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Original Research Article

Comparative study to Evaluate the Safety and Efficacy of Equine Antithymocyte Globulin with Hematopoietic Stem Cell transplant in Patients with Acquired Aplastic Anemia

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Abstract:

Background: Aplastic anemia is a hematopoietic stem cell disorders that causes cytopenias in two or more cell lines (red blood cells, white blood cells, and/or platelets), hypoplasia or aplasia of the bone marrow, and a loss of blood cell precursors. It is a fatal condition and the prognosis is highly influenced by the patient's age, severity of the disease and the effectiveness of immediate treatment. Robust treatment options include bone marrow transplantation and immunosuppressive therapies, such as cyclosporine and equine antithymocyte globulin. Notably, patients who have undergone a compatible bone marrow transplant can achieve a five-year survival rate exceeding 75%, demonstrating a strong potential for recovery and significantly enhanced quality of life. Equine anti-thymocyte globulin is a cost-effective alternative with good efficacy and safety, allowing for shorter hospital stays and fewer complications.

Materials and Methods: A retrospective comparative study was carried out in the oncology unit of the State Cancer Institute in Jaipur, Rajasthan. Following Institutional ethical committee approval, the patients' data of two years from May 2022 to June 2024 was analyzed, and a comparison of the safety and efficacy of stem cell transplant and anti-thymocyte globulin was conducted. Data was analyzed with SPSS software with latest Microsoft version.

Results: The present study was carried out among 56 patients. Out of 56, 63% (35) were given Anti-thymocyte globulin (ATG) and in 38% (21) patients bone marrow or stem cell transplant was performed. In ATG group there was a complete response and resolution of acquired aplastic anemia in 51 % (18) patients followed by partial response in 34% (12), no response in 9% (3) and death of 5% (2) patients. Similarly in stem cell transplant patients, successful engraftment was achieved in 76% (16) patients followed by graft failure in 14% (3) and death of 9% (2) patients.

Conclusion: The comparative analysis showed that anti-thymocyte globulin is safe and cost-effective treatment with efficacy comparable to stem cell transplantation. Longer-term research is required to assess the efficacy for future perspectives.

Keywords: Anti-thymocyte globulin (ATG), Stem cell transplant, Aplastic anemia, Cytopenia, Engraftment

Introduction

Severe aplastic anemia represents a critical hematological disorder characterized by bone marrow failure, leading to pancytopenia and the presence of a hypocellular bone marrow. The advent of allogeneic bone marrow transplantation coupled with immunosuppressive therapy utilizing equine antithymocyte globulin (ATG) and cyclosporine has profoundly altered the trajectory of this condition, resulting in a 10-year survival rate for patients receiving either modality of approximately 70% [1].

Aplastic anemia represents an uncommon hematological disorder characterized by a bimodal age distribution. The male-to-female ratio is approximately 1:1. The higher incidence of consanguinity, the preponderance of males, and the

prevalence of younger people suggest that genetic factors may play a role in the pathophysiology of aplastic anemia in the South Asian population [2].

Aplastic anemia affects about two people out of every million each year [3]. A number of hereditary diseases, including Shwachman-Diamond syndrome, Fanconi anemia, Diamond-Blackfan anemia, and dyskeratosis congenita, are characterized by bone marrow failure; however, acquired etiologies of marrow aplasia can also manifest similarly [4]. Medicines (such as chloraphenicol, nonsteroid anti-inflammatory medicines, and chemotherapeutic agents), radiation, hepatitis viruses, and pregnancy are some of the factors that can cause aplastic anemia. In the majority of cases, idiopathic acquired aplastic anemia is diagnosed when no etiologic cause is identified [5].

Symptoms of severe aplastic anemia are caused by reduced hematopoietic cell counts and include anemia-related fatigue and asthenia, recurrent infections (from neutropenia), and increased susceptibility to bleeding or bruises (from thrombocytopenia). Pallor (a loss in skin pigmentation), vertigo, pyrexia, cephalalgia (headache), and dyspnea are other symptoms patients may experience. [6].

