Apr 20th, 2:00 PM - 3:00 PM

Medical Advantages of Allogeneic vs Autologous Stem Cell Transplants as Treatment in Blood Related Cancer Patients

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11/1/17

Abstract

Stem cell transplants have become common treatment for certain types of cancer including multiple myeloma and acute lymphoblastic leukemia. There are two types of stem cells that are derived from different places. Autologous stem cells are taken from the body of a sick patient and put back into the same patient after treatment. Allogeneic stem cells come from a donor and are given to a person who is sick as treatment. The main focus of this paper is to analyze the two different type of stem cell treatments and to determine which one is a more effective method in treating patients with blood related cancers.

The biggest risks associated with autologous stem cell transplant are rejection of the cells and reinjecting cancer cells back into the patient if the extracted stem cells were not properly purged. The biggest risk associated with allogeneic stem cell transplant are rejection of the new stem cells and infection from them. There have been more benefits associated with allogeneic stem cells because of their ability to potentially fight off the disease. This phenomena is known as the graft vs. cancer effect, it is when the immune system cells from the donor work to kill the cancer in the recipient. The autologous stem cells can prolong someone's life but cannot keep the cancer from coming back. Allogeneic stem cells have more risks associate with them, however the benefits outweigh the risk making this the more efficient stem cell treatment.

Introduction

Stem cells have been at the heart of many controversies over the years about whether or not they should be used in medical treatments. The controversy comes in deciding where and or who the stem cells should be allowed to come from (Nisbet 2003). Despite a lot of controversy there have been major advances in stem cell research that have led to using certain types of stem

cells as treatment for numerous different diseases. The two most commonly used types of stem cells for cancer treatments are autologous and allogeneic stem cells. There are distinct differences between the two kinds of stem cell. Autologous stem cells that are being transplanted come from the same person that is receiving the stem cells, meaning that they are your own stem cells. Allogeneic stem cells are transplanted from one person to another person, so they are not your own cells (Shustov 2013).

Allogeneic and autologous stem cells are defined by where they come from. Therefore there are different major sources of the stem cells for each type. Allogeneic comes from a donor. Good sources of these stem cells for transplants in children and young adults are from placenta or umbilical cord blood. Full grown adults that need an allogeneic stem cells are usually taken from the donor's bone marrow (Gratwohl 2009). Autologous comes from the patient them self. The patient has their blood drawn and the stem cells are harvested from the blood. This is done prior to any type of treatment. The stem cells could also be taken from the bone marrow (The Leukemia & Lymphoma Society 2015). There is little ethical debate around if stem cells that can be harvested from an adult should be used as medical treatment. There is little ethical debate because these stem cells are not causing harm to the donor when they are harvested. This is different from using embryonic stem cells because when those are harvested the embryo dies. As long as both the donor and the recipient have given informed consent it is perfectly acceptable to use these stem cells (Kitzinger & Williams 2005).

Autologous stem cells are usually used to treat certain types of leukemia and myelomas. Allogeneic stem cells are usually used to treat types of leukemia, lymphomas, and myelomas (American Cancer Society 2016). Both of the stem cells are used to treat similar types of cancer which is why it is imperative to determine which one will produce the most favorable outcomes.

As previously stated currently the most common usage of stem cell therapy is using them to treat certain types of cancer. Multiple myeloma is an example of a type of cancer that can be treated with a stem cell transplantation. Multiple myeloma is formed by malignant plasma cells, which are found in the bone marrow. The most commonly reported symptoms of this disease are pain, fatigue, constipation, and tingling in the hands and feet (Ramsenthaler et. al 2016).

Treatment for multiple myeloma includes autologous stem cell transplants, which lengthens the patient's life, but isn't effective in stopping the spread of the disease (Krishnan et. al 2011). The ineffectiveness in stopping the disease could have something to do with how the stem cells were "cleaned." There may be a way that this technique could be perfected in the future that would help the immune system fight off the disease and stop it from spreading. This would make it similar to the way that allogeneic stem cells work in the capacity of the graft vs cancer effect (Shustov 2013).

