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The Effects of Stem Cells on Multiple Myeloma

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Abstract

Multiple myeloma is the second most common hematological disease characterized by uncontrollable cell proliferation of malignant plasma cells in the bone marrow. Evolution of multiple myeloma stems from asymptomatic precursor states of multiple gammopathy of undetermined significance or smoldering multiple myeloma. Standard care of newly diagnosed multiple myeloma patients includes various induction therapies of different combinations of corticosteroids, proteosome inhibitors, and immunomodulatory drugs. Stem cell transplantation into the bone marrow of myeloma patients is a regenerative therapy that possesses the capability of restoring functionality in non-functional cells. Hematopoietic stem cells and mesenchymal stem cells have shown promise in restoring functionality to non-functional cells. Clinical trials of hematopoietic stem cells and preclinical animal models have exhibited success of stem cell transplantation as a regenerative therapy for multiple myeloma.

Keywords

Clinical trials; Multiple myeloma; Stem Cells

Introduction

Multiple Myeloma (MM) is characterized as a hematological disease of malignant plasma cells in bone marrow. Uncontrolled growth of monoclonal plasma cells in the bone marrow can lead to nonfunctional immunoglobulins and immunoglobulin chains [1]. MM is the second most common hematological malignancy and accounts for about 10 percent of all hematological malignancies [2]. The evolution of MM is understood to sometimes evolve from a premalignant stage of plasma cell proliferation known as Monoclonal Gammopathy of Undetermined Significance (MGUS) or another intermediate asymptomatic stage known as Smoldering Multiple Myeloma (SMM) [3]. MGUS is characterized by an accumulation of monoclonal protein, or Protein M, in blood, less than 10 percent of plasma cells in bone marrow, and the absence of myeloma-related end-organ damage4. MGUS progressed to MM in approximately 1 percent of patients per year in the first 5 years after diagnosis, which illustrates that symptomatic malignancy is uncommon [4].

An intermediate stage, SM is present in some myeloma patients, where their levels of the serum M protein and clonal plasma cells are higher than those with MGUS [4]. MGUS patients experience serum protein M levels of less than 3 g/dl and clonal bone marrow plasma cell levels of less than 10 percent. Individuals in the SMM stage have M protein levels of greater than 3 g/dl and clonal bone marrow plasma cell levels of greater than 10 percent. Both stages experience an absence of myeloma related end-organ damage, which is characterized by hypercalcemia, renal insufficiency, anemia, and bone lesions, otherwise known as CRAB 5. About 10 percent of patients experiencing SMM progress to MM per year after the first 5 years of diagnosis, a value considerably higher than that of MGUS [4] (Table 1).

Disorder	**Criteria**
Monoclonal Gammopathy of Undetermined Significance	All criteria must be met: 1. Serum monoclonal protein <3g/dl 2. Clonal bone marrow plasma cells <10% 3. Absence of myeloma related end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions
Smoldering Multiple Myeloma	Both criteria must be met: 1. Serum monoclonal protein >3g/dl and/or clonal bone marrow plasma cells >10% 2. Absence of myeloma related end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions

Multiple Myeloma	All three criteria must be met: 1. Clonal bone marrow plasma cells ≥ 10% 2. Presence of serum and/or urinary monoclonal protein 3. Evidence of end-organ damage that can be attributed to the underlying plasma cell disorder, specifically CRAB

Table 1: Scheme for diagnostic criteria of plasma cell disorders [5].

Etiology of MM remains largely unknown; however there have been trends observed related to race, ethnicity, age, sex, and genetic factors. The incidence of MM in the United States was 6.6 per 100,000 people from 2012-2014 studies suggest that potential risk factors include male sex, genetic background, obesity, and some immunological disorders could play a role in the development of MM 6. Furthermore, MM is often observed in patients of advanced age, particularly individuals in the range of 66-70 years old [6]. In fact, individuals aged 65 years or older account for 85% of diagnoses of Multiple Myeloma [7]. Epidemiological studies indicate that incidence of the disease varies, but is higher in more-developed countries, particularly Europe and the United States [8]. This observation of increased incidence in more developed countries could be attributed to advanced diagnostic techniques and procedures. There is an increased prevalence of the disease in black individuals than white individuals, with the incidence being about 2/3 higher in those of African American origin [8]. Furthermore, a report in 2020 discussed that the prevalence of MGUS was fourfold higher in Blacks compared to Whites [9]. The observed disparity in risk of MM and MGUS between the two races is unknown, although potential risk factors could include socioeconomic status, genetic susceptibility, and obesity 9. In addition to a history of MGUS leading to MM as a precursor state, occupational and environmental risk factors could potentially play a role in development of the disease. The use of pesticides on some crops such as wheat/barley, potato and corn is associated with an increased risk in MM [10]. In the same study performed by Tual et al., there was a positive association between the use of insecticides on animals, such as cattle and horses, and an increased risk in MM [10].

