Combined procedure of vascularized bone marrow transplantation and mesenchymal stem cells graft – An effective solution for rapid hematopoietic reconstitution and prevention of graft-versus-host disease

Andrei Colităa,*, Anca Colităb, Dragos Zamfirescu c, Anca Roxana Lupu a

a Colța Hospital, 1 IC Bratianu Ave., Bucharest 030171, Romania
b Fundeni Clinical Institute, 258 Fundeni Str., Bucharest, Romania
c Floreasca Clinical Emergency Hospital, 1 Floreasca Str., Bucharest, Romania

ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is a standard therapeutic option for several diseases. The success of the procedure depends on quality and quantity of transplanted cells and on stromal capacity to create an optimal microenvironment, that supports survival and development of the hematopoietic elements. Conditions associated with stromal dysfunction lead to slower/insufficient engraftment and/or immune reconstitution. A possible solution to this problem is to realize a combined graft of hematopoietic stem cells along with the medular stroma in the form of vascularized bone marrow transplant (VBMT). Another major drawback of HSCT is the risk of graft versus host disease (GVHD). Recently, mesenchymal stromal cells (MSC) have demonstrated the capacity to down-regulate alloreactive T-cell and to enhance the engraftment. Cotransplantation of MSC could be a therapeutic option for a better engraftment and GVHD prevention.

Background

Hematopoietic stem cell transplantation (HSCT) represents an important therapeutic tool for the treatment of hematologic diseases, genetic disorders and autoimmune diseases [1,2]. The basis of this procedure is the capacity of hematopoietic stem cells (HSC) to self replicate, differentiate and generate all the different mature blood cells through a complex process known as hematopoiesis [1–4].

In order to sustain an efficient hematopoietic process (in normal subjects or hematopoietic reconstitution in HSCT recipients), hematopoietic stem cells have to reside in a specific microenvironment which is essential in maintaining and regulating their activity and survival [4,5]. This bone marrow (BM) microenvironment consists of stromal cells, extracellular matrix and factors required for the development of stem cells. Stromal cells include macrophages but also other cell types such as mesenchymal cells and osteoblasts as well as other hematopoietic cells that secrete hematopoietic cytokines and extracellular matrix components [3–5]. More than 40 different growth factors, cytokines, and chemokines interact with stem and progenitor cells through specific receptors and regulate proliferation, differentiation, and cell fate [6]. Hematopoietic growth factors are produced by mesenchymal cells and hematopoietic cells and are present in cell-bound forms, bound to the extracellular matrix (ECM) or in solution [4,7–9]. Stem and progenitor cells express adhesion receptors that provide specific cell–cell and cell-ECM interactions [4].

Recently, multipotent mesenchymal stromal cells (MMSCs) have been isolated from bone marrow and shown to differentiate in vitro into several mesenchymal lineage cell types – adipocytes, connective stromal cells, osteoblasts, chondrocytes. MSC have a striking similarity to mural vessels cells. As a part of the vascular wall compound they can be found in highly vascularized bone marrow. MMSCs have thus emerged as an important regulator of hematopoietic activity, but also as a precursor for non-hematopoietic tissue, with possible stem-cell properties. An important clinical application of MMSC within the field of HSCT is on the basis of the ability of these cells to down-regulate alloreactive T-cell responses when added to mixed lymphocyte cultures. This makes MMSCs an attractive cell source for therapeutic application in T-cell mediated autoimmune or alloimmune diseases such GVHD [3,5,10].

An increasing role in the regulation of hematopoiesis is described for the bone tissue itself through the activity of osteoblasts that sustain HSC function and homing [5].

Conventional HSCT

High-dose myeloablative radio-chemotherapy is considered as a mandatory first step in preparation for allogeneic HSCT for two
Vascularized bone marrow transplantation (VBMT)

The vascularized bone marrow transplant (VBMT) is a combined graft of bone marrow, bone and stromal environment transplanted to a recipient on a vascular pedicle. The VBMT contains hematopoietic stem cells as well as stromal cells that are able to sustain hematopoietic stem cell survival and differentiation. The concept of VBMT evolved from studies on composite tissue allotransplantation (CTA) [11]. In animals, investigation of VBMT has demonstrated several clinically relevant improvements in comparison to conventional (cellular) bone marrow transplantation (BMT): faster engraftment, reduced incidence of graft-versus-host disease (GVHD), stable (cellular) bone marrow transplantation (BMT); faster engraftment, reduced incidence of graft-versus-host disease (GVHD), stable infected proliferation of the hematopoietic elements. There are several diseases where the stromal cells are affected – MDS, myelofibrosis, genetic disorders. There is a slower engraftment and/or immune reconstitution when using alternative donors [1,2].

Several drawbacks to the current BMT procedure include obligatory host immunosuppression, risk of engraftment failure, risk of acute and chronic GVHD, relapse of the disease after the BMT, and infectious complications [11].

Hypothesis

Our hypothesis is that the cotransplantation of HSC together with their environment (as VBMT) combined with MMSC graft would determine a more rapid hematopoietic reconstitution and reduced graft rejection as compared with conventional HSCT and also due to the MMSC specific functions would prevent severe GVHD and induce immunological tolerance.

Future directions

Proving this hypothesis would be a major benefit in controlling engraftment and tolerance in patients with CTA.

This hypothesis is the subject of a postdoctoral study project of our group. We are performing a study on rats by comparing the outcome of animals given conventional HSCT, animals with VBMT and a group cotransplanted with MMSC.

Conflict of interest statement

We, Andrei Colită, Anca Colită, Dragos Zamfirescu and Anca Roxana Lupu, certificate that we do not have any financial or personal relationships that might bias the content of this work.

There is no conflict of interest between authors in this study. The manuscript has been read and approved by all the authors, and each author believes the manuscript represents honest work.

Acknowledgement

This paper is partially supported by the Sectoral Operational Programme Human Resources Development, financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/89/1.5/S/64153.

References