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Genetic testing of UGT1A1 Irinotecan toxicity

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Analysis of the UGT1A1 gene can identify patients at relatively high risk of irinotecan toxicity.

Irinotecan is a chemotherapeutic agent used to treat a variety of solid tumours, either alone or in combination with other agents. It is administered by IV infusion at intervals of one or more weeks, at a starting dose calculated on the basis of body surface area (BSA). Irinotecan is converted to an active metabolite (SN-38) by hepatic carboxylesterase enzymes. Both irinotecan and this metabolite have chemotherapeutic effects by binding to the topoisomerase I-DNA protein complex and preventing re-ligation of the DNA strand. This results in double-strand DNA breaks and cell death.

Two major toxicities arising from irinotecan are severe late-onset diarrhoea (>24 hour post-infusion) and severe myelo-suppression, both of which can be life-threatening and necessarily curtail chemotherapy.

There is a clear association between the plasma concentration of the metabolite (SN-38) and both chemotherapeutic effectiveness and the risk of these severe toxicities. However, the dose of irinotecan based on BSA does not reliably predict the serum concentration of SN-38 or the risk of toxicity.

UGT1A1 gene variants and irinotecan metabolism

The active metabolite of irinotecan, SN-38, is inactivated by the enzyme UGT1A1 and thereby excreted via the biliary tract. This enzyme converts SN-38 to SN-38-glucuronide.

5–10% of patients have a variant of the UGT1A1 enzyme which alters the usual metabolism of SN-38, with consequent changes in the plasma concentration of SN-38.

The UGT1A1 gene sequence that encodes the normal enzyme is described technically as *1. The most common variant of the UGT1A1 gene (*28) produces an enzyme with reduced activity, such that SN-38 is not excreted readily in the bile and accumulates in the plasma, with the plasma concentration being higher than would be predicted from the dose determined by BSA alone.

Homozygosity for this UGT1A1 variant, i.e. *28/*28, causes a general limitation of glucuronidation, and is the underlying cause of Gilbert syndrome.

Patients who are homozygous for the *28 variant (*28/*28) are at significantly higher risk of irinotecan-related toxicity when compared with those who have one or two copies of the normal gene (heterozygous *1/*28, or wild-type *1/*1, respectively).

Approximately 10% of Caucasians and 5% of Asians are homozygous for the variant, i.e. *28/*28, at the UGT1A1 gene.

Prescribing recommendations and UGT1A1 genotype

In current practice, the starting point for calculating the dose of irinotecan remains body surface area (BSA). This estimated dose may then be modified as follows, on the basis of the patient's UGT1A1 genotype.[1]

- If the patient is heterozygous (*1/*28) or wild-type (*1/*1), no dose adjustment is required.
- If the patient is homozygous (*28/*28), the starting dose should be reduced by at least one dose level (manufacturer's recommendation) or by 30% (Dutch Pharmacogenetics Working Group). The dose may be increased as tolerated, guided by the neutrophil count.

The US Food and Drug Administration recommends testing of the UGT1A1 gene prior to initiating irinotecan therapy.

It is important to note that UGT1A1 is not the sole determinant of irinotecan toxicity, and every patient should be carefully monitored for toxic effects.

*Screening for the UGT1A1 *28 variant is available nationally through Sonic Genetics. The cost is $200^ and a Medicare rebate is not available. The turnaround time is up to 7 business days, and results can be accessed electronically via Sonic Dx, by fax, or by phone.*

^Correct at time of printing

Reference

1. Annotation of DPWG Guideline for irinotecan and UGT1A1 [Internet]. Dutch Pharmacogenetics Working Group, 2020. [Accessed January 2020]. <https://www.pharmgkb.org/guidelineAnnotation/PA166104951>

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