Induction Treatment

Therapeutic options for MM patients have increased significantly over the past century. Treatment is largely dependent on whether a patient is eligible for autologous stem cell transplantation (ASCT). Currently, eligibility for transplants is regulated by age, performance status, and comorbidities [11]. Typically, patients undergo an induction regimen prior to ASCT to decrease tumor burden [12]. A decrease in tumor burden is likely to increase the probability of engraftment and deepen response rates among patients, while maintaining minimum levels of toxicity on normal hematopoietic stem cells [12]. Usually, patients that are able to tolerate multi-drug combination therapies are treated with a proteosome inhibitor along with immunomodulatory drugs 8. These drugs are often delivered in

combination with corticosteroids such as dexamethasone. Common immunomodulatory drugs used are thalidomide and lenalidomide, while bortezomid is used as the proteosome inhibitor [8]. The VTD regimen (bortezomid, thalidomide, and dexamethasone) has shown promise in achieving complete remission. In one study conducted by the Spanish group PETHEMA, a 35% complete remission rate was observed in patients that underwent 6 induction cycles of the VTD regimen [11]. Another study performed by the Italian group GIMEMA found a 19% complete remission rate after only 3 induction cycles of the regimen [11]. Although the Spanish group observed greater rates of complete remission, greater toxicity was also attributed to the more vigorous amount of induction cycles. Spanish group PETHEMA reported 14% grade 3-4 peripheral neuropathy in patients that received the 6 induction cycles of VTD, compared to 10% grade 3 peripheral neuropathy observed by the Italian group, which only administered 3 induction cycles of the regimen to patients [11].

The combination of bortezomid, lenalidomide, and dexamethasone is another induction treatment regimen studied (known as the VRD regimen) to reduce toxicity and increase efficacy [13]. In a 2012 study conducted by the Spanish group GEM, the VRD regimen showed similar complete remission rates (33.4%) to a 2005 study by the same group that used the VTD regimen (35%) [13]. Both studies were done using 6 cycles of their respective regimens over a 4-week period per cycle. The study found that VRD exhibited a higher rate of very good partial response (VGPR) among patients (66.6%) versus VTD (60%) 13. General toxicity profiles showed similarities between the two regimens, but there was a lower rate of grade 3/4 peripheral neuropathy observed in VRD [13] (Table 2).

Grade 3/4 Treatment Emergent Adverse Effects		
	VRD GEM 2012 (n=458)	**VTD GEM 2005 (n=130)**
Hematologic		
1. Neutropenia	58 (12.9%)	13 (10%)
2. Thrombocytopenia	29 (6.3%)	10 (8%)
Nonhematologic		
1. Peripheral Neuropathy	18 (3.9%)	17 (13%)
2. Infection	42 (9.2%)	27 (21%)

Table 2: Comparison of adverse events observed through induction of different regimens [13].

The depth of response among patients was also investigated by measuring the mean residual disease (MRD) among patients as well as VGPR. Of the 426 patients that underwent all 6 cycles of VRD regimen, there was a marked increase in VGPR after subsequent cycles of the regimen were administered, with the rate of VGPR or better at 55.6% after cycle 3, and 70.4% after cycle 6 [13]. In the intent-to-treat population (n=458), undetectable MRD rates of 28.8% were reported [13]. Multi-drug combination therapy prior to autologous stem cell transplantation has proven to be effective in obtaining complete remission, high rates of VGPR, and low rates of MRD among individuals with MM. Variants in combination therapies have been studied, such as those with cyclophosphamide (VCD) as an immunomodulator instead of thalidomide or lenalidomide, or carfilzomib as a proteasome inhibitor instead of bortezomib in conjunction with thalidomide and dexamethasone, but these therapies have

produced inferior results to the VRD and VTD regimens [11]. VRD has proven to be a highly effective pre-transplantation induction regimen, because of its low toxicity and similar efficacy compared to VTD.

Stem Cell Therapy

Stem cells are cells that possess the unique ability to differentiate into many different types of specialized cells. These undifferentiated cells are present in embryonic, fetal, and adult stages of life and have three main characteristics: their ability to self-renew, their ability to differentiate into various types of cells (potency), and clonality [14]. Stem cells can be classified based on their origin and their differentiation potential [14]. In general, stem cells can be placed in three broad categories based on their origin: embryonic stem cells, adult stem cells, and induced pluripotent stem cells [14].

