Unrelated cord blood transplantation after reduced toxicity conditioning with mesenchymal stromal cell co-infusion in patients with severe epidermolysis bullosa

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We propose a phase II study (intervention) in patients with severe generalized recessive dystrophic EB receiving reduced toxicity conditioning chemotherapy followe by cord blood transplantation with co-infusion of mesenchymal stromal cell units....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Epidermal and dermal conditions
Study type	Interventional

Summary

ID

NL-OMON41470

Source
ToetsingOnline

Brief title
CB+MSCforEB

Condition

- Epidermal and dermal conditions

Synonym
butterfly child disease, congenital bullous disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,Zeldzame ziekten fonds,Stichting Vlinderkind

Intervention

Keyword: blistering disease, cord blood, epidermolysis bullosa, mesenchymal stromal cell

Outcome measures

Primary outcome

Safety: Transplantation related mortality (TRM).

Efficacy/Biology: Investigation of phenotype status post-transplantation by clinical assessment of chronic wound healing, blister provocation testing, and photographic documentation. We aim to use diagnostic laboratory techniques in order to assess presence of missing proteins at the dermal-epidermal junction after transplantation.

Secondary outcome

* Disease specific outcomes: Clinical blister assessment: Suction test (Electronic Diversities. U.S.A) & Rub test (Kiritsi et al, personal communication)

* Acute GVHD (Grade II-IV: Gluckberg Criteria)

* Engraftment: Neutrophils > 500K/uL for 3 consecutive days and Platelet (day 180 > 50 K) engraftment.

* Loss of CB chimerism (<25%) at 6 mths post HSCT

* Event Free Survival (>6 mths follow up). Event defined as: death, graft-failure (<25% total donor chimerism) or relapse.

* Overall Survival

* Chronic GVHD: limited and extensive (Shulman Criteria)

* VOD (Seattle Criteria)

* Mucositis * CTC grade 3

* ISCOREB- Epidermolysis Bullosa Severity Score & Quality of Life Assessment (

Pope et al 2013, in preparation)

Study description

Background summary

Epidermolysis bullosa (EB) is a heterogeneous group of inherited diseases characterized by trauma-induced blistering and erosions of the skin and mucous membranes. There are over 25 different subtypes of highly variable clinical severity caused by mutations in 17 different genes.

Severe generalized recessive dystrophic EB (RDEB) is caused by absence or severely reduced type VII collagen (Col7), a constituent of the anchoring fibrils and an important protein involved in the adhesion of the basement membrane to the underlying dermis. The total loss of Col7 is caused by null mutations in the COL7A1 gene encoding for the collagenous polypeptide type Col7. Besides mutation analysis, other clues to diagnosis are electron microscopy, in which absence or reduction of anchoring fibrils is seen, and immunofluorescence antigen mapping, in which (almost) complete absence of the monoclonal antibody LH7:2 staining against Col7 is seen. Diagnosis can be made in most cases within 24 hours by IF antigen mapping. Patients with RDEB suffer from lifelong generalized painful blistering, erosions and granulation tissue. Due to mucosal involvement, patients also develop extracutaneous complications, such as mitten deformity of the hands (pseudosyndactyly), esophageal strictures, anemia, ectropion, short tongue, severe caries, painful open skin wounds, and multiple cutaneous squamous cell carcinomata. Patients with RDEB survive to adulthood and decease within the third to fifth decade of life despite optimal multidisciplinary care, mostly by fatal metastasis of skin cancer. Severe RDEB is a disease with such an expected poor life quality of hopeless, unbearable suffering, that some parents request euthanasia in the neonatal period.

To date, the care of patients with the most severe epidermolysis bullosa forms has been palliative and supportive. Since no curative treatment is available,

treatment is restricted to individual wounds. Recently in addition to various experimental settings, there has been clinical evidence that (allogeneic) hematopoietic stem cell transplantation (HSCT) influences the natural phenotype (natural course) of the disease significantly by engraftment of a substantial percentage of donor cells in the skin / mucosa. The substantial sustained engraftment (median 20%) of donor cells were from hematopoietic (CD45+) as well as from non-hematopoietic/non-endothelial (CD45-/CD34-) donor cells. In the small group of transplanted patients there is definitely an indication that the percentage of engrafted donor cells, as well as having 2 wild type genes of the donor in the skin correlates with the correction of the phenotype: the higher the percentage of donor cells- the higher the phenotypic correction. This landmark paper published in the NEJM, describes the clinical outcome of 7 patients, who had a heterozygous donor, and illustrates a worse clinical effect in comparison to the non-mutated donor. This was recently confirmed in a larger series (n=18) of EB patients transplanted in the same institute (personal communication with Dr. Jakub Tolar, Minnesota.) Furthermore, this is in line with the long-term outcome results of HSCT in patients with lysosomal storage diseases: full donor chimerism with a donor containing 2 wild-type genes is associated with the highest enzyme levels and therefore the best long term outcome.

