

Long-term survival of donor multipotent mesenchymal stromal cells implanted into the bone

There are two types of stem cells in the bone marrow, one for the formation of blood cells and another for the formation of the skeleton and the bone marrow stroma. Stromal cells (5% of all cells in the bone marrow) regulate and maintain the formation of blood cells (haematopoiesis). Multipotent mesenchymal stromal cells (MSCs) can be isolated from the bone marrow and multiplied in culture. MSCs are able to differentiate into all adult bone marrow stromal cells and maintain blood formation, as well as modulate the immune response and perform trophic functions. MSCs administered intravenously are detected in the body for approximately 2 weeks and then disappear.

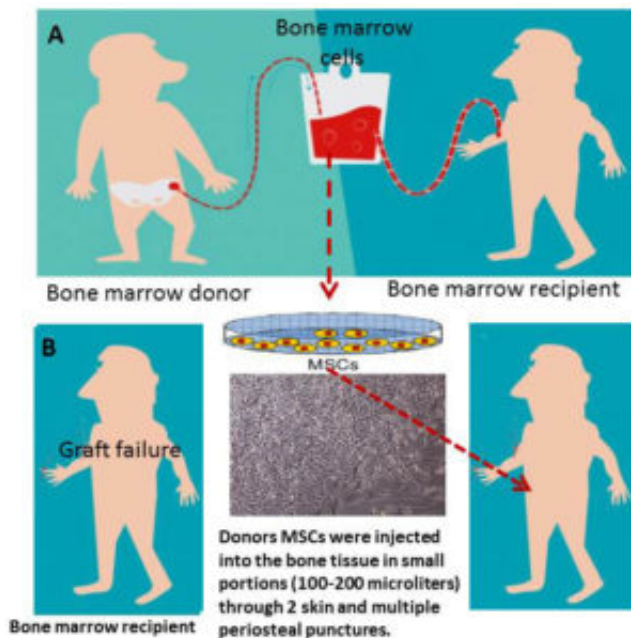


Fig. 1. Bone marrow transplantation (A) and MSCs injection (B).

A. Bone marrow was aspirated from the ilium bones of donors and injected intravenously into the patient. A small portion of the bone marrow was taken for MSC cultivation. B. Multiplied MSCs were frozen. In 3 patients, the graft failed, and thawed MSCs were implanted into the ilium bones of the patients.

Allogeneic bone marrow transplantation (allo-BMT) provides an opportunity for survival in leukaemia patients. Patients receive highly active drugs to kill tumour cells and then receive transfusions with donor haematopoietic stem cells (HSCs). The drugs destroy not only malignant cells but also those involved in normal blood formation. Usually, normal donor cell-mediated

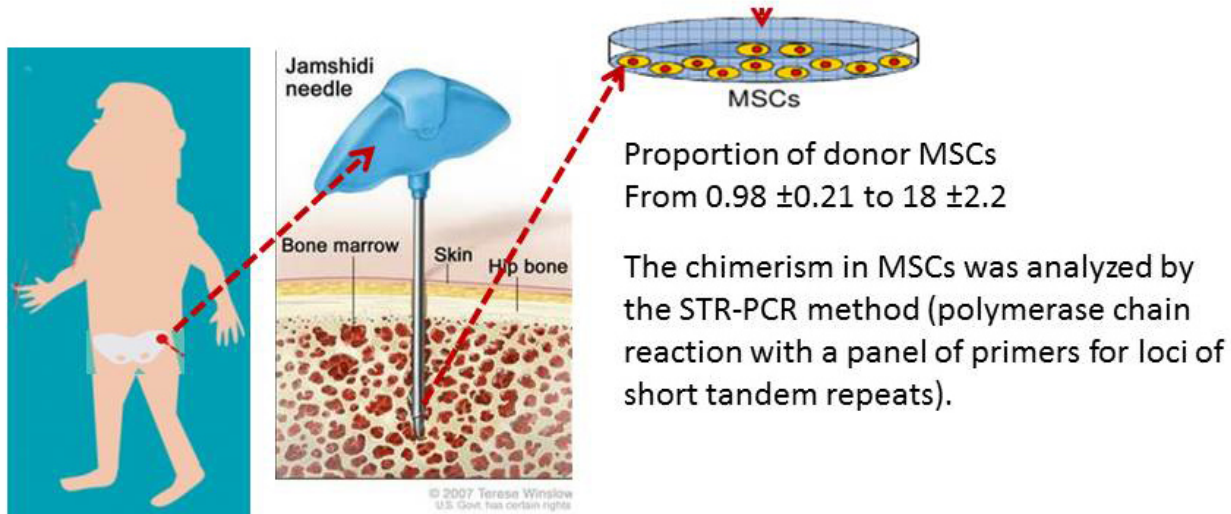
haematopoiesis recovers within one month after allo-BMT. In 3 patients observed for more than 3 months, haematopoiesis was not restored, i.e., transplanted HSCs were not engrafted. In these cases, patients require the continuous transfusion of blood components and should be kept under sterile conditions; otherwise, the patients are at risk of death from infections.

