Stem Cell Transplantation in Aplastic Anaemia

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Hematopoietic stem cell transplantation (HSCT) in Aplastic Anemia can be discussed under two main headings:

A. HLA Identical Sibling Transplant in Aplastic Anemia
B. Alternative Donor Transplantation for Aplastic Anemia

A. HLA Identical Sibling Transplant in Aplastic Anemia

Introduction

The clinical outcome for patients with aplastic anemia (AA) is dependent upon the severity of the pancytopenia and patient age. Allogeneic hematopoietic stem cell transplantation (HSCT) is the best curative treatment for severe and very severe aplastic anemia (SAA) and is the treatment of choice for those less than 50 years of age. The expected five years survivals of patients less than 20 years of age treated with HLA identical sibling HSCT is 88% and between 21-50 years is 72%. However, in patients more than 50 years survival is only 43%.1,2 Therefore HSCT is offered to this group of patients only if immunosuppressive therapy (IST) fails. IST has been effective in the acquired variety of AA with a predicted survival of 67.5% - 80% in children1-4 and overall response rates of approximately 60 - 85% in adults.5 HSCT is particularly desirable in patients with very severe aplastic anemia (VSAA) since these patients have an increased risk of infection and bleeding and are less likely to respond to IST. Human leucocyte antigen (HLA) matched sibling is the donor of choice in patients of SAA being planned for HSCT.

Conditioning

The standard conditioning regimen for HLA identical sibling HSCT uses cyclophosphamide (200mg/kg) either alone or in combination with antithymocyte globulin (ATG).8,9 This regimen has been found to be superior to other regimens particularly for patients over 20 years who have received blood transfusion products.10 This combination has got a beneficial effect on engraftment and carries a reduced risk for GVHD.11 But the use of these conditioning regimens in developing countries have however been associated with inferior outcomes mainly related to graft failure and increased mortality related to infections. In order to improve survival in older patients, the use of less cytotoxic but more immunosuppressive regimens including low-dose cyclophosphamide (below the standard dose of 200 mg/kg) in combination with ATG≤ adding fludarabine has been tried.12 Modification of conditioning regimens using a fludarabine based conditioning has shown very good long term survival in patients undergoing HSCT for severe AA.10

Stem Cell Source

The sources of stem cells from the
donor can either be from unmanipulated bone marrow or peripheral blood. EBMT analysis suggest that there are better outcomes with the use of bone marrow compared to peripheral blood as it is associated with a survival advantage. Peripheral blood may be used because of donor’s choice or in cases of second transplant after graft failure. In a retrospective analysis of 121 patients of SAA in three centers in India where peripheral blood was the source 109 patients and G-CSF stimulated bone marrow in 12 patients, all centers used fludarabine and cyclophosphamide as conditioning regimen with cyclosporine and mini methotrexate as GVHD prophylaxis. The overall survival was 64% for high risk and 95% for low risk groups. It was interesting to note that incidence of acute and chronic GVHD was similar to data from CIBMTR.10

Complications

Three major issues have limited the success of allogeneic HSCT in SAA:  

a. Graft rejection  
b. Acute and chronic graft versus host disease  
c. Regimen related toxicity

Graft Rejection

One of the major complications associated with HSCT for aplastic anemia has been graft rejection and various approaches have been used to reduce the risk of rejection. This can be done by maximizing the number of donor marrow cells infused, by giving unirradiated donor lymphocyte infusions or buffy coat cells after the marrow graft.13 This resulted in a decrease in acute GVHD but resulted in increase in chronic GVHD. The second approach involved increasing the intensity of pretransplant immunosuppression by combining cyclophosphamide with total body irradiation (TBI) or with limited field irradiation. This has resulted in a decreased risk of rejection but also has resulted in a higher incidence of radiation related toxicity causing increased transplant related mortality and secondary malignancies.14 Bean et al found that the incidence of rejection may be reduced by minimizing the recipient’s exposure to potentially immunogenic blood products before transplant and by use of leucodepleted red blood cells and platelets for transfusions.15 The main intervention that actually helps in reducing the chance of rejection is improving immunosuppression during conditioning. The use of cyclophosphamide / ATG regimens resulted in an overall survival of 88% compared to 72% survival rate after 6 years.16 Graft rejection has been noted as upto 17% in EBMT study and was mainly associated with a delay in transplant (> 2 years) from diagnosis. It was also higher in patients exposed to > 20 transfusions. Graft rejection can be reduced by refining conditioning regimen using cyclophosphamide with ATG ± fludarabine. The use of granulocyte colony stimulating factor (G-CSF) mobilized peripheral blood stem cells as the graft source of HSCT also helps in reducing the risk of in patients with SAA.

Graft Versus Host Disease (GVHD)

Acute and chronic GVHD are multisystem disorders that are common complications of allogeneic hematopoietic cell transplant (HCT). GVHD occurs when immune cells transplanted from a non-identical donor (the graft) recognize the transplant recipient (the host) as foreign, thereby initiating an immune reaction that causes disease in the transplant recipient.

