Journal of Stem Cell Research and Medicine

Review Article ISSN: 2398-6530

Mesenchymal stromal cells therapy in radiation oncology regenerative medicine

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Abstract

Mesenchymal stromal cells (MSCs) are multipotent somatic cells resident in many tissues and organs. They have specific characteristics that distinguish them from other cell types. They are self-renewing cells with multi-lineage differentiation potential. In addition, they possess anti-inflammatory and immunomodulatory properties. Studies have shown that they could be used as vehicles to deliver certain therapeutic gene products as well. These cells possess secretory capabilities of certain cytokines and growth factors that mediate various paracrine effects. They increase the secretion of the anti-inflammatory interleukin-10 (IL-10) together with lowering the availabilities of tumor necrosis factor-alpha (TNF-α), interferon-gamma (INF-γ), and interleukin -1-beta (IL-1β) by signaling to the immune system elements, e.g. dendritic cells, T-cells, B-cells, and natural Killer cells (NK cells). Recently, studies have investigated such anti-inflammatory properties of MSCs in the repair of radiation-induced normal tissue injury, also called radiation oncology regenerative medicine (RORM), supported by the recently known MSCs radiation resistance potential. In this review, we summarize MSCs radio-resistant mechanisms, anti-inflammatory properties, and their application in RORM with special attention to adipose tissue-derived MSCs (aMSCs).

Abbreviations: aMSCs: Adipose tissue-derived mesenchymal stromal cells, ATM: Ataxia telangiectasia mutated protein, b-FGF: Basic fibroblast growth factor, Chk: Check point cell cycle kinase, DSB: Double stranded DNA breaks, HGF: Hepatocyte growth factor, HR: Homologous recombination,HSCs: Hematopoietic stem cells, IL-10: Interleukine-10, IL-1β: Interleukine-1-beta, IDO: Indoleamine 2,3-dioxygenase, INF-γ: Interferon-gamma, MSCs: Mesenchymal stromal cells, NHEJ: Non-homologous end-joining, NK: Natural killer cells, NO: Nitric oxide, PGE2: Prostaglandin-E2, RORM: Radiation oncology regenerative medicine, TGF-β: Tumor growth factor-beta, TNF-α: Tumor necrosis factor-alpha

Introduction

Mesenchymal stromal/Stem cells (MSCs) are multipotent somatic progenitor cells that have been isolated from different tissues, such as bone marrow, adipose tissue, muscles and skin [1-3]. They can be expanded ex-vivo to hundreds of million cells, maintaining their phenotype and characteristics, and used as therapies in different diseases [1-3]. Another property of these cells is their homing to the site of tissue injury, an ability that widens the choices for their route of administration [2,4,5]. In addition to their multi-lineage differentiation potential [6], these cells possess anti-inflammatory and immunomodulatory properties and paracrine effects that qualified them for regenerative medicine applications (Figure 1) [7-11]. Furthermore, MSCs could be genetically engineered and used as vehicles for delivering therapeutic gene products [12-14]. Studies in radiotherapy have shown that MSCs can be recruited to the radiation injury site where they secrete many cytokines and growth factors, e.g. prostaglandin-E2 (PGE2), nitric oxide (NO), hepatocyte growth factor (HGF), interleukin-10 (IL-10), tumor growth factor-beta (TGF-β), and indoleamine 2,3-dioxygenase (IDO) [15]. These soluble mediators inhibit the major components of the immune system and inflammation, e.g. dendritic cells, T-cells, B-cells, and natural killer cells (NK cells) [15]. The final result will be an increase in the secretion of the anti-inflammatory interleukin-10 (IL-10) together with lowering the availability of pro-inflammatory mediators and cytokines, e.g. tumor necrosis factor-alpha (TNF-α), interferon-gamma (INF-γ), and interleukin -1-beta (IL-1β) [15] (Figure 1).

Mesenchymal stromal cells (MSCs) clinical trials in various disorders

MSCs have been applied for various repairs, such as of arthritis [16], cardiac muscle [17,18], lung tissue [14], diabetes [19], skin [20-23], skeletal tissue [24], and digestive tract tissue [12,25,26]. Table 1 shows 92 recent clinical trials for MSCs therapies in various disorders.

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Key words: *adipose tissue, anti-inflammatory, cell cycle, DNA repair, mesenchymal stromal cells, msc, normal tissue injury, radiation oncology regenerative medicine, radiation resistance*

Received: June 05, 2016; **Accepted:** July 04, 2016; **Published:** July 07, 2016

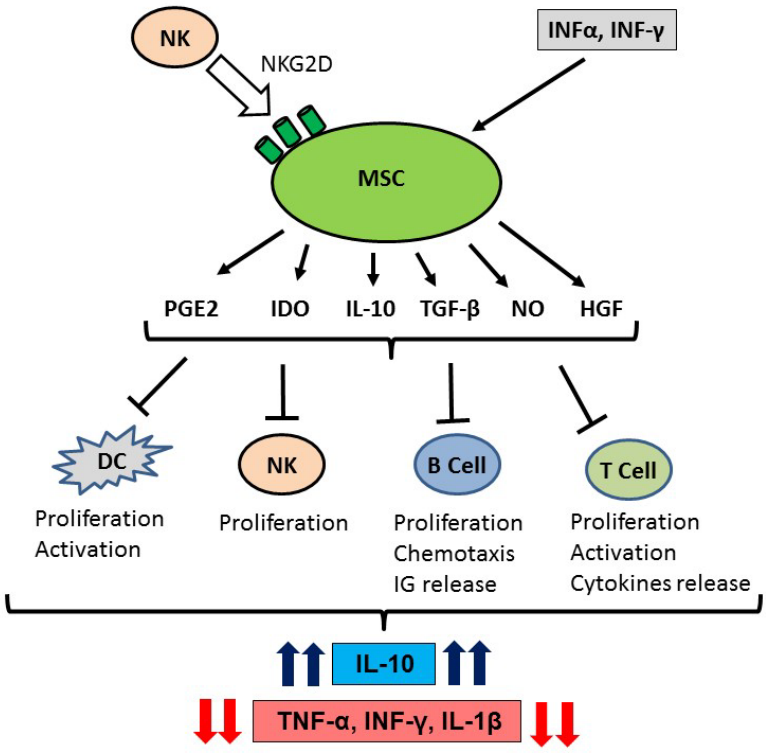

Figure 1. MSCs anti-inflammatory properties
MSCs recruited to the radiation injury site secrete many cytokines and growth factors, e.g. prostaglandin-E2 (**PGE2**), nitric oxide (**NO**), hepatocyte growth factor (**HGF**), interleukin-10 (**IL-10**), tumor growth factor-beta (**TGF-β**), and indoleamine 2,3-dioxygenase (**IDO**). These soluble mediators inhibit the major components of the immune system and inflammation, e.g. dendritic cells, T-cells, B-cells, and natural killer cells (NK cells). The final result will be an increase in the secretion of the anti-inflammatory interleukin-10 (**IL-10**) together with lowering the availability of the pro-inflammatory mediators and cytokines, e.g. tumor necrosis factor-alpha (**TNF-α**), interferon-gamma (**INF-γ**), and interleukin -1-beta (**IL-1β**) [15].

