REVIEW

Autologous Hematopoietic Stem Cell Transplantation as a Potential Treatment for Multiple Sclerosis Patients

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Abstract

Multiple Sclerosis is a severe autoimmune disorder in which the central nervous system is targeted, specifically the myelin sheath. Due to the neurodegeneration of the myelin sheath in both the brain and spinal cord, symptoms of numbness, lack of muscle coordination, and chronic fatigue are seen. Multiple Sclerosis has a devastating effect on the immune system as it causes an attack the body's own cells. Although there is currently no cure for MS, there are several treatment options available that work to improve the quality of life for affected individuals, including the use of various immunosuppressant drugs. Research suggests that there may be an alternative treatment plan which involves the use of an autologous Hematopoietic Stem Cell Transplant. Autologous HSCT has shown to halt the progression of the disease as well as reduce clinical relapses. However, it is yet to become a fully practiced procedure due to various safety concerns as well as the lack of a successful animal model. Further research on the use of autologous HSCT may help to treat Multiple Sclerosis in the future.

INTRODUCTION

Multiple Sclerosis is an aggressive autoimmune disorder that negatively affects the central nervous system (CNS). Autoimmune disorders are diseases in which the body's immune system attacks healthy cells resulting in a variety of symptoms. The defining trait of MS is the presence of demyelination areas, or MS lesions, in which an inflammatory response in the CNS is observed. Myelin is a substance that coats nerve fibers and allows for proper transmission of signals (Duncan et al. 2013). When myelin becomes damaged, nerves of the brain and spinal cord are unable to function properly, resulting in symptoms of numbness, impaired coordination, and cognitive fatigue. Cognitive fatigue is highly problematic for affected individuals as it decreases the ability to maintain task performance (Berard et al. 2014).

MS was first analyzed in great detail in 1863 by Jean-Martin Charcot, a professor at the University of Paris who is known as the "father of neurology." After analyzing the brain of a deceased woman who exhibited unusual tremors, he discovered the characteristic lesions or plaques now associated with MS. By the end of the 18th century and into the beginning of the 19th, physicians began to recognize MS as a specific disease and they made numerous discoveries. These discoveries included the various neurological symptoms that MS could produce, as well as the facts that women are impacted more often than men, and that the disease itself is not directly inherited. Neurological symptoms discovered included tremors, loss of motor coordination, and (in extreme cases) paralysis (Loren 2016).

Since the discovery of MS, advancements in the understanding of the disease have progressed. The attack on the CNS arises when various cells and proteins within the body's immune system leave the blood vessels serving the CNS and travel to the brain and spinal cord, ultimately destroying the myelin. These are the same cells and proteins that normally

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function in protecting and defending the body against infections. Although it is known that the myelin and their surrounding nerve fibers are the target in MS, much about the nature and the initial cause of the disease is still greatly unknown (Loren 2016).

Current MS treatments include various immunosuppressive drugs that modify the disease pathology. These disease modifying drugs are designed to slow the progression of MS through immune system suppression. With immune system suppression, the immune system cells are prevented from attacking the myelin surrounding the nerves. In addition to managing the disease pathology, immunosuppressive drugs also work to control symptoms and manage relapses. Through the combination of various immunosuppressive drugs, patients may experience an increase in their comfort and quality of life (National 2016). However, research suggests that there may be a more advanced treatment for MS that involves the use of stem cells.

Autologous (HSCT) is a procedure in which a patient's own (autologous) hematopoietic stem cells are intravenously extracted from the bone marrow and ultimately reintroduced to the patient in order to supply the body with a new population of healthy, normal functioning cells. Hematopoietic stem cells are self-renewing and have the ability to differentiate into specialized cells including blood and immune system cells (La Flamme et al. 2015). This procedure could be a promising treatment for MS patients as it allows for a potential "reset" of the damaging immune system cells. The use of autologous cells has also shown to decrease the risk of rejection following transplant.

This literature review article aims to explain the process of HSCT and how it can be used to treat patients suffering from MS. The immune-mediated CNS damage, degeneration of the myelin sheath, stages and symptoms of MS, as well as current treatment options will be discussed in detail. Lastly, this review article will explore HSCT and it's current limitations as well as hopes for the future.

