An open-label, uncontrolled, multicenter, multinational study on the efficacy and safety of administration of donor lymphocytes depleted of alloreactive T-cells (ATIR), through the use of TH9402 and light treatment in an ex vivo process, in patients receiving a CD34-selected peripheral blood stem cell graft from a related, haploidentical donor.

Published: 01-06-2010
Last updated: 30-04-2024

Primary objective:• To study the effects of the administration of a donor lymphocyte preparation selectively depleted of host alloreactive T cells (ATIR) to patients with hematologic malignancies on 6 months and 12 months transplant related...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON36698

Source
ToetsingOnline

Brief title
CR-AIR-004

Condition

- Haematological disorders NEC

Synonym
cancer of the blood and immune system, hematological malignancies

Research involving
Human

Sponsors and support

Primary sponsor: Kiadis Pharma Netherlands B.V.
Source(s) of monetary or material Support: Kiadis Pharma Netherlands BV

Intervention

Keyword: ATIR, Donor Lymphocytes, HSCT

Outcome measures

Primary outcome

Incidence of TRM at 6 months and 12 months after the transplantation. All

deaths during the trial will be assessed by the Central Endpoint Adjudication

Committee (CEAC) to diferrentiate between TRM and death due to other causes.

TRM is defined as death due to causes other than disease relapse or

progression, or other causes which are unrelated to the transplant procedure

(e.g. accident, suicide).

Secondary outcome

N/A

Study description

Background summary

For many end stage patients with hematological malignancies such as acute and

chronic leukemia, lymphoma and multiple myeloma, hematopoietic stem cell transplantation (HSCT) remains the only curative option. However, even though a stem cell transplant can provide a cure in contrast to most other treatments, it is not a first line treatment, because of related complications and limitations.

Transplantation is most successful if the donor is either an HLA-matched sibling or an unrelated matched donor. However, it is not always feasible to find a matched donor in a timely manner. Alternatively relatives who are only partially HLA matched to the patient (haploidentical donor) can be used as donor.

A stem cell transplant is a complicated and specialized treatment. It has many side effects and possible complications. The transplantation of haploidentical cells has been shown to be feasible in the past when specific immune cells, namely the T -cells from the donor (type of cells that help defend the body against infections) were removed from the transplant. However some immune cells always remain and when transplanted to the recipient, they can recognize certain organs of the recipient as being foreign and attack them. This causes a condition called graft-versus-host disease (GvHD), which may be severe and may even be life threatening.

The transplant in this study differs from a standard haploidentical transplant because the recipient will be provided with special treated donor immune cells approximately a month after the transplantation. In a standard haploidentical transplantation no additional infusion of immune cells is given. The treatment of the immune cells (T-cells) is done outside of the body, in a specialized laboratory facility. First the immune cells from the donor will be collected and mixed with some of the recipient's immune cells. The immune cells that can attack the body and not the disease are destroyed by exposing them to a light sensitive drug (TH9402) and light treatment. As a result, it is expected to prevent the recipient from GvHD and that the remaining cells (also called ATIR) can attack infections and possibly the cancer.

Study objective

Primary objective:
• To study the effects of the administration of a donor lymphocyte preparation selectively depleted of host alloreactive T cells (ATIR) to patients with hematologic malignancies on 6 months and 12 months transplant related mortality (TRM).
Secondary objectives:
• To study the effects of ATIR on Overall Survival (OS).
• To study the effects of ATIR on the incidence and severity of acute GvHD.
• To study the effects of ATIR on the incidence and severity of chronic GvHD.
• To study the effects of ATIR on Progression Free Survival (PFS).
• To study the effects of ATIR on the incidence and severity of bacterial,

viral or fungal infections.
• To study the effects of ATIR on immune reconstitution.
• To study the effects of ATIR on the health status of patients (including Quality of Life [QoL]).

Study design

CR-AIR-004 is an open-label, uncontrolled, multicenter, multinational study. Patients will undergo an HSCT (CD34-selected graft) from a related, haploidentical donor including corresponding conditioning regimen. Infusion with ATIR will take place 35±7 days after the HSCT. The primary analyses will be conducted using 6 and 12 months follow-up data. Patients will be assessed weekly for the first 100 days after the transplant. Patients will be assessed every month up to 6 months after the transplantation, every 2 months up to 12 months after the transplantation and subsequently every 3 months up to 24 months after the transplantation. Patients will be followed-up for 24 months to assess overall survival. See Section 6 of the study protocol for a detailed description of the assessments conducted at each visit.

Intervention

Stem cell transplant from a donor.

Study burden and risks

This information is clearly mentioned for the patient and the donor in the patient information sheet.

