

ALLOGENEIC BONE MARROW TRANSPLANTATION IN MULTIPLE MYELOMA - A REVIEW OF LITERATURE

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ABSTRACT

Multiple myeloma is a hematological malignancy of the plasma cells with evidence of bone marrow infiltration. It is accompanied with extramedullary plasmacytomas. There are a variety of possible treatment options, but this review focuses on allogeneic bone marrow transplantation for the treatment of multiple myeloma. Allogeneic bone marrow transplant is commonly known as stem cell transplantation. From the review, the results suggest that this can be used as a treatment option for fit young individuals as compared to older individuals. It also shows better results during the early stages relative to the later stages with poor prognosis. In conclusion, allogeneic bone marrow transplant can help treat multiple myeloma, but it depends on factors such as age, stage of cancer, fitness of the individual.

KEYWORDS

Allogeneic transplantation; Death rate; Hematopoietic stem cell transplantation; Multiple Myeloma

INTRODUCTION

Multiple myeloma is considered as hematological malignancy with evidence of clonal expansion of malignant plasma cells. There is evidence of plasma cell infiltration of the bone marrow and is accompanied with the presence of extramedullary plasmacytomas (Mohamed et al. 2020). Allogeneic bone marrow transplantation is also known as stem cell transplantation which aids in replacing and replenishing the lost forming cells in the bone marrow.

Allogeneic bone marrow transplantation is now being considered as an alternative to bone marrow transplant for the treatment of hematological malignancies, especially among children (Shimosato et al. 2020). Allogeneic bone marrow transplantation has been customized and tailored mainly for pediatric patients among whom the probability of veno occlusive disease to occur is significantly low (Szmit et al. 2020). This review mainly focuses on the efficiency of allogeneic bone marrow transplant for treatment of multiple myeloma. Allogeneic bone marrow transplantation just besides children, can also be performed on a selective set of elderly patients which further depends on a variety of factors. It is a selective procedure as it is not suitable for every patient. (Rashidi et al. 2016).

In similar reviews published, one of the hematological malignancies considered is multiple myeloma. According to previous studies, the authors suggest that the use of allogeneic bone marrow transplantation for the treatment of multiple myeloma can't be considered as the standard of care or the first treatment choice. This statement is suggested as this method of treatment is restricted to well-designed clinical trials only. Allogeneic bone marrow transplant is not preferred in those patients with high-risk MM and poor long-term prognosis. It is also considered as an initial course of therapy along with chemotherapy among those patients diagnosed with relapse of multiple myeloma (Dhakal, Vesole, and Hari 2016). Clinical trial for Allogeneic bone marrow transplantation suggests that this treatment modality can be considered for young, fit patients rather than those with high risk NDMM (Bensinger 2004). Another study by Venegas C et al regarding the use of Allogeneic bone marrow transplantation as a treatment option for MM confirms the previous observations that it is effective only among a subset of patients (Venegas et al. 2018). Some of the researchers also feel that the best outcomes of such a treatment is when the patient is benefitted multidimensionally.

Some of the reviews possess some latency of facts and lacunae. The limitations and difficulties faced by other authors included certain concerns such as their studies must consider an appropriate palliative care period. The risk faced by elderly patients post transplantation. Other authors expressed their concerns and stated that the best possible outcome from this method of treatment can only be achieved if the benefits to the patient are multidimensional (Lin et al. 2020). The main drawback of this method is its high selectivity- it is most successful and efficient only among young and fit patients. Another concern is the serious deleterious side effects and risks post transplantation especially among elderly population.

The main necessity for this research is, it will help one to analyze the correct situation for using allogeneic bone marrow transplantation for suitable patients and among whom the best outcomes arise so as to provide the most efficient treatment. This review also helps us to understand advantages and disadvantages of the procedure.

The aim of this study is to analyze the success rate of allogeneic bone marrow transplantation for the treatment of multiple myeloma.

MATERIALS AND METHODS

All the data that has been collected for this review article has been done so through various search engines such as PubMed , Google scholar , MeSH, core, Cochrane, bioRxiv, Semantic scholar and so on. Being a review article, there was no requirement for any approval for publication. All the articles that are included in this review are cited form previous similar studies which provide information about allogeneic bone marrow transplantation, diagnosis of multiple myeloma, uses of allogeneic bone marrow transplantation, etc. All the articles collected for this review belong within a 20 year time frame.