IMMUNE-MEDIATED CNS DAMAGE

The CNS is a system comprised of the brain and spinal cord. Its complex of nerve tissues control the activities of the body. The CNS is known to be immune-privileged, meaning it is able to tolerate the introduction of antigens without issuing an inflammatory response. The CNS is one of the few systems in the body that accepts foreign tissue grafts quite readily. Unfortunately, due to this tolerance, it is known to be susceptible to autoimmune disease (Kierdorf et al. 2010).

The CNS contains a blood-brain barrier (BBB) that functions in the filtering of the capillaries that bring blood to the brain and the spinal cord tissue. This barrier is designed to block certain substances from crossing over. In the case of CNS-invading pathogens, **T lymphocytes** cross the BBB in order to fight infection. T lymphocytes are an important component of the adaptive immune system and are responsible for remembering and responding to specific antigenic targets. Naive T lymphocytes congregate in the lymph nodes where they are first exposed to antigens. The lymph nodes act as a training site for the naive T lymphocytes to learn to discriminate foreign antigens from self-antigens. The extent by which these lymphocytes seek out the lymph nodes is determined by the expression of the lymph node homing receptor, **L-selectin**. Following specialized training, these lymphocytes then become activated T memory lymphocytes that move throughout the body in search of their specific antigen. Activated T memory lymphocytes down-regulate L-selectin expression, thus losing their lymph-node seeking tendencies. In the search for their specific antigens, it is still partly unclear which T lymphocytes are able to pass the BBB into the CNS and why (Lehmann 1998).

T Lymphocytes: A lymphocyte formed in the bone marrow which matures in the Thymus gland in order to become an immunologically proficient cell

L-selectin: A cell adhesion molecule found on Lymphocytes

Neuroantigen-specific T lymphocytes are regularly found in everyone, including individuals with MS. Everyone also has myelin basic proteins (MPB). However, in cases of MS, the T lymphocytes attack the MBP which is the most frequently targeted antigen in the CNS. This attack is what initiates MS. Using MBP-specific T lymphocyte receptor transgenic mice, Bauer et al. (1998) suggested that these T lymphocytes normally ignore the autoantigen and do not cause an immune response. However, some of these neural antigen-specific T lymphocytes responded to the autoantigen, thus inducing an immune response characterized by localized inflammation of the myelin. Bauer et al. (1998) sought to understand what made these T lymphocytes respond to the same autoantigen ignored by other T lymphocytes with the same specificity. In order to better understand this process, more studies on T lymphocytes that cross the BBB and which T lymphocytes mediate MS need to be conducted (Lehmann 1998).

The first animal model to represent MS is Experimental Allergic Encephalomyelitis (EAE) in rodents. EAE is the result of an autoimmune attack by T Lymphocytes on the CNS. The disease is triggered by the immunization with a CNS antigen or by in vitro injection of activated CNS antigen-specific T lymphocytes. Following the peak of the disease, the inflammatory T lymphocytes that crossed the BBB consisted of auto-reactive and irrelevant antigen-specific T lymphocytes. This is a puzzling discovery because it does not adhere to the rules that govern the entry of these lymphocytes into the CNS tissue. Once these cells had located their antigen, they attacked until the antigen was completely destroyed. This properly illustrates the progression of MS as an autoimmune disease (Lehmann 1998).

The interesting aspect of EAE is that most of the rodents made a full recovery from the disease before they experienced a relapse. It is hypothesized that the T lymphocytes become overworked and eventually die through apoptosis. The T lymphocytes that survive, however, proliferate and give rise to a new population. The problematic T lymphocytes that are able to cross the BBB are said to recruit the irrelevant antigen-specific T lymphocytes due to the inflammation they cause. This response is highly destructive and leads to a pro inflammatory cytokine response, resulting in the damage of the myelin sheath at lesion sites (Lehmann 1998).

