THE USE OF STEM CELLS IN CEREBROVASCULAR DISEASE

Dimitrios Karussis
Hadassah-Hebrew University, Jerusalem, Israel

Introduction/Background: To overcome the limited capacity of the CNS for regeneration, the theoretical alternative would be to use stem cells for more effective management of chronic degenerative and inflammatory neurological conditions, and also of acute neuronal damage from injuries or cerebrovascular diseases. Although the adult brain contains small numbers of stem cells in restricted areas, this intrinsic stem cell repertoire is small and does not measurably contribute to functional recovery. In addition, the migration ability of these CNS stem cells is limited and their function may also be compromised by putative inhibitory factors.

Stem cells administration was shown to promote neuronal survival in animal models of stroke, brain trauma, Parkinson's disease and Multiple sclerosis. The neuroprotective effects of stem cells are mainly related to their ability to produce neurotrophic factors that may support neuronal survival and induce the proliferation and mobilization of endogenous neural stem cell in the sites of CNS damage. Another possibility is that the neuroprotective effects could be attributed to cellular trans-differentiation of the transplanted cells and replacement of the damaged neurons (neo-neurogenesis).

Embryonic cells carrying pluripotent and self-renewal properties represent the stem cell prototype, but there are additional somatic stem cells that may be harvested and expanded from various tissues during adult life. Stem cell transplantation is based on the assumption that such cells may have the potential to regenerate or support the survival of the existing -partially damaged cells.

Mesenchymal stromal cells (MSC) are part of the bone marrow stem cells repertoire which also includes the main stem cells population of the bone marrow, the hematopoietic stem cells. The main role of MSCs is to support hematopoiesis but they can also give rise to cells of the mesodermal layers. Recently, significant interactions between MSCs and cells from the immune system have been demonstrated: MSCs were found to downregulate T and B lymphocytes, natural killer cells (NK) and antigen presenting cells through various mechanisms, including cell-to cell interaction and soluble factor production. Besides the immunomodulatory effects, MSCs were shown to possess additional stem cells features, such as the self-renewal potential and multipotency. Their debatable transdifferentiation potential to cells of the endo- and exo-dermal layer, including cells of the CNS, may explain in part their reported neuroprotective effects. Studies in vitro and in vivo (in cells cultures and in animal models) have indicated neuroprotective effects. MSCs are believed to promote functional recovery following CNS injury or inflammation, by producing trophic factors that may facilitate the mobilization of endogenous neural stem cells and promote the regeneration or the survival of the affected neurons. These immunomodulatory and neuroprotective features could make MSCs potential candidates for clinical application in immune-mediated and neurodegenerative diseases. Moreover, the use of bone marrow derived stem cells offers several practical advantages: (1) MSC can be obtained easily and safely from adult bone marrow, including from patients with advanced disease; (2) MSC which are normally present in small concentrations in the bone marrow compartment can be enriched and expanded by in vitro culturing to large numbers for therapeutic purposes; (3) autologous MSC can be administered safely without the need of immunosuppressive treatment to prevent rejection; and (4) adult MSC are less prone to genetic abnormalities and malignant transformation during multiple passages in vitro, thus implying a low risk for induction of treatment related malignancies.

Several clinical trials with stem cells in immune-mediated and degenerative diseases have been already conducted or are underway. The clinical experience has -until now- revealed the feasibility and safety of application of stem cell therapy (and especially MSC) in various neurological conditions, including cerebrovascular diseases and indicated some evidence of efficacy in various medical conditions.

Clinical experience with stem cell therapies in Cerebrovascular diseases

Early open clinical trials have provided data on the safety and feasibility of cell trans-plantation in patients with stroke. In one of them (Kondziolka et al), neuronal cells derived from neural progenitors were transplanted into 12 patients from 0.5 to 6 years after basal ganglia strokes. No adverse events were observed up to 5 years after transplantation and the patients displayed some clinical improvement. In a randomized phase II follow-up trial [55], a total 18 patients were included, 1–6 years after suffering a basal ganglia ischemic or hemorrhagic stroke. Patients were randomized to receive 5 or 10 million cultured neuronal cells by stereotactical surgery, combined with cyclosporine 1 week before and 6 months after surgery and rehabilitation. No cell-related adverse effects were observed; other side effects of the procedure included a single seizure, a syncopal episode and a subdural hematoma. Of the total 14 patients who underwent surgery, 6 showed clinical improvement at 6 months. In a separate study, 5 patients received transplanted porcine neural cells pretreated

with anti-MHC1 antibody to avoid immune rejection 1.5–10 years after a basal ganglia stroke. One patient experienced worsening of the motor deficits and another developed seizures briefly after transplantation. This trial was subsequently terminated by FDA after the inclusion of 5 patients.
Another, open-label, observer-blinded, trial evaluated the long-term (5 years) safety and efficacy of i.v. MSC transplantation in 85 patients with severe, middle cerebral artery territory ischemic stroke (Lee. et al). This study showed that the cumulative survival at 260 weeks was 72% in theMSC group and less than half (34%) in the control group. Significant side effects were not observed following MSC treatment. The occurrence of comorbidities including seizures and recurrent vascular episodes did not differ between groups. The follow-up modified Rankin Scale (mRS) in the control group score was decreased, whereas the number of patients with a low mRS (0–3) increased in the MSC group. The clinical improvement in the MSC group was associated with the serum levels of stromal cell-derived factor-1 and the degree of involvement of the subventricular region (SVZ) of the lateral ventricle (patients with less infracted SVZ area had a better outcome). Bang et al., transplanted autologous MSC in a phase I/II clinical trial in 30 patients with MCA cerebral infarcts. An intravenous infusion of autologous MSC was given to 5 patients and the rest served as controls. No adverse cell-related effects were observed, and some clinical
improvement was detected at 3, 6 and 12 months in the patients who received MSC, compared with the control population.
Cumulatively, these human trials indicate the feasibility of stem cell therapy in stroke and some elements of clinical benefits, but the currently existing clinical data are still limited and cannot provide a proof of clinical efficacy.

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