Immunosuppressive Therapy and Bone Marrow Transplantation for Aplastic Anaemia – The CMC Experience

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Abstract
This is a single centre experience on the use of immunosuppressive therapy (IST) and stem cell transplantation (SCT) in patients with aplastic anaemia. Between 1985 and December 2013, 530 patients underwent IST while 214 underwent allogeneic SCT. Overall response rate with the use of IST was 58% with higher responses seen in adults (65.1%) compared to children (35.8%) [p = 0.001]. At a median follow up of 34 months (range: 1 - 264), 5 year KM estimates for OS for the entire group is 68.2 ± 2.2%. Loss of response or relapse was seen in 27 responders while clonal evolution to PNH was seen in 8 patients and transformation to MDS or AML was seen in 3. The 5 yr OS for children (45.7 ± 4.7%) was significantly lower than the OS of age groups 16-30 (75.6 ± 3.6%), 31-50 years (76.2 ± 4.2%) and > 50 years (73.0 ± 4.2%) (p = 0.0001). SCT was performed in 214 patients with engraftment seen in 91%. The incidence of grade II-IV acute graft versus host disease (GVHD) was 38.4% with grade III-IV GVHD in 11.7%. Chronic GVHD was seen in 47.5% of evaluable patients with majority (73%) being limited chronic GVHD. At a median follow up of 32 months (range: 1 - 244), the 5 year KM estimates of OS for the entire cohort is 64.8 ± 3.3%). The 5 yr OS was significantly higher with the use of Flu/Cy (5 yr OS of 73.8 ± 3.6%) compared to Cy/ATG (5 yr OS of 44.4 ± 9.6%) or Flu/Bu conditioning (5 yr OS of 52.4 ± 8.9%) [p = 0.001].

Imp: SCT and IST offer good response rates and survival in Indian patients with AA except in children receiving IST.

Introduction

Allogeneic stem cell transplantation (SCT) and immunosuppressive therapy (IST) using a combination of Anti-thymocyte globulin (ATG) and Cyclosporine have become the cornerstone of therapy for both severe aplastic anaemia (SAA) and non-severe aplastic anaemia (NSAA). The ideal treatment for any patient below the age of 40 years with an HLA matched sibling donor is a stem cell transplant and CIBMTR data suggests that the 5 yr overall survival (OS) rates are about 82% in patients lower than 20 years of age and 70-72% in patients above the age of 20 years. In patients > 40 years, the survival rates drop to about 45%. A number of groups including the NIH, German, Japanese and EBMT have shown that immunosuppressive therapy with ATG and cyclosporine induces a response in 60-80% of patients but over a period of time, relapses are seen in 20-30% and in addition, 5-15% show evidence of clonal evolution leading to 5 year overall survival rate ranging between 50-80%. Survival rates have been lower in developing countries due to delays in diagnosis and treatment and newer protocols have helped in improving survival. We describe a single centre experience on the use of SCT and IST as modalities of treatment in patients with aplastic anaemia.

Patients and Methods

All patients diagnosed to have aplastic anaemia in the Department of haematology, CMC Vellore between 1986 and December 2013 and received either SCT or IST were included in this analysis. Data was collected from individual medical records and databases maintained in the department.
Treatment

Immunosuppressive therapy: Patients undergoing immunosuppressive therapy (IST) received either
a. ALG (Pasteur Merieux, France) at 15 mg/kg/day x 5 days (or)
b. ATGAM (Pharmacia Upjohn, USA) at 40 mg/kg/day x 4 days

Serum sickness prophylaxis with oral prednisolone 1mg/kg/day in 3 divided doses was started one day after completion of ATG/ALG for 10 days and then tapered over 7-10 days. Once there was no evidence of active infection and steroids were tapered, Cyclosporine was started at 3 mg/kg/day in 2 divided doses. Cyclosporine was given for 6 months and then slowly tapered if there was a response. In the absence of any response, cyclosporine was stopped at 6 months.

Stem cell transplantation: All patients undergoing stem cell transplantation (SCT) had transplants from HLA identical (HLA 6/6) or 1 antigen mismatched sibling or parental donors.

