Stem cell therapy in dermatology

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Abstract

Stem cells are precursor cells present in many tissues with ability to differentiate into various types of cells. This interesting property of plasticity can have therapeutic implications and there has been substantial research in this field in last few decades. As a result, stem cell therapy is now used as a therapeutic modality in many conditions, and has made its way in dermatology too. Stem cells can be classified on the basis of their source and differentiating capacity. In skin, they are present in the inter-follicular epidermis, hair follicle, dermis and adipose tissue, which help in maintaining normal skin homeostasis and repair and regeneration during injury. In view of their unique properties, they have been employed in treatment of several dermatoses including systemic sclerosis, systemic lupus erythematosus, scleromyxedema, alopecia, Merkel cell carcinoma, pemphigus vulgaris, psoriasis, wound healing, epidermolysis bullosa and even aesthetic medicine, with variable success. The advent of stem cell therapy has undoubtedly brought us closer to curative treatment of disorders previously considered untreatable. Nevertheless, there are multiple lacunae which need to be addressed including ideal patient selection, timing of intervention, appropriate conditioning regimens, post-intervention care and cost effectiveness. Further research in these aspects would help optimize the results of stem cell therapy.

Key words: Dermatology, pemphigus, stem cell therapy, systemic lupus erythematosus, systemic sclerosis

Introduction

Stem cell therapy is a novel technique which had gained significant attention over the past years. The Nobel Prize in Physiology or Medicine 2007 was awarded jointly to Mario R. Capecchi, Sir Martin J. Evans and Oliver Smithies for their discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells.[1] Stem cells have been employed in broad therapeutic indications and as a consequence, the New Drugs and Clinical Trials Rules include "stem cell derived products" under the new drug section.[2] In dermatology, stem cell therapy has been tried in several refractory conditions with some success which has widened the therapeutic armamentarium. In this article, we aim to review the current status of stem cell therapy in dermatology.

Materials and Methods

A search for relevant literature in English language was conducted using PubMed, MEDLINE, Hindawi and Google Scholar. All publications up to 2019 were identified using the following key words: stem cell therapy, dermatology, hematopoietic, autologous and allogenic. All articles, including case reports, case series, randomized controlled trials and review articles on the use of stem cell therapy in various dermatological conditions, were considered and the results of the studies including the adverse effects were tabulated. We included articles related to clinical relevance of stem cells and stem cell therapy in dermatology. We excluded articles that were outside the domain of clinical dermatology, such as those on basic science of stem cells, veterinary dermatology and use of stem cells in other fields of medicine. The guidelines by European Group for Blood and Marrow Transplantation (EBMT), British Society of Blood and Marrow Transplantation (BSBMT), American Society for Blood and Marrow Transplantation (ASBMT) and Indian Council of Medical Research (ICMR) were compiled to give a comprehensive overview of indications and current status of stem cell therapy in dermatology. We were able to review

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about 110 articles on this subject which form the basis of this review article.

Principles of Stem Cell Therapy

Stem cells are undifferentiated cells present in different organ systems with the three hallmark characteristics of self-renewal, differentiation and plasticity [Table 1].[3] Stem cells are present in a specialized microenvironment called stem cell niche which functions as a unit to maintain homeostasis and repair tissues at the time of injury.[4] Stem cells can be classified on the basis of their source and differentiating capacity [Table 2].[5-7]

Epidermal Stem Cells

In skin, stem cells are found in inter-follicular epidermis (keratinocyte), bulge of the hair follicle (keratinocyte, melanocyte and neuronal), sebaceous gland, dermal papillae, dermis and subcutaneous tissue (mesenchymal). Melanocyte stem cells can be induced by ultraviolet radiation, laser, dermabrasion and drugs including tacrolimus, hence are used in re-pigmentation of vitiligo.[8-13] Under normal circumstances, the stem cells from epidermis, hair follicle and sebaceous glands differentiate independent of each other. During injury, by virtue of plasticity, any stem cell from one location can give rise to whole cell lineage.[14]

Table 1: Defining characteristics of a stem cell[3]

Property	Definition
Self-renewal	Ability to undergo numerous cycles of asymmetrical cell division to produce differentiated cells as well as cells that are similar to the parent cell, thereby maintaining the pool of undifferentiated cells
Differentiation	Ability to differentiate into cells of the tissue in which stem cell is located
Plasticity/trans-differentiation	Ability of adult stem cells to cross lineage barriers and differentiate into cells of tissue different from the original tissue

Bone Marrow Stem Cells

Bone marrow contains hematopoietic and mesenchymal stem cells. The former can be derived from bone marrow and umbilical cord blood and are used in autoimmune disorders after immune ablation, deleting the self-reactive cells and repopulating with cells with improved self-tolerance. The hematopoietic stem cells can be derived from the same donor (autologous – as the loss of self-tolerance is at the peripheral blood level, but not the stem cell level as they are not involved in antigen recognition) or from an HLA matched donor (allogenic). Umbilical cord blood transplantation has few advantages over bone marrow transplant including lower incidence and lower severity of acute and chronic graft-versus-host disease, lower risk of transmitting latent virus infections and elimination of clinical risk to the donor during hematopoietic stem cell procurement procedures. However, disadvantages include higher risk of graft rejection and delayed hematopoietic recovery after transplantation due to a reduced number of hematopoietic progenitor cells that can further contribute to serious infections.[15]

Table 2: Classification of stem cells[5-7]

	Classification	Description
Classification on the basis of differentiating capacity	Totipotent/omnipotent	The ability to differentiate into all possible cell types including placenta Cells produced by the first few divisions of the fertilized egg, known as morula cells, are totipotent
	Pluripotent	The ability of a stem cell to turn into all mature cell types of the body of all the three germ layers, except placenta Embryonic stem cells that are isolated from an early stage embryo, called blastocyst are pluripotent cells
	Multipotent	The ability to turn into more than one mature cell type of the body, usually a restricted and related group of different cell types E.g., hematopoietic (adult) stem cells that can become red and white blood cells or platelets Mesenchymal stem cells that can become a wide variety, but related group, of mature cell types (bone, cartilage, connective tissue, and adipose tissue)
	Oligopotent	The ability to differentiate into a few cells. Example: Adult lymphoid or myeloid stem cells.
	Unipotent	Can produce only one cell type Muscle stem cells
Classification on the basis of their source	Embryonic stem cell	Pluripotent stem cells present in the inner cell mass of blastocyst which are capable of producing all organs in human body except for placenta
	Somatic/adult stem cell	Somatic stem cells (multipotent or unipotent), with limited plasticity, present in many tissues including skin and bone marrow
	iPSC	Recently, the induced pleuripotent stem cells have emerged as a distinct variety. They are produced by reprogramming of somatic cells into pleuripotent state by genetic engineering. These stem cells can be induced to form various types of differentiated cells

iPSC: Induced pleuripotent stem cells

Mesenchymal stem cells are multipotent adult stem cells derived from almost all tissues including bone marrow, umbilical cord, peripheral blood, skin, foreskin, fallopian tube, lung, fetal tissue, placenta, adipose tissue or amniotic fluid. In contrast to hematopietic stem cells, mesenchymal stem cells have low immunogenicity by virtue of their low MHC expression and also possess immunomodulatory effects, hence have utility in many diseases including inflammatory diseases. They also provide greater advantages over other stem cells including their relatively easy tissue isolation, absence of obvious risk for the donor or ethical constraints, capacity of migrating and homing to the injured site (e.g., tumor tropism), ability to expand for a relatively long period of time, ability to modify the host immune environment and higher transdifferentiation potential.[16]