It is challenging to find HLA matched donor for transplantation, and only a small percentage of patients have one. Another treatment option, immunosuppressive therapy, has emerged as a result of the scarcity of HLA-matched donors and the complications connected to transplants from alternative donors [7].

The suppression of immunological responses is largely dependent on regulatory T cells. Patients with severe aplastic anemia have a reduced number of these cells, and one way to reestablish hematopoiesis following ATG therapy may be through an increase in regulatory T cells [8].

Individuals who are not eligible for bone marrow transplantation may benefit from immunosuppressive treatment of aplastic anemia with antilymphocyte globulin, methylprednisolone, and cyclosporine, as it seems to be more effective than a combination of antilymphocyte globulin and methylprednisolone without cyclosporine [9].

Materials and Methods

A retrospective comparative study was conducted within the oncology department of the State Cancer Institute located in Jaipur, Rajasthan. Following the approval from the Institutional Ethical Committee, the patient data spanning two-year duration from May 2022 to June 2024 underwent analysis, during which a comparative evaluation of the safety and efficacy between stem cell transplantation and anti-thymocyte globulin was conducted involving a total of 56 patients. Among the 56 patients, 35 individuals received Equine Antithymocyte Globulin, Cyclosporine & Thrombopoietin analogue (Triple Immunosuppressive Therapy), while the remaining 21 patients underwent hematopoietic stem cell transplantation. Triple Immunosuppressive Therapy (IST) was administered to patients who are either unwilling to undergo hematopoietic stem cell transplantation (HSCT) or who do not possess a matched sibling donor. Data included pretreatment blood values, date, type, source, and procedures for therapy, as well as demographics, response to therapy, status at the last follow-up, causes of mortality, and complications.

Inclusion criteria include individuals aged between 12 and 60 years with a definitive diagnosis of acquired aplastic anemia characterized by a bone marrow cellularity of less than 25%. Also, absence of any previous history pertaining to hematopoietic stem cell transplantation (HSCT) and presence of a human leukocyte antigen (HLA)-matched sibling or haploidentical donor in stem cell transplant group and satisfactory organ function encompassing renal, hepatic, and cardiac systems.

Exclusionary parameters include genetic hematopoietic insufficiency syndromes. Ongoing infections that is unmanageable with antibiotic treatment, Gestation or breastfeeding female. Previous administration of immunosuppressive agents within the preceding three months.

Diagnostic Criteria: Aplastic anemia is postulated in individuals, notably in the younger demographic, exhibiting pancytopenia. A bone marrow cellularity of less than 25% (hypocellularity) and the presence of two or more of the following criteria—a neutrophil count below 500/microL (below 0.5 × 10^9/L), a reticulocyte count below 60,000/microL (below 60 × 10^9/L), and a platelet count below 20,000/microL (below 20 × 10^9/L)—are indicative of severe aplastic anemia.Very severe aplastic anemia is defined as having an absolute neutrophil count < 200/microL (less than 0.2 x 10^9/L) [10].

In immunosuppressive therapy group, response to treatment was assessed according to published criteria; Complete response (CR) was defined as haemoglobin (Hb) >10 g/dl, absolute neutrophil count (ANC) >1.5 × 10^9/l and platelet count >100 × 10^9/l. Partial response (PR) was defined when haematological parameters were not sufficient for a Complete response but there was increase from baseline values with at least Hb >7 g/dl, ANC > 0.5 × 10^9/l and platelet count >30 × 10^9/l . In general, partial response was defined as no longer meeting the criteria for severe aplastic anemia and no transfusion dependence for platelets or red blood

cells. Continuous transfusion dependency was classified as no response. Relapse was defined as a decrease in blood counts to values either requiring transfusions or needing reinstitution of immunosuppressive therapy or HSCT [11].