MSCs radio-biological response

The exposure of MSCs to ionizing radiation (IR) induces direct and indirect double stranded DNA breaks (DSB) which are detected by Poly (ADP-ribose) polymerase (PARP) and heterodimeric Ku protein complex (Ku70/80) sensor proteins [27,28]. At the DSB location, PARP started the signal amplification upon formation of the Mre11, RAD50, and NBS-1 protein complex which leads to recruitment and auto-phosphorylation of Ataxia Telangectasia mutated protein (ATM). Phosphorylated ATM (p-ATM) is a main station that leads to multiple downstream signals. P-ATM enhances the phosphorylation of histone H2X (to γ-H2AX) and DNA-PK (to p-DNA-PK), phosphorylates P53 (a tumor suppressor regulatory protein), activates the cell cycle checkpoint effector protein kinases (Chk-1 and Chk-2), and prepares for cell cycle arrest (G2/M). In addition, the Chk1 activation is augmented by the replication stress-mediated ATR pathway (through replication protein A, RPA), while the Chk2 activation is enhanced directly through Ku70/80-mediated p-DNA-PK signaling [27,28]. Cell division cycle phosphatase (Cdc25) is crucial for removing the inhibitory phosphorylation on specific residues on the cyclin-dependent kinase (Cdk). Chk1 phosphorylates Cdc25 in the presence of DNA damage resulting in the inhibition of Cdc25 activity. Chk1 and Chk2 are main inhibitors of Cdc25A and Cdc25C resulting in Cdk/cyclin-mediated cell cycle arrest [29]. It has been suggested that DSB in MSCs are repaired by activation of both the homologous recombination (HR, during S and G2 phases) and the non-homologous end-joining (NHEJ, during all cell cycle phases) DNA repair pathways [27,28,30]. Our recent study showed the activation of HR and NHEJ repair pathways in irradiated aMSCs [31]. In addition, p-ATM enhances the stabilization of the tumor suppressor regulatory protein and transcription factor P53 which up-regulates the expression and enhances the stabilization of the transcription factor and inhibitory regulatory protein p21, which potently inhibits Cdks which are needed for the G1/S transition leading to inhibition of the entry into S phase [27].

The application of MSCs in radiation oncology regenerative medicine (RORM) was enhanced by their efficient radiation-induced DNA repair machinery and their relative radiation resistance [30-34]. Such radiation resistance was mediated by many mechanisms, e.g. the ATM phosphorylation, activation of cell cycle check points (G2/M arrest), and activation of single and double stranded DNA repair by both homologous and non-homologous recombination mechanisms and other pathways [30,31] (Figure 2). DSB resulting from the direct and indirect radiation injury stimulate the phosphorylation of ATM which is the proximal step for cell cycle check point's activation (G2/M arrest). In addition, the nuclear apoptotic factor P84 (P84/53E10 = the nuclear protein encoded by the N5 gene) is up regulated, which participates in the apoptotic response of the aMSCs. It has been documented that irradiated aMSCs showed p-ATM dependent and p-ATM independent (P84-mediated) G2/M arrest [31]. Phosphorylated histone-2AX (γ-H2AX) stimulated both the HR and the NHEJ of the dsDNA breaks and other repair mechanisms [35]. Rad-51 is considered one of the mandatory proteins for HR to occur. DNA-PK is the major protein in the NHEJ repair pathway. Studies have shown that both proteins (Rad-51 and DNA-PK) were up regulated in irradiated MSCs (Figure 2) [28,30,31].

Table 1. Mesenchymal Stromal cells (MSCs) clinical trials in various disorders as listed on www.ClinicalTrials.gov by the National Institute of Health (NIH) by Nov. 2015.

NCT #	Title	Conditions	Interventions	Last Verified
NCT01589549	Mesenchymal Stromal Cells for Acute Graft Versus Host Disease	Acute GVH Disease	Biological: Mesenchymal stromal cell therapy	Jun-15
NCT02057965	Mesenchymal Stromal Cell Therapy in Renal Recipients	Renal Transplant Rejection|Fibrosis	Drug: Mesenchymal Stromal Cells	Mar-15
NCT02032446	Umbilical Cord Derived Mesenchymal Stromal Cells For The Treatment of Severe Steroid-resistant Graft Versus Host Disease	Hematologic Malignancies	Biological: UMBILICAL CORD DERIVED MESENCHYMAL STROMAL CELLS (UC-MSC)	Apr-15
NCT02012153	Mesenchymal Stromal Cells in Kidney Transplant Recipients	Kidney Transplant Rejection	Biological: Mesenchymal Stromal Cells	Oct-15
NCT01090817	An Australian Study of Mesenchymal Stromal Cells for Crohn's Disease	Crohn Disease	Drug: Mesenchymal stromal cells (MSC) for infusion	Jun-15
NCT00644410	Autologous Mesenchymal Stromal Cell Therapy in Heart Failure	Congestive Heart Failure	Biological: Mesenchymal stromal cell| Biological: Saline	Mar-15
NCT01061099	Repeated Infusions of Mesenchymal Stromal Cells in Children With Osteogenesis Imperfecta	Osteogenesis Imperfecta Type II| Osteogenesis Imperfecta Type III	Biological: Mesenchymal Stromal Cells	Apr-15
NCT02150551	Safety and Tolerability Of Allogeneic Mesenchymal Stromal Cells in Pediatric Inflammatory Bowel Disease	Inflammatory Bowel Diseases	Biological: Allogeneic bone marrow-derived mesenchymal stromal cells	Sep-15
NCT01522716	Mesenchymal Stromal Cells as Treatment of Chronic Graft-versus-host Disease	Graft-Versus-Host Disease	Biological: Mesenchymal stromal cells	Nov-15
NCT02323789	A Phase I/II Study Evaluating Allogeneic Mesenchymal Stromal Cells in Adults With Recessive Dystrophic Epidermolysis Bullosa	Recessive Dystrophic Epidermolysis Bullosa	Drug: Mesenchymal stromal cells	Dec-14
NCT02291770	Treatment of Chronic Graft-Versus-Host Disease With Mesenchymal Stromal Cells	Chronic Graft-Versus-Host Disease	Biological: Mesenchymal Stromal Cells	Nov-14
NCT01764100	Mesenchymal Stromal Cells (MSCs) for the Treatment of Graft Versus Host Disease (GVHD)	Graft vs Host Disease	Genetic: Mesenchymal stromal cells	Jan-13
NCT02230514	Mesenchymal Stromal Cells for the Treatment of Non-union Fractures of Long Bones	Atrophic Nonunion of Fracture	Drug: XCEL-MT-OSTEO-ALPHA|Other: autologous iliac crest| Procedure: Surgery	Jul-15
NCT02215811	Treatment of Severe Acute Respiratory Distress Syndrome With Allogeneic Bone Marrow-derived Mesenchymal Stromal Cells	Acute Respiratory Distress Syndrome, Adult	Biological: Mesenchymal stromal cells	Aug-14
NCT01449032	Mesenchymal STROMAL CELL Therapy in Patients With Chronic Myocardial Ischemia (My Stromal Cell Trial)	Chronic Ischemic Heart Disease	Biological: MSC| Biological: Saline	Jun-14
NCT02580695	A Study to Assess Safety and Efficacy of Umbilical Cord-derived Mesenchymal Stromal Cells in Knee Osteoarthritis	Osteoarthritis	Biological: umbilical-cord mesenchymal stromal cells| Drug: Hyaluronic Acid	Oct-15
NCT01038596	Mesenchymal Stromal Cells and Osteoarthritis	Osteoarthritis		Dec-09
NCT02495766	Autologous Mesenchymal Stromal Cells for Multiple Sclerosis	Relapsing-Remitting Multiple Sclerosis| Secondary Progressive Multiple Sclerosis	Drug: XCEL-MC-ALPHA|Drug: Placebo	Nov-15
NCT02565459	MSC and Kidney Transplant Tolerance (Phase A)	Chronic Renal Failure	Biological: Mesenchymal Stromal Cells	Sep-15
NCT01849237	Russian Clinical Trial of Mesenchymal Cells in Patients With Septic Shock and Severe Neutropenia	Septic Shock| Nonchemotherapy Drug-induced Neutropenia| Neutropenia After Chemotherapy in Oncohematological Patients| Neutropenia in Patients With Aplastic Anemia	Genetic: Mesenchymal stromal cells|Drug: Standard therapy of septic shock	May-13
NCT02387151	Allogeneic Mesenchymal Stromal Cell Therapy in Renal Transplant Recipients	Rejection|Graft Loss	Procedure: mesenchymal stem cell infusion	Mar-15
NCT01175655	A Study to Evaluate the Potential of Mesenchymal Stromal Cells to Treat Obliterative Bronchiolitis After Lung Transplantation	Bronchiolitis Obliterans|Lung Transplantation	Other: MSC	Apr-15
NCT00957931	Allo-HCT MUD for Non-malignant Red Blood Cell (RBC) Disorders: Sickle Cell, Thal, and DBA: Reduced Intensity Conditioning, Co-tx MSCs	Sickle Cell Disease| Thalassemia| Diamond-Blackfan Anemia	Procedure: Bone marrow transplantation| Biological: Mesenchymal Stromal Cells	Dec-12
NCT01742260	Cranial Reconstruction Using Mesenchymal Stromal Cells and Resorbable Biomaterials	Surgically-Created Resection Cavity	Procedure: Repair of cranial defects by tissue engineering	Jun-15
NCT02260375	MSC Therapy in Liver Transplantation	Liver Transplant Rejection	Biological: Mesenchymal Stromal Cells	Sep-15
NCT01872624	Safety Study of Bone-marrow Derived Mesenchymal Stromal Cells Associated With Endobronchial Valves in Emphysema	Pulmonary Emphysema	Procedure: Bronchoscopy	Mar-15
NCT01586312	Treatment of Knee Osteoarthritis With Allogenic Mesenchymal Stem Cells	Osteoarthritis, Knee|Arthritis of Knee|Knee Osteoarthritis	Other: Allogenic mesenchymal stromal cells injection|Drug: Hyaluronic Acid	Sep-15

