NK cells as post consolidation therapie in AML.

No registrations found.

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

Summary

ID

NL-OMON22174

Source
NTR

Brief title
PMLA25

Health condition

Hematopoietic stem cells, umbilical cord blood, NK cells, ex vivo expansion, cellular immunotherapy,acute myeloid leukemia, cancer immunotherapy, Elderly patients, Phase I, dose escalation study, safety and toxicity.

Hematopoietische stamcellen, navelstrengbloed, NK cellen, ex vivo expansie, cellulaire immunotherapie, acute myeloide leukemie, immunotherapie tegen kanker, oudere patiënten, fase I dosis escalatie studie, veiligheid en toxiciteit.

Sponsors and support

Primary sponsor: Radboud University Nijmegen Medical Centre
Source(s) of monetary or material Support: ZON/MW
Sponsor

Intervention

Outcome measures

Primary outcome

The study is designated as a phase I dose escalation study in a series of 15 patients with primary or secondary AML to evaluate the safety and 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.

Secondary outcome

1. Evaluation of the in vivo lifespan of the expanded NK cells following adoptive transfer;

2. Exploration of the biological and clinical activity of NK cell infusion in study participants.

Study description

Background summary

Rationale:

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. 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. In collaboration with Glycostem Therapeutics 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.

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.

Secondary objectives are to evaluate the in vivo lifespan of infused NK cell products and

effects on residual disease.

Study design:

This study is a phase I dose escalation study in a series of 15 AML patients who have successfully achieved CR (<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.

Study population:

AML patients with age >65 years who have achieved CR after one or two courses of standard remission-induction chemotherapy and who have completed consolidation chemotherapy.

Intervention:

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

Main study parameters/endpoints:

Primary endpoints are safety and toxicity.

Secondary endpoints are in vivo detection of the transfused NK cells, detection of biological NK cell activity and clinical response on residual disease.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

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. The Hi-Cy/Flu regimen in the AML patients (n=19) induced transient pancytopenia by the time of NK cell infusion. 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 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 (pre-study, 7 days, 3 months 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.

Study objective

This study is a phase I trial, testing the safety and toxicity of allogeneic NK cell infusions with an escalating dose of ex vivo expanded NK cells following immunosuppressive conditioning therapy in elderly patients with AML.

Study design

The primary endpoint of this study is to evaluate safety and toxicity of escalating dose infusion of ex vivo-generated NK cells following Cy/Flu conditioning. In cohorts of three patients, NK cells will be infused with an escalating dose of 3x106, 10x106, 3x107 and 10x107 NK cells/kg body weight. A total of 15 patients will be included in this study. Toxicity of the immunosuppressive conditioning regimen and NK cell infusions will be separately evaluated. Acute toxicity caused by the Cy/Flu conditioning is generally low and has proven to be safe in older patients, although the immunosuppressive state of the patient may cause severe infections caused by the transient pancytopenia induced by this regimen. All patients will be evaluated intensively for toxicity caused by the conditioning regimen using the NCI Common Terminology Criteria for Adverse Events (http://ctep.cancer.gov/reporting/ctc.html).

If the toxicity of the conditioning regimen in this population of patients exceeds the common accepted toxicity for this kind of treatment the study will be stopped. If a patient dies due to the conditioning regimen itself, the study will be stopped immediately. Toxicity caused by the NK cell infusions may predominantly consist of GVHD. In case 1 patient will experience DLT at a particular dose, the cohort will be increased to 6 patients. The maximum tolerated NK cell dose will be defined as the dose at which 2 patients experience DLT within a cohort of 3 or 6 patients.

Intervention

This study is a phase I dose escalation trial, using ex vivo-generated NK cells from CD34+ UCB cells from KIR-ligand mismatched donors. In collaboration with Glycostem Therapeutics we will generate allogeneic NK cells. These NK cells will be infused into poor-prognosis AML patients following Cy/Flu conditioning. This immunosuppressive conditioning regimen is necessary to prevent rejection and has shown to induce NK cell survival factors such as IL-15 that facilitate prolonged in vivo lifespan and expansion of the infused NK cells. The CD56+ NK

cell products will be >70% pure and almost devoid of CD3+ T cells (i.e. <1x104 cells/kg body weight), thereby minimizing donor T cell-mediated GVHD. Study participants will undergo clinical and immunological evaluation.

Prior to NK cell infusion, AML patients will receive a non-myeloablative immunosuppressive preparative regimen of cyclophosphamide (900 mg/m2/day) and fludarabine (30 mg/m2/day) on days -6, -5, -4, -3. Ample experience with this preparative conditioning regimen has been obtained in the transplant setting with patients suffering from multiple myeloma (n=22) and high-grade Non-Hodgkin's lymphoma (n=19). In this NK cell study we even use a cyclophosphamide dose which is 75% lower than we are used to in the above mentioned studies. Studies by Einsele et al. infusing gamma/delta T cells show that this lower regimen is immunosuppressive enough to create an environment in which third party cells (i.e. allogeneic gamma/delta T cells or NK cells) may survive for a longer period (Prof.dr. H. Einsele, personal communication). In eligible AML patients, three days after the Cy/Flu regimen (day 0), NK cell products will be administered to the patient i.v. using dose escalation of 3x106, 10x106, 3x107 and 10x107 NK cells per kg body weight in cohorts of three patients. The NK cell dosage is based on studies by Miller et al. who showed that following Hi-Cy/Flu conditioning IL-2-activated NK cell products could be administered to AML patients up to 2x107/kg body weight without induction of GVHD. In contrast to the study of Miller et al., we will omit IL-2 injections because these are associated with persistent fever and associated constitutional symptoms, neutropenia, hypoxemia and drug rash. Furthermore, this will provide more conclusive data whether T cell-free allogeneic NK cell infusions can induce a GVL effect without GVHD.

Contacts

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Eligibility criteria

Inclusion criteria

1. AML patients > 65 year of age;

2. Absence of a HLA-Cw ligand for an inhibitory KIR (i.e. homozygous Cw group 1 or 2);

3. CR after first line standard chemotherapy;

4. CR after second line chemotherapy;

5. WHO performance 0-1;

6. Life expectancy > 6 months;

7. Written informed consent.

Exclusion criteria

1. Patients candidates for SCT;

2. Progressive disease, no change or only minor response following induction and consolidation therapy;

3. Patients on immunosuppressive drugs;

4. 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;

5. Severe cardiovascular disease (arrhythmias requiring chronic treatment, congestive heart failure or symptomatic ischemic heart disease;

6. Severe pulmonary dysfunction (CTCAE III-IV);

7. Severe renal dysfunction (serum creatinine > 3 times normal level);

8. Severe hepatic dysfunction (serum bilirubin or transaminases > 3 times normal level);

9. Severe neurological or psychiatric disease.

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:	Pending
Start date (anticipated):	01-05-2011
Enrollment:	15
Type:	Anticipated

Ethics review

Positive opinion

Date:	22-03-2011
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 38045
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL2689
NTR-old	NTR2818
CCMO	NL31699.000.10
ISRCTN	ISRCTN wordt niet meer aangevraagd.
OMON	NL-OMON38045

Study results

Summary results

Spanholtz J, Tordoir M, Eissens D, Preijers F, van der Meer A, Joosten I, Schaap N, de Witte T, Dolstra H. High log-scale expansion of functional human natural killer cells from umbilical cord blood CD34-positive cells for adoptive cancer immunotherapy. PLoS One. 2010;5(2):e9221.