Infusion of ex vivo-generated allogeneic natural killer cells in combination with subcutaneous IL-2 in patients with acute myeloid leukemia: a phase I/IIa study*

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This study has been transitioned to CTIS with ID 2024-515357-16-00 check the CTIS register for the current data. The study is divided in two phases.The primary objective of phase I of the study is to evaluate the safety and toxicity of the infusion…

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

Summary

ID

NL-OMON55708

Source
ToetsingOnline

Brief title
NK4AML: Allogeneic NK-cell therapy for AML

Condition

- Leukaemias

Synonym
Acute myeloid leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: KWF

Intervention

Keyword: Acute myeloid leukemia, Immune therapy, Natural killer cells

Outcome measures

Primary outcome

Phase 1: All patients will be evaluated extensively for toxicity using the CTCAE toxicity criteria and graft versus host disease criteria. Based on this dose-limiting toxicities will be scored. In case 1 patient will experience DLT at a particular dose, the cohort will be increased to 6 patients. The maximum tolerated IL-2 dose will be defined as the dose at which less than 2 patients experience DLT within a cohort of 6 patients.

Phase 2: The primary endpoint of phase 2 of the study is to evaluate te effect of NK cells following adoptive transfer in combination with sc IL-2 on disease activity in patients with AML. Effect will be determined as a CR or PR according to ELN criteria.

Secondary outcome

- Evaluation of the in vivo lifespan and expansion potential of the NK cells following adoptive transfer, either with or without IL-2 administration. For phase 2: A positive expansion rate of the infused NK cells requires an absolute number of >= 100 donor-derived NK cells per µl blood at day +7 and/or +14.
- Exploration of the functional activity of the donor NK cells in PB and BM, either with and without sc IL-2 administration using flow cytometry and CD107a (LAMP-1)-based degranulation and IFNy-secretion assays

- Evaluation of IL-2 plasma levels and cytokine concentrations (IL-15, IL-7,

IFN-γ, TNFα, IL-6) pre- and post infusion of IL-2, which will be correlated

with absolute lymphocyte count and in vivo NK cells persistence and expansion

- For phase 2: amount of patients eligible for allogeneic stem cell

transplantation defined at day +28

Study description

Background summary

AML is the most common type of acute leukemia in adults and incidence increases with age. Despite (agressive) treatment progrnosis remains poor, with at the moment a 5 years survival of 35-40% in young and 5-15% in older AML patients. New treatments are necessary. Allogeneic natural killer cell based immunotherapy is a promising adjuvant treatment with less toxicity. However the therapeutic effect can en should be improved. Our previous clinical trial showed that administration of our NK-cel product to older AML patients is safe. Additionally it showed that the NK cells do not have a high expansion potential in the patient. In this study we want to combine allogeneic NK-cel therapy with IL-2, an essential cytokine for NK cell survival and proliferation.

Study objective

This study has been transitioned to CTIS with ID 2024-515357-16-00 check the CTIS register for the current data.

The study is divided in two phases.
The primary objective of phase I of the study is to evaluate the safety and toxicity of the infusion of ex vivo expanded RNK001 NK cells, both with and without sc IL-2 following immunosuppressive conditioning therapy in patients with AML. In this phase we will determine the maximum tolerable dose of IL-2.
The primary objective of phase II of the study is to evaluate the effect of RNK001 NK cell adoptive immunotherapy in combination with sc IL-2 on disease activity in patients with AML.

Study design

After written informed consent in- and exclusion criteria will be checked for.7 days before NK cell infusion the patiënt will be admitted to the hospital and will receive chemotherapy for 3 days, as preparative regimen for the NK cell

infusion. NK-cell infusion will be followed by 6 times every other day a subcutaneous injection of IL-2, starting on the day of NK-cell administration. Patients will be admitted at least until the last IL-2 administration.

Phase 1: 3 cohorts of 3 patients receiving IL-2 in increasing dose (0, 3.0, 6.0 x 10^6 IU/dose). Dose limiting toxicities (DLT*s) will be monitored till 28 days (4 weeks) after NK cell infusion. Four weeks after NK cell infusion of the last patient in a cohort, the next patient can be included in a new cohort.

Phase 2: phase 2 consists of 2 stages; If 3 or more of the 8 patients enrolled in stage 1 of phase 2 show either CR or a PR according to ELN response criteria by day +28 post NK cell infusion an additional 10 patients will be enrolled in stage 2 to obtain a precise estimate of PR/CR. If < 3 of the 8 patients show CR or PR the study will be stopped.

Intervention

As preparative regimen to NK-cell administration patients receive chemotherapy for 3 days, starting one week prior to a single intravenous administration of NK-cells. Except 3 patients, the NK cell infusion will be followed by a 6 times every other day subcutaneous injection of IL-2. Follow up consists of venapunctures and 3 times (possibly 4 times) a bone marrow aspiration, combined with two times (possibly 3 times) a bone marrow biopsy.

Study burden and risks

Due to the chemotherapy patients are vulnerable for infections which might require antibiotic treatment. In addition bloodtransfusions might be necessary. NK-cell therapy has been shown to be a less toxic treatment in published literature, including our own clinical trial. Patients experience less side effects. Although is has not been seen before, a graft versus host reaction could occur.
Administration of IL-2 subcutaneous can be accompanied by fever-like complaints, changes in blood pressure and a rash at the injection side.

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

MDS with excess blasts, MDS/AML or AML patients (de novo and secondary) according to ELN 2022 criteria, who have stable disease or non-rapidly progressive disease with or without disease controlling medication, who are not eligible for allogeneic SCT

- Age > 18 years
- WHO performance 0-2
- Life expectancy of > 4 months
- Written informed consent
- Hydrea is allowed as pre-treatment to control blast count until day -3
- Other disease controlling medication is allowed until day -7

Exclusion criteria

- Progressive disease in case of previous therapy
- Patients on immunosuppressive drugs or active GvHD
- Patients with active infections (viral, bacterial or fungal); acute anti-infectious therapy must have been completed within 7 days prior to study treatment
- Severe cardiovascular disease (CTCAE III-IV)
- Severe pulmonary dysfunction (CTCAE III-IV)

- Severe renal dysfunction (CTCAE III-IV)
- Severe hepatic dysfunction (CTCAE III-IV)
- Severe neurological or psychiatric dysfunction (CTCAE III-IV)
- Patients on concurrent chemotherapy or interferon-alpha treatment
- Pregnancy or breastfeeding

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-12-2020
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic
Product type:	Medicine
Brand name:	interleukin-2
Generic name:	proleukin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	04-03-2020
Application type:	First submission

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-05-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-09-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-09-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	27-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-05-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-06-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-10-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-10-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 25848
Source: NTR
Title:

In other registers

Register	ID
EU-CTR	CTIS2024-515357-16-00
EudraCT	EUCTR2019-001929-27-NL
ClinicalTrials.gov	NCT04347616
CCMO	NL67150.000.19