Review Article

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RECENT ADVANCES IN DIAGNOSIS AND TREATMENT OF APLASTIC ANEMIA: A REVIEW

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ABSTRACT Aplastic anemia (AA) is a rare, life-threatening condition where bone marrow failure leads to pancytopenia. It manifests with anemia, bleeding, and susceptibility to infections, impacting a wide age range but most prevalent among the young and elderly. Incidence rates vary globally, higher in Asia than in the US and Europe. AA is classified into congenital and acquired forms, with acquired often idiopathic. Diagnosis involves genetic testing, bone marrow biopsy, and specific markers. Advances in immunosuppressive therapy (IST) and stem cell transplantation (HSCT) have greatly improved survival rates, nearing 90%. Ongoing research in genetics and molecular science promises continued progress in AA treatment.

KEYWORDS : Aplastic anemia, pancytopenia, diagnosis, immunosuppressive therapy, stem cell transplantation

INTRODUCTION

Aplastic anemia (AA) is a rare and potentially fatal bone marrow failing disorder that results in pancytopenia. Patients often first present with symptoms of anemia, bleeding, and infection. Although AA can affect individuals of any age, it is most commonly observed in young people (ages 10–25) and the elderly (over 60 years), with no significant gender differences[1,2]. While the prevalence of AA is 2-3 times greater in Asia, with significant regional variation, it is less than 2.5 per million in the US and Europe: China has 7.4 million, Thailand has 3.7–5.0 million, and In Malaysia, there are 4.8 per million [3,4]. Few research from India suggests that aplastic anemia is identified in 20–30% of cases of pancytopenia[5]. In a 2015 study conducted over a seven and a half-year period at a prestigious institute in New Delhi, 1501 individuals with aplastic anemia from 20 different states were enrolled [6]. The frequency of aplastic anemia in children in Lucknow was determined to be 6.8 per million [7]. In the northern regions of West Benga, the incidence of severe and non-severe aplastic anemia was found to be 33.33% and 57.14%, respectively[8].

Incidence rates of AA is influenced by several environmental factors such as drugs, toxins, and chemicals [9]. Recent advancements in immunosuppressive therapy (IST) and hematopoietic stem cell transplantation (HSCT) have significantly improved patient survival rates up to 90%, which has been accepted from last three decades[10,11].

Classification

AA is classified into congenital and acquired forms. Congenital AA is rare and includes conditions like Fanconi anemia (FA), dyskeratosis congenita (DKC), congenital pure red cell aplasia (DBA), and Shwachman-Diamond syndrome (SDS). Acquired AA includes Idiopathic, drugs and chemicals, ionizing radiation etc. Approximately two-third cases of aplastic anemia are idiopathic [12,9]. The first case of aplastic anemia was published in 1888 by Ehrlich[13].

On the basis of the severity aplastic anemia is categorized into three types such as severe aplastic anemia (SAA), very severe aplastic anemia (VSAA) and nonsevere aplastic anemia. Camita et al, 1976 defined SAA by peripheral blood findings of at least two of the following: neutrophils less than 500cells per cubic millimeter, platelets less than 20,000 cells per cubic millimeter, and reticulocyte corrected for packed cell volume (PCV) less than 1%. Additionally, the bone marrow must show either cellularity between 25% and 50% with less than 30% hematopoietic cells [14]. Whereas, very severe aplastic anemia (VSAA) defined by Bacigalupo et al,1988 includes the same criteria as SAA but there is less than 200 cells per cubic millimeters of neutrophils[15]. Nonsevere apalstic anemia is characterized by marrow cellularity less than 25% and peripheral blood cytopenia not meeting the criteria for SAA.

