Mesenchymal stromal cells therapy in radiation oncology regenerative medicine

Osama Muhammad Maria1,4, Nicoletta Eliopoulos2,4 and Thierry Muanza1,3,5*  
1Experimental Medicine Department, Faculty of Medicine, McGill University, Montreal, Quebec, Canada  
2Surgery Department, Faculty of Medicine, McGill University, Montreal, Quebec, Canada  
3Radiation Oncology Department, Jewish General Hospital, McGill University, Montreal, Quebec, Canada  
4Lady Davis Research Department, Jewish General Hospital, McGill University, Montreal, Quebec, Canada  
5Oncology Department, McGill University, Montreal, Quebec, Canada

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 secretary 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 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) 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 millions of 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.
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 Cdk's 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 Inusions of Mesenchymal Stromal Cells in Children With Osteogenesis Imperfect | 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        |
| NCT02232789 | 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        |
| NCT02921770 | 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 Knees With Osteoarthritis | Ostearthritis | Biological: umbilical-cord mesenchymal stromal cells| Drug: Hyaluronic Acid | Oct-15        |
| NCT01038596 | Mesenchymal Stromal Cells and Osteoarthritis                          | Ostearthritis                                    | Biological: umbilical-cord mesenchymal stromal cells| Drug: Hyaluronic Acid | 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: Neutropenia After Chemotherapy | 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 | Ostearthritis, Knee|Athritis| Of Knee|Knee Osteoarthritis | Other: Allogeneic mesenchymal stromal cells| injection|Drug: Hyaluronic Acid | Sep-15        |
| NCT01860417 | Treatment of Degenerative Disc Disease With Allogenic Mesenchymal Stem Cells (MSV) Combining Intervertebral Disc Disease| Low Back Pain | 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 | 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 | Biological: Mesenchymal Stromal Cells| Other: Placebo | Oct-15 |
| NCT02033525 | Mesenchymal Stromal Cells for Degenerative Musculoskeletal 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 | Biological: Human Mesenchymal Stem Cells (hMSCs)| Other: Standard of Care | Jun-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 Myelofibrosis| Refractory Chronic Leukemia | 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: cyclophosphine| Drug: mycophenolate mofetil| 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 | Feb-15 |
| NCT02270707 | 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 MSCs for Enhancing Hematopoietic Recovery and Prophylaxis of Neutropenic Enterocolitis | NeutropenicEnterocolitis Myelosuppressive Chemotherapy Induced Bone Marrow Aplasia Procedure: Peripheral blood stem cell mobilisation and collection| Drug: High-dose chemotherapy| Drug: Bone marrow derived allogeneic MSCs 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 |
| NCT019909154 | Safety Study of Local Administration of Autologous Bone Marrow Stromal Cells in Chronic Paraplegia | Spinalepio Divele | Biological: Mesenchymal stromal cell therapy | Nov-13 |
| NCT00395200 | Mesenchymal Stem Cells in Multiple Sclerosis (MSCMS) | 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 | Sep-15 |
| NCT01659762 | A Phase I Study Evaluating Autologous Bone Marrow Derived Mesenchymal Stromal Stromal for Crohn's Disease | Crohn's Disease | Biological: autologous mesenchymal stromal cell | Jul-15 |
| NCT02382874 | Allotogenic 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 | Jan-14 |
| 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 |
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 showed decreased oxidative stress of UVB radiation. MSCs have been applied for the repair of radiation-induced normal tissue 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 secretion of 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 of 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

| Study ID | Title                                                                                     | Disease                                      | Treatment Details                                                                 | Timeframe |
|---------|-------------------------------------------------------------------------------------------|----------------------------------------------|-----------------------------------------------------------------------------------|-----------|
| NCT01071577 | Collection of Bone Marrow From Healthy Volunteers and Patients for the Production of Clinical Bone Marrow Stromal Cells (BMSC) Products | Bone Marrow| Bone Marrow Stromal Cells; Mesenchymal Stromal Cells; Blood Donors                  | Aug-15    |
| NCT00186914 | Stromal Therapy of Osteodysplasia After Allogeneic Bone Marrow Transplantization          | 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: Allogenic Mesenchymal Bone Marrow Cells (aMBMC); Drug: Lactated Ringer's Solution | Jun-15    |
| NCT02428817 | Linaagliptin and Mesenchymal Stem Cells: A Pilot Study                                      | Schizophrenia                               | Drug: Linaagliptin                                                               | Apr-15    |
| NCT02064062 | Autologous Strom 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 Oclusive 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    |
| NCT01557534 | 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    |
| NCT015849159 | 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 Transplantization           | 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 Adjacent Gastrointestinal Stromal Tumor (GIST) | Gastrointestinal Stromal Tumors            | Drug: Imatinibmesylate                                                           | Mar-15    |
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...
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.
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: Intravarian injection of aMSCs          | Nov-15        |
| NCT01449032 | MSCs Therapy in Patients With Chronic Myocardial Ischemia (MyStromaCell Trial) | Chronic Ischemic Heart Disease         | Biological: aMSCs (Biological: Saline)             | Jun-14        |
| NCT01585857 | ADIPOA - Clinical Study                                                | Osteoarthritis                         | Biological: Autologous aMSCs administered for intra-articular use | Dec-14        |
| NCT02338827 | 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 Grat 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 Intr-a-articularly in Patients With Osteoarthritis. | Osteoarthritis                         | Procedure: Autologous aMSCs harvesting              | 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)| May-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        |
| NCT02135380 | Evaluate Safety and Efficacy of Intravenous Autologous aMSCs for Treatment of Idiopathic Pulmonary Fibrosis | Idiopathic Pulmonary Fibrosis          | Biological: Autologous Stromal Vascular Fraction (SVF)| 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 | 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/Proceded: Acceller 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 transplantation/Drug: Basiliximab | Nov-14        |
| NCT02492308 | Induction With SVF Derived MSC in Living-related Kidney Transplantation | Living-related Kidney Transplantation  | Procedure: SVF-MSC induction/Drug: Basiliximab induction | Jul-15        |

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 homogeneous 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 Munanza: Conception and design, financial support and final approval of the review.

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Disclosure of potential conflict of interest

None.

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