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Case Report

First-In-Human High-Cumulative-Dose Mesenchymal Stem Cell therapy in Multiple Myeloma: A Case Report

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Abstract

Multiple myeloma (MM) is a highly malignant cancer characterized by the proliferation and accumulation of monoclonal plasma cells in the bone marrow along with end-organ damage due to the underlying disorder. Despite the remarkable progress in the treatment of MM with the availability of novel agents and hematopoietic cell transplantations (HCTs), an overwhelming majority of patients relapse and the disease is generally considered incurable. Here we report a case of a 57-year old male with relapsed MM previously treated with standard of care therapies including high-dose chemotherapy, radiotherapy, and autologous HCT. Based on our previous success with mesenchymal stem cell (MSC)-based therapy and its favorable safety profile, allogeneic MSC infusions were offered as a treatment option. A daily dose of 5.0×10^8 MSCs was slowly administered intravenously for about one and a half hours to the patient for ten consecutive days. Three months after the treatment, his laboratory results had returned to within normal ranges and MRI showed complete resolution of the lesions. There were no significant adverse effects after administration of MSCs during the course of treatment and follow-up. The patient has since been cancer-free and no longer suffers from osteoporosis, which is usually a life-long complication for patients with MM. This first-in-human study showed that a high cumulative dose of MSCs is a safe and curative treatment for MM.

INTRODUCTION

Multiple myeloma (MM) is a hematopoietic malignant disorder characterized by a clonal expansion of terminally differentiated plasma cells in the bone marrow. The plasma cells proliferate in the bone marrow and infiltrate the kidney and other organs can result in extensive skeletal destruction, renal failure, anemia, hypercalcemia and recurrent infections [1,2]. MM accounts for about 1% of all new cancer cases in the United States, and is the second most frequent blood cancer, constituting about 10% of all hematologic malignancies [3]. Various types of treatment exist for MM, including chemotherapy, corticosteroids, immunomodulators, monoclonal antibodies, histone deacetylase inhibitors, proteasome inhibitors, radiation, and hematopoietic cell transplantations (HCTs) which have contributed to a significant improvement in overall survival in the last 15 years [4]. However, despite the remarkable progress in survival, it remains a fatal disease.

Mesenchymal stem cells (MSCs) are a major constituent of the bone marrow microenvironment. They possess the ability to self-renew and differentiate into several lineages, including osteoblasts, chondrocytes, adipocytes, and fibroblasts [5-8]. Accumulating evidence indicates that MSCs in MM are phenotypically and functionally different from normal MSCs, and the aberrant MSCs promote osteolytic lesions, support MM cell growth and drug resistance through direct cell-to-cell contact, cytokine release, and exosome secretion [9-17]. In contrast, aberrant MSCs from MM patients stimulate tumor growth and disease progression. Expanded MSCs isolated from postpartum human placenta effectively suppress MM-induced bone disease and tumor growth in bone by inhibiting osteoclastogenesis and stimulating endogenous osteoblastogenesis [18]. Intrabone or sequential intravenously injected expanded human fetal bone-derived MSCs act as bystander cells to inhibit MM-induced bone disease in the mouse model [19]. The pathologic characteristics of MM-related osteolytic lesions and the acceptable safety profile of MSCs support the potential of exogenous healthy MSC-based therapies for this disease [18-22]. This case reports the results obtained from a relapsed MM patient treated with high-cumulative-dose allogeneic MSCs.

CASE REPORT

A 57-year-old male relapsed MM presented with fatigue, myalgia, anorexia, renal insufficiency, and generalized weakness. Magnetic resonance imaging (MRI) of the spine and extremities revealed a total of eighteen variable-sized, well-defined lesions. Cancer cells had invaded the orbital bone of his right eye causing the eye to spontaneously shed tears. As a result, his oncologist recommended surgical removal of his right eyeball. Laboratory findings were remarkable for a WBC of $3.28 \times 10^3/\mu l$, platelet

count of 116 × 10^3/μl and red blood cell distribution width (RDWCV) of 16.0%. Electrophoresis identified a large amount of lambda (27.6 mg/l) and kappa-free light chains (27.6 mg/l). The patient had received high-dose chemotherapy, radiotherapy, and autologous HCT but with limited response. Due to his deteriorating health, and the lack of response to prior treatments, we offered allogeneic MSC infusions as a treatment option based on our previous success with MSC-based therapy and its favorable safety profile. The patient was well-informed regarding the experimental nature of the protocol and provided written informed consent for treatment and data publication.

MSCs from human gingiva were prepared as previously described [23]. A biopsy of gingival connective tissue from a healthy donor was crushed into small pieces and were cultured in αMEM (ThermoFisher Scientific, Grand Island, NY, USA) supplemented with 10% AB serum (Sigma-Aldrich, St Louis, MO, USA). Antibiotics, 100 U/ml penicillin, 100 μg/ml streptomycin, and 0.25 μg/ml Amphotericin B (ThermoFisher) were added to the culture for the first two passages. The medium was replaced three times a week, and adherent cells were allowed to reach 85% confluent before they were sub-cultured with trypsin-EDTA. The resulting cells were harvested and expanded in vitro for 4 weeks.