The more typical treatments for multiple myeloma include medications, chemotherapy, corticosteroids, and radiation. There have been new discoveries of treatment for this disease which include bortezomib, lenalidomide and pomalidomide, and a high-dose of melphalan with autologous stem cell transplantation (Ramsenthaler et. al 2016). Bortezomib, lenalidomide, and melphalan are all different types of chemotherapy. Pomalidomide is an immunomodulator that suppresses the immune systems response so that the chemotherapy can attack the cancer cells in the body (Zhu et. al 2013). Stem cell transplantation could potentially be used in place of some of these harsh drugs such as chemotherapy. The stem cell transplant therapy could be integrated in the hopes of boosting the immunes system of the patient after intense chemotherapy. If the patient's immune system produces more white blood cells that are healthy and able to fight off the cancer cells, then prolonged use of the chemotherapy would be unnecessary. This treatment

could potentially have longer remission rates due to the shorter exposure to chemotherapy (Ramsenthaler et. al 2016).

Acute Lymphoblastic Leukemia is another type of cancer that has successfully been treated with stem cell transplantation therapy. Acute lymphoblastic leukemia is a cancer in the bone marrow that causes it to make too many immature lymphocytes. Acute means that the cancer can progress quickly, which usually happens by spreading to the blood. The major concern with this cancer is that it has a very high rate of reoccurrence post remission (Yanada et. al 2006). The most commonly reported symptoms of this disease are fever, fatigue, bone or joint pain, and easy bruising and bleeding (National Cancer Institute 2017). One type of treatment for this type of cancer is centered on allogeneic stem cell transplants. There are other modifications of this treatment such as treating the patient with a medium does of etoposide, cyclophosphamide, and a total body irradiation followed by an allogeneic transplant that have shown favorable results (Shigematsu et. al 2015). Etoposide and cyclophosphamide are both forms of chemotherapy but cyclophosphamide also contains an immunosuppressant drug. The use of an immunosuppressant drug in chemotherapy is commonly used in autoimmune diseases. This helps to control the spread of the disease and the rate at which it is multiplying. By suppressing the immune system the chemotherapy drugs are able to attach the cancer cells without the immune system trying to make more of them (Burt 1998).

Typical treatments for acute lymphoblastic leukemia vary based on the stage of the cancer but generally chemotherapy is a suggested course of treatment (Pui & Evans 2006). The risk of using chemotherapy as treatment is that exposure to chemotherapy increases your risk of getting the disease again. If allogenic stem cells are implemented more as treatment instead of

chemotherapy the length of remission could possibly be extended due to less harmful drugs in the patient's body (National Cancer Institute 2017).

Autologous stem cells are removed from the patient when they are diagnosed with a certain cancer. The autologous stem cells are then treated in hopes of removing the disease from them. This is typically done by freezing and purging them, which also keeps them viable to be implanted in the future. Purging is the process of killing remaining cancer cells collected with the stem cells. This could also cause normal cells to be killed off as well, causing the unnecessary loss of cells. This causes the body to take longer to make new blood cells and can lead to infection (American Cancer Society 2016). Another treatment to try to get rid of cancer in the stem cells is in vivo purging. This process involves giving the patient anticancer drugs after the stem cells have been transplanted back into the patient (American Cancer Society 2016). These anticancer drugs are important because if they are not taken and the cells were not properly "cleaned" of all of the cancer cells that they once had the patient could be reinfected with the cancer cells they were trying to get rid of. Purging is done in vivo by using cytotoxic therapy in order to get rid of all of the cancer cells that are mixed in with the stem cells that were taken from the bone marrow (Gulati & Acaba 2009).

There is a very specific procedure that is followed when someone is receiving or donating stem cells. For someone that is receiving the stem cells they need to make room in the bone marrow before the stem cells can be transplanted. This is done with either chemotherapy or radiation. This process likely happens one to two weeks before the actual transplant occurs. A central venous catheter is put into the patient which is how they will receive the stem cells. This procedure is painless and the patient is kept awake for the whole procedure (American Cancer Society 2016). The donation of stem cells is a little bit more invasive and requires a formal

surgery. It is important to understand how this process works in order to assess how effective the stem cells can be once they are transplanted into the patient. It is also important to know the procedure so that we can identify potential risks the might arise before, during, or after a treatment.

