Short versus extended antibiotic treatment with a carbapenem for high-risk febrile neutropenia in hematology patients with Fever of Unknown Origin: a randomized multicenter open-label non-inferiority trial.

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To assess if short antibiotic treatment (3x24 hours) with an anti-pseudomonal carbapenem (imipenem-cilastatin or meropenem) is safe (NON-INFERIOR) with regard to treatment failure in comparison with extended treatment (at least 9x24hours) of high-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON47609

Source
ToetsingOnline

Brief title
SHORT-trial

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)
- Bacterial infectious disorders

Synonym
febrile neutropenia

Research involving
Human

Sponsors and support

Primary sponsor: VUmc
Source(s) of monetary or material Support: ZonMW en FondsNutsOhra

Intervention

Keyword: antibiotic stewardship, carbapenem, febrile neutropenia, hemato-oncology

Outcome measures

Primary outcome

The primary endpoint is the percentage of patients with failed treatment.

Treatment failure is defined as

1. The occurrence of any of the following events after randomization at

3x24hours and before 9x24hours after treatment with a carbapenem:

* A clinically or microbiologically documented carbapenem-sensitive infection;

* Recurrence of fever after previous defervescence (tympanic temperature <38.0

°C during 24 hours) which is not attributable to administration of a blood

product or to a drug reaction.

o In case of clinical doubt if the fever is of infectious etiology, the

recurrence of fever will be considered as failure.

2. The occurrence of death, ARDS/respiratory insufficiency, septic shock

(systolic blood pressure <90mmHg and oliguria <500mL/day) due to any cause

until the end of neutropenia.

NOTE: The occurrence of fungal, viral or carbapenem-resistant (inherent or

acquired) bacterial infections will not be considered as treatment failure.

Examples of inherent carbapenem resistant bacteria include: E. faecium, commensal skin flora (ie. CNS), MRSA, Legionella spp., S. maltophilia, Bulkholderia cepacia, Chlamydia spp, Chlamydophilia spp., Mycoplasma spp., Ureoplasma urealyticum.

Secondary outcome

1) Treatment failure (as defined by primary endpoint) from 9x24hours until 14x24 hours after onset of fever.

2) All-cause mortality from 3x24hours of treatment until the end of neutropenia.

3) Infection related mortality from 3x24hours of treatment until the end of neutropenia.

4) All-cause mortality within 30 days after recovery of neutropenia.

5) Infection related mortality within 30 days after recovery of neutropenia.

6) Treatment strategy failure, defined as the necessity to modify the antibacterial regimen after randomization other than for antibacterial prophylaxis.

7) The incidence and prevalence of all clinical or microbiological documented infections. fungal, viral, or carbapenem-resistant (inherent/acquired) infections until the end of neutropenia.

8) The incidence and prevalence of Clostridium difficile infections until 30 days after the end of neutropenia.

9) The length of hospitalization in days.

10) Time to defervescence.

11) The total number of febrile episodes during neutropenia.

12) Bacterial resistance in blood cultures and surveillance cultures (including

minimal inhibitory concentrations (MIC)).

13) Candida spp. colonization in (surveillance) cultures;

14) Cost of antimicrobial therapy per admission

15) The percentage of patients with a MASCC-score *21 and treatment failure

(defined as in primary endpoint)

16) The percentage of patients with mucositis and positive blood cultures or

antibiotic treatment failure.

