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Reports of Severe Harm and Death Involving 5-Fluorouracil and Capecitabine: A Focus on Pharmacogenetics

Health Canada recently published an article highlighting the risk of severe toxicity associated with systemic 5-fluorouracil (5-FU) or capecitabine therapy when administered to patients with dihydropyrimidine dehydrogenase (DPD) deficiency.[1] Patients with complete or near-complete absence of DPD activity due to genetic variants are at the highest risk for severe, life-threatening, or fatal adverse reactions.[1] This bulletin describes findings from the article, as well as a qualitative analysis of incident reports submitted to ISMP Canada and adverse drug reaction reports submitted to Health Canada. In addition, recommendations are provided to help prevent or mitigate patient harm.

EXAMPLES OF INCIDENTS SUBMITTED TO ISMP CANADA

- *A patient was prescribed 5-FU and received publicly funded pharmacogenetic testing before treatment. Within 96 hours of the first dose, they presented to hospital with severe mucositis, vomiting, and diarrhea. The patient later died from 5-FU toxicity. Subsequent broader pharmacogenetic testing showed that the patient carried a gene variant not included in the pre-treatment pharmacogenetic test. The report described this gene variant as a likely factor leading to drug toxicity and death.*

- *A patient experienced copious, intermittent diarrhea after receiving capecitabine for a week and opted to complete the treatment cycle before informing the oncology team. The patient was then counselled to take loperamide. The symptoms worsened, and the patient was eventually admitted to hospital, where electrolyte abnormalities occurred, and intensive care was required. The patient died a week later. The incident report described a DPD deficiency.*

Pharmacogenetics is defined as the influence of variation in a single gene on a person's response to drugs.[2] Pharmacogenetic testing is used as an additional clinical tool to inform the most appropriate drug or dose for a given person.

BACKGROUND

Both 5-FU and capecitabine belong to the fluoropyrimidine class of chemotherapeutic agents and are metabolized by the DPD enzyme.[3] The gene that encodes for DPD is known as *DPYD*, and the presence of certain variants can be identified through pharmacogenetic testing to help predict a person's degree of DPD deficiency. Another method that is used to identify DPD deficiency is plasma uracil concentration or the ratio of dihydrouracil (a metabolite of uracil) to uracil.[4,5]

These 2 systemic fluoropyrimidines are contraindicated for patients predicted to have complete DPD deficiency.[6,7] Patients predicted to have partial DPD deficiency should have their 5-FU or capecitabine doses reduced according to established guidelines[8-11] and should be closely monitored for adverse effects. Studies have shown that reducing the dose helps to reduce severe toxicity and associated hospitalizations[12] without loss of efficacy in these patients.[13-15]

Health Canada recommends that pharmacogenetic testing for DPD deficiency be considered before treatment with 5-FU injection or capecitabine tablets, based on local availability and current guidelines.[1] This genetic testing before treatment may be referred to as pre-treatment,[16] pre-emptive,[10] or prospective[17] in different jurisdictions.

Guidance for Treatment Monitoring

Guidelines have been developed to support the monitoring of patients receiving fluoropyrimidine medications.[8,9] Current evidence indicates that therapeutic drug monitoring (TDM; i.e., measurement of drug levels) is helpful for some patients receiving 5-FU infusions.[5,8,18,19,20] There is currently an assay for 5-FU with marketed approval from Health Canada.[21]

Uridine triacetate (known by the brand name Vistogard) is an antidote indicated for emergency treatment of early-onset, severe or life-threatening fluoropyrimidine toxicity. The antidote must be given **within 96 hours** after the end of the last infusion of 5-FU or the last dose of capecitabine.[22] In Canada, it is available through Health Canada's Special Access Program.[23]

Jurisdictional Pre-Treatment Testing for DPD Deficiency

Current publicly funded genetic testing includes variants that were identified from largely European study populations and may miss *DPYD* variants in people of other ethnic origins.[24,25] Work is underway in a number of jurisdictions to implement or expand the availability and accessibility of publicly funded pre-treatment testing of *DPYD* variants.[16] Canada's Drug Agency is currently working to develop a consensus-based assessment framework as well as a health technology review to support standardized, efficient, and transparent assessment of genetic and genomic biomarkers in cancer care.[16,26]

