Safety of topical 5-FU cream in patients carrying a clinically relevant DPYD variant

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To study if patients who carry clinically relevant DPYD variants (DPYD*2A, DPYD*7, c.2846A>T, c.1236G>A/HapB3, c.1679T>G) are at a higher risk for developing severe 5-FU cream-related toxicity.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Skin neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON54797

Source
ToetsingOnline

Brief title
DPYDIX

Condition

- Skin neoplasms malignant and unspecified

Synonym
Actinic keratosis, damage from sunlight

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Stichting de Merel

Intervention

Keyword: Dihydropyrimidine dehydrogenase, Efudix, Fluoropyrimidines, Genotyping

Outcome measures

Primary outcome

Primary Objective is to prospectively study if patients carrying clinically relevant DPYD variants (DPYD*2A, DPYD*7, c.2846A>T, c.1236G>A/HapB3, c.1679T>G) are more at risk for developing moderate/severe vesicles or bullae with 5-FU cream

Secondary outcome

Secondary Objectives:

• To assess the pharmacokinetic profile of 5-FU and the metabolites in patients treated with 5-FU cream.

• To assess if the time of onset of adverse events in patients with a clinically relevant DPYD variant is earlier in than in patients without a DPYD variant.

• To assess if patients carrying a clinically relevant DPYD variant are more at risk to develop severe toxicity.

• To assess if clinically complete tumour response at 3 months is different between pa-tients with and without a clinically relevant DPYD variant.

• To determine in patients with actinic keratosis the risks for developing basal cell carci-noma and/or squamous cell carcinoma (SCC).

Study description

Background summary

Actinic keratosis (AK) is the most frequent premalignant skin lesion in patients with a Caucasian ethnicity. In a Dutch population-based study with 2063 participants, almost 38% had one or more AK. This UV-induced lesion can eventually transform into squamous cell carcinoma (SCC). The most effective treatment of actinic keratosis is topical 5% fluorouracil cream (Efudix; 5-FU cream). 5-FU cream is also registered for treatment of Morbus Bowen and superficial basal-cell carcinoma.
5-fluorouracil (5-FU) is an antineoplastic agent belonging to the fluoropyrimidines. Fluoropyrimidines can be administered as an intravenous solution (5-FU), as an oral prodrug (Capecitabine), or as a cream (Efudix). The intravenous and oral form are frequently used in the treatment of multiple cancers e.g. colorectal, gastric and breast cancer. Deficiency of dihydropyrimidine dehydrogenase (DPD), the rate limiting enzyme of fluoropyrimidines, is an important risk factor for fluoropyrimidine associated severe toxicity. About 5-8% of the population has a deficiency in DPD activity, often as a result of single nucleotide polymorphisms (SNPs) in the gene encoding for DPD, DPYD. Recently, it was shown by Henricks et al. that DPYD genotype-based dose reductions improved patient safety of fluoropyrimidine treatment. A prospective, multicentre safety analysis was performed to assess the effect of prospective screening for the four most relevant DPYD variants (DPYD*2A, DPYD*7, c.2846A>T, c.1236G>A/HapB3, c.1679T>G) on patient safety and subsequent DPYD genotype-guided dose individualization in daily clinical care. For DPYD*2A and c.1679T>G carriers, a decreased risk of severe (>= grade 3) toxicity was shown after a 50% reduction. For c.2846A>T and c.1236G>A carriers a 25% dose reduction was not enough to decrease severe treatment-related toxicity. A larger initial dose reduction of 50%, with subsequent individual dose titrations, should therefore be considered.
Despite the first case of a DPD-deficient patient who developed life-threatening toxicity after treatment with topical 5-FU was described in 1999, similar research has never been performed in patients treated with 5-FU cream. Another patient developed severe neutropenia after initiating topical 5-FU treatment. Although DPD deficiency was suspected, genotyping for the clinically relevant DPYD SNPs could not be performed. To provide more clarity, our primary aim is to prospectively study the incidence of severe 5-FU cream-related toxicity in patients with and without a clinically relevant DPYD variants, eventually to determine the most optimal dosing regime in patients treated with 5-FU cream.

Study objective

To study if patients who carry clinically relevant DPYD variants (DPYD*2A, DPYD*7, c.2846A>T, c.1236G>A/HapB3, c.1679T>G) are at a higher risk for developing severe 5-FU cream-related toxicity.

Study design

This is a prospective, observational clinical trial. The number of patients needed for this study is between 350-550, with the expectation that 27 of them carry one of the clinically relevant DPYD variants (DPYD*2A, DPYD*7, c.2846A>T, c.1236G>A/HapB3, c.1679T>G). From patients treated with 5-FU cream, one blood sample will be withdrawn before or during therapy with 5-FU cream for DPYD genotyping. Genotyping will be performed after treatment. Therefore, the genotype does not influence the treatment regime. On five time points (1, 2 and 3 weeks after start therapy, with stop therapy and 3 months after start) toxicity will be evaluated using photos of the treatment area. In addition, patients will be asked to complete diaries to obtain information about toxicity. If obtained informed consent, pharmacokinetic data will be assessed to determine if there is a difference in clearance in patients with a clinically relevant DPYD variant.

Study burden and risks

In order to determine the DPYD genotype, a total of 4 mL EDTA blood will be drawn from the patients intended to be treated with 5-FU cream, or patients who recently started with application of 5-FU cream.
If additive consent is provided, an additional blood sample will be withdrawn to determine the pharmacokinetic profile of 5-FU and its metabolites.
Both samples can be withdrawn at the same time.
Patients will be asked to complete diaries to obtain information about toxicity and a questionnaire about sun exposition in the past and their skin type. In addition, on five time points (1, 2 and 3 weeks after start therapy, with stop therapy and 3 months after start therapy) toxicity will be evaluated using photos of the treatment area. Photos of the treatment area will be sent by email to the study email address. These proceedings take some extra time for the 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

- Age >= 18 years
- Able to understand the written information and able to give informed consent
- Planned treatment with topical 5-FU cream (Efudix) for any indication
- Possibility to take photos of the treatment area at the designated times and send them digitally

Exclusion criteria

- Known allergy to (components of) 5-FU cream
- Pregnancy, breast-feeding, active child wish
- Concomitant use of systemic retinoids
- Patients with known substance abuse, psychotic disorders, and/or other diseases expected to interfere with study or the patient*s safety in the opinion of the treating physician

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-10-2019
Enrollment:	550
Type:	Actual

Ethics review

Approved WMO Date:	03-10-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-10-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-09-2022
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 20542
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL70969.078.19
OMON	NL-OMON20542