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Bone marrow-derived liver-committed stem cell mobilization by G-CSF to enhance liver regeneration after hepatectomy

Submission date
22/12/2015

Recruitment status
No longer recruiting

Registration date
08/01/2016

Overall study status
Completed

Last Edited
07/01/2016

Condition category
Cancer

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Liver tumors usually require surgical treatment. Surgery to remove part of the liver (partial hepatectomy) is commonly performed. After hepatectomy regeneration of the liver is very important to maintain liver function. Stem cells from the bone marrow could migrate from the bloodstream to the liver and contribute to liver regeneration. Granulocyte-colony stimulating factor (G-CSF) can be given to patients to stimulate the bone marrow to produce and release the stem cells. The aim of this study is to find out whether infusing G-CSF before partial hepatectomy mobilizes patients' stem cells and improves liver recovery.

Who can participate?
Patients aged 18 to 75 with benign or malignant liver tumors and undergoing partial hepatectomy.

What does the study involve?
Participants are randomly allocated to one of two groups. In one group participants are treated with G-CSF every day in the morning for five consecutive days before undergoing partial hepatectomy. In the other group participants are treated with saline (salt solution) in the same manner before undergoing partial hepatectomy. Blood samples are collected from the two groups to investigate the presence of stem cells in the blood. The results are compared with the results obtained from healthy volunteers. All patients are monitored daily by physical examination and laboratory tests. CT scans are performed to evaluate liver volume, tumor mass and liver recovery.

What are the possible benefits and risks of participating?
The benefit would be enhanced remnant liver recovery after hepatectomy. G-CSF has been used with no harm for more than 30 years.

Where is the study run from?
1. Clinic Hospital, Barão Geraldo (Brazil)
2. Haematology Hemotherapy Centre, Barão Geraldo (Brazil)

When is the study starting and how long is it expected to run for?
August 2008 to July 2015

Who is funding the study?
1. Norrbacka-Eugenia Foundation (Sweden)
2. Foundation Sunnerdahls Disability Fund (Sweden)
3. Promobilia Foundation (Sweden)

Who is the main contact?
1. Dr Ângela Luzo (scientific)
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Contact information

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Scientific

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Additional identifiers

Protocol serial number
N/A

Study information

Scientific Title
G-CSF mobilization in the pre-operatory period to enhance remnant liver recovery after hepatectomy: a randomised controlled trial

Study objectives
Pre operative G-CSF mobilization might recruit bone marrow–derived liver committed stem cells (BMDLCSC), immunophenotyped as CD34+/Lin-/CXCR4+/SDF1+ stem cells, improving remnant liver recovery in patients undergoing extensive PH.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Ethics Committee of the Faculty of Medical Sciences (State University of Campinas), 15/12 /2009, ref: 996/2008
2. Brasilian National Ethics Committee (CONEP), 29/01/2010, ref: 061/2010

Study design
Prospective double-blind randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Controlled primary neoplasia disease

Interventions
The presence of bone marrow-derived liver committed stem cells, immunophenotyping as D34+ /Lin-/CXCR4+/SDF1+ stem cells, were previously investigated by flow cytometry in the peripheral blood of 9 adult healthy volunteers, with the same median age of the eligible patients, in order to be used as healthy normal controls of these cells. All patients were hospitalized in the Liver Unit one day prior to mobilization or infusion of NaCl 0.9%. In the intervention group bone marrow stem cells mobilization was induced by G-CSF (Granulokyn, Roche), administered via subcutaneous 10 µg/kg every day, in the morning during five consecutive days. The control group received subcutaneous NaCl 0.9% in the same volume as G-CSF in the same manner (every day, in the morning during five consecutive days). Before the beginning of the mobilization protocol, blood samples were collected from the two groups to perform flow cytometry analyses to investigate the previous presence of BMDLCSC (CD34+ /Lin-/CXCR4+/SDF1 + stem cells) in the peripheral blood. The results were compared with the ones obtained from healthy donor controls. All patients were submitted to PH on the 5th day of G-CSF /NaCL 0.9% mobilization, and monitored daily by physical examination and laboratory tests. Abdominal CT was performed to evaluate hepatic volume, the amount of tumor mass pre partial liver resection and in the post surgery period, and on day 10, 30 and 60 to evaluate the remnant liver growth.

