Stem Cell Therapy as an Emerging Paradigm for Stroke (STEPS) II

Sean I. Savitz, MD; Michael Chopp, PhD; Robert Deans, PhD; S. T. Carmichael, MD; Donald Phinney, PhD; Larry Wechsler, MD

Abstract—Cell-based therapies represent a new therapeutic approach for stroke. In 2007, investigators from academia, industry leaders, and members of the National Institutes of Health crafted recommendations to facilitate the translational development of cellular therapies as a novel, emerging modality for stroke from animal studies to clinical trials. This meeting was called Stem Cell Therapies as an Emerging Paradigm in Stroke (STEPS) and was modeled on the format of the Stroke Therapy Academic Industry Roundtable (STAIR) meetings. Since publication of the original STEPS guidelines, there has been an explosive growth in the number of cellular products and in the number of new laboratory discoveries that impact the safety and potential efficacy of cell therapies for stroke. Any successful development of a cellular product will need to take into consideration several factors, including the preclinical safety and efficacy profile, cell characterization, delivery route, in vivo biodistribution, and mechanism of action. In 2010, a second meeting called STEPS 2 was held to bring together clinical and basic science researchers with industry, regulatory, and National Institutes of Health representatives. At this meeting, participants identified critical gaps in knowledge and research areas that require further studies, updated prior guidelines, and drafted new recommendations to create a framework to guide future investigations in cell-based therapies for stroke. (Stroke. 2011;42:00-00.)

Key Words: cell therapy ■ guidelines ■ stem cells ■ stroke

Cell-based therapy is a potential new treatment approach for stroke. Over the past 20 years, there have been extensive efforts to develop and translate new stroke therapies, but there remains no proven treatment aside from tissue plasminogen activator for acute ischemic stroke. When neurologic deficits persist, despite acute treatment, there is no Food and Drug Administration-approved therapy to enhance recovery. Given the difficulties of identifying new treatments for stroke and the promising results of cell therapy in animal stroke models, investigators from academia, industry leaders, the National Institutes of Health, and the Food and Drug Administration convened in 2007 to discuss research guidelines in the field following the format of the prior Stroke Therapy Academic Industry Roundtable (STAIR) meetings.¹ This meeting was called Stem Cell Therapy as an Emerging Paradigm for Stroke (STEPS).²

Since publication of the first STEPS meeting, there has been an explosive growth in the number and types of cell-based therapies for stroke. Cells have been prepared and isolated from a range of different tissues, including blastocysts, embryonic and fetal tissue, neural tissue, bone marrow, peripheral blood, umbilical cord, placenta, amniotic fluid, menstrual blood, dental pulp, and adipose. Induced pluripotent cells have emerged based on new technology to reprogram adult skin fibroblasts into pluripotent stem cells with the potential to differentiate into cells from all 3 germinal layers, including neurons and other cells that comprise the nervous system. Many types of cell-based preparations are composed of heterogeneous cell populations such as umbilical cord blood or the mononuclear fraction of bone marrow. Even some types of more purified populations of bone marrow such as marrow stromal cells may be heterogeneous depending on culture passage and isolation procedures. Not all types of cell-based preparations necessarily include stem cells and the field may be more appropriately termed cell-based therapy rather than stem cell therapy. Clinical trials testing cellular products in patients with stroke have emerged since the STEPS 1 publication and are mainly focused on the use of autologous mixed cell populations. The application of allogeneic, “off-the-shelf” cells to patients with stroke is poised for early-stage clinical testing. It is therefore timely and necessary to update preclinical and clinical trial guidelines for translating cell-based therapies for stroke. A workshop was held on crafting suggestions for preclinical studies that should be performed on any cellular product that is being developed as a potential therapeutic for stroke. A second workshop

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focused on suggestions for early-stage clinical testing of cellular products in patients with stroke. The recommendations from these workshops are described subsequently and agreed on by the participants listed at the end of this article following the format of the prior STAIR meetings.1

Updated Preclinical Guidelines

The prior STEPS document2 described recommendations on preclinical testing. We refer back to the original document regarding cell delivery (Table 1) and cell dosing (Table 2). We now provide modifications and add new recommendations regarding the following factors that apply to both ischemic stroke and intracerebral hemorrhage (Table 3).