The steps of allogenic hematopoietic stem cell therapy include stem cell mobilization, collection of stem cells, conditioning of recipient, stem cell infusion and recovery [Table 3].[17-20]

Applications of Stem Cells in Dermatology [Table 4]

Pemphigus

Even though the first-line treatment of pemphigus remains to be corticosteroids and other immunosuppressants, some patients remain refractory to therapy, making it imperative to explore other therapies. Hematopoietic stem cell therapy has been tried successfully in pemphigus as shown in a few studies.[21-24] The proposed mechanism of action is that the transplanted stem cells repopulate the immune system, the number of autoreactive immune cells decline and this helps to restore the immunological balance.

There are case reports and small case series from India and abroad on successful treatment of recalcitrant pemphigus with both autologous and allogeneic hematopoietic stem cell therapy using different mobilization and conditioning regimens [Table 5]. Infection was the most common side effect, with sepsis and occasionally death occurring in these patients.[21-24]

The available literature suggests the efficacy of hematopietic stem cell therapy in treatment of pemphigus (grade of recommendation C, level of evidence 4); however, large scale multicentric studies with longer follow-up are needed to confirm the results.

Systemic sclerosis

In search of a definite disease modifying treatment, systemic sclerosis is one of the first autoimmune diseases to be subjected to stem cell therapy. Hematopoietic stem cell therapy aims to non-specifically immunoablate aberrant self-reactive T- and B-cells through high-dose immunosuppression, with subsequent reconstitution of a renewed and tolerant immune system by means of infusing patient's previously collected hematopoietic stem cells. Autologous hematopoietic stem cell therapy is preferred over allogeneic therapy due the

Table 3: Steps and principles of allogenic hematopoietic stem cell therapy[17-20]

Step	Comments
Stem cell mobilization	Quiescent hematopoietic stem cells in bone marrow are tethered to osteoblasts, other stromal cells and the extracellular matrix in the stem cell niche through a variety of adhesive molecule interactions. Stem cell mobilization aims at disruption of these niche interactions, thereby resulting in release of stem cell from the bone marrow into the peripheral blood. Mobilization regimens include cytotoxic agents (cyclophosphamide), hematopoietic growth factors (G-CSF, GM-CSF, both are FDA approved), small-molecule chemokine analogues (Plerixafor, an inhibitor of CXCR4, FDA approved for patients who fail to mobilize sufficient CD34+ cells for ASCT), recombinant monoclonal antibody (Natalizumab)
Collection of stem cells or harvesting	The donor stem cell can be obtained by either direct bone marrow biopsy or by peripheral stem cell mobilization and collection of peripheral blood. Subsequently, either simple apheresis or stem cell manipulation with selection for CD34+ is done so as to prevent reinfusion of autoreactive cells. In autologous transplant the stem cells are stored in deep-freeze condition/in liquid nitrogen as a gap of 4 weeks is given for the cells to recover to undergo conditioning regimen, while in allogeneic transplant, collection and transplantation are done on the same day, eliminating the need for storage
Conditioning of recipient	Preparative/conditioning regimen has to be given in autologous and allogeneic transplantation to prevent graft rejection and reduce tumor burden. The agents used include both radiotherapy and chemotherapy. Total myeloablation was the norm in older days, but with recognition of graft-versus-tumor effect having a contributory role in the success of allogenic HCT, reduced intensity, nonmyeloablative conditioning regimens have been developed nowadays for better acceptance. Examples of conditioning regime include cyclophosphamide, busulfan, fludarabine, antithymocyte globulin, cytosine arabinoside, anti-CD45 antibody conjugated to I-131, high-dose TBI (800–1320 cGy). Low-dose TBI (200–400 cGy)
Stem cell infusion	Following conditioning, stem cells are thawed and reinfused, either into the bone marrow or through intravenous route. Even when given in peripheral circulation, the stem cells home to bone marrow and engraftment takes place
Recovery	Following the conditioning regimen, the patient enters a stage of intense immunosuppression/myelosuppression, which is related to increased mortality and morbidity in transplant recipient. Supportive therapy is given which includes anti-emetics, anti-diarrheal, antibiotic, antiviral, and antifungal coverage. G-CSF, red cell and platelet transfusions is done when the levels of leukocytes are <1000, hemoglobin <7 g, platelet <30,000 respectively

ASCT: Autologous stem cell transplantation, CXCR4: Chemokine receptor type 4, CD34: Cluster of differentiation 4, cGy: Centigray, FDA: Food and drug administration, G-CSF: Granulocyte-colony stimulating factor, GM-CSF: Granulocyte-macrophage colony stimulating factor, HCT: Hematopoietic cell transplantation, TBI: Total body irradiation

lower treatment-related mortality and lack of graft-vs-host disease in the former.[25] Stem cell therapy in this condition has been well studied in three randomized controlled trials (RCTs), namely, American Scleroderma Stem cell versus Immune Suppression Trial (ASSIST, phase 2, 19 patients), Autologous Stem cell Transplantation International Scleroderma Trial (ASTIS, phase 3, 156 patients) and The Scleroderma Cyclophosphamide Or Transplantation study (SCOT, phase 3, 75 patients), besides several case series and pilot studies.[26-38] Despite the slight differences in methodology, all the studies have shown autologous hematopoietic stem cell therapy as an effective, safe and feasible modality in systemic sclerosis (level of evidence-2a, 2b. 4) [Table 6]. Since severe major organ involvement (pulmonary, cardiac or renal) or serious comorbidities are an absolute contraindication for hematopoietic stem cell therapy, these patients were excluded from all the three trials. It has been found to be more effective than conventional immunosuppressive therapies and is currently the only disease modifying strategy for improving long-term survival, prevention of organ worsening and improvement of skin and pulmonary function and improving the overall quality of life of patients.[39] Data provided by the European and American registries include overall 3-year survival rates of around 80% and 5-year progression-free survival rate of 55%.[29,40] The European Society for blood and marrow transplantation and British society of blood and marrow transplantation categorize autologous hematopoietic stem cell therapy in severe resistant disease as "clinical opinion," that is, after assessing risks and benefits.[41] Guidelines from the American society for blood and marrow transplantation categorize autologous hematopoietic stem cell therapy as "standard of care, rare indication" (as a treatment option for individual patients after careful evaluation of risks and benefits) in children and "developmental" in adults.[42]

