Stem Cell Therapy in Multiple Sclerosis: Current Progress and Future Prospects

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Summary. *Background and objective.* Multiple sclerosis is a chronic inflammatory disease of the central nervous system that represents one of the leading causes of neurologic disability in young adults. Innovative treatment for multiple sclerosis is of broad current interest in the whole world, especially in Europe. Europe, including Lithuania, is considered a high prevalence region for MS. Current treatments have shown limited efficacy in patients with either a progressive or an aggressive disease course. Immunomodulatory and anti-inflammatory agents work by reducing the frequency and severity of relapses, but they are not sufficient enough to cure chronic neurological disability. Stem cells offer the promise of filling this therapeutic goal. This review aims to report the current progress in the experimental and clinical application of stem cell-based therapies, used in managing multiple sclerosis.

Materials and methods. A systematic review of the MEDLINE database and Cochrane library was conducted. A search using Medical Subject Heading (MeSH) major terms "multiple sclerosis" and "stem cells" was applied for the period from 2010 to the end of 2015.

Results. Our review identified 45 publications. The literature search and analysis provided information on the basic stem cell biology, preclinical research, and the development of innovative new stem cell-based therapies.

Conclusions. There are many types of stem cells that are undergoing research, which is producing knowledge about their potential use in the treatment of multiple sclerosis. Recent studies demonstrate that specifically hematopoietic and mesenchymal stem cell transplantation is a growing area of clinical study that shows a low risk/high reward treatment option for multiple sclerosis patients. Additionally, combined therapy of HSCT and MSCT or combination therapies which include stem cells and disease modifying agents could work synergistically to further decrease adverse side effects and increase patient outcomes.

Keywords: multiple sclerosis, stem cells, transplantation, multiple sclerosis treatment.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic immune-mediated, demyelinating, neurodegenerative disease of the central nervous system (CNS). It is one of the most common disabling neurological disorders affecting mainly young adults and leading, in the majority of cases, to physical and psychological impairment [1, 2].

In patients with MS, activated autoreactive immune system T-cells enter the CNS, attacking myelin and producing inflammatory responses which cause multifocal demyelination, axonal loss, and scarring of white matter [3]. Following an acute demyelination episode, MS progression typically follows one of four disease courses: relapsing-remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS) and progressive-relapsing MS (PRMS) [4].

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Over the past two decades, a number of immunomodulatory and anti-inflammatory therapies have been developed that are effective in the relapsing-remitting phase of the disease. Immunomodulatory and anti-inflammatory agents work by reducing the frequency and severity of relapses, and decreasing the formation of inflammatory lesions [5]. However, they do not influence the course of the disease and they are not sufficient enough to cure chronic neurological disability [2].

The current therapeutic challenge is to find an effective treatment which could be able to stop the disease progression and to reverse established neural injury [6].

Tremendous progress in the experimental and clinical applications of cell-based therapies has recognized stem cells as the potential candidates for regenerative therapy for many neurodegenerative disorders including multiple sclerosis [2]. This future therapeutic strategy is aimed to achieve neuroprotection, remyelination and regeneration of new oligodendrocytes and neurons [7].

Stem cell therapy is a growing area of research that may contribute to the additional treatment options, leading to more effective management of MS.

MATERIAL AND METHODS

This review includes literature published from 2010 to the end of 2015. The electronic databases Pub Med, Science Direct and Cochrane Database of Systematic Reviews, as well as the web search engines of Google were searched to identify relevant publications.

In order to identify any topic of interest related articles, a search using the Medical Subject Headings (MeSH) major terms "multiple sclerosis" and "stem cells" was applied. In order to get more detailed insight also other combinations of search keywords were used: "stem cell therapy", "embryonic stem cells"; "induced pluripotent stem cells", "neural stem cells"; "hematopoietic stem cells", "mesenchymal stem cell"; "transplantation", "multiple sclerosis treatment", etc.

All documents resulting from the electronic searches were evaluated and appropriate publications retrieved. The final review and the text of literature review were performed by the researchers, i.e., the authors of this paper.

WHAT TYPES OF STEM CELLS MIGHT BE USED FOR MS?

