Individualized pemetrexed dosing in patients with non-small cell lung cancer or mesothelioma based on renal function to improve treatment response - The IMPROVE-I, -II and -III studies -

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The overall main objective is to develop a safe and effective individualized dosing regimen for pemetrexed.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54624

Source
ToetsingOnline

Brief title
IMPROVE

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
asbestos cancer, lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: dose individualization, mesothelioma, non-small cell lung cancer, pemetrexed

Outcome measures

Primary outcome

IMPROVE-I

The fraction of patients safely reaching the target dose in combination with folinic acid or folinic acid and G-CSF, with the target dose being the dose most likely to result in an AUC of 164 mg*h/L.

IMPROVE-II

The fraction (percentage) of patients with attainment of therapeutic exposure defined as an AUC of 164 mg*h/l ±25%, with pemetrexed dosing based on renal function versus BSA-based dosing. AUC will be calculated based on the dose and the estimated pemetrexed clearance.

IMPROVE-III

The predictive performance of microdosing for pemetrexed clearance at therapeutic doses by assessing accuracy (MPE) and precision (NRMSE) in reference to full dose pharmacokinetics.

Secondary outcome

IMPROVE-I

•The AUC of pemetrexed reached at each dose level.

•Population pharmacokinetics in patients with renal impairment

•Comparative performance of different renal function markers to predict pemetrexed pharmacokinetics by assessing which algorithm provides best model fit and best reduction in clearance variability. Algorithms to be assessed:

•Safety of pemetrexed dosing in patients with a creatinine clearance <45ml/min.

IMPROVE-II

•Population pharmacokinetics in patients with adequate renal function

•Comparative performance of different renal function markers to predict pemetrexed pharmacokinetics by assessing which algorithm provides best model fit and best reduction in clearance variability.

•Safety of pemetrexed dosing based on renal function in patients with a creatinine clearance >45ml/min versus dosing based on BSA.

•Quality of life measured with the EORTC QLQ-C30/L13 questionnaire before start of chemotherapy and three months after start of chemotherapy

•Cost-effectiveness of renal-based dosing versus BSA-based dosing by using an in silico evaluation of neutropenic response and related costs

IMPROVE-III

No secondary endpoints are studied in IMPROVE-III

Study description

Background summary

Pemetrexed is a multi-targeted folate antagonist, which is primarily indicated for the treatment of advanced non-small cell lung cancer (NSCLC) and mesothelioma. Dosing of cytotoxic agents like pemetrexed requires balancing the dual risk of sub-therapy and toxicity. Administration of pemetrexed to patients with a creatinine clearance <45 ml/min is currently not advised. Pemetrexed is dosed based on body surface area (BSA), while renal function and dose are the sole determinants for systemic exposure. This causes 3 major issues:
1. In patients with renal dysfunction, BSA-based dosing may lead to haematological toxicity
2. Patients have to discontinue treatment due to declining renal function, and are withheld effective treatment
3. Even in patients with adequate renal function (GFR >45 ml/min) treatment may be improved by individualized dosing based on renal function, resulting in less toxicity. Also, BSA-based dosing may lead to ineffective therapy in patients with above average renal function.
We aim to address these problems.

Study objective

The overall main objective is to develop a safe and effective individualized dosing regimen for pemetrexed.

Study design

IMPROVE-I is a single arm dose finding study to assess the feasibility of renal function-based dosing of pemetrexed in combination with folinic acid or folinic acid and pegfilgrastim in renally impaired patients

IMPROVE-II is an open label, double arm, randomized study to compare renal function-based dosing of pemetrexed versus BSA-based dosing on attainment of therapeutic exposure.

IMPROVE-III is an explorative microdosing study to assess the extrapolability of microdose pharmacokinetics to the pharmacokinetics of a therapeutic dose.

Intervention

IMPROVE-I:patients will be treated with pemetrexed dose based on renal function. As a safety measure, the first dose will be calculated based on 10% exposure. If this is tolreated well,intra-patient dose escalation will be performed to 33, 66 and 100% respectively. Adiitionally, prophylactic treatment

with folinic acid will be administered to prevent toxicity, on day 2-15 of the treatment cycle. If neccesary, pefgilgrastim can be used to treat neutropenia.

IMPROVE-II: patients will be randomized in a 1:1 ratio to Arm A (BSA-based dosing according drug label) or to Arm B (renal function based dosing). The renal function-based dose will be calculated to reach the target AUC. Pharmacokinetic assessment after administration will be performed after the first pemetrexed dose in both arms.

IMPROVE-III: patients will be administered a microdose with subsequent pharmacokinetic assessment.

Study burden and risks

We consider the extra burden from participating in the planned studies limited. The extra interventions compared to routine care, consist of sampling extra blood. The pharmacokinetic assessments require placement of one additional intravenous venflon. To ensure minimal impact of study participation on daily life, we will use a limited sampling strategy. Patients may benefit from participating in IMPROVE I and -II, as they will be treated with a potentially safe and effective drug that is dosed individually, which prevents toxic exposure.

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

IMPROVE-I,
1. >=18 years old
2. Eligible for treatment with pemetrexed-based chemotherapy based on indication
3A. For the first three patients (cohort 1): estimated creatinine clearance of 30-45 mL/min
3B. For every next patient (cohort 2): estimated creatinine clearance <45ml/min
4. ECOG performance score of 0-2
5. Subject is able and willing to sign the Informed Consent Form
IMPROVE-II
1. >=18 years old
2. Eligible for treatment with pemetrexed-based chemotherapy
3. Creatinine clearance >45ml/min
4. ECOG performance score of 0-2
5. Subject is able and willing to sign the Informed Consent Form,
IMPROVE-III
1. >=18 years old
2. Planned for treatment with pemetrexed-based chemotherapy
3. ECOG performance score of 0-2
4. Subject is able and willing to sign the Informed Consent Form

Exclusion criteria

IMPROVE-I, -II and -III
1. Conditions that affect haemostasis in a way that blood drawing is complicated (to be assessed by physician)
2. Contraindications for treatment with pemetrexed in line with the SmPC (except for creatinine clearance <45 ml/min in IMPROVE-I)
a.Hypersensitivity to the active substance or to any of the excipients
b.Pregnancy or lactation
c. Concomitant yellow fever vaccine
3. The presence of clinically relevant pharmacokinetic interactions, according

to the current SmPC
4. Obesity (defined as a body mass index (BMI) >40 kg/m2)
5. Limb amputation
6. Use of trimethoprim and/or cimetidine
additional for IMPROVE-I:
7. Baseline absolute neutrophil count <1.5*109/L

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-02-2019
Enrollment:	106
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ALIMTA
Generic name:	pemetrexed
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	04-06-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-08-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-11-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-06-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-11-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-01-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-03-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EudraCT	EUCTR2018-001291-38-NL
Other	IMPROVE
CCMO	NL65481.091.18

Study results

Date completed:	29-12-2023
Actual enrolment:	100