Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Juniper Publishers
key to the Researchers

Editorial
Volume 28 Issue 2 - February 2025
DOI: 10.19080/CTOIJ.2025.28.556234

Cancer Ther Oncol Int J

Therapeutic Insights on Mesenchymal Stromal Cell Therapy

Nahla A. M. Hamed*

Professor of Clinical Hematology, Faculty of Medicine, Alexandria University, Egypt

Submission: January 19, 2025; **Published:** February 11, 2025

Corresponding author: Nahla A. M. Hamed, Professor of Clinical Hematology, Faculty of Medicine, Alexandria University, Egypt

Abstract

There are growing interest on the use of mesenchymal stromal cells (MSCs) as a therapeutic tool in hematopoietic stem cell transplantation (HSCT), as well as in regenerative cell therapy. Phase I/II clinical trials address the feasibility and safety of MSCs infusions especially in the acute graft-versus-host disease (aGvHD) treatment. No major infusional toxicity was reported after MSCs administration. Promising preliminary results in terms of efficacy have been reported in some clinical trials. FDA-approved the first MSC therapy (Ryoncil, remestemcel-L-rknd) isolated from allogeneic bone marrow of healthy adult humans. Ryoncil is indicated for the treatment of steroid refractory - aGvHD complicating allogeneic HSCT in pediatric patients 2 months of age and older. MSCs have been also successfully used to repair tissue injury in auto-immune disorders, for e.g. refractory Crohn's disease, Crohn's fistulas and lupus.

Keywords: Mesenchymal stromal cells; Ryoncil; Steroid-refractory; Regenerative medicine; Solid organ transplantation

Abbreviations: MSCs: Mesenchymal stromal cells; MHC: Major histocompatibility complex; SOT: Solid organ transplantation; DC: Dendritic cell; RC: Regenerative cell; SR- aGvHD: Steroid -refractory acute graft-versus-host disease

Introduction

Mesenchymal stromal cells (MSCs) are a subpopulation of multipotent cell characterized by their fibroblast-like appearance, and colony forming unit capacity. MSCs have the capacity to differentiate in vivo and in vitro into numerous other types of cells such as adipocytes, osteoblasts and chondrocytes. MSCs are relatively easy to isolate (from a number of tissues), culture, and expand. They rapidly adhere to tissue culture plastic [1]. The main criterion for the identification of MSCs is their ability to grow in vitro as a population adhering to the substrate [2].

Characterization of MSCs

Characteristically, these cells phenotypically express CD73, CD90, CD105 surface antigens (in more than 95%) and lack expression of CD4, CD11b, CD14, CD19, CD34, CD79a, or HLA class II. Additional markers such as vascular cell adhesion molecule (VCAM/CD106), melanoma cell adhesion molecule (MCAM/CD146), and stromal-1 antigen (STRO-1) were also identified [2].

Bone marrow was the first source from which MSCs were isolated. MSCs can be isolated in different developmental stages (fetal, young, adult and older population). Fetal sources of MSCs include umbilical cord, umbilical cord blood, placenta, chorionic villi and amniotic fluid. Adult sources of MSCs include tissues and secretions such as adipose tissue, dental pulp, peripheral blood, menstrual blood, endometrium, mother's milk and yellow ligament. MSCs from various sources have similar properties [2]. MSCs derived from different tissues have different differentiation capacity even when cultured in the same culture condition. The number of bone marrow derived-MSCs dramatically decreases with age, while fetal MSCs have a higher proliferative capacity [3]. The differentiation of MSC lineage is regulated by many signaling pathways as well as by a variety of microRNAs, transcription factors, chemical factors, biological factors and physical factors. These signaling pathways include fibroblast growth factor, transforming growth factor-beta /bone morphogenic protein signaling, Notch signaling and Hedgehogs signaling, etc. These pathways can be simultaneously activated by stimuli from specific microenvironments [3].

Role of MSCs

MSCs have various roles in the body. In addition to their key role in regulating hematopoiesis, MSCs have the following properties [4].

Immunomodulatory properties of MSCs

MSCs have low immunogenicity and create a suppressive microenvironment. Culture-expanded MSCs usually express low levels of MHC class I, and no MHC class II or costimulatory molecules. However, MSCs act as antigen-presenting cells with upregulation of both MHC-I and MHC-II antigens following exposure to interferon-γ [5]. MSCs modulate the immune responses against auto- and alloantigens. They actively interact with components of the innate immune response and with cells of the adaptive immune system [4]. MSCs have inhibitory functions on various immune cells [5].

MSCs and components of the immune system

Macrophages: MSCs influence macrophage differentiation, with a preferential shift towards an M2 phenotype (anti-inflammatory immunosuppressive).

