Determination of phenotypical and biological characteristics of mesenchymal stem cells in pediatric myelodysplastic syndromes

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1 To determine the phenotype and biological characteristics of mesenchymal stem cells derived from pediatric MDS patients as determined by flow cytometric analysis, cell culture and differentiation abilities analyzed by subtype of MDS compared to de…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON31742

Source
ToetsingOnline

Brief title
MSC's in children with MDS

Condition

- Other condition
- Leukaemias
- Miscellaneous and site unspecified neoplasms benign

Synonym
bone marrow dysfunction, pre-leukemia

Health condition

myelodysplastic syndroom op het kinderleeftijd

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,SUBSIDIEAANVRAAG GISELA THIER FONDS (WA-KJC) sept 2007

Intervention

Keyword: Mesenchymal stem cells, Myelodysplastic syndorme., Pediatrics

Outcome measures

Primary outcome

1. Determination for each patient and control the phenotypical and biological

characteristics of MSC*s by flow cytometric analysis, cell culture and

differentiation abilities.

2. Determination of functional characteristics of MSC's isolated from

pediatric MDS patients and controls:

- immune regulation of T and NK cell function

- cytokine and growth factor expression of MSC*s and the

expression of chemokine receptor profiles

3. Determination of cytogenetic abnormalities of MSC*s and HSC*s in MDS

patients and controls.

4. Determination of cell cycle control, apoptosis and differentiation by gene

array of MSC*s and HSC*s from children with MDS and controls.

5. Determination of MSC and CD34+ve HSC*s from MDS patients to support normal

hematopoiesis compared to controls.

Secondary outcome

Not applicable

Study description

Background summary

The pluripotent stromal stem cells or so called Mesenchymal Stromal Cells (MSC*s), located in the bone marrow, give rise to cells that form the structural network in support and maintenance of normal hematopoiesis. The growth and differentiation of hematopoietic stem cell progenitor cells rely on instructive signals provided by a specialized micro-environment. MSC*s provide signaling by cell-cell contact and release of soluble factors. They themselves are influenced by the developing hematopoietic stem cell. The stromal cells isolated from marrow can be expanded ex vivo for biological studies. Myelodysplastic syndrome is a heterogeneous disease characterized by hematomorphological dysplasia, cytopenia, cytogenetic abnormalities and leukemic transformation. In children, MDS accounts for less than 10% of all cancers and has some distinct characteristics that distinguish the disease from its adult counterpart. The contribution of the non hematopoietic microenvironment in MDS is controversial but there is increasing evidence to suggest that bone marrow stromal defects occur both in adult and pediatric MDS patients and that stromal cell/hematopoietic stem cell interactions may influence the initiation and/or progression of MDS. Modification of stromal precursors could be the result of infiltrating malignant cells, which generate conditions favorable to the development of leukemia. As such, precursor MSC*s may be functionally different in children with MDS and within the heterogeneity of the disease, i.e. depending upon leukemic development. If our hypothesis is true normal signaling and interaction may be restored following successful hematopoietic stem cell transplantation. If so pre and post transplant analysis may be of benefit in prediction of relapse.

Study objective

1 To determine the phenotype and biological characteristics of mesenchymal stem cells derived from pediatric MDS patients as determined by flow cytometric analysis, cell culture and differentiation abilities analyzed by subtype of MDS compared to de novo ANLL and normal pediatric controls.
2 To analyze functional characteristics of MSC's isolated from pediatric MDS patients:
a. In relation to immune regulation of T and NK cell function
b. To compare cytokine and growth factor expression of MSC*s and the expression of chemokine receptor profiles of MSC*s and HSC*s isolated from children with MDS analyzed by subtype of MDS compared to de novo ANLL and normal control marrows.

3 To compare chromosomal difference between patient HSC*s and MSC's in children with different subtypes of MDS utilizing karyotyping and/or chromosome painting techniques.
4 To analyze genetic profiles of cell proliferation, apoptosis and differentiation of MSC*s isolated form children with MDS compared to MSC*s analyzed by subtype utilizing gene array analysis compared to de novo ANLL and pediatric normal controls.
5 To determine whether or not normally functioning MSC*s impact on hematopoietic growth in MDS patients and whether MDS derived MSC*s support hematopoietic growth of normal CD34+ cells (pre and post allogeneic HSCT) by long-term culture (Dexter type).

Study design

Following informed consent 10-15 cc of additional bone marrow aspirate will be withdrawn at or around the time of diagnosis or immediately before hematopoietic stem cell transplantation (HSCT). At the same time 20 cc of EDTA blood and 5cc plasma will be withdrawn with the routine diagnostic blood sampling. All samples will be shipped to the LUMC, Leiden, the Netherlands for subsequent analysis. For children <10kg the blood sampling will be reduced to 10cc EDTA blood and 5cc plasma. CD 34+ve hematopoietic stem cells (HSC*s) will be isolated from bone marrow and used in the subsequent experiments. MSC*s will be isolated and expanded ex vivo to provide sufficient cells for analysis. Phenotypic and biological parameters will be investigated, inclusive of cytokine production, chemokine receptor analysis, chromosome changes and interaction with immune regulatory cells. These results will be compared to CD34+ve HSC*s and MSC*s obtained at the time of routine bone marrow harvest from consenting normal pediatric bone marrow donors and children with de novo acute myeloid leukemia at the time of diagnosis.

Study burden and risks

Additional blood and marrow during routine diagnostic sampling confers no additional risks.

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

Patient inclusion criteria
1 Children aged 0-18 years.
2 Patients enrolled in EWOG-MDS/JMML 2006 study.
3 Informed written consent.
Study control inclusion criteria
1 Normal fully screened donor undergoing bone marrow harvest.
2 Sufficient cells for marrow recipient.
3 Pediatric patients with de novo ANLL
4 Informed written consent.

Exclusion criteria

Patient exclusion criteria
1 Failure of bone marrow aspirate.
2 Failure of MSC expansion;Donor control exclusion criteria
1 Insufficient harvest (cell dose below target).
2 Failure of MSC expansion.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-01-2009
Enrollment:	45
Type:	Actual

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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
CCMO	NL18482.058.07