Review article

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Cell transplantation: history of development, bioetic and legal aspects, prospects for treatment traumatic brain injury

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In the modern world, a doctor of any specialty knows about a relatively new direction in the treatment of severe and previously untreatable diseases - stem cell (SC) transplantation. A scientific discussion around this is an actively developing direction. At present time laboratory studies of the cell therapy have gone beyond the limits of the experiment and began to actively find their application in practical medicine, which gives rise to scientific, ethical, legal and legislative problems. Thousands of laboratory experiments and clinical studies are carried out around the world, hundreds of stem cell culture laboratories and clinics are opened that use cell transplantation for the treatment of a wide range of diseases. The world governments start introduce SC transplantation into the medical system.

The classical dogma that CNS cells are unable to regenerate has been challenged in recent decades by studies demonstrating new mechanisms of stem cell migration in the brain in trauma models.

One of the most popular and promising areas for using cell therapy is treatment of nervous system diseases. Today, the actual problem for society is the cost of treating the consequences of moderate and severe traumatic brain injury, due to the wide prevalence (30-40% of all types of traumas), high disability rate in the working-age population and the global trend increase number of TBI cases by constant development of the technogenic environment.

The review provides information on the history of development, legal, bioethical aspects, the prospects for the use of SC in the treatment of TBI.

Key words: *traumatic brain injury; cell therapy; stem cells; transplantation; legal aspects of transplantation*

Cell transplantation development history

> … The strength of an individual is great, and if someone believes that he is able to change or improve something in a person against his natural personality, then he is poorly educated in medicine.
> Caspare Tagliacozzi, anatomist from Bologna 1597

The first attempt to use donor stem cells ((SC) or bone marrow cells (BM)) for the treatment of patients with leukemia was made in the XIX century. In 1891, two French doctors - C.E. Brown-Sequard and J.A. d'Arsonval gave such patients the human BM orally [1].

The first in the world to use the term «stem cell» was the Russian histologist, professor of the Military Medical Academy O.O. Maximow (Fig. 1). His fundamental work on hematopoietic SC «Lymphocyte as a common stem cell of various blood elements in embryonic development and post-fetal life of mammals» published in 1908 became the basis for the further development of cell transplantation (CT) [2].

In 1937 works describing the intramuscular administration of aspirated autogenous and allogeneic BM from random donors to patients with anemia were published [3]. The first BM transplantation in the clinic with the achievement of engraftment was performed by E.D. Thomas (USA) in 1959. Transplantation was performed from one identical twin to another who suffered from leukemia [4,5]. In 1965, G. Mathe (France) published an article describing the long-term engraftment of the BM transplant from a donor sibling and the antileukemic result of this procedure [6]. In 1970, a corresponding member of the USSR Academy of Sciences, Professor A. Ya. Friedenstein described and successfully cultured fibroblast-like SC, which were later called «mesenchymal stromal cells» [7,8].

In 1973, the first BM donor register was established in London on the initiative of Shirley Nolan, the father of a child who suffered from congenital immunodeficiency and required hematopoietic SC transplantation. Soon the register numbered 18 million donors, but even with such a number of donors, there were problems selecting immunologically compatible BM, since the probability of compatibility ranged from 1:100 000 to 1:1 000

Fig. 1. Professor of the Military Medical Academy O.O. Maximow, 1910 (image taken from Wikipedia https://ru.wikipedia.org/wiki/Максимов,_Александр_Александрович_(histologist))

000, forcing scientists to look for alternative sources of hematopoietic SC. A scientific breakthrough occurred in 1974 after the discovery of S. Knudtzon that umbilical cord blood in large quantities contains the same hematopoietic SC as the BM.

In 1981, a group of scientists led by Martin Evans (UK) isolated embryonic SC from the mouse embryoblast for the first time, which not only expanded the possibilities for studying genes by the gene knockout technique (gene knockout, Nobel Prize 2007), but also brought to the forefront the first of the known types of pluripotent cells, promising for tissue replacement.