Cell Characterization

The intended cellular product needs to be sufficiently described for several purposes, including cell identity and characteristics, conducting experiments by other groups for reproducibility, and evaluating safety risks. At a minimum, it is important to provide immunophenotyping in any peer-reviewed publication. For ex vivo expanded products and nonexpanded products, it is suggested to perform and publish transcriptional profiling as an open code approach to cell characterization. It is recommended that references be provided citing laboratories that have independently derived the same characterized cell therapy product using published methodologies. Guidance documents from the Food and Drug Administration on cell characterization ask for information including the identity, purity, viability, potency, stability, and dosage (www.fda.gov/cber/guidelines.htm).

Animal Species

We refer to the prior STEPS document and add the following recommendations. A stepwise approach would be useful to test a cellular product in models that address the heterogeneity of different types of stroke. Rodent models are well established and multiple strains and genetic backgrounds can be exploited. Large animal models may be helpful for specific situations in which they permit testing of specific neuroana-

Table 1. Guidance on Cell Delivery Approaches

| 1. Establish compatibility of cells with delivery device and determine optimal cell density and delivery volume necessary for efficacy |
| 2. Infracerebroventricular: requires further safety and feasibility study |
| 3. Direct intracranial injection: may be most suitable for neural stem cells |
| 4. Intra-arterial: requires demonstration that cells do not lead to microembolism and brain infarcts |
| 5. Intravenous: cells may need homing signal to brain; demonstration that cells do not cause organ toxicity or interfere with organ physiology |

Table 2. Guidance on Dosing

| 1. Determine MTD from the literature |
| 2. Determine dose–response curve |
| 3. Initial clinical trials should be based on animal studies of the optimal dose |
| 4. Dose ranges will likely be negotiated with regulatory agencies and historical MTD |

Table 3. Recommendations for an Experimental Program Testing a Specific Cellular Therapy for Stroke

| 1. Any cellular product needs to be well characterized |
| 2. Testing should be performed in multiple focal ischemic stroke or intracerebral hemorrhage models including animals with baseline conditions (aged, hypertensive, diabetic, etc) |
| 3. Safety measures include detecting tumor or ectopic tissue formation, overt behavioral abnormalities, and adverse physiological alterations according to Food and Drug Administration guidelines; assessing pulmonary function is suggested for intravenous delivery routes |
| 4. Control groups need to be well designed; examples include the vehicle solution or functionally irrelevant cells |
| 5. Studying cell deposition, migration, persistence and fate is important to investigate in the stroke model in any plan to design a potential clinical trial |
| 6. Defining the underlying mechanisms of therapeutic action may contribute to accurate clinical end point selection and appropriate biomarkers for treatment response |

tomical structures (white matter), specific types of imaging, or delivery options. Primates and other large animals also allow for testing in gyrencephalic brains. Animal models should be exploited to examine the effects of age (young versus old), gender, and comorbidities (hypertensive, diabetic, etc) on the therapy being investigated. These baseline conditions are important given that patients with stroke tend to be older and have vascular risk factors. Testing of cellular products in multiple, independent laboratories is crucial for reproducibility, robustness of effect, and to broaden the compendium of preclinical studies.

Stroke Models

There are many types of focal ischemic stroke and intracerebral hemorrhage models causing injury in cortical or subcortical areas of the brain. Evaluation of a cell-based approach is important in multiple focal ischemic stroke or intracerebral hemorrhage models using appropriate histological and behavioral tests. We recommend models that produce deficits that persist up to 4 weeks after stroke.

Preclinical Safety Indices

Safety includes tumorigenicity, immune sensitization, biodistribution, persistence, and cell fate and these issues are referenced in the following guidelines from the Food and Drug Administration (www.fda.gov/cber/guidelines.htm). As stated in the STEPS 1 document, cell therapy studies should include measures for detecting tumor or ectopic tissue formation, overt behavioral abnormalities, and adverse physiological alterations according to Food and Drug Administration guidelines. The duration of safety testing will vary depending on the cell type, but exogenous cells that die within days to weeks after injection in vivo or that already have been proven safe in patients with other clinical disorders may not require long-term testing in animals. Other types of cells with high proliferative and differentiation profiles such as embryonic or neural progenitor cells will likely require more extensive and long-term monitoring such as histopathology to assess for overgrowth and tumor formation.3

Positive controls for tumor formation or overgrowth, when available, and relevance of immunosuppression regimens
should strongly be considered. All adverse behaviors during the life of the animal after cell injection should be evaluated and tracked if observed. Acute toxicity of relevant organ systems should also be tested based on the delivery route. For example, the effects of cells on cerebrovascular blood flow or cerebral perfusion should be evaluated for an intra-arterial route of delivery. Pulmonary function should be evaluated for an intravenous delivery route for cells that accumulate within the first-pass filter of the lungs. Such tests might include respiratory rate and arterial blood gases. The rate of infusion is an important variable with respect to assessing these safety outcomes.

