UGT1A1 genotype-guided dosing of irinotecan

No registrations found.

Ethical review	Positive opinion
Status	Suspended
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON22175

Source
Nationaal Trial Register

Brief title
UGT1A1 genotype-guided dosing of irinotecan

Health condition

irinotecan

UGT1A1

toxicity

irinotecan

UGT1A1

toxiciteit

Sponsors and support

Primary sponsor: Catharina Hospital Eindhoven
Source(s) of monetary or material Support: Catharina Hospital Eindhoven

Intervention

Outcome measures

Primary outcome

incidence of febrile neutropenia (amendment 2019)

Secondary outcome

• Incidence of grade ≥3 toxicity other than neutropenia

• 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

Rationale: 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*28to 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.

Therefore we will 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

Study design: Prospective, multi-center, non-randomized clinical implementation study.

Study population: Patients with a pathologically confirmed malignancy intended to be treated with irinotecan at a dosage of ≥ 180 mg/m2 or 450-600mg flat dose.

Intervention: Patients intended to be treated with irinotecan will be prospectively genotyped for UGT1A1*28 and UGT1A1*93. Patients that prove to be wildtype or heterozygous polymorphic will be treated with the standard-dose treatment of irinotecan. In patients homozygous polymorphic for UGT1A1*28 and/or UGT1A1*93 an initial 30% dose reduction in the first cycle will be applied. Based on clinical tolerability and absolute neutrophil count (ANC), the dose in subsequent cycles may be increased or further decreased in order to optimize the dose for the individual patient. Doses of other concomitant anticancer drugs will be left unchanged. Homozygous variant allele carriers will also be asked to provide additional blood for pharmacokinetic measurement of irinotecan and SN-38 on day 1, in order to confirm adequate drug exposure following genotype-guided dosing. Furthermore, after inclusion of the last patient, the patient cohort will be retrospectively genotyped for other polymorphisms than UGT1A1*28 and *93, in order to identify additional genetic biomarkers that are associated with treatment outcome.
(amendment 2019)

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 in the first 2 cycles (amendment 2019)

Study design

During chemotherapy with irinotecan

Intervention

dosing nomogram of irinotecan in patients homozygous polymorphic for UGT1A1*28 and/or UGT1A1*93

Contacts

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Eligibility criteria

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)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Suspended
Start date (anticipated):	01-09-2017

Enrollment:	388
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	25-06-2017
Application type:	First submission

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
NTR-new	NL6270
NTR-old	NTR6612
Other	NL59765.100.17 : EudraCT

Study results