In 1988, a French scientist, professor of hematology Elian Gluckman in Paris performed the world's first transplantion of umbilical cord blood cells to a child with Fanconi anemia. In 1990, the transplantation of hematopoietic SC of umbilical cord blood was performed in the United States, in 1994 - in Japan, in 1996 - in Poland and Portugal. In 1992, a cord blood sample for long-term storage was frozen at the University of Arizona. A year later, the first umbilical cord blood banking program was established in the United States, providing free transplantation of hematopoietic SC of umbilical cord blood to patients with indications for transplantation. In 1997, the first transplantation of cultured *ex vivo* umbilical cord blood SC to a patient with myeloid leukemia was performed. This contributed to the general recognition of SC.

The development of cell transplantation (CT) continues. In 1999, the journal "Science" recognized the discovery of SC as the third most important event in the history of biology after the deciphering of DNA helices and the "Human Genome" Project. In 2003, the US National Academy of Sciences (PNAS USA) published an article in its journal on cryo-freezing of umbilical cord blood SC with complete preservation of biological properties for 15 years. In 2012, Shinya Yamanaka (Japan) and John Gurdon (UK) received the Nobel Prize for their discovery of the possibility of reprogramming mature SC into induced pluripotent stem cells (IPS) ***(Fig. 2)***, which makes their properties similar to those of embryonic SC with minimal risk of side effects [9].

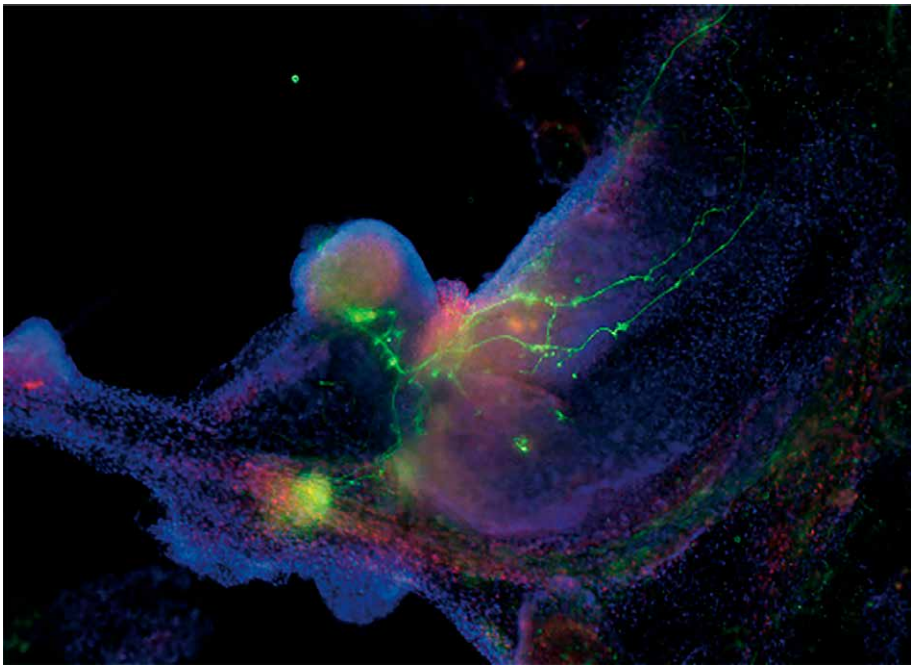

Fig. 2. Cells with induced pluripotency, differentiated into nerve cells (shown in green) and cardiac muscle cells (shown in red) [10]

This article contains some figures that are displayed in color online but in black and white in the print edition

Currently, Canada[1], USA[2], New Zealand, Japan[3] and South Korea have approved and introduced into clinical practice the use of SC in various diseases [11].