Outcome Measures
The primary goal of initial testing should be to address safety risks evaluated around cell identity, method of isolation, and expansion procedures. Once safety is established, functional end points should be the mainstay of primary outcomes. There are various behavioral outcomes within the domains of motor control, sensation, and cognition. Testing a cellular therapy using multiple different behavioral studies is favored to support robust efficacy. A battery of behavioral end points should be selected that are sensitive to the degree of injury, sites of damage, and severity of impairment. Testing should be performed multiple times in a longitudinal fashion for at least 1 month after treatment. Positive, neutral, and negative outcomes should be reported. It is also recommended to test cellular therapies in >1 laboratory to assess reproducibility of safety and efficacy.

Treatment Protocols
It is important to establish a dose–response curve and determine an optimized dose and treatment schedule as well as the minimum threshold for observed benefit. The chosen preclinical regimen should correlate with the intended clinical protocol, including delivery route and treatment schedule regimen, with single and cumulative dose greater than anticipated in clinical testing. There are limited data available regarding serial dosing for benefit or with respect to immune sensitization; further research is therefore encouraged. Negative controls are the subject of much debate. At a minimum, we recommend the vehicle solution of the cellular product. Other controls include dead cells, although cellular debris might be less desirable compared with cells that remain intact but are nonfunctional. It has been shown that freeze–thawing of grafted cells can worsen outcome after stroke. If immunosuppression will be needed in a clinical trial, it is recommended to study the cellular product with immunosuppressive agents along with a separate group receiving the immunosuppressive agents alone. Consideration may also be given to applying clinically relevant rehabilitation to all treatment groups in functional testing. Finally, comparing different therapeutic cell products would contribute greatly in this emerging field.

Biodistribution and Cell Persistence
Studying cell deposition, migration, persistence, and fate in stroke models may have value relative to defining mechanistic pathways. Because engraftment of delivered cells remains low whenever it has been examined, methods to improve

| Table 4. Recommendations for Early-Stage Clinical Trials Testing a Cellular Therapy in Patients With Stroke |
|--------------------------------------------------|--|
| 1. Confirmation of pivotal preclinical results in at least 2 laboratories and 2 species; identifying the key mechanisms of action is not essential before initiating a clinical trial |
| 2. Including heterogeneous stroke types improves recruitment and provides robust safety information, whereas a more homogeneous stroke population may be more desirable for detecting early efficacy signals or determining a biological target |
| 3. Route of delivery should be based on preclinical data regarding mechanism, biological target, and cell type |
| 4. Preclinical data and the proposed mechanisms of action should drive decisions regarding timing of therapeutic delivery |
| 5. Imaging should be used to establish the size and location of the infarct |
| 6. Safety end points and the duration of patient monitoring will be negotiated with regulatory agencies and should be driven around cell type, delivery routes, biodistribution of cells, and other preclinical data |
| 7. Intravenous delivery of exogenous cells should be monitored for acute infusional toxicities and pulmonary complications |

engraftment should be evaluated for those cellular products in which engraftment is necessary to achieve benefit. Noninvasive imaging to address these issues is insightful and could be developed as a surrogate biomarker for translation to the clinical arena.

Mechanisms of Action
Defining the underlying mechanisms of therapeutic action may contribute to timing and duration of therapy, accurate clinical end point selection, and appropriate biomarkers for treatment response. Epigenetics, tissue microarray, and other emerging technologies are providing insight into mechanism of action of cellular therapeutics. Studies should consider cell–host interactions, including the site of injury, immune system effects, interaction with parenchymal cells, and remodelling of the microenvironment. Such approaches may also rule out irrelevant pathways and give insight to clinical trial design. Although some studies suggest that certain cell types when injected into the brain after stroke may lead to differentiation of donor cells into host brain cells, the majority of exogenous cells under investigation at the present time exert so-called “nursing functions” to the injured brain such as cytoprotection or stimulation of endogenous repair mechanisms. Clarifying the mechanisms of action is generally useful but is not a prerequisite for proceeding to human clinical trials provided sufficient, encouraging, and reproducible preclinical evidence of efficacy exists.

