Stem cell transplantation – new treatment approaches

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STEM CELL TRANSPLANTATION – NEW TREATMENT APPROACHES

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A b s t r a c t: Stem cell research still remains one of the most controversial fields of science today on account cell plasticity and its capability of transdifferentiation or de-differentiations to certain tissue types, as well as the clinical application of this scientific concept. Stem cells derived from bone marrow, peripheral blood or the umbilical cords are a common therapeutic approach for treatment of haematological malignancies as part of established transplant procedures (allogeneic, autologous, syngeneic stem cell transplantation). But recent clinical data have revealed the potential role of stem cells in the treatment of other nonhaematological diseases, degenerative disorders, cardiovascular diseases and autoimmune diseases. The experience with stem cell transplantation in haematological malignancies at the Hematology Department, Skopje, has been established since it was set up 7 years ago, with more than 130 patients undergoing transplant procedures (87 autologous and 43 allogeneic recipients). Encouraging results were also reported from the Skopje Cardiology Clinic in the field of intracoronary application of bone marrow derived stem cells for the treatment of patients with acute myocardial infarction. But this new rout in tissue regeneration should still be further extended and evaluated in clinically randomized studies that will confirm the therapeutic potential of stem cells.

Key words: stem cell transplantation.

Background

Stem cells are defined as a population of undifferentiated cells with the capacity to divide for indefinite periods, for cell division, for self-renewal, differentiation and transdifferentiation into highly specific cells. The immuno-

phenotypic characteristics of stem cells are CD 34+, CD 133+, c-kit and protein BCRP-1.

A fertilised egg (zygote) represents a totipotent stem cell, a cell with unrestricted differentiation potential and the only cell with the capacity to give rise to all the cells necessary for the development of foetal and adult organs. Embrionic stem cells forming a cluster of cells inside the blastocyst are pluripotent stem cells, capable of generating a variety of specialized cell types, but limited in their differentiation potential by their inability to support the development of a foetus. Further specialization results in the generation of multipotent stem cells residing in adult somatic tissues. Their physiological functions are to replenish mature cell populations of the given tissue or organ, and to respond to stress by repairing the damage. Haematopoietic stem cells represent the prototype of multipotent adult tissue stem cells [1]. In humans, HSCs can be found in cord blood as a result of stem cell migratory properties during foetal development, whereas post-natally the only organ harbouring HSCs and pursuing active multilineage haematopoiesis is the bone marrow.

More than 40 years of research on bone marrow derived stem cells, initiated in the 1960s by Till and McCulloch, marked an ongoing improvement in methods to quantitate and isolate these cells. Assays for clonogenic presursors of the myeloerythroid lineages *in vitro*, defined as long-term culture-initiating cells (LTC-ICs) and commited colony forming units (CFUs) were followed by the development of a model of immunocompromised non-obese diabetic cross severe combined immunodeficiency (NOD/SCID) mice, which allows the study of the repopulating ability of human haematopoietic cells *in vivo* [2]. These functional assays are paralleled by progress in the phenotypic characterization of haematopoietic cells by flowcytometry, owing to monoclonal antibodies specifically recognizing cell surface molecules.

Haemopoietic stem cells are defined by their dual ability to self-replicate into erythroid, myeloid, megacariocytic and lymphoid lineages. They are thus distinguishable from commited haemopoietic progenitors which have lost their ability to self-replicate and are restricted in their developmental potential. This ability of the stem cells had been hypothetical since the 1950s. Almost six decades have elapsed since the experiments of Jacobson, Lorenz and their colleagues clearly demonstrated that mice could be protected against otherwise lethal irradiation by an intravenous infusion of marrow. Soon thereafter it was convincingly shown that the protective effect was due to the colonization of the recipient marrow by donor cells. About 40 years ago, bone marrow transplantation was an experimental procedure carried out as a last resort in terminally ill patients. Successful reports of transplants from HLA-identical siblings in children with congenital immune deficiency disorders in 1968 encouraged the protagonist of that period to forge ahead.

Stem cell transplantation was pioneered using bone marrow derived cells by a team at the Fred-Hutchinson Cancer Center from the 1950s to 70s, led by E. Donnel Thomas, whose work was later recognized with a Nobel Prizes in Physiology and Medicine. Thomas's work showed that bone marrow cells infused intravenously could repopulate the bone marrow and produce new blood cells. His work also reduced the likelihood of developing a life-threatening complication, graft-versus-host disease.