Stem cells can be very effective as a treatment method for various types of cancer. Autologous and allogeneic are different in nature and therefore are used to treat different things. Their treatment do however sometimes overlap. As previously stated the purpose of this paper is to analyze if it more effective to treat a person with a blood or immune system cancer with autologous stem cell transplant or an allogeneic stem cell transplant. There are both benefits and limitations to both however, allogeneic stem cell transplants are more beneficial due to the graft-vs-cancer effect that could be produced.

Benefits of Autologous and Allogeneic Stem Cell Transplants

Autologous and Allogeneic have their own unique benefits as to why someone should use one over another as a form of treatment. There are a few factors that could be considered advantages of autologous. These factors include that fact that you would be getting your own cells back. This factor might seem obvious but because they are your own cells that the chance of your body rejecting the cells decreases immensely (The Leukemia & Lymphoma Society 2015). Another benefit of getting your own cells back is that you chances getting a different infection for an unknown donor are also reduced (American Cancer Society 2016). The screening process for donors is very extensive but there is still a chance that the recipient could get a disease from

the donor. If the chance of that is reduced this could be very appealing to the patient who does not want to get more sick from something that is supposed to be making them better.

Allogeneic stem cells have their own advantages too. A particular type of advantage for allogeneic stem cells is a graft versus cancer effect. The graft versus cancer effect is when the stem cells from the donor use their own immune system cells to kill of the cancer cells in the body of the person receiving the stem cells. These immune system cells from the donor might be stronger than the recipient's immune system and will try to fight off the cancer in the recipient (Shustov 2013). The donor stem cells are tested prior to being transplanted and must be cancer free in order for the transplant to take place.

A metaanalysis done by Ram et al. (2010) was done to determine the best course of treatment for patients who are in the remission phase of acute lymphoblastic leukemia. The measure of failure that was being measured in this study was the all- cause mortality of the patients. The result of the metaanalysis showed that allogeneic stem cell transplants had much better outcomes than that of the autologous transplants and the chemotherapy treatment. The results also concluded that there was no statistical difference between receiving autologous stem cell transplant or chemotherapy. This means that using allogeneic stem cell transplants could become the new norm in treating patients in remission because it is allowing them to live longer healthier lives post remission (Ram et.al 2010).

There would be a dramatic change in medicine if allogeneic stem cell transplants were able to be used in place of chemotherapy. Chemotherapy has a long list of unpleasant side effects that most patients would want to avoid if at all possible. Stem cell transplants also have their own list of side effects but it isn't half as long as the one for chemotherapy, and the side effects are not as severe (Ramirez et. al 2009). The fact that both autologous and allogeneic were both

compared in this study reaffirms the idea the allogeneic transplants are more beneficial to the patient in the long term.

There was a study done by Van Kampen et. al (2011) where allogeneic stem cell transplant were used as treatment after a failed autologous stem cell transplant was done in patients with lymphoma. This study acknowledged that graft-vs- cancer effect which could potentially benefit the patients and lead to better outcomes (Van Kampen et. al 2011). If the graft vs cancer effect was to work on those patients it would mean that allogeneic stem cells are more beneficial as a treatment method because of this effect that the autologous stem cells cannot produce.

There can be direct donations made for stem cell transplants. This means that if someone in your family was a match they could offer to donate some of their stem cells to you. There was a study done by Cornelissen et. al (2008) that was run on patients with acute lymphoblastic leukemia comparing the disease free survival rates between related and nonrelated donors. The related donor group had significantly better results than the nonrelated donor group. This supports the idea that allogeneic stem cells can produce a positive effect as treatment but it also touches on the specificity of the donor. The more closely related the donor is the higher the chance of survival. This is most likely due to a lower rejection rate of the cells because the donor cells are very similar to the cells of the patient. This would mean that patients with sibling donors for allogeneic transplants have the most favorable survival rate.

There are conflicting studies on if the relationship between the donor and the recipient makes an impact on the success rate of the allogeneic stem cell transplant. Solomon et al. (2016) analyzed the relationships between the donor and recipient in depth and found no definitive proof that the relationship mattered to the success of the transplant. The research done by Solomon et

al. (2016) looked at patients who were in their first remission from acute lymphoblastic leukemia and were treated with allogeneic stem cells. The treatment proved to be successful which could provide patients with an alternative treatment to the traditional treatments such as chemotherapy. If the relationship of the donor does not matter then it makes it that much easier for people to have access to the stem cells they need for treatment. However, because there was a lot of conflicting information on the topic of the donor relationship more research needs to be done in order to fully understand it. In the meantime it would be best to have a related donor, if that is possible, to be on the safe side.

