Allogeneic Stem Cell Transplantation of NiCord, Umbilical Cord Blood-derived Ex Vivo Expanded Stem and Progenitor Cells, in Adolescents and Adult Patients with Hematological Malignancies

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The overall study objective is to evaluate the safety and efficacy of NiCord®: single ex-vivo expanded cord blood unit transplantation in patients with hematological malignancies following myeloablative therapy.

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

Summary

ID

NL-OMON43606

Source
ToetsingOnline

Brief title
GC P# 03.01.020

Condition

- Leukaemias

Synonym
bone marrow cancer, leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Gamida Cell ltd.
Source(s) of monetary or material Support: Gamida Cell Ltd. Stem Cell Therapy Technologies

Intervention

Keyword: Gamida Cell, hem. malignancies, Phase I/II, Stem Cell Transplantation

Outcome measures

Primary outcome

• Incidence of NiCord®-derived neutrophil engraftment at 42 days following transplantation

• Incidence of secondary graft failure at 180 days following transplantation of NiCord®

Secondary outcome

• Time from infusion to neutrophil engraftment

• Time from infusion to platelet engraftment

• Incidence of platelet engraftment at 100 days

• Proportion of non-relapse mortality at 100 days

• Incidence of acute GvHD grade II-IV and III-IV at 100 days

• Incidence of chronic GvHD (limited or extensive) at 180 days and 1 year

• Incidence of secondary graft failure at 1 year following transplantation of NiCord®

• Overall survival at 180 days and 1 year

• Safety and tolerability of NiCord® transplantation

Study description

Background summary

Successful blood and marrow transplantation (BMT) requires the infusion of a sufficient number of hematopoietic stem/progenitor cells (HSPCs), capable of both homing to the bone marrow and regenerating a full array of hematopoietic cell lineages with early and late repopulating ability in a timely fashion.Despite the development of large international volunteer donor registries, less than 50% of unrelated donor searches result in identification and availability of a suitably matched donor graft. Umbilical cord blood (UCB) is an alternative stem cell source for hematopoietic stem cell transplantations (HSCT) and is clinically in use for the treatment of diverse life-threatening diseases, such as hematological malignancies or genetic blood disorders. UCB grafts have been used in over 20,000 stem cell transplant recipients and provide an alternative source of stem cells in cases where a matched related or unrelated stem cell donor are unavailable. There are numerous advantages to UCB as a transplantable graft source. These include the ease of procurement, the absence of risk to the donor, the reduced risk of transmissible infections, and the availability for immediate use, potentially reducing a long wait and risk of disease progression - particularly important for patients with acute leukemia. However, a major drawback of UCB is the low stem cell dose available for transplantation, compared to mobilized peripheral blood (PB) or bone marrow. This low stem cell dose can compromise the chances of engraftment and contributes to delayed kinetics of neutrophil and platelet recovery. The delay in graft function may negatively impact transplant outcome and prolong the duration of hospitalization and costly supportive care measures. The transplant community has been actively engaged in developing methods to address the cell dose issue in cord blood transplantation (CBT), which is most acute in adolescent and adult recipients. Several approaches were developed, including dual umbilical cord blood transplantation (DCBT) and ex vivo expansion of UCB stem cells. Although to date no prospective clinical trials on the efficacy of single cord versus double cord in adults have been published, the DCBT has become standard practice in CBT for recipients in whom a single CBU of adequate cell dose is unavailable. Ex vivo expansion is still an experimental approach.

Study objective

The overall study objective is to evaluate the safety and efficacy of NiCord®: single ex-vivo expanded cord blood unit transplantation in patients with hematological malignancies following myeloablative therapy.

Study design

Open-label, non-randomized, interventional, single group assignment study of

NiCord® in adolescent and adult patients suffering from hematological malignancies.

Intervention

Allogeneic Stem Cell Transplantation of NiCord®, Umbilical Cord Blood-derived Ex Vivo Expanded Stem and Progenitor Cells

Study burden and risks

Compared to a standard umbilical cord stem cell transplantation, patients participating in the trial will have more blood tests and questionnaires done.

Currently there is no evidence that NiCord® transplantation is any more dangerous than standard umbilical cord blood transplantation. However, there may be unknown risks involved with the transplantation of NiCord®, which include graft failure, secundary blood cancers, transmissable spongiform encephalopathy, allergic reaction to DMSO, nicotinamide, contamination.

NiCord® may however improve the chances of successful umbilical cord blood transplantation by speeding up the recovery of blood cell production. It may also reduce the risk of infections or bleeding complications.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1.Patients must be 12-65 years of age
2.Patients with one of the following hematologic malignancies:
Acute lymphoblastic leukemia (ALL) at one of the following stages:
a.High risk first complete morphologic remission (CR1), defined as one or more of the following:
*The presence of t(4;11), t(9;22), t(1;19) or MLL rearrangements t(11q23)
*Extreme leukocytosis (WBC >30,000/µl for B-ALL or >100,000/µl for T-ALL)
*Longer than 4 weeks to achieve complete remission after induction therapy
b.Second or subsequent remission
*Acute myelogenous leukemia (AML) at one of the following stages:
a.First complete morphologic remission (CR1) that is NOT considered as favorable-risk:
Favorable risk is defined as having one of the following:
*t(8,21) without cKIT mutation
*inv(16) without cKIT mutation or t(16;16)
*Normal karyotype with mutated NPM1 and no FLT-3 Internal Tandem Duplication
*Normal karyotype with double mutated CEBPA
*APL in first or second molecular remission at end of consolidation
b.Second or subsequent remission
*Chronic myelogenous leukemia (CML) at one of the following phases:
a.Chronic phase with one or more of the following characteristics:
*Failure to achieve a primary hematologic or cytogenetic response to either nilotinib or dasatinib (following European LeukemiaNet timelines)
*Intolerance to/failure of two tyrosine kinase inhibitors (TKI)
*Any T3151 mutation
b.Accelerated phase with one or more of the following characteristics:
*Newly diagnosed patients who do not achieve an optimal response to TKIs
*TKI-treated patients who progress from chronic phase
c.Blast crisis (myeloid or lymphoid) with disease control
*Myelodysplastic Syndrome (MDS) with International history of International Prognostic Scoring System (IPSS) risk category of INT-1 or greater. On screening morphologic analysis

