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EXPERT OPINION

Clinical cell therapy guidelines for neurorestoration (China version 2016)

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On behalf of the Chinese Association of Neurorestoratology and Chinese Branch of the International Association of Neurorestoratology

Abstract: Cell therapy has been shown to be a key clinical therapeutic option for central nervous system disease or damage, and >30 types of cells have been identified through preclinical studies as having the capacity for neurorestoration. To standardize the clinical procedures of cell therapy as one of the strategies for treating neurological disorders, the first set of guidelines governing the clinical application of neurorestoration was completed in 2011 by the Chinese Branch of the International Association of Neurorestoratology. Given the rapidly advancing state of the field, the Neurorestoratology Professional Committee of Chinese Medical Doctor Association (Chinese Association of Neurorestoratology) and the Chinese Branch of the International Association of Neurorestoratology have approved the current version known as the "Clinical Cell Therapy Guidelines for Neurorestoration (China Version 2016)". We hope this guideline will reflect the most recent results demonstrated in preclinical research, transnational studies, and evidence-based clinical studies, as well as guide clinical practice in applying cell therapy for neurorestoration.

Keywords: cell therapy, neurorestoration, China, clinical application

Introduction

Neurorestoratology is an emerging discipline at the intersection of clinical medicine and neuroscience. Its goal is to restore, promote, and maintain the integrity of impaired or lost neuronal functions and/or structures.[1]

The "Beijing Declaration of IANR" (agreed upon at the International Association of Neurorestoratology [IANR] 2015 Conference in Tehran) declared as its fundamental tenet that "functional recovery is possible after central nervous system (CNS) injury and neurodegeneration" and noted that "cell therapies may become a key clinical therapeutic option for acute, subacute, and/or chronic CNS disease or damage".[1] More than 30 types of cells have been identified through preclinical studies as having the capacity for neurorestoration.[2–62]

Cells that have been tested to date in clinical neurorestorative treatments can be classified into the following three categories: 1) immature or mature neural functional or supporting cells, some of which are still able to proliferate (including neural progenitor or precursor cells, olfactory ensheathing cells, Schwann cells, oligodendrocytes, and neurons); 2) stromal cells (including bone marrow, umbilical cord or peripheral blood mononuclear cells, umbilical cord stromal cells, and adipose stromal cells); 3) totipotent, pluripotent, multipotent, or unipotent stem cells, which include embryonic stem cells, induced pluripotential cells, and adult stem cells.[63–67]

The guidelines presented in this document are intended for clinical applications utilizing cells in the first two categories described earlier. To date, clinical trials and

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treatments based on the first and second categories of cells have been established in >30 countries. Clinical studies have documented the safety and efficacy of treatments based on the first two categories of cells, with many demonstrating neurological function improvement for patients.[68–107] Because of concerns over tumorigenicity and the difficulties in controlling the cellular differentiation process, clinical applications of the third category of cells require additional scrutiny and thus fall outside the scope of this current set of guidelines. We recommend that any clinical studies utilizing the cells from the third category should strictly comply with the following draft regulations issued by the Science and Educational Division of the National Health and Family Planning Commission of China (NHFPC): "Stem cell quality control and pre-clinical research guideline principles (Trial) (Document 2015 No.46)" and "Stem cell clinical research management measures (Trial) (Document 2015 No.48)".

The first set of guidelines governing the clinical application of neurorestoration, "Chinese clinical standard of neurorestorative cell therapy", was formulated in 2011 by the Chinese Branch of the International Association of Neurorestoratology.[108] These guidelines were revised, translated into English, and published in 2012.[109] The guidelines were further revised as "Chinese clinical application guideline of neurorestorative cell therapy (2015 version)".[110] These guidelines have played a significant role in standardizing treatment protocols and setting up an international set of professional standards agreed upon by leading experts in this emerging field. Given the rapidly advancing state of the field, the Neurorestoratology Professional Committee of Chinese Medical Doctor Association (Chinese Association of Neurorestoratology) and the Chinese Branch of the International Association of Neurorestoratology have jointly collaborated to amend and update the existing guidelines to reflect the most recent results demonstrated in preclinical research, transnational studies, and evidence-based clinical studies. The current version, known as the "Clinical Cell Therapy Guidelines for Neurorestoration (2016)", was approved by the executive boards of the Chinese Association of Neurorestoratology and the Chinese Branch of the International Association of Neurorestoratology on June 18, 2016.

