Transfusion and Apheresis Science xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

Emerging stem cell based strategies for treatment of childhood diseases

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ARTICLE INFO

Keywords:
Stem cells
Cell therapy
Adoptive therapy
Regenerative medicine
Research translation
Regulation
Ethics

ABSTRACT

Cell therapy is an important regenerative medicine approach, in which either differentiated cells or stem cells capable of differentiation are transplanted into an individual with the objective of yielding specific cell types in the damaged tissue and consequently restoring its function. The most successful example of cell therapy is hematopoietic stem cell transplantation, leading to regeneration of patient's blood cells, now a widely established procedure for many hematopoietic diseases. Development of cellular therapies for other tissues then followed in the footsteps of the hematopoietic experience. Nowadays, there are numerous ongoing clinical trials using various types of stem cells and some of them become approved cell-based products for use by patients.

The aim of this review is to highlight some of advances and challenges of cell-based therapies including:

- New trends in HSCT.
- Clinical applications of new biopharmaceuticals and cell sources.
- New frontiers in regenerative and gene therapies.
- Broadening perspectives for adoptive immunotherapy.
- Collaboration between medical science, health care providers, governing bodies and biopharmaceutical industry.
- Challenging global issues; accessibility to effective therapy, concerted effort to coordinate regulation processes, ethical concerns and financial costs.
- Future dynamics of regenerative medicine including ethical, financial and global issues associated with these developments.

1. Introduction

Advances in cell and gene therapy are opening up new avenues for regenerative medicine. New cell sources, developments in cell generation and reprogramming and new platform technologies are opening up new avenues for regenerative medicine. Human mesenchymal and induced pluripotent stem cells are promising sources of cells for future therapeutic uses. The safe engineering and engraftment of these cells are the keys to treating a vast spectrum of genetic and acquired disorders that affect various tissues. Emerging cellular therapies are changing treatment models and dynamics of relationships between patients, health care providers, regulatory agencies and biopharmaceutical companies. Implementation of innovative computational programs for assembling clinical data and generation of risk-benefit profiles to gather compelling evidence that is based on sound science would expedite licensure and ultimate safe and effective stem cell based therapies availability to patients in need.

2. New trends in hematopoietic stem cell transplantation (HSCT)

Hematopoietic stem cell transplantation (HSCT) is most established and extensively used stem cell therapy in children and adults. It is the only curative therapy for many inherited or acquired malignant and nonmalignant disorders. Once used as a last-resort therapy, it is now recognized as a standard of care. More than 70,000 hematopoietic cell transplants are currently performed each year, and this trend continues to increase every year. Expansion in utilization of marrow, cord and peripheral blood stem cell sources, novel transplant methods, and sophisticated supportive care has simultaneously made giant strides toward improving safety and efficacy of this cell therapy. Post HSCT complications resulting from conditioning and immunosuppressive regimens such as graft rejection (GL), graft versus host disease (GVHD)

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https://doi.org/10.1016/j.transci.2018.05.011

and infections are better combated in this modern era of transplant, with decreased late effects and better survival.

There have been dramatic improvements over the past two decades that have enhanced HSCT efficacy and improved patient overall survival. Greater donor options and better control of regimen-related toxicities, graft-versus-host disease and infections significantly led to increase in the utilization of this procedure. Many challenges remain, including prevention as well as treatment of disease relapse and prediction of severity or treatment outcome of GVHD. Currently, research studies are conducted to evaluate the new diagnostic, prognostic and therapeutic approaches. These studies include a broad range of important topics in HSCT, from the evaluation of reduced intensity conditioning regimens, use of different stem cell sources, use of modified cells, preventive cell therapies for acute and chronic GVHD, gene and regenerative cell therapies. Progress in implementation of the clinical applications from these studies has been accomplished to a concerted effort of researchers, care providers, biopharmaceutical companies and artificial intelligence.

3. Haploidentical HSCT sources

Only 25% of individuals have an HLA-identical sibling who could serve as donor of stem cells derived from bone marrow, peripheral blood or umbilical cord blood. Alternative stem cell sources are matched unrelated volunteers, unrelated umbilical cord blood, and HLA haplotype mismatched (“haploidentical”) family members. HSCT from these sources carried increased risk of the morbidity resulting from graft failure (GF), GVHD, veno-occlusive disease, and infections [1]. Haploidentical (Haplo-HSC) transplantation protocols that were implemented in 1990s used ex-vivo manipulated grafts to deplete T-cells. Depletion of T-cells was associated with slow post transplant immune reconstitution and led to rejection or GVHD. More recent transplantation protocols use non-manipulated Haplo-HSC) grafts, which is combined with enhanced post transplant immunosuppression, to help prevent GVHD (combined with new strategies to attenuate/modulate donor T-cell alloreactivity). These include post transplant high-dose cyclophosphamide, in-vivo T-cell depletion of recombinant granulocyte growth factor (GCS-F) mobilized peripheral blood stem cell grafts, or GCS-F primed hematopoietic grafts combined with in-vivo T-cell depletion. Non-manipulated hematopoietic transplants relay on the high T-cell content of the graft for engraftment and immune reconstitution.