NK-cells: MSCs inhibit proliferation and cytotoxicity of NK cells. Conversely, MSCs secrete ligands activating NK cell receptors and express low levels of MHC molecules class I which make them susceptible to NK cell lysis.

DCs: MSCs can affect activation, differentiation, maturation, and antigen presentation of the DCs. MSCs may favor reprogramming of mature stimulatory DC into a more protolerogenic lower immunogenicity DC phenotype, characterized by a higher interleukin (IL)-10 secretion, lower IL-12 production, their ability to inhibit proliferation and function of allo-reactive T-cells and to generate allo-antigen specific Treg.

T-cells: MSCs suppress T-cell proliferation triggered by allogeneic, mitogenic, or antigen-specific stimuli; impair activation and differentiation of T-cells; decrease T-cell cytotoxicity; regulate Th1/Th2 balance and favor the differentiation of CD4+ T-cell subsets with a Treg phenotype. MSCs do not activate allogeneic lymphocytes [5].

B-cells: MSCs inhibit B-cell proliferation, especially through their arrest in G0/G1 phases [5].

Tissue repair effects of MSCs

MSCs are likely to contribute to repair of tissues through several mechanisms, such as (i) reducing apoptosis, by preventing oxidative stress and via activation of protein kinase B pathway (ii) promoting angiogenesis by MSC paracrine factors, especially vascular endothelial growth factor, angopoietin-1, tumor growth factor-β, hepatocyte growth factor, and stromal cell–derived factor 1-α and (iii) enhancing survival, migration and proliferation of endogenous cells [3]. MSCs have a predominant paracrine role in establishing a regenerative microenvironment through their interactions with many cells, including fibroblasts, endothelial cells, epithelial cells, and macrophages [3]. In addition, MSCs have the ability to home to inflamed sites, where they may promote repair of injured tissues through their immunoregulatory properties [4].

Anti-inflammatory effects of MSCs

MSCs display both pro-inflammatory and anti-inflammatory effects [4]. Their anti-inflammatory effects results from the production of anti-inflammatory cytokines, such as IL-10 and tumor necrosis factor-α–induced protein-6 and a reduction of proinflammatory molecules, such as IL-1α and interferon-γ. In addition, MSC-derived extracellular vesicles (EVs) may help rapid restoration of ATP supply by transferring mitochondria into the damaged cells following ischemia/reperfusion (I/R) injury associated with solid organ transplantation (SOT) [5].

Clinical challenges and therapeutic opportunities of MSCs

i. MSCs have been tried in the setting of hematopoietic stem cell transplantation (HSCT) to facilitate engraftment of hematopoietic stem cells (HSCs) after HLA-haploidentical, T cell-depleted allografts and umbilical cord blood transplantation, to prevent graft failure, as well as to treat severe steroid resistant - acute graft-versus-host disease (GvHD) [4].

ii. MSC treatment has been successfully used as a therapeutic tool in regenerative cell (RC) therapy. MSCs have been employed to repair tissue injury in autoimmune disorders, for e.g. refractory Crohn's disease, Crohn's fistulas [4] and lupus [3]. The therapeutic potential of MSCs include also other diseases such as myocardial infarction, liver cirrhosis, multiple sclerosis, stroke, diabetes, lung injury, and cancer [3].

iii. Drug-loaded MSCs, genetically modified MSCs and MSC-derived EVs are attractive cellular carriers to deliver drugs and therapeutic cytokines to the site of inflammation or injury due to their inherent homing ability [3].

iv. There is a growing interest in the use of MSCs as an innovative cell-based approach in SOT. MSCs administration in SOT mostly concern with (i) preventing or treating acute rejection or interstitial fibrosis and tubular atrophy, (ii) attenuating the inevitable ischemia/reperfusion (I/R) injury associated with SOT, (iii) minimizing the adverse effects of immunosuppressive drugs and (iv) inducing long-term graft tolerance. These expectations arise from the results of a significant number of preclinical experimental studies which demonstrate the ability of MSCs to inhibit T-cell proliferation, DC maturation and to induce regulatory T-cell expansion [5].

How to cite this article: Nahla A. M. Hamed. Therapeutic Insights on Mesenchymal Stromal Cell Therapy. Canc Therapy & Oncol Int J. 2025; 28(2): 556234. DOI: 10.19080/CTOIJ.2025.28.556234

MSCs and solid organ transplantation tolerance

The difference in MSCs localization dictates the immunomodulatory properties of MSCs. Timing of MSCs infusion may impact their localization. In rats, infusion of MSCs for four days before heart transplantation induced transplant tolerance and acceptance of the transplanted heart while, rejection of the transplanted heart was observed when MSCs infusion was performed three days after heart transplantation. Post-transplant MSCs infusion leads to migration of MSCs to the transplanted organ rather than to the secondary lymphoid organs resulting in stimulation of proinflammatory phenotype characterized by neutrophil infiltration, complement deposition and graft rejection. Furthermore, post-transplant MSCs infusion decreases the immunomodulatory ability of MSCs i.e. MSCs are unable to convert conventional T cells to immunoregulatory Treg population and has reduced inhibitory effect on DC maturation. However, pre-transplant MSCs infusion leads to the localization of MSCs in the secondary lymphoid organs promoting the protolerogenic effects and the prolonged graft survival [5].