At the time of bone marrow collection from donors, a small quantity of bone marrow cells was taken, and MSCs were separated and cultured (Fig. 1).

Cryopreserved MSCs were thawed and implanted into the bone. After 2 weeks, 2 patients exhibited recovery of their own haematopoiesis, and 1 patient exhibited recovery in 2.5 months. All patients survived. At 3 and 5 months after MSC implantation, bone marrow puncture was performed for routine investigations. The sites of puncture were located closely to the sites of intraosseous MSC administration. From patients' bone marrow cells, MSCs were cultured and tested for the presence of donor cells (Fig. 2).

It appeared that 1–18% of MSCs were of donor origin. Samples of MSCs containing donor cells grew better than those consisting of only patient cells. This can be explained by the fact that the stromal cells of the patient were subjected to the damaging effects of the drugs used before and during allo-BMT, whereas donor MSCs were intact. The detection of donor MSCs in patients demonstrated, for the first time, the possibility of their long-term engraftment and function. Perhaps the lack of restoration of haematopoiesis in some patients was due to damage to their own stromal cells. Donor HSCs could not find a niche and were not engrafted. The introduction of donor MSCs into the bone supported the partial restoration of the stroma. MSCs probably performed trophic functions that allowed patient HSCs to begin producing mature blood cells. An individual's own haematopoiesis is rarely destroyed completely, and some HSCs survive, but a long time is needed to restore blood cell production. In these patients with graft failure, MSC implantation enabled patient HSCs to start functioning.

Bone marrow punctures 3 and 5 months after donor MSCs implantation.



Bone marrow recipient

Fig. 2. Analysis of MSCs from bone marrow of patients.

Bone marrow punctures were performed at 3 and 5 months after donor MSC implantation into the bone.

Two important conclusions could be inferred by these results:

1. MSCs implanted into the bone survived and functioned in the patient's bone marrow for more than 5 months.
2. These findings open new possibilities for the treatment of patients with graft failure after allo-BMT.

Kuzmina L.A., Petinati N.A., Sats N.V., Drize N.J., Risinskaya N.V., Sudarikov A.B., Vasilieva V.A., Drovkov M.Y., Michalzova E.D., Parovichnikova E.N., Savchenko V.G
National Research Center for Hematology, Moscow, Russia
Noviy Zikovskiy pr, 4, Moscow, 125167, Russia

Publication

[Long-term survival of donor bone marrow multipotent mesenchymal stromal cells implanted into the periosteum of patients with allogeneic graft failure.](#)

Kuzmina LA, Petinati NA, Sats NV, Drize NJ, Risinskaya NV, Sudarikov AB, Vasilieva VA, Drovkov MY, Michalzova ED, Parovichnikova EN, Savchenko VG

Int J Hematol. 2016 Sep