Safety of mesenchymal stem cells therapy

More than 10 years mesenchymal stem cells (MSCs) have been used in treatment of different diseases, most importantly in tissue degeneration, irradiation damage, hematopoietic and posttransplant diseases as well as in refractory chronic inflammatory, fibrosing and fistulizing diseases. They have unique properties such as immunomodulatory, proangiogenic and antifibrotic, therefore, MSCs inhibit inflammation, fibrosis and promote regeneration of tissue damage. These cells can be isolated from bone marrow, adipose tissue, cord blood and potentially from muscle, gingiva and fetal liver. In addition they are non-immunogenic and can be transplanted without conditioning and without immunosuppressive prophylaxis. Therefore, MSCs represent an attractive clinical approach for the treatment of chronic inflammatory, fibrosing and fistulizing diseases[1].

It is considered that the microenvironment of damaged tissues produces factors that attract stem cells to the site of injury and enhances their differentiation into desired cells. Thus, MSCs promote tissue regeneration by differentiating into the injured cells[2]. Moreover, in the presence of MSCs, immature or partially immature antigen presenting cells are produced which turn off T cells leading to down-regulation of activated immune cell reactivity. Due to their immunomodulatory potential, MSCs reduce tissue damage[3].

There are data which were obtained on animal models that MSCs due to their immunosuppression ability can promote tumor growth. It is crucial to specify that it was demonstrated on animals with preexisting malignancies[4]. Moreover, it has been showed that MSCs don’t undergo malignant transformation in long-term culture[5]. Also, oncogenic transformation of MSCs and induction of malignancy by them wasn’t seen in vitro or in vivo. Tarte K. et al. in 2010 demonstrated that MSCs with or without chromosomal alterations showed growth arrest and entered senescence without evidence of transformation[6].

In 2005 the report that described escape of MSCs from senescence and generation of malignant cells as the MSC were expanded in culture was published[7]. At that time it was unexpected results because numerous laboratories which had studied the cells for more than a decade hadn’t observed such phenomenon[8,9]. Later the authors indicated the reason of observed data. The transformation of MSCs was explained by contamination of cultures with a small number of malignant cells[10]. Therefore, it is important to emphasize that according to the data obtained by Tarte K. et al. in 2010 and Bernardo M.E. et al. in 2007 MSCs don’t undergo malignant transformation in vitro in long-term culture as well as in vivo. Hence, using of mesenchymal stem cells in clinical practice is safe and don’t increase the risk of malignant transformation in patients. Also, now it is well documented the conditions for safe expansion of MSCs[11].

In 2012 Lalu M.M. et al. published the results of a systematic review and meta-analysis of clinical trials in which the safety of mesenchymal stem cells (MSCs) therapy were examined. It was the first systematic review and meta-analysis which have given comprehensive assessment of all available data related to the safety of systemic MSCs administration.

The analysis of 36 clinical trials in which 1087 patients had participated didn’t reveal association between MSCs and tumour formation. It means that administration of MSCs is safe and doesn’t increase the risk of malignant transformation in patients. Also, systemic review of clinical trials demonstrated that malignancy occurred only in patients with ongoing or previous malignancies. It is important to note that de novo malignancies weren’t observed in all reviewed clinical studies.

It is important to emphasize that associations between MSCs treatment and the development of acute infusional toxicity, organ system complications, infection, death weren’t detected. Therefore, according to existing data using of mesenchymal stem cells in the treatment of patients with diverse pathologies is safe[12].

In 2014 Fisher S.A. et al. published the results of systemic review of randomized controlled clinical trials in which the safety and efficacy of autologous bone marrow-derived stem cells as a treatment for chronic ischemic heart
disease and heart failure had been researched. Nineteen clinical trials in which 947 patients received stem cells treatment showed no long-term adverse events associated with bone marrow-derived stem cells therapy[13].

It is necessary to mention the results of clinical trial in which a long-term safety of the MSCs therapy was proved. There were nineteen patients with amyotrophic lateral sclerosis who received autologous MSCs treatment. The patients were monitored during nearly 9 years. Every 3 months clinical, psychological and neuroradiologic assessments were conducted. The greatest value of this clinical trial is the neuroradiologic demonstration of the lack of tumor formation or abnormal cell growth after MSCs therapy. During the entire follow-up period the MRI didn’t show any evidence of new tissue formation[14].

The long-term safety of MSCs administration was showed also in the clinical trial conducted by Giannotti S. et al. in which MSCs were used in the treatment of upper limb non-unions. Patients with atrophic pseudarthrosis of the upper limb were enrolled in the clinical trial. All of them were implanted MSCs with bone grafts at the non-union sites. The follow-up period was 6 years. Satisfactory integration of the new bone was confirmed by X-ray. All patients recovered limb function. No evidence of ectopic neoformation, tissue overgrowth, neoplastic transformation were observed in all patients[15].

Another clinical trial which has demonstrated long-term safety of using autologous MSCs was published by Waki0ani S. et al. There were 41 patients who had received autologous MSCs for repair of articular cartilage. The patients were followed for up to 11 years and 5 months. It was demonstrated that no tumor formation was observed in all patients during all observational period[16].

Therefore, the obtained data have provided strong evidence for the safety of autologous MSCs treatment.

References


20 YEARS OF CLINICAL EXPERIENCE

3 INTERNATIONAL CLINICS

ADVANCED MEDICAL EQUIPMENT

50 HIGHLY SKILLED MEDICAL EXPERTS

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