Mesenchymal Stromal Cells from Bench to Bedside: Current Use in Hematopoietic Stem Cell Transplantation and Future Prospect

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Mesenchymal stromal cells (MSCs) are multipotent cells that can be isolated from several human tissues and expanded \textit{ex vivo} for clinical use. MSCs are identified by their adherent properties, immunphenotype and differentiation potential. MSCs display immunological properties that have been demonstrated both \textit{in vitro} and \textit{in vivo}, in animal models and in humans, although the exact mechanisms underlying these effects remain largely unknown. MSCs preferentially home to damaged tissue and secrete paracrine factors with anti-inflammatory properties. The immunomodulatory and reparative/anti-inflammatory properties of MSCs have been tested in a variety of animal models and have been applied in specific clinical settings.

The ability of MSCs to enhance the engraftment of HSCs after transplantation has been demonstrated both in animal models and in clinical trials. The experimental data \textit{in vivo}, together with the known physiological role played by MSCs in sustaining haematopoiesis, have provided the rationale for testing the capacity of these cells to facilitate haematological recovery after HSCT in humans. Expansion of donor-derived MSCs proved to be feasible and their clinical use safe in children given a T-cell depleted HLA-disparate allograft from a relative. Indeed, all patients given MSCs showed sustained hematopoietic engraftment, without any adverse reaction. This study suggests that co-transplantation of hematopoietic stem cells (HSCs) and MSCs may modulate host alloreactivity and/or promote better engraftment of donor hematopoiesis, reducing the risk of early graft failure when HLA disparity is present in the donor/recipient pair. Similarly, co-transplantation of MSCs and umbilical cord blood (UCB)-derived HSCs is under investigation as a strategy aimed at improving engraftment and reducing transplant-related mortality in UCB transplantation recipients.

The most impressive clinical effect of MSCs \textit{in vivo} has been observed in the treatment of acute graft-versus-host disease (GvHD) developing after allogeneic hematopoietic stem cell transplantation (HSCT). The first striking report of this effect was reported by Le Blanc \textit{et al.} who described a pediatric patient experiencing grade IV acute GvHD of the liver and gut after allogeneic HSCT from an unrelated volunteer and resistant to multiple lines of immune suppressive therapy. The child was rescued by the infusion of bone marrow (BM)-derived MSCs isolated from the mother. More recently, the benefit deriving from the infusion of MSCs in patients with steroid-resistant acute GvHD has been confirmed in a study reporting 55 patients, both adults and children, treated in 6 different institutions. Infusion of MSCs appeared to be safe and no major toxicities were observed. Treatment with MSCs resulted in a response in the majority of patients with a significant difference in survival between complete responders and partial/non-responding patients. The real efficacy of MSC infusion in the management of patients with GvHD remains to be proved in a randomized trial comparing this innovative treatment with more conventional approaches. Likewise, it remains to be defined the number of infusions to be performed, the optimal dose of MSCs to be administered for each infusion and the possible synergisms of MSCs with other therapies demonstrated to be active in patients with acute GvHD.
In view of the promising experimental results on the use of MSCs for the treatment of autoimmune diseases, their role in the clinical setting is now beginning to be explored. Both in animal models and in patients, it has been shown that BM-derived cells play a role in the healing process following intestinal injury and in the regeneration of various cellular components of the mucosa. Recently, in a phase-I clinical trial, autologous, adipose tissue (AT)-derived MSCs have been successfully employed for the treatment of 4 patients with fistulizing Crohn's disease (CD). Based on these encouraging results, a phase-II trial on autologous AT-derived MSCs and a phase-III trial on third-party, BM-derived MSCs in CD patients refractory to conventional therapies, are underway.

In conclusion, at present MSCs are extensively characterized in a culture-expanded state, and relatively little is known on their biological properties in vivo. The immunosuppressive and reparative properties of MSCs hold great promise for treating immune-mediated and inflammatory disorders. Clinical results obtained so far have demonstrated the feasibility and safety of MSC use in vivo. Larger randomized clinical trials have been started in Europe and in the USA. To completely exploit the potentiality of this new treatment modality more in vivo work is required to increase our knowledge on how MSCs mediate their suppressive effect and reduce inflammatory responses. Moreover, in vivo tracking studies to examine the survival, distribution and homing of MSCs after infusion in humans are necessary. The identification of a universal MSC marker is warranted both to dissect the hierarchy of the different MSC subsets and to facilitate the generation of homogenous cell products at different sights. Once more largely defined, these in vivo biological activities of MSCs could be properly employed as a novel therapeutic strategy to stimulate tissue repair and modulate immune responses in a variety of immune-mediated and inflammatory diseases.