

BC Cancer Agency Management Guidelines

Management of 5-fluorouracil (5FU) infusion overdose

Rationale: 5-FU is an analog of uracil and acts as a pyrimidine antagonist. It is widely used to treat solid tumors and is often administered via infusion devices at or near its maximum tolerated dose. The common use of infusion devices containing 5FU for infusion over several days increases the possibility of potentially lethal overdoses due to device malfunction, dose calculation errors, device selection errors or misprogramming. Toxicities resulting from delivery of 5FU at greater than the intended dose or dose rate can range from mild to life-threatening depending upon the rate of infusion and total dose delivered. Presently, no standard guidelines exist regarding the definition of a 5FU infusion overdose and the recommended management. This guidance serves as a directive regarding the overdose management for 5FU infusors at the BC Cancer Agency (BCCA). [More detailed management information can be found in POISINDEX management of fluorouracil and related agents.](#)

Directive: Prescribing medical staff, pharmacy and nursing must ensure that every effort is made to minimize the risk of an error in dose calculation or infusor misprogramming. In the event of a 5FU overdose, appropriate and timely measures to anticipate and implement supportive management of patients at risk for severe 5FU toxicity should be implemented per the procedures outlines below. Anticipated toxicities of 5FU can include but are not limited to myelosuppression, nausea, vomiting, stomatitis, diarrhea, ileus, and ileitis. Less common but severe effects can include hepatotoxicity, cardiogenic pulmonary edema, seizures, shock, gastrointestinal bleeding and perforation.

Procedures:

- For the purposes of this guidance, a 5FU infusor overdose will be empirically defined as administration of 5FU via infusor at greater than or equal to 2 times the intended rate with completed delivery of greater than 50% of the intended total 5FU dose.
- Upon identification of a potential overinfusion, the 5FU infusor should be discontinued and the total administered dose of 5FU should be determined.
- The prescribing medical oncologist (or responsible Doctor of the Day) should be paged and informed of the potential infusion error, with details regarding the over-infusion rate, the total dose delivered and the patient's current clinical status and vitals.
 - Ensure administration, medical, nursing and pharmacy leadership are informed of the patient event
- **If the overdose rate is between 2-10X intended rate (with completed delivery of greater than 50% of the intended total 5FU dose):**
 - Hospitalization at discretion of medical team.
 - Factors to consider:
 - Degree of overdose – greater vigilance may be required for overdoses between 8-10X intended rate
 - Patient factors which may be associated with impaired clearance including advanced age, impaired baseline renal function (Creatinine clearance [CrCl] < 60 mL/min) and impaired hepatic function (AST > 2.5X ULN, Bilirubin > 1.5X ULN).
 - Patient's ability to return for close outpatient follow-up and monitoring
 - Patient's access to home and social supports
 - Initiate filgrastim (G-CSF)* at a dose of 5 mcg/kg subcutaneous daily beginning within 24 hours of overdose and continuing for a minimum of 7 days or until past nadir to $ANC \geq 1.0$ (1,2)
 - Discontinue concomitant medications which may impair clearance of 5FU: cimetidine, metronidazole, thiazide diuretics (3)

- If managed as an outpatient
 - Clinical assessment every 1 to 2 days for 7 days then as required
 - Labs every 1 to 2 days for 7 days then as required: CBC, electrolytes, liver function tests (LFTs) and creatinine monitoring
- If on combined modality therapy – notify responsible Radiation Oncologist and hold radiation therapy.
- **If the overdose rate is greater than 10X intended rate (with completed delivery of greater than 50% of the intended total 5FU dose):**
 - Patient should be hospitalized for monitoring and supportive management including assessment of hemodynamic status and intravenous hydration (minimum of 2 L/day to encourage diuresis) (2)
 - Obtain a baseline ECG
 - Daily CBC, electrolytes, LFTs, creatinine
 - Discontinue concomitant medications which may impair clearance of 5FU: cimetidine, metronidazole, thiazide diuretics (3)
 - Initiate filgrastim (G-CSF)* at a dose of 5 mcg/kg subcutaneous daily beginning within 24 hours of overdose and continuing for a minimum of 7 days or until past nadir to ANC > 1.0 (1,2)
 - Initiate glutamine 18 g PO daily for prevention of 5FU intestinal toxicity (4)
 - Consider Uridine triacetate (Vistonuridine, Wellstat) available for emergency use (5)
 - Vistonuridine is an oral prodrug of uridine, a specific pharmacologic antidote for 5FU poisoning
 - It is recommended that treatment with vistonuridine commence as soon as possible after a suspected severe 5FU overdose
 - Health Canada Special Access Programme (SAP) approval required (BCCA clinical pharmacist should be contacted to assist with this request)
 - Availability of vistonuridine is dependent upon supply from the US manufacturer (Wellstat) and may be considered by Wellstat on a case-by-case basis.
 - Consider an ACE inhibitor (ACEI) to reduce risk of 5FU-related cardiac dysfunction
 - Initiate fluoroquinolones in the event of diarrhea.
 - If on combined modality therapy – notify responsible Radiation Oncologist and hold radiation therapy.

**Inpatient or outpatient Filgrastim use for this indication would be covered by the BCCA Systemic Therapy Program*

References

1. Poisindex Summary monograph – Fluorouracil and related Agents (abstracted from Micromedex®, Aug 17, 2010)
2. Appendix 5, Institute for Safe Medication Practices Canada: Fluorouracil Incident Root Cause Analysis Report, Safety Bulletin 7(4) 2007
3. Fluorouracil monograph, BCCA Cancer Drug Manual© (revised May 2007).
4. Daniele B, Perrone F, Gallo C, et al. Oral glutamine in the prevention of fluorouracil-induced intestinal toxicity: a double blind, placebo controlled, randomized trial. *Gut* 2001;48:28-33.
5. Barmat MK, Tremmel R, O'Neil JD, von Borstel R. Uridine triacetate: an orally administered, life-saving antidote for 5-FU overdose. *Proc Am Soc Clin Oncol* 2010 (abstr 9084).
6. McEvilly M, Popelas C, Tremmel B. Use of uridine triacetate for management of fluorouracil overdose, *Am J Health Syst Pharm* 2011;68(19):1806-9.