NCT01860417	Treatment of Degenerative Disc Disease With Allogenic Mesenchymal Stem Cells (MSV)	Degenerative Disc Disease| Intervertebral Disc Disease|Low Back Pain	Biological: Allogenic Mesenchymal Stromal Cells| Drug: Mepivacaine	Sep-15
NCT02384018	Mesenchymal Stem Cell and Islet Co-transplantation	Chronic Pancreatitis| Diabetes	Biological: autologous mesenchymal stromal cell	Dec-14
NCT01306513	Safety and Feasibility Study of Administration of Mesenchymal Stem Cells for Treatment of Emphysema	Emphysema	Biological: autologous bone marrow derived mesenchymal stromal cells	Nov-12
NCT02359929	BMT Auto MSCs GvHD Ph1	Graft Versus Host Disease|Acute Graft Versus Host Disease|Chronic Graft Versus Host Disease	Biological: Autologous mesenchymal stromal cells (MSCs)	Aug-15
NCT02585622	Novel Stromal Cell Therapy for Diabetic Kidney Disease	Diabetic Kidney Disease	Biological: Mesenchymal Stromal Cells| Other: Placebo	Oct-15
NCT02033525	Mesenchymal Stromal Cells for Degenerative Meniscus Injury	Chronic Meniscal Injury	Drug: XCEL-M-ALPHA and standard rehabilitation| Other: Rehabilitation	Jul-15
NCT02589119	Stem Cell Fistula Plug in Cryptoglandular Perianal Fistulas (MSC-AFP)	Perianal Fistula| Cryptoglandular Perianal Fistula	Drug: MSC-AFP	Oct-15
NCT02421484	Cellular Immunotherapy for Septic Shock: A Phase I Trial	Septic Shock	Biological: Allogeneic bone marrow derived mesenchymal stromal cells	Apr-15
NCT02055625	Mesenchymal Stem Cells as a Treatment for Oral Complications of Graft-versus-host Disease	Graft -Versus-host-disease	Biological: Mesenchymal stromal cells	Mar-15
NCT02408432	Intravenous Administration of Allogeneic Bone Marrow Derived Multipotent Mesenchymal Stromal Cells (MSCs) in Patients With Recent Onset Anthracycline-Associated Cardiomyopathy	Cardiomyopathy	Biological: Human Mesenchymal Stem Cells (hMSCs)|Other: Standard of Care	Jun-15
NCT02181478	Intra-Osseous Co-Transplant of UCB and hMSC	Acute Lymphoblastic Leukemia| Acute Myelogenous Leukemia| Myelodysplastic Syndromes| Myelofibrosis| Relapsed Non-Hodgkin Lymphoma| Refractory Non-Hodgkin Lymphoma| Hodgkin Lymphoma| Refractory Hodgkin Lymphoma| Relapsed Chronic Lymphocytic Leukemia| Refractory Chronic Lymphocytic Leukemia| Lymphoid Malignancies| Chronic Myelogenous Leukemia	Drug: cyclophosphamide| Drug: fludarabine phosphate| Radiation: total-body irradiation|Drug: cyclosporine|Drug: mycophenolatemofetil|Procedure: umbilical cord blood transplantation| Procedure: mesenchymal stem cell transplantation	Jul-15
NCT02351011	Human Autologous MSCs for the Treatment of Mid to Late Stage Knee OA	Osteoarthritis of Knee	Biological: 1 x 10^6 MSCs|Biological: 10 x 10^6 MSCs|Biological: 50 x 10^6 MSCs	Feb-15
NCT02270307	MSC and Cyclophosphamide for Acute Graft-Versus-Host Disease (aGVHD) Prophylaxis	Leukemia| Multiple Myeloma	Drug: Cyclophosphamide| Biological: Mesenchymal stromal cells	Oct-14
NCT01922908	Mesenchymal Stromal Cells for Ischemic Stroke	Ischemic Stroke	Biological: MSC Infusion|Biological: Placebo Comparator	May-15
NCT02145923	Effectiveness and Safety of MMSCs for Enhancing Hematopoietic Recovery and Prophylaxis of Neutropenic Enterocolitis	NeutropenicEnterocolitis| Myeloablative Chemotherapy Induced Bone Marrow Aplasia	Procedure: Peripheral blood stem cell mobilisation and collection|Drug: High-dose chemotherapy| Drug: Bone marrow derived allogeneic MMSCs infusion|Procedure: Autologous peripheral blood stem cells infusion	Jun-15
NCT01275612	Mesenchymal Stem Cells In Cisplatin-Induced Acute Renal Failure In Patients With Solid Organ Cancers	Solid Tumors| Acute Kidney Injury	Biological: Mesenchymal stromal cell infusion	Oct-15
NCT01909154	Safety Study of Local Administration of Autologous Bone Marrow Stromal Cells in Chronic Paraplegia	Spinal Cord Injury	Biological: Mesenchymal stromal cell therapy	Nov-13
NCT00395200	Mesenchymal Stem Cells in Multiple Sclerosis (MSCIMS)	Multiple Sclerosis	Procedure: MSC Treatment	Oct-11
NCT00260338	Stem Cell Therapy for Vasculogenesis in Patients With Severe Myocardial Ischemia	Myocardial Ischemia| Coronary Heart Disease	Biological: stem cell	May-13
NCT01659762	A Phase I Study Evaluating Autologous Bone Marrow Derived Mesenchymal Stromal for Crohn's Disease.	Crohn's Disease	Biological: autologous mesenchymal stromal cell	Jul-15
NCT02382874	Allogenic AD-MSC Transplantation in Idiopathic Nephrotic Syndrome (Focal Segmental Glomerulosclerosis)	Focal Segmental Glomerulosclerosis	Biological: Intravenous injection	Mar-15
NCT02448849	Autologous BM-MSC Transplantation in Combination With Platelet Lysate (PL) for Nonunion Treatment	Bone Fracture	Biological: Percutaneous injection| Other: Percutaneous injection	Sep-15
NCT01915927	Stem Cell Fistula Plug in Perianal Crohn's Disease	Perianal Crohn's Disease	Drug: MSC-AFP	Jun-15
NCT01686139	Safety Study of Stem Cells Treatment in Diabetic Foot Ulcers	Type I Diabetes Mellitus With Ulcer| Type II Diabetes Mellitus With Ulcer	Biological: ABMD-MSC	Jan-14
NCT02017912	Phase 2, Randomized, Double Blind, Placebo Controlled Multicenter Study of Autologous MSC-NTF Cells in Patients With ALS	Amyotrophic Lateral Sclerosis (ALS)	Biological: Autologous MSC-NTF cells	Jul-15