Embryonic stem cells (ESCs) are derived from a stage of the pre-implantation embryo called the blastocyst, which is usually about 5-6 days after fertilization [14]. This type of stem cell has been the topic of serious ethical controversy in recent decades due to the destruction of the human embryo to facilitate research initiatives [15]. The blastocyst contains two cell layers, the inner cell mass which makes up the embryo, and an outer mass of cells called trophoblasts, that nourishes the embryo and eventually forms the placenta [14]. Adult stem cells arise from all types of adult tissue and are also termed somatic stem cells [16]. These resident stem cells possess the ability to regenerate and repair damaged tissue in the tissue they reside [17]. The growth and development of these cells is maintained by a specific “niche” where these stem cells are located [17]. This niche is essentially a microenvironment that provides a series of extrinsic signals to maintain the development of somatic stem cells, and thus the homeostasis and repair mechanisms of the resident tissue [16,17]. Adult stem cells are not of ethical concern because of their derivation from adult tissue, therefore they are of important research interest in stem cell therapy [14]. Induced pluripotent stem cells are derived from adult stem cells and genetically reprogrammed to exhibit an ESC-like condition [14]. This “reprogramming” to a pluripotent state is done through ectopic co-expression of a defined set of transcription factors identified in 2006 by Kazutoshi Takahashi and Shinya Yamanaka to be Oct 3/4, Sox 2, c-Myc, and Klf4 18. Induced pluripotent stem cells are of extreme clinical and research importance, because of their role in regenerative medicine and ability to model life-threatening diseases that can aid in the understanding of pathogenic mechanisms [14,18]. Furthermore, induced pluripotent stem cells avoid the ethical concerns of the destruction of blastocysts, considering they can be derived from adult tissue and then genetically modified.

Stem cells can also be classified based on differentiation potential. Differentiation classification includes totipotent, pluripotent, multipotent, oligopotent, and unipotent stem cells [14]. Totipotent cells have the highest differentiation potential and are able to differentiate into cells of an entire organism [19]. The zygote is an example of a totipotent cell, as it can develop into any of the three germ layers (endoderm, mesoderm, and ectoderm) or form the placenta (extra-embryonic structure) [19]. Pluripotent stem cells are able to specialize into cells from all three germ layers but cannot form extra-embryonic structures like the placenta [19]. ESCs are a common example of pluripotent stem cells.

Multipotent stem cells have a narrower range of differentiation but can still differentiate into all cell types of a particular cell lineage (a single germ layer) [14]. Mesenchymal stem cells are perhaps the most popular example of multipotent stem cells. Mesenchymal stem cells can differentiate into tissue derived from the mesoderm, such as bone, muscle, adipose tissue, and cartilage [14]. Hematopoietic stem cells (HSCs) are a common example of oligopotent stem cells, which are stem cells that can only differentiate into closely related cell type [19]. HSCs can differentiate into cells of myeloid and lymphoid lineages [14]. Finally, unipotent stem cells are classified as having the narrowest differentiation capabilities and a common example of this type of stem cell are epidermal stem cells, which give rise to layers of the epidermis [20].

Autologous Stem Cell Transplantation

As aforementioned, if deemed medically fit, newly diagnosed multiple myeloma (NDMM) patients often undergo autologous stem cell transplantation after they undergo some sort of multi-drug combination therapy [21]. A conditioning regimen is introduced in NDMM patients and currently, intravenous high-dose melphalan (200 mg/m2) is the accepted standard for high-dose therapy (HDT) [12]. This currently accepted standard is due to a randomized clinical trial performed by the Intergroupe Français du Myélome in 2002 where the group compared the two most widely used conditioning regimens: 200 mg/m2 Melphalan versus 8 Gy total body radiation in conjunction with a reduced 140 mg/m2 Melphalan [22]. The study found that the group that received the full melphalan dose (200 mg/m2) experienced greater overall survival at 45 months (65.8%) compared to the group that received the reduced dose (45.5%) [22]. Furthermore, reduced toxicity, concerning neutropenia, thrombocytopenia, and severe mucositis among others, was observed in the full dose Melphalan group compared to the reduced dose Melphalan group [22].