MSCs and minimization of immunosuppressive drugs in solid organ transplantation

The development of a protolerogenic environment, the complement of the tolerogenic potential of induction therapies for prevention of acute graft rejection as well as the repair of chronic allograft damage by MSC therapy has enabled its use in the minimization of induction and maintenance immunosuppressive drugs in kidney transplantation [2]. The attenuation of acute kidney injury could result from MSC-mediated modulation of renal metabolism and prevention of lipotoxicity [5]. Identification of biomarkers of response to MSC therapy could aid in selection of patients who are amenable to safe immunosuppressive drug withdrawal [5].

Efficacy and limitation of MSCs

Phase I/II clinical trials especially in the treatment of acute GvHD do not report major toxicity after administration of MSCs infusion and address the safety and feasibility of MSCs infusion. Preliminary results have reported their efficacy in some clinical trials [4]. Factors posing a barrier in MSC-based therapy are the retention and survival of MSCs. Long-term transplanted MSCs have very low levels at best. Less than 5% of the injected MSCs cells remained at the injection site for several hours after their local administration due to their rejection by the recipient's immune system, or failure to survive and transplant after intravenous injection. It appears that MSCs exert their function in damaged tissues through a brief "hit and run" mechanism, rather than through continuous implantation. MSCs encapsulation by biomaterials can improve their retention and survival ability in vitro, but further studies are still needed to investigate their effects in vivo [3]. Another factor thought to influence MSC immunomodulatory properties is the mode of administration. Different modes of administration can produce different pharmacokinetics. Also, the microenvironment to which MSCs are exposed have a role. Variability in cell culture and expansion conditions, tissue origin, activation signals, cryopreservation and the MSC-to-immune cell ratio may result in heterogeneous outcomes in MSC-based therapy [5]. Cryopreserved MSCs have decreased ability to suppress immunosuppression and inhibit T cell proliferation [3]. Moreover, MSC-derived EVs have shown that they retain the biological characteristics of their parental MSCs and have similar therapeutic effects in some animal models. MSC-derived EVs have a lower yield so a larger dose is required [5].

MSCs as a promising candidate in medicine

i. Alofisel is an allogeneic stem cell therapy approved by the European Union for treatment of Crohn's disease (CD) with refractory, draining, and complex perianal fistulas in adult patients. It showed marked remission compared to placebo, with a higher remission rate at 52 weeks of follow-up [3].

ii. Ryoncil (remestemcel-L-rknd) is the first FDA-approved MSC therapy isolated from allogeneic bone marrow of healthy adult human. It is indicated for the treatment of SR-aGvHD) complicating allogeneic hematopoietic stem cell transplantation (allo-HSCT) in pediatric patients 2 months of age and older. Ryoncil was evaluated in a study on 54 pediatric participants with SR-aGvHD post allo-HSCT. Sixteen participants (30%) had a complete response to treatment 28 days after receiving Ryoncil, while 22 participants (41%) had a partial response. The most common adverse reactions in the study were infections, fever, hemorrhage, edema, abdominal pain and hypertension. Complications such as hypersensitivity and acute infusion reactions, transmission of infectious disease and ectopic tissue formation may occur following Ryoncil treatment. Ryoncil is contraindicated in patients with known hypersensitivity to dimethyl sulfoxide or porcine and bovine proteins [6].

Conclusion

In recent years, MSCs have gained attention due to their desirable properties including immune regulation, homing ability and tumor tropism. MSC therapy is considered promising candidate for cancer therapy, tissue regeneration, inflammatory and other fields. The therapeutic potential of MSCs is being investigated in genetic engineering and drug delivery due to their inherent homing ability.

References

1. English K, Wood KJ. Mesenchymal stromal cells in transplantation rejection and tolerance. Cold Spring Harb Perspect Med 2013;3:a015560.