Intervention Type
Procedure/Surgery

Primary outcome(s)
The effectiveness of recruitment and release of bone marrow-derived liver-committed stem cells to the peripheral blood by granulocyte colony stimulating factor (GCSF) bone marrow mobilization at improving remnant liver recovery in patients undergoing extensive liver resections.

The recruitment and release of bone marrow-derived liver-committed stem cells was measured by flow cytometry analysis with specific labeled antibodies: IgG FITC/ IgG PE; CD45 Percp; CD14 FITC CD33 APC; CD34 APC; CD19 FITC ; CD3 PE; cySDF1 Alexa fluor 488; CD184 PE(CXCR4); cyCD184 PE, disposed for the analyses as: cySDF1 Alexa fluor 488/ CD184 PE/ CD45 Percp/ CD34 APC; CD14 FITC/ CD34 PE/ CD45 Percp/ CD33 APC and CD19 FITC/ CD3 PE/ CD45 Percp/ CD34 APC. Flow cytometry analyses were performed on days 0, 5, 10-15, and 30. Results on day 0 were compared with results obtained from nine adult healthy volunteers, with the same median age as the eligibility patients.

The improving remnant liver recovery was analyzed by a 64-slice Scanner CT. Pre surgery CT analysis was performed with four consecutive acquisitions (pre and post contrast medium injection). Post surgery analysis was carried out on days 10, 30 and 60, one acquisition, post contrast medium injection, during portal phase. The following parameters were used; voltage 120 kVp, current of 200-275 mAs, and section thickness of 5 mm in order to optimize liver volumetry analyses. Results were analyzed by two radiologists specialized in liver images. CT results were analyzed by Vitrea Advanced Software.

Key secondary outcome(s))
Patient clinical and laboratory exams were performed during the recruitment phase and on day 0 before GCSF/NaCl 0.9% administration, and days 5, 10 and 60.

The following exams were performed: Hemoglobin (Hb); Hematocrit (HT); Leucocytes; Platelets; Albumin; Prothrombin Time/international normalized ratio (PT/INR); Activated partial tromboplastin time/ratio (APTT/R), aspartate aminotransferase (AST) alanine amino transferase (ALT); alkaline phosphatase (Alkaline Phos); gamma glutamil transferase (GGT); urea (U); creatinine (C); glycemia (mg/dL) and ferritin.

Some clinical and laboratorial data were also analyzed post surgery on day 10: days spent in the Intensive Care Unit (ICU), bleeding volume during the surgeries, and blood usage.

Completion date
01/07/2015

Eligibility

Key inclusion criteria
1. Aged between 18 and 75 years
2. Controlled primary neoplasia disease
3. Absence of clinical, laboratorial and radiological evidence of tumor metastasis

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Chronic hepatic insufficiency
2. Hepatic encephalopathy
3. Coagulopathy
4. Presence of hepatoblastoma
5. Disseminated intravascular coagulation
5. Renal or cardiac insufficiency
5. Acute infection
6. Sepsis (defined by the criteria of the Society of Critical Care Medicine and American College of Chest Physicians, 1992)
7. Those enlisted for liver transplantation.

Date of first enrolment
01/02/2010

Date of final enrolment
01/03/2011

Locations

Countries of recruitment
Brazil

Study participating centre
Clinic Hospital
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Study participating centre
Haematology Hemotherapy Centre
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Sponsor information

Organisation
State University of Campinas (Brazil)

ROR
https://ror.org/04wffgt70

Funder(s)

Funder type
Research council

Funder Name
Brazilian National Counsel of Technological and Scientific Development

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Available on request