

PHARMACOGENETICS NEWSLETTER

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Podcast

Take Home Points

Setting Considerations

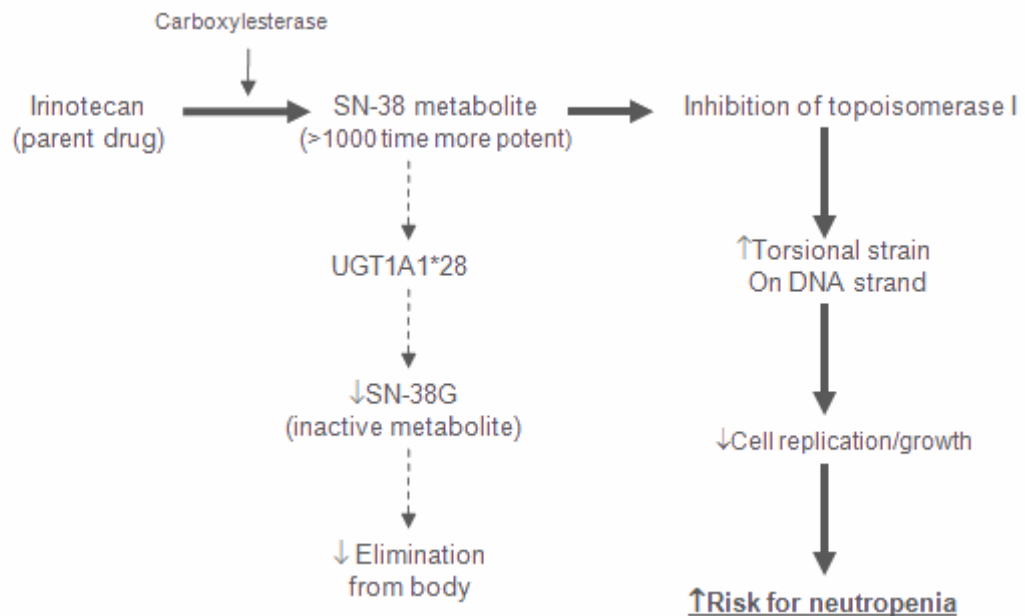
Counseling Points

Legal Points

Take CE

Question: How do genetic polymorphisms to UGT1A1*28 increase the risk for life-threatening neutropenia when receiving irinotecan (Camptosar®)?

Answer: It is well known that the chemotherapeutic regimen of irinotecan (CPT-11, Camptosar®) in combination with 5-fluorouracil and leucovorin is an effective treatment for one of the most common forms of cancer in the western world, metastatic colorectal carcinoma.¹ Like many chemotherapeutic agents, irinotecan is known to cause a number of adverse drug events (ADE). Of greatest concern is the development of severe myelosuppression (in particular neutropenia) that may be life-threatening. Patients at greatest risk for this are those over the age of 65, those having previously received pelvic/abdominal irradiation, patients with low performance status, and patients heterozygous (TA6/TA7) or homozygous (TA7/TA7) for UGT1A1*28 allele.^{1,2} What does heterozygous and homozygous mean? Since all humans have 2 copies of a gene coding sequence (or allele), a person is heterozygous if they carry 1 copy of the normal gene and 1 copy of the mutant gene and are homozygous if they have two identical copies of the mutant gene (or gene variation).³ It is this genetic polymorphism (or variation) or risk factor that is the focus of this newsletter issue. It is estimated that approximately 10% of the North American population is homozygous for this allele.¹ So what role does UGT1A1*28 polymorphism play in causing irinotecan-induced myelosuppression?