Recommended standards for personnel and institutions conducting cell therapies in China

Equipment

Personnel and institutions conducting cell therapies in China must have laboratory facilities and equipment that comply with the relevant national standards for ensuring cell quality control.

Personnel

Clinical personnel

Physicians performing cell transplantation procedures should have acquired relevant professional training and certification required to ensure high-level competency in this field. Supervising clinicians should have attained a rank of associate chief physician or above. They should have also passed all certification examinations recommended by the relevant professional societies or associations.

Laboratory personnel

Directors of cell preparation laboratories should have attained at least a master's degree in a relevant scientific field and have achieved a high professional rank; technicians involved in cell preparation should have undergone all relevant professional training and passed all certification examinations in cell preparation recommended by the relevant professional societies or associations.

Oversight personnel

Inspectors assessing cell quality should have attained at least a bachelor's degree in a relevant scientific field, undergone all relevant professional training, and passed all certification examinations in cell preparation recommended by the relevant professional societies or associations.

Institutional board of reviewing

All clinical studies or treatment conducting cell therapies and involving human participants should be reviewed and approved by the institutional board of ethics committee.

The Chinese Association of Neurorestoratology is responsible for offering professional training and establishing standardized assessment and credentialing procedures to ensure the integrity and quality of neurorestorative cell therapy procedures conducted in China.

Provisions

This revised set of guidelines includes the following set of provisions: guiding principles of neurorestorative cell therapy, the cell types governed by these guidelines, cell quality control procedures, cell dosages, informed consent procedures for patients and other participants, indications for undergoing cell therapy, contraindication for undergoing cell therapy, operating procedures (including surgical procedures

and key points for cellular injection), and recommendations for evaluating safety and efficacy.

Guiding principles of the neurorestorative cell therapy

The guiding principles for the neurorestorative cell therapy are timeliness, adequate dosage, multiple routes, multiple cell types, multiple courses, and combined treatment. The optimization of personalized treatment should be highlighted and explored more by precise mechanism.

Cell type nomenclature

Cells are the basic unit of structure and function of organisms, including all the various stages of development and various cellular functions. From the cell development period, the cells can be divided into stem cells and premature (immature) or mature functional cells. The stem cells include totipotent, pluripotent, multipotent, or unipotent stem cells. The premature (immature) or mature functional cells include the neural progenitor or precursor cells, olfactory ensheathing cells, Schwann cells, oligodendrocytes, neurons, mesenchymal or stromal cells, and so on. The difference between the stem cells and progenitor cells is that the former can proliferate without limitation and the latter can proliferate with limitation and only differentiate into special kinds of the cells or target cells. Stem cells are one of the most important cell lines. Defining the concept of stem cells or replacing the term of cells by stem cells, has risked using stem cells in cell therapy. Therefore, the description of cell therapy should strictly normalize the cell type nomenclature.

We suggest that each cell type should be named after its derived source, such as the olfactory ensheathing cells derived from olfactory mucosa, the Schwann-like cells derived from sciatic nerve, the progenitor/precursor cells derived from brain, the olfactory ensheathing cells derived from olfactory bulb, the mononuclear cells derived from bone marrow, the peripheral blood, or umbilical cord blood, and the stromal or mesenchymal cells derived from the adipose tissue or umbilical cord.