NCT01463475	University of Wisconsin hMSC Cell Bank: Bone Marrow Donor Protocol	Graft Versus Host Disease (GVHD)|Acute Myocardial Infarction (AMI)	Procedure: Bone marrow aspirate	Dec-14
NCT02195323	Autologous Bone Marrow Derived Mesenchymal Stromal Cells (BM-MSCs) in Patients With Chronic Kidney Disease (CKD)	Chronic Kidney Disease	Biological: Intravenous injection	Oct-13
NCT02409940	To Elucidate the Effect of Mesenchymal Stem Cells on the T Cell Repertoire of the Kidney Transplant Patients	Renal Transplant Rejection	Biological: Mesenchymal Stem Cells	Apr-15
NCT00908856	Autologous Cell Therapy After Stroke	Stroke	Biological: autologous bone marrow mononuclear cell transfusion| Biological: marrow stromal cells| Drug: placebo	Dec-14
NCT02247973	Mesenchymal Stem Cells Co-transplantation in Alternative Donor Transplantation of Severe Aplastic Anemia.	Severe Aplastic Anemia	Biological: mesenchymal stem cells| Biological: mesenchymal stem cells	Sep-14
NCT01446614	Mesenchymal Stem Cells Transplantation to Patients With Parkinson's Disease	Parkinson's Disease	Biological: bone marrow derived mesenchymal stem cells	Oct-11
NCT01446640	Mesenchymal Stem Cells Transplantation to Patients With Spinal Cord Injury	Spinal Cord Injury	Biological: bone marrow derived mesenchymal stem cells	Oct-11
NCT01305694	Mesenchymal Stem Cells Transplantation to Patients With Relapsed/Refractory Aplastic Anemia.	Aplastic Anemia	Biological: bone marrow derived mesenchymal stem cells	Feb-11
NCT01051882	Autologous Cultured Mesenchymal Bone Marrow Stromal Cells Secreting Neurotrophic Factors (MSC-NTF), in ALS Patients.	Amyotrophic Lateral Sclerosis	Biological: MSC-NTF cells transplantation (i.m.)| Biological: MSC-NTF cells transplantation (i.t.)	Aug-12
NCT01624701	Clinical Ex Vivo Expansion of Human Umbilical Cord Blood Stem and Progenitor Cells	Acute Leukemia| Chronic Leukemia| Myelodysplastic Syndrome| Lymphoma| Myeloma	Other: Ex-vivo expanded cord blood cells	Jun-12
NCT02336230	A Prospective Study of Remestemcel-L, Ex-vivo Cultured Adult Human Mesenchymal Stromal Cells, for the Treatment of Pediatric Patients Who Have Failed to Respond to Steroid Treatment for Acute GVHD	Grades B-D aGVHD	Drug: Remestemcel-L	Jan-15
NCT02525432	Autologous Stem Cell Study for Adult TBI (Phase 2b)	Brain Injuries, Traumatic| Brain Injuries, Acute| TBI (Traumatic Brain Injury)	Biological: Placebo Infusion| Biological: Autologous BMMNC Infusion| Device: Ultrasound	Oct-15
NCT02209311	Effectiveness and Safety of Method of Maxilla Alveolar Process Reconstruction Using Synthetic Tricalcium Phosphate and Autologous MMSCs	Partially Edentulous Maxilla| Alveolar Bone Atrophy| Alveolar Bone Loss	Procedure: Oral mucosa biopsy| Procedure: Sinus lift with implantation of tissue engineered construction| Device: Dental implant	Sep-15
NCT02379442	Early Treatment of Acute Graft Versus Host Disease With Bone Marrow-Derived Mesenchymal Stem Cells and Corticosteroids	Graft-Versus-Host Disease	Biological: MSC	Feb-15
NCT01144962	Dose-escalating Therapeutic Study of Allogeneic Bone Marrow Derived Mesenchymal Stem Cells for the Treatment of Fistulas in Patients With Refractory Perianal Crohn's Disease	Crohn's Disease| Fistula	Procedure: Localization, curettage of the fistulous tract and closure of the internal opening without MSC injection.| Procedure: Localization, curettage of the fistulous tract and closure of the internal opening with local MSC injection.	Dec-14
NCT02448121	Autologous Bone Marrow Stem Cell Transplantation for Hip Osteonecrosis in Sickle Cell Disease	Avascular Necrosis of Femur Head| Sickle Cell Disease	Procedure: Stem Cell Graft Group| Biological: Autologous bone marrow stem cell	Aug-15
NCT01892514	Randomized Clinical Trial for the Treatment of Osteonecrosis of the Femoral Head	Osteonecrosis	Procedure: core decompression	Apr-14
NCT02249676	Autologous Mesenchymal Stem Cells for the Treatment of NeuromyelitisOptica Spectrum Disorders	Devic's Syndrome| Devic'sNeuromyelitisOptica| Devic Syndrome| Devic's Disease| Devic Disease	Biological: Autologous mesenchymal stem cells	Sep-14
NCT02482194	Autologous Mesenchymal Stem Cells Transplantation for Spinal Cord Injury- A Phase I Clinical Study	Spinal Cord Injury	Biological: mesenchymal stem cells	Jun-15
NCT00731744	Generation of Dendritic Cell Precursors From Cord Blood Stem Cells	Normal Full-Term Deliveries	Procedure: Normal full-term deliveries	Aug-08
NCT02037204	IMPACT: Safety and Feasibility of a Single-stage Procedure for Focal Cartilage Lesions of the Knee.	Foreign-Body Reaction| Inflammation| Effusion (L) Knee| Knee Pain Swelling	Other: Cartilage repair surgery	Jul-14
NCT01993368	Analysis of Osteoimmune Interactions Linking Inflammation and Bone Destruction in Aggressive Periodontitis	Aggressive Periodontitis| Chronic Periodontitis	Other: flow cytometry	Sep-15
NCT01777646	Autologous Cultured Mesenchymal Bone Marrow Stromal Cells Secreting Neurotrophic Factors (MSC-NTF), in Patients With Amyotrophic Lateral Sclerosis (ALS)	Amyotrophic Lateral Sclerosis	Biological: MSC_NTF cells transplantation by multiple intramuscular injections at 24 separate sites, in addition to a single intrathechal injection into the CSF	Jan-14
NCT01468064	Autologous Bone Marrow Stromal Cell and Endothelial Progenitor Cell Transplantation in Ischemic Stroke	Stroke| Infarction, Middle Cerebral Artery	Genetic: Autologous BMSCs transplantation| Genetic: Autologous EPCs transplantation| Genetic: IV infusion of placebo	Nov-15