ALLOGENEIC BONE MARROW TRANSPLANT

Allogeneic Bone Marrow Transplant [ABMT] refers to the transplantation of hematopoietic stem cells (Bosi and Bartolozzi 2010). These stem cells can be obtained from the cord blood immediately after birth. It can help a patient during times of emergency. This acquisition of cord blood will depend on the awareness of its benefits among mothers (Rose and Ellappan 2019, Balaji 2015). It is found through a structured interview that 77% of the mothers had inadequate knowledge and only 3% of the mothers were aware of the uses and benefits of saving cord blood (Kalabarathi, Khanpam, and Gowri 2019). With the current problem being lack of awareness, it is important to teach young women the importance of saving

cord blood. This can be taught in schools and colleges using fun online learning platforms. This can provoke the interest of gaining knowledge out of the curriculum and at the same time improve awareness (Brundha and Nallaswamy 2019, Prashaanthi and Mp 2018). Another source of stem cells from adults is the dental pulp. If cord stem cells are not available, the host dental pulp is the next best source for stem cells (Timothy, Samyuktha, and Brundha 2019). One of the main risks of allogeneic bone marrow transplant is the incidence of post translational graft v/s host disease. From older studies it shows that the use or addition of anti-thrombocyte globulins can significantly reduce the severity of graft versus host disease. This transplantation is a possible treatment option for various hematological malignancies, but it is also associated with severe risks after transplantation (Theurich et al. 2012). It is a possible treatment option in the control of myelofibrosis too (Lwin et al. 2019). Previously, the use of allogeneic bone marrow transplant was specific and preferred only for younger patients. But, recent advances promise the use of allogeneic bone marrow transplant even for elderly with minimum toxicity, especially the elderly patients suffering from Severe Aplastic Anaemia [SAA] (Georges 2019). Allogeneic bone marrow transplant is used for the treatment of leukemia. It is accompanied with supportive and palliative care. For leukemia, the success of the treatment is based on the grade of cancer and the age of the patient receiving treatment (Sivakumar, Sukumaran, and Ganapathy 2019).

MULTIPLE MYELOMA

Multiple myeloma is a hematological malignancy involving the clonal expansion of malignant plasma cells and which is also associated with extramedullary plasmacytoma (Mohamed et al. 2020). Multiple myeloma is considered to account for about 1% of cancers worldwide and upto 10-15% among hematological neoplasms. The major risk groups are the elderly people. The average age of onset is about 71 years for men and 74 years of age for women (Heikenwalder and Heikenwalder 2019, Gerecke et al. 2016). It is important that the correct diagnosis is made as early as possible. Being aware of the prevalence of diseases among men and women. It has been proved in previous studies about the high prevalence of macroglossia in men than among women. Such studies provide evidence of gender selective prevalence of many diseases (Harsha and Brundha 2017). It is important to keep in mind that the reproductive health and the reproductive history of a woman can vary the risk of being associated with multiple myeloma (Kalaiselvi and Brundha 2016, Wang et al. 2013). Histopathological examination is crucial for diagnosis of multiple myeloma. Finding the characteristic myeloma cells in the bone marrow. It is a highly important stem in diagnosis of the disease (Hannah et al. 2019). It can provide a confirmatory result and diagnosis (Fujino 2018, Brundha 2015). One such case report mentioned that the patient had headache, and bilateral hip pain. Later on, pain began in the lower back which irradiated to the posterior aspect of both his legs. Despite such pain and even development of fever, the patient was prescribed only analgesics when he consulted a doctor. One of the first diagnostic manifestations of multiple myeloma can be seen in the oral cavity. One of the most common findings for multiple myeloma in the oral cavity is macroglossia (Parathan K.K. et al. 2015). It is thus of utmost importance that the dentist is quick to identify and make the accurate diagnosis (Sachidanandan et al. 2012). Multiple myeloma can sometimes represent itself with rare symptoms such as nocturia. This is seen in a rare condition called plasmacytosis, affecting the B lymphocytes. The differential diagnosis is usually prostate cancer. Thus it is also necessary to be aware of such rare symptoms too (Ashok Kumar and Brundha 2016). Another such confusion arises with breast cancer and breast plasmacytoma, hence awareness of the same is important (Balaji, Brundha, and Path 2016). A new diagnostic tool is used popularly for non invasive diagnosis of various carcinomas. It is called the Fourier Transform InfraRed (FTIR) diagnosis. It uses Spectrum One Perkin-Elmer FTIR Spectrophotometer for spectral analysis. This allows for continuous blood examination results during and after chemotherapy. This continuous blood screening proves to be very helpful for diagnosis and treatment