Cell quality control

Quality control is the basis of the cell therapeutic safety and efficacy. The whole process includes the cell collecting, culturing, identifying, amplifying, detecting composition and the content of various cytokines, transmission, and passage number, adding exogenous factors, cell storing, testing biological effects (dynamics proliferation), cell transporting, managing before clinical use, operating procedure of cell transplantation or therapy, and etc. Serum-free cultures are recommended; otherwise, the fetal bovine sera should be washed or removed. The standard of the quality control should include at least the following: the total number of cells, the passage number in vitro, cell purity, cell viability (at least 95%), biological effects (at least 80%), the proportion of special surface markers, and the detection of infectious disease and endotoxin. In certain low-temperature conditions, the optimal time from the clinical laboratory to transplantation of cells to the patient should not exceed >2 hours.[111]

Cell dosage

Cells must be used at an effective dose. With more clinical treatment studies, the cell dosage will be more accurate. Currently, we recommend that the maximum injection volume of cell suspension will not exceed 200 μL for the brain parenchyma,[73,112–114] 25 μL for the spinal cord parenchyma,[68,69,115] 10 mL by the cerebrospinal fluid route,[116] and 10–100 mL by vascularity.[114,117–121]

The current recommendation of the prescription for the commonly used single dose of cells is as below:

1. Glial cells, such as olfactory ensheathing cells and Schwann cells, $(2.0–3.0)\times10^6$ for the intrathecal injection; $(1.0–2.0)\times10^6$ for the spinal cord injection; and $(2.0–4.0)\times10^6$ for the brain parenchymal injection.[68,69,73,114,122]
2. Neural progenitor/precursor cells: $(5.0–6.0)\times10^6$ for the intrathecal injection; $(5.0–6.0)\times10^6$ for the spinal cord injection; and (1.0×10^7) for the brain parenchymal injection.[114,119,123]
3. Mesenchymal or stromal cells derived from umbilical cord: $(0.5–0.8)\times10^6$/kg body weight for intravenous infusion (the elderly and frail patients should reduce to 1/3 to 1/2 dosage); $(5.0–8.0)\times10^6$ for the intrathecal injection; and 1.0×10^7 for the brain parenchymal injection.[73,124–130]
4. Mononuclear cells derived from cord blood: $(1.0–2.0)\times10^6$/kg body weight for intravenous infusion, the elderly and frail patients should reduce to 1/3–1/2 dosage; and $(5.0–6.0)\times10^6$ for the intrathecal injection.[75,81,84,88]
5. Mononuclear cells derived from bone marrow: $(3.0–9.0)\times10^8$ for intravenous infusion and $(5.0–6.0)\times10^6$ for the intrathecal injection.[78,80,117,118,120,121]

Patient informed consent

Patients and their families have the right to know about all the possible benefits and potential risks of matters related with the cell transplantation and procedures. Physicians should continue to learn and master the latest cell therapy-related knowledge in order to give objective answers and explanation.

All participants should fill and sign a consent form before the clinical study or treatment is performed.

Indications for undergoing cell therapy

Neurological system diseases and damages, which include the neurotrauma, neurodegeneration, ischemic/hypoxic brain injury, demyelination, sensory motor disorders, neuropathic pain, as well as nerve damage caused by intoxication, physical/chemical factors, immune, infectious, inflammatory, hereditary, congenital, developmental factors, etc.

Contraindications for undergoing cell therapy

Patients with poor general condition or major organ dysfunction cannot tolerate cell therapy procedures. There are the infections or pressure sores in the surgical site, bleeding tendency, coagulation disorder that cannot be corrected, and emotional disturbance. Patients with hypersensitivity, >90 years old, or pregnant are not recommended for the procedure.

Operating record and key points

The operating record of the cell therapy methods includes anesthesia methods, transplanting approach, surgical procedure, transplanting method, transplanting site, transplanted cell type, quantity of transplanted cells, and the concentration and volume.

