Direct Healthcare Professional Communication

October 2022

Irinotecan – Recommendation for Reduction in Starting Dose to Reduce Risk of Irinotecan-induced Neutropenia and Diarrhea in Patients with UGT1A1 *28*6 Variant

Dear Healthcare Professional,

The General Administration for Pharmaceutical Vigilance of the Central Administration for Pharmaceutical Care at The Egyptian Drug Authority would like to inform you of the following:

Summary:

- UGT1A1 genotyping may be helpful in identifying patients at increased risk of severe neutropenia and diarrhea.
- Patients who are UGT1A1 poor metabolizers (e.g., homozygous for UGT1A1*28 or *6 variants, as in Gilbert's syndrome) are at increased risk of severe neutropenia and diarrhea following treatment with irinotecan. This risk increases with the dose of irinotecan.
- A lower starting dose of irinotecan should be considered in patients with reduced UGT1A1 activity. This applies in particular to patients who are given doses in excess of 180 mg/m² or who are debilitated.
- Subsequent doses can be increased if well tolerated.

Background on the Safety Concern

Medicinal products containing irinotecan are indicated for the treatment of patients with advanced/ metastatic colorectal cancer, either as monotherapy or in combination.

The recommended dose of irinotecan hydrochloride trihydrate for monotherapy is 350 mg/m2 body surface area every three weeks. The recommended dose of irinotecan hydrochloride trihydrate in combination therapy is 180 mg/m2 body surface area every two weeks. Irinotecan is a prodrug that is activated by carboxylesterases in the liver and blood to SN-38, which in turn is activated in the liver and gut by UDP-glucuronosyltransferase 1A1 (UGT1A1) is glucuronidated to SN-38 glucuronide (SN-38G). UGT1A1 is the main enzyme responsible for inactivating SN-38.

Patients who are UGT1A1 poor metabolizers are at increased risk of severe neutropenia and diarrhea following treatment with irinotecan. This risk increases with the dose of irinotecan.

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A lower starting irinotecan dose should be considered in patients with reduced UGT1A1 activity. This applies to patients receiving doses greater than 180 mg/m² body surface area or who are debilitated. An exact reduction of the initial dose has not yet been determined. In the affected patient group, the current clinical guidelines for dose recommendations should therefore be taken into account. If well tolerated, subsequent doses can be increased.

UGT1A1 genotyping can be performed in patients receiving > 180 mg/m2 body surface area and in debilitated patients to identify those with reduced UGT1A1 activity. However, the prognostic value of genotyping prior to treatment to avoid severe neutropenia and diarrhea is limited because the UGT1A1 polymorphism does not determine the overall toxicity of irinotecan therapy.

The benefit-risk balance of irinotecan remains positive.

References

Bfarm

https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/EN/RHB/2021/rhb-irinotecan.html

Call for reporting

Healthcare professionals are asked to report any suspected adverse reactions via the Egyptian reporting system:

Name: General Administration for Pharmaceutical Vigilance

Email: pv.followup@edaegypt.gov.eg

Online reporting: https://primaryreporting.who-umc.org/EG
QR Code:

Hotline: 15301

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