Clinical Trials of Stroke Therapy
Which Cells, Which Patients?

Lawrence R. Wechsler, MD

Despite recent advances in stroke prevention and acute stroke therapy, few treatments exist for reversal of fixed neurological deficits after stroke. Cellular therapy offers the possibility of improving neurological deficits months or even years after stroke. Animal studies provide evidence that such treatment may be effective. Many questions, however, remain unanswered regarding cellular therapy for stroke. In view of the significant differences between animal models and human stroke, some questions might be best addressed with clinical trials.

Clinical Trials of Cellular Therapy

Completed clinical trials of cellular therapy for stroke are summarized in the Table. Kondziolka et al reported the results of a Phase I study of 12 patients with completed stroke involving the basal ganglia treated with human neuronal cells derived from an immortalized tumor cell line (LBS cells). Either 2 or 6 million cells were implanted stereotactically between 6 months and 6 years after stroke. Patients were followed clinically as well as with MRI and positron emission tomography scans. The same group subsequently performed a Phase II study with randomization of 18 patients to either implantation of 5 or 10 million cells and rehabilitation (14 patients) or rehabilitation alone (4 patients). Follow-up neurological evaluations were blinded to treatment status. Savitz et al reported the results of transplantation of fetal porcine cells implanted stereotactically in 5 patients with basal ganglia stroke 3 months to 10 years after onset. The study was discontinued due to adverse events in 2 patients. In a study by Bang et al, autologous mesenchymal stem cells were given intravenously to 5 patients with middle cerebral artery territory strokes 4 to 5 weeks and again at 7 to 9 weeks after onset. An additional 25 patients served as control subjects. All patients were followed for functional outcome and adverse events.

The clinical studies of cell transplant for stroke performed to date are limited by the few patients treated, varying cell types and minimal controls. The results, however, provide preliminary insights into clinical questions that may be difficult to approach with animal studies and may help guide design of future trials of cell therapy.

Stroke Location

Three of the 4 completed studies included patients with stroke involving the basal ganglia. The basal ganglia provide a convenient target for stereotactic implantation of cells because a relatively small infarct in this area may cause significant and measurable motor deficits. The circumscribed area of infarction can be treated with small infusion volumes at several locations in one or more passes through the area. In the existing studies, infusions were targeted to surround the infarct with implanted cells, but the optimal location for stereotactic placement of cells may ultimately depend on cell type and mechanism of repair. Bang et al infused cells intravenously. In animal studies, bone marrow stromal cells localize to areas of brain injury, but whether this results in survival of functioning cells after human stroke is unclear. It is also unclear whether sufficient numbers of cells can be delivered intravenously to achieve clinical effectiveness in patients with extensive areas of infarction in the territory of the major cerebral arteries.

Stroke Etiology

The completed studies provided little information regarding stroke mechanism in the enrolled patients. In the phase I LBS study, 8 patients had infarcts restricted to the basal ganglia and in 4, the cortex was involved. Only one patient had atrial fibrillation. The phase II LBS trial included 9 ischemic strokes and 9 hemorrhages. Six of the 7 patients receiving 10 million cells had hemorrhagic strokes, whereas 5 of 7 strokes in the 5 million cell group were ischemic. A dose–response was not observed in this study with 4 of 7 patients in the 5 million cell group and 2 of 7 in the 10 million cell group improving at 6 months. The imbalance in hemorrhagic strokes and lack of improvement in the patients receiving higher numbers of cells suggest hemorrhagic and ischemic stroke may respond differently to cell therapy. This very preliminary observation requires confirmation in future trials.

Safety

Safety was the major focus of these early clinical trials. In the phase I and II LBS trials, no adverse events occurred directly attributable to the cell implants up to 2 years after treatment. One patient in the phase I study suffered a seizure at 6 months...
and in one patient, a brainstem stroke occurred 6 months after implantation. Two patients died of unrelated causes. In the phase II trial, a seizure occurred in one patient postoperatively and another was found to have a subdural hematoma 1 month after surgery requiring surgical drainage. In the study of intravenous mesenchymal stem cells, no procedure-related adverse events or complications related to the cells were observed up to 1 year after treatment.

Adverse events occurred in 2 of the 5 patients receiving fetal porcine transplants. One patient had transient weakness resolving after 10 days due to cortical vein occlusion. Another patient had seizures in the setting of hyperglycemia and a ring-enhancing lesion on MRI remote from the transplant site. This was resolved in 3 months. The relationship between these 2 complications and the transplants is uncertain and there is no clear indication that the cells were responsible.

Most adverse events observed in these trials were transient and reversible. Some were attributable to the stereotactic implantation procedure. The advantages of specific targeting of the stroke location and maximal delivery of cells must be weighed against the possibility of procedural complications. Fortunately, no cell-related complications such as tumors or abscess formation have been observed to date.

