An open-label, randomized clinical trial on teicoplanin infection prophylaxis in pediatric patients with acute myeloid leukemia

Published: 17-07-2020
Last updated: 07-09-2024

This study has been transitioned to CTIS with ID 2023-506546-23-00 check the CTIS register for the current data. Objectives safety run-in: The primary objective is:• To assess the safety of i.v. teicoplanin prophylaxis three times per week with a...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON54113

Source
ToetsingOnline

Brief title
Pro-Teico study

Condition

- Leukaemias

Synonym
AML, blood cancer

Research involving
Human

Sponsors and support

Primary sponsor: Prinses Máxima Centrum voor Kinderoncologie

Source(s) of monetary or material Support: KiKa

Intervention

Keyword: Acute myeloid leukemia, Antibiotic prophylaxis, Childhood leukemia, Teicoplanin

Outcome measures

Primary outcome

Safety run-in:

The number of DLTs observed.

Randomized controlled trial:

The (first) occurrence of culture-proven BSIs with VGS during initial AML

treatment;

Date(s) of BSI(s) with VGS

Secondary outcome

Safety run-in:

PK parameters of teicoplanin, e.g.,

Css,max; Css,min; Tss,max; Area under the curve

T1/2; Clearance (inter-compartmental, total, renal fraction); Volume of

distribution (central and peripheral)

Randomized controlled trial:

1. the number of BSIs with culture-proven bacteria

2. Results of all positive blood cultures

3. Infection-related (pediatric) intensive care admissions;

4. The number of episodes/admissions with (neutropenic) fever; days with fever

(with or without neutropenia), days with FN, days with neutropenia

5. Infection-free survival time, i.e., time from diagnosis till first

culture-proven BSI;

6. Infection-related mortality;

7. Number of days until neutrophil recovery (ANC of >=0.5 x10^9/L following the

nadir)

8. Resistance patterns of pathogenic isolates from blood cultures;

9. Incidence of resistant bacteria in (routine) throat and rectal surveillance

cultures, e.g.,; VRE

10. AEs of special interest (see section 8.2.4),

11.Serious adverse events (SAEs) (see section 8.2.3);

12. Use of (other) antibiotics, antifungals and antivirals;

13. Serum creatinine levels

14. Serum levels of teicoplanin

15. Cumulative incident of relapse

16. Event-Free survival

17. Overall survival

Study description

Background summary

As a result of an impaired immune system and severely impaired mucosal barriers due to chemotherapy (in particular high-dose cytarabine), pediatric patients with AML are at high risk of developing severe infections. Viridans Group Streptococci (VGS) are a prevalent cause of Gram-positive bloodstream infections (BSIs) in pediatric AML patients, with an incidence up to 30%. BSIs with VGS are associated with severe complications and often result in sepsis,

which is associated with intensive care admission rates up to 60% in some series, and mortality rates up to 20%. Nonetheless, no antibiotic VGS prophylaxis is recommended by (inter)national guidelines in pediatric AML patients, because of the lack of supporting evidence.

Recently, a retrospective cohort study conducted by the Berlin-Frankfurt-Münster (BFM)-AML-Austria Study Group (SG) reported a complete eradication of VGS sepsis and a decrease of approximately 40% in episodes of febrile neutropenia (FN) in pediatric AML patients whom received prophylactic i.v. teicoplanin.

Is this study the results of the BFM-AML Austria SG will be validated prospectively.

Study objective

This study has been transitioned to CTIS with ID 2023-506546-23-00 check the CTIS register for the current data.

Objectives safety run-in:
The primary objective is:
• To assess the safety of i.v. teicoplanin prophylaxis three times per week with a two to three days interval in children with newly-diagnosed AML.
A patient will be considered evaluable for safety if they experience a DLT during a prophylactic cycle with teicoplanin or, in case no DLT occurs, if exposure to teicoplanin is either at least 2 consecutive weeks with at least 5 doses of teicoplanin or at least 3 weeks in total with at least 6 out of 9 doses of teicoplanin, or 8 out of 12 doses in case of 4 weeks, or 10 out of 15 doses in case of 5 weeks.
The secondary objective is:
• To (preliminary) characterize the PK parameters of teicoplanin in children with newly-diagnosed AML.