Table 4: Dermatological conditions in which stem cell therapy has been tried

Good results	Promising results	Results with low evidence	Discouraging results
Systemic sclerosis	Psoriasis	Wound healing Scleromyxedema	Epidermolysis bullosa
SLE	Vitiligo	Alopecia	
Pemphigus		HIV Melanoma Aesthetic medicine	Merkel cell carcinoma

SLE: Systemic lupus erythematosus

Table 5: Studies on stem cell therapy in treatment of pemphigus

Author, year	Indication and inclusion	Methods	Results	Side effects
Oyama *et al*., 2004[21] Case report	Refractory pemphigus foliaceus. BSA - 20% Resistant to topical betamethasone, oral prednisone, azathioprine, MMF, dapsone, cyclophosphamide 75 mg/day, for 9 months	Autologous HSCT Mobilization - cyclophosphamide and G-CSF Conditioning regimen: Cyclophosphamide and rATG. Methylprednisolone 1.0 g/day before each dose of rATG	Skin lesions resolved over 2 months; maintained till 10 months Prednisone tapered off over 4 months	Culture negative neutropenic fever, nausea, anorexia Relapse: Few erythematous plaques on nose and scalp, responded to topical steroids No systemic therapy for 19 months post-HSCT
Suslova *et al*., 2010[22] Case report	Pemphigus vulgaris. BSA - 30% Resistant to steroids, methotrexate, dapsone, chlorambucil, azathioprine	Allogeneic HSCT Conditioning regimen: Alemtuzumab, 300 cGy of TBI Adjuvant: oral sirolimus	Severity decreased by 9th month post-transplantation	Arthralgia arthritis Relapse: None at 24 months
Vanikar *et al*., 2012[23] Case series, 11 patients	Clinical and biopsy proven pemphigus vulgaris, resistant to prednisolone and topical steroid	Cytokine-stimulated allogeneic HSCT	Recovery began (skin lesions started regressing) within 24 h of HSCT and new lesions stopped erupting after 6 months. Over a mean follow-up of 8.02 years, all patients were well without recurrence/new lesions	No GVHD/AE observed in any patient/donor
Wang *et al*., 2017[24] Case series, 12 patients	Nine of pemphigus vulgaris, three of pemphigus erythematosus, one of pemphigus foliaceus Persisting disease after high doses of steroids, or at least one kind of immunosuppressant, for <6 months; or patients with steroid-related diseases or severe contraindications and complications to steroids	Autologous peripheral HSCT	Overall survival was 91.6% at 80.33 months, complete remission was achieved and maintained in 90.9% (10/11); 81.8% (9/11) and, 75% (6/8) patients at 6 months, 1 year and 5 years, respectively, two patients developed relapse at 5 and 6 months post-transplant	Infection (most common side effect) in 8 (66.7%) cases, with sepsis in 2 (16.7%), of which one died at 2 months post-transplant. Other AE: Pyrexia, headache and transaminitis

BSA: Body surface area, cGy: Centigray, G-CSF: Granulocyte-colony stimulating factor, GVHD: Graft versus host disease, HSCT: Hematopoietic stem cell transplantation, MMF: Mycophenolate mofetil, rATG: Rabbit antithymocyte globulin, TBI: Total body irradiation, AE: Adverse event

Table 6: Studies on stem cell therapy in systemic sclerosis

Author, year	Indication and inclusion	Methods	Results	Side effects (number of patients)
Oyama *et al*., 2007[26] Case series, 10 patients	Diffuse systemic sclerosis with an mRSS >13 and internal organ involvement	Autologous HSCT Mobilization: cyclophosphamide and G-CSF Conditioning regimen: cyclophosphamide plus rabbit anti-thymocyte globulin Outcome measures: mRSS, PFT, HRCT, cardiac and renal	Significant improvement in mRSS at 6, 12 and 24 months Cardiac, pulmonary and renal functions - Stable	Neutropenic fever - 5 Clostridium difficile colitis, culture negative pulmonary infiltrate, fluid overload, acute renal failure, engrafment syndrome - 1 patient each chemotherapy-related nausea, vomiting, diarrhea, asthenia and mild liver enzyme elevation - Most of the patients
Nash *et al*., 2007[27] Case series, 34 patients	Early (<4 years) diffuse scleroderma (mRSS >15) and internal organ involvement	Autologous HSCT Mobilization: G-CSF Conditioning regimen: Total body irradiation with cyclophosphamide and equine anti-thymocyte globulin Post-transplant - prednisone	One-year survival - 79% Significant improvement in mRSS and FVC	CMV gastroenteritis - 1 Bacteremia - 11 Herpes zoster - 6 Fatal pulmonary toxicities - 2 Renal crisis - 6 Supraventricular arrhythmias - 2 patients Heart failure - 2 Treatment related death - 8 (23%) cases
Vonk *et al*., 2008[28] Retrospective study, 26 patients	Rapidly progressive disease (2 years duration), mRSS >20 or a disease duration >2 years, progression of mRSS (>20%) plus major organ involvement	Autologous HSCT Mobilization: Cyclophosphamide and G-CSF Conditioning regimen: cyclophosphamide plus anti-thymocyte globulin Outcome measures: mRSS, PFT, survival	mRSS - significant decrease in mRSS in 19 (73%) cases after 1 year and in 15/16 (94%) patients after 5 years No significant change in FEV_1 or DLCO Progression/event free survival 64.3% at 5 years and 57.1% at 7 years	Transplant related mortality: 1 (3.8%) case Relapse: 6 (28%) patients at 2–4 years
Farge *et al*., 2010[29] Retrospective study, 175 patients	Systemic sclerosis	Autologous HSCT Myeloablative (total body irradiation)/ non-myeloablative (cyclophosphamide/ busulfan/carmustine, cytarabine, melphalan, and etoposide/antithymocyte globulin) Outcome measures: survival	Overall survival: 72.6% at 5 years Progression/event free survival: 55% at 5 years	Transplant related mortality: 12 (6.8%) cases
Burt *et al*., 2011[30] Phase 2 ASSIST trial. 19 patients Single center randomized controlled trial	Diffuse systemic sclerosis mRSS ≥15 with internal organ involvement, disease duration ≤4 years, age <60 years	Autologous peripheral blood HSCT (ten patients) versus cyclophosphamide pulse (nine patients) HSCT group: mobilization with cyclophosphamide and G-CSF Conditioning regimen: cyclophosphamide plus anti-thymocyte globulin Control group: Cyclophosphamide 1 g/sq.m monthly pulse for 6 months. Outcome measures: improvement in mRSS (>25%) and FVC (>10%) Mean follow up period of 2.6 years	All patients of stem cell group improved at or before 12 months follow-up. No patient had disease progression. Improvement in FVC and mRSS persisted at follow-up. In control group, none had improvement. Seven patients switched to receive stem cell transplantation, after which 4 were followed up for at least 1 year, with all showing improvement. No mortality in both groups at 12 months and overall	Arrythmias (2 patients), volume overload (two patients), reactivation of CMV infection (1 patient)
Henes *et al*., 2012[31] Case series, 26 patients	Systemic sclerosis with inefficacy of cyclophosphamide or rapidly progressive diffuse disease	Autologous stem cell transplantation Mobilization: cyclophosphamide and G-CSF Conditioning regimen: cyclophosphamide plus antithymocyte globulin Outcome measures: mRSS, PFT	Response rate 25% improvement in mRSS score in 21/23 (91%) patients	3 deaths before transplantation. Transplant-related mortality: 4% Treatment-related mortality: 11% Relapse: 7 patients (4.4 years of follow-up)
Burt *et al*., 2013[32] Retrospective study, 90 patients	Diffuse systemic sclerosis (mRSS >14) and internal organ involvement (pulmonary, cardiac or gastrointestinal)	Autologous HSCT Mobilization: cyclophosphamide and G-CSF Conditioning regimen: cyclophosphamide and rATG Outcome measures: mRSS and PFT	mRSS and FVC improved. Total lung capacity and DLCO not improved	Treatment related mortality: 5 (6%) cases