QUALITATIVE FINDINGS

Three scenarios were described in the reports submitted to Health Canada (n = 10)* and the incidents submitted to ISMP Canada (n = 3):

- Unknown risk of DPD deficiency before 5-FU or capecitabine treatment
- Lack of pre-treatment pharmacogenetic testing to identify the extent of DPD deficiency in the presence of known risk factors (e.g., family history, ethnicity)
- Inability of pre-treatment pharmacogenetic testing to detect clinically relevant gene variant(s)

Most of the reports described the onset of severe symptoms within a week of the first cycle of therapy. Among patients who died, the death occurred within 1 to 2 weeks of symptom onset. None of the reports mentioned the antidote.

Contributing Factors

Analysis of the adverse reaction reports (submitted to Health Canada) and the medication incident reports (submitted to ISMP Canada) identified the following potential contributing factors:

- Limited health care providers' awareness of pre-treatment pharmacogenetic testing and its limitations
- Missed opportunities for early identification of toxicity and treatment of overdose
- Limited patient and caregiver knowledge related to DPD deficiency and availability of testing, and when to seek immediate medical attention

* Adverse drug event report information (submitted between January 2019 and February 2025) was provided by Health Canada.

RECOMMENDATIONS

The analysis yielded 6 key system-level safeguards that can be put in place to help prevent and mitigate harm due to fluoropyrimidine toxicity (Figure 1):

- Health care provider awareness and education
- Patient and caregiver engagement
- Pre-treatment testing and interpretation
- Therapeutic drug monitoring
- Early recognition of signs and symptoms of toxicity
- Consideration of the antidote and rapid access to it

Provincial/Territorial Health Ministries

- Review the accessibility of and payment coverage for *DPYD* pharmacogenetic testing (including increasing the number of gene variants tested) for patients who are starting 5-FU or capecitabine therapy.[9,27]

Provincial/Territorial Cancer Care Organizations and Health Care Organizations

- Develop or update standardized, evidence-informed guidelines[8,9] to support care teams to
  - provide individualized patient care with consideration of pharmacogenetic testing limitations (e.g., when treating patients from underrepresented ethnic backgrounds)
  - interpret pharmacogenetic test results for dose determination (e.g., partial DPD deficiency would warrant dose reductions of 5-FU and capecitabine)
  - consider TDM for optimizing the efficacy and safety of 5-FU dosing.[5,8,18,19,20]
- Advocate for more patient-oriented research to advance the safety and efficacy of 5-FU dosing in patients from underrepresented ethnic backgrounds.
- Review and update (as needed) treatment protocols in relevant care areas (e.g., emergency, critical care, oncology) to support identification and management of fluoropyrimidine toxicity.