Conditioning regimens used for SCT included Cyclophosphamide 200 mg/kg/day x 4 days and ALG 90 mg/kg/day x 3 days (Cy/ATG) from 1986 to 2001. From 1999, conditioning regimen consisted of Fludarabine 180 mg/m² over 6 days with Oral Busulfan 8 mg/kg x 2 days (Flu/Bu) and ATG 10 mg/kg/day x 4 days. Busulfan was changed to Cyclophosphamide 60 mg/kg x 2 days from 2004 (Flu/Cy) and low dose ATG was stopped subsequently. In a few patients with active infection at the time of SCT, other regimens were used including Fludarabine 90 mg/m² with TBI 200 Cgy, Fludarabine 180 mg/m² over 6 days alone or Cyclophosphamide with Fludarabine (Others)

Graft versus Host disease (GVHD) prophylaxis consisted of Cyclosporine and short course methotrexate on Day 1, 3, 6 and 11 followed by folic acid rescue 24 hours later. Cyclosporine was given at full doses for 6 months and in the absence of GVHD, tapered and stopped by 12 months post BMT. Twenty patients received post transplant cyclophosphamide as sole GVHD prophylaxis as a part of an ongoing study protocol. Acyclovir was given as antiviral prophylaxis from day +1 while oral penicillin and cotrimoxazole was started after engraftment. No antifungal prophylaxis was used unless patient had previous fungal infection. Colony stimulating factors (G-CSF) was not routinely used and was given at physician’s discretion if there was severe sepsis or delayed engraftment.

Statistical analysis: Overall survival was calculated from the time of ATG or BMT till date of last follow up. Patients who received ATG and had less than 6 months of follow up were considered dead for this analysis. Individual variables were compared using a Fishers 2 tail test. Overall survival was calculated based on Kaplan Meir estimates. All statistical analysis was performed using SPSS 13.0 version.

Results

The baseline characteristics for patients having IST and SCT are described separately.

Immunosuppressive therapy (IST) - A total of 530 patients underwent treatment with ATG or ALG between 1985 and December 2013. Cyclosporine was not given after ALG in 32 patients in the early period of treatment. The baseline characteristics of this cohort are described in Table 1. There were 343 males and 187 females with a median age of 30.1 years (range: 1.5 to 74). This included 120 children (22.6%) aged less than 15 years. Three hundred and fifteen patients (59.4%) were diagnosed to have severe aplastic anaemia (SAA) while 105 (19.8%) had very severe aplastic anaemia (VSAA) and 110 (20.8%) had non-severe aplastic anaemia (NSAA). Majority of the children were tested for Fanconi anaemia using stress cytogenetics and were found to be normal. The median time from diagnosis of aplastic anaemia to initiation of ATG was 3 months (Range: 1 – 120). Two hundred and seventy eight patients received ATGAM (Pharmacia Upjohn, USA) while 252 received ALG (Pasteur Merieux, France) or similar products.

Stem cell transplantation (SCT): Two hundred and fourteen patients underwent stem cell transplantation between 1990 and December 2013 (Table 1). There were 140 males and 74 females with a median age of 22 years (range: 3 - 57). This included 73 children...
Response rates and survival: Immunosuppressive therapy (IST) – Response to IST was assessed at 6 months post ATG and classified as complete response (CR), partial response (PR) or no response (NR) based on standard response criteria. An overall response (CR + PR) was seen in 58.3% of patients with CR in 23.3% and PR in 35% (Table 2). The overall response was significantly lower in children (35.8%) compared to adults (65.1%) [p = 0.0001]. Overall responses were higher in patients who received ATGAM (65.1%) compared to ALG (51.1%) [p = 0.001]. There was no difference in the response rates among patients who had NSAA (65.4%) and SAA (61.5%) [p = 0.491] but both had significantly better response rates than patients with VSAA (45.7%) [p = 0.006]. The overall response rates for the various age groups were as follows: < 15 years [35.8%], 16 – 30 years [66.8%], 31 – 50 years [67.3%] and > 50 years [60%]. Among 44 patients aged > 60 years, the overall response rates were 59%. The median follow up of the entire group is 34 months (range: 1 – 264). Loss of response or relapse was seen in 27 responders while clonal evolution to PNH was seen in 8 patients and transformation to MDS or AML was seen in 3 patients. Repeat ATG was given to 14 patients while BMT was performed in 7 patients. The 5 year KM estimates for OS for the entire group is 68.2 ± 2.2% [Figure 1a]. The 5 yr OS for children (45.7 ± 4.7%) was significantly lower than the OS of age groups 16-30 (75.6 ± 3.6%), 31-50 years (76.2 ± 4.2%) and > 50 years (73.0 ± 4.2%) [p = 0.0001] [Figure 1b].

