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How Does Graft Versus Host Disease React to the Heart, Lungs, and Liver After an Allogeneic Stem Cell Transplant?

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Abstract

E. Donnall Thomas performed the first allogeneic transplantation in 1957. Since then, the field has grown and evolved all around the world. Allogeneic transplantation has become much more accessible thanks to the utilization of matched unrelated donors, umbilical cord blood units, and partially matched related donors. (Henig I. et al, 2014) Research in stem cells has helped doctors and scientists increase their understanding of how disease occurs, the process behind regenerative medicine, and testing drugs for safety. Over a million individuals have benefited from stem cell transplants for the treatment of leukemias, anemias, and immunodeficiencies around the world. (Dulak J. et al, 2015) On the other hand, disease relapse and graft-versus-host disease remain to be the two leading causes of death. (Henig I. et al, 2014) In this systematic review, the effects of graft-vs-host-disease were looked at and how it affected the heart, lungs and liver. When an allogenic transplant occurs there is a chance for the body's tissues to view the donor tissues as foreign and attack them. The body is a complex and intricate system, when tissues are fighting off what they perceive as threats, at the same time it is harming other organs. (n=26) sources were evaluated and used to assess these effects.

Keywords: graft-versus-host-disease, allogenic, stem cell, organs

Introduction

Stem cells, in simple terms, are the body's raw materials. All cells with specialized roles are created from stem cells, which are the body's basic resources. When stem cells are given the correct conditions in the body or lab, they can multiply and produce daughter cells. The new daughter cells that are made can either become new stem cells or for more specialized cells, ones with specific functions. These include brain cells, blood cells, heart muscle cells or bone cells. Stem cells are the only cells in the body with the ability to generate new types of cells. (Dulak J. et al, 2015) Stem cells can originate from different places, three of the main sources are embryonic stem cells, adult stem cells, and perinatal stem cells. Pluripotent stem cells, also known as embryonic stem cells, come from embryos that are three to five days old. These types of cells can become a type of cell in the body or divide into more stem cells. Most adult tissues, such as bone marrow and fat, contain a limited amount of adult stem cells. They are more limited to various cells of the body. Adult stem cells can create bone or heart muscle cells as well as blood cells. Perinatal stem cells have been found in amniotic fluid and umbilical cord blood, these cells can specialize

into other types of cells. (American Cancer Society, 2021).

Autologous and Allogeneic Stem Cell Transplant

There are two main methods of stem cell transplant: autologous transplant and allogeneic transplant. Autologous transplant uses cells from the body and allogeneic transplants use cells from a donor. In an autologous transplant, high doses of chemotherapy or radiation are given after stem cells are removed. Once that happens, stem cells are put back in the body to make normal blood cells, also known as rescue transplants. (The Mayo Clinic, 2020) An allogeneic transplant is similar, but instead, the stem cells are donated from a healthy person, the donor. After high-intensity chemotherapy or radiation — a conditioning treatment — donated stem cells from either a related or an unrelated donor are transplanted into the recipient. The conditioning treatment is used to kill any cancer cells that remain in the body, weakening the patient's immune system and allowing the body to reject the donor cells following the transplant. It also enables donor cells to travel via the bloodstream to the bone marrow, where they will begin to grow and generate new blood cells such as red blood cells, platelets, and white blood cells. Engraftment is the term for this procedure. (Leukemia and Lymphoma Society, 2021) When a transplant is successful, donor stem cells can take the place of bone marrow stem cells. It could also possibly be the patient's only hope for a long-term cure. One of the advantages of allogeneic stem cell transplantation is that the given cells form a new immune system when they engraft in the recipient's body. White blood cells are produced by the donor cells, fighting off any cancer cells left in the patient's body. This process is known as the "graft-versus-tumour effect," a process important as the conditioning treatment used to kill cancer cells. (Leukemia and Lymphoma Society, 2021)