NCT01071577	Collection of Bone Marrow From Healthy Volunteers and Patients for the Production of Clinical Bone Marrow Stromal Cell (BMSC) Products	Bone Marrow| Bone Marrow Stromal Cells| Mesenchymal Stem Cells| Blood Donors		Aug-15
NCT00186914	Stromal Therapy of Osteodysplasia After Allogeneic Bone Marrow Transplantation	Osteodysplasia	Biological: Marrow stromal cell infusion	Feb-08
NCT00781872	Mesenchymal Stem Cells for the Treatment of MS	Multiple Sclerosis	Biological: injection of autologous stem cells	Oct-08
NCT02467387	A Study to Assess the Effect of Intravenous Dose of (aMBMC) to Subjects With Non-ischemic Heart Failure	Non-Ischemic Heart Failure	Drug: Allogeneic Mesenchymal Bone Marrow Cells (aMBMC)| Drug: Lactated Ringer's Solution	Jun-15
NCT02442817	Linagliptin and Mesenchymal Stem Cells: A Pilot Study	Schizophrenia	Drug: Linagliptin	Apr-15
NCT02064062	Autologous Stem Cells in Achilles Tendinopathy	Achilles Tendinitis, Right Leg| Achilles Tendinitis| Achilles Degeneration| Achilles Tendon Thickening| Tendinopathy| Achilles Tendinitis, Left Leg	Biological: Autologous Mesenchymal Stem Cells	Feb-14
NCT01840540	MSC for Occlusive Disease of the Kidney	Atherosclerotic Renal Artery Stenosis| Ischemic Nephropathy| Renovascular Hypertension	Drug: Arterial infusion of autologous mesenchymal stem cells	Oct-15
NCT01795950	Safety Study of PLX-PAD Cells to Treat Pulmonary Arterial Hypertension (PAH)	Pulmonary Arterial Hypertension	Drug: PLX-PAD	Sep-15
NCT01377870	Evaluation of Autologous Mesenchymal Stem Cell Transplantation (Effects and Side Effects) in Multiple Sclerosis	Multiple Sclerosis	Biological: intravenous injection of mesenchymal stem cells| Biological: injection of cell free media	Aug-10
NCT01557543	Stem Cell Injection to Treat Heart Damage During Open Heart Surgery	Heart Disease| Ischemic Heart Disease| Coronary Artery Disease| Coronary Artery Disease (CAD)	Other: Cell Therapy	Nov-15
NCT00919958	Safety of Intramuscular Injection of Allogeneic PLX-PAD Cells for the Treatment of Critical Limb Ischemia	Peripheral Artery Disease| Peripheral Vascular Disease| Critical Limb Ischemia	Biological: PLX-PAD IM injection	Jun-12
NCT00951210	Safety of Intramuscular Injections (IM) of Allogeneic PLX-PAD Cells for the Treatment of Critical Limb Ischemia (CLI)	Peripheral Artery Disease| Peripheral Vascular Disease| Critical Limb Ischemia	Biological: PLX-PAD	Nov-11
NCT02323477	Human Umbilical Cord Stroma MSC in Myocardial Infarction	Chronic Ischemic Cardiomyopathy| Coronary Artery Bypass Surgery	Biological: stem cell transplantation	May-15
NCT01849159	Clinical Study of the Efficacy and Safety of the Application of Allogeneic Mesenchymal (Stromal) Cells of Bone Marrow, Cultured Under the Hypoxia in the Treatment of Patients With Severe Pulmonary Emphysema	Pulmonary Emphysema	Biological: Mesenchymal stem cells| Other: Reference therapy: 400 mL of 0.9% NaCl solution	Oct-15
NCT00821470	Treatment of Osteonecrosis of the Femoral Head by Bone Marrow Transplantation	Necrosis	Procedure: core decompression| Procedure: Bone marrow implantation into the necrotic lesion	Jan-09
NCT01172548	Safety and Efficacy Evaluation of Two Year Imatinib Treatment in Adjuvant Gastrointestinal Stromal Tumor (GIST)	Gastrointestinal Stromal Tumors	Drug: Imatinibmesylate	Mar-15

MSCs applications in radiation oncology regenerative medicine (RORM)

Adding up all their beneficial characteristics, MSCs have been investigated in RORM preclinical and clinical studies (Table 2). Nevertheless, the few clinical data representing the therapeutic benefits of the application of MSCs in radiation-induced normal tissue injury are promising. Among these, in radiation-induced bone injury, MSCs therapy caused early hematopoietic recovery with improved osteonecrosis. In radiation-induced intestinal injury, MSCs therapy produced significant repopulation of intestinal epithelium with reduced pain, diarrhea, and hemorrhage. In radiation-induced skin injury, MSCs therapy showed significant improvement and repopulation of skin tissue [29]. The following are the clinical studies that have been investigating the potential application of MSCs in RORM.

Skin repair application after radiation exposure

MSCs have been used in the repair of radiation-induced skin injuries where they were administered systemically and led to decreased radiation-induced skin fibrosis through enhancing the secretion of IL-10 and increasing the infiltration of anti-inflammatory regulatory CD163(+) macrophages, in addition to decreasing the secretionof IL-1 beta and the number of infiltrated pro-inflammatory CD80(+) macrophages [36]. It was suggested that the autologous grafting of MSCs is more efficient than the allogenic grafting in cutaneous radiation syndrome [20]. MSCs secrete growth factors and anti-inflammatory mediators that can be combined with other external growth factors, e.g. basic fibroblast growth factor (b-FGF) in order to improve the healing in radiation-induced skin damage [37]. The improved migration of fibroblasts and collagen production will protect the fibroblasts from the oxidative stress of UVB radiation [37].