The introduction of ASCT became the foremost advancement in MM therapeutics approximately 30 years ago following a randomized clinical trial performed by the French group, Intergroupe Français du Myélome [21]. The group compared the effects of conventional chemotherapy versus HDT combined with ACST and found significant results in terms of complete remission and VGPR [23]. Patients in the HDT group saw 38% complete remission or VGPR, compared to only 14% of patients in the conventional chemotherapy group [23]. Additionally, the conventional-dose group reported 43% of patients did not observe partial responses, compared to only 19% of the HDT group [23]. This randomized trial demonstrates the benefit of ASCT in conjunction with HDT compared to the utilization of conventional chemotherapy for treating NDMM patients.

Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) are adult precursor cells that usually reside in the bone marrow or peripheral blood [24]. HSCs retain the capacity to self-renew and differentiate into mature cell types within the myeloid and lymphoid cell lineages [24]. Myeloid progenitor cells are able to differentiate into monocytes (from which dendritic cells and macrophages can develop), megakaryocytes (from which platelets can develop), basophils, neutrophils, and erythrocytes, among others [24]. Cells derived from

lymphoid progenitors include B cells (thus new plasma cells), T cells, and natural killer cells [24].

In NDMM patients, hematopoietic stem cells are essential in restoring hematopoiesis. Patients undergoing ASCT after HDT require adequate harvesting of hematopoietic progenitor cells (HPCs) for transplantation to be successful. To do this, CD34+ cells must be mobilized from the bone marrow compartment to the peripheral blood 25. CD34+ is a transmembrane phosphoglycoprotein that serves as a marker for HSCs and HPCs 26. A minimum cell dose of 2x106 CD34+ cells/kg is required for a single ASCT, while 3 to 6x106 CD34+ cells/kg is considered ideal [27]. Due to possible mobilization failures or other risk factors, it is recommended to harvest at least 3-4x106 CD34+ cells/kg for subsequent transplants, where the cells will be stored for later use [28].

Several mobilization options exist in steady-state mobilization with only growth factors, growth factors in conjunction with chemotherapy, and growth factors in conjunction with plerixafor [27]. Criteria for choosing a mobilization method is based on stem cell yield, least toxicity, and cost 25. Common steady-state mobilization factors are granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF) [27]. The use of G-CSF alone is favored over GM-CSF alone due to a greater yield with lower toxicity, as well as earlier neutrophil and platelet recovery [27]. For patients with active disease, chemotherapy-based mobilization is likely the preferred method for mobilization of cells because of antitumor applications and a promotion of stem cell mobilization [29]. Proliferation of HSCs is common when bone marrow is recovering from chemotherapy, so a higher amount of progenitor cells in the peripheral blood will be observed [27]. A common chemotherapeutic agent used for this method is cyclophosphamide, which will cause neutropenia and thrombocytopenia, so patient monitoring for infection, fever, and the possibility of a transfusion is essential [29]. Lastly, a chemokine called plerixafor can be used with G-CSF to disrupt the interactions between stromal derived factor 1 and chemokine receptor 4 which will enhance stem cell mobilization and provide a greater yield [25].

In 2020, Plerixafor in conjunction with G-CSF was evaluated for its efficacy in collection of hematopoietic stem cells from the peripheral blood based on different CD34+ cell counts. Evaluation of the efficacy of Plerixafor used after high dose melphalan was based on mean plerixafor utilization, number of apheresis procedures, and assessment of the overall cost to the patients [30]. The study, performed by Shah et. al., conducted 344 mobilization procedures over three time periods with three different peripheral blood CD34+ thresholds (<15/µL, <20 µL, <40/µL) intended to guide Plerixafor use [30]. Plerixafor use was determined after peripheral blood CD34+ cell counts were evaluated after the fourth day of G-CSF use. The group found that Plerixafor utilization increased among each cohort: 80.3% (<15/µL) to 83.1% (<20 µL) to 91.2% (<40/µL) [30]. The group took the mean number of Plerixafor doses per patient in each cohort and found that administration increased from 1.32 to 1.65 to 1.74, respectively over each cohort with a significant difference observed in the <15/µL and <40/µL cohorts [30]. Average days of apheresis procedures increased from 2.15 days for the <15/µL cohort to 2.17 days for the <20 µL cohort but decreased to 1.89 days for the <40/µL cohort, with a significant difference observed between the <20 µL and <40/µL cohorts [30]. Single-day collection yields were observed to be greatest in the <40/µL

threshold, and across all cohorts, at least 89% of patients achieved a total stem cell collection yield of ≥4 x 106 CD34+ cells/kg [30]. There was no significant difference observed in mobilization costs among the three cohorts, although the 40/µL threshold cohorts exhibited the cheapest mean cost ($37,182 per patient) [30]. The group concluded that a relatively lenient threshold of <40/µL peripheral blood CD34+ cell counts was an optimal strategy for reducing apheresis days among patients.