of the cancer. For multiple myeloma, it continuously scans the various plasma protein levels in the blood (Sankari et al. 2011). The pathophysiology of the disease involves a sequence of changes that occur not only in the malignant cells, but also in the surrounding microenvironment of bone. The sequence of events that occur before it transforms into active myeloma has been extensively researched. Currently, there is no specific sequence of events found. The main understanding from these various studies is the presence of heterogeneity among the various patients, leading to difference in expression of the disease (George, Mangesh, and Dhanraj 2017). One of the novel treatment methods suggested for multiple myeloma is through epigenetic pathways which are druggable and customisable (Amodio et al. 2017). Another novel approach is through target secretory apparatus through target secretory apparatus through plasma cells (Auner and Cenci 2015).

TREATMENT EFFICIENCY

The use of allogeneic bone marrow transplant in multiple myeloma is restricted to a well designed clinical trial and is not considered as the standard of care. Those patients with high risk of multiple myeloma and thus naturally have poor prognosis cant have allogeneic marrow transplant as their treatment plan as it is not an efficient option, it will not help improve the quality of life to a great degree. Whereas, on the other hand, allogeneic bone marrow transplantation can be a part of the initial course of therapy for the patients initially diagnosed with relapse. Such a treatment shows high success rates. Newer drug based treatment for MM involves drugs like pomalidomide, carfilzomib, elotuzumab, PI3K pathway inhibitors, and heat shock protein 90 inhibitors (Rajkumar 2011). Further complications arise in patients during treatment when they are also suffering from diabetes mellitus. Thus understanding the link between the two diseases is also necessary (Preethikaa and Brundha 2018).

ADVANTAGES

The method can provide for a tumor free graft. Allogeneic bone marrow transplant when successful has prolonged actions, where they have ability to produce immune cells even after chemotherapy (Khaddour, Hana, and Mewawalla 2020). It is recommended as a first line treatment modality among pediatric patients. Studies have shown that allogeneic bone marrow transplant success can be improved when combined with drug therapy. Allogeneic bone marrow transplants help in controlling and also in the treatment of a few childhood neurodegenerative disorders such as adrenoleukodystrophy (Uddin and Amran 2018). In another study, it proved that allogeneic bone marrow transplantation can be considered as the first line treatment option for myeloid sarcoma. It was suggested that 17% of the patients did not have a relapse and the survival rate was 5 years average for 33% of the patients. It was suggested that Allo BMT be used as a treatment for myeloid sarcoma for long term survival.(Brundha and Saivignesh 2019)

DISADVANTAGES

The newly devised treatment options in order to reduce severity of graft versus host disease, but there is no method to stop the occurrence of the disease. This in the long run leads to extreme immunodepression. It is also contraindicated among elderly patients and highly selective only for younger and fit patients. It is also very difficult to reduce these severe side effects after transplantation. Research suggests that patients suffer from anaemia as an iatrogenic effect to myelosuppressive radiotherapy and chemotherapy (Brundha, Pathmashri., and Sundari 2019, Shreya and Brundha 2017). Bisphosphonates is the common drug prescribed to control the lytic lesions. The drawback is the severe deleterious side effects of the drug (Muthukrishnan and Sekar 2015). One of the reasons for increased risk for such treatment methods can be attributed to the lack of awareness and knowledge of regular health checkups (Ferdioz and Brundha 2016,

Shenoy and Brundha 2016). A recent survey suggests that only 32% of the population surveyed are aware of the necessity and importance of regular health check ups (Varshini, Rani, and Brundha 2020). One of the controversies stated in a survey paper suggest that stem cell is abortion politics and human cloning (R, V, and Gayathri 2017).

USE OF ALLOGENEIC BONE MARROW TRANSPLANTATION

The survival rate of patients who received allogeneic bone marrow transplantation is significantly better than those who received an autologous transplantation. It has been used as a treatment option for pediatric patients suffering from acute myeloid leukemia with successful results (Woods et al. 2001). Allogeneic bone marrow transplantation is considered to have better results than peripheral bone marrow or blood stem cell transplant for hematological malignancies (Shimosato et al. 2020). Pre- allo bone marrow transplant > 20% hinders engulfment. It is considered as a treatment for chronic myeloid leukemia (Paul et al. 2020). Allogeneic bone marrow transplant can also be considered as a treatment option and also to control the progression of myelofibrosis (Palmer et al. 2019, Georges 2019).