(Contd...)

Table 6: *(Continued)*

Author, year	Indication and inclusion	Methods	Results	Side effects (number of patients)
van Laar *et al*., 2014[33] ASTIS trial, 156 patients Multicenter randomized controlled trial, Phase 3	Diffuse systemic sclerosis, mRSS ≥15 and internal organ involvement, disease duration ≤4 years, age 18–65 years	Autologous HSCT (79 patients) versus cyclophosphamide pulses (77 patients). Mobilization: cyclophosphamide and G-CSF Conditioning regimen: cyclophosphamide plus anti-thymocyte globulin Control group: cyclophosphamide 750 mg/sq.m monthly pulse for 12 months Outcome measures: event free survival till death/persistent major organ failure Median follow up 5.8 years	HRCT group - significant improvement in MRSS, total lung capacity, FVC HSCT was associated with increased treatment-related mortality (8 cases, 10%), none in control group in the first year after treatment. However, HCST conferred significant long-term event-free survival benefit	Grade 3 or 4 AEs in first 2 years of follow-up: 51 (62.9%) patients in HSCT group and 30 (37%) in control group
Henes *et al*., 2014[34] Case series, 6 patients	Progressive systemic sclerosis with cardiac manifestations (biopsy proven myocardial fibrosis)	Autologous HSCT Mobilization: Cyclophosphamide and G-CSF Conditioning regimen: thiotepa, cyclophosphamide and rATG Outcome measures: mRSS, HRCT chest and PFT	Significant improvement in mRSS score at 6 and 12 months. In 4 patients - >25% improvement Median lung density and total lung volume improved Non-significant improvement of FVC	Aspergillus pneumonia - 2 patients No transplant related mortality Relapse: 2 patients
Del Papa *et al*., 2017[35] Retrospective study, 18 patients	Rapidly progressing diffuse systemic sclerosis with disease duration <4 years Control group (36 patients) treated with conventional therapies	Autologous HSCT Mobilization: cyclophosphamide and filgrastim Conditioning regimen: Cyclophosphamide and rATG Outcome measures: mRSS, DLCO, disease activity using the ESSG scoring system follow-up of 60 months	Statistically significant reduction in mRSS and DLCO in autologous HSCT group compared to control group at 1 year and maintained at the end of follow-up. Significantly lower mortality in autologous HSCT group (5.8%) compared to control (61%)	Only one patient died during follow-up due to systemic sclerosis related manifestation (fatal cardiac arrhythmia occurring after 34 months)
Sullivan *et al*., 2018[36] SCOT trial, 75 patients Multicenter randomized, open-label, phase 3 trial	Diffuse systemic sclerosis, mRSS ≥16 and internal organ involvement, disease duration ≤4 years, age 18–69 years	Autologous HSCT (36 patients) versus cyclophosphamide (39 patients) Mobilization: G-CSF Conditioning regimen: Fractionated total-body irradiation, cyclophosphamide and equine antithymocyte globulin Control group: cyclophosphamide 500 mg/sq.m followed by 750 mg/sq.m monthly pulse for 11 months Outcome measures: Global rank composite score at 54 months Follow up to 4.5 years	Rate of event-free survival at 54 months was 79% in transplantation group and 50% in cyclophosphamide group (P=0.02). At 72 months, Kaplan–Meier estimates of event-free survival (74% vs. 47%) and overall survival (86% vs. 51%) also favored transplantation (P=0.03 and 0.02, respectively). Treatment-related mortality in the transplantation group was 3% at 54 months and 6% at 72 months, as compared with none in cyclophosphamide group	Rate of serious AEs in person-years: 0.38 (transplantation group) and 0.52 (cyclophosphamide group). Rate of infections (of any grade) per person-year: 0.75 (transplantation group) and 0.79 (cyclophosphamide group) Rate of infections of grade 3 or more per person-year: 0.21 (transplantation group) and 0.13 (cyclophosphamide group)
Nakamura *et al*., 2018[37] 14 patients Long-term follow-up in a phase II Trial	SSc patients with disease duration <3 years, with at least one of the following: mRSS) ≥15, refractory digital ulcer or interstitial lung disease	HSCT were performed after conditioning using cyclophosphamide Median follow-up period was 137 months	Overall survival 93%, event-free survival rate 40% at 10 years. Eight patients (57%) achieved more than 50% decrease in mRSS from baseline within 6 months after HSCT	AEs related to HSCT occurred in 6 patients (43%). Severe cardiomyopathy occurred in 2 patients, and one of them had a fatal course
Nair *et al*., 2018[38] Case series, 4 patients	Diffuse systemic sclerosis with mRSS of 15 and one internal organ involvement	Autologous HSCT Mobilization: cyclophosphamide and G-CSF Conditioning regimen: cyclophosphamide plus fludarabine plus anti-thymocyte globulin Outcome measures: mRSS, PFT	Mean mRSS reduced to 22.2 after 1 year and 18.5 at 4 years of follow-up from baseline 24.5. Mean FVC increased from 65% to 78.5% at 4 years follow-up, while DLCO increased from 55% to 77.73%	No significant procedure-related side-effects

ASSIST: American scleroderma stem cell versus immune suppression trial, ASTIS: Autologous stem cell transplantation international scleroderma trial, CMV: Cytomegalovirus, DLCO: Diffusing capacity of the lungs for carbon monoxide, ESSG: European scleroderma study group, FEV_1: Forced expiratory volume during first second, FVC: Forced vital capacity, G-CSF: Granulocyte-colony stimulating factor, HSCT: Hematopoietic stem cell transplantation, mRSS: modified Rodnan skin score, rATG: Rabbit antithymocyte globulin, PFT: Pulmonary function test, HRCT: High-resolution computed tomography, AEs: Adverse events

Patients with acute onset rapidly progressive disease refractory to conventional therapy and mild initial organ damage carry a better prognosis after hematopoietic stem cell therapy, while long standing disease, indolent course and irreversible organ damage are contraindications to this therapy.[43] Hence, the challenge is to identify patients who are most likely to be benefitted, and the timing of hematopoietic stem cell therapy is to be tailored based on the phase of disease.