Reconstitution of platelets and WBCs in patients as early as possible is optimal. Mobilization techniques are hence vital to successful engraftment in NDMM patients. In one study conducted in 2020, a group compared the efficacy of Pegfilgrastim (PEG) to Filgrastim (FIL) in mobilization [31]. FIL is a recombinant G-CSF and PEG is a conjugate of FIL [31]. Their results concluded that mobilization with PEG yielded higher levels of CD34+ cells and mononuclear cells per milliliter of blood [31]. In addition, the PEG group also experienced significantly earlier engraftment of WBCs and platelets after ASCT compared to the FIL group [31] (Figure 1).

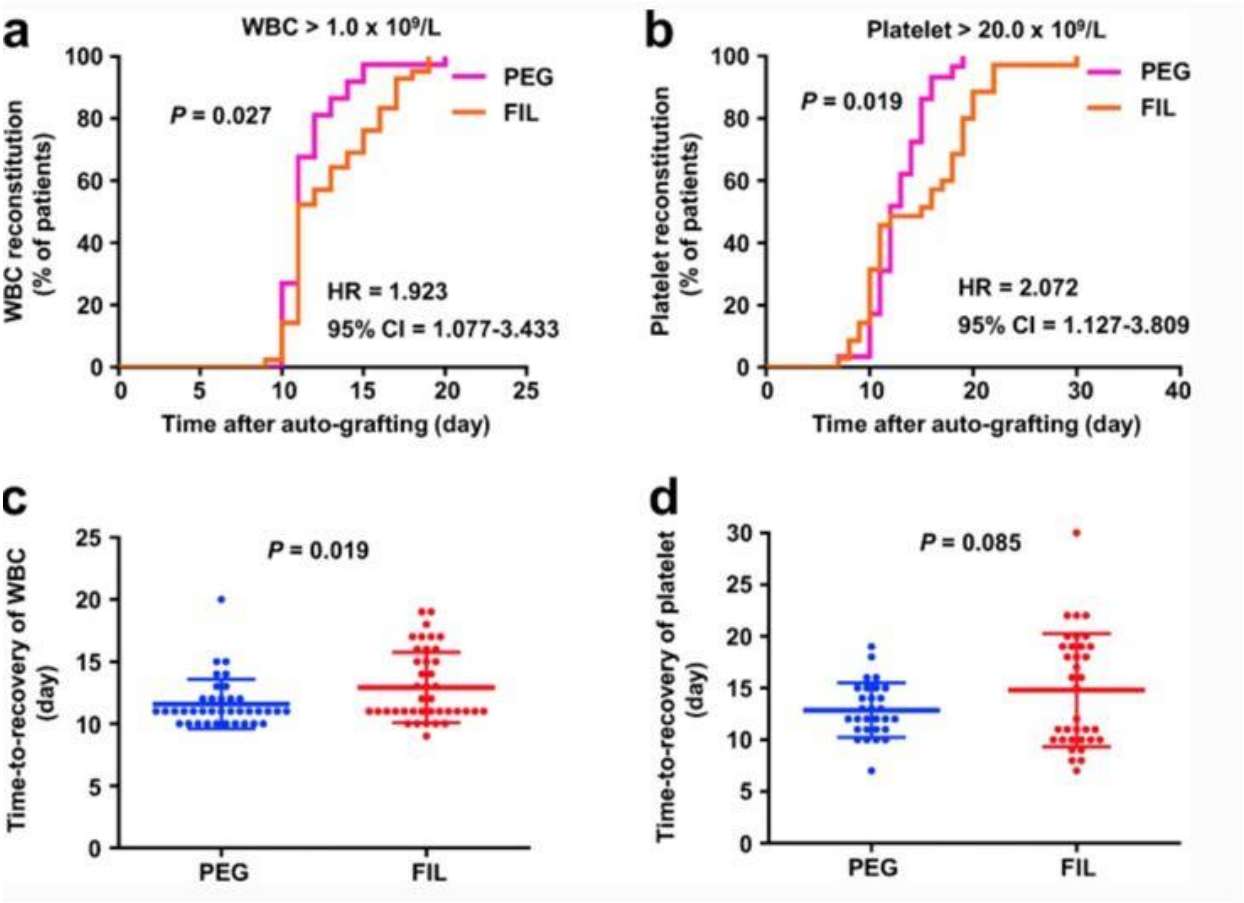


Figure 1: Hematopoietic recovery between PEG and FIL groups [31].

