Early Tissue Distribution of Bone Marrow Mononuclear Cells After Intra-Arterial Delivery in a Patient With Chronic Stroke

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A 24-year-old man with a cerebral infarct within the left middle cerebral artery (MCA) territory was enrolled in a study to assess the safety of autologous bone marrow mononuclear cell (BMMC) transplantation in patients with ischemic stroke (NCT00473057). His National Institutes of Health Stroke Scale score was 7. Computed tomography (Figure 1A) and technetium-99m ethyl cysteinate dimer (99mTc ECD) single photon emission computed tomography (SPECT) (Figures 1B and 2 and Movie I in the online-only Data Supplement) indicated the location of the infarct. Sixty-seven days after onset of symptoms, the patient underwent BMMC transplantation. Bone marrow blood was aspirated under local anesthesia from both iliac crests and processed to isolate the mononuclear cell fraction. A total of $5 \times 10^9$ BMMCs was suspended into a volume of 10 mL, and 1 mL of the cell suspension was radiolabeled with $99mTc$ (radioactivity 111 MBq, physical half-life 6 hours), as described previously, and then added back to the unlabeled cell suspension. After catheter navigation via femoral artery access under local anesthesia and conscious sedation, cells were injected into the M1 portion of the MCA, and the infusion was completed within ~10 minutes. To monitor the fate of transplanted BMMCs, whole-body and planar scintographies were performed at 2, 24, and 48 hours after cell therapy. The patient had no complications during the procedure or follow-up.

Planar and SPECT views revealed uptake and retention of the labeled BMMCs in the territory of the left MCA for up to 48 hours (Figures 1C, 3, and 4 and Movie II in the online-only Data Supplement). The remaining uptake occurred mainly in the liver and spleen (Figure 4). To our knowledge, there has been only 1 report of BMMC homing in cerebral infarction, which indicated the retention of BMMCs 8 hours after intra-arterial injection in 1 patient in the subacute phase, 9 days after stroke. We here report for the first time the migration and homing of BMMCs to the brain of a patient in the chronic phase of stroke, >2 months after the onset of symptoms. The mechanisms involved in the possible therapeutic effect of BMMC therapy are still largely unknown, but accumulating evidence from animal studies suggests that these cells may behave as minipumps producing cytokines and/or trophic factors that support cell survival in the penumbra area and stimulate neurogenesis and angiogenesis, increasing brain remodeling and functional regeneration after ischemia. In vivo tracking of BMMCs after grafting is of great importance because the retention of transplanted cells at the site of the lesion may be critical for the success of cell therapy. In animal models, different methods have been used to track the transplanted cells, and it has been suggested that signals that are involved in the transit of inflammatory cells to injured tissue may also direct the transplanted bone marrow–derived cells. Our results indicate that labeling BMMCs with $99mTc$ is feasible and that noninvasive imaging may be used to study the migration and homing of transplanted cells in vivo in the setting of chronic stroke.

Figure 1. A, Computed tomography showing ischemic lesion in the left MCA territory. B, Brain perfusion $99mTc$ ECD SPECT showing left hypoperfusion. C, $99mTc$ BMMC brain SPECT revealing accumulation of the BMMCs in the left brain hemisphere 2 hours after cell transplantation.


The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/120/7/539/DC1.


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Disclosures

None.

References

Figure 4. Anterior whole-body scans performed 2 (A), 24 (B), and 48 hours (C) after infusion in the territory of the MCA show the distribution of BMMCs labeled with $^{99m}$Tc. Uptake in the left brain hemisphere is well visualized. The remaining activity was distributed mainly to the liver and spleen.
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