

Cell therapy in Brazil: time for reflection

Milton Artur Ruiz

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Cell therapy, known in the media and among laypeople as stem cell treatment, has been under debate on several totally different fronts. The main confusion, which still persists even though it has been about for many years, is related to the use of embryonic stem cells in experimental and pre-clinical studies; today this occurs in most countries^(1,2) but great difficulties exist in Brazil until now⁽³⁾. This issue was debated extensively for four years in the Brazilian society and in 2008 the Supreme Court legalized studies using human embryonic stem cells. Subsequently, this measure allowed the first line of human embryonic stem cells to be obtained in Brazil⁽⁴⁾. Notwithstanding the controversial source of the embryo, in its strict sense cell therapy is a medical procedure that is not new as it goes back centuries to the time when human and even animal blood first began to be used for therapeutic purposes. Landsteiner's discovery of the ABO blood group system in 1900, complemented by the Rh blood group system, paved the way for the incorporation of transfusion medicine in the medical practice⁽⁵⁾. Cell replacement therapy using red blood cells and blood components enabled the treatment of many diseases and allowed a leap in surgical techniques including solid organ transplants.

The fear of nuclear war and its foreseeable immediate and long-term consequences on human beings helped the progression of research which aimed to minimize the effects with the evolution of reparative cell therapy using bone marrow transplants, which are now called hematopoietic stem cell transplantation (HSCT). This procedure is today common practice. Hereditary and acquired hematologic diseases including onco-hematology, autoimmune and immunodeficiency diseases are on the list of indications for HSCT with this list still expanding⁽⁶⁾. At the start of this millennium, the studies and results of cell therapy in degenerative and chronic diseases, the emergence of the concepts of cellular plasticity⁽⁷⁻⁹⁾, transdifferentiation and fusion⁽¹⁰⁻¹²⁾, and the description of the paracrine effect of cells⁽¹³⁾, opened new perspectives for research in regenerative therapy using different sources of cells including the bone marrow, peripheral blood and umbilical cord blood. So began the era of regenerative cell therapy, a movement that has caught the imagination of the scientific, academic and lay communities with the idea of new approaches to treat incurable diseases and common diseases that lack good therapeutic options⁽¹⁴⁾. Auspicious results have been described using several experimental models including in myocardial infarction after the use of cell therapy in a small sample of patients⁽¹⁵⁾. The number of publications on the use of stem cells has been expanding geometrically and so publications in all areas of medicine are becoming commonplace.

The same has occurred in respect to heart disease in Brazil and after the publication of promising results in Chagasic cardiomyopathy⁽¹⁶⁾, a large double-blind, randomized clinical trial was designed involving 1200 patients with diverse heart diseases^(17,18).

Subsequently, after 2005 government resources are being allocated to research projects; the National Network of Cell Therapy was created resulting in the establishment of several cell therapy Centers (Figure 1)⁽¹⁹⁾. Investment by the Brazilian Government in the area of cell therapy is shown in Table 1.

Despite these advances, several questions remain unanswered and the pressure of the community continues in light of the positive results that have been observed in different diseases⁽²⁰⁻²⁵⁾. These results do not go unnoticed in the electronic communication age; they quickly become common knowledge. This issue was reviewed and discussed in presentations on the theme during the congress of the *Sociedade Brasileira de Transplante de Medula Óssea* recently held in São Paulo. Among the topics presented, the potential of using mesenchymal stem cells (MST) was debated with their possible use in patients with graft-versus-host disease (GVHD) being stressed. This common adverse reaction after allogeneic HSCT is frequently difficult to control and so the use of MST is indicated in these situations. In Brazil the use of MST is restricted to patients enrolled in clinical trials, which makes it difficult for centers around the country, that are both competent and technically prepared, to offer this type of therapy to a larger number of patients⁽²⁶⁾. The compassionate use of MST in these cases, when necessary, is based on the data available in the medical literature. This topic has been discussed by Medical and Research Ethics Committees with great repercussions; as in countless other

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Corresponding author:

Milton Artur Ruiz
Rua Catarina Nucci Parise, 760,
Jardim Vivendas
15090-470 São José do Rio Preto, SP, Brazil
milruiz@yahoo.com.br

www.rbhh.org or www.scielo.br/rbhh

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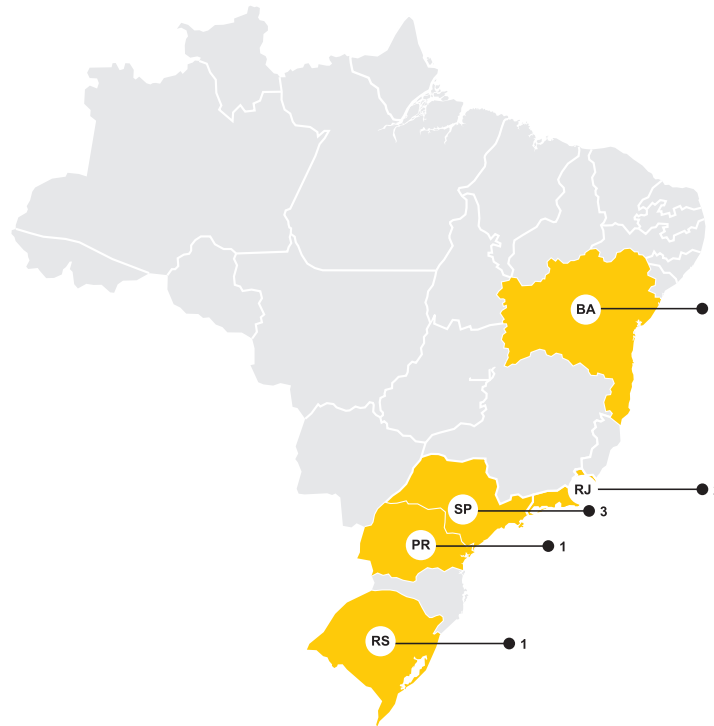


Figure 1 – Number of new cell therapy centers by state established after the creation of the National Network of Cell Therapy. Adapted from Mendez-Otero et al.⁽¹⁹⁾

BA: Bahia; RJ: Rio de Janeiro; SP: São Paulo; PR: Paraná; RS: Rio Grande do Sul

Table 1 - Funding Research for Stem Cell Therapy in Brazil

Grant	Amount (million US\$)	Projects
Miheart trial 2005	7.5	5
Requests for applications - 2005	5.8	45
Requests for applications - 2008	6.4	51
Cell Technology Centers 2008	22.7	8
Cell Therapy Network 2008	1.4	1
Brazil/Argentina	8.0	10
Requests for applications - 2012	5.0	30
Total	56.8	150

*DECIT - Prof. Antonio Carlos Campos de Carvalho

situations involving clinical or surgical procedures, cell therapy cannot be postponed at the expense of the patients' health. In Brazil there is a legal inadequacy in respect to compassionate treatment. And do not forget that the patients cannot wait^(23,26-28).

Cell therapy has flourished in respect to heart diseases in experimental studies on acute myocardial infarction. Soon clinical trials and case reports related to other heart diseases proved the benefits of the procedure. However ten years after the first reports there are still uncertainties about cell therapy^(29,30). Doubts related to cell therapy also extrapolate to the clinical parameters employed in previous studies. These include the use of the left ventricle ejection fraction as a clinical outcome as in many studies. Even without improvements in this parameter being observed, increases in survival and quality of life in many patients subjected to this procedure were

demonstrated. The review presented at the congress makes us reflect on the interpretation of results obtained using cell therapy in heart disease. The benefits of the use of cell therapy in the treatment of autoimmune, central nervous system and ophthalmological diseases and for orthopedic complications among others were also demonstrated during the scientific event thereby proving the importance of cell therapy as a new modality of therapy.

In conclusion, cell therapy has proven to be safe and effective in many situations, in particular in peripheral arterial diseases when there is a risk of amputation⁽²³⁾. This latter example makes us reflect on the current status of the treatment of diverse diseases in which cell therapy may play a leading or supporting role. This procedure remains crucial to relieve the suffering and benefit patients for whom there is no therapeutic option.

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