Figures 1a and 1b represent hematological reconstruction curves of the two treatment groups (PEG and FIL) for WBCs and platelets, respectively. Clearly, the group treated with PEG achieved earlier engraftment than the FIL group. Figures 1c and 1d demonstrate the average time-to-recovery of WBCs and platelets, respectively. Average time-to-recovery of WBC ($\geq 1x10^9$/L) was approximately 11.59 days for PEG compared to about 13 days for FIL, while time-to-recovery of platelets ($\geq 20x10^9$/L) was about 12.9 days for PEG compared to almost 15 days for FIL [31].

Following mobilization, HSCs are collected via apheresis, which is a technique designed to separate blood compartments and select for the needed white blood cell (WBC) layer [29]. HSC product is then cryopreserved using dimethyl sulfoxide until the patient is ready for transplant [29]. Following a conditioning regimen of HDT with melphalan that was discussed earlier, patients undergo transplantation of harvested HSCs [29]. Signs of engraftment usually occur 7-10 days and complete engraftment usually does not occur for at least 3 weeks [29].

Following ASCT, consolidation therapy is often introduced to improve disease response in patients while limiting toxicity. The phase 3 PETHEMA clinical trial discussed previously investigated how consolidation therapy influenced complete remission rates among NDMM patients [13]. Patients received 2 additional cycles of the VRD regimen 3 months after ASCT [13]. Complete remission rates increased from 44.1% to 50.2% following consolidation therapy 13. The European Myeloma Network published a study in 2020 in which they conducted a similar phase 3 trial. Patients undergoing transplantation with HSCs were randomly assigned to either receive 2 cycles of the VRD regimen for consolidation therapy or no consolidation therapy [32]. The group reported that patients that underwent consolidation therapy had significantly higher rates of median progression-free survival (58.9 months) compared to those with no consolidation (45.5 months), after a median follow up of 42 months [32].

Overall, the use of HSCs as a treatment for MM through ASCT has shown to be very effective and is currently still considered standard for NDMM patients. There are a variety of induction regimens, mobilization methods, and consolidation therapies that can influence the efficacy of ASCT with HSCs. Still, it is important to consider whether other stem cells can play a therapeutic role in the treatment of MM.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are multipotent progenitors derived from the bone marrow that possess the capacity to self-renew [33]. MSCs can differentiate into osteoblasts (bone-forming cells), fibroblasts (collagen-forming cells), and adipocytes (fat-storing cells), which make up the majority of the bone marrow compartment [33]. There is increasing interest on the therapeutic capabilities of MSCs for treating patients with MM bone disease. Studies suggest MM bone disease is due to osteoblast deactivation from certain proteins and cytokines [34]. One study in 2012 investigated the use of placenta-derived adherent cells (PDACs) for antimyeloma therapeutic potential in a severe combined immunodeficiency (SCID)-model of mice [34]. PDACs are mesenchymal-like stem cells that are isolated from the postpartum human placenta [34]. In the study, myeloma cells were obtained from patients

with active MM via bone marrow aspirates; the cells (1x106 cells) were injected into a rabbit bone that had been previously implanted in the mice [34]. After indication of myeloma growth from changing levels of human Ig of the M-protein isotype and detection of tumor growth approximately 3 weeks after myeloma injection, intra-bone injections of PDACs (0.1-1x106 cells per mouse) and MSCs (1x106 cells per mouse) followed [34] (Figure 2).

