Abstract

Stem cell research has a promising role and the potential to yield novel medical therapies. Many researchers have been working in various disciplines such as Cardiology, Neurology, ophthalmology, ENT, Gastroenterology, Immunology, Hematology, Oncology and several others to identify the etiology of the disease process and to eventually develop appropriate treatment by utilizing different types of stem cells, either fetal or the adult stem cells thereby trying to address and minimize the symptoms in each disease. Hence an attempt has been made in this article to give an update about the recent developments in regenerative medicine.

Introduction

Stem cells are unspecialized cells that can self renew and differentiate into more mature cells with specialized functions. They can be unipotent, multipotent or pluripotent depending on various characteristics that they exhibit.

Types of Stem cells

**Embryonic stem cells (ESCs):** These are derived from early stage of embryo. They need to be cultured and differentiated into various tissues before they can be implanted.

**Fetal stem cells (FSCs):** These are primitive cells that have been isolated from the fetuses.

**Adult stem cells (ASCs):** These are multipotent undifferentiated cells. They are found in eye, brain, blood, skeletal muscle, pancreas, bone marrow, skin and dental pulp.

**Clinical application of stem cells:** Many preclinical studies and clinical trials using stem cells have been conducted across the globe to come up with effective treatment strategies for both acute and chronic diseases. Recent research in various clinical diseases give a ray of hope to the ailing patients to overcome their disease and progress in life. Some of these applications have been described below.

**Autism spectrum disorders**

Autism spectrum disorders (ASDs) are heterogeneous neuro developmental pathologies characterized by behavioral symptoms. Bradstreet et al in 2014 investigated the
safety and efficacy of fetal stem cell (FSC) transplantations in treating children diagnosed with ASDs. Two doses of intravenously and subcutaneously administered FSCs were transplanted. The Autism Treatment Evaluation Checklist (ATEC) test and Aberrant Behavior Checklist (ABC) scores were performed before transplantation and then at 6 and 12 months. Treatment safety was ensured by laboratory examinations and clinical assessment of adverse effects. Statistically significant differences (p < 0.05) were shown on ATEC/ABC scores for the domains of speech, sociability, sensory, and overall health, as well as reductions in the total scores when compared to pretreatment values without any adverse effects.

Retinal Regeneration

Many diseases of the outer retina are due to the degeneration of the retinal pigment epithelium (RPE). Stem cell-derived RPE cells are ideal for transplantation into retinas for the treatment of degenerative diseases that do not have any cure so far such as age-related macular degeneration (AMD), Stargardt's disease (STGD) and Retinitis pigmentosa (RP), (Ramsden et al 2013). Pluripotent stem cells and multipotent stem cells of fetal and adult tissues are potential sources of cellular therapy of AMD. The cells, known as MA09-hRPE, developed by Advanced Cell Technology (ACT), California, USA (Schwartz et al., 2012) were injected into the submacular space following a vitrectomy procedure in two individuals (one with dry AMD and one with STGD). Four months after transplantation, no loss of vision was reported in either individual. New pigmentation near the injection site in the patient with STGD was evident of the RPE function.

Janssen Research and Development (Philadelphia, PA, USA), have initiated a clinical trial of a hUTSC cell line, termed CNTO 2476, in individuals with dry AMD. These cells are delivered using a catheter delivery system through the white fibrous sclera and the vascular choroidal tissue to the subretinal space. There are no results from this phase I/II trial as yet. In humans, intravitreal injection of BMHSCs into three individuals with RP was shown to have no adverse side effects, although visual parameters in these cases did not improve significantly (Siqueira et al., 2011). The same group is currently recruiting to use this therapy on subjects with AMD and vascular retinopathies such as retinal vein occlusion and diabetic retinopathy, both of which result in retinal ischaemia.
Myocardial Infarction

Zwetsloot PP et al in the year 2016 used meta-analysis to establish the overall effect of Cardiac Stem Cells in preclinical studies and assessed translational differences between and within large and small animals in the CSC therapy field.

The overall effect observed in Cardiac Stem Cells treated animals was 10.7% (95%CI 9.4-12.1 p<0.001) improvement in ejection fraction (EF) compared to placebo controls. Interestingly, CSC therapy had a greater effect in small animals compared to large animals (p<0.001). Meta-regression indicated that cell type was a significant predictor for EF improvement in small animals.