Intestinal repair application after radiation exposure

MSCs have been applied for the repair of radiation-induced intestinal injury [26,38]. When MSCs were given before irradiation, treated mice showed higher body weight, thicker intestinal submucosal and muscle layer, significant higher survival rates and stromal derived factor-1 (SDF-1) expression, and lower numbers of radiation-induced ulcers [25,38]. Another study reported that MSCs therapy showed better maintenance of epithelial homeostasis, neovascularization, high anti-inflammatory IL-10, increased expression of VEGF, b-FGF and EGF in irradiated intestine, and increased the homing of CD31-positive hematopoietic stem cells or hematopoietic progenitor cells to the irradiated intestine [39]. MSCs therapy showed decreased

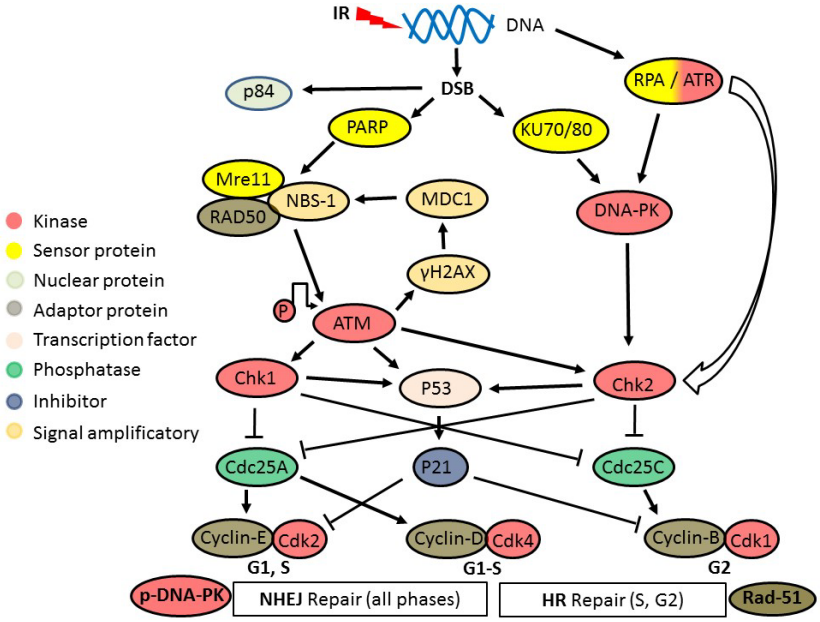

Figure 2.MSCs radiobiological response

Double stranded DNA (**dsDNA**) breaks (**DSB**) resulting from the direct and indirect radiation injury stimulate the phosphorylation of Ataxia Telangectasia Mutated protein (**ATM**) which is the proximal step for cell cycle check points activation (**G2/M arrest**). The nuclear apoptotic factor **P84** is up regulated, which participates in the apoptotic response of the cells. DSB stimulate the phosphorylation of histone-2AX through the Mre11, RAD50, NBS1 complex and p-ATM with a feedback loop amplification. Phosphorylated histone-2AX (**γ-H2AX**) stimulated both the homologous recombination repair (**HR, active in S and G2 phases only**) and the non-homologous end-joining repair (**NHEJ, active in all cell cycle phases**) of the DSB. **Rad-51** is considered one of the mandatory proteins for **HR** to occur. **DNA-PK** is the major protein in the **NHEJ** repair pathway. Both proteins were up regulated in irradiated MSCs. P-ATM and p-DNA-PK activate the cell cycle check point kinases (**Chk1 and Chk2**) resulting in cyclin/Cdk-mediated G2/M cell cycle arrest by inhibiting the Cell division cycle phosphatase (**Cdc25**). P-ATM also stabilizes the tumor suppressor regulatory protein and transcription factor **P53** which up-regulates the expression and enhances the stabilization of the inhibitory regulatory protein **p21**, which potently inhibits **Cdks** needed for the G1/S transition leading to inhibition of the entry into S phase.

activation and proliferation of T-lymphocytes together with increased local corticosterone secretion at the intestinal mucosa that highlighted an immunosuppressive effect of MSCs mediated by glucocorticoid receptors [40]. It was found that MSCs reparative and paracrine effects in radiation-induced intestinal injury were enhanced by pretreating them with TNF-alpha, IL-1 beta, and nitric oxide [41].

Lung tissue repair application after radiation exposure

MSCs therapy was shown to reduce radiation-induced lung tissue injury. Administration of MSCs resulted in decreased radiation-induced inflammatory response in terms of reduced pro-inflammatory mediators (IL-1 beta, IL-6, TNF-alpha), increased anti-inflammatory mediators (IL-10), reduced expression of TGF-β, alpha-smooth muscle actin (Alpha-SMA) and type 1 collagen level, and control of the pro- and anti-apoptotic mediators (Bcl-2, Bax, and caspase-3) protecting the lung tissue from apoptosis [42]. Moreover, MSCs therapy reduced bronchial epithelium senescence and lowered the risk of metastatic spread in lung tissue [43]. In addition, MSCs therapy decreased the mortality rate in mice with radiation-induced lung injury [44]. These cells showed a proven beneficial therapeutic effect in radiation pneumonitis as well [45].

Hematopoietic system homeostasis radiation injury

MSCs therapy has been shown to reduce the radiation-induced bone marrow apoptosis, and enhancemegakaryopoiesis and platelet recovery [46]. Moreover, MSCs therapy resulted in improved recovery of the hematopoietic system through decreased apoptosis and radiation-induced oxidative stress [47,48].

Radiation-induced cardiac injuries

A case report of a patient suffering from late radiation cardiomyopathy and radiation exudative pericarditis after radiotherapy of Hodgkin lymphoma showed that systemically transplanted MSCs partially differentiated to cardiomyocytes [49].

Radiation-induced salivary gland injury

In irradiated mice, systemically transplanted MSCs resulted in improvement of the saliva flow rate, lower salivary gland damage and atrophic acini, and higher mucin and amylase production [50].

Radiation-induced oral mucositis

Bone marrow-derived mesenchymal stromal cells (bmMSCs) therapy have been applied in fractionated radiation-induced oral mucositis where the administration of a systemic single dose of 6 million MSCs resulted in a significant decrease in ED50 (the RT dose that produces ulcer in 50% of irradiated mice) [51]. The first MSCs therapy for RIOM was done in 2014 by Schmidt et al. and concluded that transplantation of bone marrow (BM) or bmMSCs could modulate RIOM in fractionated RT, depending on the time of plantation [52]. Nevertheless, in another study they also concluded that bmMSCs plantation had no therapeutic benefits on RIOM in single dose RT when compared to the therapeutic gain by the mobilization of endogenous BM stem cells [53]. Further studies are needed in this field since the initial studies showed significant clinically relevant therapeutic effects.

Liver tissue protection

MSCs therapy reduced the radiation-induced liver injury by anti-oxidative, vascular protection, hepatocyte differentiation, and

Table 2. Mesenchymal stromal/stem cells (MSCs) preclinical and clinical studies in RORM [53,55].