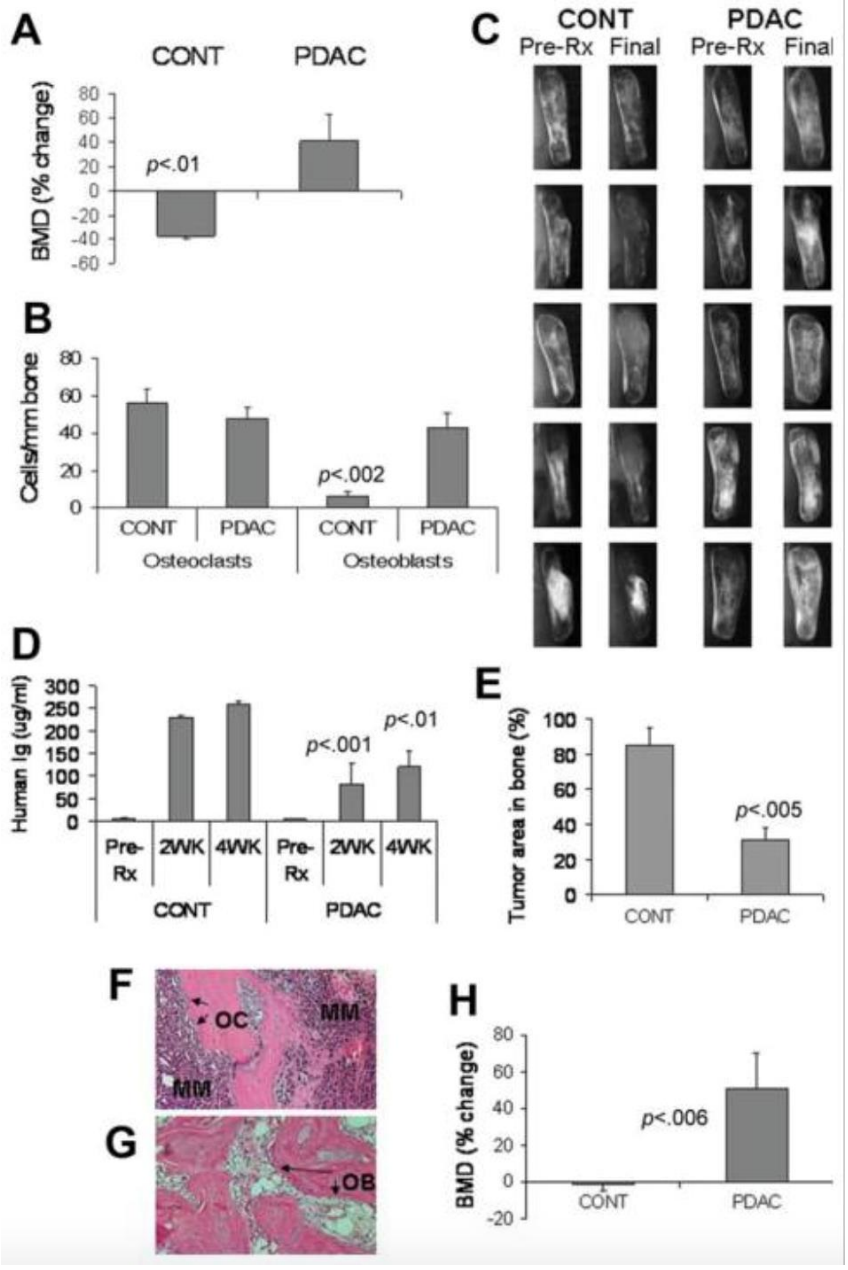


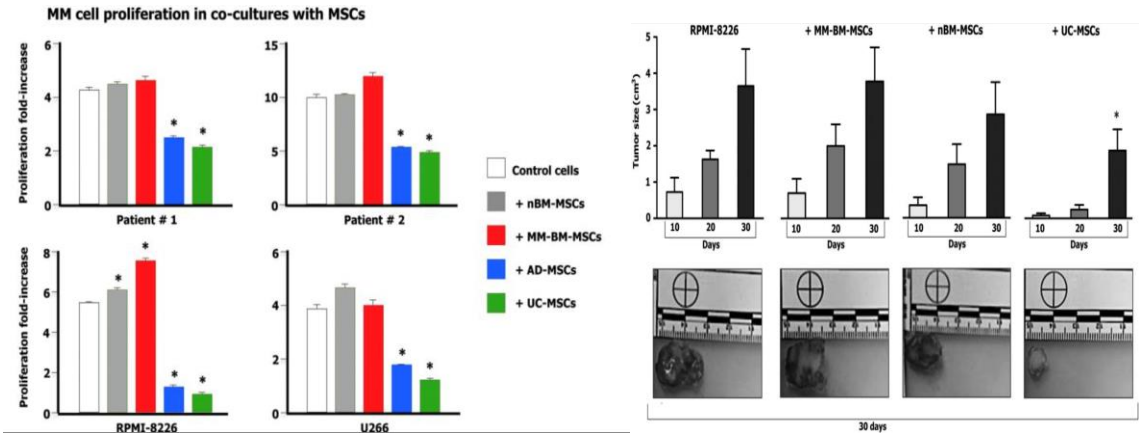
Figure 2: Mouse Model of Treatment of Myeloma with Mesenchymal-like Stem Cells.

