequently, toxic levels of cytotoxic metabolites (Ma et al., 2017).

TABLE 1.
SYMPTOMS ASSOCIATED WITH 5-FLUOROURACIL AND CAPECITABINE ADMINISTRATION

SYMPTOM	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Diarrhea	Increase of fewer than 4 stools per day over BL; mild increase in ostomy output compared to BL	Increase of 4–6 stools per day over BL; moderate increase in ostomy output compared to BL	Increase of 7 or more stools per day over BL; incontinence; hospitalization indicated; severe increase in ostomy output compared to BL; limiting self-care ADLs	Life-threatening consequences; urgent intervention indicated
Dysphagia	Symptomatic; able to eat a regular diet	Symptomatic; altered eating and swallowing	Severely altered eating and swallowing; tube feeding or total parenteral nutrition or hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Oral mucositis	Asytomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated
Palmar-plantar erythrodysesthesia/ hand-foot syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, hyperkeratosis) with pain; limiting instrumental ADLs	Severe skin changes (e.g., peeling, blisters, bleeding, edema, hyperkeratosis) with pain; limiting self-care ADLs	–
Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADLs	Severe symptoms; limiting self-care ADLs	Life-threatening consequences; urgent intervention indicated
Vomiting	1–2 episodes (separated by 5 minutes) in 24 hours	3–5 episodes (separated by 5 minutes) in 24 hours	5 or more episodes (separated by 5 minutes) in 24 hours	Life-threatening consequences; urgent intervention indicated

ADL—activity of daily living; BL—baseline
Note. Faster onset of severe symptoms is a red flag for overexposure. Grade 5 is death.
Note. From *Common Terminology Criteria for Adverse Events* [v.4.03], by National Cancer Institute Cancer Therapy Evaluation Program, 2010. Retrieved from www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Overdose

Overdose of 5-FU can stem from various issues, including those related to the infusion pump (e.g., misprogramming of the pump, pump malfunction, use of incorrect pump or filter) (Ma et al., 2017) or the pharmacy (e.g., incorrect dose, transcription or order error, dose prescribed for infusion given as a bolus). Capecitabine overdose can be intentional or accidental. Overdose can saturate the clearance that would normally occur via the DPD enzyme, resulting in greater quantities of 5-FU being metabolized into cytotoxic metabolites. Much higher levels of 5-FU (than the expected 1%–3%) are metabolized to fluorouridine monophosphate (FUMP) and the downstream toxic metabolite FUTP; this is the primary cause of 5-FU toxicity and the dose-limiting factor in 5-FU treatment (Mir, 2016).

Metabolic Defects

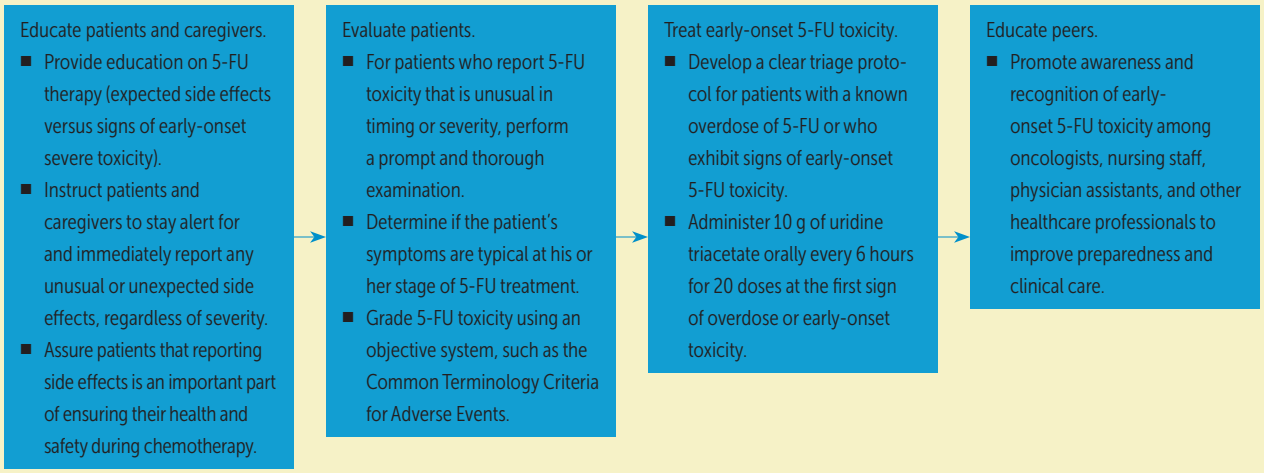
Patients with certain genetic or metabolic defects can develop lethal overexposure at standard doses of 5-FU or capecitabine. Orotate phosphoribosyltransferase (OPRT) is a principal enzyme that converts 5-FU to toxic intracellular 5-fluorouridine nucleotides (Boisdron-Celle et al., 2017). Overexpression of OPRT results in greater quantities of toxic FUTP. When FUTP replaces UTP in the synthesis of RNA, protein synthesis is disrupted, and this a major source of 5-FU toxicity.