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

Recipient Inclusion Criteria (any of the following)
Initially, both patients with primary and secondary indications are eligible for the trial. During the trial accrual may be limited to the primary indications based on a recommendation made by the Independent Data Monitoring Committee (IDMC). ;Group 1: Primary Indications
• Acute Myeloid Leukemia (AML): AML in first remission with high risk features (secondary AML, FLT-3 mutation, complex karyotype, abn(3q), -5/5q-, -7/7q-, abn(12p), abn(17p), or other cytogenetic anomaly of similar poor prognosis, or need for 2 induction regimens to achieve a complete remission (CR)). All AML in second remission.
• Acute Lymphoblastic Leukemia (ALL): ALL in first remission with high-risk features (presenting leukocyte count > 30,000/mm3 for B-cell ALL or > 100,000/mm3 for T-cell ALL, karyotypes t(9;22), t(11;19), and t(4;11) biphenotypic leukemia, pro-B-ALL, late CR after induction therapy, rising MRD markers). All ALL in second remission.
• Myelodysplastic Syndrome (MDS): Transfusion-dependent MDS with low or intermediate-1 IPSS score, and all MDS with intermediate-2 or high IPSS score. Patients with more than 20% blasts in the marrow will be considered AML.
• Ph-positive chronic myeloid leukemia (CML): Patients with Ph-positive CML in first chronic phase (CP) who have failed (either resistant or intolerant) at least 2 tyrosine kinase inhibitors and any patient with the T315I mutation (irrespective of prior tyrosine kinase inhibitors).;Group 2: Secondary Indications
• AML:
- All AML not belonging to Group 1 in subsequent remission or with evidence of chemo-sensitive disease or,
- Patients requiring 3 or more induction regimens to achieve a first remission or,
- Patients with AML in hematologic remission who relapsed more than 2 years after allogeneic stem cell transplantation.
• ALL: All ALL not belonging to Group 1 in subsequent remission or with evidence of chemo-sensitive disease. Patients with ALL in hematologic remission who relapsed more than 2 years after allogeneic stem cell transplantation.

• Non-Hodgkin Lymphoma (NHL): All high grade and low grade Non-Hodgkin lymphoma (other than CLL and MM) in 2nd or 3rd remission (at least PR) after standard of care treatments including autologous stem cell transplantation.
• Chronic Myeloid Leukemia (CML): Patients with accelerated phase CML or CML in second or later chronic phase.
• Multiple Myeloma (MM): Secretory MM with or without osteolytic lesions concurrently not featuring extramedullary disease responsive to prior autologous stem cell transplantation(s) or at least one standard of care treatment (defined as 50% reduction of paraprotein in serum/plasma and/or 75% reduction of paraprotein in urine).
• Chronic Lymphocytic Leukemia (CLL):
- CLL non-responsive or early relapsed (within 12 months) after a previous fludarabine- or equivalent purine-based regimen or,
- CLL relapsed (within 24 months) after purine analogue combination therapy or treatment of similar efficacy (i.e. autologous stem cell transplantation) or,
- CLL with p53 deletion/mutation (i.e. del 17p-) requiring treatment.
• CLL transformed to high grade lymphoma (Richter transformation) having demonstrated at least PR.
• MPS: Myeloproliferative disorders in transformation to acute leukemia or with progressive transfusion requirements or pancytopenia including atypical (Ph negative) chronic myeloid and neutrophilic leukemias, and progressing myelofibrosis. Patients with more than 20% blasts in the marrow will be considered AML.;Other Inclusion Criteria
• Male or female, age >= 18, <= 65 years.
• Ability to comprehend the investigational nature of the study and provide informed consent. ;Donor Inclusion Criteria
• Haploidentical family donor with 2 to 3 mismatches at the HLA-A, -B and/or -DR loci of the unshared haplotype.
• Male or female, age >= 16, <= 75 years.
• Donors must be fit to receive G-CSF and undergo apheresis (normal blood count, normotensive and no history of stroke).
• Donor must have Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less.
• Donor must provide written informed consent.

Exclusion criteria

Recipient Exclusion Criteria (any of the following)
• AML in 1st CR with good risk karyotypes: AML M3 (t15; 17), AML M4Eo (inv 16), AML t (8; 21).
• MM featuring concurrent extramedullary disease or being non-responsive to prior therapy
• CML in blast crisis.
• CLL concurrently transformed into high-grade lymphoma and failing to demonstrate at least PR.
• NHL with concurrent bulky disease (>= 5 cm).
• Diffusing Capacity for Carbon Monoxide (DLCO) < 40% predicted.
• Left ventricular ejection fraction < 40% (evaluated by echocardiogram or MUGA).

• AST/SGOT > 2.5 x ULN (CTCAE grade II v3.0).
• Bilirubin > 1.5 x ULN (CTCAE grade II v3.0).
• Creatinine > 1.5 x ULN (CTCAE grade II v 3.0).
• HIV positive (Recipients who are positive for hepatitis B (HBV), hepatitis C (HCV) or human T-cell lymphotropic virus (HTLV-I/II) are not excluded from participation).
• Positive pregnancy test for women of childbearing age.
• Prior haploidentical PBSC or cord blood transplantation.
• Less than 2 years from a prior allogeneic stem cell transplantation.
• Estimated probability of surviving less than three months.
• Major anticipated illness or organ failure incompatible with survival from transplant.
• Severe psychiatric illness or mental deficiency sufficiently severe as to make compliance with the transplant treatment unlikely and informed consent impossible.
• Known allergy to any of the components of ATIR* (e.g., dimethyl sulfoxide).
• Any other condition which, in the opinion of the investigator, makes the patient ineligible for the study.;Donor Exclusion Criteria
• Medically uncontrolled coronary heart disease.
• Myocardial infarction within the last 3 months.
• History of uncontrolled seizures.
• History of malignancy (except basal cell or squamous carcinoma of the skin, positive PAP smear and subsequent negative follow up).
• Positive test result for any of the mandatory viral tests in the applicable region, except for a positive cytomegalovirus (CMV) result, which does not lead to exclusion.
• Presence of a transmissible disease (such as HIV positive), a major illness, a suspected systemic dysfunction and/or an active inflammatory or autoimmune disorder.
• Female donors who are pregnant or nursing.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-02-2011

Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	01-06-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-07-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-07-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-08-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-04-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-08-2011
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-10-2011
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	EUCTR2008-008198-73-NL
ClinicalTrials.gov	NCT00967343
CCMO	NL32446.000.10