Acute GVHD

Clinical manifestations of acute GVHD include a classic maculopapular rash; persistent nausea and/or emesis; abdominal cramps with diarrhea; and a rising serum bilirubin concentration. Acute GVHD occurring in transplanted patients reduces their survival rates. Risk factors for GVHD include increased patient age and post pregnancy female donor transplants. GVHD prophylaxis using a combination therapy of methotrexate and cyclosporine has been most effective in reducing acute GVHD.18 T cell depletion has also been shown to reduce incidence of acute GVHD but had a higher risk of graft failure.

Chronic Graft Versus Host Disease

Patients with chronic GVHD commonly demonstrate skin involvement resembling lichen planus or the cutaneous manifestations of scleroderma; dry oral mucosa with ulcerations and sclerosis of the gastrointestinal tract; and a rising serum bilirubin concentration. Chronic GVHD was more common in presence of risk factors like preceding acute GVHD, increasing age, use of radiation based conditioning or use of supplemental buffy coat preparations. Various agents have been used for prevention of chronic GVHD including prednisone, azathioprine, thalidomide, tacrolimus or mycophenolate. Chronic GVHD has significantly decreased by with the use of cyclophosphamide and ATG conditioning and with methotrexate and cyclosporine prophylaxis.19

Delayed Effects of Transplantation

Growth and development

Decreased growth may be seen in patients transplanted with cyclophosphamide and TBI while it is less common with high dose cyclophosphamide based regimens. It is also seen in patients with chronic GVHD.

Fertility

Fertility is a concern in patients treated with IST
especially cyclophosphamide and may result in reduced gonadal function and amenorrhea in females.

Secondary Cancers

Secondary cancers were common with radiation based treatment protocols and with patients having chronic GVHD with included solid tumors or leukemia.

Survival of patients transplanted has improved over the last few decades due to
a. Decreased graft rejection
b. Improve conditioning regimens
c. Better transfusion practice
d. Availability of newer antibiotics
e. Decrease in acute and chronic GVHD

B. Alternative Donor Transplantation for Aplastic Anemia

Alternative donor HCT is reserved for patients who do not respond to immunsuppressive therapy and do not have a HLA-matched sibling donor. This modality is generally not preferred as first line therapy for following reasons-
1. Regimen related toxicity
2. Increased incidence of GVHD
3. Graft Failure
4. Availability of Matched Unrelated Donor (MUD) in short time frame
5. Unrelated Cord HCT may not be feasible for adults

Only 30% patients have Matched Related donor (MRD) available and can be offered Allogeneic HCT as first choice therapy. MRD HCT have become fairly routine norm at some places. However, the family size is shrinking and there is more need to explore the possibilities of alternate approaches in the field of HCT.

We have following options for alternate donors –
1. Matched Unrelated Donor (MUD) from various donor registries in the world
2. Haplo (Half Matched) Identical Donor – generally parents / children
3. Unrelated cord Transplant – Single or Double cord

The need for alternate donor transplants is on the increase and outcomes have improved over time due to refined conditioning regimens and improved supportive care.

Recent changes in
1. Pre-transplant conditioning regimens have lowered the risks of organ toxicity and graft failure.
2. Advances in donor HLA typing and selection practices and improved GVHD prophylaxis have lowered the risk of GVHD
3. Expanded donor pool - 22 million donors available in the registries.
4. Haplo Identical transplants and Double cord transplant approach

These changes have definitely increased the possibilities and outcome of these HCTs.

Generally Alternate HCT would be reserved for following
1. Non availability of a HLA matched sibling donor.
2. Failed IST without active infection
3. Age less than 50 years
4. Good performance score

MUD Transplant

There are a number of donor registries functioning worldwide. In India we have a functioning registry in DATRI from Chennai since 2011 and they have completed 51 donations in total. Total donors available are 22 million worldwide (NMDP source – 2013). NMDP in the US is the largest registry.

Identifying the Optimal Unrelated-Adult Donor:

Selecting an appropriately matched donor for HCT is an important factor. Donor-recipient matching at HLA-A, HLA-B, HLA-C, HLA-DRB1 and HLA-DQB1 (a 10/10 HLA match) offers the highest likelihood of survival. Approximately 60% patients have a chance of finding a donor. Donor Graft Sources
1. Bone Marrow – (BM)
2. Peripheral Blood Stem Cells (PBSC)
3. Umbilical cord (UCB)

CIBMTR data suggests that the graft source is 60% BM, 25% PBSC and 15% UCB. Through PBSC has a faster engraftment with less Graft failure this is offset by a higher incidence of GVHD. Graft failure is highest with UCB but data is awaited from Double UCB studies. Similarly, in an analysis of MUD HSCTs reported to the CIBMTR, mortality risks were higher with PBSC than with bone marrow grafts (RR 1.74; p = 0.05), with 2-year probabilities of overall survival of 76% and 55% with BM and PBPC, respectively (Figure 1).