Study description

Background summary

Episodes of fever are very common in patients undergoing intensive chemotherapy treatment for malignant hematological disease. More than 80% of patients experience one or more episodes of fever after their first cycle of chemotherapy. Only 20-30% of these patients have a clinically documented focus and mostly include infections of skin, intestinal tract and lung, while at most 10-25% of these patients have microbiologically proven bacteremia during these episodes. Most protocols advice treatment with very broad-spectrum antibiotics. These antibiotics are administered for variable durations, often at least 9 days or until fever or neutropenia have resolved. In 56% of cases no infectious agent can be cultured and the fever remains of unknown origin. Current clinical guidelines bring about the use of large amounts of antimicrobials, while clinical evidence regarding optimal length of antibacterial therapy is lacking. Prolonged continuation of treatment may induce bacterial resistance. In view of the possible emergence of bacterial resistance due to prolonged antibiotic administration, continuation until recovery of neutropenia is suboptimal. Moreover, it is costly because of longer hospital admissions, higher antibiotics costs and more possible adverse reactions. Recent, observational studies have shown that discontinuation of broad-spectrum antibiotics is safe if no clinical or microbiological infection has been found after 3 days. However, no randomized clinical trial has yet been performed to support this data.
We therefore propose a randomized clinical trial investigating whether the duration of empiric antibacterial therapy in these patients can be safely reduced to 3x24 hours if no bacterial explanation has been found by that time. This study compares the safety (non-inferiority) of short treatment (3x24hours) versus extended treatment (at least 9x24 hours) with an anti-pseudomonal

carbapenem for hematology patients with unexplained high risk febrile neutropenia. We hypothesize that a more restrictive use of broad-spectrum antibiotic use of three days in unexplained fever in neutropenic hematology patients is non-inferior to the present extended use during at least 9 days which would lead to a more restrictive use of antibiotics and less multiresistent strains of bacteria, costs and hospitalization length in the future.

Study objective

To assess if short antibiotic treatment (3x24 hours) with an anti-pseudomonal carbapenem (imipenem-cilastatin or meropenem) is safe (NON-INFERIOR) with regard to treatment failure in comparison with extended treatment (at least 9x24hours) of high-risk febrile neutropenia in hematology patients receiving standard antimicrobial prophylaxis.

Study design

Multicenter open-label randomized non-inferiority clinical trial

Intervention

In patients in the short treatment arm (intervention) the intravenous empirical antibiotics will be discontinued if no clinical, radiological or microbiological documented infection has been found that could explain the fever after 3 days of treatment. After this, the patients will resume their standard oral antibiotic prophylaxis. In the extended treatment arm (control), the empirical antibiotics will be continued at least 9 days until fever resolved at least consecutive 5 days. The treatment in this arm will be up to 14 days, in case of unexplained fever.

Study burden and risks

In patients in the short treatment arm the intravenous empirical antibiotics will be discontinued if no clinical, radiological or microbiological documented infection has been found that could explain the fever after 3 days of treatment. After this, the patients will resume their standard oral antibiotic prophylaxis. There is a small chance a bacterial infection appears after discontinuation of intravenous antibiotics. Because neutropenic patients are more vulnerable to infectious disease there is a bigger chance of complications of bacteremia and/or sepsis than in immunocompetent patients.

Contacts

Public
VUmc

De Boelelaan 1117
Amsterdam 1081 HV
NL
Scientific
VUmc

De Boelelaan 1117
Amsterdam 1081 HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1.Patients with malignant hematological diseases being treated with cytotoxic chemotherapy or stem cell transplantation;;2.High-risk neutropenia;;3.Fever;;4.Age 18 years or older;;5.Written informed consent.

Exclusion criteria

1.Contraindications to use of imipenem-cilastatin or meropenem such as allergy, previous severe side-effects or previous microbiological cultures with carbapenem-resistant microorganism(s).;2.Corticosteroid use *10 mg per day prednisolone or equivalent for more than 3 consecutive day during the previous 7 days.;3.Clinically or microbiologically documented infection. ;4.Symptoms of septic shock (systolic blood pressure <90 mm Hg

unresponsive to fluid resuscitation and/or oliguria (urine production <500mL/day)).;5.Previous enrollment in this study during the same episode of neutropenia. ;6.Any critical illness for which Intensive Care Unit treatment is required.;7.Legal incompetency

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-12-2014
Enrollment:	276
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	meropenem
Generic name:	meropenem
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	tienam
Generic name:	imipenem-cilastatine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-10-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-01-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-03-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2014-001546-25-NL
ClinicalTrials.gov	NCT02149329
CCMO	NL48960.029.14