Risks of hematopoietic stem cell therapy include gonadal failure, secondary autoimmune diseases and malignancies. The European registries analyzed mortality after autologous hematopoietic stem cell therapy for severe autoimmune disease from 1996 to December 2007 and reported 5% mortality by day 100 following transplantation. The commonest cause of death included SSc recurrence, and transplant-related mortality, with others being cardiotoxicity, hemorrhage, secondary malignancies and infections.[29] As systemic sclerosis has complex cardiac manifestations and cyclophosphamide is also associated with cardiotoxicity, a comprehensive pre-transplant cardiac assessment is recommended even in patients without cardiac symptoms.[44] Hematopoietic stem cell therapy can induce gonadal failure in both sexes, therefore semen, oocyte or embryo cryopreservation/hormone replacement in case of gonadal failure should be considered as appropriate.[45] The cumulative incidence of secondary autoimmune diseases was 9.8% after 5 years of treatment.[46] In view of the high risk of treatment related side effects and early treatment-related mortality, the new EULAR treatment recommendations advise for careful selection of patients and highlight the experience of the medical team to be of utmost importance.[47]

Systemic Lupus Erythematosus

Hematopoietic stem cell therapy had been tried in patients with refractory systemic lupus erythematosus (SLE). The first case report of a successful autologous hematopoietic stem cell therapy in SLE was published in 1997, subsequent to which many observational studies and clinical trials have been conducted [Table 7].[48-60] The current literature suggests that hematopoietic stem cell therapy is an option in refractory disease of short duration.[61] European society for blood and marrow transplantation and British society of blood and marrow transplantation categorize autologous hematopoietic stem cell therapy in severe resistant disease as "clinical opinion," that is, it can be undertaken after assessing risks and benefits.[41] Guidelines from the American society for blood and marrow transplantation categorize the treatment as "developmental" in adults.[42]

Therapeutic potential of mesenchymal stem cells has been explored in various autoimmune diseases including SLE.[62] It has been found to be safe and effective in SLE, with decrease in disease activity, improvement in renal function, reduction in autoantibody production, peripheral Treg upregulation and re-establishment of balance between Th1- and Th2-related cytokines.[63] Their immunomodulatory and regenerative characteristics make them a promising novel therapy for SLE.

Psoriasis

Although recent years have seen considerable progress in elucidating psoriasis pathogenesis, the exact mechanism is yet not fully known. At present, attention has been drawn to the possibility of dysfunction of certain types of stem cells to be the main cause of dysregulation of the inflammatory response in psoriasis.[64] The idea originated while noticing psoriasis patients undergoing hematopoietic stem cell therapy and subsequently achieving long-term remission.[65,66] In contrast, cases of acquired psoriasis after bone marrow transplantation from donors with psoriasis have also been reported.[67-69] This suggests that hematopoietic stem cells have a significant role in disease pathogenesis. Mesenchymal stem cells have also been tried in few studies with success.[70] Clinical benefits may be attributed to mesenchymal stem cell engraftment or to their paracrine or immunomodulatory effects. However, the availability of cost-effective, safe alternatives prevent the use of stem cell transplantation as a viable option in psoriasis.

Epidermolysis Bullosa

Although there is no specific treatment for this genetic condition till date, various therapeutic modalities are being studied that aim at correction of the underlying genetic defect and restore skin barrier. Stem cell therapy is one such cell based therapy. Either mesenchymal stem cells from the donor can be introduced intradermally or intravenously, bone marrow transplant can be done from allogeneic donor, or patient's stem cells can be genetically modified and transplanted. While hematopoietic stem cell therapy has failed to live up to its initial promise, allogenic mesenchymal stem cells therapy may be useful in alleviating some symptoms.

In a study by Conget *et al*., two patients with severe generalized recessive dystrophic epidermolysis bullosa (EB) treated with intradermal administration of allogenic mesenchymal stem cells from bone marrow showed complete healing of ulcers around the treated site by 12 weeks.[71] One week after intervention, type VII collagen was detected along the basement membrane zone and the dermal–epidermal junction was continuous in the treated site. However, the clinical effect lasted for only 4 months in both the patients.

A case of junctional EB treated with primary keratinocyte culture had normal morphology and absence of spontaneous and induced blisters or erosions at 21 months of follow-up.[72]

Studies by El-Darouti *et al*. and Wagner *et al*. using stem cells have also shown promising results.[73,74] Petrof *et al*. studied ten recessive dystrophic EB children treated with intravenous allogeneic bone marrow-derived mesenchymal stem cells and found that the procedure was well tolerated and the adverse effects were minimal at nine months of follow-up.[75] However, skin biopsy performed at day 60 showed no increase in type VII collagen and no new anchoring fibrils.

Although the initial clinical improvement was promising, it did not sustain with time due to lack of production of

long lasting proteins (collagen and laminins). The current evidence of the use of stem cell therapy in EB is limited as the total number of patients treated with this modality is low, thus warranting further research to evaluate the efficacy and the potential risk to benefit correlation.[76]

Wound Healing

Epidermal stem cells have the potential to regenerate the epidermis and differentiate into various cell types and tissues, under appropriate stimuli.[77] This property can be utilized to advantage in initiation and acceleration of healing of chronic non-healing wounds. Mesenchymal stem cells have been shown to promote wound healing by decreasing inflammation, promoting angiogenesis and decreasing scarring.[78] Falanga *et al*. successfully applied human mesenchymal stem cells to non-healing and acute wounds, using a specialized fibrin spray system.[79] Lu *et al*. demonstrated efficacy of stem cell therapy in diabetic foot ulcers.[80]

Vitiligo

Medical management is the first-line therapy for vitiligo and when it fails surgical therapies are considered.

