TK008:Randomized phase III trial of haploidentical HCTwith or without an add back strategy of HSV-Tk donor lymphocytes in patients with high risk acute leukemia

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Primary objective:-To compare disease-free survival (DFS) in high risk leukemia patients who underwent haploidentical HCT followed by an add back strategy of HSV-Tk donor lymphocytes or standard haploidentical HCTSecondary objectives:- To compare...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON35966

Source
ToetsingOnline

Brief title
TK008

Condition

- Leukaemias

Synonym
AML or ALL in complete remission at high risk of relapse; High risk acute leukemia

Research involving
Human

Sponsors and support

Primary sponsor: MolMed S.p.A
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: -genetically modified HSV-Tk donor lymphocytes, -haploidentical HCT, -high risk acute leukemia

Outcome measures

Primary outcome

Primary efficacy parameter:

- Disease-Free Survival (DSF) will be measured for all patients from the date

of randomization until the date of relapse or death from any cause, whichever

occurs first

Secondary outcome

Secondary efficacy parameters:

- Overall Survival (OS) will be measured for all patients from the date of

randomization until death from any cause

- Non-relapse mortality (NRM) will be defined for all patients as any death

without previous occurence of a documented relapse

- Immune Reconstitution (IR) will be defined as the time to reach a level of

circulating CD3+ >= 100/µl

- Engraftment rate will be defined as the persistent blood cells count above a

predefined level (ANC >= 1 x 109/L per 3 consecutive days with evidence of donor

haematopoiesis; platelets >= 50 x 109/L, unsupported by transfusions, for 7 days)

- Cummulative incidence of grade 2, 3 or 4 acute GvHD, diagnosed and graded

according to standard criteria, will be computed from the transplantation

- Cummulative incidence extensive chronic GvHD, diagnosed and graded according to standard criteria, will be computed from the transplantation

- Cummulative incidence of relapse will be defined on the basis of morphologic evidence of leukaemia in bone marrow or other sites.

Safety and tolerability parameters:

- Adverse Events (AE) and laboratory abnormalities graded according tot the CTCAE v 4.02

- laboratory assessments (urinalisis, hematology, blood chemistry, immunophenotype, PCR-TK, RCR analysis), bone marrow asprirate

- physical examination and vital signs

- Serious Adverse Events (SAE)

- Suspected Unexpected Serious Adverse Reactions (SUSARs)

- Long term follow up

Quality of life: FACT-BMT to summarize and evaluate patient convenience and satisfaction

Pharmacoeconomics on medical care utilization. To summarize and evaluate treatment group differences.

Study description

Background summary

Many patients with high risk acute leukemia potentially curable by tranplantation of haematopoietic cells are generally not considered for such treatment because an HLA identical family donor is lacking. For these patients the only curative option is represented by a transplant obtained from a haploidentical donor (haploidentical HCT).
T-cell depletion of the allograft is usually performed to reduce the risk of GvHD. Although this is a successfull strategy for GvHD prophylaxis, it often results in an increased risk of delayed immune reconstitution, thus leading to relapse and post transplant infections.
Recent clinical trials confirmed that immune recovery following haploidentical HCT could be improved by the infusion of T lymphocytes engineered to express the thymidine kinase of the Herpes Simplex Virus (HSV-Tk), a suicide gene activated upon ganciclovir administration.

Study objective

Primary objective:
-To compare disease-free survival (DFS) in high risk leukemia patients who underwent haploidentical HCT followed by an add back strategy of HSV-Tk donor lymphocytes or standard haploidentical HCT

Secondary objectives:
- To compare overall survival (OS) in the two treatment arms
- To compare the cumulative incidence of non-relapse mortality (NRM)
- To compare the time to T-cell immune reconstitution
- To compare the engraftment rate
- To compare the cumulative incidence of grade II-IV acute GvHD
- To compare the cumulative incidence of extensive chronic GvHD
- To compare the cumulative incidence of relapse (CIR)
- To compare incidence and duration of infectuous episodes and infectious disease mortality
- To evaluate the acute and long-term toxicity related to the HSV-Tk infusion
- To assess quality of life (QoL) and Medical Care Utilization (MCU) in both arms

Study design

This is an open label, randomized (3:1) phase III study, with a comparison of an add back strategy of HSV-TK donor lymphocytes versus standard stategy in high risk acute leukemia patients who underwent haploidentical HCT.