Graft-versus-host-disease

In the case of an allogeneic transplant, the body may be susceptible to graft-versus-host disease (GVHD). (The Mayo Clinic, 2021) This develops when the new immune system's donor stem cells perceive the body's tissues and organs as foreign and attack them. (Graft-versus-host disease, 2021) “The recipient’s immune system has mostly been destroyed by a conditioning treatment and cannot fight back, so the new stem cells make up most of the immune system after transplant.” (American Cancer Society, 2021) GVHD can arise at any point following a transplant. The risk of GVHD is slightly higher if the stem cells originated from an unrelated donor, but it can happen to anyone who has a bone marrow transplant from a donor. (The Mayo Clinic, 2021) The chance of GVHD developing is “around 35% to 45% when the donor and recipient are related and 60% to 80% when the donor and recipient are not related.” (Graft-versus-host disease, 2020) There are two types of GVHD: acute and chronic. Acute GVHD usually develops in the first few months after a donation, affecting the skin, digestive system, or liver. Chronic GVHD appears later in life and can affect many organs. Joint or muscle discomfort, shortness of breath, persistent cough are some symptoms of chronic GVHD. (The Mayo Clinic, 2019) Acute GVHD is characterized by inflammation, whereas chronic GVHD is characterized by autoimmune symptoms. (Rai V. et al, 2016)

How graft-versus-host-disease affects the human organs

A stem cell transplant can affect the body in different ways, both emotionally: depression, stress, and anxiety, and physically: fatigue, pain, hair loss, and infertility. To date, the heart has rarely been a target for GVHD, affecting mostly the mouth, joints, liver, eyes, gastrointestinal tract, and lungs. Several people with acute or chronic GVHD have developed bradycardia, coronary artery disease, or cardiac myolysis and have been reported. These symptoms ranged in severity from asymptomatic to deadly. Although these cardiac symptoms are unusual, they are crucial to detect since they may indicate GVHD

activity and may be reversible. (Rackley C. et al, 2005)

Chronic GVHD of the lungs develops when the donor's cells attack the tiny airways in the lungs. Lungs may become inflamed (red and swollen) and scarred as a result of this. Scarred lungs are no longer thin and lacey, instead, they are thick and stiff. (American Lung Association, 2016). The lungs stop working properly and shortness of breath is very common. It is likely that exercise or engaging in strenuous physical activity gets harder, resulting in coughing, chest tightness, or the inability to take a deep breath. With chronic GVHD there is an increased risk of lung infections. Early stages of chronic GVHD of the lungs are harder to detect, PFTs (pulmonary function tests) are the only tests that can find chronic GVHD of the lungs in earlier stages. (Fast Facts - GVHD of the Lungs, 2021) Infectious and non-infectious pulmonary problems affect 40 percent to 60 percent of all BMT recipients, resulting in significant morbidity and mortality. (Khurshid I. et al, 2002)

Another one of the major organs that are affected by graft-versus-host-disease is the liver. Chronic GVHD of the liver frequently manifests as "indolent cholestatic illness" in patients with skin, mouth, and eye involvement. Hepatic GVHD can be difficult to identify from other conditions such as infection and drug-induced liver injury in some circumstances. The combined effects of pretransplant chemoradiotherapy, immunotherapy, GVHD prevention, and infection, commonly complicate clinical indications and symptoms. As a result, it's often critical to pay attention to and link clinical observations and laboratory data while making a diagnosis. (Karen E. et al, 2016)

Methods

When reviewing data for this research analysis, a series of search engines were used to support the findings. These included PubMed, Postgraduate Medical Journal, Mayo Clinic, MedlinePlus Medical Encyclopedia, and the National Center for Biotechnology Information. To find more relevant information, keywords such as ‘graft-vs-host-disease,’ ‘stem cells,’ allogenic,’ and ‘organs’ were used. When put through Pubmed, (n=669) related searches were found, of these searches (n=13) were screened and (n=6) were used in the final paper. The Postgraduate Medical Journal showed (n=14) results, (n=6) were further looked into and (n=1) was used. MedlinePlus Medical Encyclopedia gave (n=151) results, from here (n=25) were reviewed and (n=2) were used. The National Center for Biotechnology Information generated (n=1088,) (n=33) were reviewed and (n=6) were used in the final paper. Mayo Clinic showed (n=46) results, (n=6) were screened and (n=2) were used. Other than the five main search engines (PubMed, Postgraduate Medical Journal, Mayo Clinic, MedlinePlus Medical Encyclopedia, and the National Center for Biotechnology Information) other smaller independent sources were used. These were used to add clarification to the paper and have more detail. (n=8) sources were from independent sources such as sciencedirect.com, the European Respiratory Journal, cancer.org and more.

The sources that were used were focused on allogeneic transplants. Leaving the spectrum to include all types of stem cell transplant, allogeneic, autologous, and umbilical cord blood transplant, the searches were coming up broad and did not entail enough detail relating to the topic. Many of the studies that were screened were eliminated because of the sample size being too small — less than ten people— or because some of them were performed on animals, such as rats and mice. Since the focus was how graft-versus-host-disease affected human organs those sources were excluded.