Diagnosis

Aplastic anemia (AA) is a rare and complex blood disorder characterized by pancytopenia and hypocellular bone marrow, requiring accurate diagnosis to distinguish it from other conditions and develop an effective treatment plan. Laboratory markers, such as GPI-deficient blood cells and HLA class I allele-lacking leukocytes, aid in diagnosis and prognosis [16]. However, diagnosis is challenging due to the need to differentiate between acquired AA and inherited bone marrow failure disorders (IBMFD), with evolving techniques and genetic underpinnings adding to the complexity [17]. It is critical to identify hereditary disorders that affect AA diagnosis and therapy, as evidenced by recent advances in genetics and molecular science, which offer diagnostic and prognostic information. Essential bone marrow biopsy, clearing out infections and genetic illnesses, pancytopenia with hypocellular bone marrow, and the exclusion of other conditions such as congenital marrow failure and myelodysplasia syndromes are critical diagnostic points. Myelodysplastic syndrome (MDS), paroxysmal nocturnal hemoglobinuria (PNH), and hereditary marrow failure syndromes such as Fanconi anemia and telomere illnesses are examples of differential diagnoses. The diagnosis of AA is based on peripheral blood pancytopenia and bone marrow hypoplasia/aplasia [18,19,20]. The disease has an incidence of 2-3 per million per year and is characterized by pancytopenia with hypocellular marrow[21,22].

Clinical Presentation

Aplastic anemia (AA) is marked by reduced levels of red blood cells, white blood cells, and platelets. Neutropenia, which is defined as abnormally low neutrophil levels, contributes to the clinical picture [23,24]. Neutropenia is associated with infections but the infections are less common at presentation despite severe neutropenia [25]. Patients with AA often present with fatigue, pallor, petechiae (small red or purple spots), and bleeding due to thrombocytopenia. Acquired AA is usually idiopathic and peaks in the elderly and young adults. Pancytopenia may be discovered by accident, and a history of single lineage cytopenia can occur before the diagnosis of severe aplastic anemia[26]. In aplastic anemia, there is no enlargement of lymph nodes, liver or spleen. If it is found to be enlarged, diagnosis other than aplastic anemia should be considered[27].

Treatment, Studies And Recent Advances

Allogeneic HSCT with HLA-matched sibling donor is the main treatment for severe aplastic anemia. If no donor is available, IST with ATG and CsA is the preferred initial therapy. This combination is the standard regimen for aplastic anemia patients [28]. A study analyzed 91 patients with aplastic anemia, focusing on the efficacy of Immunosuppressive Therapy (IST) using horse ATG and CsA. Most patients had severe symptoms, and around 70% could achieve prolonged survival rates with IST, especially using indigenous hATG. In 60–75% of cases, IST with horse ATG CsA produced hematologic responses; younger patients fared better than older ones. Horse ATG is the most studied preparation for severe aplastic anemia. Rabbit ATG is popular for SAA treatment. It was first used in refractory cases and

showed good activity. Because of its greater lymphocytotoxicity, rabbit ATG protects kidney allografts better than horse ATG. This implies that as a first SAA treatment, rabbit ATG may be better than horse ATG. [29]. The combination of hATG and CsA is commonly used for severe aplastic anemia patients not eligible for HSCT due to various reasons. Hematologists often face challenges like lack of suitable donors, financial constraints, procedural limitations, and facility accessibility. However, the high cost and uncertain availability of hATG remain a significant barrier to treatment for these patients [28,30].

Advancements in technology for HLA-typing in the late 1990s led to improvements. Current centers now match for 10 alleles using high-resolution technology instead of six. Some small studies show promise with low-dose TBI or fludarabine, but more extensive trials are needed. A proven treatment for severe aplastic anemia in young people is hematopoietic stem cell transplantation from an HLA-identical sibling. Young patients with severe neutropenia benefit from a proactive transplant approach. If patients do not respond to immunosuppressive therapy and have a suitable donor, transplantation should be considered. Unrelated donor transplantation has historically been suggested for younger patients after unsuccessful rounds of immunosuppressive therapy [31].