Guidelines on Designing Early-Stage Clinical Trials
When to Start Clinical Trials
We encourage confirmation of pivotal preclinical results in at least 2 laboratories and 2 species (Table 4). Understanding the mechanism of action is not essential before initiating clinical trials but such information is desirable to plan strategies, including treatment regimen, route of administration, and outcome measures.
**Patient Selection**

We highly encourage initial testing in patients with stroke, not healthy control subjects, and enroll patients who will be informative based on safety profile and the anticipated biological effect of the cellular product. The selection of heterogeneous (eg, all types of ischemic stroke) versus patients with homogeneous stroke (eg, middle cerebral artery stroke) depends on a number of factors. Including patients with heterogeneous stroke improves recruitment and provides more robust safety information, whereas a more homogeneous stroke population may be more desirable for detecting early efficacy signals or determining a biological target. The size and location of the infarct may be important to use as selection criteria, particularly when efficacy is a consideration. Inclusion and exclusion criteria may vary with the cell type, delivery, and treatment time window.

**Route of Therapy and Biocompatibility of Devices**

We refer to the STEPS 1 document and add that the route of delivery should be based on preclinical data regarding mechanism, biological target, and cell type. Assessing the biocompatibility of devices with the cell product is useful and important. More information can be found in the STEPS 1 guidelines.

**Timing of Cell Therapy**

Preclinical data and the proposed mechanisms of action should drive decisions regarding timing of therapeutic delivery. In addition to exploring the optimal timing for effective cell therapy, the window for enrollment should also consider any information regarding when after stroke the cell product is not effective. A well-defined therapeutic window in animals is therefore highly encouraged.Classifying the timing of injury into categories such as acute, subacute, and chronic based on biological activity will eventually be necessary, but, at the present time, there is insufficient knowledge to fully define these temporal categories.

**Role of Imaging in Clinical Trials**

It is important to clarify the intended purpose of imaging methods, which can be applied for various purposes, including patient selection, surrogate end points, safety, and exploration of mechanism (eg, repair measures). We advise incorporating imaging to establish the size and location of the infarct. When feasible, advanced imaging techniques may be considered for exploring the mechanisms of action or surrogates of activity of the cellular therapy. Several imaging biomarkers of recovery are actively being explored. Further studies are needed, however, to validate imaging end points as surrogate outcomes measures. To this end, a stroke recovery neuroimaging consortium is highly recommended. Imaging is also very useful in the preclinical setting to monitor biodistribution of delivered cellular products. Although there are no accepted techniques to label and monitor cells for clinical testing, several approaches are currently available, including iron, indium, thallium, gadolinium-based agents, etc. More investigation is urgently needed to develop safe and reliable labeling techniques for deployment in clinical trials. Whatever labeling approach is chosen, it is important to assess that the label does not impair viability of the cellular product. It is also recommended to test the effects of the label on various in vitro functional assays of the cellular product.

**Immunosuppression**

The decision to consider immunosuppression is based on a number of factors, including whether the cellular product is autologous or allogeneic. At present, it is unknown whether immunosuppression in a stroke clinical trial is necessary for some allogeneic cells that have been shown to exert immunomodulatory effects. Immunosuppression may be more relevant if long-term engraftment of the cellular product is thought to be required for effectiveness. If immunosuppression is used, there should be a robust monitoring plan and follow-up in all early-phase trials. Another consideration is HLA matching, the benefits of which are well known in transplantation biology.

**Controls in Cell Therapy Trials**

Comparison of outcomes to a placebo arm may be useful, particularly for detecting initial evidence for efficacy, but no early-phase study would likely be sufficiently powered to detect a difference. However, in early-phase studies, safety issues are most important and control subjects reduce the sample size of informative patients. Placebo control subjects, nevertheless, may allow a reasonable comparison of safety outcomes with a similar population treated under the same conditions with the vehicle as patients treated with active cells. One way of addressing this issue is to use an uneven randomization scheme, which assigns a higher number of active to placebo subjects. We therefore recommend justification for incorporating a placebo arm in Phase I/IIa testing. An alternative approach is to use historical data from a database such as Virtual Stroke International Stroke Trial Archive (VISTA). Standard of care should be provided to all control patients. We recommend using American Heart Association guidelines for rehabilitation to ensure standardization of poststroke care. Capturing and controlling for confounding factors is highly encouraged.