Stem cell research still remains one of the most controversial fields of science today on account of cell plasticity and its capability of trans-differentiation or de-differentiation to certain tissue types, as well as the clinical application of this scientific concept. Each organ and tissue is perceived to possess a subpopulation of cells capable of self-maintenance, indefinite proliferative potential and the ability to give rise to a large family of descendants, i.e. to be clonogenic. These stem cells usually give rise to a limited number of different cell lineages within their normal environs, such multipotentiality being a future of tissue- and organ-specific stem cells. This review focuses on a hitherto unsuspected property of tissue-specific stem cells, i.e. the ability to give rise to cell types in a new location that are not normally present in the organ in which the stem cells are located – a property we refer to as stem cell plasticity. The stem cells that are thought to be most flexible come from the inner cell mass of the blastocyst: these cells are essentially pluripotential, being capable of giving rise to cells found in all three germ layers. However, the ethical issues surrounding the use of embryonic stem cells from early human embryos have caused concern.

There may, however, be alternatives to the use of embryonic stem cells, as certain adult stem cells appear to be more flexible than has previously been thought. Numerous papers have challenged the long-held belief that organ-specific stem cells are lineage-restricted. In particular, haematopoietic and neural stem cells appear to be the most versatile at cutting across lineage baundaries. Of course, it is one thing for a circulating cell to engraft in another organ and assume some or all of the phenotypic traits of that organ; this is known as trans-differentiation – the acquisition of a new phenotype. It is quite another to claim that the engrafted cell is a stem cell for its new-found home. Ideally this would require the isolation and transplantation of single cells that self-renew and produce a large family of descendants (clonogenicity) that eventually become fully functional; these robust criteria have been met in one or two cases. However, some commentators have added that this phenomenon should be observed to occur "naturally" in organs not forced to undergo organ degeneration before accepting that stem cells jump lineage boundaries. Although this does occur to a limited extent, we will argue that it is precisely because of severe organ damage that trans-differentiation occurs more readily, and that the likes of haematopoietic stem cells (HSCs) can act as a back-up system when an organ's own regenerative capacity is overwhelmed. Thus, they lack the trans-

differentiation in the absence of organ damage that we would envisage exploiting the use of stem cells with a trans-differentiating potential. Also, there is the evidence that some adult stem cells may even be pluripotential, albeit in the context of creating chimaeric animals, for example in the ability of adult HSCs to contribute to all three germ layers in pre-immune foetal sheep and NOD/SCID (non-obese diabetic/severe combined immunodeficient) mice after an injection into the blastocyst.

In the 1990s stem cells were predominantly collected from the bone marrow. The ability to mobilize and harvest large numbers of haematopoietic progenitors from the peripheral blood has significantly altered the practice of clinical transplantation in the last 15 years. As a consequence more than 90% of autologous transplants are now performed using progenitors harvested from the peripheral blood rather than the bone marrow and mobilized progenitors are also increasingly used in allogeneic transplantation.

The other currently available source of stem cells is cord blood. In contrast to adult bone marrow, purifed progenitors obtained from umbilical cord blood undergo clonogenic maturation even in the absence of added growth factors. In addition there is growing evidence that the difference between adult and foetal haemopoiesis is not just a quantitative difference, but there are ontogeny-related differences related to differences of cell signalling and growth receptor requirements.

According to relations between donor and recipient, stem cell transplantation can be:

1. Autologous (tweens)
2. Allogeneic (related and unrelated)
3. Xenogeneic (in experimental phase)

Table 1 – Табела 1

Established indication for treatment with haematopoietic stem cell transplantation (23):
Индикации за третман со ТХМК

Allogeneic stem cells transplantation	**Autologous stem cells transplantation**
Severe aplastic anaemia	**ALL**
CML	**Hodgkin's disease**
AML	**Non-Hodgkin Lymphomas**
MDS	**Multiple myeloma**
Severe congenital immunodeficiency	**Solid tumours**
ALL (1 CR)	
AML and ALL (2CR)	

Temporary indications for stem cells transplantation:

Allogeneic stem cell transplantation	Autologous stem cell transplantation
Sickle cell anemia	**Autoimmune diseases**
Congenital metabolic disorders	**CLL**
Osteopetrosis	**CML**
Multiple myeloma (NMAT)	**AML**
Hodgkin's disease (NMAT)	**Hodgkin diseases (1 CR)**
Non-Hodgkin Lymphomas (NMAT)	**Non-Hodgkin Lymphomas (1CR)**

Experimental indications for haematopoietic stem cells transplantation:

Allogeneic stem cell transplantation	Autologous stem cell transplantation
CLL	**Amyloidosis**
Renal carcinoma	**Other solid tumours**
Breast carcinoma	**Juvenile rheumatoid arthritis**

The total numbers of transplanted patients according to the EBMT (the European Bone Marrow Transplantation Organization) data base are 165,000 patients and 188,703 procedures.

Our department has been a member of the EBMT since 2003.

Today stem cells transplantation has became a new therapeutical option for many neurological and cardiovascular disorders, brain and spinal cord injuries and others.

Material and methods

From September 2000 to September 2007 at our clinic we have treated 130 patients with different haematological and nonhaematological diseases. Gender: Male: 70 Female: 60 Median age: 34 years (from 12 to 64 years). Autologous: 90 (Male: 50 Female: 40) Allogeneic: 40 (Male: 20 Female: 20) from HLA identical sibling.

Table 2 – Табела 2

Transplantation according to source of stem cells
Број на трансплантации во зависност од изворот на матични клетки

Source of stem cells	*Autologous*	*Allogeneic*	*Total*
Bone marrow	24	4	28
Peripheral blood	64	36	100
Combined BM+PB	2		2

Table 3 – Табела 3

Transplantation according to diagnosis
Број на трансплантации во зависност од основната дијагноза

Diagnosis	*AML*	*ALL*	*CML*	*CLL*	*NHL*	*HD*	*MM*	*SAA*	*MP*	*ES*
Allogeneic	27	2	7	1	1	/	/	1	1	/
Autologous	37	4	/	/	12	16	20	/	/	1
Total	64	6	7	1	13	16	20	1	1	1

AML: acute myeloblastic leukaemia; ALL: acute lymphoblastic leukaemia; CML: chronic myeloic leukemia; CLL: chronic lymphocytic leukemia; NHL: non-Hodgkin's lymphoma HD: Hodgkin's disease; MM: multiple myeloma; SAA: severe aplastic anemia; MP: myelofibrosis primaria; ES: Ewing sarcoma.

Table 4 – Табела 4

Chemotherapeutic conditioning protocols used
Употребени хемиотераписки кондиционирачки протоколи

Conditioning regimen:

Regimen	*Allogeneic*	*Autologous*	*Total*
Busulfan/Cyclophosphamide	21	16	37
Busulfan/Cyclophosphamide/Melphalan	6	2	8
BEAM	2	42	44
Melphalan	/	20	20
Flag/Ida	4	1	5
ICE	/	3	3
Cyclophosphamide	1	/	1
Fludarabine/Melphalan	2	/	2
Busulfan/Melphalan	1	/	1
Other regimen	3	6	9

Median infused CD 34+cells: 3.84×10^9/Kg.b.w.

Table 5 – Табела 5

Cumulative proportion of survival after allogeneic transplantation in patients treated at the Haematology Department in the period 2000–2007

Вкупно преживување на пациентите третирани со алогена трансплантација на матични клетки во периодот 2000–2007

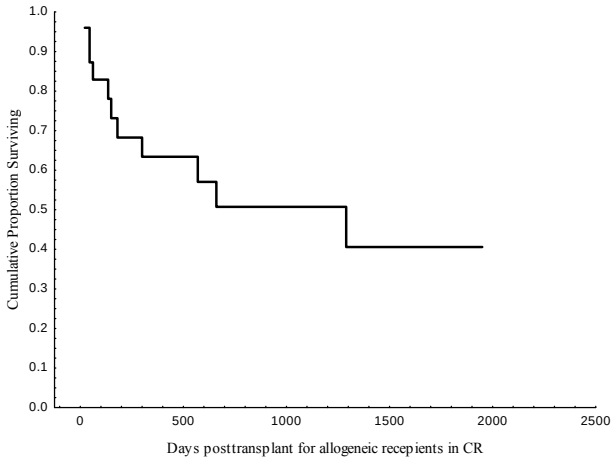
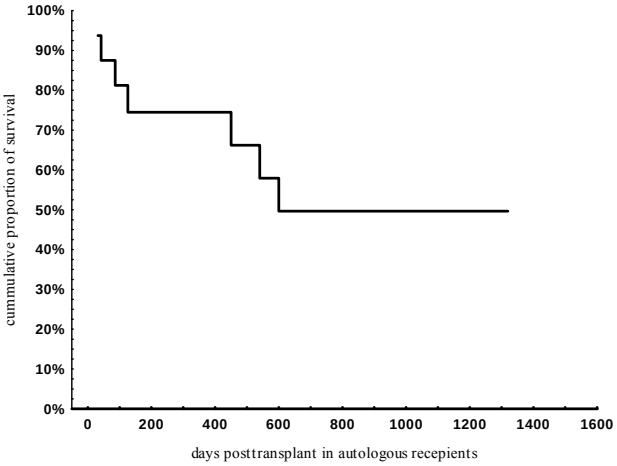