DEGENERATION OF THE MYELIN SHEATH

The specific damage resulting from MS is to the myelin sheath, which normally functions as the protective covering on neurons in the brain, spinal cord, and optic nerves within the CNS (Grigoriadis et al. 2015). The insulation of the nerve fibers by the myelin sheath is essential in order for nerves to conduct electricity and transmit signals from the brain and spinal cord to the rest of the body. When this insulation is degraded and damaged, the myelin sheath is considered demyelinated and the sites of damage are termed MS lesions. The colossal damage is caused by excessive inflammation due to the release of **pro-inflammatory cytokines** from autoimmune MBP specific T lymphocytes. Due to the release of pro-inflammatory cytokines, other immune system cells, including naive T lymphocytes, are able to cross the BBB (Lehmann 1998). They then congregate at the MS lesion sites and assist in the attack of the body's own tissues. The demyelination results in a lower rate of action potential, or nerve conduction, and leads to the characteristic symptoms of numbness as well as loss of coordination and cognitive ability in MS patients (Bo et al. 2013).

Pro-inflammatory cytokine: Cytokines that initiate systemic inflammation

STAGES AND SYMPTOMS OF MS

The stages of MS are as follows: Relapse-remitting (RR-MS), secondary-progressive (SP-MS), and primary-progressive (PP-MS) (National 2016). RR-MS occurs in 80% of individuals who initially develop the disease. This stage of MS is categorized by an asymptomatic period followed by relapses of new symptoms. About 50% of patients with RR-MS will develop SP-MS which is categorized by a steady progression of the disease as well as steady deterioration of the myelin sheath. PP-MS is the most severe stage and occurs in 10-15% of MS patients. This stage, which is characterized by rapid progression of the disease, occurs after the disease's onset (National 2016).

Due to the multiple stages of MS, severity of the disease as well as associated symptoms varies from patient to patient. A few of the potential symptoms associated with the disease are decreased motor coordination, muscle fatigue, cognitive ability, numbness, and partial or total paralysis. The symptoms and signs that a patient will display are directly correlated with the sites at which the MS lesions have developed within the CNS. Early in the course of the disease, patients will generally display lesion distribution limited to one or two regions. After many years, however, lesions may become widely distributed throughout the CNS and therefore produce more extreme symptoms such as paralysis (La Flamme et al. 2015).

CURRENT TREATMENT OPTIONS

Current treatment of MS works to reduce nerve inflammation, reduce fatigue, and increase muscle activity. First-line drugs Interferon β (IFN-β) and Glatiramer Acetate are used in order to inhibit the immune system's attack on its own cells (King 2011). These first-line drugs are given via injection under the skin or into the muscle and aim to reduce the severity of relapses. Several oral medications (Table 1) are also used in order to manage the course of the disease.

TABLE 1: The most common oral medications used in the treatment of patients with Relapse-Remitting Multiple Sclerosis. Adapted from Mayo (2016).

Treatment Option for RR-MS	Mechanism of Action	Potential Side-Effects
Tecfidera	Reduces Relapses	Diarrhea, nausea, lowered white blood cell count
Gilenya	Reduces Relapses	Headache, high blood pressure, blurred vision
Aubagio	Reduces Relapses	Linked to liver damage and hair loss
Tysabri	Blocks damaging immune cells from entering the bloodstream to the brain and spinal cord	Increased risk of viral infection of the brain
Lemtrada	Targets proteins on the surface of immune cells in order to reduce relapses	Increased risk of infections and autoimmune diseases
Mitoxantrone	Last resort medication for patients with severe, advanced MS	Harmful to the heart and linked to the development of various blood cancers

Due to disease unpredictability from patient to patient, careful consideration of medication choice is crucial. Medications will not affect every patient in the same way. Several immunosuppressive drugs have been shown to produce unfavorable side effects. Injected medications, such as the first-line drugs, have been shown to produce flu-like symptoms as well as a reaction at the site of injection. A major concern with these drugs in MS treatment is that the efficacy of the medication is unclear. Many of the disease modifying medications have little impact on how a patient feels day to day. This lack of apparent impact could mean that the medication is, in fact, succeeding in its efforts to manage the disease. However, it could also mean the symptoms are not being managed. Many patients suffering from un-alleviated symptoms begin to lose confidence in medications and fail to take their doses correctly. This results in a bigger problem; no drug is effective if patients do not take it (King 2011).