**Outcomes**

Safety end points will likely be negotiated with regulatory agencies and should be driven around cell type, delivery routes, biodistribution of cells, and other preclinical data. Similarly, the duration of monitoring for safety end points needs to be negotiated with regulatory authorities. For cell types that die within days after administration, long-term monitoring beyond 6 months is likely unnecessary. Intravenous delivery of exogenous cells should be monitored for acute infusional toxicities and pulmonary complications. The selection of functional end points in stroke is the subject of much debate. The traditional outcome measures of the National Institute of Health Stroke Scale, modified Rankin Scale, or Barthel Index still have merit but other, more novel end points should be developed and considered. Domain-specific modalities such as language or hand function may also be suitable or even more desirable outcome measures in efficacy studies. Any novel outcome measures should be validated and peer-reviewed.
Table 5. Areas That Require Further Research That Would Advance the Field

1. Develop cell labeling techniques that are safe for clinical testing and are reliable to monitor and track cells administered to patients
2. Develop and validate surrogate markers of stroke recovery
3. Stroke recovery imaging consortium is needed to develop imaging endpoints that could guide Phase IIb testing

Conclusions

Cell-based therapies may represent a new therapeutic modality for stroke. Not all types of cell-based preparations necessarily include stem cells. Therefore, this emerging field may more appropriately be termed “cell-based therapy” rather than solely “stem cell therapy.” Nevertheless, all of these approaches fall under the rubric of “regenerative medicine,” which represents a cutting-edge approach to ischemic injury of the nervous system. To accelerate the field of cell therapy for stroke, we have updated the recommendations from the prior STEPS meeting and identified key translational barriers that need further study, including cell labeling, imaging, biodistribution of exogenous cells in patients, and identifying imaging biomarkers of stroke recovery (Table 5). Given the monumental failures of neuroprotective agents for acute stroke over the past 20 years, these guidelines are based, in part, on the lessons learned from those prior failures in the hopes of facilitating the successful development of cellular therapies for stroke from preclinical studies to early-stage clinical trials.

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References
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脳卒中に対する新たな治療パラダイムとしての幹細胞療法（STEPS）II

Stem Cell Therapy as an Emerging Paradigm for Stroke (STEPS) II [Special Report]

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脳細胞療法は、脳卒中の新たな治療パラダイムを形成する可能性が示唆されている。脳卒中により脳の機能が障害されるが、幹細胞療法はその再生を可能にすることを目指している。幹細胞療法の開発には、前臨床における安全性および有効性の確認が求められる。その結果、Stem Therapy Academic Industry Roundtable (STAIR) 会議において、幹細胞療法の開発が推進されている。STAIR 会議では、幹細胞療法の安全性と有効性評価が行われ、臨床試験の実施が計画されている。

Keywords: 細胞療法, ガイドライン, 麻酔, 脳卒中

細胞療法は、脳卒中の新たな治療パラダイムを形成する可能性が示唆されている。脳卒中により脳の機能が障害されるが、幹細胞療法はその再生を可能にすることを目指している。幹細胞療法の開発には、前臨床における安全性および有効性の確認が求められる。その結果、Stem Therapy Academic Industry Roundtable (STAIR) 会議において、幹細胞療法の開発が推進されている。STAIR 会議では、幹細胞療法の安全性と有効性評価が行われ、臨床試験の実施が計画されている。

Keywords: 細胞療法, ガイドライン, 麻酔, 脳卒中
表1 前向き研究に関するガイドライン

1. 研究は適切なレベルの自信を得、効果を示すのに必要な統計的
   精度基準を満たす必要があります。
2. 研究が本質的に異なるものを含む場合、比較検討が必要です。
3. 研究者が既存の研究を基にしているとされる。
4. 研究者が確立された効果が証明されない場合には、実施する必要が
   ありません。
5. 研究者が線形の関数関係が示されない場合には、実施する必要が
   ありません。