Stem cells are unspecialized cells in the body that retained the ability to generate cells of undifferentiated state identical to themselves, or of differentiating into other types of body cells with specialized functions [2]. Stem cells have the potential of unlimited numbers of progeny. All these characteristics are both a strength and a liability for stem cell-based therapies in the CNS [8].

There are multiple types of stem cells that arise at different stages in the development. Functional recovery in the pathologies of central nervous system can be achieved using multiple different classes of stem cells [9].

1. Embryonic stem cells (ESCs)

Conceptually, they are the most effective stem cell population for therapeutic applications. **Embryonic stem cells** (ESCs) have been extensively studied in several models of neural injury and disease. ESCs have the advantage of being potentially the most plastic and therefore capable of generating the most diverse cell populations [8].

These pluripotent stem cells are derived from the inner cell mass of a blastocyst, an early-stage preimplantation embryo. The number of studies of embryonic stem cells and their use in clinical practice are limited by ethical issues and national legislation limits [10].

Besides, this is a controversial and uncertain area of research as ESCs have the potential to develop into tumours. For the moment, ESCs are extremely useful in the laboratory – to identify and test potential drugs before they are tested in clinical trials [11].

2. Induced pluripotent stem cells (iPSCs)

It would be ideal to use the patient's own cells for transplantation in order to avoid rejection of the new tissue by the immune system. Recent developments in the area of stem cell research have resulted in generating stem cells from human tissue. These cells, known as induced **pluripotent stem cells** (iPSCs), have the potential to become any cell type of the body, similar to the human embryonic stem cells (hESC) [2].

A recent method of generating patient-specific pluripotent stem cell is based on the discovery that somatic cell nucleus can be genetically reprogrammed to an embryonic stem cell-like pluripotent state without the need for eggs through introduction of a quartet of transcription factors. Somatic cell nucleus is being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells. iPS cells are made in the laboratory by reprogramming specialised adult cells, for example skin cells, so that they function as stem cells capable of generating other types of tissue, such as brain [11].

This approach offers minimal ethical dilemmas and allows unlimited expandability of the cells, broad patterning potential and patient DNA match (autologous transplantation). Nevertheless, there is a concern related with tumor formation and also genetic and epigenetic instability [12].

This method has only recently been developed and is the subject of much ongoing research. Currently there are no clinical trials underway using ESCs or iPSCs for MS [9].

3. Neural stem cells and their derivatives

Neural stem cells (NSCs) are multipotent cells that have the capacity to self-renew and generate the main phenotype of the nervous system. Studies over the last two decades have demonstrated the presence of neural stem cells in both the developing and adult CNS, proving the existence of adult neurogenesis [12]. These cells are found in specific regions of the CNS. Under non-pathological conditions endogenous neural stem cells generate new neurons that populate the hippocampus and the olfactory bulb. NSCs primarily give rise to neurons, astrocytes, and oligodendrocytes [8].

Recent studies provided the definitive proof that neural stem cells are the main remyelinating cells in the CNS following a demyelinating injury. In response to inflammation and demyelination, neural precursor cells (NPCs) promote migration, glial differentiation, survival of endogenous NSCs thereby enhancing self-repair. Transplantation of OPCs (oligodendrocyte progenitor cells) and various types of neural precursor cells has shown their potential in remyelinating the CNS. Unfortunately, remyelination activated in MS is insufficient to repair severe and long-lasting demyelination [13]. Additional NSCs transplantation could boost remyelination.

Currently, the acquisition of autologous NSCs requires a brain biopsy. The likelihood of brain biopsy on a neuro-

logically impaired patient in order to obtain NSCs becoming a generalized practice is relatively low.

In spite of these concerns, multiple studies have confirmed a significant functional improvement in the animal models of multiple sclerosis following treatment with NSCs. It is believed that NSCs can have an effect through immunomodulation and a direct effect on remyelination. A new promising perspective for the future could be therapies targeting the stimulation of endogenous NSCs with growth factors [8].

4. Hematopoietic stem cells (HSCs)

Hematopoietic stem cells (HSCs) are found within bone marrow in niches created by surrounding stromal cells. HSCs have the potential to differentiate into the main hematopoietic and lymphopoietic precursors which then differentiate into mature cells. They are generated in large numbers throughout our lives and continually repopulate our blood and immune system [4].