Impaired clearance of 5-FU is caused by various mechanisms, such as DPD enzyme deficiency, mutations, renal impairment, and hepatic dysfunction (Meulendijks et al., 2016). DPD enzyme deficiency can greatly increase exposure to 5-FU because DPD catabolizes from 80%–85% of a normal 5-FU dose (Boisdron-Celle et al., 2017). Capecitabine and 5-FU have similar toxicity profiles in patients with a *DPD* mutation. DPD deficiency occurs in 3%–5% of patients who are treated with 5-FU or capecitabine (Boisdron-Celle et al., 2017). In patients with severe rapid-onset toxicities from 5-FU or capecitabine, DPD may be deficient; however, few tests to determine DPD deficiency are available (Sahu et al., 2016). Other potentially important gene mutations include thymidylate synthase (*TYMS*) and methylenetetrahydrofolate reductase (*MTHFR*), but these deficiencies are not routinely tested (Amstutz, Froehlich, & Largiadèr, 2011). Although 5-FU metabolites are involved in severe cardiac and neurologic or CNS toxicities, the specific mechanisms of their involvement are not well defined.

Standard Supportive Care for Overexposure

The first step in addressing 5-FU overexposure is reducing, holding, or discontinuing 5-FU dosing (Ison et al., 2016; Ma et al., 2017). Traditional supportive care measures for 5-FU overexposure include the administration of supportive medications (e.g., filgrastim, oral rinses, antibiotics, antifungals, antivirals, antidiarrheal agents, antiemetics, antianxiety agents, pain management, pressors) and procedures (e.g., IV hydration; electrolyte replacement; whole blood, red blood cell, and platelet transfusions), and the provision of life support (e.g., intensive care unit care, neutropenic precautions [isolation], intubation for airway support, ventilator

FIGURE 2.
5-FU TOXICITY CLINICAL PREPAREDNESS ACTION PLAN



5-FU—5-fluorouracil
Note. From *Vistogard (Uridine Triacetate) Oral Granules. Early-Onset 5-FU Toxicity: Clinical Indicators of a Life-Threatening Emergency. A White Paper and Clinical Action Plan*, by BTG International, 2017. Retrieved from https://www.vistogard.com/Vistogard/media/Main-Media/Landing-Page/PDFs/Vistogard_White_Paper.pdf. Copyright 2017 by BTG International. Adapted with permission.

TABLE 2.
5-FU AND CAPECITABINE EARLY-ONSET SEVERE TOXICITY DECISION ALGORITHM

REPORTED OR OBSERVED SYMPTOM	ACTION REQUIRED
■ Grade 3 or 4 nausea and vomiting or diarrhea not relieved by anti-nausea and/or anti-diarrheal medications while still on therapy or within 96 hours of last dose ■ Immediate grade 3 or 4 fatigue; patient unable to get out of bed or only with assistance ■ Blistering and/or peeling skin ■ Mouth sores so severe that the patient is unable to eat, drink, or swallow; patient has trouble managing own secretions	■ Patient should be seen; stop 5-FU and capecitabine, and provide supportive care, including emergency treatment with uridine triacetate.[a]
■ Altered mental status ■ Cardiac symptoms (chest pain, shortness of breath, patient report of possible arrhythmia)	■ Immediate attention required; patient should be seen; stop 5-FU and capecitabine, and provide supportive care, including emergency treatment with uridine triacetate.[a]
■ Severe drop in white blood cell count or platelets during or within 96 hours of therapy (white blood cell count of less than 3,500; absolute neutrophil count of less than 1,000; and/or platelet count of less than 75,000); a drop in counts is expected, and the nadir most commonly occurs about 7 days after the end of therapy.	■ Intervention, including emergency treatment with uridine triacetate[a], is required.