### Survival of Transplanted Cells

Although transplantation of cells has been successful, it is unclear whether the cells survive and function. In an attempt to assess the function of transplanted cells, all patients in the phase I LBS trial had positron emission tomography scans before and 6 and 12 months after the procedure. Increases of at least 10% in relative 18F fluorodeoxyglucose uptake in the area of the stroke were observed in 7 of 11 patients at 6 months, although at 12 months only 3 had sustained increases. In the area surrounding the stroke, 5 of 11 had increased activity at 12 months. There was a significant correlation between positron emission tomography changes from baseline and the motor subscore of the European Stroke Scale in both the area of the stroke and the surround ($P=0.009$ and $P=0.02$). Increased activity on positron emission tomography scans may be due to causes other than transplanted cells such as inflammation or increased activity of native cells in response to the transplant. The correlation with improvement in motor function and the persistence in some cases to 12 months favors a functional contribution of the implanted cells rather than inflammation.

One patient in the phase I LBS study treated with 2 million cells 34 months after stroke died of a myocardial infarction 27 months after transplantation. Neuropathological examination of the brain identified the site of transplantation adjacent to a lacunar infarct. Histochemical staining and subsequent DNA probes of cells in this area identified neuronal cells polyploid for chromosome 21 characteristic of LBS neurons. No tumors were found throughout the brain. These findings confirm survival of at least some transplanted cells more than 2 years after implantation.

### Efficacy

Conclusions regarding efficacy are limited in the completed studies due to small numbers of patients, minimal controls, and relative insensitivity of outcome measures to small changes in neurological function. In the phase I LBS study, 7 of 12 patients improved on the European Stroke Scale at 2 years. In the phase II study, 6 of 14 patients improved at 6 months, but there was no difference in the mean change in European Stroke Scale motor scores between treated patients and control subjects. Improvement in gross movement measured by the Action Research Arm Test was observed in treated patients compared with control subjects and between pretreatment and posttreatment evaluations. Four of 7 patients with nondominant hemisphere strokes showed improvements on tests of visuospatial ability and nonverbal memory. In both studies, several patients reported subjective changes, including improved walking, reduced stiffness, and improved memory. Similar findings were reported by Savitz et al after fetal porcine cell transplants. Improvement in Barthel Index was observed in patients treated with mesenchymal stem cells compared with control subjects after 1 year. Although there was no difference in infarct volume, patients receiving mesenchymal stem cells had less peri-infarct atrophy and less ventricular dilation. These preliminary observations suggest future studies should include detailed motor end points to detect small changes in function. Cognitive testing may also be an important outcome measure in future cell therapy trials.

### Summary

Only a few small clinical trials of cellular therapy for stroke have been reported. No direct cell-related complications occurred, and most of the observed issues were attributable to the stereotactic procedure. The results indicate that stroke location and etiology should be studied as possible variables affecting response to therapy and modes of infusion or cell types. Very limited efficacy data suggest that standard stroke study outcome measures such as the National Institutes of Health Stroke Scale score and modified Rankin score may not

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**Table. Clinical Trials of Cellular Therapy for Stroke**

<table>
<thead>
<tr>
<th>No. of Patients/Control Subjects</th>
<th>Cell Type</th>
<th>Source</th>
<th>Location</th>
<th>Delivery</th>
<th>Stroke Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kondziolka et al Phase I LBS</td>
<td>hNT</td>
<td>Immortalized cells</td>
<td>BG</td>
<td>IS</td>
<td>6 months to 6 years</td>
</tr>
<tr>
<td>Kondziolka et al Phase II LBS</td>
<td>hNT</td>
<td>Immortalized cells</td>
<td>BG</td>
<td>IS</td>
<td>1–6 years</td>
</tr>
<tr>
<td>Savitz et al</td>
<td>LGE</td>
<td>Fetal porcine</td>
<td>BG</td>
<td>IS</td>
<td>3 months to 10 years</td>
</tr>
<tr>
<td>Bang et al</td>
<td>MSC</td>
<td>Bone marrow</td>
<td>MCA</td>
<td>IV</td>
<td>4–5 weeks</td>
</tr>
</tbody>
</table>

LGE indicates lateral ganglionic eminence; MSC, mesenchymal stromal cells; BG, basal ganglia; MCA, middle cerebral artery; IS, intrastraital; IV, intravenous.
be sensitive to the magnitude of changes in function expected with cellular therapy and more detailed motor assessments are needed.

**Disclosures**

None.

**References**


**Keywords:** clinical trials # stroke therapy
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Stroke. 2009;40:S149-S151; originally published online December 8, 2008; doi: 10.1161/STROKEAHA.108.533208
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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