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Stem Cell Therapy from Clinical Trial to Clinical Practice

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ABSTRACT

Stem cell therapy is great alternative for disorders of the CNS, which are associated with limited regenerative potential. Neurological disorders are distinct and generally not understood clearly. Stem cell therapy may reduce the anxiety of these disorders. Stem cell therapies provide promising results to Parkinson's disease, Huntington's disease, stroke, traumatic brain injury, amyotrophic lateral sclerosis, multiple sclerosis, and multiple system atrophy, The stem cell transplantation increases with excellent results in animal clinical trials. However, human clinical trials revealed the probable severe side effects. The treatment of individual neurological disorders will be associated with different pathophysiological conditions. Hence, transplantation therapy must be executed under optimal conditions with essential liability. The hypothesis that brain cells can never re-establish has been demanding by the discovery of newly formed neurons in the human hippocampus or the migration of stem cells in the brain in animal models. These observations bring about hope for regeneration of neuronal diseases by using exogenous stem cell sources to restore the stem cells in the brain. Human pluripotent stem cells such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) provide unprecedented opportunities for cell therapies against intractable diseases and injuries. Both ESCs and iPSCs are used in clinical trials.

INTRODUCTION

Fortunately, the prospect of regenerative medicine as an alternative to conventional drug-based therapies is becoming a tangible reality by the day owing to the vigorous commitment of the research communities in studying the potential applications across a wide range of diseases like neurodegenerative diseases and diabetes, among many others (1).

Stem cell therapies to patients become a hope to treat a wide range of vexing diseases (2).

Exponential advancement in clinical trials revolving around stem cell-based therapies (3).

For example, a case of Epidermolysis Bullosa manifested signs of skin recovery after treatment with keratinocyte cultures of epidermal stem cells (4).

Also, a major improvement in eyesight of patients suffering from macular degeneration was reported after transplantation of patient-derived induced pluripotent stem cells (iPSCs) that were induced to differentiate into pigment epithelial cells of the retina (5).

(MSC)-based therapies in Europe have turned the wheel of regenerative medicine to become prominent treatment modalities. Cell-based therapy, especially stem cells, provides new hope for patients suffering from incurable diseases where treatment approaches focus on management of the disease, not treat it. (6,7)

Stem cell-based therapy is an important branch of regenerative medicine with the ultimate goal of enhancing the body repair machinery via stimulation, and modulation (8).

Stem cell therapy is a novel therapeutic approach that utilizes the unique properties of stem cells, including self-renewal and differentiation, to regenerate damaged cells and tissues in the human body or replace these cells with new, healthy and fully functional cells by delivering exogenous cells into a patient (9).

Stem cells for cell-based therapy can be of (1) autologous, also known as self-to-self therapy, an approach using the patient's own cells, and (2) allogeneic sources, which use cells from a healthy donor for the treatment (10).

The term "stem cell" were first used by the eminent German biologist Ernst Haeckel to describe the properties of fertilized egg to give rise to all cells of the organism in 1868 (11).

The clinical applications of stem cell-based therapies for heart diseases have been recently discussed comprehensively in the reviews (12,13).

The G I T is protected from adverse substances in the gut environment by a single layer of epithelial cells that are known to have great regenerative ability in response to injuries. (14)

Research has been conducted on the effects of stem cells on animal models of brain degeneration, such as in Parkinson's disease, Amyotrophic lateral sclerosis, and Alzheimer's disease(15).

Facing a large number of patients with migraines who have not responded to a variety of treatments and following the publication of 4 case reports of refractory headaches being successfully treated with stem cells (16).

Preliminary studies related to multiple sclerosis have been conducted, and a 2020 phase 2 trial found significantly improved outcomes for mesenchymal stem cell treated patients compared to those receiving a sham treatment.(17,18)

In January 2021 the FDA approved the first clinical trial for an investigational stem cell therapy to restore lost brain cells in people with advanced Parkinson's disease (19).

Healthy adult brains contain neural stem cells, which divide to maintain general stem-cell numbers, or become progenitor cells.(20)

History

Historically, the first pluripotent cell lines to be generated were embryonic carcinoma (EC) cell lines established from human germ cell tumors and murine undifferentiated compartments (21).

Although EC cells are a powerful tool in vitro, these cells are not suitable for clinical applications due to their cancer-derived origin and aneuploidy genotype (22).

The first murine ESCs were established in 1981 based on the culture techniques obtained from EC research (23).

Murine ESCs are derived from the inner cell mass (ICM) of the pre-implantation blastocyst, a unique biological structure that contains outer trophoblast layers that give rise to the placenta and ICM (24).

In vivo, ESCs only exist for a short period during the embryo's development, and they can be isolated and maintained indefinitely in vitro in an undifferentiated state. The discovery of murine ESCs has dramatically changed the field of biomedical research and regenerative medicine over the last 40 years.(25)

What are stem cells?

Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. In addition, in many tissues they serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive.

