

Stem Cell Transplantation for Treatment of Intractable Diseases

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Abstract

Hemopoietic stem cells (HSCs) can be harvested from the bone marrow, peripheral blood or umbilical cord blood. HSC transplantation is used to treat hematologic and lymphoid cancers and other disorders. Some reports have indicated that Bone Marrow Transplantation (BMT) might cure these intractable diseases—including hematological disorders, autoimmune diseases and age-associated diseases. Intra bone marrow- BMT (IBM-BMT) has been proven to be a powerful strategy for allogeneic BMT due to the rapid hemopoietic recovery and the complete restoration of T cell functions. In this review, we summarize the findings of our studies of IBM-BMT to treat some intractable diseases, including cancers such as leukemia, autoimmune diseases such as rheumatoid arthritis and autoimmune pancreatitis, age-related diseases such as osteoporosis and Alzheimer's disease in mouse models.

Keywords: Intra-bone marrow; Bone marrow transplantation; Mesenchymal stem cell; Cancer; Autoimmune diseases; Age-related diseases

Introduction

Hemopoietic Stem Cell (HSC) transplantation is used to treat hematologic and lymphoid cancers and other disorders [1]. HSCs are isolated from the bone marrow, peripheral blood or umbilical cord blood for allogeneic transplants. Bone Marrow Transplantation (BMT) was able to cure these intractable diseases, including 1) hematological disorders such as aplastic anemia [2], leukemia [3] and malignant lymphomas [4]; 2) congenital immuno deficiencies such as severe combined immune deficiency [5]; 3) metabolic disorders [6] such as enzyme deficiencies and amyloidosis; 4) Autoimmune Diseases (ADs) [7] such as Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE); 5) age-associated diseases such as osteoporosis [8], diabetes mellitus [9] and myocardial infarction [10]. Intra-Bone Marrow-BMT (IBM-BMT) [11] has been proven to be the most effective approach, since it can be used to replace not only HSCs and but also Mesenchymal Stem Cells (MSCs).

In this review, we summarize our studies of ADs, age-related diseases and leukemia treated with IBM-BMT in mouse models.

IBM-BMT

IBM-BMT was used first in our laboratory to treat chimeric-resistant MRL/lpr mice in 2001 [11]. We have reported that donor-derived c-kit (+) cells were significantly greater in number at 2 to 6 days after IBM-BMT. Meantime, the number of colony-forming units in spleen was significantly higher than with intravenous BMT (IV-BMT). Higher accumulations of both hemopoietic cells and stromal cells were observed after IBM-BMT than with IV-BMT during this early period [12]. Abnormal HSCs can proliferate in allogeneic microenvironments, while normal HSCs can proliferate in collaboration with Major Histocompatibility Complex (MHC)-compatible stroma cells, not MHC-incompatible MSCs [13]. Because IBM-BMT can be used to replace both HSCs and MSCs, the process avoids the risk of graft rejection and allows the use of a mild conditioning regimen, and hemopoietic recovery is rapid.

MSCs can be differentiated in vitro and in vivo into various cell types of mesenchymal origin, such as osteoblasts, adipocytes and chondrocytes [14,15]. Recently, more reports have demonstrated that MSCs secrete a variety of factors that promote tissue repair, stimulate proliferation and differentiation of endogenous tissue progenitors, and

decrease inflammatory and immune reactions [16-18]. MSCs have the ability to modify and influence almost all the cells of the innate and adaptive immune systems, to interfere with and affect cellular proliferation, differentiation, maturation, and function to induce an anti-inflammatory phenotype and to modulate the immune response [18-21]. MSCs delay and prevent the development of acute Graft Versus Host Disease (GVHD) [22,23].

Some reports have shown that antibody response is lower in the older than younger humans and the efficacy of vaccinations is reduced [24,25] and that morbidity and mortality are increased in aged mice and humans [26]. B lineage precursors function decreased with aging resulting from the decreasing function of HSCs. IBM-BMT of young marrow cells reversed the reduction of pro-B cells and pre-B cells. The frequency of follicular-B cells in the IBM-BMT group was significantly increased compared to those in the older group [27].

IBM-BMT Plus Thymus Transplantation (TT) Treats Leukemia

Allogeneic BMT is a viable therapeutic option to treat leukemia via Graft-Versus-Leukemia (GVL) responses. The GVL effects induced by the alloreactive T cells transferred along with the bone marrow graft respond to antigenic differences expressed on host tissues and appear to have a significant antitumor benefit [28,29].

The thymus regulates the production, proliferation and functions of T cells [30]. It plays a crucial role in the elimination of the auto reactive clones involved in the development of ADs [31]. TT supplies mature lymphocytes in one direction, and significantly regulates the immune function of T cells in vivo for the benefit of the host [32]. The combination of BMT plus TT can treat the ADs in the MRL/lpr mouse, because the allogeneic T cells newly developed by TT are naïve T cells, which show less fas expression and more resistance to apoptosis than

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the activated memory T cells with their high Fas expression [33]. IBM-BMT plus TT is effective in restoring donor-derived T cell function in aged, chimeric-resistant mice [34]. Moreover, we found that allogeneic IBM-BMT plus adult TT from the same donor is effective in mice bearing solid tumors; it can induce high thymopoiesis, preserving strong Graft-Versus-Tumour effects without severe graft-versus-host reaction [35]. In tumor-bearing mice, tumor growth was more strongly inhibited by IBM-BMT plus adult TT than by IBM-BMT alone. The number of CD8+ T cells that infiltrated the tumors, and the number of apoptotic tumor cells both significantly increased in the mice treated with IBM-BMT plus adult TT.