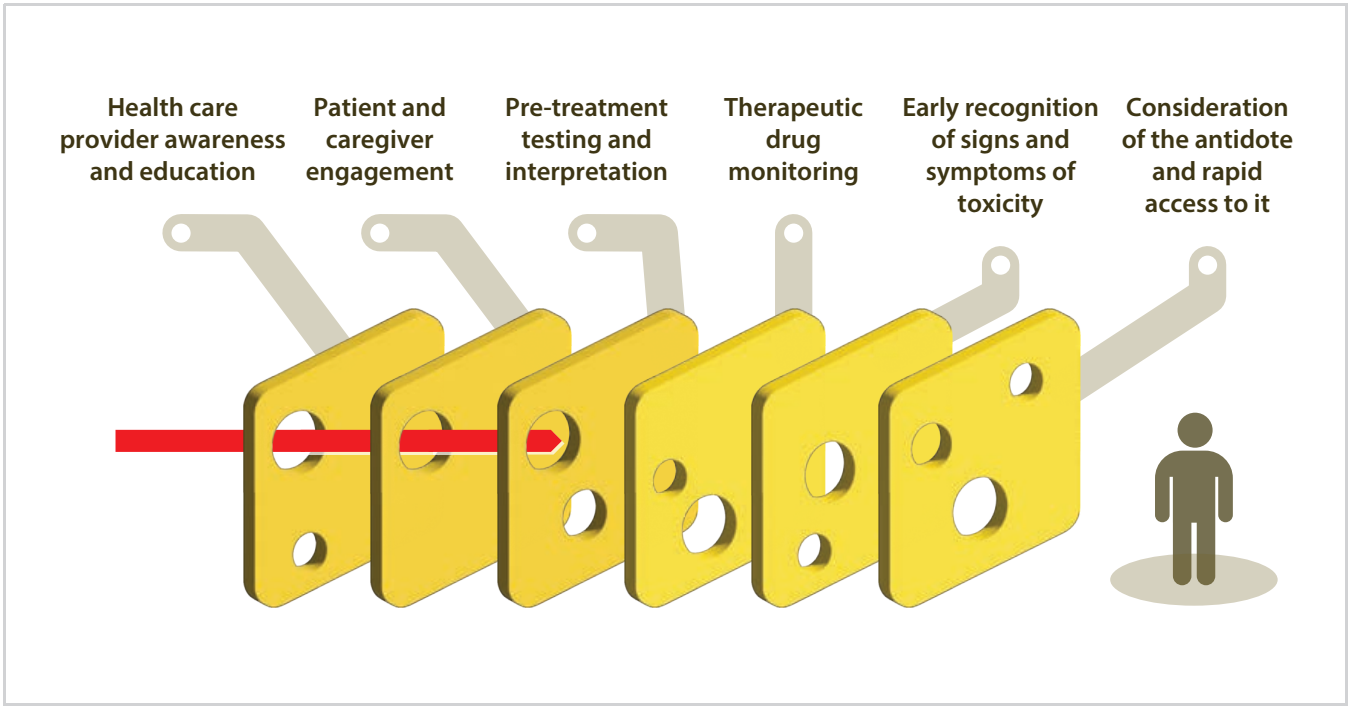

FIGURE 1. Key safeguards to prevent or mitigate harm from toxicity from 5-fluorouracil or capecitabine. Based on Reason J. Human error: models and management.[28]

These may include the following:
- Contact the patient's oncology team if the patient presents to the emergency department.
- Contact your local **poison centre** (1-844-POISON-X [1-844-764-7669], or 1-800-463-5060 in Quebec)[29] to seek advice.
- Use of a rescue protocol with uridine triacetate (Vistogard) that supports rapid procurement (through Health Canada's Special Access Program [**1-613-941-2108**]) and prompt administration (within 96 hours of the patient's last dose) when early-onset, severe or life-threatening fluoropyrimidine toxicity is recognized.

Manufacturer of Uridine Triacetate

- Consider pursuit of market authorization in Canada to enable easier access and use of the antidote for Canadians.

Oncology Care Teams

- Incorporate pharmacogenetics information into an electronic health record with clinical decision support (if available).[8] This may include:
  - documentation of test orders and results
  - recommendations for appropriate prescribing
  - support for early identification and treatment of toxicity.
- Engage patients/caregivers regarding
  - the potential for serious or life-threatening adverse reactions to systemic fluoropyrimidine medications[1]
  - pre-treatment *DPYD* pharmacogenetic testing and its limitations[30]
  - results of any pharmacogenetic testing to support shared decision-making about treatment options[27] and the potential benefit of TDM
  - severe, early-onset signs and symptoms of 5-FU and capecitabine toxicity that require immediate medical attention (e.g., emergency department care), such as stomatitis, diarrhea, vomiting, neurotoxicity, and/or neutropenia.[1,31,32]

  *Note: A 1-page **newsletter** designed for patients can be shared to facilitate discussion.*
- Provide each patient with a documented care plan to support emergency care in cases of toxicity. Consider specifying in the plan the name of the fluoropyrimidine medication that the patient is receiving, the symptoms of toxicity of that medication (to support early recognition at home and in the emergency department), and a treatment protocol.

CONCLUSION

Incident reporting and feedback to provincial/national bodies support the recognition of important risks to patients and inform actions for improvement. The multiple system safeguards described here, some of which were adopted or adapted from a recent Health Canada article,[1] support the coordinated work of policy-makers, researchers, oncology and health care organizations, oncology care teams, and patient and caregiver advocates, to prevent or mitigate harm from fluoropyrimidine toxicity.

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