

## 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, proangiogenetic 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 Wakitani 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

1. **Voswinkel J et al.** Use of Mesenchymal Stem Cells (MSC) in Chronic Inflammatory Fistulizing and Fibrotic Diseases: a Comprehensive Review. Clin Rev Allergy Immunol. 2013 Oct;45(2):180-92. doi: 10.1007/s12016-012-8347-6
2. **Caplan A.I., Dennis J.E.** Mesenchymal stem cells as trophic mediators. J Cell Biochem 2006;98:1076-84.
3. **Beyth S., Borovsky Z., Mevorach D. et al.** Human mesenchymal stem cells alter antigenpresenting cell maturation and induce T-cell unresponsiveness. Blood .2005; 105:2214-9.
4. **Djouad F., Plence P., Bony C. et al.** Immunosuppressive effect of mesenchymal stem cells favors tumor growth in allogeneic animals. Blood. 2003 Nov 15;102(10):3837-44. Epub 2003 Jul 24.
5. **Bernardo M.E., Zaffaroni N., Novara F. et al.** Human bone marrow derived mesenchymal stem cells do not undergo transformation after longterm in vitro culture and do not exhibit telomere maintenance mechanisms. Cancer Res. 2007;67:9142 – 9.
6. **Tarte K., Gaillard J., Lataillade J.J. et al.** Clinical-grade production of human mesenchymal stromal cells: occurrence of aneuploidy without transformation. Blood. 2010 Feb 25;115(8):1549-53. doi: 10.1182/blood-2009-05-219907. Epub 2009 Dec 23.

7. **Wang Y., Huso D.L., Harrington J. et al.** Outgrowth of a transformed cell population derived from normal human BM mesenchymal stem cell culture. *Cytotherapy*. 2005;7:509 – 19.
8. **Pittenger M.F., Mackay A.M., Beck S.C. et al.** Multilineage potential of adult human mesenchymal stem cells. *Science*. 1999;284:143 – 7. 11.
9. **Digirolamo C.M., Stokes D., Colter D. et al.** Propagation and senescence of human marrow stromal cells in culture: a simple colony-forming assay identifies samples with the greatest potential to propagate and differentiate. *Br J Haematol*. 1999;107:275 – 81.
10. **Garcia S., Mart í n M.C., de la Fuente R. et al.** Pitfalls in spontaneous in vitro transformation of human mesenchymal stem cells. *Exp Cell Res*. 2010;316:1648–50.
11. **Prockop D.J., Brenner M., Fibbe W.E. et al.** Defining the risks of mesenchymal stromal cell therapy. *Cytotherapy*. 2010 Sep;12(5):576-8. doi: 10.3109/14653249.2010.507330.
12. **Lalu M.M., McIntyre L., Pugliese C. et al.** Safety of cell therapy with mesenchymal stromal cells (SafeCell): a systematic review and meta-analysis of clinical trials. *PLoS One*. 2012;7(10):e47559. doi: 10.1371/journal.pone.0047559. Epub 2012 Oct 25.
13. **Fisher S.A., Brunskill S.J., Doree C. et al.** Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. *Cochrane Database Syst Rev*. 2014 Apr 29;4:CD007888. doi: 10.1002/14651858.CD007888.pub2.
14. **Mazzini L, Mareschi K, Ferrero I et al.** Mesenchymal stromal cell transplantation in amyotrophic lateral sclerosis: a long-term safety study. *Cytotherapy* 2012; 14(1), 56–60.
15. **Giannotti S., Trombi L., Bottai V. et al.** Use of autologous human mesenchymal stromal cell/fibrin clot constructs in upper limb non-unions: long-term assessment. *PLoS One*. 2013 Aug 30;8(8):e73893. doi: 10.1371/journal.pone.0073893. eCollection 2013.
16. **Wakitani S., Okabe T., Horibe S. et al.** Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months. *J Tissue Eng Regen Med*. 2011 Feb;5(2):146-50. doi: 10.1002/term.299.



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