表2 前向き研究に関するガイドライン

1. 研究は適切なレベルの自信を得、効果を示すのに必要な統計的
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   ありません。
5. 研究者が線形の関数関係が示されない場合には、実施する必要が
   ありません。

表3 脳卒中の特異的経験療法を検証する臨床プログラムに関する

1. 研究は適切なレベルの自信を得、効果を示すのに必要な統計的
   精度基準を満たす必要があります。
2. 研究が本質的に異なるものを含む場合、比較検討が必要です。
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5. 研究者が線形の関数関係が示されない場合には、実施する必要が
   ありません。

生命体、力値、安定期、用量に関する情報が必要である（www.fda.gov/cber/guidelines.htm）。

動物群

動物群については、過去のステップスガイドラインを参考に、さらに以下の検討を追加する。動物間のプローブは、さまざまな条件設定を含む脳卒中での一相対性に向けたモデルを用いた動物実験で有用である。がん種類モデルは十分に確立されたモデルであり、複数の系統や遺伝的背景のものを利用可能である。特定の神経伝達物の構造（回）の試験や血行動態、あるいは迅速方法の選択が可能であるが、脳梗塞の脳卒中モデルを用いた方法がよい場合がある。また、発症例数やその他の条件下では、脳梗塞脳卒中モデルを用いた実験が可能である。動物モデルは、年齢（若齢・高齢）、性別、保険機関（高血圧、糖尿病）などが負担を及ぼす影響を調べる場合に利用すべきである。こうした動物実験の状態は、脳卒中患者の高齢で、血管性脳卒中を有する傾向であることからも重要である。細胞内刺激の試験を複数の独立した研究施設で実施することは、再現性や効果の再現性を検証して、前臨床試験を拡張するのに不可欠である。

脳卒中モデル

脳の反応または脳皮質領域が損傷された、さまざまな種類の脳卒中脳卒中モデルや脳卒中脳卒中モデルがある。

細胞療法の評価は、複数の時相変動性脳卒中モデルや脳卒中脳卒中モデルにおいて、適切な組織学的検査および行動学検査の検査を行うことが重要である。脳卒中後 4 週間程度の障害が持続するモデルが望ましい。
前臨床試験における安全性の指標

安全性の問題には、腫瘍形成性、免疫不応、生体内分布、持続性、細胞毒性などがあり、FDAのガイドラインでもこれらの問題が取り上げられている(www.fda.gov/sher/guidelines.htm)。STEPSのガイドラインでは、腫瘍形成性、免疫不応、生体内分布、持続性、細胞毒性などが問題として取り上げられている。

治療プロトコル

用量反応曲線を設定し、効果の強さを検討するための基準値を設定することが重要である。用量反応曲線は、用量と効果の関係を示す図であり、用量の増加に伴い効果が増加するか、それ以前から一定の効果を示す場合がある。

生体内分布および細胞の存続

脳卒中のモデルを用いた臨床試験は、用量反応曲線を設定し、効果の強さを検討するための基準値を設定することが重要である。用量反応曲線は、用量と効果の関係を示す図であり、用量の増加に伴い効果が増加するか、それ以前から一定の効果を示す場合がある。

作用機序

治療の基礎となる作用機序が明らかになれば、治療の有用性を検討するための基準値を設定することが重要である。用量反応曲線を設定し、用量と効果の関係を示す図であり、用量の増加に伴い効果が増加するか、それ以前から一定の効果を示す場合がある。
初期臨床試験のデザインに関するガイドライン

初期臨床試験開始時期

中間的な臨床試験の結果は、2.3所以上の研究施設で数種類以上の動物種を用いて確認することを推奨する（表4）。

患者の選択

臨床試験の対象は健康成人ではなく脳卒中患者を対象とし、安全性、効果性をも及ぼしている細胞間転写因子の抑制剤を用いた効果学的評価に基づき推奨されるほど優れた群を優先的に選択する。もしくは、数種類の脳卒中患者（あらゆる種類の虚血性脳卒中など）を含む、それらのうち脳卒中患者（中大脳動脈脳卒中など）を選択するか、種々の要因によって決定される。平均値の脳卒中患者を試験に就けた場合、登録と比較して選択する Jinping 枚を検討した後に、生物学的特性をも考慮して選択する。特に効果性が検討項目となっている場合は、統制の大きさや変動が重要な選択基準となるだろう。選択基準は除外基準は、細胞の種類や達成度、調査データに基づいて評価される。
タリングに関しても、一般的に強く認められている方法は少ないが、今後も、抗TNFα薬、パセプセン、サルコペネミン、イミダゾラジングリュタミンを用いた治療などを、複数のアプローチが利用可能である14,15。安全性と有効性に優れた臨床試験用の標識技術を用いるために、より一層の研究が急務である。

