Infusion of ex vivo-cultured allogeneic NK cells in acute myeloid leukemia patients not eligible for stem cell transplantation (a phase I dose escalation study)

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

Summary

ID

NL-OMON38045

Source
ToetsingOnline

Brief title
Allogeneic NK-cell therapy in AML

Condition

- Leukaemias

Synonym
Acute Myeloid Leukemia, Blood cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: NWO

Intervention

Keyword: Acute Myeloid Leukemia, Escalating dose infusion, ex vivo-cultured allogeneic NK cells, Stem cell transportation

Outcome measures

Primary outcome

The primary study parameters are to evaluate the safety and dose-limiting

toxicity of allogeneic NK cell infusions with an escalating dose up to

10x107/kg body weight ex vivo-expanded NK cells following immunosuppressive

conditioning therapy in patients with AML not eligible for stem cell

transplantation

Secondary outcome

The secondary study parameters are to evaluate the in vivo lifespan of the

expanded NK cells following adoptive transfer and to determine the biological

and clinical activity of NK cell infusion in study participants

Study description

Background summary

Patients with acute myeloid leukemia (AML), older than 60 years, treated with intensive chemotherapy achieve complete remission (CR) rates of about 50%. However, over 75% of the patients relapse thereafter despite CR and only 15% of those patients are still alive after 3 years. Although allogeneic stem cell transplantation (SCT) can be curative, this option is unavailable for the majority of patients due to age and co-morbidity. Interestingly, it has been demonstrated that Natural Killer (NK) cell alloreactivity can control relapse of AML without causing graft-versus-host disease (GVHD) in the setting of HLA-mismatched haploidentical allogeneic SCT. Furthermore, in a non-transplant setting it has been demonstrated that allogeneic NK cell infusions can induce CR in poor-prognosis AML patients (Miller et al Blood 2005). In this study, we

plan to further investigate adoptive immunotherapy of NK cells in poor-prognosis AML patients who are not eligible for allogeneic SCT due to age. Unlike the procedure chosen by Miller et al. we will generate allogeneic NK cell products ex vivo from CD34+ hematopoietic progenitor cells. Conform GMP-regulations these CD34+ cells will be enriched from umbilical cord blood (UCB) units from the Cord Blood Bank Nijmegen. NK cell therapy is a novel experimental treatment for these AML patients.

Study objective

The primary aim of our study is to evaluate safety and toxicity of ex vivo-expanded NK cell infusions following a non-myeloablative conditioning regimen in elderly AML patients who are no candidates for allogeneic SCT. Moreover there is also a second aim; how long do the administered NK-cellen remain in life and what is the impact on the sickness (AML).

Study design

The study is designed as a prospective phase I dose escalation study in a series of 15 AML patients with age * 55 years who have successfully achieved CR (i.e. <5% blasts in the bone marrow) after standard intensive chemotherapy. Prior to NK cell infusion, patients will receive non-myeloablative immunosuppression with cyclophosphamide and fludarabine on 4 consecutive days. On day 0, four cohorts of 3 patients will receive 3x106, 10x106, 3x107 and 10x107 allogeneic NK cells per kg body weight generated ex vivo from CD34+ cells obtained from an allogeneic UCB unit.

Intervention

Allogeneic NK cell products generated ex vivo from CD34+ UCB cells will be transfused into patients in a single escalating dose up to 10x107 donor NK cells/kg body weight after completing standard chemotherapy and preparative immunosuppressive conditioning consisting of fludarabine (30 mg/m2/day) and cyclophosphamide (900 mg/m2/day) on days -6, -5, -4, and -3 in order to prevent rejection. Monitoring will be done for toxicity, biological parameters and remission status.

Study burden and risks

In other clinical studies up to 2x107 allogeneic NK cells ex vivo purified and activated with IL-2 have been administered to patients with several malignancies including AML (Miller et al. Blood 2005; Shi et al. Br J Hematol 2008). The Hi-Cy/Flu regimen in the AML patients (n=19) induced transient pancytopenia by the time of NK cell infusion (Miller et al. Blood 2005). The NK cell infusions were well tolerated without evidence of induction of GVHD. Toxicity was limited to constitutional symptoms consisting of low-grade fever,

chills and myalgias mostly due to low-dose IL-2 injections given post-NK cell infusion. Therefore, in our study escalating dose NK cell infusions will be given without IL-2 infusions. For follow-up peripheral blood will be collected from patients (pre-study, at 4 hr, day 1, 2, 5, 7, 14, 28 and 56 after NK cell infusion) and bone marrow aspirates (after concolidation treatments, and 7 days, 3 and 6 months after NK cell infusion). UCB units stored in the Cord Blood Bank Nijmegen will be used to enrich CD34+ cells for ex vivo expansion and differentiation of NK cells.

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

* AML patients * 55 year of age
* Absence of anti-HLA antibodies

* CR after first line standard chemotherapy
* CR after second line chemotherapy
* WHO performance 0-1 (see appendix 3)
* Life expectancy > 6 months

Exclusion criteria

- Patients candidates for SCT
- Progressive disease, no change or only minor response following induction and consolidation therapy
- Patients on immunosuppressive drugs
- Patients with active infections (viral, bacterial or fungal) that requires specific therapy. Acute anti-infectious therapy must have been completed within 14 days prior to study treatment
- Severe cardiovascular disease (arrhythmias requiring chronic treatment, congestive heart failure or symptomatic ischemic heart disease (appendix 2)
- Severe pulmonary dysfunction (CTCAE III-IV) (appendix 2)
- Severe renal dysfunction (serum creatinine > 3 times normal level) (appendix 2)
- Severe hepatic dysfunction (serum bilirubin or transaminases > 3 times normal level) (appendix 2)
- Presence of anti-HLA antibodies

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-10-2011
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	03-05-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-06-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-12-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-01-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-11-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-11-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	24-01-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-02-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-04-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-06-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	03-07-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-05-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	28-04-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-06-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	22-07-2015
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: 22174
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2010-018988-41-NL
CCMO	NL31699.000.10
OMON	NL-OMON22174