Primitive Hematopoietic Stem Cells

Research on stem cells is advancing knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. This promising area of science is also leading scientists to investigate the possibility of cell-based therapies to treat disease, which is often referred to as regenerative medicine. Stem cells are one of the most fascinating areas of biology today. But like many expanding fields of scientific inquiry, research on stem cells raises scientific questions as rapidly as it generates new discoveries (26).

Stem cells and cell cycle control

With a few notable exceptions, our understanding of the mechanisms governing cell cycle regulation in SCs and the effect of mitotic control on SC development and biology currently canters on cues such as cytokine/growth factor-triggered signal transduction pathways and asymmetric distribution of intrinsic cell fate determinants. For the most part, the fascinating questions of how phenomena translate into distinct molecular signals and how those signals mesh with the intricacies of cell cycle phase and specific components of the cell cycle machinery have yet to be answered (27).

Safeguarding valuable biological stem cells to cure neurological diseases

The embryos used in these studies were created for infertility purposes through in vitro fertilization procedures and when they were no longer needed for that purpose, they were donated for research with the informed consent of the donor. Stem cells are important for living organisms for many reasons (28).

It has been hypothesized by scientists that stem cells may, at some point in the future, become the basis for treating diseases such as Parkinson's disease, diabetes, and heart disease. Scientists want to study stem cells in the laboratory so they can learn about their essential properties and what makes them different from specialized cell types (29).

Unique properties of stem cells

Stem cells differ from other kinds of cells in the body. All stem cells — regardless of their source — have three general properties: they are capable of dividing and renewing themselves for long periods; they are unspecialized; and they can give rise to specialized cell types.

Stem cell therapy comes to the rescue of many patients, says specialist

Mumbai-based NeuroGen Brain and Spine Institute has achieved a 90 percent success rate in treating "non-curable" neurological disorders with Stem Cell Therapy, said head of the Institute and pioneer in the therapy Alok Sharma.

Safeguarding a valuable biological resource': Know all about umbilical cord and stem cell banking in India

They can be used in transplantation procedures to replace damaged or diseased cells, stimulating the body's natural healing processes, said Dr. Pradeep Mahajan, regenerative medicine researcher and founder, StemRx BioScience Solutions – India (Indian express,01/07/2023).

Parkinson's disease

Parkinson's disease, Huntington's disease, stroke, traumatic brain injury, amyotrophic lateral sclerosis, multiple sclerosis, and multiple system atrophy, continue to pose a significant societal and economic burden (30,31).

Parkinson's disease (PD) is a very common neurodegenerative disorder that affects more than 2% of the population over 65 years of age. PD is caused by a progressive degeneration and loss of dopamine (DA)-producing neurons, which leads to tremor, rigidity, and hypokinesia (abnormally decreased mobility). It is thought that PD may be the first disease to be amenable to treatment using stem cell transplantation. Factors that support this notion include the knowledge of the specific cell type (DA neurons) needed to relieve the symptoms of the disease. In addition, several laboratories have been successful in developing methods to induce embryonic stem cells to differentiate into cells with many of the functions of DA neurons (32).

In a recent study, scientists directed mouse embryonic stem cells to differentiate into DA neurons by introducing the gene Nurr1. When transplanted into the brains of a rat model of PD, these stem cell-derived DA neurons reinnervated the brains of the rat Parkinson model, released dopamine and improved motor function. Regarding human stem cell therapy, scientists are developing a number of strategies for producing dopamine neurons from human stem cells in the laboratory for transplantation into humans with Parkinson's disease.

Stem cell therapy for neurological disorders

However, since they are located deep within the adult brain, NSCs are not accessible for harvesting and hence for autologous therapeutic applications. They are therefore procured from aborted foetuses and prepared for allogeneic transplantation purposes. (33)

With recent advances in our understanding of stem cell biology, it is possible to differentiate pluripotent stem cells (both ESCs and iPSCs) into neural progenitor or NSC-like cells for therapeutic purposes. Protocols for differentiating bone marrow-derived MSCs into NSC-like cells have also been developed and translated for clinical application in patients with multiple sclerosis (34).

Both forms of derivation (from foetal tissue and differentiated) are being investigated in clinical studies to treat several neurological conditions.

A database of registered clinical trials was created based on data outputs using the following search terms: ‘embryonic stem cells’, ‘induced pluripotent stem cells’, ‘neural stem cells’, ‘mesenchymal stem cells’, ‘mesenchymal stromal cells’, ‘bone marrow stromal cells’, ‘umbilical cord mesenchymal stem cells’, ‘adipose stem cells’, ‘adipose-derived regenerative cells’ and ‘stromal vascular fraction’. To capture trials using HSCs, we based our search on the use of ‘hematopoietic stem cells and ‘umbilical cord blood’ together with disease indications listed in one of our previous reports (35).

