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Sapporo Medical University: Cellular therapy for stroke and spinal injury

One of the missions of Sapporo Medical University is to develop regenerative medicine and to provide innovative therapies for patients. The university began clinical trials of autologous mesenchymal stem cells (MSCs) for stroke and spinal cord injury in 2007 in Japan.

Novel therapeutic mechanisms of MSCs for neurological diseases and their implications

MSCs are capable of self-renewal and multipotent differentiation along distinct lineage pathways, including the neural lineage. MSCs have shown multiple therapeutic effects at various sites and stages of disease both in and outside the target lesion. This is because MSCs respond to a gradually developing pathological microenvironment. Although initially stem cells were thought to replace injured cells during treatment for neurological disease, studies suggest there are additional therapeutic mechanisms[1,2]. Only a few days after infusion, MSCs release neuromodulators such as brain-derived neurotrophic factor, which modulates excitability. MSCs may also provide trophic support for vulnerable neurons and anti-inflammatory responses, including reduction of oedema that leads to enhanced tissue sparing. MSCs may contribute to neovascularization, vascular stabilization and remodelling of the blood–brain barrier, thereby protecting the central nervous system (CNS) and limiting oedema over time. Local axonal sprouting and new synaptic connections could also be stimulated. Finally, MSCs could facilitate mobilization of resident progenitor cells, which might contribute to neurogenesis and remyelination of demyelinated axons. Thus, MSC therapies promote improved functional outcomes or enhance endogenous regenerative processes in which compensatory neural plasticity or remodeling may contribute to time-dependent functional improvements.

Clinical studies of intravenously delivered MSCs for stroke

We recently conducted a clinical study with 12 stroke patients who received systemic administration of autologous bone marrow–derived MSCs that were cultured and expanded in auto-serum[1,2]. All patients showed improved neurological functions on the National Institutes of Health Stroke Scale (NIHSS). Magnetic resonance imaging (MRI) following MSC infusion showed an absence of tumours and abnormal cell growth in all of the patients over one year. Time-locked, accelerated improvement in the NIHSS score was observed soon after MSC infusion. The fastest recovery period was during the initial phase (first 1–2 weeks) after MSC infusion. Functional improvement continued, but at a slower rate — some patients continued to improve for the next few months and the improvement was maintained for the year in all patients. Based on the promising outcomes of this clinical study, a phase III, double-blind, placebo-controlled clinical stroke trial was launched at Sapporo Medical University in 2013 (JMA-IIA00117).

Clinical trial of intravenously delivered MSCs for spinal cord injury

We previously demonstrated that intravenous infusion of MSCs in experimental contusive spinal cord injury (SCI) improved functional outcomes[3]. Based on these encouraging results, a phase II clinical trial for patients with SCI has been ongoing at Sapporo Medical University since late 2013 (JMA-IIA00154).

Our application for intravenously delivered MSCs for SCI was recently designated as a 'SAKIGAKE' breakthrough therapy in Japan, which has prompted priority review and expedited drug approval.

Prospects

Systemically infused autologous MSCs have been tested in clinical studies, and their safety profile supports their therapeutic utility in both stroke and SCI. Intravenous infusion of MSCs seems to be a more tractable route for clinical application. Several other delivery routes could be considered but have limitations. Intra-arterial injection may cause systemic embolism and require specific interventional devices. Direct injection of MSCs into the CNS may cause additional intracerebral or intraspinal trauma or haemorrhage. Intracerebral stereotactic injection could be complicated by the amount of human tissue, possibly causing targeting problems and necessitating multiple injections that are undesirable in the vulnerable CNS. Intracerebral injection could also cause an epileptic attack. Thus, an intravenous route may be the safest and most effective.

Autologous MSCs cultured in auto-serum also have advantages compared with allogeneic MSCs. This is because MSCs express human leukocyte antigen class I and II, which can initiate immunorejection that requires immunosuppression[1]. Importantly, a single preparation of 10^8 MSCs grown under standard conditions in fetal bovine serum (FBS) retains approximately 7–30 mg of FBS protein, and humoral immune responses against FBS have been observed in recipients of MSC infusions[1].

In summary, intravenous infusion of autologous MSCs cultured in auto-serum might be the best candidate regenerative therapy for CNS diseases, such as stroke and SCI. Sapporo Medical University is working towards developing MSCs as an innovative drug for practical use in the clinic.

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