The study reported that diseased mice treated with PDACs saw a much higher percent change of bone

mineral density (41% higher than pre-treatment levels) than those in the control group (37% lower than pre-treatment levels) (Figure 2a); increased osteoblast activity (Figure 2b); x-ray radiographs showed an increase in bone mass (Figure 2c); a decrease in tumor activity and inhibition of myeloma growth via an immunosorbent assay of human Ig (Figure 2d-e) [34]. Figures 2f and 2g represent H&E staining of the control group (2f) and the PDAC-treated group (2g) of mice [34]. Clearly, there is a more normal marrow composition, reduction in MM cells, and increase in osteoblast activity in the PDAC-treated image. This animal model demonstrated that mesenchymal-like stem cells isolated from the postpartum placenta can promote bone formation via stimulation of osteoblasts and inhibit growth of myeloma cells [34]. The study shows promise for treating bone disease in MM patients, but more research needs to be conducted to improve understanding of the therapeutic potential of MSCs in MM patients.

Another study in 2013 utilized a similar mouse model to investigate the use of MSCs from fetal bone for recovery of osteolytic lesions and inhibition of MM disease [35]. Intra-bone injections of MSCs were delivered in vivo to myeloma-diseased mice [35]. The results reported from this animal model were similar to the study previously discussed: the group treated with MSCs experienced an increase in bone mineral density, increase in bone mass, decrease in osteoclast activity with an increase in osteoblast activity, as well as significantly lower serum levels of human Ig (which can be used as an indicator of MM burden), when compared to the control group that received no treatment [35].

Currently, there are no clinical trials involving therapeutic use of MSCs derived from bone marrow for treatment of MM, however preclinical models do exist. Reasoning for this lies in the fact that bone marrow derived MSCs contribute to MM cell proliferation and chemoresistance 33. MM cell proliferation is aided by MM-MSCs because of secretion of high levels of a potent growth factor for MM cells termed Interleukin (IL)-6 [33]. MM cells secrete DKK1 protein that halts MSC differentiation into osteoblasts, where undifferentiated MSCs will then produce more IL-6, which in turn stimulates DKK1 production [33]. Thus, research into MSCs from sources other than bone marrow is necessary for therapeutic treatment. In one study from 2015, a group explored if MSCs derived from adipose tissue and umbilical cord have any effect on MM cell growth when compared to normal marrow MSCs and myelomatous MSCs [36]. This study conducted experiments in vitro and in vivo with SCID-mice [36]. The group found that adipose-derived and umbilical cord-derived MSCs significantly suppressed MM cell proliferation when compared to normal marrow-derived and myelomatous marrow-derived MSCs in culture [36]. Similar findings were reported on the in vivo effect of different MSCs on MM tumor growth in SCID mice [36] (Figure 3).



Figures 3 (left) and 4 (right): Effect of adipose-derived and umbilical cord-derived MSCs on cell proliferation and tumor growth compared to normal marrow-derived and myelomatous-derived MSCs *in vitro* and *in vivo*.

The histograms in (Figure 3) show how cell proliferation of RPMI-8826 MM cells and U226-MM cells decreased when cultures were treated with adipose-derived and, more significantly, with umbilical cord-derived MSCs. (Figure 4) illustrates how significantly umbilical cord-derived MSCs decreased tumor size in relation to the other MSCs. Interestingly, there was a 20-fold decrease in tumor size when mice were treated with umbilical cord-derived MSCs compared to the control group treated with PBS [36]. These findings illustrate the capacity to which different sources of MSCs can have on decreasing tumor size and cell proliferation of malignant myeloma cells. They demonstrate the need for more research on potential candidates for reducing MM progression, in particular umbilical-cord derived MSCs.

Mesenchymal stem and progenitor cells possess the unique capability to differentiate into various types of cells that aid in osteoblastogenesis and the production of adipocytes and fibroblasts [37]. The ability of MSCs to migrate towards tumor sites indicates that they potentially play a role in tumor suppression [37]. Differentiation of MSCs into osteoblasts provides reasoning for MSC therapeutic treatment of MM patients, due to the life-threatening conditions that bone disease causes in MM patients, even after remission [35]. Although some preclinical animal models have shown promise in the utilization of MSCs for treatment, further research needs to be conducted before clinical trials can ensue.

Conclusion

Although treatment options have improved dramatically in the past few decades, multiple myeloma remains an incurable disease. There are a variety of induction therapies that have undergone clinical trials to show promise in preparing NDMM patients for ASCT after HDT. ASCT of HSCs remains the mainstay for NDMM patients in terms of achieving complete remission or VGPR. HSCs ability to self-renew and differentiate yield potential to repair damaged tissue and treat diseases related to MM. MSCs have shown promise in animal models for treating bone diseases related to MM, but MSCs involvement in myeloma cell proliferation remains an issue for the utilization of MSCs as a therapeutic option for NDMM patients. For this reason, further research needs to be conducted before clinical trials can ensue.

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