Melissa Losasso, a MS patient of twelve years, described her experience with the first-line injected medications as anything but satisfactory. She, like others, experienced excruciating side effects: "I would start to become agitated and depressed long before I needed to take it. I would sit holding the needle for 30 minutes or more trying to make myself inject, knowing I was going to have body aches, fever and pain within hours. Mentally, I was wearing down, angry at my disease and angry with myself for putting my family through this." (King 2011)

Much research is currently being conducted on the production of new drugs and therapies for individuals suffering from resistance to current drugs. There is a need for a new therapy that targets MS's neurodegenerative components, rather than only suppressing the immune system (Lutz 2014). Part of MS research is going into an entirely new approach to treating the disease. This new approach focuses on whether there is a way to rid the body of the damaging MBP specific T lymphocytes exhibited in MS. For patients with severe MS who are unresponsive to immunosuppressive drugs, the use of autologous HSCT proves to be a step in the right direction.

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

Autologous (HSCT) involves an intravenous infusion with a patient's own cells in order re-establish function of the damaging cells present in the patient. This is a way to perhaps "reset" the patient's immune system. HSC are adult stem cells that are able to differentiate and are found in most self-renewing tissues (Abrahamsson et al. 2013). Hematopoietic cells are extracted from the bone marrow and cryopreserved in liquid nitrogen while the patient undergoes aggressive chemotherapy or radiation to completely destroy the damaging lymphocytes (Hohlfeld 2002). One or more chemotherapy drugs or immune-depleting agents are used in order to destroy the auto-reactive T lymphocytes. Following chemotherapy and/or radiation, the autologous HSC graft is thawed and then reintroduced into the body to replace the destroyed lymphocytes and to rebuild blood cells (Atkins et al. 2013). The goal is to introduce new blood cells that will begin to function normally in the immune system. A diagram outlining the autologous HSCT procedure is shown in Figure 1.

Research suggests that the use of autologous HSCT is beneficial because it reduces the severity of a patient's relapses. Additionally, by using the patient's own cells, it greatly minimizes the risk of rejection (MacNeil 2004). Autologous HSCT also provides a way to repair the immune system rather than suppress it (Atkins et al. 2013). Few HSCT clinical studies have been performed, as the procedure is intense and there are many ethical and safety concerns.