Autologous hematopoietic stem cells (HSCs) can be collected directly from bone marrow or by leukapheresis from the peripheral blood [3].

The concept behind HSCT or autologous stem cell transplantation (ASCT) is the ablation of an aberrant or self-reactive immune system by chemotherapy (typically using granulocyte colony-stimulating factor (G-CSF) and cyclophosphamide (CY)). The immune system is rebooted by re-infusing the stem cells into patient's blood, hoping for regeneration of a new and hopefully self-tolerant immune system. Hematopoietic stem cells (HSCs) are already used to treat leukaemia, lymphoma and several inherited blood disorders [4, 14].

5. Mesenchymal stem cells (MSCs)

A leading candidate of stem cell population for clinical neurological applications is MSCs – multipotent stromal cells or mesenchymal stem cells [8, 15].

MSCs are a heterogeneous population of stromal cells that can be isolated from various sources such as bone marrow, amniotic fluid, dental pulp, adipose tissue [16], umbilical cord [17], synovial membranes, and peripheral blood, among which the main and the most frequently studied source is the bone marrow [2].

MSCs can differentiate into cells of the mesenchymal lineage, such as bone, cartilage and fat. It has been recently reported that MSCs are able to differentiate into non-mesenchymal cell lineages, such as skeletal myocytes, neurons and cells of the visceral mesoderm, both *in vitro* and *in vivo* [1, 2].

Being relatively accessible, easily isolated and grown, mesenchymal stem cells are an attractive cell population for a range of therapeutic interventions [8]. They have a therapeutic role through strategies other than tissue replacement in diseases such as MS. These strategies include tissue protection, augmentation of endogenous axonal and myelin repair processes, and immunomodulatory activity [5, 18].

Though MSCs are unable to improve the clinical course of disease and recover neurological functions when chronic neural damage and subsequent disability have occurred, MSC interventions should be used in patients with acute neurological disorders to target inflammatory mechanisms, promote tissue protection and repair [10].

PRECLINICAL STUDIES

Stem cell therapy in axonal demyelination and neurological disability has had promising results in animal models [19].

ESCs

Experimental autoimmune encephalomyelitis (EAE) is the most commonly used experimental animal model to study multiple sclerosis, its etiology and pathogenesis. This model can also be used to investigate therapeutic mechanisms in order to develop more efficacious therapies for MS than are currently available. A recent study conducted by A. S. Fazeli (2013) studied molecular mechanisms of EAE after stem cell transplantation. Researcher has treated an EAE mouse model with an embryonic stem cell-derived neural precursor. Clinical analysis showed recovery of the EAE model following transplantation. The analysis of the proteome of spinal cords in healthy and EAE samples before and after transplantation was made. Proteome results revealed that the expression levels of differentially expressed proteins in EAE samples returned to normal levels after transplantation. Clinical signs of EAE in transplanted mice also decreased suggesting a possible correlation between changes at the proteome level and clinical signs. Results provided a proteomic view of the molecular mechanisms of EAE recovery after stem cell transplantation [19].

iPSCs

Wang et al. (2013) successfully used human induced pluripotent stem cell (hiPSC) to treat congenital myelin loss disorder in mice. Using hiPSCs, researchers generated glial precursor cells, namely OPCs, which efficiently differentiated into myelinogenic oligodendrocytes. Neonatally engrafted human iPSC-OPCs myelinated the brains of myelin basic protein (MBP) deficient mice, and were able to rescue a hypomyelinated mouse model and increased its life span. The efficiency of myelination by human iPSC-OPCs was higher than that previously observed using fetal tissue-derived OPCs, and no tumors from these grafts were noted as long as 36 weeks after transplant [20].

In 2014, myelinating oligodendrocytes were generated not from healthy individuals, but from subjects with primary progressive MS, through iPSC technology. It demonstrated that the MS-iPSCs derived from disease-state patients can successfully differentiate into mature astrocytes, oligodendrocytes and neurons with normal karyotypes [21].

