Infusion of IL-15 activated NK cells after allogeneic stem cell transplantation in children transplanted for relapsed/refractory leukemia: a feasibility study

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Primary: The main objective of the study is to evaluate the feasibility, safety and tolerability of allogeneic IL15-activated NK cell infusions in children transplanted for refractory or relapsed leukemia.Secondary: To document immune reconstitution...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON43758

Source
ToetsingOnline

Brief title
NK cell infusions after allogeneic stem cell transplantation

Condition

- Leukaemias

Synonym
blood cell cancer, Leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,KWF,Miltenyi Biotec, korting op isolatie kits voor NK cellen

Intervention

Keyword: allogeneic, leukemia, NK cells, stem cell transplantation

Outcome measures

Primary outcome

To document the feasibility to generate sufficient numbers of IL-15 activated NK cells from HSCT donors in real time, i.e. the Investigational Medicinal Product (IMP), meeting the release criteria and the safety of infusion and tolerability of the IMP post HSCT in children transplanted for refractory/ relapsed leukemia.

Secondary outcome

1. The anti-leukemic/cytolytic reactivity and cytokine producing potential, e.g. IFN-gamma, of NK cells ex vivo prior to and after NK infusion (intra-individual control).

2. The 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 and of NK cell function. The latter will also be analysed for NK cells present in the HSCT graft (if not CD34+ enriched), donor leukapheresis material and the IMP.

3. Incidence of disseminated (viral) infections in children undergoing NK cell infusions post HSCT compared to controls.

4. Incidence and severity of acute and chronic GvHD in children undergoing NK cell infusions post HSCT compared to controls.

5. Incidence of relapses of hematological malignancies in children undergoing NK cell infusions post HSCT compared to controls.

6. Survival in children undergoing NK cell infusions post HSCT compared to controls.

7. To study the relevance of mismatched KIR ligands (HLA types) and KIR genotype/phenotype of donor/recipient pairs for observed biological effects.

Control group:

Patients transplanted for leukemia with stem cells from an MMFD or UD donor between 2005 and 2012 at our unit will be the (historical) control group.

Study description

Background summary

For many children with high risk leukemia hematopoietic stem cell transplantation (HSCT) is the only curative option. Due to ongoing improvements in HLA typing technology, graft manipulation and supportive care, a matched unrelated (UD) or mismatched family donor (MMFD) is nowadays a feasible and widely accepted alternative in children lacking a HLA identical sibling donor. However, leukemia relapse remains the main reason for transplant failure. Following HSCT with UD 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.

Study objective

Primary: The main objective of the study is to evaluate the feasibility, safety and tolerability of allogeneic IL15-activated NK cell infusions in children transplanted for refractory or relapsed leukemia.

Secondary: To document immune reconstitution with a focus on the phenotype and function of NK cells, rates of acute and chronic graft versus host disease (GvHD), (viral) infections, relapse, overall and disease free survival compared to historical controls.

Study design

This study is an open-label, non-randomized, phase I, feasibility study, designed to treat children and adolescents, up to 18 years of age at the time of transplantation for refractory/ relapsed pediatric hematological malignancies. Following standard UD/MMFD HSCT, recruited patients will receive at 4-16 weeks after HSCT one intravenous infusion of ex vivo IL-15 activated donor NK cells.

Intervention

Patients will receive at 4-16 weeks after HSCT one intravenous infusion of ex vivo IL-15 activated donor NK cells (dose: 5-10 x 10e6 IL-15-activated NK cells per kg b.w. with a maximum total dose of 200 x 10e6 NK cells; children > 40 kg receive one dose of 200 x 10e6 NK cells)

Study burden and risks

Burden:
Extra burden consists of infusion of NK cells.
The frequency of post HSCT site visits and concomitant blood sampling is similar to the standard post HSCT procedures.
Risk:
Based on the reported clinical experience with autologous as well as allogeneic NK cell infusions, treatment related toxicity appears very limited.
Particularly, the risk to develop GvHD is reported to be negligible.
The possible benefit involves enhanced immune reconstitution and associated reduction in infectious complications.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Aged between 1-18 years at the time of HSCT;
2. Undergoing HSCT for ALL or AML according to existing indications;
3. Receiving a stem cell graft from a mismatched family (MMFD) or volunteer unrelated (MUD) donor;
4. Life expectancy > 3 months.
5. Availability of a stem cell donor willing to donate white blood cells by means of a non-mobilized leukapheresis procedure.

Exclusion criteria

1. Progressive uncontrollable malignant disease after HSCT but before or at the day of NK cell infusion, defined as overt leukemia relapse, i.e., >= 25% blasts in the marrow and/or 5% circulating blasts in the peripheral blood or progressive extra-medullary disease;
2. Lack of evidence for donor myeloid engraftment at the day of infusion (< 0.5 x 106 neutrophils/L);
3. Active acute GvHD >= grade II (overall grade);
4. Patient is receiving (or received less than 2 weeks before IMP infusion) pharmacological GvHD prophylaxis or immunosuppressive drugs used for non-GvHD indications;
5. 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).
6. Cord blood stem cell donor.
7. Patient received a second cellular product after the stem cell graft;Donor exclusion criteria:
1. Donor cord blood;
2. Lack of consent for leukapheresis.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-07-2013
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	09-03-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-04-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-03-2014
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-001514-34-NL
CCMO	NL38836.000.12
Other	NTR 16086