The above mentioned clinical evidence is hopefully the first step to more sophisticated and *targeted stem cell therapies* for EB resulting in better correction of the disease. For these future therapies targeting cells towards skin engraftment and differentiation into type VII collagen producing cells; cord blood transplantation may be an interesting cell source. Over the last decade classical HSCT has become much safer and more effective also due to the emergence of cord blood (CB). CB has many advantages above the conventional bone marrow grafts (e.g. prompt availability, less stringent HLA-typing criteria, less graft-versus-host disease (GvHD) notwithstanding a stronger graft-versus-leukaemia effect, but is also suggested having more trans-differentiation abilities because it contains younger pluripotent stem cells. Long term outcomes in patients transplanted with unrelated cord blood for lysosomal storage disease appears better then in those transplanted with the more conventional sources i.e. bone marrow and peripheral blood. The prompt availability (transplant possibility <4weeks of life), lower GvHD rates as well trans-differentiation abilities makes cord blood an interesting cell source for transplantation in EB as well as a platform for future adjuvant stem cell based therapies.

Mesenchymal stromal cells (MSC), also known as mesenchymal stem cells are non-hematopoietic cells that reside in the bone marrow stroma. In vitro studies showed that MSC have an important interaction with hematopoietic stem cells (HSC). MSC express ligands for surface molecules of HSC, form cell clusters with HSC in co-culture experiments and secrete cytokines necessary for HSC homing, proliferation and differentiation. The speculated role of MSC in the

bone marrow has been examined in vivo, and it was observed that co-transplantation of MSC with HSC promotes engraftment of the donor cells. Besides this supportive role of MSC for HSC growth and differentiation, the main benefit comes from their immunomodulatory ability. Results suggest that MSC promote a shift from a pro-inflammatory environment to an anti-inflammatory environment. Infusion of mesenchymal stroma cells thus offers adjuvancy to two very important aspects of the procedure. Firstly, the additional anti-inflammatory effect will help reduce toxicity of conditioning prior to procedure, minimizing the chance of GvHD. This in turn facilitates not only proper engraftment of transplanted cord blood, but will allow for better correction of the disease phenotype itself through decreased inflammation and improved wound healing

Study objective

We propose a phase II study (intervention) in patients with severe generalized recessive dystrophic EB receiving reduced toxicity conditioning chemotherapy followe by cord blood transplantation with co-infusion of mesenchymal stromal cell units. Next to safety (transplantation - related mortality), the outcomes (biology, halting of progression of severe physical deformities) will be compared with the natural course of the disease.

Study design

Phase II intervention study

Intervention

Reduced toxicity chemotherapy conditioning followed by cord blood transplantation with co-infusion of mesenchymal stromal cells for severe generalized recessive dystrophic EB

Study burden and risks

The burden of the therapy is associated with HSCT itself (less likely to be associated with the MSC infusions). Cord blood stem cells will be from an unrelated donor, while the mesenchymal stroma cells will be from 3rd party donors. Despite a reduced toxicity myeloablation will be used, EB patients, due to the nature of EB and it*s characterizing chronic wounds, will be of increased susceptiblity for GvHD. MSC infusion may potentially impact this susceptibility, due to the immune-modulation potential. All other acts, measurements, follow-up and level of care are similar to off-study patients undergoing allogeneic HSCT.

Potential Risks:
1) Potentially risk of aGVHD and cGVHD resulting in death

2) Infections associated with allogeneic HSCT resulting in death
3) Death due to transplantation associated mortality (e.g. due to 1,2)
4) Passagere worsening of skin disease due to effects of conditioning (toxicity)
Potential Benefits:
1) Enhanced wound healing and reduction of pain with
potentially less scar formation as a result of protein expression in the skin
2) Clinical improvement of severe EB that is expected or has become a misery
3) Potential prevention/prolongation of onset of *mitten deformity* by
RDEB-sev-gen patients
4) Better *quality of life* due to less pain, less disease burden on a
psychosocial level*

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

(1) Diagnosed genetically & molecularly Epidermolysis Bullosa type recessive dystrofische severe generalized
2) having a single matching (* 5/6) umbilical CB unit available with sufficient cell count total NC count > 3 * E7/kg for the 8-10/10 matched units and >5*10e7/kg for the 6-7/10 matched units
(3)Lansky,Karnofsky >40
(4)Age <18
(5) approval of eligibility by "international expert panel" & UMCU kernteam HCT
(6) Signed informed consent

Exclusion criteria

(1) Creatinine clearance < 40 ml/min
(2) Cardiac dysfunction (SF < 30%) (Ejection fraction < 45%), unstable angina, or unstable cardiac arrhythmias
(3) Pulmonary function test VC, FEV1 and/ or DCO< 50%
(4) Subjects with medical history of evidence of malignancy, including cutaneous squamous cell carcinoma
(5) Allergy to any of the known constituents of the investigational product
(6) HIV seropositive infection

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):	01-11-2013
Enrollment:	11

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Fludarabine
Product type:	Medicine
Generic name:	Somatic cels allogenic
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	busulfan
Generic name:	Busilvex
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Mesenchymal stromal cells (TC-MSC)
Generic name:	not applicable
Product type:	Medicine
Brand name:	Thymoglobuline
Generic name:	ATG
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-03-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-02-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-04-2015
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-01-2017
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	EUCTR2012-000605-72-NL
CCMO	NL41471.000.13