Conditioning Regimen

MUD HCTs have higher rates of graft failure, regimen-related toxicity, and GVHD than HLA-matched sibling transplants for SAA, even when the donor and recipient are 10/10 HLA matched.

The introduction of ATG and Fludarabine have definitely lowered the incidence of both Graft Failure and GVHD. In younger patients with no matched sibling donor MUD, HSCT should be considered as results have improved in recent years, with some reports in children suggesting that transplantation outcomes in this age group rivals that of an HLA Identical Sibling Transplant in Aplastic Anemia. 20-22
Unpublished data from the CIBMTR indicate that approximately 15% of unrelated-donor transplants for aplastic anemia performed in recent years have used umbilical cord blood (UCB) grafts. UCB as an alternative to unrelated-adult donor grafts is an attractive option. Placental lymphocytes are immunologically naive, allowing for transplantation of UCB units with degrees of donor-recipient HLA disparity that would be associated with prohibitively high risk GVHD, otherwise. Although UCB transplantation is used for aplastic anemia, the data thus far are not as encouraging. Forty-five patients with aplastic anemia who received a single UCB unit as their first allograft were reported to the CIBMTR with high Graft failure rate. However, this may change with the use of DOUBLE UCB graft this is definitely an attractive option in children.

Haplo Identical HCT for Aplastic Anemia

Even after expanding donor registries 40% patient may not find a HLA matched donor and this situation led to the use of Haplo HCTs in Malignant disorders. This approach is being explored for Aplastic Anemia and MDS over recent years.

Every patient is 50% match with parents and children. Thus the donor is rapidly available and lot of time can be saved that occurs in MUD search. Thus theoretically every patient has a potential donor rapidly available.

The major problems with Haplo HCT include graft versus host disease (GVHD) and Graft failure.

There are two types of graft available –
1. T cell depleted ie. manipulated
2. T cell nondepleted or Unmanipulated

T cell depletion techniques are very expensive and cumbersome. Thus making this type of graft unavailable for third world countries. John Hopkin’s introduced the concept of Post HCT Cyclophosphamide as GVHD prophylaxis without T-Cell Depletion, and this is very feasible in majority of the centers. Malignant diseases data is very widely available and shown comparable results with MUD HCT. Data is getting generated and various groups are trying to use novel approaches. Early data suggests that this is feasible and an attractive option in aplastic anemia.23-25

India Specific Issues for HCT in Aplastic Anemia

Aplastic anemia is a very common disorder in India and the median age of presentation is around 25 years. Unfortunately very few patients can afford curative treatment strategies such as allogeneic Allo HCT or ATG based IST. In majority of situations, patients get referred at a very late stage.

High Risk factors for Transplant outcome in Aplastic Anemia -
1. More than 20 transfusions prior to HCT
2. Active infection esp Pneumonia at the time of HCT
3. Failed Prior immunosuppressive therapy
4. More than six months to HCT from diagnosis

If we look carefully, we realize that all these risk factors are directly proportional to the DELAY IN HCT. Thus by delaying the HCT we are converting LOW RISK patient to a HIGH RISK group. Indian data published at ASH 2009 by George B et al, showed that if HCT is done without any of the above risk factors the long term disease free survival is around 90%. Lot of our patients are infected at the time of HCT or are heavily transfused and this forces us to use PBSC as the graft source (EBMT/CIBMTR data suggests better outcome with BM source, however majority of the patients are Low Risk in this data base) for rapid engraftment. With the use of PBSC as a source the issue of Chronic GVHD is a major concern. A low risk transplant is generally cheaper than the ATG based IST and has a far better outcome. Majority of our patients cannot afford two curative options due to financial restraints and then ALLO HCT done early will be better option for patients below the age of 50 years.

We need to improve on –
1. Early referral
2. HCT when patient is Low Risk category
3. To Tackle Graft versus Host Disease and develop new approach in MRD
4. Non ATG based conditioning regimens. To use Fludarabine in pre transplant conditioning regimen
5. To do more collaborative work
6. Young patients to be offered Allo HCT as First Line therapy

Few patients may need second line therapy and then Haplo or MUD may be a better option than second
ATG based treatment. Haplo transplant may be cost effective in our country and will definitely be faster than MUD transplant as early transplant is crucial for Aplastic Anemia. However this issue has to be resolved and we may be in a position to resolve this issue. MUD transplant becomes difficult due to finances available. John Hopkin’s protocol for Haplo HCT may be a good option for Haplo transplants in India. Issue of UCB HCT is still being debated for adult HCT in Aplastic anemia, however UCB HCT is definitely a good option for very young children even as a first line option. Double UCB data may be different than single UCB data. Mixing UCB with Haplo identical transplant is being explored in Aplastic Anemia.

References

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