Table 6 – Табела 6

Cumulative proportion of survival after autologous transplantation in patients treated at the Haematology Department in the period 2000–2007

Вкупно преживување на пациентите третирани со автологна трансплантација на матични клетки во периодот 2000–2007



Results

Our first experience in the intracoronary application of bone marrow derived stem cells in the patients with acute myocardial infarction was made in collaboration with Mystar project led by AKH Wien (Prof. Dietke and Prof. Lang). Two patients were randomized for group A (early treatment with intracoronary injection, means 21–42 days after acute myocardial infarction, according to the criteria of the Myocardial Stem Cell Administration After Acute Myocardial Infarction (MYSTAR) study. Stem cells were collected from autologous bone marrow with multiple aspirations from the posterior iliac crest, under general anesthesia in the operating theatre, to a total volume of 1 litre bone marrow. The bone marrow was processed and stem cells were separated in two buffy coats with a volume of 69ml. (Cobe Spectra apheresis system). Buffy coat: 69ml was enriched with mononuclear cells = 3.9×10^8/kg; CD34 + cells = 1.2×10^6/kg., after which it was ready for intracoronary application. There were no major cardiac events after the transplantation and during a further follow-up period (30–120 days after infarction). The NYHA function class improved: from NYHA II to NYHA I class. Control myocardial perfusion scintography for detection of ischemia showed improvement in myocardial perfusion in our two patients. Echocardiographic assessment also showed an improvement in the left ventricular function 3 months after the infarction.

Discussion

Studies of the regenerating haematopoietic system led to the definition of many of the fundamental principles of stem cell biology. Therapies based on a range of tissue stem cells have been widely touted as a new treatment modality, presaging an emerging new speciality called regenerative medicine that promises to harness stem cells from embryonic and somatic sources to provide replacement cell therapies for genetic, malignant and degenerative conditions. Most of the enthusiasm surrounding embryonic stem cells owes directly to the perceived need for cell replacement therapy for a host of degenerative diseases. Indeed, disorders of organ failure are not reversible, and organ transplantation cannot meet the needs of an ever-aging population. Primary pump failure in the heart, alcoholic or viral liver failure, beta-cell deficient type I diabetes and Parkinson's disease are frequently cited as examples of monocellular deficiency states that might be amenable to cell replacement strategies, if a suitable and inexhaustible cell source could be found. Human ES cells might represent such a source, but the over-riding challenge is to achieve efficient directed differentiation of ES cells into therapeutically relevant cells, followed by proof-of-principle for the effective restoration of tissue function in animal models.

ES cells are derived from the inner cell mass of the preimplantation embryo. When placed in culture ES cells proliferate indefinitely and yet retain their potential to form all of the tissues of the developing organism [1]. Murine ES cells have been intensively studied for over 20 years, yet the first derivation of ES cells from the human embryo was only reported in 1998. Although advances in ES cell biology have revolutionized the creation of mouse models of disease, generating and breeding mice is time-consuming and costly. For addressing questions in cell and developmental biology, ES cells represent an excellent *in vitro* model system. While ES cells have been touted as an inexhaustible resource for cell replacement therapies, they have also already proved to be highly valuable as a research and discovery tool. By analysing the effect of targeted gene deletions on the formation of specific lineages of cells, ES cells provide a tool for validating potential therapeutic targets for small molecule drug development. ES cells are emerging as a platform technology around which chemical screens can be built, providing for identification of compounds that promote or block cell differentiation. Schultz and colleagues recently performed a chemical screen to identify agents that induce neurogenesis in ES cells, thereby establishing the proof-of-principle for using stem-cell differentiation in assays for drug discovery [2]. Kamp and collegues have convincingly shown that human ES cells differentiate into a number of cardyomyocyte classes, including embryonic atrial, ventricular, and nodal subtypes, each faithfully recapitulating their respective electrophysiologic properties and pharmacologic responses [3]. Gauging the effects of compounds on the differentiation of a specific cell population from ES cells would provide a screen for potential drug toxicities, prior to clinical development. Assembly of a genetically diverse bank of human ES cells, together with the detailed knowledge of human genetic variation emerging from the international haplotype mapping project ("the hap map"), could be translated into a discovery platform for pharmacogenomics [4].