Table 7: Studies on stem cell therapy in systemic lupus erythematosus

Author, year	Indication and inclusion	Methods	Results	Side effects
Marmont *et al*., 1997[48] Case report	A 48 year old woman, severe SLE since 20 years. Despite being on azathioprine, she required 40 mg of methylprednisolone to be in remission, recurrent chest pain (costochondritic) requiring intravenous corticosteroids	Autologous BMT Conditioning: 15mg/kg Thiotepa followed by 100 mg/kg of cyclophosphamide over 2 days	7 months after transplant, corticosteroid requirement reduced to 10 mg methylprednisolone daily, and ANA/anti-DNA antibodies not demonstrable. Chest pain did not recur	Post-transplant course was uneventful
Burt *et al*., 1998[49] Case series, 2 patients	Patient 1: malar rash, arthralgias, hematuria, diffuse abdominal pain, pancytopenia ascites and pericardial effusion. Renal function was declining Patient 2: active pneumonitis, pulmonary infiltrates, hypoxia, WHO class IV glomerulonephritis. Positive ANA	Source: bone marrow and peripheral blood stem cells Mobilization: Cyclophosphamide and G-CSF Conditioning regimen: cyclophosphamide and antithymocyte globulin Outcome: 50% improvement in serology, SLEDAI, serum creatinine, 24 h urine protein, creatinine clearance, left ventricular ejection fraction, chest radiograph and pulmonary function without any deterioration	Patient 1: At 12 months, malar rash, cytopenia, arthralgia, pericardial effusions resolved and renal function improved. Patient off all immunosuppressant medications Patient 2: at 6 months follow-up, pulmonary infiltrates improved. PFTs and creatinine values static. ANA decreased. Steroids tapered from 80 mg/day to 25 mg/day	Cell lysis effect, acid base and electrolyte disorders, volume disturbances
Fouillard *et al*., 1999[50] Case report	A 35-year old woman with Raynaud's phenomenon, arthritis, cutaneous vasculitis, proteinuria (WHO class III renal involvement) and ANA positivity (1:4096), anti-ds-DNA and anti-SSA antibodies, right homonymous hemianopia (left occipital ischemia)	Autologous HSCT Mobilization: cyclophosphamide and G-CSF Conditioning regimen: BEAM	At 1-year follow-up, clinical remission – No Raynaud's phenomenon, arthritis, cutaneous vasculitis. ANA and anti SSA negative at 1st and 6th month but become positive at 9 months. Renal - Reduced to class Ii Steroid requirement - 12.5 mg/day of prednisone	Grade II mucositis
Brunner *et al*., 2002[51] Case report	Treatment resistant SLE with severe nephrotic syndrome and recurrent pneumonitis Resistant to steroids, azathioprine, cyclophosphamide	Autologous HSCT Mobilization: Cyclophosphamide and G-CSF Conditioning regimen: cyclophosphamide and ATG	At 21 months follow-up, disease under remission. Not on immunosuppressive drugs CT chest - No SLE related pulmonary activity	Sepsis - *Pseudomonas aeruginosa* Moderate intermittent fluid overload, mild mucositis
Lisukov *et al*., 2004[52] Case series, 6 patients	Recalcitrant SLE (cyclophosphamide pulse), with Class III or IV glomerulonephritis, CNS lupus, vasculitis involving the lung or heart, or life threatening cytopenias	HSCT Source: Bone marrow (4 patients) and peripheral (2 patients) Mobilization: Cyclophosphamide and G-CSF Conditioning regimen: BEAM with ATG	Case 1: Complete remission. Steroid stopped at 10 months Case 3: Improvement in CNS lupus. Low dose steroids (7.5–10 mg/day), azathioprine and cyclosporine Case 6: Complete remission after 6 months	3 patients died. 1 - on day 11. Sepsis and multiple organ failure, hemorrhage 1 - on day 22. Sepsis followed by multiple organ failure, hemorrhage pneumonia 1 - on day 63. CMV infection (treated), pancytopenic. Sepsis and pneumonia followed by multiple organ failure

(Contd...)

Table 7: *(Continued)*

Author, year	Indication and inclusion	Methods	Results	Side effects
Burt *et al*, 2006[53] Case series, 49 patients	Patients with class III or IV glomerulonephritis or lung involvement (vasculitis, pneumonitis, alveolar hemorrhage), CNS involvement (cerebritis or transverse myelitis), vasculitis (biopsy proven or angiogram), biopsy proven myositis, transfusion-dependent autoimmune cytopenia, symptomatic pericardial or pleural effusions, ulcerative mucocutaneous disease, antiphospholipid syndrome refractory to treatment	Autologous HSCT Mobilization: Cyclophosphamide and G-CSF Conditioning regimen: Cyclophosphamide and equine antithymocyte globulin	At 5 years Overall survival - 84% Disease free survival - 50% No remission - 4 patients SLEDAI score improved and remained lower till 5 years Creatinine clearance - Stable	Deaths: Disseminated mucormycosis before transplantation, but after stem cell mobilization - 1, non-treatment related - 6, SLE related - 4 Infections: Pneumocystis jiroveci - 1, esophageal candidiasis - 1, gram positive bacteremia - 4 during mobilization, 14 during transplantation; peritoneal fluid: *Candida parapsilosis* – 1; blood: *Candida glabrata* – 1; immune mediated hematological: acquired factor VIII deficiency – 2, ITP – 1
Gualandi *et al*., 2007[54] Case series, 8 patients (blood - 4, marrow - 1, mobilized stem cell - 3)	Severe SLE	Autologous HSCT Mobilization: Cyclophosphamide and G-CSF Conditioning regimen: Reduced intensity protocol thiotepa and cyclophosphamide	Complete remission following transplant SLEDAI index improved from 90 to 9	Fever - All patients Relapses - 2 patients
Loh *et al*., 2007[55] Case series, 13 patients	Mean SLEDAI - 20 Impaired left ventricular ejection fraction (6), pulmonary hypertension (5), mitral valve dysfunction (3), pericardial effusion (1)	Autologous HSCT Mobilization: Cyclophosphamide and G-CSF Conditioning regimen: Intravenous cyclophosphamide with equine ATG or alemtuzumab	Disease remission Impaired LVEF - Stable or improved Mitral valve disease improved Elevated pulmonary Pressures paralleled disease activity	5 patients - Fluid overload (mobilization or transplant course) Deaths - 2 (post-transplant SLE progression). No cardiac events or transplant related deaths Relapse - 2 patients
Vanikar *et al*., 2007[56] Retrospective cohort study, 27 patients	Biopsy proven lupus nephritis with high dsDNA antibodies, ANA and low serum C3	Allogenic HSCT Mean follow-up 4.9 years	Average disease-free interval was 7.35 months (range, 2.1–12.7 months)	No GVHD in any patient
Farge *et al*, 2010[29] Multi-centre observational study, 85 patients	All consecutive patients with autoimmune diseases who underwent stem cell transplantation	Autologous HSCT Mobilization: cyclophosphamide and G-CSF or G-CSF alone Conditioning regimen: total body irradiation or single-agent chemotherapy or combinations based on cyclophosphamide, busulfan, and BEAM ± anti-thymocyte globulin	At 5 years, overall survival – 76% Progression-free survival – 44%	At 100 days, transplant-related mortality – 11%
Alchi *et al*, 2012[57] Retrospective study, 28 patients	Patients reported to EBMT registry from 2001 to 2008	Autologous HSCT	5 years overall survival: 81±8% Disease free survival: 29±9% Nonrelapse mortality: 15±7% Relapse incidence: 56±11%	Severe/life threatening AEs: 31 (15 - infections, 3 - severe immune events, 1 – post-transplant EBV associated lymphoproliferative disorder, secondary autoimmune disease - 2, cardiovascular events- 2) Deaths: 5 (3 - infections, 1 - autoimmune hemolytic anemia, 1 - disease progression)

(Contd...)