Similarly, in HSCT group, Hematopoietic stem cells (HSC) move to bone marrow niches, multiply, and maintain long-term hematopoiesis through a process known as engraftment. It is essential for general post-transplant survival. Platelet engraftment (platelet count >20 × 10^9/L without transfusion for 7 days) and neutrophil engraftment (>500 × 10^6/L for 3 days in a row) are among the definitions. The absence of hematopoietic cell engraftment (primary graft failure) or the loss of a formerly functional graft (secondary GF) is two significant complications associated with a poor prognosis. HLA discrepancy, ABO mismatching, the graft source, cell dosage, graft manipulation, infections, reduced-intensity conditioning, and primary diagnosis (e.g., severe aplastic anemia, hemoglobinopathies, myeloid diseases) are risk factors. Graft rejection, which exclusively applies to allogeneic transplants, is the immune system's reaction to donor cells being rejected by remaining host cells [12].

Treatment regimen: (a)**Triple Immunosuppressive Therapy**: The standard dosage is 40 mg/kg of equine ATG per day for four days, along with 5–12 mg/kg of cyclosporine per day, adjusted to reach blood trough levels of 150–250 ng/mL, with thrombopoeitin analogue. (b)

Hematopoietic Stem Cell Transplant: Stem cell infusion on Day 0. The conditioning regimen consists of ATG, fludarabine, and cyclophosphamide. Accordingly, Methotrexate and Cyclosporine were used for GVHD Prevention and Prophylaxis [13,14]

The resulting study groups were categorized as Triple Immunosupressive therapy (Triple IST) and Hematopoeitic Stem Cell Transplantation (HSCT). Triple IST was given to patients who did not have a matched sibling donor or who were unwilling to have hematopoietic stem cell transplantation (HSCT). The relevant data was analyzed with appropriate statistical tools.

Results:

Patients were categorized into two main groups after applying inclusion & exclusion criteria's , one group consisting of 35 patients from a total of 56 patients that were given a combination of equine ATG, Cyclosporine, and Thrombopoietin Receptor Agonists (TPO-RA) like Eltrombopag or romiplostim symbolisized as Triple Immunosuppressive therapy or Triple IST. Gender predisposition in these patients was 66% (23) Males and 34% (12) females with an average age of 32 years **[Figure 1]**.

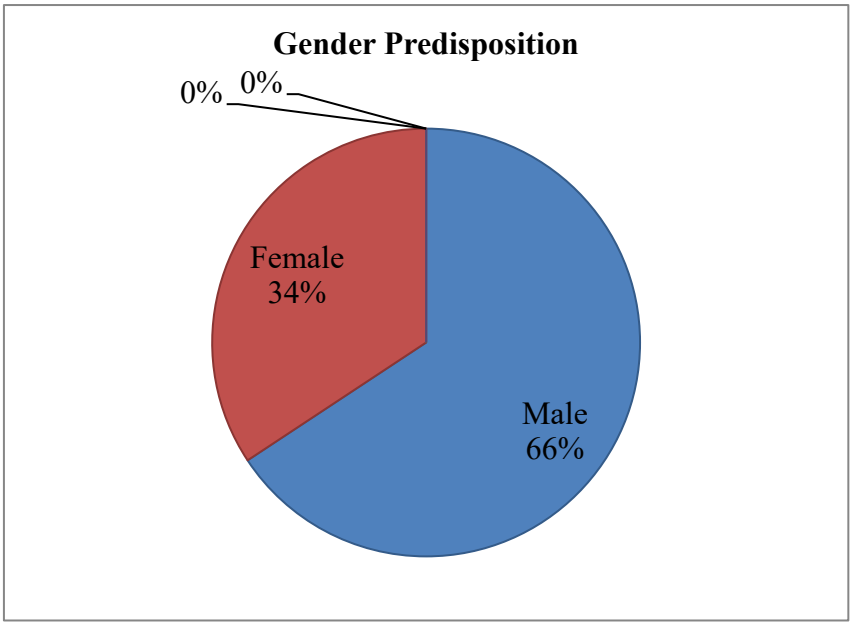

Figure 1: Gender Predisposition in Triple IST group

Among the patient population 23% (8) patients were diagnosed with very severe Apastic anemia, 26% (9) with severe and 51% (18) with non-severe type of Apastic Anemia **[Figure 2]**.