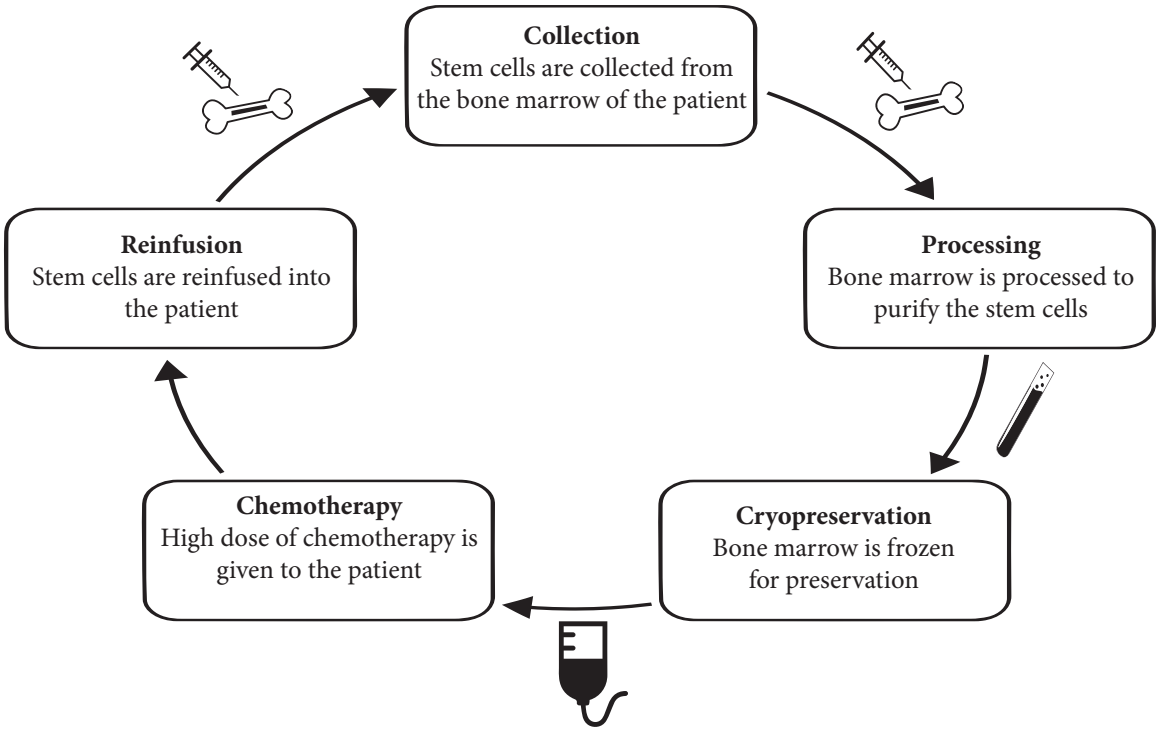

FIGURE 1: Illustration of Autologous Hematopoietic Stem Cell Transplantation. Adapted from Barts & The London (2014).

One set of researchers who have performed a clinical trial of autologous HSCT on patients are from the University of Ottawa (Macneil 2004). Their study consisted of patients 26 to 40 years old, who had been diagnosed with RP-MS within 83 months of the trial. Additionally, none of these patients had responded to interferon therapy, the usual first-line drugs. Patients were treated with immune ablation followed by autologous HSCT. The purpose of the immune ablation was to disarm MS by depleting the patient's immune system cells, specifically the autoimmune MBP specific T lymphocytes. Autologous HSCT was done thereafter in order to ultimately rebuild a new immune system with stem cells that have no immune memory. The hope was that these cells would not be auto-reactive (Macneil 2004).

The patient's stem cells were harvested from their bone marrow after mobilization and then purified and re-infused into the body. Patients were hospitalized on average 26.5 days, and their average platelet recovery time was 9.5 days*. Side effects of the treatment were the typical effects of toxicity following a stem cell transplant. Hepatic toxicity, perhaps the most common following stem cell transplantation, only occurred in one patient and was only early-stage toxicity. MRIs were taken, and the MS lesions appeared to be getting better over time, suggesting that the procedure halted the progression of the disease (MacNeil 2004).

Although this clinical study yielded several positive results, the mechanism of action of autologous HSCT is still greatly unknown. One of the patients passed away 72 days after the treatment, due to regimen-related **Veno-Occlusive disease** of the liver. Due to this, the trial was stopped. There are many safety concerns surrounding the use of this treatment because of its intensity. It was found that the patients' immune systems rebuilt at a slow pace, taking more than a year. Drawbacks of this clinical study included its small sample

Veno-Occlusive disease: A condition resulting in the obstruction of veins within the liver. A complication in patients undergoing hematopoietic cell transplantation

* All patients had experienced a relapse during a 24 month time frame before undergoing the trial. However, zero patients reported having a relapse or drastic side effects in any of the 12-30 month follow ups

size. Dr. Atkins, the lead researcher, hopes to conduct more trials but more research must first study the effects of stem cell transplantation (MacNeil 2004).

Although the use of autologous HSCT appears to have promising benefits to patients, many variables must be considered before it becomes a standardized procedure. Among these variables are safety, ethics, and patient selectivity. Autologous HSCT is an aggressive, multi step therapeutic procedure that is typically only suggested for patients with very severe forms of MS who are refractory to conventional MS therapies (Atkins et al. 2013). Patients with these severe forms have been found to be more motivated to accept such an aggressive treatment (Guimaraes et al. 2010). Additionally, patients must be experiencing active inflammation in order to be a candidate for autologous HSCT. Research has shown that without active inflammation, there will be no response following treatment (Burt et al. 2012). Although transplantation displays a low percentage of fatal complications, is it still hard to take safety issues lightly. These safety issues stem from not fully understanding the mechanism of differentiating cells and their effect on the body (Silani et al. 2008).

