**UGT1A1 Genotype-Guided Dosing of Irinotecan: a Prospective Safety and Cost Analysis in Poor Metaboliser Patients**

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Background
Irinotecan is commonly prescribed for various types of tumours. The active metabolite, SN-38, is inactivated by UGT1A1 through glucuronidation. The UGT1A1*28 and UGT1A1*93 genetic polymorphisms are significantly associated with severe irinotecan-associated adverse events.

Aim
To determine the safety, feasibility, pharmacokinetics, and cost of UGT1A1 genotype-guided dosing of irinotecan.

Methods
In this prospective, multicentre, non-randomised study, patients intended for treatment with irinotecan were pre-therapeutically genotyped for UGT1A1*28 and UGT1A1*93. Homozygous variant carriers (UGT1A1 poor metabolisers; PMs) received an initial 30% dose reduction. The primary endpoint was the incidence of febrile neutropenia. UGT1A1 PMs were compared to a historic cohort of UGT1A1 PMs treated with full dose therapy, and to UGT1A1 non-PMs treated with full dose therapy in the current study. Secondary endpoints were pharmacokinetics, feasibility, and costs.

Results
Of the 350 evaluable patients, 31 (8.9%) patients were UGT1A1 PM and received a median 30% dose reduction. The incidence of febrile neutropenia in this group was 6.5% compared to 24% in historical UGT1A1 PMs (P= 0.04) and was comparable to the incidence in UGT1A1 non-PMs treated with full dose therapy. Systemic exposure of SN-38 of reduced dosing in UGT1A1 PMs was still slightly higher compared to a standard-dosed irinotecan patient cohort (difference: +32%). Cost analysis showed that genotype-guided dosing was cost-saving with a cost reduction of €183 per patient.

Conclusion
UGT1A1 genotype-guided dosing significantly reduces the incidence of febrile neutropenia in UGT1A1 PM patients treated with irinotecan, results in a therapeutically effective systemic
drug exposure, and is cost-saving. Therefore, *UGT1A1* genotype-guided dosing of irinotecan should be considered standard of care in order to improve individual patient safety.

**What is new?**

To the best of our knowledge, this is the first, prospective study investigating the safety, feasibility, pharmacokinetics, and cost of *UGT1A1* genotype-guided dosing of irinotecan. We demonstrate that *UGT1A1* genotype-guided dosing significantly improves patient safety, without a risk of underdosing. Moreover, it is cost-saving and feasible in daily practice. With that, there is finally a safe and effective irinotecan dosing advice for UGT1A1 PMs.