2. Deo D, Marchioni M, Rao P. Mesenchymal stem/stromal cells in organ transplantation. Pharmaceutics 2022;14:791.

How to cite this article: Nahla A. M. Hamed. Therapeutic Insights on Mesenchymal Stromal Cell Therapy. Canc Therapy & Oncol Int J. 2025; 28(2): 556234. DOI: 10.19080/CTOIJ.2025.28.556234

3. Mei R, Wan Z, Yang C, Shen X, Wang R, Zhang H, Yang R, Li J, Song Y, Su H. Advances and clinical challenges of mesenchymal stem cell therapy. Front Immunol 2024;15:1421854.
4. Bernardo ME, Fibbe WE. Mesenchymal stromal cells and hematopoietic stem cell transplantation. Immunol Lett 2015;168(2):215-21.
5. Vandermeulen M, Erpicum P, Weekers L, Briquet A, Lechanteur C, Detry O, et al. Mesenchymal stromal cells in solid organ transplantation. Transplantation 2020;104: 923–36.
6. FDA news release. FDA approves first mesenchymal stromal cell therapy to treat steroid-refractory acute graft-versus-host Disease. Released 18 December, 2024.
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann T, et al. (2020) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 29: 372: n71.
8. Moons KGM, Wolff RF, Riley RD, Whiting PF, Westwood M, et al. (2019) PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. Ann Intern Med 170(1): W1-W33.
9. Kim HM, Lee SJ, Park SJ, Choi IY, Hong SH (2021) Machine learning approach to predict the probability of recurrence of renal cell carcinoma after surgery: prediction model development study. JMIR Med Inform 9(3): 1-12.
10. Kim HM, Byun SS, Kim JK, Jeong CW, Kwak C, et al. (2022) Machine learning-based prediction model for late recurrence after surgery in patients with renal cell carcinoma. BMC Med Inform Decis Mak 22(1): 241.
11. Khene ZE, Bigot P, Doumerc N, Ouzaid I, Boissier R, et al. (2023) Application of Machine Learning Models to Predict Recurrence After Surgical Resection of Nonmetastatic Renal Cell Carcinoma. Eur Urol Oncol 6(3): 323-330.
12. Guo Y, Braga L, Kapoor A (2019) Machine learning to predict recurrence of localized renal cell carcinoma. The Journal of Urology.
13. Shu J, Wen D, Xi Y, Xia Y, Cai Z, et al. (2019) Clear cell renal cell carcinoma: Machine learning-based computed tomography radiomics analysis for the prediction of WHO/ISUP grade. Eur J Radiol 121: 108738.
14. Sun X, Liu L, Xu K, Li W, Huo Z, et al. (2019) Prediction of ISUP grading of clear cell renal cell carcinoma using support vector machine model based on CT images. Medicine (Baltimore) 98(14): e15022.
15. Bektas CT, Kocak B, Yardimci AH, Turkcanoglu MH, Yucetas U, et al. (2019) Clear Cell Renal Cell Carcinoma: Machine Learning-Based Quantitative Computed Tomography Texture Analysis for Prediction of Fuhrman Nuclear Grade. Eur Radiol 29(3): 1153-1163.
16. Nazari M, Shiri I, Hajianfar G, Oveisi N, Abdollahi H, et al. (2020) Noninvasive Fuhrman grading of clear cell renal cell carcinoma using computed tomography radiomic features and machine learning. Radiol Med 125(8): 754-762.
17. Li Q, Liu YJ, Dong D, Bai X, Huang QB, et al. (2020) Multiparametric MRI Radiomic Model for Preoperative Predicting WHO/ISUP Nuclear Grade of Clear Cell Renal Cell Carcinoma. J Magn Reson Imaging 52(5): 1557-1566.
18. Wen R, Huang J, Gao RZ, Wan D, Qin H, et al. (2021) CT Radiomics for the Prediction of Synchronous Distant Metastasis in Clear Cell Renal Cell Carcinoma. J Comput Assist Tomogr 45(5): 696-703.
19. Bai X, Huang Q, Zuo P, Zhang X, Yuan J, et al. (2021) MRI radiomics-based nomogram for individualised prediction of synchronous distant metastasis in patients with clear cell renal cell carcinoma. Eur Radiol 31(2): 1029-1042.
20. Bhalla S, Chaudhary K, Kumar R, Sehgal M, Kaur H, et al. (2017) Gene expression-based biomarkers for discriminating early and late stage of clear cell renal cancer. Sci Rep 7: 44997.
21. Barkan E, Porta C, Rabinovici-Cohen S, Tibollo V, Quaglini S, et al. (2023) Artificial intelligence-based prediction of overall survival in metastatic renal cell carcinoma. Front Oncol 13: 1021684.
22. Maier-Hein L, Eisenmann M, Reinke A, Onogur S, Stankovic M, et al. (2018) Why rankings of biomedical image analysis competitions should be interpreted with care. Nat Commun 9(1): 5217.

DOI: 10.19080/CTOIJ.2025.28.556234

How to cite this article: Nahla A. M. Hamed. Therapeutic Insights on Mesenchymal Stromal Cell Therapy. Canc Therapy & Oncol Int J. 2025; 28(2): 556234. DOI: 10.19080/CTOIJ.2025.28.556234