Tissues that actively regenerate from stem cell pools in adults maintain the appropriate stem cell niche, providing the signals for stem cell self-renewal, survival, and differentiation. The haematopoietic system, skin, gut, islets, liver, and parts of the central nervous system (CNS) fall in that category. Diseases or conditions that deplete stem cell pools while leaving the niche intact would represent the lowest hurdle for stem cell-based therapeutics and there is clear proof-of-principle for such treatments in clinical settings. The successful transplantation of bone marrow, skin, pancreatic islets, liver, and to a lesser extend foetal mesencephalic dopaminergic tissue provides important confirmation that stem cell replacement therapies are a viable goal and an opportunity, given the paucity of donor organs.

In many instances of disease, however, we have a relatively poor understanding of the pathophysiology of cell degeneration. This is particularly true

for the neurodegenerative and autoimmune diseases, making it difficult to predict whether stem cell based replacement therapies can be successful without first interrupting the systemic disease process. In cases where stem cell depletion is a consequence of cell-extrinsic forces like an autoimmune attack, stem cell replacement must be accompanied by immune suppression. Despite the inadequate knowledge about the diseases' etiology and pathogenesis, neurodegenerative diseases like PD, Alzheimer's, Huntington's, Amyotrophic lateral sclerosis, stroke, and anoxic brain injury as well as all host lysosomal storage diseases with CNS pathology, represent poorly managed diseases that are worthy targets for cell replacement therapy. The hippocampus and the olfactory bulb maintain self-renewing populations of neural stem/progenitor cells, but there is scant evidence for cell renewal beyond these limited regions the CNS. Given the likelihood that many classes of highly specialized neurons develop only during the critical period of embryogenesis, ES cells might in principle be directed to differentiate into specialized neuronal subtypes for use in cell replacement therapy.

Type I diabetes represent a major disease entity that has tremendous appeal as a target for cell replacement therapy. The disorder, which results from loss of mass of the insulin-producing beta cells of the pancreatic islets due to autoimmune attack, can be reversed by pancreatic or islet cell transplantation together with steroid-sparing immunosupression [5]. Diabetes is particularly attractive because, unlike in Parkinson's disease where precise connections may be necessary, beta cells can function autonomously, even outside the pancreas. Several groups have reported differentiation of murine and human embryonic stem cells into insulin-secreting cells, [4, 13, 14] with one group claiming normalization of hyperglicaemia in a streptozotocin-treated diabetic model by transplanted cell clusters [6]. These reports are provocative, but much additional work remains to characterize the functional nature of the cells as glucose regulators, and to document adequate, regulated production of insulin, which in one case was some 50-fold less than native beta cells [8, 9].

The past 5 years have witnessed an explosion in interest in using somatic stem cells, particularly those derived from adults, for cell and gene therapy [10]. This has been driven by a number of discoveries, but in particular the possibility that some somatic stem cells can differentiate into non-autologous cell types, and also the discovery of multipotential stem cells in adult bone marrow [11]. Stem cells are thought to be present in most adult tissues, and are responsible for replenishment of those tissues throughout life. By far the best known is the HSC that resides primarily in the bone marrow. However, lesser known but potentially of equal importance are stem cells from the CNS, the liver, the skin, the intestine and so on. With the resurgence of interest in stem cells in general, some researchers are turning their attention to these systems in order to determine how different stem cells compare with each other, and to exploit these stem cells for repopulation or reconstruction of their parent

