Translational Research Informatics Center (TRI)

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Transplantation of CD34⁺ cells for patients with nonunion fractures

The Translational Research Informatics Center (TRI) was founded in 2002 as the first data centre in Japan to promote academia-originated medical innovation. The Academic Research Organization (ARO) network was established in 2013 by TRI and is transforming into an Asian ARO network in conjunction with Korea, Taiwan and Singapore. We plan to expand the network globally to Europe and the United States. Our aim is to develop an infrastructure to support the launch of global clinical trials of academia-originated projects and to obtain regulatory approval worldwide.

Failures in fracture healing are caused by many systemic and local factors. Among them, severe skeletal injuries consisting of fractures with a compromised blood supply result in either delayed unions or established nonunions. An essential requirement for such fractures to heal is to restore the local blood flow, which is traditionally performed through complex vascular procedures or soft tissue transfers. One emerging strategy in the regeneration and repair of bone and surrounding tissue is the use of stem cells, including bone marrow mesenchymal stem cells. We have proven the first proof-of-principle by elucidating the collaborative multilineage differentiation of circulating CD34⁺ cells into endothelial cells and osteoblasts. On the basis of *in vitro* experiments and a preclinical study using *in vivo* animal experiments, we started a clinical trial of autologous transplantation of granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood CD34⁺ cells for patients with tibial or femoral nonunion.

We demonstrated that systemic infusion of human circulating CD34⁺ cells into immunodeficient rats with non-healing fractures contributes to fracture healing. This CD34⁺ cell transplantation and healing produced two main mechanisms: the osteogenic and endothelial differentiation potential of CD34⁺ cells; and the paracrine effect of CD34⁺ cells by secreting vascular endothelial growth factor[1]. Next, we attempted local transplantation of CD34⁺ cells with atelocollagen gel, a bioabsorbable scaffold, in the same animal model and demonstrated the similar effect at a lower dose when compared with systemic administration[2]. In this series, we confirmed that effective fracture healing occurred as long as there were more than 1×10^4 CD34⁺ cells per rat implanted along the fracture site. Our findings provide feasible alternatives to current clinical strategies for treating delayed unions and established nonunions.

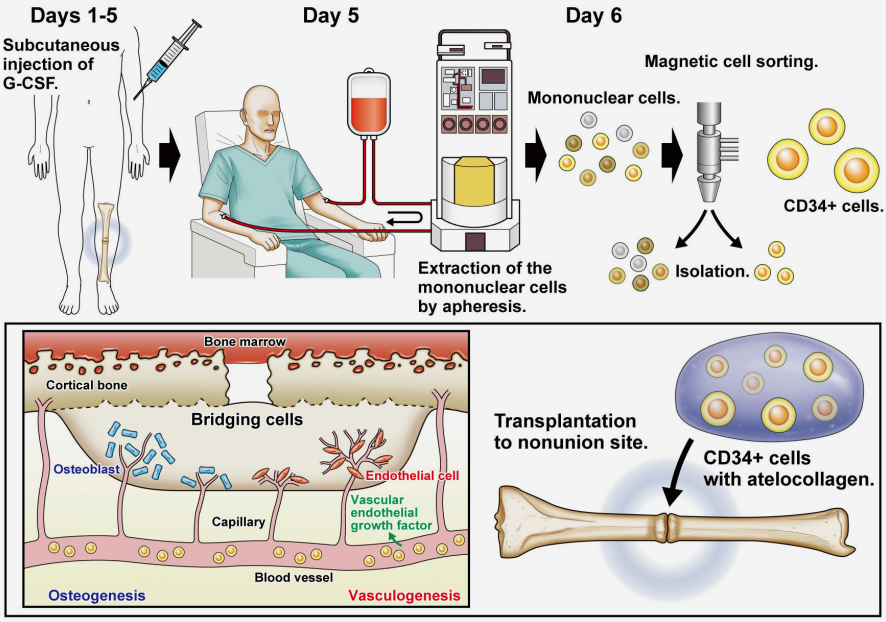

Figure 1. A schematic of the treatment procedure. Peripheral blood CD34⁺ cells, which are sorted from mononuclear cells following administration of granulocyte colony-stimulating factor (G-CSF) and leukapheresis, dissolve in the atelocollagen gel and are locally administered into the fracture site. Fractures are healed via the osteogenic and endothelial differentiation potential of CD34⁺ cells and the paracrine effect of CD34⁺ cells by secreting vascular endothelial growth factor.

We started a phase I/IIa clinical trial of autologous local transplantation of G-CSF-mobilized peripheral blood CD34⁺ cell for patients with tibial or femoral nonunion. After leukapheresis following a course of one injection per day, for five days of G-CSF, patients received magnet-sorted CD34⁺ cells. Treatment was a conventional operation for nonunion combined with autologous transplantation of G-CSF-mobilized peripheral blood CD34⁺ cells (10^6 cells/kg) suspended with atelocollagen gel (Fig. 1). Radiological fracture healing at week 12, the primary endpoint of this study, was achieved in 5 of 7 patients (71.4%). Two patients without fracture healing at week 12 had femoral fractures, and in those patients radiological healing was observed at weeks 19 and 36. The intervals between cell transplantation and union, the secondary endpoint, were 12.6±5.4 (range 8 to 24) weeks for clinical healing and 16.1±10.2 (range, 8 to 36) weeks for radiological healing.

Promising outcomes in the phase I/IIa clinical trial[3] encourage the application of transplanting CD34⁺ cells for nonunion as a novel therapeutic modality. A multicenter clinical trial has been initiated to further elucidate the safety and efficacy of CD34⁺ cell transplantation for bone fracture healing.

REFERENCES

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