At the Institute of Neurosurgery named after acad. A.P. Romodanov, Ukraine clinical transplantation of nervous tissue was first performed in 1989 for severe traumatic brain injury (TBI) by E.G. Pedachenko, G.A. Kevorkov, O.V. Kop'iov, for infantile cerebral palsy – by V.I. Tsymbaliuk and L.D. Pichkur. In 2005 two monographs were published on the study of neuronal SC in humans and animals: «Neurogenic differentiation of stem cells» (Yu.P. Zozulia, M.I. Lisianyi, V.I. Tsymbaliuk) and «Neurogenic stem cells» (V.I. Tsymbaliuk, V.V. Medvedev). The staff of the institute published more than 300 scientific articles, conducted more than 40 experimental studies on the use of SC, defended more than 20 dissertations on this topic.

Bioethical principles of stem cell use in clinical research

In 1969, V. Potter defined the concept of «bioethics», associated with traditional and medical ethics, law, natural sciences and philosophy, which became a determining factor for its formation as independent direction. The main task of bioethics is to resolve problems in the field of interdisciplinary research concerning the moral aspect of human activity in medicine and biology. On the basis of bioethical paradigm, the study of the environment by the human in conditions of scientific and technological progress and preservation of human health, the basic principles of conducting clinical research have been determined [12–14]:

1. Providing complete, objective information about the clinical trial to the patient (subject), on the basis of which an informed decision can be made. In case of patient's incapacity, his guardian should be informed in accordance with current legislation.

2. The need to obtain consent for the patient's participation, which is confirmed by the signing of a bilateral agreement between the principal investigator and the patient. In case of patient's incapacity, the guardian assents to participate in the study in accordance with the law.

3. The patient has the right to refuse to participate at any stage of the clinical trial, while reserving all rights to receive quality medical care.

4. Conducting a clinical study is justified in the case when new scientific data cannot be obtained in other ways.

5. Clinical studies are permissible in the case when the expected result is justified as probable in terms of medical achievements.

6. Clinical research should correspond (in terms of morality, expediency, methodology) to the development of modern medical science.

7. The degree of risk in conducting a clinical study for the life and well-being of the patient should not exceed the scientific significance of obtained results.

8. Clinical trials should be carefully planned to minimize the risk of adverse effects.

9. Clinical trials may be conducted only by a team of specialists led by the doctor who are appropriate to the nature of the study.

The main controversies, conflicts and resistance are associated with studies that use embryonic SC. Bioethical, religious and legal problems are caused by heterogeneity of views, in particular religious denominations, legal and ethical principles. Studies simulating TBI on laboratory animals using embryonic SC have shown low efficiency or lack of positive dynamics in the restoration of motor and cognitive functions, as well as the emergence of mass in the injection site of SC [15]. According to the authors, these problems are the reason for the formation of different views in society on the phenomenon of embryonic SC use, while the use of other types of SC in clinical research does not contradict ethical, bioethical and other value systems.

Legal aspects of cell use in clinical transplant research on the territory of Ukraine

Legal regulation of the use of SC therapy on the territory of Ukraine has undergone systemic changes in recent years and is currently carried out in accordance with the requirements of the Constitution of Ukraine, the Law of Ukraine « Fundamentals of Health Care Legislation of Ukraine «, Information of Verkhovna Rada of Ukraine (IVR), 1993, № 4, Art. 19), the Law of Ukraine «On Application of transplantation of anatomical materials to a person» from 17.05.2018 № 2427-VIII with appropriate amendments, the Civil Code of Ukraine, the Criminal Code of Ukraine, the Resolution of the Cabinet of Ministers of Ukraine dated March 25, 2020 № 257 «On approval of the Procedure for obtaining and providing hematopoietic stem cells and exchange of information on available human anatomical materials intended for transplantation», Resolution of the Cabinet of Ministers of Ukraine dated August 5, 2020 № 720 «On approval of the Procedure for transportation of human anatomical materials within Ukraine, import of such materials into the customs territory of Ukraine and their export outside the customs territory of Ukraine» and other normative legal acts in this area.

The adoption of the Law of Ukraine «On Application of transplantation of anatomical materials to a person» with changes at the state level was an attempt to regulate the procedure for carrying out cell therapy taking into account international rules, recommendations of the World Health Organization, EU Directives, in particular Directive № 2010/45/EU of the European Parliament and the EU Council on the quality and safety standards of human organs intended for transplantation, to create favorable conditions for carrying out cell therapy in Ukraine, in particular SC therapy.