Stem cell transplantation (SCT): Engraftment was seen in 195 patients (91%) while 6 had primary graft failure and 13 expired due to sepsis prior to engraftment. The median time to engraftment (absolute neutrophil count > 500/mm³) was 14 days (range: 9 – 24). The incidence of grade II-IV acute graft versus host disease (GVHD) was 38.4% with grade III-IV GVHD in 11.7%. Chronic GVHD was seen in 47.5% of evaluable patients with majority (73%) being limited chronic GVHD. The median follow up of the entire cohort is 32 months (range: 1 - 244). Ten patients had secondary graft failure; of these 7 had a repeat transplant. The 5 year KM estimates of OS for the entire cohort is 64.8 ± 3.3% [Figure 2a]; It was 68.3 ± 5.5% for children (45.7 ± 4.7%) was significantly lower than the OS of age groups 16-30 (75.6 ± 3.6%), 31-50 years (76.2 ± 4.2%) and > 50 years (73.0 ± 4.2%) [p = 0.0001] [Figure 2a].

**Table 2: Response to immunosuppressive therapy (n = 530)**

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<tr>
<th></th>
<th>Complete response (CR)</th>
<th>Partial response (PR)</th>
<th>No response (NR)</th>
<th>Overall response (CR + PR)</th>
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<tr>
<td>Total group (n=530)</td>
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<td>&lt; 15 yrs</td>
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<td>15%</td>
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<td>16 – 30</td>
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<td>31-50 yrs</td>
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<td>&gt;50 years</td>
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<td>60%</td>
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<tr>
<td>Adults</td>
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<tr>
<td>Children</td>
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<td>30%</td>
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<td>40%</td>
<td>38.5%</td>
<td>61.5%</td>
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<tr>
<td>VSAA</td>
<td>16.1%</td>
<td>29.6%</td>
<td>54.3%</td>
<td>45.7%</td>
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Discussion

This retrospective analysis of a large cohort of patients from a single centre examining the role of immunosuppressive therapy and stem cell transplantation in patients with aplastic anaemia demonstrates that between 60-75% of patients can have long term survival with both SCT and IST. Data on IST seems to suggest that adults > 16 years have a 60-65% chance of response to ATG and cyclosporine with low rates of clonal evolution and 5 yr OS ranging between 72-75%. This data seems to reflect data available in literature from around the world where response rates of 60-70% are seen with 5 yr survival rates ranging from 60-85%. The paediatric population seems to be a distinct population with much lower response rates which then translates into lower survival rates. The low response rates have also been reported from other centres in India (response rates of 40-50%) though one centre alone reported very high response rates of 80%.10-13 It is not clear why this population, where inherited or congenital bone marrow failure syndromes have been ruled out in most using a combination of physical examination, radiology and stress cytogenetics, have such low response rates. It is possible that other factors including environmental toxins or other congenital defects may play a role in the pathogenesis of AA in these patients thus reducing the “immune” component in these patients.

With the use of stem cell transplantation, one can cure about 70-75% of patients especially with the use of fludarabine based conditioning. The utility of fludarabine based conditioning has also been demonstrated by other transplant centres from within India.14,15 The CIBMTR data suggests that 80% of patients below the age of 20 years and 65-70% of patients above the age of 20 years have good long term survival and this is what we would aim to achieve. One of the biggest obstacles is the time delay between diagnosis and referral to transplant thus leading to recurrent transfusions, repeated admissions for infection and occasional major bleeds. This delay is partly related to financial constraints towards SCT but also related to slow referrals to a higher centre that can take up a patient quickly for a transplant. In our series, the median time from diagnosis to transplant was 4 months. The ideal goal would be to get patients into transplant within a month but this may be practically difficult to achieve in a country like ours. The use of fludarabine based conditioning regimens has led to a marked reduction in the rejection rates but chronic GVHD remains a major concern especially with the widespread use of PBSCs as the graft source. Newer modalities of GVHD prophylaxis need to be studied which would prove to be efficient but still economical.

In conclusion, both SCT and IST offer good response rates and survival in Indian patients with aplastic anaemia except in children < 15 years who receive IST. Better markers are needed to identify patients who would show response to IST. Overall survival after SCT need to be improved further but more so, the need to reduce the incidence of acute and chronic GVHD.

References