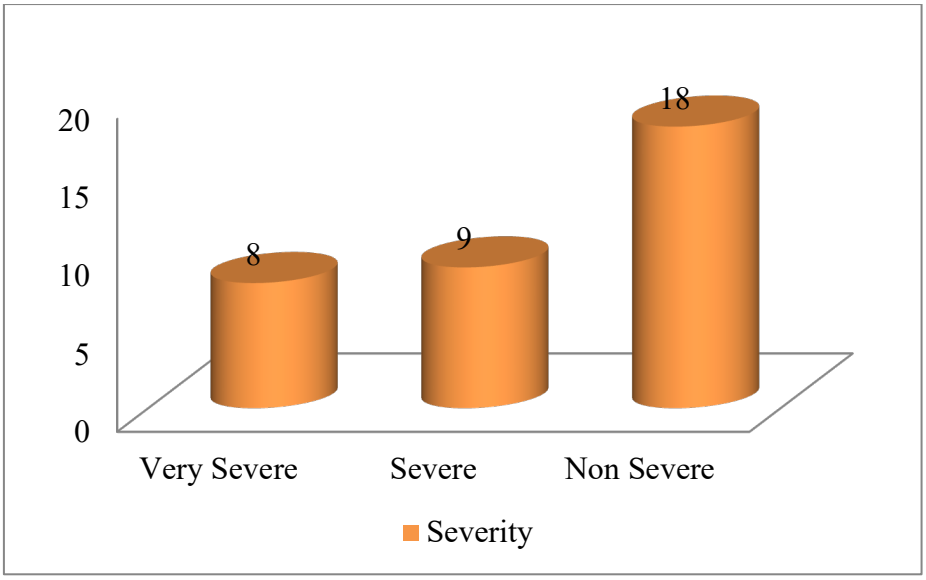

Figure 2: Severity of Aplastic Anemia in Triple IST group

In Triple IST group 51.4% (18) patients demonstrated complete response, 34.2% (12) attained partial response and 8.5% (3) showed no response and 5% (2) patients succumbed to death due to disease severity and complications **[Figure 3].**

