Dysfunction of bone marrow progenitor cells in chronic kidney disease

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1. To quantify and characterize BM progenitor cells in patients with CKD as compared to healthy controls. 2. To explore strategies to improve BM stem and progenitor cell function ex vivo.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal disorders (excl nephropathies)
Study type	Observational invasive

Summary

ID

NL-OMON41569

Source
ToetsingOnline

Brief title
Dysfunction of BM progenitor cells in CKD

Condition

- Renal disorders (excl nephropathies)

Synonym
chronic kidney disease, chronic renal failure

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: NWO: Vidi grant Marianne Verhaar

Intervention

Keyword: bone marrow, chronic kidney disease, dysfunction, endothelial progenitor cells

Outcome measures

Primary outcome

1. Quantify and characterize BM stem and progenitor cells

Using flow cytometry, we will quantify the levels of CD34, CD31, KDR, CD133, CD45, CD184, CD140b, CD14 and CD26 positive cells in BM and PB, to determine EPC (CD34, CD31, CD133 and KDR (also known as VEGFR-2)) and stem cells of leukocyte (CD45), stromal cell(CD184, CD26), mesenchymal (CD140b) or monocyte (CD14) origin.

BM-cells will be studied for migration-capacity in response to angiogenic factors and for their in vitro capacity to differentiate into EPC. EPC will be studied with respect to proliferative-, adhering-, and angiogenic capacity. Human MSC will be cultured according to clinical protocol in our Gene & Cell Facility. BM-cells, EPC, SPC and MSC from CKD patients and controls will be studied for differences in gene expression and secretion of growth factors.

2.Functional assessment of BM stem and progenitor cells

The in vivo neovascularization capacity will be compared of BM cells obtained from patients with CKD and BM cells from healthy controls in a hind limb ischemia animal model.

3.Laboratory testing

Laboratory testing will be performed according to the transplantation protocol.

In addition we will study progenitor cell mobilizing factors, as well as

markers for endothelial cell dysfunction/activation, inflammation and oxidative

stress (e.g. Cytokines IL1b, IL2, IL6, SDF, VEGF etc.).

BM biopsy

The biopsy specimen will be used for histological analysis on the composition

and microscopic architecture of the BM.

Secondary outcome

Not applicable

Study description

Background summary

CKD is a growing health problem, affecting up to 10% of the population, mainly due to the increase in diabetes, hypertension en obesity. CKD may lead to end stage renal disease (ESRD), is associated with an increase in cardiovascular risk and has great health and economic impact. Slowing CKD is therefore a major health priority.

CKD is characterized by reduced renal and vascular regenerative capacity. In 1997 Asahara et al. discovered the putative EPC, which is derived from the BM and present in the adult circulation. EPC have been shown to home to sites of neovascularization and differentiate into endothelial cells in situ. We previously reported that BM-EPC can also contribute to regeneration of the highly specialized glomerular microvasculature. These observations have raised much interest in BM cell therapy for the treatment of cardiovascular as well as renal diseases.

BM-cell therapy for cardiovascular and renal disease
In recent years many studies have been performed to test the therapeutic potential of BM-derived cells in cardiac and limb ischemia. Two recent

meta-analyses of clinical trials in ischemic heart disease confirmed safety of BM-cell therapy and reported modest yet significant and clinically relevant benefits on cardiac function and remodelling. Small human clinical trials in patients with limb ischemia suggested improved clinical outcome of BM-cell administration.
BM-progenitor cell therapy has also been shown to induce renal recovery in animal models of acute renal failure. We recently showed that that injection of healthy BM-cells can reduce progression of CKD in a rat model of established, progressive CKD.

BM cell dysfunction in cardiovascular and renal disease
Several studies have demonstrated that circulating BM-derived EPC are reduced and dysfunctional in the presence of risk factors for cardiovascular disease. We and others demonstrated that this dysfunction of circulating EPCs is also present in patients with predialysis CKD, cardiorenal syndrome and patients with end stage renal disease on hemodialysis or peritoneal dialysis. In patients with chronic ischemic heart disease such functional impairment has been shown to extend to BM stem and progenitor cells. A small clinical study, comparing the angiogenic potency of the BM cells of patients undergoing thoracic surgery, suggests that in patients with renal failure, the angiogenic potency of the BM cells is significantly compromised. In line, our recent data show that whereas administration of healthy rat BM cells in a rat model of established CKD significantly reduced CKD progression, administration of BM cells obtained from a rat CKD BM donor had a markedly attenuated effect.

It is important to note that when considering BM cell therapy, this will involve autologous BM cells. A functional impairment of BM stem and progenitor cells may limit the therapeutic potential of autologous BM cell therapy in CKD patients. Our objective is to study the functional characteristics of the BM progenitor cells obtained from patients with CKD (preemptive and on dialysis) as compared to healthy controls, relate BM cells* dysfunction to clinical parameters and to explore methods to improve BM progenitor cell function in vitro and in vivo.

Hypothesis

In CKD, despite standard medication, dysfunction of BM stem and progenitor cells is present, which may hamper the clinical applicability of current progenitor cell based strategies to reduce CKD progression.

Study objective

1. To quantify and characterize BM progenitor cells in patients with CKD as compared to healthy controls.

2. To explore strategies to improve BM stem and progenitor cell function ex

vivo.

Study design

A cross-sectional case-control study.

After obtaining informed consent, BM-aspirates will be drawn from 20 patients with CKD (recipients from our donor kidney program) and 20 controls.
The controls will consist of donors from our living-donor program and healthy patients undergoing surgery who agree to donate BM to UMCU BioBank. For the latest a separate proposal will be prepared and submitted to the Biobank Scientific Advisory Board (BSAB; WARB in Dutch) for approval.
Human BM-samples will be compared for cell composition, migration-capacity in response to angiogenic factors and differentiation capacity to EPC and human mesenchymal stem cells (MSC). EPC will be studied with respect to proliferative-, adhering-, and angiogenic capacity. MSC will be cultured according to clinical protocol in our Gene & Cell Facility. BM-cells, EPC, and MSC from CKD patients and controls will be studied for differences in gene expression and secretion of growth factors.

Study burden and risks

BM punction (taking 20ml BM aspirate and a BM biopsy) and peripheral blood collections (20 ml) will be performed in the operating room, under general anaesthesia, before start of the operative procedure. Large studies have shown that complications during this procedure, rarely occur (<0.1%). The patient will not have direct potential benefits by participating in this research.
However the patient will contribute to innovating stem cell technologies which will be a significant improvement to current existing techniques to treat cardiovascular and kidney diseases.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584CX

NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

CKD patients/kidney recipients:
Inclusion criteria:
• CKD patients undergoing renal transplantation procedure
• Age>18 yrs
• Written informed consent.;Donors/healthy controls:
Inclusion criteria:
• Healthy controls undergoing renal transplantation donor procedure or voluntarily donate BM during surgery
• Age > 18 yrs
• Written informed consent.

Exclusion criteria

CKD patients/kidney recipients:
Exclusion criteria:
1. Patients undergone stem cell transplantation in the past
2. Based on the exclusion for renal transplantation for CKD:
• Active infection (hepatitis B and C, tuberculosis, HIV);
• Life expectancy <2 years;
• Malignancy not curatively treated;;Donors/healthy controls:
Exclusion criteria:
• Kidney disease.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-07-2013
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	17-10-2012
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-07-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-12-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-05-2015
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	05-08-2015
Application type:	Amendment
Review commission:	METC NedMec

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	NL38857.041.12

Study results

Date completed:	01-07-2016
Actual enrolment:	38