One of the setbacks to autologous HSCT is that only a few studies have monitored auto-reactive T lymphocytes following the treatment. In the animal model (EAE) using ablative therapy and transplantation was able to clear auto-reactive T lymphocytes from the CNS in a short 3 weeks. MS patients who were followed after transplantation showed suppression of the MBP auto-reactive T lymphocytes for at least 20 months. Interestingly enough, some of these cells were able to respond differently to the myelin antigen, suggesting possible mutation. It is widely unknown how these cells are able to differentiate following transplantation. In order to overcome this discovery, DNA labeling of stem cells in the autologous graft has been suggested. The goal is to be able to differentiate physiological from pathogenic auto-reactive cells. Studying the T lymphocyte grafts of patients whose transplantation failed may make the differentiation clear (Openshaw et al. 2002).

The development of a second autoimmune disease following transplantation, or worsening of the current one, is another major safety concern with this treatment. In few rare cases, patients with MS undergoing transplantation developed myelitis with MRI-viewed abnormalities of demyelination. It was found that these complications could be brought on by Cyclosporin, which is given early after transplantation (Openshaw et al. 2002).

Patients with autoimmune disorders such as MS, Systemic Sclerosis, Systemic Lupus, Erythematosus, and Rheumatoid Arthritis must meet eligibility requirements in order to go through with transplantation. Criteria is based on the severity and progression of the disease despite current treatments and therapies. In the case of MS, the expanded disability status scale (EDSS) is used in order to determine eligibility. MRIs are used frequently to measure disease activity and MS lesions. The more severe a patient's condition is, the more likely they will meet the requirements for transplantation (Openshaw et al. 2002).

Due to the fact that all autoimmune disorders differ from each other, results of autologous HSCT differ from one disorder to the next. Patients with Systemic Lupus Erythematosus or Systemic Sclerosis have a high risk of mortality from their disease with or without autologous HSCT. This is not the case in MS. The mortality rate of 85 patients following autologous HSCT was 8%. However, it is difficult to evaluate the few clinical trials that have been done because follow ups are still short and the disease itself is quite difficult to predict (Openshaw et al. 2002).

EAE has greatly advanced research for treatment. However, it has not successfully shown that the inflammation caused by MS will cease following the removal of damaging MBP auto-reactive T lymphocytes. As previously stated, more studies need to be conducted on these T lymphocytes that cross the BBB, and which T lymphocytes mediate MS. Further research in this animal model will help to implement the use of autologous HSCT

as treatment for patients with aggressive MS (Openshaw et al. 2002). Overall, increasing knowledge and experience on the use of autologous HSCT will help to yield less toxic ways of repairing the immune system, thus moving closer to the application of this potential treatment (Atkins et al. 2013).

DISCUSSION / CONCLUSION

Multiple Sclerosis is a severe auto-immune disorder that attacks the myelin sheath of the central nervous system. The attack on the myelin is due to immune system cells, T-lymphocytes, being unable to recognize self antigen. These cells cross the BBB of the CNS and begin attacking the body's healthy cells. The damage done to the myelin and the nerves results in highly unfavorable symptoms of disease. Current and widespread treatment of MS include the use of immunosuppressant drugs, with hope of decreasing the inflammation caused by the over-reaction of the immune system.

MS is known to be unpredictable and highly variable between patients. In the case of severe and advanced MS, the body becomes unaffected by the use of immunosuppressants. Research suggests that the use of autologous HSCT may greatly benefit patients with these severe forms. It has been concluded that this treatment induces a long lasting suppression of inflammation, but whether or not it is effective in managing the course of the disease is still unknown. More research is currently being conducted in this field as several factors, such as the safety of the patient and the ethics behind the procedure, need to be taken into consideration. Future goals aim to improve patient safety by gaining experience using more sophisticated strategies, and further conducting clinical experiments. Advancements in EAE need to be made in order to further understand the mechanism of action in MS.

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BIOGRAPHY

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