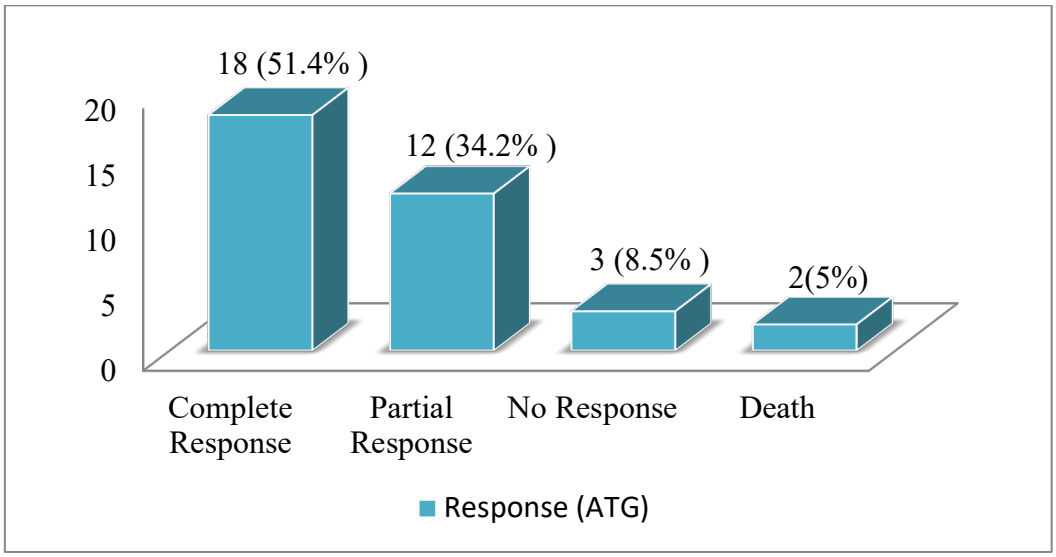

Figure 3: Response seen in Triple IST group

Another group was Hematopoietic Stem Cell Transplant (HSCT group) in which 38% (21) patients were enrolled who were willing to undergo bone marrow transplant. Out of 21, the donor and patient sharing all the same human leukocyte antigen (HLA) markers also known as Full Match siblings or Matched Sibling Donor (MSD) were 57% (12) and 43% (9) were haplo-identical or half match from a donor who is a 50% genetic match, often a parent, child or sibling [Figure 4]. The average age in this group was 26 years.

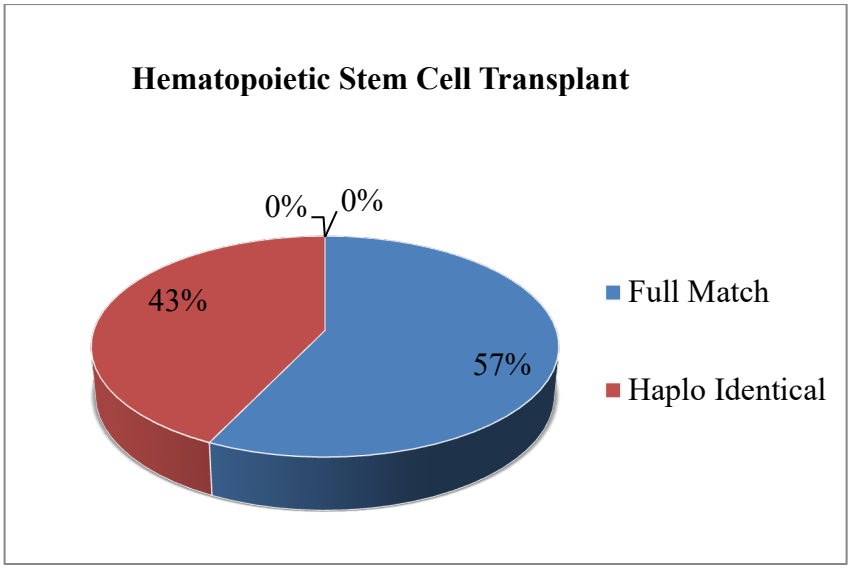

Figure 4: Hematopoietic Stem Cell Transplant (HSCT) group

Table 1: Reponse after Hematopoetic Stem Cell Transplant (HSCT)

Total Patient	Full Match	Haplo identical	Average Age (In Years)	Response		
21	12	09	26	Successful engraftment	16	76.1%
				Graft failure	03	14.2%
				Death	02	09%

In bone marrow transplant patients, there was a successful engraftment in 76% (16) patients, graft failure was reported in 14% (3) patients and 9% (2) patient were not able to survive due to disease progression or complications.

The overall comparative status of both the groups revealed that although the survival rate of both the groups was similar but overall HSCT provides a more favorable opportunity for achieving a curative result and enhanced failure-free survival but graft failure, graft versus host disease, economic burden and long hospital stays are major challenges associated with HSCT. Conversely, patients undergoing immunosuppressive therapy (IST) face the potential for incomplete recovery, relapse, or the development of late-onset clonal disorders. Successful engraftment was seen in 76% of the patients whereas 51% patients showed complete response and 34% showed partial response with immunosuppressive therapy.

During treatment in both the groups all individuals received prophylactic measures against infectious diseases and standard supportive interventions, which encompassed the administration of red blood cell transfusions and platelet concentrates, alongside the initiation of broad-spectrum intravenous antibiotics in response to febrile episodes and infections. The patients of both the groups were either managed within laminar airflow environments or in single rooms equipped with reverse isolation protocols.