A study aimed to validate Thiotepa-based PTCY approach in haploidentical HSCT for aplastic anemia. All 15 patients had successful implantation, with engraftment times of 14 days for neutrophils and 12 days for platelets. Main toxicity was canker sore, three patients had hemorrhagic cystitis. Incidence of acute and chronic GVHD was 13.3% and 6.7%, respectively, with no severe cases. All 15 patients survived with no GVHD relapse, 14 had complete remission. Low CMV and EBV reactivation rates were observed due to prevention strategy. Thiotepa-based haplo-HSCT had positive outcomes for aplastic anemia patients, leading to prolonged survival and reduced complications [32]. In Japan, umbilical cord blood transplantation is studied as an option for aplastic anemia. A comparison showed similar survival outcomes between UCBT and haploidentical HSCT with PTCY, but PTCY-haplo had quicker engraftment [33].

Thrombopoietin receptor agonists were tested in IST-refractory SAA, first in a pilot study on 25 patients and then in an extension with 43 patients, resulting in a 40% hematologic response with multilineage improvements from eltrombopag. Studies focused on raising platelet counts found unexpected bi- and tri lineage recoveries, with clonal evolution observed in certain patients, especially non-responders, in line with historical reports of 15% incidence and no significant increases in marrow reticulin deposition or thrombosis. In a 40-patient study, eltrombopag at 150 mg on day 1 for 6 months resulted in a 50% hematologic response, leading to some patients stopping the drug successfully while others needed to restart due to declining blood counts. The combination of data from two studies involving 83 patients showed 19% developing abnormal karyotype, mostly within the initial 6 months of eltrombopag treatment, indicating a possible association between eltrombopag and abnormal progenitor cell stimulation. This connection is further supported by retrospective studies on refractory SAA [34].

Some centers use upfront MUD HSCT. Recent trials explored alternative donor HSCT for severe aplastic anemia. Concerns include GVHD, graft rejection, mortality, and infertility. NAPAAC is conducting an RCT comparing upfront MUD transplants to IST for pediatric patients with severe aplastic anemia [35].

The ACCESS study showed positive outcomes for adults with hematologic malignancies. Interim results were presented at the European Haematology Association Annual Meeting by NMDPSM and CIBMTR. Patients who received post-transplant cyclo-phosphamide (PTCy) prophylaxis after receiving a peripheral blood stem cell (PBSC) transplant from an HLA-mismatched unrelated donor (MMUD) had good overall survival (OS) and GvHD-free, relapse-free survival (GRFS) rates one year after the transplant[36].

Progress in understanding AA pathophysiology made through gene sequencing. Gene sequencing and flow cytometry useful for assessing T-cell genetic abnormalities. Single cell RNA sequencing allows direct analysis of cell transcriptomes. Technique provides insight into AA pathophysiology and gene-targeted therapy strategies. Progenitor cell scarcity hampers AA molecular pathophysiology study. iPSCs hold potential in overcoming this challenge by becoming hematopoietic cells. Combining iPSCs with RNA splicing and CRISPR/Cas9 may aid in studying genetic events in AA biology. Development of an appropriate animal model for AA research possible [37].

CONCLUSION

Pancytopenia and bone marrow failure are hallmarks of the rare and potentially fatal disease known as aplastic anemia (AA). Due to environmental variables, Asia has a higher incidence of it than either Europe or the United States. There are two types of AA: congenital and acquired, the latter of which is primarily idiopathic. The diagnosis process includes utilizing genetic testing, bone marrow biopsies, and laboratory markers to differentiate AA from related disorders.

Patient outcomes have greatly improved with recent treatment developments, such as immunosuppressive therapy (IST) using antithymocyte globulin (ATG) and cyclosporine A (CsA) and hematopoietic stem cell transplantation (HSCT) from HLA-matched sibling donors. Promising outcomes have been observed in innovations such as rabbit ATG, haploidentical HSCT, umbilical cord blood transplantation, and thrombopoietin receptor agonists such as eltrombopag.

Despite persistent challenges including as treatment-related mortality and graft versus host disease, ongoing research in genetics and molecular science is improving our knowledge of and ability to treat AA. These developments give patients with AA hope for improved care and higher survival rates.

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