Table 7: *(Continued)*

Author, year	Indication and inclusion	Methods	Results	Side effects
Leng *et al*., 2017[58] Prospective cohort study, 27 patients	Severe SLE (WHO class III or IV lupus nephritis progressive pulmonary dysfunction or pulmonary fibrosis, recurrent flares of lupus encephalopathy, transverse myelitis or catastrophic antiphospholipid syndrome)	High-dose immunosuppressive therapy and autologous peripheral blood stem cell transplantation	21 (87.5%) cases achieved remission at 6 months 2 achieved partial remission and 1 patient died, 14 patients completed 10 years follow-up. The 10-year overall survival rate and 10 years remission survival rate were both 86%, 16 (66.7%) patients remained in remission, four were lost to follow-up, two died, and one patient remained active	Infections (CMV, bacterial, both) - 12 (44.4%) patients, nausea, vomiting, alopecia, transaminitis
Burt *et al*., 2018[59] Prospective cohort study, 30 patients	Refractory SLE, steroid dependent, having organ damage, and at high risk of mortality	Autologous HSCT using two different non-myeloablative conditioning regimens four patients (Group 1): cyclophosphamide (200 mg/kg) and alemtuzumab (60 mg) 26 patients (Group 2): cyclophosphamide (200 mg/kg), rATG (Thymoglobulin) (5.5 mg/kg), and rituximab 1000 mg	Group 1: None entered remission Group 2: Disease remission (defined as no immune suppressive drugs except hydroxychloroquine and/or ≤10 mg/day of prednisone) was 92% at 6 months, 92% at 1 year, 81% at 2 years, 71% at 3 years, and 62% at 4 and 5 years post-HSCT Conclusion- Autologous HSCT outcome is dependent on conditioning regimen	No treatment related deaths Infection - sinusitis (5), UTI (6), VZV (3), URTI (7), clostridium difficile (3), influenza (3), cellulitis (2) Others, hip AVN, adrenal insufficiency, acute ITP
Cao *et al*., 2018[60] Prospective cohort study, 22 patients	SLE with failed previous therapy (prednisolone 0.5 mg/kg at least 2 months, or methylprednisolone pulse treatment for 6 months, or cyclophosphamide 500 mg/m^2/month × 3 months)	Autologous HSCT Conditioning regimen of cyclophosphamide and ATG	3-year and 5 years Progression-free survival was 77.27% and 67.9%, respectively Overall survival rate was 95.2%. The titers of ANA, anti-dsDNA, anti-Sm antibody, and 24-h urinary protein significantly decreased, while complements 3 (C3) and C4 normalized at 100 days after transplantation (P<0.05)	Infections (virus, bacteria, PCP and TB) The incidence of CMV reactivation was 59.09% post-transplantation in 3 years

ANA: Anti-nuclear antibody, AVN: Avascular necrosis, anti dsDNA: Anti-double stranded deoxyribonucleic acid, anti-Sm: Anti-smith antibody, anti-SSA: Anti–Sjögren's-syndrome-related antigen A autoantibodies, BEAM: Carmustine, cytarabine, melphalan and etoposide, BMT: Bone marrow transplant, CMV: Cytomegalovirus, CNS: Central nervous system, EBMT: European group for blood and marrow transplantation, EBV: Epstein–Barr virus, GVHD: Graft versus host disease, CSF: Colony stimulating factor, G-CSF: Granulocyte-CSF, HSCT: Hematopoietic stem cell transplantation, ITP: Immune thrombocytopenic purpura, LVEF: Left ventricular ejection fraction, ATG: Antithymocyte antiglobulin, rATG: Rabbit ATG, PCP: Pneumocystis carinii pneumonia, SLE: Systemic lupus erythematosus, SLEDAI: SLE disease activity index, TB: Tuberculosis, URTI: Upper respiratory tract infection, UTI: Urinary tract infection, VZV: Varicella zoster virus, WHO: World Health Organization, PFTs: Pulmonary function tests, CT: Computed tomography, AEs: Adverse events

Significant progress has been made in development of novel surgical techniques in vitiligo. The surgical modalities can be broadly divided into tissue and cellular grafts. Autologous non-cultured outer root sheath hair follicle cell suspension (NCORSHFS) is a recently described cellular graft technique. It is based on principle that hair follicle melanocytes have remarkable regenerative capacity which makes them a coveted source of melanocytes, instead of epidermis, for cell based therapies in vitiligo.[81] Mohanty *et al*. in their pioneering study reported the use of NCORSHFS and reported a mean repigmentation of 65.7%.[82] More than 75% repigmentation was achieved in 9/14 (64.2%) patients. The mean repigmentation rate was significantly less in patients with disease stability of less than 12 months duration. Vinay *et al*. studied the treatment variables determining therapeutic outcome in 30 patients with 60 target lesions undergoing NCORSHFS.[83] Optimum repigmentation (> 75%) was seen in 21 of 60 (35%) lesions. The number of melanocytes (P = 0.04) and hair follicle stem cells (P = 0.01) transplanted was significantly higher among patients achieving optimum repigmentation. This, along with absence of dermal inflammation was significant predictors of achieving optimum repigmentation.

Moreover, multilineage-differentiating stress enduring (MUSE) cells are other type of stem cells that can have utility in treatment of vitiligo. *Ex vivo* studies in three-dimensional skin culture model have identified factors that induce MUSE cells to differentiate into melanocytes, which get integrated in the epidermis and lead to melanogenesis.[84] The *in vivo* effect is yet to be determined.

Scleromyxedema

Scleromyxedema is a rare chronic fibro-mucinous disorder that may result in high mortality due to respiratory complications. Lacy *et al*. studied five patients who were given high-dose chemotherapy with stem cell rescue and found that it offers durable remission in most patients, although it is not curative.[85] Illa *et al*. successfully treated scleromyxedema with chemotherapy and autologous stem cell transplantation.[86] Full recovery was achieved at six months and the patient continued to be in remission three years after the transplantation.

Alopecia

Although application of stem cell therapy in hair restoration is relatively new and the stem cell isolation techniques are varied, the results to date are promising in both androgenetic alopecia (AGA) and alopecia areata (AA). Anderi *et al*. harvested autologous adipose-derived stromal vascular cells through lipoaspiration and injected into the scalp of 20 patients with AA.[87] At three and six months of follow-up, they found statistically significant hair growth in all the patients. Adipose-derived stem cell conditioned medium (ADS-CM), known to be rich in growth factors such as vascular endothelial growth factor, hepatocyte growth factor, platelet-derived growth factor, and insulin-like growth factor ILGF, has also be utilized to treat hair loss.[88] Gentile *et al*. isolated human adult stem cells by the centrifugation of human hair follicles obtained through punch biopsy and injected them into the scalps of 11 AGA patients resulting in an increase in hair density and count compared to baseline and placebo.[89] Elmaadawi *et al*. who randomly assigned 40 patients (20 with AGA and 20 with AA) to receive either autologous bone marrow-derived mononuclear cells or autologous follicular stem cell injections into the scalp, found significant improvement in hair loss with no significant difference between the two preparations.[90] Li *et al*. introduced a novel stem cell method, termed "stem cell educator therapy" in which patient's mononuclear cells are separated from whole blood and allowed to interact with human cord blood–derived multipotent stem cells, and these "educated" cells are returned to patient's circulation.[91] Of nine patients with severe AA, all but one experienced improved hair regrowth of varying degrees. Two patients (one with alopecia totalis and one with patchy AA) experienced complete hair regrowth at 12 weeks without relapse after two years. A combination of platelet-rich plasma and stem cell technology has also shown promising results.[92]