There are four types of leukemia, including acute lymphoblastic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia and chronic myelogenous leukemia. Allogeneic hematopoietic stem cell transplantation is an effective immunotherapy for childhood leukemia. One report has demonstrated that BMT can be used to treat all subtypes of pediatric leukemia and provides consensus guidelines for transplantation of acute leukemia [36]. Although allogeneic BMT has been used for the treatment of leukemia, there were some side effects such as GVHD. IBM-BMT has been proven to reduce the incidence of GVHD and to provide a greater engraftment of donor-derived cells, including MSCs [37,38]. EL-4 cells are derived from thymoma of mice, and can induce the mimicking of leukemia in mice. We recently reported that IBM-BMT plus adult TT prevented the growth of leukemia as a result of the improved mitogen responses to both T and B cells, and significantly increased IL-2 production, and donor-derived T cells in mice with leukemia [32]. Our report showed that allogeneic IBM-BMT plus adult TT induces strong GVL effects with mild GVHD. It could thus become a viable strategy for the treatment of leukemia in humans.

IBM-BMT Treats ADs

ADs represent a heterogeneous group of disorders with genetic, environmental and individual etiological factors [39]. There are a number of reports of BMT being used to treat ADs such as insulin-dependent diabetes mellitus, RA, SLE, multiple sclerosis, and Autoimmune Pancreatitis (AIP) in various mouse models [40-44].

One report has demonstrated that serum IL-10, TGF β -1, and IL-2 concentrations were significantly increased compared to the control group when treated with N-acetyl-D: -glucosamine, indicating that this has suppressive effects on experimental RA in the SKG/Jcl mouse [45]. There was no evidence of arthritis 12 months after the bone marrow cells of C57BL/6J mice were transplanted into SKG/Jcl mice using IBM-BMT, and the hematolymphoid cells in the recipient mice were reconstituted by donor-derived cells. Moreover, IBM-BMT has been shown to normalize the percentages of treg (Foxp3+/CD4+) cells, the percentages of receptor activator of NF-kB ligand+ cells on the CD4+ T cells and the serum levels of TNF α , IL-1 and IL-6. This report demonstrated that IBM-BMT is a viable method of immunological manipulation that suppresses the severe joint destruction and bone absorption in SKG/Jcl mice, and lends further credence to the use of this methodology in humans with intractable RA [44].

AIP has been reported to show chronic pancreatitis with pancreatic duct stenosis, raised levels of serum IgG4, responsiveness to immunosuppressive therapy, and no apparent underlying cause such as chronic alcoholic pancreatitis [46,47]. The male Wistar Bonn/Kobori (WBN/Kob) rat is used as a unique animal model for chronic pancreatitis because it shows widely distributed fibrosis and degeneration of parenchyma because of infiltration of lymphocytes. These findings have been shown to be related to sex hormone [48], genetic factor [49] and

immune disturbances [50]. We previously reported that WBN/Kob rats develop dacryoadenitis, sialadenitis, thyroiditis, sclerotic cholangitis and tubulointerstitial nephritis, and that this rat is a useful animal model for AIP and Sjögren-like syndrome in humans. Moreover, IBM-BMT has been shown to prevent these ADs in this animal model [42].

IBM-BMT Improves Age-related Diseases

The Senescence-Accelerated Mouse (SAM) strain shows senescence acceleration and age-associated disorders. The SAMP6 spontaneously develops osteoporosis, and SAMP8 develops cognitive deficits that mimic Alzheimer's disease with aging [51]. Osteoporosis is one of the most common bone disorders, and is classified into primary and secondary types. Though primary osteoporosis usually occurs in both sexes at any age, it is often observed in postmenopausal women and even in men later in life. IL-6, TNF α and TGF β might be involved in osteoporosis through the regulation of osteoblastogenesis and osteoclastogenesis. Osteoclast formation and bone resorption via TNF- α has been recently reviewed [52]. The bone marrow microenvironment was normalized after IBM-BMT, and increased production of IL-11 and IL-6 ameliorated the imbalance between bone absorption and formation, resulting in the prevention of osteoporosis in SAMP6 [8,53,54]. RANKL, RANK and osteoprotegerin have been shown to be essential for controlling the osteoclast development and functions in bone remodeling, and the inhibition of RANKL activity by osteoprotegerin injection results in significantly reduced bone loss in arthritis [55] and osteoporosis [56].

The SAMP8 is an acceptable rodent model for cognitive deficits that mimic Alzheimer's disease with aging and is found to have age-related deficits in learning and memory that could not be explained in terms of differences in sensorimotor or motivational capabilities [57,58]. Heme Oxygenase (HO)-1 is a very sensitive marker of oxidative stress; chronic over-expression of HO-1 in the Alzheimer's disease brain, possibly in response to excessive amyloid provocation, may account for the (transferrin receptor-independent) iron overload and mitochondrial insufficiency observed in this disorder [3]. The higher oxidative stress status is observed to be partly caused by mitochondrial dysfunction in the SAM, resulting in the excessive production of reactive oxygen species and neurodegeneration [4]. Our studies indicated that IBM-BMT increased the antioxidant effect by increasing the expression of HO-1 and decreasing the expression of inos, thus ameliorating the impaired cognitive ability of SAMP 8 mice [59]. We have no data about which cognitive areas are primarily recovered; our aim is to clarify this in further studies.

Conclusion

BMT is a routine and successful method performed in humans in HLA-matched combinations. Most intractable diseases are not only HSC disorders but also MSC disorders. IBM-BMT can efficiently transplant both HSCs and MSCs, and may in the future be useful for treating various intractable diseases.

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