Of the (n=83) sources that were screened, the ones excluded (n=23) were because of the date they were published (older than 20 years,) checking if there was a substantial amount of information and making sure there were solutions

and discussions included. The sources that were screened and eliminated, were due to the fact that the information was generalized and wasn't giving specific information. Though one source from the Mayo Clinic was used even though the specificity of the type of stem cell transplant wasn't included. This source was included because it worked as a good base and provided key facts for the paper. Next, the (n=60) sources that were included in the second screening were all put into a spreadsheet and were skimmed to see the author's credibility, sources used, and relevance to the topic. The (n=26) that were used in the final search was determined by reading the abstract of the paper and/or the conclusion. Here several were eliminated again because they were either too broad or didn't provide the relevant information. Oftentimes, instead of talking about an allogenic transplant, they would discuss the effect of GVHD from an autologous transplant, or it would go into detail about how to help cope with it and not the chronic effects. The credibility of the author and publisher were also both taken into account during this process. In the spreadsheet, other than having just the title of the source and a citation, some jot notes were taken below it to have an easy visual of what information was on each website.

Results

a study was performed at the Erciyes University Medical Faculty from May 2008 through June 2010. In this study, they looked at and studied the "Cardiac Effects of Chronic Graft-versus-Host Disease after Stem Cell Transplantation." This analysis included 40 patients who had received bone marrow transplantation: 14 with chronic GVHD and 26 without. Before bone marrow transplantation, all patients had baseline echocardiograms and were closely monitored. Following the estimated time for GVHD after transplantation had passed — 100 days — these patients were split into two groups based on whether they developed chronic GVHD. It was found that chronic GVHD is linked to an increase in left ventricular mass and deterioration in left ventricular diastolic function in patients. In addition, it demonstrated that in these patients, inflammatory markers rose to higher levels. Inflammatory markers such as C-reactive protein (a protein made by the liver), erythrocyte sedimentation rate (type of blood test that measures how quickly red blood cells settle at the bottom of a test tube), and plasma viscosity (a measurement of the amount of protein in the blood's liquid portion) are frequently used in primary care to diagnose and monitor inflammatory illnesses such as infections, autoimmune diseases, and cancerous growth. (Dogan A. et al, 2013)

In 2014 a study was conducted by the European Respiratory Society looking at "Pulmonary graft-versus-host disease (GVHD) post stem cell transplant." Serial pulmonary function tests were performed on patients having stem cell transplantation for hematological malignancies, cancers that affected the blood, bone marrow, and lymph nodes. A high-resolution CT scan was used to investigate symptoms of increasing breathlessness or a decline in pulmonary function. Adjuvant chemotherapy was given to six patients, and complete body radiation was given to seven others. Breathlessness worsened in 10 of the participants. Within a year of their stem cell transplant, three people experienced pulmonary GVHD. (Jayaraman B. et al, 2012) Graft-versus-host disease was discovered to target the small airways in the lungs, causing them to become inflamed, red, and swollen, scarring them. (Fast Facts - GVHD of the Lungs, 2021)

In 2000, a study was conducted looking at the liver condition of 130 patients before and after bone marrow transplants at the Catholic Hematopoietic Stem Cell Transplantation Center. Liver dysfunction occurred in 85 of the 130 patients. GVHD and medication hepatotoxicity were the leading causes of allogeneic bone marrow transplant failure. Before the transplant, 18 out of 130 patients, 13.8%, had abnormal liver function tests. These patients showed no higher

risk of post-transplant liver dysfunction, GVHD, or death as compared to patients who had normal liver function tests prior to their transplant. (Kim B. et al, 2000) Hepatic graft-versus-host disease is a common complication following bone marrow transplantation that commonly leads to death. When dealing with this type of scenario, a liver biopsy is necessary to confirm the diagnosis in patients of liver impairment that developed within 100 days of transplantation. To avoid chronic GVHD in patients with acute hepatic GVHD, substantial immunosuppression is required. (Chiba T. et al, 2005)