[a] Treatment with uridine triacetate should be administered within 96 hours after the end of 5-FU infusion or the last dose of capecitabine.
5-FU—5-fluorouracil
Note. These symptoms are not normal or expected, and they should not be observed in patients still on therapy or who are within 96 hours of administration.
Note. Based on information from BTG International, 2017; Cordier et al., 2011; Davis et al., 2014; Hickey & Newton, 2012; National Cancer Institute, 2010, 2017; Polk et al., 2016; Territo, 2018; Teva Parenteral Medicines, Inc., 2017.

support, cardiac assist devices). In this instance, supportive care treats symptoms but not the underlying problem (a large quantity of toxic metabolites in the body); despite the extent of supportive care that can be provided, supportive care alone has been associated with mortality rates of 84%–100% among patients with 5-FU overexposure (Ison et al., 2016; Ma et al., 2017).

Uridine Triacetate as Emergency Treatment

Uridine can reverse 5-FU toxicity (Ma, 2017). Uridine competes with the toxic 5-FU metabolite FUTP for incorporation into RNA. Oral uridine has poor bioavailability, and parenteral uridine presents safety concerns (Ma et al., 2017), but uridine triacetate has bioavailability that is four- to six-fold greater than that of uridine. Uridine triacetate absorbs quickly in the GI tract and rapidly converts to free uridine as it circulates. Uridine increases levels of UTP, which competes with FUTP for incorporation into RNA. As a result, toxicity and cell death are reduced. A uridine triacetate intervention is most effective if administered within 96 hours of the end of 5-FU administration, before the majority of toxic FUTP has had the time to cause cellular damage (Ma et al., 2017).

In an examination of uridine triacetate use involving a total of 173 patients in two clinical studies (6 of whom were pediatric patients), 26 had early-onset toxicity from 5-FU and 147 had 5-FU or capecitabine overdose (Ma et al., 2017). In these studies, the most common reasons for overdose were infusion pump misprogramming or malfunction. Follow-up was possible for 168 patients; 94% of patients survived to day 30, and 34% restarted chemotherapy prior to day 30 (primary end point of the study). Among the 26 patients with early-onset toxicity, 81% survived. Uridine triacetate treatment was started within 96 hours in 18 patients, and all survived; however, only 38% of those who started treatment after 96 hours survived, which highlights the importance of timely treatment. Among the 147 patients who experienced an overdose of 5-FU or capecitabine, the outcome was known for 142, and 96% of them survived. Among patients treated with uridine triacetate (n = 142), chemotherapy was restarted within 30 days in 12% of patients with early-onset toxicity and in 38% of those with overdose.

Among 25 patients with 5-FU overdose, 21 died after treatment with traditional supportive care only (Ma et al., 2017). These results compelled reviewers at the FDA to approve uridine triacetate for the emergency treatment of adult and pediatric patients following overexposure to 5-FU or capecitabine (Ison et al., 2016; Wellstat Therapeutics Corporation, 2015).

Patient Education and Assessment

Nurses are often the first among healthcare providers to communicate with patients or their caregivers about changes in patient status. As a result, nurses aware of the rare but life-threatening consequences of 5-FU and capecitabine overexposure or intolerance can best advise patients and families about these risks (Ma et al., 2017). It is important for nurses to educate patients and caregivers prior to the start of treatment with 5-FU or capecitabine because of the potential severe toxicities, which need to be addressed within 96 hours of treatment to ensure the best patient outcome.

IMPLICATIONS FOR PRACTICE

- Recognize uncommon early-onset severe toxicities in patients treated with 5-fluorouracil or capecitabine.
- Educate patients to be aware of the potential for early-onset toxicity.
- Facilitate immediate intervention in early-onset severe toxicities and cases of overdose to decrease morbidity and mortality.

Clear and detailed patient information should also be obtained by nurses. A patient's survival may depend on the assessment and evaluation skills of a clinic nurse, a nurse navigator, or a telephone triage nurse. A focused patient assessment helps to identify the signs of early-onset severe 5-FU and capecitabine toxicity; nurses can then advocate for treatment with uridine triacetate when indicated. Figure 2 presents a clinical preparedness action plan to empower nurses to facilitate the identification and treatment of 5-FU overdose or early-onset toxicity.

Three main considerations exist for nurses when educating patients and caregivers and evaluating patient response to therapies containing 5-FU or capecitabine:

- Change from baseline performance status
- Time from delivery of chemotherapy to start of symptoms
- Severity of symptoms

Initial patient assessment often begins when a patient or caregiver calls to report chemotherapy side effects. Telephone triage questioning requires focus because visual assessment is not possible. Knowing what to ask during an assessment and when to pursue more detailed information is a valuable skill. Gathering pertinent details, applying critical thinking skills, diagnosing symptom severity, planning interventions, and evaluating outcomes—all parts of the nursing process—must occur before escalating to an in-person evaluation or an immediate intervention. Table 2 presents a decision algorithm to use when assessing early-onset 5-FU or capecitabine toxicity.