The Law of Ukraine «On Application of transplantation of anatomical materials to a person» approved a centralized procedure for keeping records of potential

[1] https://www.canada.ca/en/innovation-science-economic-development/news/2020/03/government-of-canada-invests-in-regenerative-medicine-research-to-support-canadians-health.html
[2] https://www.fda.gov/vaccines-blood-biologics/consumers-biologics/consumer-alert-regenerative-medicine-products-including-stem-cells-and-exosomes
[3] http://www.mhlw.go.jp/file/06-Seisakujouhou-10800000-Iseikyoku/0000030847.pdf

donors who gave consent to transplant organs and/or anatomical materials, including information about them in the Unified State Information System of Organ and Tissue Transplantation and the State Information System transplantation of hematopoietic SC, there is a possibility of data exchange between the State information system for hematopoietic SC transplantation and international, foreign and Ukrainian information systems of other forms of ownership, registers of potential hematopoietic SC donors in order to facilitate the search and selection of potential donors. These registers began operating on January 1, 2021. In addition to the issue of taking into account the consent of potential donors for transplantation, Ukraine needs to address the problem of insufficient awareness of the population about transplantation and cell therapy in general, about donation, which raises concern. The law also provides not only legal regulation of procedures related to transplantation, but also active state information policy aimed at creating a positive attitude towards intravital and cadaveric donation of anatomical materials by informing the public about transplantation as a non-alternative method of medical care necessary for saving lives and restoring health, in particular through social advertising and outreach.

Prospects for the use of cell transplantation in clinical trials to improve the prognosis and treatment of the consequences of traumatic brain injury

Traumatic brain injury is one of the most common non-infectious diseases, which depending on the severity, is characterized by high mortality and disability of the working-age population. According to WHO forecasts, starting in 2021, TBI will rank first among the causes of death and morbidity. This will lead to an increase in the cost of treatment, rehabilitation, social benefits for the state, patients and their families [16,17]. Currently in Ukraine the problem of TBI is relevant in connection with the joint forces operation (anti-terrorist operation) in the east of the country, since TBI in the structure of combat injuries (including gunshot wounds to the skull and brain) accounts for 24.2% [18].

According to the modern clinical classification, the following types of TBI are distinguished: concussion, cerebral contusion of mild, moderate and severe degree, diffuse axonal damage to the brain and compression of the brain against the background of its contusion (acute intracranial hematomas, hydromas, depressed fractures of the skull) or without contusion (chronic subdural hematomas, hydromas) [19]. Traumatic brain injury can be primary or secondary. During TBI, the following periods are distinguished [20]:

- acute: from the moment of injury to stabilization of dysfunction (interaction of traumatic substrate, damaging reactions and defense reactions) (from 2 to 10 weeks);

- intermediate: from the moment of stabilization of functions to their full or partial recovery or stable compensation (resorption and organization of injuries, development of compensatory-adaptive processes (in mild TBI – up to 2 months, in moderate – up to 4 months, in severe - up to 6 months));

- long-term period: clinical recovery or the maximum possible recovery of impaired functions, or the emergence or progression of new pathological conditions caused by TBI. The duration of long-term period in case of clinical recovery is up to 2 years, in case of progressive - unlimited (completion or existence of local and remote degenerative-destructive and regenerative-reparative processes).

The consequences of TBI can be observed at any time. According to the Glasgow outcome scale, the following consequences of TBI are distinguished [21]:

1. Good recovery.
2. Moderate disability.
3. Gross disability.
4. Vegetative state.
5. Death.

At the Institute of Neurosurgery named after M.M. Burdenko on the basis of the Glasgow outcome scale a differentiated scale of consequences of TBI [20] taking into account the following combinations of the patient's condition and his working capacity has been developed:

1. Recovery. Complete recovery of working capacity, the patient works at the same place. No complaints, sense of well-being, social behavior, work and study are the same as before the injury.

