Anakinra: safety and efficacy of interleukin-1 pathway inhibitor anakinra for the management of fever during neutropenia and mucositis in patients with multiple myeloma receiving an autologous hematopoietic stem cell transplantation after high-dose melphalan - A randomized controlled trial

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

Summary

ID

NL-OMON48856

Source
ToetsingOnline

Brief title
HEMSC42 / AFFECT-2

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)
- Gastrointestinal inflammatory conditions

- Body temperature conditions

Synonym
and fever during neutropenia), mucositis and febrile neutropenia; (inflammation of the lining of the digestive system

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,KWF-subsidie

Intervention

Keyword: anakinra, autologous stem cell transplantation, febrile neutropenia, mucositis

Outcome measures

Primary outcome

Primary endpoint:

- Reduction of incidence of fever during neutropenia

Secondary outcome

Secondary endpoints:

- Incidence of mucositis-related fever

- Maximum CRP level on day +9-10

- Daily mean CRP level

- Intestinal mucositis as measured by the area-under-the-curve of reciprocal

citrulline levels

- Clinical mucositis as determined by the daily mouth and gut scores

- Days with fever ((>= 38.2° C)

- Days with fever (>= 38.5° C)

- Mean daily morning temperature

- Area under the curve of daily morning temperature

- Incidence of bloodstream infections i.e. bacteremia

- Type of bloodstream infections

- Incidence of persistently positive blood cultures on day +4

- Quality of life according to the EORTC QLQ-C30

- Severity of fatigue as the score measured by the validated FACIT-Fatigue scale

- Tumor response evaluation (100 days and 1 year)

- Short term overall survival (100 days and 1 year)

- Length of hospital stay in days

- Use of systemic antimicrobial agents (incidence and duration)

- Use of analgesic drugs (incidence and duration)

- Use of total parenteral nutrition (TPN) (incidence and duration)

Study description

Background summary

Mucosal barrier injury (MBI) of the mouth (oral mucositis) and gut (intestinal mucositis) is an important side effect of treatment with intensive chemotherapy and radiotherapy. The occurrence of mucositis is a major risk factor for fever during neutropenia (febrile neutropenia, FN) and the development of bloodstream infections (BSI) with microbes residing at the integument. These complications often require dose reductions or cause delay in and even cessation of treatment, all precluding optimal treatment for patients with cancer with a lower chance for cure. Currently, however, there are no effective strategies to prevent or treat mucositis. Therefore, there is an unmet need for effective treatment and prevention strategies for mucositis and fever during neutropenia. Cytokines that belong to the interleukin-1 family are involved in multiple inflammatory and immune responses, but also play a crucial role in the pathogenesis of mucositis. Inhibition of the IL-1 pathway has proven to be effective in a number of IL-1 mediated diseases, such as rheumatoid arthritis (RA), gout and Cryopyrin-associated Periodic Syndromes (CAPS). Recently, studies in murine models of chemotherapy-induced mucositis demonstrated that

anakinra, a recombinant human interleukin-1 receptor antagonist, significantly ameliorated intestinal mucositis. Therefore, we hypothesize that inhibition of the IL-1 pathway, in patients receiving intensive chemotherapy in the context of hematopoietic stem cell transplantation, can decrease the incidence of intestinal mucositis and consequently fever during neutropenia.

Study objective

The primary objective is to evaluate the efficacy of anakinra in patients with multiple myeloma receiving high-dose melphalan (HDM) in the preparation for an autologous hematopoietic stem cell transplantation (SCT). The primary endpoint is the reduction of the incidence of fever during neutropenia. Secondary objectives are the gathering of blood and microbiota samples for translational research.

Study design

A multicenter phase IIb double-blind randomized placebo-controlled study.

Intervention

Subjects will be randomized between the intervention group (Arm A: anakinra intravenously once daily, in dose defined in pilot study AFFECT-1), and the control group (Arm B: placebo intravenously once daily) with a 1:1 ratio. Investigators, healthcare providers and subjects will be blinded to both the randomization schedule and subsequent treatment allocation.