In 2014, Douvaras et al. reported the generation of iPSCs from skin biopsies from primary progressive MS patients and their efficient differentiation to functional oligodendrocytes demonstrated by in vivo myelination in the shiverer mouse. Primary progressive MS patients derived OPCs also differentiated into mature oligodendrocyte which formed dense compact myelin resembling normal myelin in mice, as efficiently as iPSC-derived OPCs from healthy subjects [22].

NSCs

Recent studies have shown that grafted oligodendrocyte progenitor cells (OPCs) obtained from neural stem cells can differentiate into oligodendrocytes and develop compact myelin supplies to repair the injured white matter of rodents [23].

In animals with experimental autoimmune encephalomyelitis (EAE), NSC transplantation led to significant improvement of the clinical severity of the disease and reduction in the pathological parameters of inflammation [5, 7, 10, 14]. Importantly, the immunomodulatory function of NSCs proved to be neuroprotective. Inhibition of the injurious autoimmune process by NSC transplantation prevented accumulation of acute axonal injury and chronic axonal and myelin loss [1].

Other study reported that injection of neural stem cells from the adult spinal cord into the mice with induced experimental autoimmune encephalomyelitis (EAE) enhanced remyelination in the CNS. In addition, the number of CD3+ T cells in areas of spinal cord demyelination was reduced. In vivo studies indicated that in EAE, neural stem cells stimulated endogenous repair while in vitro they responded to inflammation by differentiating into oligodendrocytes. These results suggested that adult stem cells represent a useful cell population for promoting neural repair in a variety of different demyelinating diseases such as MS [12]. An interesting study was provided by Brustle et al., in which human NSCs were implanted into the ventricle of embryonic rat brains. The human cells appeared to incorporate into all major compartments of the host cerebrum and differentiated into neurons, astrocytes and oligodendrocytes [24].

MSCs

Recent evidence from preclinical studies submits MSCs transplantation as an effective cell therapy for EAE. In EAE, intravenous injection of MSCs improves the clinical evolution of the disease and reduces demyelination, immune infiltrates and axonal loss. These effects do not require grafting of MSCs in the CNS, but are based on the MSCs' ability to inhibit the pathological response of T and B cells and on the tissue protection, myelin repair processes, and immunomodulatory activity. These results led to the conclusion that the administration of MSCs should focus on individuals with ongoing inflammation and before they develop irreversible disability [5].

HSCT

Preclinical studies of autologous HSCT in experimental autoimmune encephalomyelitis (EAE) contributed to the optimization of autologous HSCT and to the understanding of its effect on CNS pathology. While transplantation during high EAE severity resulted in fast recovery [11], protection from disability was not seen when autologous HSCT was carried out in the chronic stages of EAE [3].

Animal studies have shown that immunosuppressive therapy followed by hematopoietic cell transplantation (HCT) can cure autoimmune diseases in mice and rats. These studies showed that high-dose immunosuppressive therapy eliminates the components of the immune system that cause the autoimmune disease. Then, the patient's full health is restored by rebooting the immune system with a transplant of hematopoietic stem cells, either from a compatible donor (allogeneic) or from previously stored bone marrow or blood cells from the patient (autologous) [25].

The results of HSCT in an animal model of EAE have shown that all types of HSCT may stabilize clinical MS or induce high remission rates and cures of EAE, when intensive conditioning regimens are administered [25].

CLINICAL EXPERIENCE

MSCs

The past several years saw an increase in clinical trials which confirmed the efficacy, feasibility and safety of MSC therapy [2, 7].

In 2012 Connick et al. published the results of their open label study with ten SPMS patients who had optic nerve disabilities. They were intravenously injected with autologous MSCs and were followed up to 20 months pre-treatment and 10 months post-treatment. The authors' conclusion was that MSCs were proven safe for use in patients with SPMS because there were no significant side effects. Furthermore, the study showed structural and functional improvement of patients' visual function [5, 15, 26]. The results mentioned previously coincide with the neuroprotective effect of MSCs by promotion of endogenous oligodendrogenesis and remyelination [2].