2. Mild asthenia. Increased fatigue, but no memory loss or difficulty concentrating. Works at full load in the same place. Children show a pre-traumatic level of learning capacity and academic performance.

3. Moderate asthenia with difficulty remembering. Works at his previous job, but working capacity is reduced compared to that before TBI. Children may have a slight decline in academic performance.

4. Severe asthenia: quickly gets tired physically and mentally, decreased memory, attentiveness, headaches and other manifestations of discomfort occur. Works at a less skilled job; III group of disability status. Children have a marked decline in academic performance.

5. Expressed mental disturbance and / or motor functions. Able to self-care; II group of disability status. Children have a pronounced decrease in learning ability, only the special school program is available.

6. Severe mental disturbance, motor functions or vision. Needs self-care; I group of disability status. Children are only capable to learn basic knowledge.

7. Vegetative state.

8. Death.

According to L.B. Lichterman, the classification constructions of the consequences of TBI are among the most unprocessed and confusing. He proposed a classification based on structural changes in the intracranial space [22]. It is known that the intracranial space is occupied by brain matter (about 85%), cerebrospinal fluid (about 10%) and blood (about 5%), which are influenced by mechanical energy (both on the hard and soft scalp). Accordingly, three groups of structural consequences of TBI are identified:

- clinical forms of tissue consequences of TBI:

1. Post-traumatic brain atrophy:

a) local;

b) diffuse.

2. Post-traumatic arachnoiditis.

3. Post-traumatic pachymeningitis.

4. Meningeal scars: without foreign bodies, with foreign bodies.
5. Damage to the cranial nerves.
6. Skull defects.
7. Post-traumatic skull deformity.
8. Combined;

- clinical forms of cerebrospinal fluid consequences of TBI:

1. Hydrocephalus: active, passive.
2. Porencephaly.
3. Meningoencephalocele.
4. Chronic hygromas.
5. Cerebrospinal cysts.
6. Liquorrhea:
a) without pneumocephalus;
b) with pneumocephalus.
7. Combined;

- clinical forms of vascular consequences of TBI:

1. Ischemic lesions.
2. Chronic hematomas.
3. Aneurysms:
a) real;
b) erroneous.
4. Arterio-sinus fistula:
a) carotid-cavernous fistula;
b) other arterio-sinus fistulae.
5. Sinus thrombosis.
6. Combined.

It should be noted that not only moderate and severe cerebral contusion, but also «mild» injuries lead to the consequences of disability, which are combined into three main groups of symptom complexes [23,24]:

1. Behavioral:
- apathy;
- frequent mood swings;
- change of personality;
- impulsiveness;
- anxiety;
- depression;
- irascibility;
- slowing down the reaction in response to a stimulus.

2. Cognitive:
- memory impairment;
- impaired concentration;
- disorientation in time and space;
- problem with communication;
- difficulties with processing the received information;
- repeat patterns.

3. Neurological and somatic:
- sleep disorder;
- cephalgia;
- impairment of consciousness;
- convulsive disorder;
- motor dysfunction;
- digestive dysfunction;
- increased fatigue;
- coordination dysfunction.

Also, there are often symptoms that are not included in the above classification, but characteristic for this group of patients:

1. Syncopal state of unknown etiology.
2. Altered sense of taste.
3. Dystonia.

Recent studies have shown that TBI can start the initiation of molecular cascades at the cellular level, leading to Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, hypogonadotropic hypogonadism, and chronic traumatic encephalopathy (dementia pugilistica).

One of the most promising treatment landscape of TBI and its consequences is CT of SC, as evidenced by a large number of publications and studies.

There are two main phases/periods in the pathogenesis of TBI. The first phase is due to the direct physical action of the traumatic factor, which leads to mechanical damage to the macro- and microanatomical structures of the brain, which triggers a cascade of pathophysiological processes [25,26]. The second phase begins a few hours after TBI and lasts from several hours to several weeks. It is characterized by secondary pathophysiological changes that lead to necrosis and apoptosis of nerve cells in the brain [25,26].

