The Possibilities of Harvesting and the Modalities of Processing Hematopoetic Stem Cells

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Hematopoietic stem cells are defined as cells with self-renewing capabilities that can differentiate into multiple cell liniages. In adults, the stem cells are part of the tissue-specific cells into which they are committed to differentiate. The embrionic stem cells are derived from embryos and have the ability to generate any cell in the body.

The adult hematopoietic stem cells are organized in a hierarchic tree, with multipotent, self-renewing stem cells at the base, the committed progenitor cells as the main branches and lineage restricted precursor cells as terminal branches. The lineage restricted stem cells give rise to terminally differentiated cells. The classic paradigm of organ-restricted stem cell differentiation is challenged by the possibility of the hematopoietic stem cells to retain a degree of plasticity that allows them to differentiate into any cell of the adult human body, according to the microenvironment [1].

The initial source for stem cells was the bone marrow. After transplantation of unselected cells in animals previously conditioned with chemotherapy/radiotherapy treatment there was evidence that not only hematopoietic tissue was generated by the transplanted cells, but also non-lymphohematopoietic tissue, such as hepatocytes, muscle fibers and neuronal tissue.

Since 1990 the main source of stem cells was the peripheral blood after mobilization with cytokine (granulocyte colony stimulating factor – G-CSF) with or without chemotherapy. Several investigators reported that human peripheral blood stem cells can generate also non-lymphohematopoietic tissue in the same way the cells from the marrow did.

There are some differences between marrow and peripheral blood stem cells. The marrow stem cells are in a higher proportion non-cycling, quiescent stem cells, have a lower expression of proapoptotic genes (caspases) and have increased activity of proteinase 3. In human clinical transplantation protocols the recovery is faster when peripheral blood stem cells are transplanted, with a slightly increased incidence of graft versus host disease.

The mechanisms involved in stem cells homing and mobilization are regulated by a complex interplay of chemokines, integrins, proteolytic enzymes, cytokines and stromal cells. CXCR4 is the stem cell receptor for SDF-1 (stroma derived factor 1) from the stromal cells. VLA-4 is the receptor for VCAM from the endothelial cells and fibronectin. The blockage of these receptors favors the mobilization of the stem cells from the bone marrow. G-CSF is probably blocking CXCR4, and release the CD34+ cells from the action of SDF-1. SDF-1 is considered the single most potent chemoatractant of stem cells. The antagonists of CXCR4 (known as AMD 3100) and SDF-1 (known as CTCE0021) are used for the mobilization of bone marrow stem cells into the peripheral blood [2].

Hematopoietic stem cells (HSCs) exist within the bone marrow in a specialized microanatomic space named the niche. The surrounding microenvironment is responsible for maintaining a balance between stem cell pool and proliferation. The exact location of the stem cell niche is debatable. It is suggested that HSCs exist in an endosteal niche close to the bone. Others suggest the HSCs niche is intimately associated with vasculature [3]. In fact endosteal and vascular HSCs niches are not mutually exclusive in the metaphysis [4]. The transplanted hematopoietic stem and progenitor cells (HSPCs) preferentially home close to the trabecular rich metaphysis in the femur of the non ablated mice recipients. Within the metaphysis all HSPCs exist in the endosteal niche in close proximity of the blood vessel.

The study of Tănase et al. in this issue of Acta Medica Marisiensis, reporting on mobilization of stem cells in human healthy adults is of particular interest. The investigators performed 86 hematopoietic stem cell harvest procedures in 64 healthy volunteer donors. The series of donors included 10 children. The procedure was done by leukapheresis after subcutanously administration of G-CSF (filgrastim-Neupogen, Amgen) and counting of the WBC and CD34+ cells in the peripheral blood. Twenty-four apheresis were performed with Haemonetics separator and 62 with Cobe Spectra separator. The product obtain by apheresis was cryopreserved and thawed according to the protocol. The results for viability and clonogenic capacity testing were well between reccommended limits. 50 patients were transplanted with stem cells from peripheral blood.

Hematopoietic stem cell transplantation has significant possibility to cure a variety of hematologic (neoplastic and non neoplastic) and nonhematologic diseases. It has a well established value in the setting of hematological malignancies – leukemias, acute and chronic, lymphoma, myeloma and in some eligible cases of myelodisplasia and myelofibrosis. It is also curative in thalasemia major. Due to a long period of clinical practice, of at least 3–4 decades, it is possible now to transplant also the older patients, using myeloablative or non-myeloablative (reduced intensity conditioning – RIC) conditioning regimens. The posttransplant morbidity and mortality is decreasing continuously by better understanding of immune mecanisms, more efficient supportive care, including antibiotic and antifungic therapy and better selection of related and unrelated donors.

However the role of stem cell transplantation remains to be validated in clinical practice, considering the potential plasticity of adult stem cells, and the possibility to treat neurological degenerative disorders and cardiac muscle diseases.

References

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