CURRENT TREATMENT FOR MULTIPLE MYELOMA

Initial course of treatment is autologous bone marrow transplant, which is not a specific treatment plan. Drugs for chemotherapy like Bortizomib can also be administered for eligible patients (Jewell et al. 2015). Most recent treatment modalities include specific target immunotherapy. It is seen to have good results due to its target specificity (Branagan et al. 2020). It is necessary for the doctors and nurses to use appropriate PPE while administering chemotherapy drugs for protection against cytotoxic drugs (Swetha and Brundha 2017). The disposal of the waste also needs careful handling. Thus, it is important that cleaners also are aware of the proper use of personal protective equipment (Ravichandran and Brundha 2016). For treatment of patients with multiple myeloma, who have been newly diagnosed and for those with early stage of cancer and also with first relapse diagnosis, allogeneic bone marrow transplant is considered. Multiple myeloma is known to be associated with lytic lesions. Combination drug therapy such as filanesib with dexamethasone is considered as a convincing supportive therapy for treatment of multiple myeloma (Algarín et al. 2020). Consensus of multiple myeloma in India suggested in the state of the art 2016 conference that the patients were first categorised into transplant eligible and transplant ineligible. The common course of treatment included a triplet with two novel agents as part of the upfront therapy. The consensus also suggested that the most important part of management of Multiple Myeloma is the supportive and palliative therapy (Rajkumar 2016, Yanamandra et al. 2017).

EFFICIENCY OF ALLO-BONE MARROW TRANSPLANT FOR MULTIPLE MYELOMA

Another study suggests that there is no statistically significant result in the difference of survival rates when comparing the patients who have been transplanted for the first time with standard risk with the high, poor or ultra high risk cytogenetics (Sonneveld et al. 2013). The use of allogeneic bone marrow transplantation has been restricted mainly to well designed clinical trials. Among the patients who have later stage of cancer disease, and diagnosed with very poor prognosis aren't treated with allogeneic bone marrow transplantation due to its inefficiency. Significant improvement after allo bone marrow transplant can be seen only in a selected set of patients. The same results can't be acceptable among all patients (Greil et al. 2019). Once the patient has been given the transplant, the effects of that will be prolonged.

ASSOCIATED RISKS

The main concern for this treatment method is the toxicity. It is believed that the risks associated is mostly because the toxicity overpowers and compromises survival after the transplantation (Mehta et al. 1998). It was suggested by Chhabra et al, that the median time of relapse diagnosed during follow ups is approximately 2.2 years after treatment with allo bone marrow transplant. They also suggested that there is a 1.8 year extended survival time after relapse with a 95% confidence interval (Chhabra et al. 2020). Powles R et al concluded from their study that the majority of the patients after transplantation were alive and disease free for a minimum of a decade, or sometimes longer. All the patients who survived had a relatively normal, standard quality of life. If it is not possible for a 100% success rate due to the associated risks. Hence, it is inevitable for relapse among patients. For such relapsed conditions, there is heightened requirement for salvage therapy (Powles et al. 2002).

Allogeneic bone marrow transplant must be accompanied with other treatment methods like drug therapy for positive synergistic effects. Newer studies are developing alternative non toxic transplant options, but the statistical significance in their success rates are absent. The toxicity overplays treatment and survival for allogeneic bone marrow transplantation.

In the future, the limitations of the current studies can be overcome by reducing toxicity, discovering newer methods of reduction of graft v/s host disease.

CONCLUSION

This review compiles the various advantages and disadvantages of allogeneic bone marrow transplantation for treatment of Multiple Myeloma. Allogeneic bone marrow transplantation can be used to treat the younger age groups as compared to the older age groups with best post transplantation results. It is restricted to a clinical trial and thus cant be used as a first line treatment option. Alternatively, drug therapy combinations may be provided and novel treatment methods are being designed to overcome limitations of Allo-Bone marrow transplantation and its side effects such as the graft versus host disease. It can be concluded from this review that allo bone marrow transplant is an age selective procedure, favoring the younger patients due to its toxicity and side effects. It is not the preferred treatment of choice for multiple myeloma.

AUTHOR CONTRIBUTIONS

Deepthi Sogasu, contributed to the data acquisition, and drafting of manuscript. Dr. M.P.Brundha, contributed to design, editing, and critical revision of the manuscript. Dr. Smiline Girija, contributed to supervision and proof reading of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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