# Korte versus lange behandeling met een carbapenem voor onverklaarde koorts tijdens hoog risico neutropenie bij hematologische patiënten: een gerandomiseerde non-inferiority studie.

No registrations found.

| | |
|---|---|
| **Ethical review** | Not applicable |
| **Status** | Pending |
| **Health condition type** | - |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON26213

**Source**
NTR

**Health condition**

Hematologic malignancy
Neutropenia
Neutropenic fever
Unexplained fever
Stem-cell transplantation
Chemotherapy

### Sponsors and support

**Primary sponsor:** VU university medical center
**Source(s) of monetary or material Support:** follows

### Intervention

## Outcome measures

### Primary outcome

The primary endpoint is the percentage of patients with failed treatment. Treatment failure is defined as the occurrence of one of the following events after 3x24hours of treatment with a carbapenem.

The patient:

1. Has fever at the first day of the end of the neutropenic episode (defined as the first day with neutrophil count >0.5*109/L).

2. Has experienced recurrence of fever after more than 24 hours of defervescence.

3. Is diagnosed with a clinically or microbiologically documented infection.

4. Shows signs or symptoms of septic shock (systolic blood pressure <90mmHg unresponsive to fluid resuscitation and/or oliguria <5mL/kg/hour).

5. Dies between the start of the investigational treatment protocol and recovery of neutropenia.

### Secondary outcome

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

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

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

4. Infection related mortality within 30 days after recovery of neutropenia.

5. The length of hospitalization in days.

6. Unexpected re-admission within 30 days after discharge other than for planned chemotherapy or other elective treatment.

7. The recurrence of fever within 24 hours after discontinuation of intravenous antibiotic therapy.

8. The total number of febrile episodes during neutropenia.

9. Time to defervescence.

10. Antibiotic or antifungal treatment within 30days after discharge other than standard

antibiotic prophylaxis.

11. Bacterial resistance in blood cultures and surveillance cultures (including minimal inhibitory concentrations (MIC)).

12. Incidence and prevalence of Clostridium difficile infection.

13. Incidence and prevalence of liver and kidney dysfunction during intravenous antibiotic treatment.

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

15. Cost of antimicrobial therapy per admission

16. MASCC-score (appendix C)

17. The percentage of patients with mucositis and positive blood cultures or antibiotic treatment failure.

# Study description

### Background summary

Randomized clinical trial aimed at investigating whether the duration of empiric antibacterial therapy in patients with hematologic malignancies and unexplained neutropenic fever can be safely reduced. A multicenter randomized clinical non-inferiority trial comparing safety of short (3 days) vs extended treatment (9 or more days) with an anti-pseudomonal carbapenem for hematology patients receiving standard antimicrobial prophylaxis is proposed.

### Study objective

Short empirical treatment with a anti-pseudomonal carbapenem in hematology patients with unexplained fever during neutropenia is non-inferior to extended treatment with regard to treatment failure.

### Study design

The investigational treatment protocol will end after any of the following events:

1. End of the neutropenic episode (ANC <0.5*109/L)

2. Diagnosis of a clinically, microbiologically documented infection after randomization.

3. In case the patient shows symptoms of septic shock (systolic blood pressure <90mm Hg unresponsive to fluid resuscitation and/or oliguria <5mL/kg/hour)

4. Death due to any cause.

5. Lack of patient compliance or withdrawal of informed consent (especially refusal to continue treatment according to protocol).

6. Major protocol violation

7. Contra-indication to administer imipenem-cilastatin or meropenem due to allergy, side effects or carbapenem-resistant microorganism(s) in a microbiological culture.

8. Recurrence of fever after defervescence after randomization.

**Intervention**

TREATMENT:

Patients will be included in the first 3x24hours hours after the start of antibiotic treatment and will receive standard diagnostic investigations and empirical treatment with imipenem-cilastatin 500mg QID or meropenem 1000mg TID during this period. If, intensive clinical, radiological and microbiological evaluation yields no explanation for fever, patients are eligible for randomization between 2x24 hours and 3x24hours after start of empirical antibiotic treatment. Patients will be randomized into two groups.

INFORMED CONSENT AND RANDOMISATION:

Within 72hours after onset of fever every eligible patient will be asked for informed consent. Each consenting patient is then randomized to either the short treatment arm or the extended treatment arm. This will be the start of the investigational treatment protocol.

EARLY DISCONTINUATION ARM:

In the short treatment group, imipenem-cilastatin or meropenem will be discontinued after 3x24 hours irrespective of presence of fever. If fever has resolved by this time, no further action will be undertaken. If fever persists after 3x24hours, antifungal treatment with voriconazole (or anidulafungin in case of azole-resistant fungi in surveillance cultures) will then be started after 4x24 hours and will be continued until recovery of neutropenia (ANC >0.5*109/L).

EXTENDED TREATMENT ARM:

In the extended treatment arm, the duration of imipenem-cilastatin or meropenem treatment depends on the presence of fever. Patients who are afebrile after 3x24hours after appearance of fever will continue for at least 6 more days. If fever persists after 3x24hours, antifungal treatment with voriconazole (or anidulafungin in case of azole-resistant fungi in surveillance cultures) will then be started after 4x24 hours and will be continued until recovery of neutropenia (ANC >0.5*109/L). The treatment with a carbapenem will be continued until patients have been treated for at least 9x24 hours and have been afebrile (tympanic membrane temperature <37,5°C) for at least five consecutive days or until resolution of neutropenia (ANC > 0,5 x109/L), whichever comes first.

# Contacts

**Public**
VU Medisch Centrum
N.A. Jonge, de
Amsterdam
The Netherlands
**Scientific**
VU Medisch Centrum
N.A. Jonge, de
Amsterdam
The Netherlands

# Eligibility criteria

## 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 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 <5mL/kg/hour)).

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 type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Single blinded (masking used) |
| Control: | Active |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-07-2014 |
| Enrollment: | 224 |
| Type: | Anticipated |

# Ethics review

Not applicable
Application type: Not applicable

# 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 |
|---|---|
| NTR-new | NL3499 |
| NTR-old | NTR3675 |
| Other | NCT: 02149329 : EudraCT: 2014-001546-25 ABR: NL48960.029.14 |
| ISRCTN | ISRCTN wordt niet meer aangevraagd. |

# Study results

**Summary results**
N/A