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Toxicity outcomes of patients who received UGT1A1 genotype-guided irinotecan dosing: A multicentre real-world study

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Background

UGT1A1 gene variations are known to reduce UGT1A1 enzyme activity, increasing the risk of severe irinotecan-related toxicity by 2-6 fold in patients with a poor metaboliser (PM) phenotype. Our previous trial showed that an initial 30% irinotecan dose reduction in UGT1A1 PM significantly reduced severe toxicity (Hulshof *et al.* EJC 2022). The aim of the present study was to assess the impact of this approach on toxicity outcomes in a real-world clinical setting after national implementation of *UGT1A1*-guided irinotecan dosing.

Methods

We retrospectively evaluated toxicity outcomes in adult patients who received *UGT1A1*-guided irinotecan dosing in 6 Dutch hospitals (Dec 2020–Apr 2024). Patients were eligible if irinotecan was dosed in cycle 1 according to genotype (i.e. 100% dose intensity for IM/EM and 70% for PM; ± 10% deviation allowed). Toxicities were collected for cycles 1-3 and graded according to CTCAE v5, and hospitalisations due to irinotecan toxicity were recorded. The primary endpoint was overall grade ≥ 3 toxicity. Endpoints were compared between PM with an initial 30% dose reduction and fully dosed intermediate and extensive metabolisers (IM/EM) using χ^2/Fisher's exact test.

Results

A total of 501 patients were included; 54 of whom were PM (10.8%). Colorectal and pancreatic cancer were the predominant cancer types (51% and 47%). Baseline characteristics, including treatment regimens, were evenly distributed between groups. Toxicity rates were comparable between IM/EM and PM (Table). Nine UGT1A1 PM received a full irinotecan dose and developed more overall severe toxicity than PM with an initial dose reduction (77.8% *vs* 29.6%; p=0.009).Table: 805P

	UGT1A1 PM 30% dose reduction N = 54	UGT1A1 IM/EM Full dose N = 447	p-value
Relative dose intensity cycle 1 in %, median (IQR)	70 (69-72)	100 (98-101)	<0.001
Toxicity in cycles 1-3, No. (%) Overall grade ≥ 3 toxicity Grade ≥ 3 febrile neutropenia Grade ≥ 3 neutropenia Grade ≥ 3 diarrhoea	16 (29.6) 2 (3.7) 9 (17.0) 7 (13.0)	152 (34.0) 26 (5.8) 79 (17.8) 67 (15.0)	0.520 0.756 0.884 0.687
Irinotecan-related hospitalisation in cycles 1-3, No. (%)	8 (14.8)	97 (21.7)	0.240
Early toxicity-related treatment modification, No. (%) Dose reduction Treatment delay Treatment discontinuation	9 (16.7) 15 (27.8) 3 (5.6)	156 (34.9) 146 (32.7) 36 (8.1)	0.007 0.468 0.787
Toxicity-related death, No. (%)	1 (1.9)	4 (0.9)	0.436

Conclusions

UGT1A1-based dose reductions improve patient safety of irinotecan treatment in routine clinical practice. For UGT1A1 PM, a 30% dose reduction is adequate to decrease severe toxicity risk to the level of IM/EM. International implementation of *UGT1A1* genotype-guided dosing should be the new standard of care.

Legal entity responsible for the study

Catharina Hospital Eindhoven.

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Disclosure

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