The stem cell transplant process

Identification of the appropriate type of transplantation

Autologous (from the patient), syngeneic (from an identical twin), or allogeneic (from a related, unrelated or cord blood donor).

- **Obtaining stem cells from the patient or a donor** —

- **Blood stem cells** are taken through a painless process called apheresis. Blood is taken from a vein and circulated through a machine that removes the stem cells and returns remaining blood and plasma back to the patient.

- **Bone marrow stem cells** are harvested from the donor in an operating room. Stem cells are collected through a needle placed in the soft center — or marrow — of the bone. The donor may feel some pain after this procedure.

- **Conditioning treatment** — administration of chemotherapy and/or radiation to the patient in order to destroy all of the diseased cells in the body and to create space in the bone marrow for the transplanted stem cells to populate.

- **Infusion of healthy stem cells into the patient** — a painless process in which stem cells are transplanted into the patient through intravenous (IV) infusion. Side effects from this procedure are rare.

- **Engraftment and recovery** — transplanted stem cells begin to grow and reproduce healthy blood cells. For bone marrow or blood stem cell transplant, engraftment takes between two and three weeks; for cord blood transplant, the process takes three to five weeks.

- **Post-transplant care** — Regular examinations to monitor allogeneic transplant patients for signs of graft vs. host disease (GVHD) and to watch autologous and allogeneic patients for immune system recovery, complications related to chemotherapy or radiation and cancer recurrence.

'Stem cell therapy a boon for patients'

Stem cells which have the ability to clone themselves indefinitely by cell division will be an effective alternative to transplantation of damaged body organs in future, said Dr.

G.Subrahmanyam, eminent cardiologist and Research Director in Narayana Medical Institutions, Nellore.

Stem Cell technology offers new hope for treating rare genetic disorders:

Stem cell technology has witnessed advancements that open new hopes for the treatment of rare genetic disorders which otherwise are largely undetected and also untreated. Recent research has shown exciting possibilities of having a direct intervention method for effective treatment, said Tata Institute for Genetics and Society (TIGS) Director Rakesh Mishra.

'Advances made in stem cell therapy in Asia far more than those made in U.S.'

Indigenously developed therapeutic modules for neurodevelopment disorders like autism have demonstrated a higher rate of recovery and improvement among sufferers, Nandini Gokulchandran, a Mumbai-based researcher in the field of stem cell therapy said that while the response rate for autism was as high as 91%, the recovery was significantly higher than expected in Down Syndrome, Cerebral palsy, intellectual disability, and spine injury.

Do stem cells grow better in space?

Scientists are researching whether stem cells grow faster in a zero-gravity environment by sending their own stem cells to space. Stem cell therapies could be used to treat a variety of illnesses in the future.

Stem cell therapy for spinal cord injury patients unethical, say experts

Stem cell therapy has potential to repair and regenerate the spinal nerves damaged in an injury. But has not been proven yet. Research in the field is mostly at experimental stage said Dr H S Chabra, chief of Indian spinal injuries Centre (ISIC), The times of India,2019.

Summary

Given the enormous potential of stem cells for the novel treatment of many of the major diseases that affect mankind, it is clearly imperative to go forward on all fronts; ES cells, umbilical cord blood, and adult sources of stem cells all have their admirers and detractors. In terms of adult stem cell plasticity, a more rigorous proof of clonogenicity and the function of apparently trans differentiated cells is probably required (36,37).

The 'gold standard' of CFU-S like activity of bone marrow cells in a new environment has only been convincingly demonstrated in one instance (38).

These are clearly exciting times to be in the field of stem cell research. Whether the newly discovered pathways of tissue regeneration will lead to novel therapies or a deeper understanding of pathological mechanisms will become clear over the next few years. The combination of stem cell and tissue engineering techniques overcomes the limitations of stem cells in therapy of human diseases, and presents a new path toward regeneration of injured tissues.

CONCLUSION:

The road of stem cell therapy from clinical trials to clinical practice has shown great potential for revolutionizing pharmacotherapy. On a bright note, it can provide personalized and targeted therapy options in autologous stem cell therapy. This can reduce not only chances of rejection and minimal adverse effects, but also ethical concerns with such procedures. As already mentioned, the therapy areas are diverse, like cardiovascular diseases, neurodegenerative disorders, cancers and others. Over the long run, it has a potential to reduce healthcare costs as well. Patients can avoid the lifelong medications or repeated surgeries and hospitalization in certain diseases. Robust research, standardization, validation and establishing evidence-based frameworks for stem cell therapy is the way forward. Affordability, accessibility and regulatory factors will pose certain socioeconomic and ethical considerations which have to be looked into. Long term adverse effects profiles like tumour formation and immune reactions have to be monitored closely. Despite all challenges, the progress made in stem cell therapy is substantial. This is made possible by continuing research, collaborative work between scientists, clinicians and regulatory bodies. Stem cell therapy can carve the path for a new era of regenerative medicine, bringing hope and health to humanity.

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