BERLIN 2025 ESMO congress

2238P

Survival outcomes after UGT1A1 genotype-guided dosing of irinotecan: Results of a multicentre survival analysis

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Background

UGT1A1 genotype-guided dosing significantly reduces the incidence of febrile neutropenia in UGT1A1 poor metaboliser (PM) patients treated with irinotecan, and results in a therapeutically effective systemic drug exposure (Hulshof *et al.* Eur J Cancer 2022). However, the impact of *UGT1A1* genotype-guided dosing of irinotecan on survival outcomes is unknown. In the current study, progression-free (PFS) and overall survival (OS) were compared between PMs treated with an initial 30% dose-reduction and fully dosed intermediate/extensive metabolisers (IM/EMs).

Methods

We performed a survival analysis in patients treated with *UGT1A1* genotype-guided irinotecan dosing for pancreatic (PC) or colorectal cancer (CRC) at 6 Dutch hospitals (Aug 2017 – Apr 2024). All treatment regimens were eligible for inclusion. Patients were eligible if irinotecan was dosed in cycle 1 according to genotype (i.e. 100% dose intensity for IM/EMs and 70% for PMs; ±10% deviation allowed). PFS events were defined as either radiological progression (RECIST 1.1), clinical progression or death from any cause. Kaplan Meier and multivariable Cox regression analyses, stratified per tumour type, were performed to assess impact of dose reductions in PMs on PFS and OS.

Results

In total, 779 patients were included, of whom 76 (9.8%) were PM. The median follow-up was 27.8 months. All baseline characteristics were evenly distributed across genotype groups. No significant differences in median PFS or OS were found (Table). In multivariable analysis, the hazard ratio (HR) for PFS in PMs *vs* IM/EMs was 1.015 (95%CI: 0.781-1.319; *P* = 0.91). For OS, the HR in PMs *vs* IM/EMs was 1.109 (95%CI: 0.828-1.487; *P* = 0.49).Table: 2238P

Tumour type	*UGT1A1* Genotype	No. of patients	Median PFS in months (95%CI)	*P* value	Median OS in months (95%CI)	*P* value
PC	IM/EM	355	8.3 (7.2 – 9.4)	0.542	14.8 (12.7 – 16.8)	0.419
	PM	41	9.0 (6.2 – 11.8)		11.6 (6.6 – 16.7)	
CRC	IM/EM	348	6.0 (5.3 – 6.7)		14.9 (12.9 – 17.0)	
	PM	35	6.2 (5.1 – 7.3)		13.4 (9.4 – 17.5)	
Total	IM/EM	703	6.9 (6.3 – 7.4)	0.611	14.8 (13.4 – 16.1)	0.417
	PM	76	6.5 (5.0 – 8.0)		13.4 (9.9 – 17.0)	

Conclusions

Survival of UGT1A1 poor metabolisers is not affected by an upfront 30% dose reduction of irinotecan. Therefore, *UGT1A1* genotype-guided dosing of irinotecan can be safely performed and should become the new standard-of-care dosing strategy for irinotecan in both PC and CRC regimens.

Clinical trial identification

NL-OMON49649.

Legal entity responsible for the study

Catharina Hospital Eindhoven, the Netherlands.

Funding

Has not received any funding.

Disclosure

H. Gelderblom: Financial Interests, Institutional, Local PI: Deciphera, Sanofi, Servier; Financial Interests, Institutional, Coordinating PI: Boehringer Ingelheim, AmMax Bio, Abbisko. R.H. Mathijssen: Financial Interests, Institutional, Invited Speaker: Bayer, Novartis; Financial Interests, Institutional, Advisory Board: Servier, NaDeNo Nanoscience; Financial Interests, Institutional, Research Grant, Investigator-initiated research: Astellas, Bayer, Cristal Therapeutics, Pfizer, Roche, Sanofi, Servier, Boehringer-Ingelheim, Novartis, Nordic Pharma; Financial Interests, Institutional, Coordinating PI: Pamgene; Financial Interests, Institutional, Funding: Echo Pharmaceuticals, Deuter Oncology. All other authors have declared no conflicts of interest.