In the same 2012 another open-label study, which was carried out by Bonab et al and included 25 patients who had progressive MS, confirmed positive results of a single intrathecal injection of autologous MSCs. After re-evaluating the 12 months post-treatment, the mean (SD) expanded disability status scale (EDSS) score of 22 patients changed from 6.1 to 6.3. 15 patients showed no change in the MRI evaluation in the first years after injection. Besides, there were no reports of serious adverse events except transient low-grade fever, nausea/vomiting, weakness in the lower limbs and headache. It can be concluded that MSC therapy can improve and/or stabilize the course of the disease in progressive MS in the first year after injection with no serious undesired harmful effects, because up

to 70% of the patients showed some signs of transient disease stabilization [5, 28].

The safety and tolerance of treatment with MSCs in 15 MS patients was also assessed by Karussis et al in 2010. This trial showed immunomodulatory effects of MSCs therapy and non important side effects apart from, e.g. headache and/or fever in those who were intrathecally injected with MSCs. There were no reports of infection as a side effect of this injection [5].

Similar results were reported by Odinak and co-workers in their study which included 8 patients with MS. The patients were evaluated 4, 8, and 12 months after intravenous treatment with autologous MSC. Also, there were no significant side effects either in the early or the late phases after-treatment. This study showed improvement on EDSS 0.5–1 point in six of the 8 patients; one of them showed disease stabilisation, another one – progression of disease [29].

Recently, in 2014, nine RRMS patients, who received bone marrow MSCs infusion for 6 months showed a trend to lower cumulative number of gadolinium-enhancing lesions (GEL) on magnetic resonance imaging (MRI). Furthermore, there was observed a non-significant decrease of the frequency of Th1 cells in peripheral blood of MSCs treated patients [17]. Intravenous infusions of autologous MSC were tolerated well by all patients after the completion of the 12 months protocol [5]. The ameliorative effects were observed in a study carried out by Yamout et al. with the intrathecal injection of ex vivo expanded autologous bone marrow derived MSCs to ten MS patients [19]. Intrathecal MSCs were generally well-tolerated [31].

The combination of both allogenic human umbilical cord-derived MSCs and autologous bone marrow-derived MSCs therapy also showed similar results [32].

The outcomes of the study conducted in 2015 are intriguing as they involve the initial use of autologous MSC-derived neural progenitors (MSC-NPs) that were never tested clinically before [34].

It seems that MSC therapy can improve or at least stabilize the course of the disease in progressive MS without serious adverse effect [5, 28].

However, another study which tested intravenous MSCs in 24 patients with active-relapsing MS and which was carried out recently in the USA showed no therapeutic benefit, although the primary outcome of safety was met [27].

HSCT

The past 15 years saw the use of autologous hematopoietic stem cell transplantation (HSCT) which has been stabilizing or even curing patients with refractory MS who failed other available therapies and had a very poor prognosis [3].

At the time HSCT was introduced, back in 1995, it was viewed as quite an extreme method of healing patients [35]. In the following years, HSCT therapy became a very effective treatment for RRMS, and even in particular highly aggressive RRMS [36].

Richard K. and colleagues in Chicago carried out their research of the association of nonmyeloablative HSCT with neurological disability and other clinical outcomes in patients with RRMS (n=123) or secondary-progressive MS (n=28) for 11 years, between 2003 and 2014. The results of this research showed a meaningful improvement in EDSS in 41 patients (50% of patients tested at 2 years) and in 23 patients (64% of patients tested at 4 years). There were noticeable improvements in cognitive and physical function, as well as in quality of life. Reduction of brain lesions related with MS was also seen on magnetic resonance imaging (MRI). Four-year relapse-free survival was 80% and progression-free survival was 87% [37].

In the Italian experience a reduction in EDSS occurred in 27% of HSCT recipients with more than 7 years of follow-up. In the research carried out by Fassas, 16 out of 35 patients had improvement in their EDSS immediately after treatment; however just 2 out of 35 patients achieved improvement in EDSS after longer time [3, 6]. A similar result was seen in a cohort study in Russia, where EDSS score dropped from a score of 3.5 before HSCT to 2.0 score after 3 years of HSCT procedure. In a study in China EDSS score was reduced by 3.1 among 10 out of 25 HSCT recipients [6].

Despite the fact that scholars are still lacking clinical evidence that would support the idea of a complete freedom from disease activity after HSCT, the outcomes are nevertheless promising because of the fact that the majority of patients with progressive disease who participated in the studies experienced confirmed disability progression in the year before HSCT, despite conventional treatments [3].