Brain Ischemia or Cerebrovascular accident

Is due to interrupted supply of blood to the brain. Stem cells have immense self-replication and self-differentiation potentials and can differentiate into various types of cells, such as neural stem cells (NSC) which may further differentiate into neurons, astrocytes, and oligodendrocytes, and so forth, with lower stem cells immunogenicity and better histocompatibility. It has been considered as the most promising natural resource for the treatment of brain stroke Thereafter, meta-analysis was performed by Chen L et al in 2016. Sixteen studies and eighteen independent treatments were included in themeta-analysis. The results based upon the pooled mean difference from baseline to follow-up points showed that the stem cell transplantation group was superior to the control group with statistical significance in the neurologic deficits score (NIHSS, MD = 1.57; 95% CI, 0.64–2.51; I^2=57%; p = 0.001), motor function (FMA, MD = 4.23; 95% CI, 3.08–5.38; I=0%; p<0.00001), daily life ability (Barthel, MD = 8.37; 95% CI, 4.83–11.91; I=63%; p<0.00001), and functional independence (FIM, MD = 8.89;95% CI, 4.70–13.08; I^2=79%; p< 0.0001).

Stem cell transplantation therapy for patients with brain ischemic stroke can significantly improve the neurological deficits and daily life quality, with no serious adverse events. However, higher quality and larger data studies are required for further investigation to support clinical application of stem cell transplantation.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease. It is frequently sporadic and characterized by the progressive degeneration of both upper and lower motor neurons in the brain, brainstem and spinal cord (Moura et al 2016).
In 2012, Lee et al replaced microglia with a mutant SOD1 gene with microglia that expressed the wild-type gene using an injection of clodronate liposome and bone marrow transplants into the fourth cerebral ventricle and subsequently observed a 51.03% increase in survival.

In 2014, Sun et al reported the behavioral improvement and extended lifespan of ALS model mice transplanted with fetal human neural cells into the spinal cord. It was suggested that intrathecal transplantation of motor neurons into the lumbar spinal cord of animals migrated into the ventral horn area and improved ambulatory function and survival.

Also in 2014, Nizzardo et al showed that survival in an animal model significantly benefited from both intrathecal and intravenous injections of specific neural stem cells that were derived from induced pluripotent stem cells. These positive effects are attributed to the activity of multiple mechanisms, including the production of neurotrophic factors and the reduction of microgliosis and macrogliosis.

**Parkinson's disease**

Parkinson’s disease is a degenerative neurogenic disorder wherein symptoms typically appear when a large proportion of brain cells containing dopamine have been destroyed. The International Stem Cell Corporation (ISCO) has reported that four patients have successfully received the transplant of neural stem cells, called ISC-hpNSC, into their brains. Researchers are now preparing for the next stage, in which patients will receive a higher number of cells. So far, researchers have not recorded any adverse events among these four patients. The Phase 1 clinical trial (NCT02452723) was launched in March 2016, and expects to enroll 12 patients with moderate Parkinson’s disease. Patients will be divided into three groups of four patients each. The groups will receive increasing doses, ranging between 30,000,000 to 70,000,000 neural stem cells. The main goal of the trial is to assess the safety of the treatment, with patients followed for 12 months after the transplants. But researchers will also use brain scans to assess whether the cells survive once transplanted, and if they contribute to making the patients better. Participants are assessed using the Unified Parkinson Disease Rating Scale (UPDRS) and other tools, and although the study is small, researchers will evaluate any potential improvements in symptoms. The cells are thought to provide neurotrophic support to brain cells still alive. This means they secrete factors that help dying neurons survive. They are also thought to replace the dead and dying dopamine neurons.
Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is a genetic X-linked disorder, mainly affecting boys and very rarely girls. Cardiovascular disease is one of the serious complications in DMD, and often these patients develop cardiomyopathy. Weakness of respiratory muscles is another debilitating complication, limiting chest mobility (muscle weakness, skeletal deformities) thereby causing chronic respiratory failure.

Sychev et al in 2014 conducted a study to demonstrate the impact of fetal stem cells (FSCs) on functional capacity and life quality of DMD patients and the ability of FSCs to prevent DMD-related complications in order to inhibit the disease progression.

All patients of the study group underwent transplantation of mesenchymal and ectodermal FSC suspension containing both hematopoietic stem cells and other stem cell types. After FSCT, the study group patients reported improved respiratory status as early as day 2 after the treatment. Six months after FSCT, forced vital capacity (FVC) increased by a mean of 4.2% and forced expiratory volume (FEV1) by 4.5% (P>0.05). One year after FSCT, there was reliable increase of FVC and FEV1 by 13.2% and 15.3%, respectively. Treatment also resulted in end-diastolic volume (EDV) reduction by 15.6% and 25.8% 6 and 12 months later, respectively (P<0.05). In the control group, a significant LVEF increase by 12.42% and EDV reduction by 21.19% was reported 12 months after the treatment (P<0.05).

Intervertebral disc Degeneration

More than 70 percent of people age 50 or younger and more than 90 percent of people older than 50 experience intervertebral disk (IVD) degeneration.