いずれの標識法を選択する場合でも、標識によって細胞性質の生化学が損なわずにいかなる影響を評価することが重要である。さらに、標識が細胞質物質の各種in vitro機能試験に及ぼす影響を調べることが望ましい。

免疫制限

免疫抑制剤の選択は、細胞性質が自体細胞と同様細胞という点も含め、多くの条件に基づいて判断される。今

のところ、脳卒中の臨床試験において、免疫抑制剤が認められている一部の同種細胞に対し免疫抑制剤が必要かつ

きわめて必要である。免疫抑制剤は、治療効果を得るためには、細胞性質の長期生長が必要であることが示唆される場合により重要である。免疫抑制剤を行う場合には、初期期のあらゆる試験において、可能なモニタリング計画と連絡調査が必要である。1つの検討事例はHLA適合であり、移植後生の利得はよく知られている67。

細胞療法試験における対照

プラセプト群との比較の有用性は、特に新規療法に見られるが、初回の試験では差を実証するための十分な検出力が得

られない可能性が高い。しかし、初期期の試験では安全性の問題が対照群を設定すると、標識制限の数が少なくなる。ただし、プラセプト群を設けることで、実際に細胞を投与した患者と同一条件下で同様の患者群に治療を施すことによって、安全性評価項目の合理的な比較を行うことができるだろう。この問題に基づく対照群の設け方は、無作為割り付けを含む等の方法が考えられる。しかし、このように第1/2相試験におけるプラセプト群を投与される場合は、ロン対を示すことが望ましい。もう1つの方法は、Virtual Stroke International Trial Archive (VISTA)などのデータベースに収められた臨床的データを用いることである。対照群の患者にいずれも標準治療を行う。脳卒中後のケアの基準化は、医療機関協会（AHA）のリハビリテーションガイドラインを推奨する。交絡因子の把握及び管理も強く推奨される。

評価項目

安全性評価項目については、おそらく規制当局と協議することになるほど予想され、細胞の種類、送達方法、細胞の生体内分布、その後の臨床データに基づいて評価

項目を決定すべきである。同様に、安全性評価項目のモニタリング計画も、規制当局と協議することになる。安全性評価項目は、6か月以上長期のモニタリングは不要であると思われる。外来細胞の関与内で送達を行う場合には、観察期間の入院率や術後合併症を監視する必要がある。脳卒中における機能的評価項目の選択は、多様な通院が的である。従来の評価項目指標であるNIHSSスコア、およびRanks尺度、Barthel


指数にもメリットはあるが、さらに新しい他の評価項目を考案し、検討する必要がある。効果在発表では、両群が手機能の機能での領域を評価する新たな評価項目も組み

ており、評価項目としてより望ましいと考える。新

規の評価項目については、妥当性確認とピレーブが

必要である。

結論

細胞療法は、脳卒中の新たな治療様式となる可能性がある。必ずしもすべての種類の細胞性質に幹細胞が含まれているわけではないため、この新規療法の名称は「幹細胞療法」に限定するよりも、「細胞療法」とする方が適切である。いずれにせよ、これらのアプローチはすべて「再生医療」という名で呼ばれる、細胞の発達性損傷に対する先進的な治療アプローチである。脳卒中に対する細胞療法の努力を準備するために、我々は過去のSTEPSE会で提唱された推奨を改訂し、今後さらに研究が必要である。トランスニーシャルリウチの助けで

になっている重要な問題を明らかにした。こうした問題に

は、細胞療法、神経再生の観点から、患者に投与されたエキスペリシング細胞の生

体内分布、脳卒中からの復帰に関する画像上のバイオマーカーの特定などがある（表5）。過去20年間において、急性

脳卒中の幹細胞療法はここごく少数に終わってきたが、本ガイドラインではそうした過去の失敗も、ある程度処

調として取り入れており、脳卒中の細胞療法の開発が臨床試験段階から初期の臨床試験段階へと進むことを期待している。
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関係

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