The previous research done by Solomon et al. (2016) is one of the many projects that has been successful in demonstrating how allogeneic stem cell transplants can be used as treatment for acute forms of leukemia. That study done by Solomon et al. (2016) discussed all of the different treatments for acute leukemia. In this study they used allogeneic hematopoietic stem cell transplantation, and in the results it concludes it is an effective treatment for adults who were in the remission phase of the disease. It also states that the allogeneic stem cell transplant is directly related to survival rates (Solomon et. al 2016). The remission periods were much longer in the patients treated with the allogeneic stem cells which shows that if administered properly can be an effective treatment for people in the remission phase of acute forms of leukemia.

A metaanalysis was performed by Yanada et al. (2006) with the main focus on adult patients that suffered from acute lymphoblastic leukemia, and what the most effective post remission treatment would be. The main focus is on the role of allogeneic stem cells in treating people with acute lymphoblastic leukemia. The measure they were looking at was the overall survival rate post remission. The metaanalysis by Yanada et al. (2006) concluded by saying that the allogeneic stem cell transplant increases the chance of survival. The research done by Yanada

et al. (2016) also noted that they did not observe any beneficial effects in patients who had received autologous stem cell transplants. It also touches upon that fact that a related donor, more specifically a sibling, as the allogeneic stem cell donor produce even more favorable outcomes. The information that was compiled by Yanada et. al (2016) is important because it deduces that the best way to prevent the acute lymphoblastic leukemia from continuing to come back is by treating it in the remission phase with allogeneic stem cells. The reason that this might be so effective in keeping the disease away could be due to the graft vs. cancer effect. The allogeneic stem cells that are used to treat the patient in remission are allowing their body to rebuild its immune system. The allogeneic stem cells are also working to kill the cancer cells that they recognize as foreign cells. If the body is able to fight off the cancer cells before they are able to multiply and spread then it will lead to longer remission periods.

There was a metaanalysis done by Messori et. al (2013) was done with its focus on treatment for people with acute lymphoblastic leukemia that are in remission. Their control group was a group of patients that received autologous stem cell transplants, and the experimental group was a group of patients that received allogeneic stem cell transplants. The conclusion of the metaanalysis is that survival is more likely when the patient received an allogeneic transplant rather than an autologous transplant (Messori et. al 2013). This is a direct comparison between the two types of stem cells for this particular type of cancer. The conclusion that the allogeneic stem cells were more beneficial in treatment of acute lymphoblastic leukemia clearly demonstrates that the type of stem cells matters when it comes to effective treatment.

Limitations of Autologous and Allogeneic Stem Cells

Just as there are benefits to both types of stem cells there are also limitations. In order to properly analyze which type of stem cell is more beneficial as a course of treatment we need to

evaluate the potential limitations and risks fully. First we will examine the limitations of autologous stem cells. A major concern is that when your stem cells are harvested you will have cancer in your body. There is a chance the cancer that you are trying to get rid of could be accidently collected along with the stem cells. There is also the chance that the stem cells won't get properly cleaned and will still have cancer cells when they are later put back into your body after treatment (American Cancer Society 2016). This is a major concern because no one would want to intentionally infect themselves with cancerous cells. There are ways to test the cells to make sure they are cancer free before transplanting them back into the body, but things could always go wrong with the testing. The way to test the cells is by using a monoclonal antibody as a marker for the cancer cell. If there is cancer present then the monoclonal antibody will attach to the cancer and is able to deliver targeted radiation to the cell (Weiner et. al 2010).

When someone is battling a serious disease such as cancer it take big toll on their body. Your immune system tries to work so hard that it eventually shuts down because it can no longer keep up with the fast rate at which the cancer is replicating. Immune systems can also be compromised from other treatment the patient might have received such as chemotherapy. If the body's immune system was not able to kill the cancer before it was further compromised it would most likely not able to kill then either (The Leukemia & Lymphoma Society 2015). Your immune system will be familiar with the autologous stem cells that are being replenished, but that could also make them more susceptible to being reinfected with the cancer.