Baseline Activity

A dramatic change from baseline activity may be one of the first signs of severe toxicity from 5-FU or capecitabine. When educating patients, specific examples of how toxicities may manifest can help patients understand the differences between expected side effects and unexpected severe toxicities. For instance, an active and independent patient who starts a planned 14-day cycle of capecitabine and cannot walk to the bathroom independently by day 10 of treatment is experiencing severe and unexpected toxicity.

Change may be more difficult to determine if the patient's baseline functional status is low; however, listening to the patient and his or her caregiver's concern about status changes can alert nurses to a decline from baseline. Change in performance status or in the ability to perform activities of daily living may be the first sign of severe toxicity. Performance of activities of daily living is not expected to change after 5-FU or capecitabine administration. Drastic changes in patients' baseline activity level or their inability to perform routine activities of daily living may indicate 5-FU or capecitabine toxicity.

Time to Onset of Toxicity Symptoms

Another important consideration is the time from the start of treatment with 5-FU or capecitabine and the onset of symptoms. Most patients receiving these therapies experience only mild side effects (e.g., mild nausea and diarrhea controlled with medication, mild fatigue, mild mucositis) for the first few months of therapy. These side effects should not result in weight loss, dehydration, or inability to perform activities of daily living.

When patients experience side effects within 96 hours or 4 days of therapy with 5-FU or capecitabine, the medical team should consider intolerance or genetic enzyme deficiency. For example, a patient experiencing grade 3 mucositis and diarrhea at four days after the onset of therapy should be evaluated for consideration of treatment with uridine triacetate and additional supportive care. Nurses should encourage patients to report any unexpected side effects with rapid onset and advise them of the availability of a rescue drug (drug to immediately relieve symptoms). Uridine triacetate should be administered within 96 hours of the emergence of early-onset toxicities for the best possible outcomes.

Severity of Side Effects

The severity of side effects among patients receiving 5-FU or capecitabine should also be considered. Early-onset grade 3 and 4 toxicities may indicate that a patient is experiencing life-threatening toxicities. Nurses should be aware that severity is subjective.

Conclusion

Severe toxicity to 5-FU or capecitabine is rare but can be deadly. Knowing the differences between expected, normal side effects and uncommon early-onset severe toxicities enables nurses to provide patient education prior to 5-FU or capecitabine treatment. Recognizing the early onset of severe toxicities will facilitate early intervention. Although GI, hematologic, and dermal toxicities are expected, the rapid onset of these toxicities at a grade of 3 or 4 requires immediate in-person nursing assessment and, if needed, appropriate escalation. Toxicity can result from accidental overdose or metabolic and clearance issues. Early emergency treatment with uridine triacetate greatly improves survival rates when administered within 96 hours of the last dose of 5-FU or capecitabine. Nurses are typically the first healthcare providers to communicate with patients or caregivers about changes in their status. Careful assessment using Common Terminology Criteria for Adverse Events is crucial (National Cancer Institute, 2010). Assessments, followed by the use of an algorithm and the establishment of protocols, can facilitate timely treatment and improve patient outcomes.

Edith Brutcher, RN, MSN, APRN-BC, AOCNP®, is a medical oncology nurse practitioner at the Winship Cancer Institute of Emory University in Atlanta, GA;

Deb Christensen, MSN, APRN-BC, AOCNS®, HNB-BC, is an oncology nurse navigator and system lead at the Intermountain Cancer Center in St. George, UT; **Melissa Hennessey Smith, MSN, AGPCNP-BC,** was, at the time of this writing, a nurse practitioner at Tufts Medical Center in Boston, MA; **Judy B. Koutlas, RN, MS, OCN®,** is a manager of oncology nurse navigation at the Vidant Cancer Center in Greenville, NC; **Jean B. Sellers, RN, MSN,** is an administrative clinical director at the University of North Carolina Lineberger Comprehensive Cancer Center in Chapel Hill; **Tahitia Timmons, MSN, RN-BC, OCN®,** is a clinical nurse educator at Cooper University Health Care in Camden, NJ; and **Joanna Thompson, RN, BSN,** is a medical science liaison for BTG International in Hartselle, AL. Brutcher can be reached at edith.brutcher@emoryhealthcare.org, with copy to CJONEditor@ons.org. (Submitted March 2018. Accepted June 27, 2018.)

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