Objectives randomized phase:
The primary objective is:
• To evaluate whether i.v. teicoplanin prophylaxis in children with newly-diagnosed AML decreases the occurrence of culture-proven BSIs with VGS during treatment.

See for the secondary objectives protocol section 2.2

Study design

Prospective, international, multicenter, open-label, randomized clinical trial, preceded by a safety run-in. The design for the safety run-in includes the Rolling 6 design based on dose-limiting toxicity (DLT). The number of patients

to be included in the safety run-in depends on the occurrence of DLTs and may vary from 6 to 24 patients. The sample size for the randomized phase of the study is 122 patients.

An interim analysis will be performed after inclusion of 75% of the evaluable patients (n=92). See protocol section 9.4.

Intervention

Intervention group: The safety run-in cohort will receive i.v. teicoplanin prophylaxis 20 mg/kg/once daily three times per week via the central venous line (CVL), which all AML patients have. The interval between two administrations should be no less than 48 hours and no longer than 72 hours (e.g., Monday, Wednesday and Friday or Tuesday, Thursday and Saturday).

The start of a cycle with teicoplanin is planned to start within 24 hours after the last day of a chemotherapy course (i.e. on the last day of a chemotherapy course or within 72 hours thereafter), and will be continued until the first of the following events: an absolute neutrophil count of >=0.5 x10^9/L following the nadir and/or the start of the next chemotherapy course.
Consecutive eligible patients in the randomized phase allocated to the intervention arm will continue with this dosing schedule if considered safe, or with a de-escalated dose of 15 mg/kg/once daily three times per week if toxicity occurs.

Control group: The control group will receive standard of care (SOC), which does not include teicoplanin prophylaxis in accordance with local guidelines.

See protocol for details.

Study burden and risks

Consequences of study participation include the administration of teicoplanin, the risk of adverse reactions and events, and the additional PK blood samples drawn from the CVL. Considering the broad experience with therapeutic teicoplanin in the treatment of both adults and children and its generally mild toxicity profile, risk of participating in this study is considered low. The PK sampling strategy is minimally invasive, since all pediatric AML patients require a CVL.
Given the differences in pharmacodynamics, infection-risk, treatment protocols and survival between adults and children with AML, a similar study conducted in adults cannot be extrapolated to children. This rectifies the use of minors, under the strict regulations that are available and will be applied.
See protocol section 12.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

- Newly diagnosed with AML
- Being registered and starting treatment according to the NOPHO-DBH AML 2012 study protocol, or a consecutive protocol
- Age 0-19 years
- Written informed consent by the patient and/or legal guardians (whatever applicable according to the patients age)

Exclusion criteria

- Acute promyelocytic leukemia
- Secondary AML
- Down Syndrome
- Preexisting primary immunodeficiency
- Patients who receive regular antibiotic prophylaxis against Gram-positive bacteria for other conditions than leukemia-related
- Patients with a history of an anaphylactic reaction (CTCAE grade >=3) to teicoplanin and/or vancomycin
- Patients with an eGFR of <30 ml/min/1.73m2 at the start of the study
- Patients with a history of severe impaired hearing (CTCAE grade >=3)
- Pregnant or breast-feeding patients
- Patients that are participating in another clinical study with an IMP, that interferes with the study objectives.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-05-2021
Enrollment:	55
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Targocid
Generic name:	Teicoplanin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-07-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-10-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	23-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-02-2022

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-02-2023
Application type:	Amendment
Review commission:	METC NedMec

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
EU-CTR	CTIS2023-506546-23-00
EudraCT	EUCTR2020-000508-13-NL
CCMO	NL72779.041.20
Other	NTR nummer: Trial NL8130