Organ/ system	RT dose (Gy)	Normal Tissue Endpoint	Paradigm	Stem cell type therapy (preclinical studies)	Stem cell type therapy (clinical trial)	Follow up time
Bone marrow	12	Bone marrow aplasia	Hematopoietic stem cell/progenitor depletion and stem cell ''niche'' destruction	BM, hSC, bmMSC	BM (81)	30 years
Brain	>57	Brain radio-necrosis, cognitive dysfunction	Inflammation, vascular breakdown, disruption of BBB, CNS progenitor depletion, stem cell ''niche'' destruction, hypoxia, demyelination, necrosis	hESC, hNSC	No	_
Salivary glands	> 35	Xerostomia, salivary flow	Stem cell/progenitor depletion	BM, bmMSC, salivary gland stem cell	No	_
Bone	>60	Bone growth alteration, bone weakening, and osteo-radionecrosis	Hypocellularity, hypovascularization, hypoxia, and fibro-necrosis	BM, bmMSC	BM associated to biomaterial (Phase I)	Few months
Skin	>50	Skin radionecrosis, pain	Chronic inflammation, damage to the microvasculature, epidermis stem cell/ progenitor depletion, ischemia, fibroblast death, and fibro-necrosis	bmMSC, aMSCs, EPC	bmMSC (local injection, 2 x 10^6/ kg, repetitive injections, curative startegy) (compatio-nnal treatment) and lipoaspira-te (PhaseI)	8 years and 13 months
Liver	>35	Radiation-induced liver disease, sinusoidal obstructive syndrome	Vascular (sinusoidal) breakdown, hepatocyte cell death, and inhibition of hepatocellular regeneration	Hepatocyte	Hepatocy-te (intraspel-nic transplan-tation, 6 x10^6 cells) (Phase I)	_
Heart	>30-40	Atheroscler-osis, cardiac attack	Inflammation, damage to the microvasculature, ischemia, myocardial cell death, and fibro-necrosis	_	No	_
Colon-rectum	>35	Pelvic radiation disease, colo-rectal ulceration, rectitis, cystitis, and fistulae	Chronic inflammation, damage to the microvasculature, epithelial stem cell/progenitor depletion, ischemia, myofibroblast death, and fibro-necrosis	bmMSC	bmMSC (i.v. injection, 2 x 10^6/kg, repetitive injections) (compass-ional treatment)	4 years

aMSCs = adipose-derived mesenchymal stromal cell, **bmMSC** = bone marrow MSCs; **BBB** = blood brain barrier; **BM** = bone marrow; **CNS** = central nervous system; **EPC** = endothelial progenitor cells; **GFAP** = glial fibrillary acidic protein; **hESC** = human embryonic stem cell; **hSC** = human stem cells; **hNSC** = human neural stem cell, **RT** = radiation.

trophic mechanisms. There was decreased expression of Nrf2 and superoxide dismutase (SOD) in MSCs-treated irradiated liver which showed decreased apoptotic cells as well.These findings suggested that, these effects were mediated by an anti-oxidative mechanism. The increased expression of VEGF and Angiopoietin-1 (Ang-1) in the perivascular region, associated with an increased expression of VEGFr1, r2 suggested the vascular protection mechanism in the livers of MSCs-treated animals. After engrafting, MSCs showed expression of cytokeratin CK18 and CK19 and alpha-fetoprotein (AFP) genes which suggested hepatocyte differentiation. The increased secretion of nerve growth factor (NGF), hepatocyte growth factor (HGF), and anti-inflammatory molecules IL-10, IL1-RA suggested MSCs' trophic effects [40, 54]. MSCs conditioned media improved the viability of liver sinusoidal endothelial cells (SECs) in vitro. Infusion of MSCs conditioned media significantly reduced the radiation-induced SECs apoptosis and improved the histopathological picture of irradiated livers. In addition, there was increased secretion of anti-inflammatory cytokines and decreased secretion of pro-inflammatory cytokines [40,55].

Studies with gene-modified MSCs for RORM

Genetically modified MSCs have been applied in RORM studies. HGF-expressing MSCs have improved the radiation-induced intestinal injury where they increased the expression of anti-inflammatory mediators and improved the histopathological picture of irradiated intestine [12]. Hepatocyte growth factor gene-modified adipose-derived mesenchymal stem cells improved the radiation induced liver damage in a rat model [13]. A similar picture was noted with TGF-beta-expressing MSCs therapy in radiation-induced lung injury [14].

Summary

Although limited data are available for the clinical application of MSCs in radiation-induced normal tissue injury, promising therapeutic benefits have been shown in a small number of isolated clinical studies [29].

Isolated clinical case reports showed promising beneficial effects of MSCs therapy; e.g. regenerating hematopoiesis and osteoradionecrosis, improved breathing parameters and lung immune function, improved intestinal mucosal inflammation, hemorrhages, fistulization, pain and diarrhea, and regenerated skin ulceration, in ionizing radiation-induced injury of bone, lung, intestine, and skin, respectively [29,40,56,57]. Table 2 summarizes the recent preclinical and clinical studies conducted in RORM applying MSCs therapies.

Adipose tissue-derived MSCs (aMSCs)

Adipose tissue-derived mesenchymal stem/stromal cells (aMSCs) are multipotent progenitor cells located in the stromal vascular fraction (SVF) of adipose tissue [2]. They are characterized by expressing cell surface antigens Sca1, CD106, CD105, CD73, CD29, and CD44, and lacking the expression of hematopoietic stem cells (HSCs) surface antigens (e.g. CD11b and CD45) [2,3,58]. In addition to their multi-lineage differentiation potential, they have anti-inflammatory/ immune-modulatory and paracrine effects [59-61]. In addition, MSCs can home to the site of tissue injury that is caused by irradiation and inflammation [2,5,62].These advantages, in addition to their source abundance, ease of isolation and high cell count after expansion, render aMSCs promising for cellular therapies [63]. Table 3 lists 22 clinical trials using aMSCs therapy for various disorders, with no trial yet found for their application in RORM, following a search on the clinical trials website of the NIH, i.e. https://clinicaltrials.gov/, in Nov. 2015.

MSCs mechanisms of action in RORM

There are proposed mechanisms of action of MSCs radio-protective properties in radiation-induced normal tissue injury repair. Homing and paracrine effects with anti-inflammatory/immunomodulatory

Table 3. Adipose Mesenchymal stromal cells (aMSCs) clinical trials www.ClinicalTrials.gov by the national Institute of Health in RORM.