Conclusions and Discussions

The goal of this systematic review was to assess the effects of graft versus host disease on the three main human organs. The effect GVHD had on the heart, lungs, and liver after an allogeneic stem cell transplant were evaluated through (n=26) sources. Cardiac effects of GVHD are seen to be rare as compared to the effects of it on an organ like the lungs, but after the study in 2010 by the Erciyes University Medical Faculty, it has been proved crucial to detect since they may indicate irreversible effects. When fourteen out of forty people developed chronic GVHD, long-lasting effects were shown in the heart. (Dogan A. et al, 2013) Left ventricular mass was increased, which oftentimes is an indicator of death and heart failure caused by coronary artery disease. (Greater left ventricular mass increases the risk of heart failure, 2019) Diastolic function was damaged in the left ventricle which has been linked to mortality, heart failure, and hospitalization. (Sherif F. et al, 2020) As well as inflammatory markers rising post GVHD in the heart and it can cause a number of things, ranging from infection to cancer. High C- reactive protein was also found and signals inflammation in the heart's arteries which may lead to an increased risk of a heart attack. Through these three main effects on the heart, it can be seen that even though it may be uncommon for there to be cardiac effects, it is important to monitor any changes that occur in the body, which may lead to something much more full scale and fatal.

When looking at the respiratory effects of GVHD, a study conducted in 2014 by the European Respiratory Society, it was seen that small airways were targeted, inflaming them and making them red and swollen. Breathlessness worsened and rigorous physical activity was also harder than usual for most. Small tasks like breathing may be subconscious but are one of the most important functions of the body. (Jayaraman B. et al, 2012) Having identified the effects of GVHD on the lungs can change a patient's lifestyle and could make the most significant difference.

Hepatic effects of GVHD were shown as high serum aminotransferase levels (“the most common causes of elevated transaminase levels are nonalcoholic fatty liver disease and alcoholic liver disease.”) (Oh R. et al, 2017) reflecting severe viral hepatitis. Tests revealed damaged and degenerative small bile ducts, typical with GVHD. (Strasser S. et al, 2000) The liver being a very important organ of the body, identifying the effects it has on the liver after an allogeneic transplant is vital to the patients’ health. It was shown that with progressive cholestatic symptoms there was evidence towards loss of tiny bile ducts and portal fibrosis in situations where the diagnosis was not made and therapy was delayed. (Strasser S. et al, 2000)

After assessing all the potential risks of getting an allogeneic stem cell transplant the question comes up of whether or not the transplant is more or less favourable. Looking through the data and findings, an autologous transplant looks like a much better option. If an individual isn’t getting donor stem cells, then the risk of getting GVHD wouldn’t even be present. Keep in mind however that everything has a positive and negative side. In the scenario that an individual is getting an autologous transplant, there isn’t the risk of GVHD but there is still the chance that the problem is reduced but not eliminated or for it to work as a

combination of therapies. Looking on the opposite side, in an allogeneic transplant even though there is the risk of GVHD there is still the complete replacement of host cells with donor cells and elimination of reservoirs for the disease. Whether or not to get an allogenic transplant would differ from person to person. The best way to see which type of transplant would work best, it would be essential to look at what is important to the individual and take into account their unique scenario. Oftentimes, allogeneic transplants are preferable for those who are at risk of relapse and who can take medication to prevent GVHD. While an autologous transplant might be a better option if the body is producing enough healthy bone marrow cells for the transplant to be successful.

The future of medicine is very bright, by just looking at the past hundred years there have been countless discoveries in medicine, hepatitis C treatment, updated cystic fibrosis treatment, 'smart' defibrillators, and more. The transplant of organs and how the rest of the body reacts is an important topic that warrants more research. In the future, I think it would be important to see if GVHD is somehow avoidable. The current strategies for preventing acute GVHD are very effective. Chronic GVHD, on the other hand, is less understood and more difficult to prevent. Could we possibly re-code our immune system to not see donor cells as a threat without compromising the immunologic benefits? This would need to be heavily considered and looked more into with regards to how it could affect people in the long term, — genetic mutations can lead to many disorders and illnesses so that would have to be taken into consideration — and with discussions of ethical problems. In regards to ethics, there are many points to look at, safety, justice and equity where it can be argued that it will only be accessible to the wealthy, and religious objections. The importance of this topic can be seen through this paper, further proving that additional research will greatly benefit the field of regenerative medicine and make it will be very worthwhile in the future.

Limitations

While writing this research paper the focus was the effect of graft-versus-host-disease on the three main organs, focusing on three organs limited the reader from getting an in-depth view of the effects. While I was looking at the general effect of the disease alternatively by looking at just one specific organ there would have been more information about the signs and symptoms, effects, and how it changes someone's lifestyle. Larger sample size could have also been evaluated. Having more people as well as age, race, gender, would have helped in getting a broader view and a more accurate conclusion. There were also a limited number of sources that were accessible, many had a subscription fee or required identification. Having these financial resources and extra aid also would have helped in broadening the search and getting more accurate and in-depth results.

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