Mayo researchers focused on the outcomes related to the effect and mechanism in IVD regeneration, which include disk height index, MRI T2 signal intensity, type II collagen expression and histologic disk degeneration grade. Animals of any species or breed with any type of model in IVD degeneration secondary to IVD trauma were included (Wang et al 2015).

In 13 studies, Mayo researchers found that disk height index in the stem cell transplantation group was significantly higher than the control group (SMD = 3.64, 95 percent CI: 2.49, 4.78, p < 0.001, l² = 91.3 percent). The 14 studies that reported MRI T2 signal intensity outcomes showed a significant increase of MRI T2 signal intensity in the stem cell transplantation group when compared with the control (SMD = 2.28, 95 percent CI: 1.48, 3.08, p < 0.001, l² = 88.5 percent). In 11 studies, stem cell transplantation was associated with significantly
reduced histologic disk degeneration grades when compared with the control group (SMD = -2.97, 95 percent CI: -3.97, -1.97, p < 0.001, I² = 80.1 percent). Increased expression of type II collagen was identified in nine studies (SMD = 3.68, 95 percent CI: 1.66, 5.70, p < 0.001, I² = 95.8 percent).

**Crohns disease**

The immune system of the host has been implicated for the etiology of crohns disease. Mesenchymal stem cells and hemopoeitic stem cells are beneficial for patients with crohns disease. 6 clinical trials using HSCs and 12 using MSCs have been conducted so far and stem cells seemed to significantly benefit patients with refractory Crohns disease in terms of both primary and second end points (Ye Lie et al 2016).

**Diabetes Mellitus**

Diabetes is a devastating disease that affects millions of people worldwide. The major forms of the disease are type 1 and type 2 diabetes. In type 1 diabetes, the body's immune system aberrantly destroys the insulin-producing beta cells (β-cells) of the pancreas. Type 2 diabetes, the more common form, is characterized both by insulin resistance, and by subsequent progressive decline in β-cell function.

In animal models, Mesenchymal Stem Cells treatment demonstrated therapeutic effects on glycemic control by restoring islet function and ameliorating insulin resistance. These results have now been translated into clinical practice. A total of 96 registered phase I/II clinical studies among T2DM patients can be found with the clinical trials registry (http://www.clinicaltrials.gov). Thirteen papers evaluating the clinical effects of MSC treatment in the management of T2DM have been published, including four randomized, placebo-controlled studies. HbA1c reduction and insulin requirements were frequently used as measures to assess the efficacy of MSC treatment for T2DM (Zang et al 2017).

**Leukemia**

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the most effective post remission treatment for leukemia, resulting in lower relapse rates than alternative therapies. Co-infusion of third-party donor stem cells with a CBT/haplo-SCT, which is called "dual transplantation," has been reported to improve the outcome of HSCT by accelerating hematopoietic reconstitution and reducing the incidence of graft-versus-host disease.
(GVHD). In addition, infusion of HLA-mismatched donor granulocyte colony-stimulating factor-mobilized donor peripheral blood stem cells after chemotherapy, the so called "microtransplantation", has been shown to promote the graft-versus-leukemia effect and hasten hematopoietic recovery without amplifying GVHD(Tian et al 2016).

**Chronic Obstructive Pulmonary Disease.**

COPD is progressive illness that makes it very difficult to breathe properly. Emphysema is a type of chronic obstructive pulmonary disease that displays abnormal and permanently enlarged the terminal bronchioles of the lungs. One of the most common symptoms with this condition is heavy coughing. Most patients with mild to moderate pulmonary disease require a combination therapy consisting of endogenous lung epithelial cells, cord blood cells, amniotic membrane derived progenitor cells and pulmonary alveolar epithelial cells needed for tracheal regeneration. For elderly patients or candidates with progressive respiratory diseases an aggressive combination protocol is required. All lung epithelial cells are screened and certified for strength and sterility documentation of using good cellular manufacturing processes at time of treatment. The Regen Center Lung disease treatment does not require invasive surgeries and the cells are delivered painlessly using a combination of Intranasal inhalation, Guided CT Scanners / Ultrasounds (when necessary) through an IV “Intravenous” Drip and/or Intrathecally depending on the patients needs.(Mora and Rojas 2013).

**Cancer**

Stem cell transplants are in use for treating various types of cancer such as leukemias, lymphomas, and multiple myeloma. They may be either of the following:

**Autologous:** The stem cells come from the same person who will get the transplant.

**Allogeneic:** The stem cells come from a matched related or unrelated donor. (Kompally 2013).

**Conclusion:**

Although stem cell research has made great progress, it still has a long way to go. More economical and effective treatments on a large scale is the hour of the need to cover all categories of patients with no potential side effects in the long run.
References