Patients with malignant MS faced quite drastic outcomes after HSCT procedure. The decrease of EDSS score from a mean of 6.8 prior to HSCT to a mean of 3.1 was received in 13 patients with disability which progressed rapidly after diagnosis [6].

Several registry reports and cohort studies have showed that HSCT can achieve the cessation of progressive accumulation of disabilities and stabilize disease for a long time in patients with SP-MS, without disease-modifying agents. Approximately 45% of patients have a stable EDSS score at 5 to 7 years after HSCT [6].

MS patients who have active inflammatory disease are likely to expect better outcomes, e.g. a short disease duration, and a lower EDSS score. Positive results are seen in studies including RRMS rather than PPMS or SPMS patients. This means that the role of HSCT in arresting disability progression is closely tied with the control of the peripheral immunity rather than to a direct effect on CNS-confined pathology [3]. Patients who have SP-MS (secondary progressive MS) and advanced disability were chosen for HSCT. Nevertheless, patients that had an Expanded Disability Status Scale [EDSS] score 6.0 had poor results in comparison with patients who entered HSCT with less disability. European Bone Marrow Transplant registry analysed their data in which patients were listed by age and duration of MS. According to this data, the results of the

patients who were younger than 40 years and who had been diagnosed in the last 5 years were better than the results of the older recipients who had longstanding MS. It is reasonable to believe that younger and healthier patients might have active neuroinflammation and may benefit from HSCT [6] if they were diagnosed earlier.

The Spanish research proved that the number of relapses decreased from 48 to 7 in only 2 patients after HSCT. In the study of Burman and co-workers, in a population with an ARR of 4, 1 before HSCT, the proportion of relapse-free patients at five years of follow-up was 87%. The Italian study of the GITMO group came to similar conclusions. In the US, 21 people with relapsing remitting MS were treated with HSCT between 2003 and 2005. After three years of treatment, people on the trial did not face impairment, and 16 patients had not experienced any relapses. A certain amount of patients suffered from issues related with immune suppression, e.g. herpes, diarrhoea and internal bleeding. There was a report that came out in the US in 2014 which included 25 people with relapsing remitting MS. It stated that 3 years after HSCT, disability rates did not drop in 91% of patients while 86% did not experience a relapse [3, 36, 38].

The European Group for Blood and Marrow Transplantation analysed and summarised the results of various research which included more than 340 people with both RRMS and PPMS-SPMS who received HSCT treatment between the years 1996 and 2007. After 5 years of treatment, MS had not progressed in 45% of patients. Nevertheless, 2% of patients who underwent this treatment died as a result of transplant-related issues. In 2011, a report following up a trial of 35 people with RRMS and progressive MS stated that 15 years after HSCT, MS had not progressed in 25% of people, and the improvement of disability was seen in 7 people [38].

The early and late toxicity from HSCT depends on particular drugs in the conditioning regimen and not the infused autologous hematopoietic stem cells [25]. Generally, the less intense the conditioning regimen, the less myeloablative it is, with low intensity regimens being considered truly non-myeloablative [4]. Several initial studies utilized cancer-specific high-risk and extreme regimens, some of which were complicated by treatment-related mortality due to increased risks of infections, late leukemia or myelodysplasia, solid tumors and, in the case of high-dose treatment, disease of the liver. In contrast, non-myeloablative regimens are much safer with less short or long-term toxicity [25]. A clinical study which compared the efficacy of low and intermediate intensity HSCT in treating MS patients concluded that the low intensity HSCT reveals lower toxicity and side effects, but similar clinical outcomes as the intermediate regimen [39]. Systematic review shows that transplant related mortality (TRM) in early clinical trials was 5–6% from 1995–2003, but dropped from 2003–2008 to 1–2% when low intensity trials first began. The outcomes of patient are also extremely encouraging. In a 5 year prospective trial, 95 MS patients with different disease severity underwent low intensity HSCT. Progression-free survival after HSCT, measured by neurological improvement, decreased EDSS, and improved quality-of-life (QOL), was 82% at 5 years and at long term follow-up overall clinical response was 80% [40].

Although the follow-up of patients in the majority of the clinical studies is too short to achieve definitive conclusions, but very few malignancies have been reported [41].