patients must have no circulating myeloblasts and <10% myeloblasts in the bone marrow. MDS patients categorized as INT-1 on primary presentation must have life threatening neutropenia or thrombocytopenia.
*Lymphoma fulfilling one of the following criteria:
a.Chemotherapy-sensitive (complete or partial response) lymphomas that have failed at least 1 prior regimen of multi-agent chemotherapy and are INELIGIBLE for an autologous transplant.
b.Marginal zone B-cell lymphoma or follicular lymphoma that has progressed after at least two prior therapies (excluding single agent Rituxan).
3.Patients must have a partially HLA-matched CBU: the unit must be HLA-matched at 4-6/6 HLA class I (HLA-A & HLA-B, low resolution) and II (HLA-DRB1, high resolution) loci with the patient. The CBU must have a pre-cryopreserved (post-processing), total CD34+ cell count of >=8 x10^6 as well as a pre-cryopreserved (post-processing) total nucleated cell count of >=1.8x10^9 and total nucleated cell dose >=1.8x10^7 TNC/kg. The CBU will have undergone volume reduction (both plasma and red blood cell depletion) prior to cryopreservation.
4.Patients must have an additional partially HLA-matched CBU, or two CBUs, reserved as a backup in case of batch failure. The backup CBU/s must be HLA-matched at 4-6/6 HLA class I (HLA-A & HLA-B, low resolution) and II (HLA-DRB1, high resolution) loci with the patient, and must have a pre-cryopreserved, total nucleated cell dose of at least 2x10^7 per kilogram, in case of one CBU, or 3x10^7 per kilogram, in case of two CBUs.
5.Patients must have a related, haplo-identical family member who is suitable for bone marrow or peripheral blood stem cell donation and has agreed to do so in the event of graft failure.
6.Subjects* Performance score >=70% by Karnofsky/Lansky
7.Patient has sufficient physiologic reserves including:
a)Cardiac: Left ventricular ejection fraction (LVEF) of < 40% by echocardiogram, radionuclide scan or cardiac MRI
b)Pulmonary function tests demonstrating FVC and FEV1 of >50% of predicted for age and DLCO > 50% of predicted
c)Renal: Creatinine clearance test (by Cockcroft-Gault equation) >=60 mL/min
d)Hepatic: Serum Bilirubin < 2.0 mg/dl; Hepatic transaminases (ALT and AST) < 3 x upper limit of normal range
8.Females of childbearing potential, defined as any female who has experienced menarche and is not postmenopausal (defined as not having a menstrual period for at least 24 months) or permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy), agree to use an appropriate method of contraception from at least 7 days prior to myeloablative therapy until completion of follow-up procedures. An appropriate method of contraception is defined as one that results in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUDs), sexual abstinence, or a vasectomized partner.
9.Patient (or legal guardian) signs the written informed consent after being aware of the nature of the patient*s disease and willingly consents to the treatment program after being informed of alternative treatments, potential risks, benefits, and discomforts.
For the Netherlands, subjects will be enrolled in the event that they are unable to be transplanted with a single CBU as per UMCU procedure (Donor Hierarchy SOP 116) for single CBU transplantation.

Exclusion criteria

1. NK cell lymphoma, Burkitt's lymphoma
2. CLL/SLL diagnosis
3. MDS or CML with "marked" or "3+" fibrosis
4. CCMoL or MDS/CMMoL overlap
5. Less than 21 days have elapsed since initiation of the patient's last chemotherapy regimen and the initiation of the stem cell transplant preparative regimen (intrathecal agents, hydroxyurea, tyrosine kinase inhibitors, hypomethylating agents and rituximab, not considered chemotherapy)
6. Persistent clinically significant toxicities that, in the investigator's opinion, make the patient unsuitable for transplant
7. Evidence of anti-HLA antibodies to the selected NiCord® CBU (MFI>3000)
8. Evidence of HIV infection or HIV positive serology
9. Evidence of active Hepatitis B, Hepatitis C or EBV as determined by serology or PCR
10. Pregnancy (βHCG +) or lactation
11. Active malignancy other than that for which the UCB transplant is being performed within 12 months of enrollment. Fully resected cutaneous squamous cell or basal cell carcinoma or cervical carcinoma in situ within 12 months of enrollment will be permitted.
12. Evidence of uncontrolled bacterial, fungal or viral infections or severe concomitant diseases, which in the judgment of the Principal Investigator indicate that the patient could not tolerate transplantation
13. Patients with signs and symptoms of active central nervous system (CNS) disease, including CNS leukemia or lymphoma
14. Patients with an 8/8 allele level HLA-matched and readily available related or unrelated donor, e.g. patients who have haploidentical related donors will not be excluded
15. Prior allogeneic hematopoietic stem cell transplant
16. Allergy to bovine, gentamicin, or to any other product which may interfere with the treatment
17. Psychiatric illness and/or social situations that would limit compliance with study requirements
18. Enrolled in another clinical trial or received an investigational treatment during the last 30 days, unless documented approval obtained from Sponsor

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):	23-03-2015
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	28-11-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-02-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-06-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-09-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	22-06-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-07-2016
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	EUCTR2014-000074-19-NL
CCMO	NL51151.000.14