There was a study done by Björkstrand et. al (2011) that was done on patients with myeloma. This specific study looked at the effects of autologous stem cell transplants. Some patients only had an autologous stem cell transplant and the other half had an autologous transplant followed by an allogeneic transplant. The group that received both types of transplants

showed more favorable outcomes than the group who only had autologous transplant (Björkstrand et. al 2011). This study shows that the long term efficiency of the autologous transplant alone is not as successful as combining the two types of stem cell transplants. Seeing as when it is combined with autologous the long term efficiency was much more favorable it makes the readers question if there was another group that only received allogeneic stem cell transplant would that have had the best outcomes?

Allogeneic stem cell transplants also have their own set of limitations which will now be analyzed. The major concern that comes with any type of transplant is that the organ, tissue, cell, etc. could potential be rejected by the body it is being transplanted into. The same goes for allogeneic stem cells which potentially could be rejected by the recipient's body (American Cancer Society 2016). In the case of the transplant failing and the body rejecting the stem cells, all of the stem cells that were transplanted would die in the recipient's body. This is a concern for patients because they want this treatment in order to get better and it could also be an expensive procedure which would be a waste of money if it did not work. This is also a concern for doctors and hospitals because they do not want to waste their resources or cause undue stress on the patient.

Similar to the risk of getting an infection after any major surgery there is also a risk that with a stem cell transplant that the recipient could develop and invasive fungal infection (IFI). This type of infection can occur because of a diminished red blood cell count combined with the drugs a patient is given after receiving an allogeneic stem cell transplant in order to prevent the graft vs host disease (Neofytos et. al 2009). There have been drugs used to effectively treat this infection but if left unnoticed it could potentially be fatal. In the study done by Neofytos et. al (2009) one third of all the patients that they were studying who received the allogeneic stem cell

transplant developed some form of graft vs host disease. Graft vs host disease is a major limitation to using allogeneic stem cells. This is when the immune system cells from the donor could attack healthy cells in the recipient and not just the diseased cells (Neofytos et. al 2009). When the donor immune cells are placed into the recipient everything is foreign to them. The purpose of immune cells are to kill off anything foreign. If the immune cell from the donor do not adjust properly then they could do more harm than good by killing any cells it comes into contact with, including the recipient's healthy cells.

There are other limitations that are less likely to happen from allogeneic stem cell transplants but are still worth discussing. One of these limitations is potentially getting an infection from the donor (American Cancer Society 2016). This is a relatively small risk now because of the thorough screening process that donors have to go through, but before we had the technology to screen blood this was a much higher risk. Another minor limitation is that an infection that the recipient had previously could come back due to a change in the body's immune system (American Cancer Society 2016). The body now has to adapt to new stem cells which could cause the already weakened immune system to malfunction.

The donor's relationship to the recipient could be seen as either a benefit or a limitation. If a donor is considered to be a matched donor than they are usually family members or close relatives of the recipient. Having a matched donor helps reduce the risk of rejection of the stem cells in the recipient (The Leukemia & Lymphoma Society 2015). As previously stated, if you have someone who is a matched unrelated donor then this transplant is generally a little bit more of a risky. This risk is associated with human leucocyte antigens which are proteins found of the surface of our cells. These are unique to each person and comprise an individual's tissue type. These are what have to be matched to a donor in order to get a stem cell transplant from them.

Matching the Human Leucocyte antigens plays a big role in the successfulness of the procedure (Boyton & Altmann 2007). If the donor seems to be a match, but does not express the correct human leucocyte antigen, then there is a high chance of rejection. This is not as common anymore due to technological advances that allow us to test for this antigen, to make sure the donor and the recipient are a good match.

There was study done by Solomon et. al (2016) that examined if the relationship of the donor makes an impact on the survival rate. It compared related and unrelated donors and it showed no major differences in survival rate between the two. The results of this study could have been due to the small sample size of the study. The sample size was a total of 172 participants, when broken up into their respected groups. The groups that the patients were broken up into for this study were matched related with 54 participants, unrelated with 67 participants, and haploidentical with 51 participants. There is a very comprehensive way to screen someone to tell if they are a match for someone in need of a transplant. This has eliminated a lot of the guess work that use to be associated with transplants. There can still be rejection even if the donor and recipient are a perfect match but it is much less likely. If this study is correct then the potential donor pool is much bigger than just people in the recipient's immediate family.