tissues after disease or surgery. Although many questions clearly remain that must be addressed by basic research, we can begin to think about using BMT for therapy of nonhaematopoietic disease [12]. There has been a relatively long history of using BMT to treat certain inherited metabolic diseases, e.g., Hurler's disease and other mucopolysaccharidoses. In such storage diseases, blood-derived cells are not used for cell replacement but rather as "pumps" for lisosomal enzymes that are taken up by impaired host cells and thereby restore their normal metabolism. As a strategy for cell replacement, BMT has been used with some success for treatment of osteogenesis inperfecta, a brittle bone disease [7]. And clinical trials are underway in several countries to determine whether bone marrow stem cells could enhance cardiac repair after infarction, either by direct injection of bone marrow cells into the heart or by mobilization through the circulation. Hopefully, good trial design will allow the outcomes of these trials to be rigorously evaluated. In some experimental settings, improvements in cardiac function following the use of bone marrow mesenchymal cells in myocardial infarction can be attributed not to trans-differentiation of such cells into cardiomyocytes, but rather to the non-cardiac cells occupying necrotic spaces that would otherwise have become scarred [17, 18]. Thus, improvement in cardiac contractility occurs via effects on Starling forces. In such cases, bone marrow-derived cells played an important therapeutic role, albeit not via cell replacement or trans-differentiation. Our first experience in this field is positive but further randomized studies are necessary. Many questions must be answered like: intracoronary or intramyocardial applications of stem cells, dose of stem cells, the best timing of stem cell applications, etc.

Conclusion

Studies of human embryonic stem cells will lead to major advances in human biology

- Embryonic stem cell research will provide critical insights into mechanisms of cell differentiation, growth and death
- Understanding stem cells may provide keys to why people age
- Limitations on the study of human embryonic stem cell research will hold back biomedical research
- Human embryonic stem cell therapies can save lives and restore people's functions
- Human embryonic stem cell can replace damaged or lost cells
- These include diabetes, degenerative neurological diseases, demyelinative diseases, brain and spinal cord injury
- These conditions are the most common and costly causes of disability in Europe and USA.

Table 7 – Табела 7

Advantages and disadvantages of adult and embryonic stem cells
Предности и недостатоци на адултните и ембрионалните матични клетки

	Advantages	*Disadvantages*
Human ES cells	Can make virtually any tissue	Allogeneic only
	Some tissues "easy" to generate	Teratoma formation
	Can be propagated indefinitely	Some tissue difficult to generate
	Amenable to genetic manipulation	Ethical issues
Adult stem cells	Autologous	Most have limited self-renewal
	Many types and sources	Differentiation outside lineage
	Not tumourigenic	Autologous
	Default differentiation	
	Amenable to gene transfer	
	Potential delivery methods attar-ctive	
	No ethical issues	

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Р е з и м е

ТРАНСПЛАНТАЦИЈА НА МАТИЧНИ КЛЕТКИ – НОВИ ПРИСТАПИ НА ТРЕТМАН

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Истражувањето на матичните клетки сè уште претставува едно од најконтроверзните полиња на науката и денес, особено врз основа на клеточната пластичност и способноста за трансдиференцијација и де-диференцијација во различни ткива, како и клиничката апликација на овој научен концепт. Матичните клетки со потекло од коскениот мозок, периферната крв или папочната врвца се тераписки избор за многу хематолошки малигноми, како дел од етаблираните тераписки процедури (алогена, автологна, сингена матично-клеточна трансплантација). Но, најновите клинички податоци ја потенцираат улогата на матичните клетки во терапија на други, нехематолошки, дегенеративни, кардиоваскуларни и автоимуни болести. Искуството со матично-клеточната трансплантација кај хематолошки малигни болести на Клиниката за хематологија во Скопје започнува од септември 2000 година. До сега се трансплантирани 130 пациенти, од кои 87 автологни и 43 алогени (од ХЛА – идентичен сроден дарител) трансплантации. Охрабрувачки резултати за примената на матичните клетки кај други заболувања доаѓаат од Клиниката за кардиологија. Во соработка со нив извршени се 2 успешни интракоронарни апликации на матични клетки од коскена срцевина, кај пациенти со акутен миокарден инфаркт. За да се потврди терапискиот потенцијал на матичните клетки, сепак се потребни понатамошни иследувања во клинички рандомизирани студии.

Клучни зборови: трансплантација на матични клетки.

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