One of the main secondary pathophysiological processes that affect neuronal damage is the development of immune inflammation (sometimes prolonged) [27,28]. The primary and secondary phases of brain damage trigger the stimulation of regenerative processes and the activation of neurogenesis and angiogenesis by endogenous SC, which are localized in the hippocampus and subventricular zone. Neurotrophic growth factors are of great importance in the regeneration process, in particular NGF (nerve growth factor), brain derived neurotrophic factor (BDNF), interleukin-10, transforming growth factor-β (TGF -β), able to secrete SC. In this case, the efficiency of regeneration process after TBI is often reduced due to the influence of immune and inflammatory processes. This necessitates a multifactorial effect in treatment aimed at slowing down the immune and inflammatory processes, stimulation of endogenous SC, introduction of exogenous SC, which will improve treatment outcomes and prognosis for patients with TBI [29–31].

SC of all types of differentiation (totipotent, pluripotent, multipotent, oligopotent, progenitor cells at different stages of maturation, brain cells of embryos and adult animals, BM cells) were used for CT in the consequences of TBI in the experiment and clinical studies [17,30]. Analysis of experimental studies with modeling of TBI in animals and the introduction of SC intravenously and stereotactically into different brain structures revealed the most promising results when using allogeneic concentrated supplements of neurogenic SC obtained from various brain structures and mesenchymal SC (MSC), adipose and bony tissue, placenta and umbilical cord, human amniotic membrane [17,30,32]. According to research data, using of neurogenic SC (NSC) can achieve a positive result (restoration of cognitive functions, improvement of motor function and learning ability). When using preliminary immunosuppression or BGF transfection with the genome 9–25% of NSC were differentiated into mature neurons [33,34]. With the introduction of NSC the volume of brain damage decreased. The migration of cells to the area of brain damage was noted. The effectiveness of the use of NSC was observed during their introduction within the first 24 hours after TBI [35]. A large number of studies have been performed using embryonic SC,

but a sustainable improvement in cognitive and motor impairment was not achieved, and the emergence of mass in the injection site was noted [36,37]. Also, many experiments were performed using MSC. It was established that MSC are able to transform into nerve cells, secrete the humoral factor, that promotes the regeneration of nervous tissue, reduces edema of the nervous tissue, as well as suppresses immune and inflammatory reactions [32,38]. In animals in the experiment with MSC transplantation, an improvement of neurological function, learning ability, and rapid memory recovery were reported [39].

Placebo-controlled trials of allogeneic and autogenous SC derived from BM, adipose tissue and umbilical cord blood in CNS damage after TBI, stroke, as well as in spinal cord injury and neurodegenerative diseases are ongoing [40,41]. Studies of the use of SC in TBI have been carried out since 2004. Groups are formed from patients aged from 5 to 75 years. SC transplantation is performed in the acute period (<48 h), intermediate (>1 month) and long-term (>6 months). The introduction of SC is performed intravenously, intrathecally, endolumbarly and intranasally. For the CT autogenous cells are used – progenitors of BM (PBM) (mononuclear cells containing MSC and hematopoietic SC), MSC derived from umbilical cord blood and adipose tissue, and modified SC [41,42]. In case of using PBM in the study, the collection of BM is carried out in the period from 12 to 30 hours after injury in the amount of 3–5 ml / kg of the body weight. The infusion is carried out once or repeatedly at a concentration of from $6 \cdot 10^6$ to $12 \cdot 10^6$ cells / kg of the body weight. When using PBM, suppression of tumor necrosis factor, a decrease in the content of interleukins-1β, 10 and interferon-γ was noted, which leads to suppression of the neuroinflammatory reaction. The correlation between functional and cognitive indicators and data of neuroimaging studies is revealed [42]. The greatest efficacy was noted in the groups of patients who received the maximum doses of cells [41,42]. Modified SC are of great interest.