When cells replicate, each strand of their DNA is copied. In order to prevent “knotting” of the unwinding DNA, topoisomerase I is present to relieve torsional strain on the negative supercoiled DNA and to help reconnect the broken DNA strands.³ Without topoisomerase I, DNA replication and cell division would

cease and the cell would be rendered dysfunctional and die. Thus, functional topoisomerase I is highly desirable for unregulated, rapidly replicating cancer cells. Irinotecan and its main active metabolite, SN-38, bind to topoisomerase I-DNA complex impairing division of cancer cells.⁴ Normally irinotecan is metabolized to its active and lipophilic metabolite, SN-38, which is known to be about 1,000 more potent at inhibiting topoisomerase I than its parent drug.^{1,4} As such, anything that prevents the metabolism or elimination of SN-38 can have a profound impact on cell division and lead to pronounced toxicities. SN-38 is metabolized via glucuronidation to SN-38G by uridine diphosphate glucuronosyltransferase (UGT) to a more water soluble metabolite that is readily available for renal elimination. UGT1A1 is the enzyme primarily responsible for the conversion of SN-38 to SN-38G. In addition, UGT1 is responsible for conjugating bilirubin. Unfortunately, UGT1A1 is subject to genetic polymorphisms that can directly impact its gene expression resulting in both a decreased availability for metabolizing irinotecan and familial unconjugated hyperbilirubinemia diseases such as Gilbert's syndrome and Crigler-Najjar syndrome types I and II.⁵ It appears that UGT1A1*28 polymorphism results in the promoter region of a gene coding sequence that has a greater number (TA7/TA7 or TA6/TA7) of TA (thymine and adenine) repeats than normal (TA6/TA6) wild-type patients.⁷ This directly affects the ability of RNA polymerase binding to the promoter region just prior to the gene coding sequence of interest and thereby prevents the gene from being transcribed and produced.³ Therefore, patients with UGT1A1*28 make less UGT1A1 than normal patients and thus cannot efficiently metabolize the potent irinotecan metabolite, SN-38.^{1,2} As a result, a more profound inhibition of DNA replication occurs. Since the bone marrow is a place for both continual white blood cell replication and turnover, these cells (in addition to the cancer cells) are significantly impacted.^{1,2} The prevalence of developing grade 4 neutropenia (neutrophil count < 1000 cells/microliter) has been reported to be 50% in TA7/TA7 patients and 12.5% in TA6/TA7 patients for UGT1A1*28.² It is apparent that other risk factors or variables also contribute to the risk of developing neutropenia since the prevalence is not 100%. These other variables will be covered in a future newsletter.

Fortunately, there are now genetic tests that can be done to determine a patient's genotype (genetic makeup or profile) for various genes to determine if there are variations compared to the norm. One example of an FDA-approved test is the [Invader® UGT1A1 Molecular Assay](#) by Third Wave Technologies.⁸ This test is recommended by the manufacturer and can be used in clinical practice to determine if the patient will require a dose reduction for irinotecan. Lastly, the National Comprehensive Cancer Network clinical guidelines for the treatment of colon cancer state, "Irinotecan should be used with caution and with decreased doses in patients with Gilbert's disease or elevated serum bilirubin. There is a commercially available test for UGT1A1. Guidelines for use in clinical practice have not been established."⁶

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Take Home Points:

- It is well known that irinotecan (CPT-11) is a chemotherapeutic agent for the treatment of metastatic colorectal carcinoma and that irinotecan is associated with severe myelosuppression (in particular neutropenia).
- Irinotecan and its main active metabolite, SN-38, bind to topoisomerase I-DNA complex preventing cellular replication. SN-38 is more than 1,000 times more potent at inhibiting this step in replication than irinotecan.
- The active metabolite, SN-38, is primarily metabolized (or glucuronidated) by UGT1A1 to facilitate elimination from the body. Patients with the genetic polymorphism (or variation) UGT1A1*28 will have a decreased ability to metabolize or glucuronidate SN-38, thereby exposing themselves to greater inhibition of cell division. This can result in life-threatening myelosuppression.
- Pharmacogenetic testing is FDA-approved and is being used in clinical practice to determine a patient's candidacy for and/or need for dose reduction with irinotecan.