Discussion

An immune-mediated condition known as acquired aplastic anemia (AA) is characterized by hypocellular bone marrow and pancytopenia. Deregulated T-cells destroy the marrow's hemopoietic cells, which results in bone marrow hypocellularity. Although hematopoietic stem cell transplantation (HSCT) offers a chance for recovery, most patients are not suitable candidates for this treatment because of their old age, comorbidities, or inability to find a donor who is histocompatible. Immunosuppressive therapy (IST) with cyclosporine and anti-thymocyte globulin (ATG) can achieve similar long-term survival for these individuals [15].

A bimodal age distribution of 15–25 years or ≥60 years was identified for the median age at presentation from western countries. The median age at presentation in India was 25 years (range 2–83 years) and 36.5 years (range 19–77 years), which is younger than in western nations, according to the majority of research [16].

The final analysis in the Jain A et al. study included 93 AA patients who received hATG between January 2003 and December 2021. The study population's mean age was 33.4 years (SD ± 15.3). Men made up sixty (64.5%) of the patients [17]. Similary in our study the study group receiving equine ATG had an average age of 32 years consisting of 66% (23) Males and 34% (12) females.

According to Iqbal A. et al., immunosuppressive medication (Thymogam 40 mg/kg/d for four days with oral Cyclosporine from Day 1) was administered consistently to all 18 patients, 14 of whom were severe and four of whom were very severe. In 94.44% of the patients, cyclosporin A was taken concurrently. At two-year follow-up, the death rate was 11.1% and 66.7% of patients showed improvement [18]. In our study, 35 patients were given triple immunosuppressive therapy that included equine ATG, Cyclosporine and TPO analogue. 51.4% (18) patients achieved complete response, 34.2% (12) showed partial response.

In another study conducted by Huang Li et al, the ratio of surviving patients at the last follow-up and sex did not significantly differ between the two groups. Patients in the IST/EPAG (immunosuppressive therapy/eltrombopag) group, on the other hand, were significantly older than those in the MSD-HSCT group (matched sibling donor- hematopoietic stem cell transplantation) median age of 29.5 years (P =.001) [19]. Similar to this in our study, patients undergoing HSCT have a mean age of 26 years and were comparatively younger than Triple IST group.

In Wilfred G et al analysis of 80 patients was done. 49 patients (61.3%) experienced complete remission at a median follow-up of 54 months, while 8 patients (10.0%) experienced partial remission during stem cell transplant. Among patients who had HSCT within three months of diagnosis, the projected 5-year overall survival was 63% or higher. Pre-engraftment death was the primary cause of mortality for twenty-two patients (27.5%) who passed away within 100 days following transplantation [20]. In contrast, 76% (16) of the bone marrow transplant patients in our study experienced effective successful engraftment, 14% (3) experienced graft failure, and 9% (2) succumbed to death due to disease progression or various complications during transplant.

Immunosuppressive treatment and stem cell transplantation produced similar overall results in our comparative analysis of acquired aplastic anemia. Because of its affordability and reduced risk of complications, IST has proven beneficial and can be used for a wider range of patients. Despite being linked to greater response rates, HSCT was limited by longer hospital stays, more problems, and the requirement for a qualified donor. Individualized treatment decisions should take into account the patient's characteristics, the availability of resources, and the treatment's long-term viability.

Conclusion

Our study demonstrates that both immunosuppressive therapy (IST) and hematopoietic stem cell transplantation (HSCT) are effective treatment options for patients with acquired aplastic anemia with comparable overall outcomes. IST offers significant advantages in terms of cost-effectiveness, fewer complications, and reduced hospital stay, making it a more practical and accessible option for majority of patients. In contrast, HSCT provides a higher response rate but it is associated with longer hospitalization, higher complication rates, and the critical challenge of HLA matched donor availability. Therefore, treatment selection should be individualized, taking into account patient profile, donor accessibility, financial feasibility and institutional expertise.

Limitations: A limited sample size was taken as well as the study was single-centered.

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