Additionally, further advances were made to enhance the effectiveness of T cell–depleted Haplo-HSCTs by transferring donor T-cell immunity, which will be discussed in the section on Adoptive Immunotherapy.

The resurgence Haplo-HSC transplantation over the last decade is one of the most important advances in the field of hematopoietic stem cell transplantation. Non-manipulated grafts, without ex vivo T cell depletion substantially extended the use of Haplo-HSCT with results that compare to those of matched transplantation. Haplo- HSCT that does not need the specialized laboratory and personnel has provided additional curative options for pediatric patients with malignant and non-malignant diseases, who have no suitable related or unrelated donor. Further improvements to decrease the rates of GF and GVHD, enhance immune recovery, reduce serious infections and develop effective prevention and management strategies of relapse will enable Haplo- HSCT to become an established therapy for pediatric patients with non-malignant disorders such as primary immune deficiencies, inborn errors of metabolism, bone marrow failure syndromes, thalassemia and sickle cell disease as well as for a variety of malignant disorders. In addition, future clinical trials with larger number of pediatric patients will help to establish the most effective conditioning regimen, the best donor source, and the optimal regulation of donor T cells, thus maximizing the outcome of this newer approach.

4. Mesenchymal cells

Other approaches to autologous and allogeneic treatments involve the cells that have potentials to form all different cell types in the body and offer an exciting opportunity to develop new treatment strategies. In the last decade, regenerative medicine has become an emerging field, which focuses on repair, replacement, or regeneration of cells, tissues and the entire organs.

Experimental and early clinical data suggest that, due to several unique properties, mesenchymal stem cells (MSCs) may be more effective than other cell types in therapy of diseases that are difficult to treat or untreatable. MSCs are also known as mesenchymal stromal stem cells, multipotent adult progenitor cells, medicinal signaling cells, and mesenchymal progenitor cells [2].

MSCs are self-renewing and multi-potent cells distinguishable by CD73 and CD90 surface markers, moderate HLA class I expression and absence of HLA class II expression. They exhibit immunosuppressive properties by down regulating pro-inflammatory cells and production of pro-inflammatory cytokines. Rather than being conventional HSCs that differentiate into effector cells, which directly trigger the regeneration of damaged tissues, they appear to act as governing cells that secrete mediators and/or directly interact with other cells and subsequently stimulate or recruit those cells to perform regenerative actions. These particulars make them unique and promising therapeutic agents, in the field of stem cell research and therapy.

Among the sources of MSCs, bone marrow and adipose tissue have been the most commonly studied to date. However, MSCs are also found in umbilical cord blood, dental pulp, synovial fluid, amniotic fluid, and urine. Most of clinical applications of MSC would require a large number of cells for transplantation. Therefore, abundance, easiness of isolation, and proliferative potential may be deciding factors while choosing a source of MSC. Amounts of MSCs, which can be obtained from the bone marrow are limited to 0.001–0.01% of its mononuclear cell content, while 1 g of adipose tissue yields approximately 5×10^3, which is 500-fold greater than in the bone marrow. Researchers from Lund University in Sweden demonstrated that large volumes of amniotic fluid with high yields of MSCs having high expansion capacities and features similar can be collected in less than 3 are less exposed to mutagens than adult MSC’s capable to differentiate towards various cell lineages and are easily reprogrammable. They represent a valuable material for induced pluripotential stem (IPS) cell generation that could be used for disease modeling, drug discovery and testing and regenerative medicine. Lastly, these cells could be banked and used for either allogeneic or autologous transplantation.

Umbilical cord Wharton's jelly (WJ)-derived MSCs has recently been gaining significant attention, owing to some of their unique properties and their feasibility as an allogeneic source of regenerative cell. The isolation efficiency from Wharton’s jelly ranges from 1 to 5×10^4 cells/cm of umbilical cord. Side-by-side comparison of MSC from bone marrow, adipose tissue and Wharton’s jelly demonstrated that WJ-MSCs have the highest proliferative capacity among tested cell types.

Although MSCs from various sources share several common characteristics, they also exhibit several important differences. These variations may reflect, in part, specific regional properties of the niches from which the cells originate. As described above, AF and WJ-MSCs express the highest proliferative potential. Only adipose tissue-MSCs are able to produce collagen. Moreover, morphological and functional features of MSCs are susceptible to variations across isolation protocols and cell culture conditions. These observations suggest that careful preparation of manufacturing protocols will be necessary for the most efficient use of MSCs in future clinical trials.

Owing to their ease of isolation and culture as well as their secretory and immunomodulatory abilities, MSCs are the most promising option in the field of cell-based therapies. One example is the treatment of GVHD, which will be discussed in details under the topic of adoptive immunotherapy. Another clinical application is the regenerative