Considerations for Clinicians Based on Setting:

Outpatient Setting:

Due to the specific indication for the use of irinotecan and its intravenous route of administration, this medication is predominantly used in an oncology infusion clinic. However, it would be prudent to do pharmacogenetic testing prior to administration of irinotecan given the severity of neutropenia that may result if the patient is homozygous for the UGT1A1*28 allele. Patients should receive a baseline white blood count and bilirubin assessment to ensure levels are acceptable prior to initiation of irinotecan therapy. Irinotecan should be administered with extreme caution in patients with elevated serum bilirubin levels at baseline.

Inpatient Setting:

If a patient receiving irinotecan has been admitted to the hospital for febrile neutropenia, testing the patient for the UGT1A1*28 allele should be considered to determine the etiology and whether or not therapy should be continued in future. However, similar to what the clinicians may do if the test returned positive, they may forgo genetic testing and simply choose to reduce the dose according to the manufacturer's recommendations.

Important Counseling Bullet Point(s):

- Patients should be given adequate counseling to monitor for the signs and symptoms of infection or neutropenia such as (but not limited to): fever, new onset shortness of breath, sore throat, shaking, chills, unusual fatigue, diarrhea and to notify their physician or oncologist immediately. It would also be prudent to recommend avoiding purposeful contact with anyone who is ill.

Medical/Legal Consideration(s):

- There were no cases identified in the 2008 edition of LexisNexis' Drugs in Litigation regarding irinotecan. Although such claims against healthcare providers and/or manufacturers have not occurred to date, because of the risk of severe and life-threatening neutropenia when given to the wrong patient medical professionals should be cautious in prescribing such medications and document appropriate risk factor assessment and counseling of the patient in the medical chart.⁹ According to the National Comprehensive Cancer Network clinical guidelines for the treatment of colon cancer, "Irinotecan should be used with caution in patients with Gilbert's disease or elevated serum bilirubin. There is a commercially available test for UGT1A1. Guidelines for use in clinical practice have not been established."⁶

Test Questions for CE:

Irinotecan (CPT-11, Camptosar®) is primarily indicated for the treatment of which condition?

- a. Diabetes mellitus
- b. Metastatic skin cancer
- c. HIV infection
- d. Colorectal cancer

Which of the following is the main metabolite of irinotecan?

- a. SN-38
- b. T20
- c. 3A4
- d. SN-21

What side effect is a patient at greatest risk of developing if they are homozygous for UGT1A1*28 and receiving irinotecan?

- a. Congestive heart failure
- b. Depression
- c. Severe neutropenia
- d. Arthritis

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References:

1. Irinotecan (Camptosar®) product package insert. Pfizer and Pharmacia & Upjohn Co. New York, NY. July 2008. Last accessed on 1-27-09: [Click here for link](#)
2. Innocent F, Undevia SD, Iyer L et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004;22:1382-8. [PubMed](#)
3. Leiberman M, Marks AD, eds. *Mark's Basic Medical Biochemistry A Clinical Approach*. 3rd Ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009:479-566.
4. Kawato Y, Aonuma M, Hirota Y et al. Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. *Cancer Res* 1991;51:4187. [PubMed](#)
5. Sampietro M, Iolascon A. Molecular pathology of Crigler-Najjar type I and II and Gilbert's syndrome. *Haematologica* 1999;84:150-7. [PubMed](#)
6. National Comprehensive Cancer Network (NCCN). Guidelines for the treatment of colon cancer. Last accessed on 1-29-2009. [NCCN](#)
7. Beutler E, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism. *Proc Natl Acad Sci USA* 1998;95:8170-4. [PubMed](#)
8. Food and Drug Administration. FDA News. August 22, 2005. Last accessed on 1-27-09: [FDA](#)
9. Patterson, RM, Hoyle PC, Editorial Staff of the Publishers of Lawyers' Medical Cyclopedias eds. *Drugs in Litigation: Damage Awards Involving Prescription and Nonprescription Drugs*. 2008 Edition. LexisNexis. San Francisco, CA.

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