There was a direct comparison study done by Neofytos et. al (2009) which evaluated the risk factors of both autologous and allogeneic stem cell transplants in terms of potential invasive fungal infections post-transplant. The allogeneic transplants were a mixture of matched related and unrelated donors. The patients were diagnosed with an invasive fungal infection and were then treated and monitored and checked in on the 6 and 12 week marks post diagnosis. Invasive fungal infections do not discriminate between the autologous and allogeneic stem cell

transplants. There were actually more infections in the autologous transplants, which was 77 patients, than there were in the matched related donor allogeneic transplants, which was 71 patients. The most common infection among all stem cell transplant patients is invasive aspergillosis. There was not a statistically difference between the allogenic and autologous stem cells transplants however the study did note that there was a trend where allogeneic stem cells had a worse outcome at week 6 compared to the autologous stem cells (Neofytos et. al 2009).

It was discovered the previously stated study done by Neofytos et. al (2009) that the outcome was worse for the patients who were subjected to the allogeneic stem cell transplant (Neofytos et. al 2009). This conclusion makes sense because the risk of getting an infection from your own cells compared to that of another person's cells is much slimmer. The fact that this was the conclusion of the study does not take away from allogeneic transplants but rather from the autologous. If the appeal of receiving the autologous stem cells is that your body is less like to reject the stem cells and prevent infection this study proves this is not the case. With any type of procedure there is going to be a risk of infection. As the medical field technology is advancing they are coming up with new techniques and procedures to minimize all possible risks of getting these infections.

Direct comparisons of treatment with autologous and allogeneic stem cells are hard to come by but there was a study that used them sequentially as a form of treatment. The study run by Van Kampen et. al (2011) was done on patients who relapsed with the disease B-cell Non-Hodgkin's Lymphoma. The first time they had the disease they were treated with an autologous stem cell transplant. The second time they got the disease, when they relapsed, they were treated with an allogeneic stem cell transplant. These patients could not have chemotherapy so the allogeneic stem cell transplant replaced it as the course of treatment. The study acknowledges

that there are disadvantages to this type of treatment due to a high percentage of nonrelapse mortality rate (Van Kampen et. al 2011). The findings concluded that this was an effective method in treating the patients who had relapsed after receiving the autologous stem cell transplant. This shows that the autologous stem cells can prolong a patient's life, but cannot stop the cancer from coming back. The allogeneic stem cells were able to treat the people who relapsed and get rid of their cancer, proving to be the more efficient method of stem cell transplant. Even though there are limitations of using the allogeneic stem cells as treatment they are a better option than the autologous stem cells, which proved to be ineffective as a treatment method for this particular cancer.

Conclusion

As previously stated there are distinct differences between autologous and allogeneic stem cells. The key differences include where they come from, what they are used to treat, and their ability to fight off disease. The biggest benefit of the allogeneic transplants are the graft versus cancer effect and the biggest risk is the rejection of the donor stem cells. The associated risk can be improved by finding a way to get exact matches of the stem cells, or by finding a way to reduce the chance of rejection such as a medication the patient could take before and after the transplant takes place.

The most beneficial part of an autologous transplant is that there is less chance of rejection and the biggest risk is that you will be reinjecting the cancer into your body that was just removed. In my opinion the risk of the autologous stem cell transplant far outweighs the potential benefits of it. In order for autologous to be as good of a treatment as allogeneic there needs to be a better protocol put into place in order to get rid of the disease from the stem cells. If there was a way to separate the stem cells from the diseased cells then the chance of relapse after

the transplant would be much lower. There needs to be more research done to determine the most efficient method in doing this.

Allogeneic stem cell transplants are more beneficial to the patient because of the graft vs cancer effect. This is what sets allogeneic apart from autologous, which can prolong a person's life but cannot stop the spread of the disease like the allogeneic stem cells potentially can. Patients with cancers such as multiple myeloma and acute lymphoblastic leukemia would have better outcomes if they were treated with allogeneic stem cells opposed to autologous stem cells.

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