COMBINED THERAPIES

According to various studies discussed above, the best treatment some MS patients should get is a combination of several therapies.

In 2013 researchers conducted a pilot study which gave results that MSC co-transplantation during HSCT could be a safe as well as an effective way to increase HSCT efficiency. Patients who received MSCs compared to a control group which underwent only HSCT recovered noticeably faster [4].

Researchers in Brasilia concluded that a combination of non-myeloablative HSCT with a consolidation therapy of Mitoxantrone is proven safe and effective for use in patients with MS. This trial included 55 MS patients (32 RRMS, 13 SPMS, 9 PPMS and 1 PRMS). After re-evaluating the 26 months post-treatment, improvement was achieved in 58% of patients in the group with RRMS, stabilization in 42%. 82% of patients of progressive MS (PPMS, SPMS, RPMS) group demonstrated an improvement, 18% – stabilization of disease. Furthermore, there were no relapses during this whole follow-up [39].

The trials mentioned above prove that although combination therapies which include stem cells are still quite new, they nevertheless offer hope of a safe and effective way to improve patient outcomes [4].

DISCUSSION

We reviewed 45 publications to expound the progress of the stem cell therapy in multiple sclerosis. The literature search and analysis provided information on the basic stem cell biology, preclinical research and the development of new and innovative stem cell-based therapies in the period from 2010 to 2015. Heading of “multiple sclerosis” and its combination with “stem cell therapy” were the most common among the publications.

There is an exciting progress being made through innovative research of stem cells. Hematopoietic stem cell transplantation, or HSCT is a type of therapy that has been explored for many years in MS. There is more experience using HSCT in MS than any other cell therapy approach [42]. With the time, there has been a marked reduction in HSCT transplant-related mortality. The reduction in mortality can be attributed to the selection of patients with better performance status for HSCT, known to correlate with regimen related mortality, combined with improve-

ments in supportive care and the increasing experience of caring for MS patients at transplant centers [5]. Additional studies are needed to fully understand benefits and risks of HSCT in MS, and who might benefit most from this therapy [42].

MSC transplantation also shows great promise as a possible treatment for MS. Several pilot clinical trials in a small number of subjects with advanced MS have indicated that MSC administration is safe, and have provided clinical effectiveness. Current aim of clinicians and scientists interested in the development of MSC-based strategies for the treatment of MS is to have the ultimate demonstration in large clinical trials [45].

Another approach being explored involves using an individual's own cells, which are reprogrammed to turn them into stem cells. These cells are called "induced pluripotent stem cells" or iPSC. These cells as well as embryonic stem cells do not yet meet the safety and purity standards that would be needed for transplantation into patients. But they do give researchers a valuable opportunity to test the effects of potential new drugs and speed up the progress of drug development, as well as to investigate therapeutic mechanisms in order to develop more efficacious therapies [43].

Concerning stem cell therapy, there are many issues and limitations that need to be resolved. The specific cell stage to be transplanted, proper characterization of the cell type to be administered, dose, route of administration, duration of therapeutic effect and genomic stability of stem cells need further exploration and quantification [2]. Another future investigation area could be the role of cell therapy in relation to the use of approved disease-modifying therapies.

CONCLUSION

The amount of interest, both scientific and media, in stem cells as a way of handling multiple sclerosis (MS) is high and still rapidly growing. Although scientific research uncovers promising findings, there is still work to be done in order to prove the effectiveness and safety of the treatment for people with MS.

Currently, various types of stem cells are analysed in order to gain knowledge about the possibilities of using them in treating MS.

Despite the fact that embryonic stem cells (ESCs) are considered to be the most plastic and capable of producing the most diverse cell populations, due to ethical issues, national legislation limits and their potential to develop into tumours, usually they are used to identify and test potential drugs.

In the future, a way of replacing autologous stem cells for clinical applications could be derived from the emerging induced pluripotent stem cell (iPSC) field. This research area, which depends on the reprogramming of somatic cells, is growing quite speedily. Research with animals has already developed protocols that allow the directed differentiation of iPSC derived neural cells down particular lineages and have shown their functional capabilities. However, one has to bear in mind that such a technique has only recently been developed and is still under research.

