Natural killer cell infusion after stem cell transplantation for leukemia

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON26066

Source
Nationaal Trial Register

Brief title
IL-15 activated NK cells

Health condition

Acute lymphoblastic leukemia (ALL)
Acute myeloid leukemia (AML)
Allogeneic stem cell transplantation

Sponsors and support

Primary sponsor: Leiden University Medical Center
Source(s) of monetary or material Support: Dutch Cancer Society
Miltenyi Biotec GmbH

Intervention

Outcome measures

Primary outcome

In addition to the standard evaluation following HSCT of children treated for leukemia, the following investigations will be performed in the context of the investigational NK cell

infusion:
- To determine the number of patients for whom an investigational medicinal product (IMP), meeting all release criteria, can be generated. The protocol is considered feasible if:
> 50 % of transplanted patients can be included
> 66 % of included patients can be infused with the IMP.
- Registration of post infusion status of the patient, fever, nausea, chills, rash, erythema, and all serious adverse events, potentially linked to infusion. The IMP is considered safe and well-tolerated if no more than 2 out of 12 patients develop severe adverse reactions that are likely due to the NK cell infusion.

Secondary outcome

- The anti-leukemic/cytolytic reactivity and cytokine producing potential, e.g. IFN-ã, of NK cells ex vivo prior to and after NK infusion (intra-individual control)
- Immune reconstitution after NK cell infusion. Apart from detailed investigation of T- and B-lymphocyte recovery, the focus will be on analysis of the surface expression patterns of activating and inhibitory receptors on NK cell subpopulations. The latter will also be investigated on NK cells present in the donor HSCT graft (if not CD34+ enriched), donor leukapheresis material and the IMP.
Patients who will not be included in this study for logistic reasons as well as matched historic controls will be used for the functional and phenotypical studies indicated above
- The incidence of disseminated (viral) infections in children undergoing NK cell infusions post-HSCT compared to aforementioned controls
- The occurrence and severity of acute and chronic GvHD in NK cell recipients compared to aforementioned controls
- The incidence of relapses of leukemia in children undergoing NK cell infusions post HSCT compared to controls.
- Survival in children undergoing NK cell infusions post-HSCT compared to controls.
- The relevance of mismatching KIR ligands (HLA types) and KIR genotype/phenotype of donor/recipient pairs for observed biological effects

Study description

Background summary

Children with leukemia are treated with standardized chemotherapy and in most cases this treatment is curative. However, and in accordance with international guidelines, patients are eligible for allogeneic hematopoietic stem cell transplantation (HSCT) in case of leukemia characterized by well defined high-risk parameters and in case of relapsed disease following initial successful remission induction therapy. Historically, HLA-matched sibling donors were the first donors to be used, but due to ongoing improvements in HLA typing technology, graft manipulation and supportive care, a matched unrelated (MUD) or mismatched family donor (MMFD) is nowadays a feasible and widely accepted alternative. However, leukemia relapse after HSCT remains the main reason for treatment failure. Following HSCT with MUD and

MMFD, T cell reconstitution is delayed up to 6-12 months post transplant, and thus a potential T cell mediated graft versus leukemia (GvL) effect may be impaired. In contrast, there is rapid recovery of natural killer (NK) cells, which have been reported to exert an anti-leukemic effect. Still, the functional capacity of the early regenerating NK cells seems limited. In vitro, the functional and cytolytic properties of NK cells can be augmented by stimulation with cytokines, e.g. interleukin 15 (IL-15). We aim to exploit this NK-cell mediated potential by adoptive transfer of ex vivo IL15-activated donor NK cells with the final aim to enhance immune reconstitution and reduce residual tumor burden in the early post transplant setting when tumor levels are low.

Study objective

Adoptive transfer of ex vivo IL15-activated donor NK cells enhance immune reconstitution and reduce residual tumor burden in the early post transplant setting.

Study design

During the first year after transplantation and NK cell infusion, patients will be monitord frequently, according to our current standards for follow-up of pediatric HSCT recipients, to address primary and secondary objectives. Timepoints are pre-SCT, weekly after SCT in the first 10 weeks, 12, 16, 20, 24, and 52 weeks post-SCT. Thereafter, patients will be followed until adulthood and subsequently transferred to the late feects clinic according to our standard procedures for allogeneic stem cell tranplantation recipients.

Intervention

Patients will receive one infusion of 5-10x10e6 ex vivo IL-15-activated donor NK cells per kg body weight (maximum dose: 200x10e6) at 4-12 weeks after transplantation.

Contacts

Public
Pediatric Immunology Laboratory
Department of Pediatrics
Leiden University Medical Center
Albinusdreef 2
M.W. Schilham
Leiden 2333 RA
The Netherlands
+31(0)71 526 4462
Scientific
Pediatric Immunology Laboratory
Department of Pediatrics
Leiden University Medical Center

Albinusdreef 2
M.W. Schilham
Leiden 2333 RA
The Netherlands
+31(0)71 526 4462

Eligibility criteria

Inclusion criteria

- Aged between 1-18 years at the time of hematopietic stem cell tranplantation (HSCT)
- Undergoing HSCT for acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) according to existing indications
- Receiving a stem cell graft from a mismatched family or volunteer unrelated donor
- Life expectancy>3 months
- Availability of a stem cell donor willing to donate white blood cells by means of a non-mobilized leukapheresis procedure

Exclusion criteria

- Progressive uncontrollable malignant disease after HSCT but before or at the day of NK cell infusion, defined as overt leukemia relapse, i.e., ¡Ý 25% blasts in the marrow and/or 5% circulating blasts in the peripheral blood or progressive extra-medullary disease
- Lack of evidence for donor myeloid engraftment at the day of infusion (< 0.5 x 10e6 neutrophils/L);
- Active acute GvHD ¡Ý grade II (overall grade)
- Administration of steroids >1 mg/kg/day for any indication at the day of infusion
- Any medical condition, which in the opinion of the treating physician, would interfere with the adequate evaluation of the patient (e.g. end-stage irreversible multi-system organ failure)
- Cord blood stem cell donor

Study design

Design

Study type:	Interventional
Intervention model:	Parallel

Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-07-2013
Enrollment:	12
Type:	Anticipated

Ethics review

Positive opinion

Date:	17-01-2014
Application type:	First submission

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	NL4267
NTR-old	NTR4403
Other	Leiden University Medical Center, CCMO, EUdract : P12.022, NL38836.000.11, 2011-001514-34

Study results