The University of California (Los Angeles, USA) conducted the study on the efficacy and safety of modified MSC derived from BM that were subjected to genetic modification (SB623) [43]. A two-stage randomized, double-blind, placebo-controlled study with sham surgery was carried out for 12 months. SB623 cells were implanted around the area of brain damage. Criteria for involving patients in the study were:

1) age from 18 to 75 years;

2) at least 12 months after TBI;

3) 3–6 points on the expanded Glasgow outcome scale (GOS-E) (moderate or severe disability).

Motor disorders were assessed using the Fugl-Meyer motor scale (FMMS) before and after the clinical study. The study involved 61 patients from the United States, Japan and Ukraine. Patients who underwent SB623 transplantion, achieved improvement of 8.3 points on average compared to baseline according to FMMS 24 weeks after ($p = 0.040$). An improvement of ≥10 points according to FMMS was noted in 39.1% of patients who received SB623, while in the control group - in 6.7% ($p = 0.039$).

In the clinical study conducted in China (2008), patients who underwent TBI were injected with allogeneic MSC into the damaged area of the brain, including 7 patients who received MSC injections during craniotomy /skull defect plastics, the second dose of SC was injected intravenously [40]. The follow-up lasted 6 months. There was a significant improvement in neurological status (according to the Barthel index). The authors noted the absence of any side effects associated with SC therapy. In clinical study in traumatic brain injury, MSC were used, the source of which was umbilical cord blood. Positive results were obtained due to improved motor and sensory functions, increased level of self-care, sphincters control, communication and social adaptation 6 months after treatment compared with the control group ($p < 0.05$) [44].

Clinical trials of MultiStem, a mesenchymal stem cell-based product approved by the FDA, which is planned to be used for the treatment of stroke in the United States, are ongoing [45,46]. Many clinical trials using allogeneic MSC have been carried out by Athersys (USA) and Osiris therapeutics (USA). None of these studies reported side effects associated with SC. Study outcomes indicate the safety and efficacy of administering allogeneic BM MSC to patients during clinical trials (preliminary data) [47,48]. Clinical studies aimed at stimulating neurogenesis and intrinsic SC are continued, which is a promising area in the treatment of the consequences of TBI [41]. Stimulation of regenerative processes is achieved through the administration of drugs, exercises, the use of the effect of hypoxia and hyperbaric oxygenation. The following articles will discuss in detail the clinical trials on the use of SC in TBI.

Thus, the positive result obtained with the use of SC, indicates the effectiveness of the use of CT in patients after TBI.

Conclusions

The history of CT development is more than 100 years old. Currently, an active phase of CT development is observed. Developed countries, such as the USA, Japan, Canada, and South Korea, introduce SC CT for the treatment of certain nosologies, which is reflected in recommendations.

A large number of ethical and medical problems in the use of SC is associated with the use of embryonic SC, in particular, a high probability of tumors emergence and the absence of a positive result in modeling TBI were found, which makes their use inappropriate at the present stage of medical science development.

The safety of using CT of MSC of various origins has been proven in many experimental and clinical studies. The use of this method is approved by the FDA for clinical research in certain nosologies. Ukrainian legislation does not prohibit the transplantation of autogenous and allogeneic biomaterials, as evidenced by the large regulatory framework on the basis of which algorithms for the introduction of CT into clinical practice have been developed. This direction of treatment requires systematic public awareness.

The search for new treatment of TBI that may affect the outcome and consequences is an urgent international challenge, since even mild TBI can lead to disability-related consequences and can be life-threatening.

Studies outcome analysis in animals and humans using SC of various origins in TBI has shown its

effectiveness in the treatment of TBI. MSC of various origin are the most promising for clinical research for a number of reasons, since they are capable of slowing down secondary pathophysiological processes and promoting the processes of nerve tissue regeneration, as well as differentiating into nerve tissue in different periods of TBI.

Given the positive results obtained in studies of multifactorial mechanisms of influence, SC CT in TBI is the most promising method and requires additional clinical studies.

Disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical norms

This article is a literature review, therefore no ethics committee approval was required.

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