SAFETY, FEASIBILITY AND COST-ANALYSIS OF UGT1A1 GENOTYPE-GUIDED DOSING OF IRINOTECAN

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To develop a dosing nomogram of irinotecan in patients homozygous polymorphic for UGT1A1*28 and/or UGT1A1*93 in order to reduce the incidence of severe irinotecan-associated toxicity, defined as febrile neutropenia during the first two cycle of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Observational invasive

Summary

ID

NL-OMON49649

Source
ToetsingOnline

Brief title
UGT1A1 genotype-guided dosing of irinotecan

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Adverse events, toxicity

Research involving
Human

Sponsors and support

Primary sponsor: Catharina-ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: irinotecan, toxicity, UGT1A1

Outcome measures

Primary outcome

The primary endpoint of the study is the incidence of febrile neutropenia of UGT1A1 genotype-guided dosing during the first two cycle of irinotecan treatment.

Secondary outcome

* Incidence of grade *3 toxicity

* Incidence of toxicity-related hospital admissions

* Number of patients with treatment delay, defined as a delay of more than 2 days

* Incidence of early treatment withdrawal

* Pharmacokinetics of irinotecan and its metabolite SN-38 in UGT1A1*28 and/or *93 homozygous variant allele carriers.

* Incidence of treatment delay due to prospective screening of UGT1A1

* Direct medical costs of irinotecan-based treatment

* Progression free survival and overall survival

* Bilirubin / conjugated bilirubin concentration ratio

* The effect of additional polymorphisms other than UGT1A1*28 and *93 on treatment outcome in terms of toxicity and efficacy (survival and progression-free survival)

Study description

Background summary

Irinotecan is a commonly prescribed anti-cancer drug that is registered for the treatment of advanced colorectal and pancreatic cancer. Irinotecan is metabolized to inactive metabolites by the enzyme UGT1A1. The gene encoding UGT1A1 is polymorphically expressed. The polymorphism UGT1A1*28 is significantly associated with reduced metabolism capacity of irinotecan with subsequent increased systemic exposure and irinotecan-associated severe toxicity such as (febrile) neutropenia and diarrhea. Severe toxicity of irinotecan is undesirable as it may lead to hospitalization for treatment of toxicity, treatment delay and/or even treatment discontinuation. Based on multiple clinical trials and meta-analyses, the Food and Drug Administration (FDA) and international clinical guidelines therefore suggest dose reductions for patients homozygous polymorphic for UGT1A1*28 to be treated with irinotecan (at doses of 180 mg/m2 or higher) in order to prevent severe toxicity; nonetheless, prospective screening is not yet routinely performed internationally. Another polymorphism, i.e. UGT1A1*93, is in partial linkage with UGT1A1*28 and is also strongly associated with irinotecan-induced severe toxicity. We hypothesize that prospective screening for UGT1A1*28 and UGT1A1*93 prior to start of treatment with irinotecan followed by genotype-based dose adjustment in homozygous variant allele carriers improves patient safety by decreasing the risk of severe toxicity and hospitalization, and is cost-effective.

Study objective

To develop a dosing nomogram of irinotecan in patients homozygous polymorphic for UGT1A1*28 and/or UGT1A1*93 in order to reduce the incidence of severe irinotecan-associated toxicity, defined as febrile neutropenia during the first two cycle of irinotecan treatment.

Study design

Prospective, multi-center, non-randomized clinical implementation study

Study burden and risks

In order to determine the UGT1A1*28 and *93 genotype prior to start of therapy, a total of 4 mL of EDTA blood will be drawn from the patients intended to be treated with irinotecan. This will not however require an extra venepuncture, as it is combined with other standard laboratory pre-treatment tests, such as determination of white blood cell count and liver and renal function. Therefore, the risk and burden associated with genotyping is minimized. It is

hypothesized that genotype-guided dosing improves patient safety of treatment by reducing the risk of severe toxicity and toxicity-associated hospitalization. There is no risk of under dosing as previous pharmacokinetic measurements have demonstrated the increased (toxic) systemic exposure of irinotecan/SN38 in UGT1A1 poor metabolizers, and the dose is further individualized in subsequent cycles of treatment based on clinical tolerability and absolute neutrophil count.
By use of a limited sampling strategy, the pharmacokinetics of irinotecan and its metabolite SN-38 will be measured on day 1 and day 3 of therapy in patients homozygous polymorphic for UGT1A1*28 and/or *93. To this purpose, 2 additional venapunctures will be performed in an expected total of 15 patients. There is no significant risk associated with this venepuncture, besides a small risk of thrombophlebitis, which is similar to the risk of other venapunctures performed during routine treatment of the patient.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

1. Pathologically confirmed malignancy for which treatment with irinotecan is indicated at a dosing regimen of * 180 mg/m2 or 450-600mg flat dose in 2- or 3-weekly treatment schedules (see table 1)
2. Age * 18 years
3. Able and willing to give written informed consent
4. WHO performance status 0-2
5. Minimal acceptable safety laboratory values defined as
a. ANC of * 1.5 x 109 /L
b. Platelet count of * 100 x 109 /L
c. Hepatic function as defined by serum bilirubin * 1.5 x ULN, ALAT and ASAT * 2.5 x ULN; in case of liver metastases ALAT and ASAT * 5 x ULN.
d. Renal function (eGFR) * 50 ml/min OR creatinine * 1.5 x ULN

Exclusion criteria

1. Prior treatment with irinotecan
2. Patients with known substance abuse, psychotic disorders, and/or other diseases expected to interfere with study or the patient*s safety
3. Patients of Asian origin
4. Patients unable or unwilling to stop the use of (over the counter) medication or (herbal) supplements which can interact with irinotecan (e.g. by induction of inhibition of CYP3A4) (see Appendix 2 study protocol).

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped

Start date (anticipated):	01-09-2017
Enrollment:	388
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Onivyde
Generic name:	irinotecan
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-05-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-07-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-03-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-07-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	24-07-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	27458 (Nederlands Trial Register)
EudraCT	EUCTR2016-004576-22-NL
CCMO	NL59765.100.17