Study burden and risks

Burden associated with participation:
Subjects will receive study treatment with either placebo or anakinra intravenously once daily. In all subjects, as compared to standard treatment outside study context, three times a week additional blood tests will be obtained (total volume 100 mL), as well as stool samples and oral swabs twice a week. Also, from day +4 until day +12, additional blood cultures will be obtained (total volume 120 mL). Finally, subjects will be asked to complete a number of questionnaires (2 questionnaires, both on 4 time points) related to quality of life and fatigue severity.

Risks associated with the investigated product:
The impact of anakinra on mucositis and therewith the expected reduced incidence of fever and infections has not been established yet. Being an anti-inflammatory drug, the signs of infections may be masked and the immunosuppressive effects may increase the risk for infections. In addition, neutropenia and headache are documented side effects of anakinra. However, in previous studies in allogeneic SCT recipients the use of anakinra was not

accompanied by untoward side effects and no detrimental effects of engraftment post-SCT have occurred. Currently, we are performing the AFFECT-1 study, in which the safety and maximum tolerated dose (100, 200 or 300 mg) of anakinra is determined. In this study, so far (actual dose level 300 mg reached), no side effects related to anakinra have occurred.

Benefits: In murine models of chemotherapy-induced mucositis, treatment with anakinra was associated with decreased signs and symptoms of mucositis. Therefore, treatment with anakinra in our study population at high risk for MBI might result in decreased incidence and severity of mucositis, with possibly a lower incidence of febrile neutropenia and infections related to MBI. In addition, patients might experience less pain related to MBI, require less antibiotics and opioids and have lower symptom scores and better quality of life. Also, participation in the study may facilitate the development of an effective drug in the management of fever during neutropenia and mucositis for future SCT recipients.

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

- Aged >=18 years
- Diagnosed with multiple myeloma
- Scheduled to receive an autologous SCT after myeloablative therapy with high-dose melphalan
- Managed with a central venous catheter (triple- or quadruple lumen)
- Is able and willing to participate
- Has provided written informed consent
- Has negative serology for active hepatitis B and C
- Has negative serology for HIV
- Has no known hypersensitivity to Escherichia coli derived products or any components of anakinra
- Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation (during treatment with study medication), and for 30 days after the last dose.

Exclusion criteria

- Inability to understand the nature and extent of the trial and the procedures required
- Enrolment in any other investigational treatment study or use of an investigational agent during the stem cell transplantation (this means studies in multiple myeloma regarding induction or maintenance treatment are permitted).
- Women who are pregnant or nursing
- Diagnosed with amyloidosis or light-chain deposition disease
- ALT or AST greater than 2.0 x upper limit of normal (ULN) of the local laboratories values.
- Bilirubin levels greater than 2.0 x upper limit of normal (ULN) of the local laboratories values, except for benign non-malignant indirect hyperbilirubinemia such as Gilbert syndrome
- Impaired renal function with eGFR <40 ml/min
- Received a live vaccine during the 3 months prior to baseline visit
- Recent use of IL-1 antagonist, such as anakinra, rilonacept or canakinumab, within three months prior to baseline visit
- Treatment with TNFα inhibiting agents (such as etanercept, adalimumab, infliximab, certolizumab and golimumab).
- Uncontrolled bacterial or viral infections, or fungal infections, at the start of therapy
- Documented colonization with methicillin-resistant Staphylococcus aureus (MRSA), carbapenemase-producing Enterobacteriaceae (CPE) or vancomycin-resistant enterococci (VRE) prior to registration

- Gram-negative colonization resistant to prophylaxis with ciprofloxacin or colistin/cotrimoxazole
- Subjects who are not able to receive antibacterial prophylaxis with ciprofloxacin or colistin/cotrimoxazole (because of hypersensitivity or drug interactions)
- Subjects with an active solid malignancy prior to registration, with the exception of cutaneous basal or squamous cell carcinomas
- History of mycobacterial infection.
- Subjects with intrinsic disorders of the gastro-intestinal (GI) tract, including, but not limited to: Crohn*s disease, ulcerative colitis, celiac disease, short bowel syndrome.
- Subject has any concurrent medical or psychiatric condition or disease that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-10-2019
Enrollment:	90
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kineret
Generic name:	anakinra
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-07-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-07-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-12-2020
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	EUCTR2018-005046-10-NL
CCMO	NL66297.091.19