Examples for the therapeutic methods are described below:

1. Stereotactic brain parenchyma (× target) neural progenitor/precursor cell transplantation through the frontal approach under local anesthesia.
2. × × cell transplantation through ventricle puncture under local anesthesia.
3. × × cell transplantation by cisterna magna puncture under local anesthesia.
4. Intrathecal × × cell transplantation through cervical, thoracic, or lumbar puncture under local anesthesia.
5. Subarachnoid × × cell transplantation in cervical, thoracic, or lumbar puncture under local anesthesia by X-ray guidance.
6. Spinal cord parenchyma × × cell transplantation in cervical, thoracic, or lumbar puncture under general anesthesia.
7. Myelography computed tomography (CT)-guided spinal cord parenchyma × × cell transplantation in cervical, thoracic, or lumbar puncture under local anesthesia.
8. Myelography CT-guided spinal subarachnoid × × cell transplantation in cervical, thoracic, or lumbar puncture under local anesthesia.
9. CT-guided spinal cord parenchyma × × cell transplantation in cervical, thoracic, or lumbar puncture under local anesthesia.
10. CT-guided spinal subarachnoid × × cell transplantation in cervical, thoracic, or lumbar puncture under local anesthesia.
11. Intravenous × × cell transplantation.
12. × × cell intravascular transplantation by ultra-artery catheterization.
13. Intramuscular × × cell transplantation.

Each different kind of cells should have the best route for the most therapeutic effect. The therapeutic effect depends mainly on the different route for each different cell type. With more preclinical and clinical treatment studies, the best therapeutic route with the most effect and safety may be found in the future. Current first options of operating key points are suggested as below according to a series of clinical and basic studies.[68,69,73,114,124–126,131–134]

In brain local disorders (brain injury or stroke) cells should be injected into the edge of lesion. In non-special or diffuse disorders (cerebral palsy, amyotrophic lateral sclerosis) cells should be injected into "the key point for neural network restoration (KPNNR)". Its anatomic structure locates at anterior 1/4–1/3 of the lateral ventricle and 23–27 mm away from the midline, where the pyramidal tract in frontal corona radiate through and represents a point at which numerous projection fibers, association fibers, and commissural fibers converge.

In spinal cord disorders cells should be injected into the spinal cord below and above the junction of normal and damaged tissue.

In peripheral nerve disorders cells should be injected into the lesion site.

Safety evaluation

Detailed records must be kept for the cell therapy-related adverse events by using standardized terminology, such as fever, headache, nausea, vomiting, anorexia, infection, rash, poor wound healing, dyspnea, increased/decreased blood pressure, increased/decreased heart rate, neurological deterioration, cerebrospinal fluid leakage, twitch, and so on.

Efficacy evaluation

Uniform evaluation standards or scales are currently used in the national community to assess the patients' functions for

different diseases (referring Neurorestoratology[133] or CNS Neurorestoratology[134]). Chinese Association of Neurorestoratology regularly decides the national training courses for the physicians to assess patients. They should be trained with the uniform evaluation, pass the examination, and acquire professional certification.

Policy of further treatment and data collection

The active exploration of individual treatments must be based on the clinical standard cell therapy for continually improving efficacy. It is recommended to accurately collect the patients' information that includes brain functional magnetic resonance imaging (MRI), brain or spinal cord MRI–diffusion tensor imaging, peripheral magnetic resonance angiography, and the electrical physiological examination.

Basic principle of cell therapy

According to the previous data from clinical practice,[73,100,119,124–126,133–135] the combination of different cells, combined transplanting approaches, setting treatment course, and comprehensive strategies are the current main study direction. The Chinese Association of Neurorestoratology will revise and release the program of safety and better efficacy in future and actively organize multicenter studies for different diseases. Randomized, double-blind, controlled clinical studies should be carried out preferentially; if unsuitable, other types of clinical studies or trials should be started.

Publishing duty

All groups that carry out the clinical cell therapy should promptly analyze, summarize, and share their data for publications to other physicians as reference, for further evaluation and validation.

Disclosure

The authors report no conflicts of interest in this work.

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