Human Immunodeficiency Virus

Till date, there is no curative therapy for HIV. HIV binds to CD4 receptor, after which it needs CXCR4 or CCR5 as a co-receptor for gaining entry into the target cell. In 2009, Hütter *et al*. reported a case, known as the "Berlin patient", of acute myeloid leukemia with HIV-1 infection who received allogenic HSCT twice from a donor with homozygous CCR5 delta32 allele. After transplantation, highly active anti-retroviral therapy (HAART) was stopped and the patient remained in remission at 20 months follow-up.[93]

Ten years later, another HIV patient of Hodgkin's lymphoma underwent allogenic transplantation from donor with homozygous CCR5 delta32 allele following which antiretroviral therapy could be stopped after 16 months post-transplant and the patient was in remission after 18 months of stopping ART.[94]

Merkel Cell Carcinoma

It is a rare cutaneous tumor with no standard treatment protocol of metastatic disease. In recent years, there has been an increased understanding of Merkel cell carcinoma biology, especially with regard to the Merkel cell polyomavirus as the causative agent, suggesting that healthy human skin harbors resident or transient polyomavirus capable of neoplastic transformation. Significant differences between polyomavirus-positive and polyomavirus-negative Merkel cell carcinomas in terms of morphology, gene expression, signaling pathways, genomic and epigenetic alterations, microRNA profiles, dysregulated immune surveillance, aberrant protein expression and post-translational modifications have been reported, which influence the overall prognosis of Merkel cell carcinoma.[95] Recent works suggest that polyomavirus-positive and negative Merkel cell carcinomas arise from two different cells of origin: the virus-negative carcinoma from epidermal stem cells and the virus-positive Merkel cell carcinoma from dermal stem cells.[96] Further research on possible involvement of Merkel cell carcinoma stem cells could provide platform significant basis for preclinical development of targeted therapeutics. Anecdotal report of polychemotherapy with autologous peripheral blood stem cell transplantation resulted in remission, though it lasted only six months.[97]

Melanoma

Melanoma is an aggressive, relatively radio- and chemo-resistant tumor which is difficult to treat even with novel therapies including oncogene-directed therapy and immunotherapy. Recently, it has been suggested that cancer is a disease in which the persistence of the tumor relies on a small population of tumor-initiating cells, the tumor stem cells. This concept, though initially established for human myeloid leukemia, has been recently considered for melanoma (melanoma stem cells).[98] These tumor stem cells are capable of self-renewal and thereby possess the ability for unlimited proliferation, are resistant to many therapeutic approaches and induce tumor relapse. Therefore, future therapies can be targeted at melanoma stem cell biomarkers, microenvironment and melanoma stem cells as a treatment option. Melanoma stem cells have been shown to express CD20 surface marker, ABCB5 (an ABC transporter protein), along with other markers including CD133, CD271 and aldehyde dehydrogenase.[99] Since melanoma stem cells express CD20, rituximab, has been attempted in clinical trials to treat melanoma, producing regression in chemotherapy-refractory melanoma. Similarly, a monoclonal antibody against ABCB5+ melanoma stem cells in mouse models showed tumor inhibitory effects.[100] Molecules involved in the mitogen-activated protein kinase (MAPK) signaling could represent interesting targets to overcome melanoma resistance as it has been shown that MAPK activation by mutant B-RAF drives melanoma tumor proliferation and that resistance to B-RAF inhibitors can be (or not) associated with reactivation of the MAPK pathway ("escape route").[101] The tumorigenic potential of tumor stem cells may be reduced by inhibition of essential stem cell factors or the therapeutic administration of differentiation factors.[102]

Aesthetic Medicine

Adipose-derived stem cells have been shown to activate fibroblasts and secrete various growth factors which lead to antioxidant, pigment lightening and wound-healing effects in the skin.[103] They have been used effectively to treat wrinkles in animal models.[104] Fibroblasts play a crucial role in wound healing and by their ability to restore lost dermal constituents; cultured autologous fibroblasts show promising future in aesthetic medicine.[105]

Current Status of Stem Cell Therapy in India

National Guidelines for Stem Cell Research, 2017, brought out by Indian Council of Medical Research (ICMR) and Department of Biotechnology (DBT), provides the basic guidelines needed for stem cell research in India.

These guidelines enumerate the various ethical issues, screening, categorization of research, levels of stem cell manipulation, stem cell research, manufacturing and release criteria for stem cells, procurement and banking, therapeutic uses, publicity and advertisements. The guidelines state that "The commercial use of stem cells as elements of therapy is prohibited. It must be emphasized that no stem cell administration to humans is permissible outside the purview of clinical trials".[106]

At present, only hematopoietic stem cell therapy has been approved in India as per National Guidelines formulated by ICMR and DBT. According to the Ministry of Health and Family Welfare in 2017, there are 60 centers offering stem cell therapy in India. Western railway hospital, Vadodara, IKDRC, Ahmedabad and New Civil Hospital, Surat are the government institutions in the list of centers.[107] The list of all the centers is included as an addendum.

According to the american society for blood and marrow transplantation, hematopoietic stem cell therapy is approved in about 31 diseases in adults and 43 diseases in children.[42] The approved indications include hematological malignancies, solid tumors, non-malignant diseases (e.g., aplastic anemia, Fanconi's anemia, dyskeratosis congenita and juvenile rheumatoid arthritis). Among dermatological diseases, the use of hematopoietic stem cell therapy had been approved in systemic sclerosis in children (<18 years of age) but not in adults by the Task force of ASBMT.

Difficulties in Stem Cell Therapy

- Ethical considerations: These include issues of consent, confidentiality, screening for transmissible diseases and procedural risks.
- Legal issues: There are many unauthorized centers in India that offer unproven stem cell therapies. The limitation is that, currently, the best available is only guidelines and not laws, due to which there is a gap between recommendation and implementation. A way to curb this practice is by making stringent rules and considering all stem cells and its products as drugs requiring drug trials before approval for a particular disease management.[108]
- Possibility of graft rejection in allografting.
- Tumorigenicity of pluripotent stem cells – Undesirable mutations may occur in stem cells when maintained for prolonged periods in culture and they may aberrantly differentiate to form tumors.
- The consequence of preservation of stem cells or their products on their viability and potency must be assessed.
- The quality control of cell processing and manufacturing must conform to the rules lain in Schedule M of Drugs and Cosmetics Act, 1940, which is sine qua non for all clinical trials.
- Future research regarding ideal patient selection, timing of intervention, appropriate conditioning regimens, post-intervention care and cost effectiveness would help to optimize the results of stem cell therapy.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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