Intracellular drug measurements to predict toxicity in high-dose methotrexate therapy in leukaemia and central nervous system lymphoma: a pilot study

Published: 17-12-2015
Last updated: 19-04-2024

A) To investigate the pharmacokinetics and determinants of MTX-PG accumulation in plasma and erythrocytes in adult CNS lymphoma and leukemia patients treated with HD-MTX;B) To investigate whether intracellular MTX levels are related to toxicity in...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON47317

Source
ToetsingOnline

Brief title
HAL study

Condition

- Other condition
- Lymphomas non-Hodgkin's B-cell

Synonym
leukaemia and central nervous system lymphoma

Health condition

Bloed- en Lymfestelsel aandoeningen: leukemiën

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: high-dose methotrexate, Intracellular drug measurements, toxicity

Outcome measures

Primary outcome

intracellulair MTX levels (polyglutamates)

Secondary outcome

toxicity

Study description

Background summary

High-dose Methotrexate (HD-MTX) chemotherapy is the cornerstone of the treatment of central nervous system lymphoma (PCNSL) and acute lymphoblastic leukaemia (ALL).The anti-folate MTX is cytotoxic by depleting folate co-factors necessary for RNA and DNA synthesis with consequent arrest of cellular proliferation. MTX is an effective drug because high plasma levels are relatively well tolerated resulting in penetration of the blood brain barrier and increased bioavailability.Although MTX is a relatively safe and quite effective drug, there is a large inter-individual variation in MTX pharmacokinetics and treatment outcome is variable.[3-6] Moreover, >35% of patients experience adverse events such as renal dysfunction, neurotoxicity, and severe mucositis. Especially nephrotoxicity, which has been reported in 26% of patients may necessitate delay or abortion of subsequent cycles and is not always reversible. Dosing algorithms have been developed to target an area under the curve (AUC) for plasma MTX between 1000 and 1100 *mol/L. However, there is little information what plasma dose/AUC is optimal to reach remission of the disease without adverse events. Moreover, conflicting data exist regarding association between plasma MTX levels, AUC, and clinical outcome. In contrast, intracellular MTX levels are difficult to measure but are probably

better related to efficacy and also toxicity. Scarce data also exist about the relation between the maximum plasma MTX levels and accumulation of intracellular MTX in target tissue or cerebral spinal fluid (CSF).

Study objective

A) To investigate the pharmacokinetics and determinants of MTX-PG accumulation in plasma and erythrocytes in adult CNS lymphoma and leukemia patients treated with HD-MTX;
B) To investigate whether intracellular MTX levels are related to toxicity in adult HD-MTX therapy.

Study design

open label

Study burden and risks

Most of the patients treated with MTX for lymphoma or leukemia have a central line or Hickman catheter. During routine blood tests, extra blood samples for this study will be withdrawn, in most cases this will be done via the central line / Hickman.
Burden and risks for the patient is very limited

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Wytemaweg 80
Rotterdam 3015 CN
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Wytemaweg 80
Rotterdam 3015 CN
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- All adult patients treated in the Erasmus MC with HD-MTX for a CNS lymphoma or ALL
- Written informed consent

Exclusion criteria

age < 18 years
no written informed consent

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2015
Enrollment:	60
Type:	Anticipated

Ethics review

Approved WMO Date:	17-12-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-07-2018
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

No registrations found.

In other registers

Register	ID
CCMO	NL54566.078.15