Real-world exploratory evaluation of the potential drug-drug interaction between anticancer small molecule inhibitors and direct oral anticoagulants in patients with solid tumours, and exploration of the role of therapeutic drug monitoring

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Primary Objective: to explore the effect of SMIs on the pharmacokinetics of DOACs in patients with solid tumours who receive a DOAC and SMI concurrently. Secondary Objective(s): - To determine the percentage of patients with DOAC peak and trough...

Ethical review	Approved WMO
Status	Completed
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON52100

Source
ToetsingOnline

Brief title
Exploratory drug interaction study between SMIs and DOACs

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Solid tumours, thrombo-embolic events

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: DOAC, Drug interaction, SMI, Therapeutic drug monitoring

Outcome measures

Primary outcome

The primary endpoints are DOAC trough and peak concentration before and after start of concomitant use with an SMI (group 1) and DOAC trough and peak concentration during concomitant use with an SMI (group 2).

Secondary outcome

Secondary endpoints are percentage of patients with a DOAC concentration within the expected range, percentage of patients with a DOAC concentration outside the expected range, percentage of patients in whom DOAC treatment is modified, SMI trough concentration during steady state and percentage of patients who develop a thromboembolic and/or bleeding event during follow-up.

Study description

Background summary

Patients with a solid tumour who are treated with oral anticancer small molecule inhibitors (SMIs) and simultaneously use a direct oral anticoagulant (DOAC) potentially hav ean increased risk on thromboembolic complications and bleeding events due to interfering drug-drug interactions. As some SMIs influence CYP3A4 and/or p-glycoprotein (p-gp) for which DOACs are substrate, concurrent use of SMIs and DOACs may increase or decrease DOAC exposure.

However, data on the clinical relevance and subsequent safety consequences of these potential drug-drug interactions (pDDI) is lacking.

Study objective

Primary Objective: to explore the effect of SMIs on the pharmacokinetics of DOACs in patients with solid tumours who receive a DOAC and SMI concurrently.

Secondary Objective(s):
- To determine the percentage of patients with DOAC peak and trough concentrations within and outside the expected ranges (table 1 - 4).
- To determine the percentage of patients in whom DOAC treatment during routine care is modified by the treating physician, based on DOAC plasma concentration measurements, obtained during the study period.
- To evaluate steady-state SMI trough concentration during concurrent DOAC treatment.
- To exploratively evaluate the effect of SMIs on the pharmacokinetics of DOACs.
- To evaluate the frequency of thrombo-embolic and bleeding events in this population, using both an SMI and a DOAC.
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Additional exploratory objectives
- To explore the feasibility of pharmacokinetic guided dosing of DOACs (when used in combination with potentially interacting co-medication).
- To explore if the extent of drug interaction between SMI and DOAC may be SMI exposure dependent.
- To evaluate the effect of SMIs on the functional activity of DOACs measured by in vitro thrombin generation.

Study design

In this prospective, multicentre, real-life, basket study, patients with solid tumours who are treated with or start treatment with an SMI in combination with a DOAC will be included. Trough and peak DOAC plasma concentration in steady state will be measured, before and after SMI initiation (or vice versa), to study the pDDI between SMIs and DOACs. Additionally, SMI trough plasma concentrations will be measured, when steady-state is reached. Results of the DOAC plasma concentration analysis will be reported to the treating physician after which patients continue with regular care. If considered necessary by the treating physician to change DOAC treatment (i.e. DOAC dose adjustment or switch to another DOAC) based on the reported DOAC plasma concentrations and regular care advice from a hospital pharmacist and/or internist-vascular medicine, the patient may re-enter the protocol for additional DOAC plasma concentration analysis. All patients will be followed to evaluate the safety and efficacy of their DOAC therapy by evaluating the occurrence of any thromboembolic or bleeding events.

Study burden and risks

Patients participating will be asked to give blood samples for trough and peak concentration measurements and thrombin generation analysis. This can be done using a venepuncture and will be combined with regular outpatient clinic appointments as much as possible. Patients will receive or continue treatment with an SMI (and, if necessary, supportive) treatment as planned and therefore will not be at significantly increased risk. Furthermore, DOAC treatment will be initiated as per regular care, but may be optimized, since therapeutic drug monitoring (TDM) has the potential to facilitate more effective use of DOACs in individual patients using potentially interacting SMIs. Therefore, the risk of study participation is negligible. Additionally, patients are asked to keep a medication diary (only group 1) between the first and second day of drug plasma concentration measurements or until the day of the last drug plasma concentration measurements to monitor treatment adherence which is not burdensome or time-consuming for patients.

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

Treatment of a solid tumour with a SMI
18 years of age or older
Already receive or start treatment with a SMI-DOAC combination that may cause a potential clinically significant DDI at the level of CYP3A4 and/or P-gp
Combined use of a DOAC-SMI combination is expected to be continued at the same dose for at least three weeks from start of the combined intake
DOAC is used for at least 7 days and SMI for at least 21 days before the first blood sampling

Exclusion criteria

Any concurrent medication besides the SMI and DOAC that is known to strongly inhibit or induce CYP3A4 or P-gp
Patients who are pregnant or lactating

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	22-12-2021
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	11-10-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-07-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
CCMO	NL78003.068.21