Research nowadays has already proven that neural stem cells are the main remyelinating cells in the CNS following a demyelinating injury. Animal studies revealed the potentional of neural precursor cells (NPCs) to attenuate inflammation and promote CNS repair [13]. To obtain autologous NSCs a brain biopsy is required. The likelihood of brain biopsy on a neurologically impaired patient in order to obtain NSCs becoming a generalized practice is relatively low.

MS treatment sees some promising signs due to the use of stem-cell therapy, especially hematopoietic and mesenchymal stem cell transplantation. Progressive MS might be controlled by autologous HSCT. HSCT, when used to treat patients with aggressive highly active multiple sclerosis, can reduce or eliminate ongoing clinical relapses, halt further progression, and reduce the burden of disability. Given MSCT's positive potential on neural restoration and immunomodulation, MSCT offers a low risk/high reward treatment option for MS patients. Additionally, combined therapy of HSCT and MSCT could work synergistically to further decrease adverse side effects and increase patient outcomes [4].

Research carried out with stem cell transplantations provides positive results that are worth considering. What is more, they may not only suggest a viable treatment option with improved therapeutic benefit but also provide hope for further progress in MS treatment.

Conflict of interest

The authors state no conflicts of interest.

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GYDYMAS KAMIENINĖMIS LĄSTELĖMIS: NAUJAUSI PASIEKIMAI IR ATEITIES PERSPEKTYVOS

Santrauka

Įvadas. Išsėtinė sklerozė (IS) – lėtinė, autoimuninė, uždegiminė centrinės nervų sistemos (CNS) liga. Tai viena dažniausių jaunų suaugusiųjų netrauminį neurologinį neįgalumą sukeliančių priežasčių. Inovatyvaus išsėtinės sklerozės gydymo paieška yra aktuali ir plačiai aptarinėjama tema pasaulyje, ypač Europoje. Šiaurės Europos šalys, tarp jų ir Lietuva, priskiriamos didelio išsėtinės sklerozės paplitimo zonai. Nors dabartinis priešuždegiminis ir imunomoduliuojantis gydymas sumažina paūmėjimų dažnį bei jų sunkumą, gydymas nėra pakankamas progresuojančios ir agresyvios išsėtinės sklerozės eigos aveju. Šiame apžvalginiame straipsnyje aprašomi naujausi eksperimentiniai ir klinikiniai pasiekimai, taikant kamieninių ląstelių terapiją gydant išsėtinę sklerozę. Ši tema yra ypač aktuali, nes šiuo metu kamieninių ląstelių terapija, sergant IS, yra pradedama ir Lietuvoje.

Tiriamieji ir tyrimo metodai. Atlikta sisteminė literatūros apžvalga, naudojantis MEDLINE ir Cochrane library duomenų bazėmis. Apžvelgti straipsniai nuo 2010 iki 2015 metų, pagrindiniai terminai, naudoti paieškoje, – „išsėtinė sklerozė“ ir „kamieninės ląstelės“.

Rezultatai. Buvo išnagrinėtos 45 anglų kalba parašytos mokslinės publikacijos. Šioje literatūros apžvalgoje pateikiama informacija apie kamieninių ląstelių biologines savybes, atliktus ikiklinikinius tyrimus ir klinikinę praktiką, taikant gydymą kamieninėmis ląstelėmis.

Išvados. Daugiausia ikiklinikinių ir klinikinių tyrimų atliekama siekiant įvertinti kamieninių ląstelių terapijos galimybes, gydant išsėtinę sklerozę. Gydymas hematopoetinėmis ir mezenchiminėmis kamieninėmis ląstelėmis teikia daug vilčių, kadangi klinikiniuose tyrimuose matomas jo itin žemas rizikos ir aukštas efektyvumo lygis. Kombinuotos kamieninių ląstelių terapijos taikymas galėtų sumažinti nepageidaujamų poveikių kiekį ir pagerinti gydymo efektyvumą. Toks pats efektas tikėtinas kartu vartojant ligos eigą modifikuojančių vaistų ir kamieninių ląstelių derinį.

Raktažodžiai: išsėtinė sklerozė, kamieninės ląstelės, transplantacija, išsėtinės sklerozės gydymas.

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