Intervention

ARM A (experimental group):
Haploidentical HCT with the infusion of CD34+ cells plus a fixed dose of T cells (1 x 10/4/Kg), followed by:

- Infusion of approximately 1 x 10/7 HSV-Tk genetically modified CD3+ cells/Kg between day +21 and day 49 after haploidentical HCT in the absence of spontaneous immune reconstitution (IR has to be documented by two consecutive findings of circulating CD3+ cells >= 100/µl) and/or development of GvHD.

In absence of immune reconstitution and GvHD further infusion will be administered wih the following dosages and timelines:
- 30 days after 1st infusion: in the absence of GvHD and immune reconstitution genetically modified lymfocytes will be infused at a dose of 1x 10* cells/ Kg
- 30 days after 2nd infusion: in the absence of GvHD and immune reconstitution genetically modified lymfocytes will be infused at a dose of 1x 10* cells/ Kg
- 30 days after 3rd infusion: in the absence of GvHD and immune reconstitution genetically modified lymfocytes will be infused at a dose of 1x 10* cells/ Kg

ARM B (control group):
Haploidentical HCT with the infusion of CD34+ cells plus a fixed dose of T cells (1 x 10/4/Kg).

Study burden and risks

Participation in the trial may involve the risk of developing acute and/or chronic GvHD. In a recent clinical trial carried out wit the HSV-Tk-donor lymphocytes, GvHD presented in approximately 30% of the patients treated and was resolved in all cases after treatment with ganciclovir. Furthermore, approximately 13% of the patients developed fever, which quickly cured after appropriate drug treatment.

The use of gene therapy products exposes the patient to a risk of cell abnormality secondary to the gene manipulation itself. The safety of lymfocytes modified with HSV-Tk gene has been documented both in the recent study (TK007) and in more than 100 patients treated throughout the world since the 1990s.

Where necessary, the administration of ganciclovir or vanganciclovir is planned to eliminate the transduced lymphocytes. Ganciclovir/valganciclovir is a drug that has been used for many years to combat certain viral infections. Ganciclovir/valganciclovir can be teratogenic. Therefore female patients of childbearing age should have a negative pregnancy test at screening and patients should be taking an effective contraceptive up to three months after the last infusion. Moreover, ganciclovir/valganciclovir can be frequently associated with serious granulocytopenia and thrombocytopenia and is less frequently associated with severe allergic dermatitis, allergic reactions, anaemia, fever, alteration of liver enzymes, loss of appetite, mental and mood alterations, nausea, phlebitis, erythema, gastralgia and vomiting.

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

• Age >= 18 with HCT comorbidity index < 3 (Appendix I);• Any of the following conditions:;• AML and ALL in 1st complete remission (CR) at high risk of relapse based on negative prognostic factors (for the definition of high-risk of relapse see Appendix H);• AML and ALL in 2nd or subsequent CR;• secondary AML in CR;• Absence of timely and suitable fully HLA matched or one HLA locus mismatched family or unrelated donor and, at Investigator*s discretion, absence of other possible therapeutic alternatives;• Stable clinical conditions and life expectancy > 3 months;• PS ECOG < 2;• Serum creatinine < 1.5 x ULN;• Bilirubin < 1.5 x ULN; transaminases < 3 x ULN;• Left ventricular ejection fraction > 45%;• QTc interval < 450 ms;• DLCO > 50%;• Patients and donors, or independent witnesses must sign an informed consent indicating that they are aware this is a research study and have been told of its possible benefits and toxic side effects.

Exclusion criteria

• Patients with life-threatening condition or complication other than their basic disease;• Contraindication to haploidentical HCT as defined by the Investigator;• Patients with active CNS disease;• Pregnant or lactation. Patients both males and females with reproductive potential (i.e. menopausal for less than 1 year and not surgically sterilized) must practice effective;contraceptive measures throughout the study. Women of childbearing potential must provide a negative pregnancy test (serum or urine) within 14 days prior to registration.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Genetic modified organism
Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	26-07-2011
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-02-2012
Application type:	First submission
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	EUCTR2009-012973-37-NL
CCMO	NL36045.000.11