The cells are prepared by resuspending them in 2 mL of patient's own serum and injected into a bag of Lactated Ringer IV solution before slowly administered intravenously intravenously over one and a half hours to the patient. The patient received a daily dose of 5.0 × 10^8 MSCs for ten consecutive days. After each infusion, the patient was closely monitored for the following symptoms: fever, chillness, nausea, vomiting, skin rash, cough, dyspnea, wheezing, chest pain, cyanosis, sputum production, hemoptysis, palpitation, and pain of extremity signs of tumor development. During the entire course of treatment, none of these symptoms were reported. Prior to MSCs treatment, the patient experienced complete hair loss and involuntarily trembling fingers after receiving multiple cycles of chemotherapy and radiotherapy. Two weeks after treatment, his fingers stopped shaking uncontrollably and his scalp hair started to grow back. The patient's skin hyperpigmentation cleared and his right eye no longer spontaneously shed tears. All laboratory tests returned to within normal ranges and MRI showed no residual cancer three month after the MSC treatment. The patient has since been cancer-free and suffered no symptoms to date. In addition, he no longer suffered from osteoporosis, which is usually a life-long complication for patients with MM.

DISCUSSION

The main treatment options for MM are chemotherapy alone or chemotherapy plus HCT. Although allogeneic HCT may be a potentially curative treatment for MM, initial high dose chemotherapy followed by allogeneic HCT cannot commonly be employed due to the fact that the majority of patients are older age and/or have comorbidities which makes them ineligible. Moreover, this regimen is associated with high rates of overall mortality and the probability of cure is very low [24-26].

MSCs from patients with MM possess aberrant genomic, phenotypic, and functional properties [9,13,16,17]. Cross-talk between tumor cells and MSCs in the bone marrow microenvironment has been shown to increase the metastatic potential and promote epithelial-to-mesenchymal transition [27]. It is well-established that abnormalities in MM bone marrow MSCs play a vital role in myeloma cell growth, progression, and relapse [11, 28,29]. Altering the bone marrow microenvironment by administering exogenous MSCs has been shown to suppress the growth of MM, prevent bone loss, and stimulate bone formation [18]. The inhibitory effect of MSCs on tumor growth has been reported in various animal tumor models including breast cancer [30], Kaposi's sarcoma [31], hepatoma [32] and melanoma [33]. An immunodeficiency SCID-rab MM model showed that exogenous MSCs act as bystander cells to inhibit MM-induced bone disease and tumor growth. Furthermore, systemically injected MSCs are attracted to bone by MM cells and inhibit bone disease [19]. MSCs express Fas-L which induce MM cell apoptosis in vivo, and inhibit the growth and metastasis of MM in vitro and in vivo [34]. Based on these findings, a novel MSC-based cytotherapy may be a promising therapeutic approach for myeloma osteolysis.

Human gingival-derived MSCs are a class of cells with unique self-renewal and multilineage differentiation properties [35]. These cells display stable morphology, maintain normal karyotype and telomerase activity at high passages, and are not tumorigenic [36]. We previously demonstrated that gingival MSC-based cytotherapy was safe and curative for the management of severe psoriasis [23]. In this study, we showed that a significantly more intensive intervention with respect to both the individual MSCs dose and the frequency of dose administration is an effective treatment strategy for MM. This report is the first to show the safety and curative effect of high-cumulative-dose MSCs in MM. The patient has been monitored for four years and has remained cancerfree.

In contrast to the research described above, MSCs have also been implicated in tumor growth, progression, and metastasis [21, 27, 37]. The potentially supportive role of MSCs in tumor growth and metastasis raises concerns about the safety of their use in a clinical setting. MSCs reside in the bone marrow stroma alongside hematopoietic stem cells (HSCs) and play a supportive role for HSCs. Capable of suppressing T-cell activation, human MSCs have previously been used to enhance long-term HSC engraftment in human transplantation [38]. To date, data from human clinical trials performed with allogeneic MSCs have shown mixed therapeutic outcomes; however, no evidence of tumor formation and severe adverse events has been reported in over 1000 patients treated with MSC for a variety of indications.

The treatment of MM is progressing rapidly with advances being made in autologous and allogeneic transplantation and the development of novel anti-MM agents. The results of this first-in-human study revealed that a high cumulative dose of MSCs is a safe and curative treatment for MM, and these findings warrant further clinical exploration toward a new step in stem cell transplantation. Combining standard of care therapies with novel strategies to achieve synergistic responses is a particularly

promising approach in MM. Future research should validate the safe/efficacy of combined application of transplantation, novel agents, and cytotherapy for the treatment of MM. The evidence presented in this report supports the notion that MM could be a manageable chronic disease and perhaps a curable disease for some.

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