NCT #	Title	Conditions	Interventions	Last Verified
NCT02603744	Autologous Adipose Derived Mesenchymal Stromal Cells (aMSCs) Transplantation in Women With Premature Ovarian Failure (POF)	Premature Ovarian Failure	Biological: Intraovarian injection of aMSCs	Nov-15
NCT01449032	MSCs Therapy in Patients With Chronic Myocardial Ischemia (MyStromalCell Trial)	Chronic Ischemic Heart Disease	Biological: MSCs|Biological: Saline	Jun-14
NCT01585857	ADIPOA - Clinical Study	Osteoarthritis	Biological: Autologous aMSCs administrated for intra-articular use|Biological: Autologous aMSCs administrated for intra-articular use	Dec-14
NCT02382874	Allogenic aMSCs Transplantation in Idiopathic Nephrotic Syndrome (Focal Segmental Glomerulosclerosis)	Focal Segmental Glomerulosclerosis	Biological: Intravenous injection	Mar-15
NCT02240823	Can Fat Derived Stem Cells (SVF) be Used in the Treatment of Erectile Dysfunction After Prostatectomy	Delayed Graft Function	Other: aMSCs	Oct-15
NCT02326935	Multi-Center Study Safety of aMSCs for the Treatment of Multiple Sclerosis	Multiple Sclerosis	Biological: Autologous aMSCs	Jan-15
NCT00913289	Liver Regeneration Therapy Using Autologous aMSCs	Liver Cirrhosis	Biological: aMSCs	Oct-12
NCT01062750	Liver Regeneration Therapy by Intrahepatic Arterial Administration of Autologous aMSCs	Liver Cirrhosis	Biological: aMSCs dosage	Sep-15
NCT02338271	Autologous aMSCs Therapy for Intervertebral Disc Degeneration	Low Back Pain	Other: autologous aMSCs	Jan-15
NCT01709279	Clinical Trial of Autologous aMSCs Therapy for Ischemic Heart Failure	Ischemic Heart Failure	Biological: aMSCs dosage	Oct-12
NCT01739504	Autologous aMSCs Delivered Intra-articularly in Patients With Osteoarthritis.	Osteoarthritis	Procedure: Autologous aMSCs harvesting through Liposuction for Intra-articular Injection	Oct-15
NCT02145897	To Evaluate the Safety and Efficacy of IM and IV Administration of Autologous aMSCs for Treatment of CLI	Critical Limb Ischemia (CLI)	Biological: Autologous Stromal Vascular Fraction (SVF)|Biological: Autologous aMSCs| Other: Control	May-14
NCT01840540	MSC for Occlusive Disease of the Kidney	Atherosclerot-ic Renal Artery Stenosis| Ischemic Nephropathy|Renovascular Hypertension	Drug: Arterial infusion of autologous mesenchymal stem cells	Oct-15
NCT02135380	Evaluate Safety and Efficacy of Intravenous Autologous aMSC for Treatment of Idiopathic Pulmonary Fibrosis	Idiopathic Pulmonary Fibrosis	Biological: Autologous Stromal Vascular Fraction (SVF)|Biological: Autologous aMSCs |Other: Control	May-14
NCT01548092	Stromal Vascular Fraction (SVF) for Treatment of Recto-vaginal Fistula	Recto-vaginal Fistula	Drug: aMSCs without expanded	Mar-12
NCT01771913	Immunophenotyping of Fresh Stromal Vascular Fraction From aMSCs Enriched Fat Grafts	Breast Reconstruction|Contour Irregularities|Volume Insufficiency	Genetic: centrifuged fat graft| Genetic: aMSCs enriched fat graft	Jul-15
NCT01849159	Clinical Study of the Efficacy and Safety of the Application of Allogeneic Mesenchymal (Stromal) Cells of Bone Marrow, Cultured Under the Hypoxia in the Treatment of Patients With Severe Pulmonary Emphysema	Pulmonary Emphysema	Biological: Mesenchymal stem cells|Other: Reference therapy: 400 mL of 0.9% NaCl solution	Oct-15
NCT01532076	Effectiveness of aMSCs as Osteogenic Component in Composite Grafts	Osteoporotic Fractures	Procedure: Cellularized composite graft augmentation|Procedure: Acellular composite graft augmentation	Sep-14
NCT02387723	CSCC_ASC Therapy in Patients With Severe Heart Failure	Clinical Patient Safety of Allogeneic Stem Cell Therapy	Biological: Allogeneic aMSCs (CSCC_ASC)	Mar-15
NCT01730547	Mesenchymal Stem Cells for Multiple Sclerosis	Multiple Sclerosis	Biological: Autologous mesenchymal stem cells	Jan-15
NCT02492490	Effect of SVF-derived MSC in DCD Renal Transplantation	Uremia	Other: SVF-derived MSC transplantations|Drug: Basiliximab	Nov-14
NCT02492308	Induction With SVF Derived MSC in Living-related Kidney Transplantation	Living-relative Kidney Transplantation	Procedure: SVF-MSC induction|Drug: Basiliximab induction	Jul-15

mechanisms are supported by in-vitro data from radiation-induced intestinal injury studies and [59-62]. MSCs therapy in radiation-induced intestinal injury showed the homing of systemically administered MSCs in measurable numbers at the intestinal injury site [25,26,41]. There were increased levels of IL-10, VEGF, b-FGF, and EGF. Histopathological studies showed improved intestinal epithelial homeostasis that may be due to MSCs overexpressing stromal cell-derived factor receptor CXCR-4 [29]. These findings suggest that the paracrine and the anti-inflammatory effect of MSCs is the expected radio-protective mechanism of action of MSCs in RORM [29].

Challenges facing MSCs therapy

The fear of MSCs-mediated radioprotection of tumor tissues has been a raised concern after the availability of in-vitro data suggesting that breast cancer cells grow and proliferate more with MSCs-therapy owing to high insulin-like factor production [53]. Also, MSCs have some angiogenic properties evident by increased secretion of platelets derived growth factor (PDGF), VEGF and TGF-β at the tumor perivascular area and parenchyma in low dose irradiated mice owing to MSCs infiltration at the tumor site [53]. MSCs angiogenic properties might counteract the anti-angiogenic cancer therapies, a question that needs to be answered with solid in-vitro and in-vivo studies [28,29].

Another challenge appeared in MSCs therapies. MSCs have been found to have heterogeneous radiation resistant populations, both in human and mouse MSCs [53]. A finding that might interfere with the overall radio-protective and tissue regenerative properties of MSCs.

Nevertheless, studies may find molecular biomarkers for isolating homogenous populations of MSCs with uniform high RT resistance profile [28,29].

A further challenge that has been found to be more frequent in mouse MSCs than in human MSCs, is MSCs in-vitro transformation (the tumorigenic potential of MSCs) [53]. Such challenge carries a significant worry for MSCs therapies, since MSCs are radio-resistant cells. Thus, their transformation may signify the generation of a severe form of radio-resistant tumor that is extremely hard to control. Tight and fine validation of MSCs before each single dose therapy is recommended for preventing the use of any potentially transformed cells [28,29,34].

Conclusion

MSCs have been widely used in preclinical studies of radiation oncology regenerative medicine. MSCs have been shown to be reliable candidates in radiation oncology regenerative medicine translational and clinical research. The strong potential of MSCs therapy in RIOM is supported by their relative radiation resistance and robust DNA repair mechanisms, multi-lineage differentiation potential, and anti-inflammatory/immunomodulatory properties. Nevertheless, few but considerable challenges in MSCs therapies are requiring more research in order to develop solid solutions. However, the overall data collected from preclinical and clinical studies with MSCs therapy promise with cell therapy choices competing the traditional therapies. Adipose-tissue derived mesenchymal stromal/stem cells are reliable candidates for radiation oncology regenerative medicine applications owing to the advantages they possess, e.g. source abundance, enhanced anti-inflammatory effects, robust IL-10 secretion, easy isolation, high expansion.

Authorship and contributions

Osama Maria: Conception and design, collection and/or assembly of data, review writing, final approval of the review.

Nicoletta Eliopoulos: Conception, design and final approval of the review.

Thierry Muanza: Conception and design, financial support and final approval of the review.

Acknowledgements

Osama Muhammad Maria is an awardee of the LDI/TD studentship, and Fonds de Récherche du Quebec - Santé (FRQS) doctoral fellowship. This study was supported partially by Ride to Conquer Cancer (RTCC, Jewish General Hospital Foundation) and FRQS grants. This work was partially supported by Canadian Institutes of Health Research (CIHR) Operating Grant MOP-15017 (N. Eliopoulos).

Disclosure of potential conflict of interest

None.

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