Review on Aplastic Anemia

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***Abstract*- Aplastic Anemia (AA) is a rare condition with the probability of 2-6 cases per million per year occurrence. In this condition, bone marrow is not capable of forming new blood cells. There are various causes reported, e.g. Radiation, Chemicals, NSAIDS, as well as it can be a result of genetic alterations. It was discovered by Dr. Paul Ehrlich and named by Anatole Chauffard. Primary symptoms of AA are fatigue, weakness, dizziness, excessive bleeding and quick response to infection. The diagnosis of AA is a bone marrow biopsy. Though it is a serious condition with high life- threatening risk but it can be controlled and treated successfully although there is no definite cure found yet. Immunosuppressive agents and hematopoietic stem cell transplant (HCT) are majorly offered treatment along with other medications like antibiotics and bone marrow stimulators. The patient also must go through regular blood transfusions. As there are improvements in the provision of treatment and supportive measures, they have contributed to the increase in survival rate of patients**

***Keywords*: Aplastic Anemia (AA), Bone Marrow Biopsy, Immunosuppressive agents, Hematopoietic stem cell transplant (HCT), Bone marrow stimulator, Pancytopenia, striking hypocellular, Fanconi Anemia, Dyskeratosis congenita (DC), Shwachman Diamond Syndrome, Diamond Blackfan Anemia, Allogeneic hematopoietic cell transplant, Anti thymocyte globulin (ATG), Acquired Aplastic Anemia, Autologous bone marrow transplant, Lymphoproliferative disorders.**

Introduction

Aplastic Anemia (AA) is a rare condition which occurs due to hematopoietic failure, in which bone marrow fails to produce new blood cells due to injury. This condition further leads to pancytopenia.[1] Aplastic refers to the inability of the bone marrow to produce new blood cells along with the Anemia (excessive loss of blood from the body). Bone marrow biopsy remains the primary preference for the diagnosis; however, it is critical to differentiate between acquired and inherited condition.[2],[3] This was firstly discovered by Dr. Paul Ehrlich, who diagnosed the hypocellular bone marrow condition in a young female Her bone marrow was studied and labeled as "striking hypocellular". Further, this Condition was analyzed by French internist, Dr. Anatole Chauffard. And in 1904 he introduced the term "Aplastic Anemia". [5],[6] AA can occur in males as well as females of any age group, but majorly it occurs between 15- 25 and after 60s. However, its etiology is yet to be understood. Although it occurs rarely According to the incidence studies in Europe and north America is estimated 2-6 cases /million /year. Still, it can be cured with the proper care and treatments with Immunosuppressive agents and transplants. As the treatment faces challenges and high risk. Eventually AA is a life-threatening condition [3],[5]

History

Dr. Paul Ehrlich firstly discovered this rare disease by narrating the case of a pregnant lady in 1888 whose cause of death was bone marrow failure. In 1904, this condition is named Aplastic Anemia by Anatole Chauffard. In between 1920s to 1930s, Alice Hamilton and Harrison found out the reason of bone marrow failure in workers in United State who continuously comes into the exposure of Benzene. Furthermore, in the late 1940s and early 1950s, findings stated that consumption of Chloramphenicol is another cause of AA Fortunately Neal young from John Hopkins introduced an immunosuppressive regime which provides effective treatment for AA.[6],[7]

Classification

There are two main types of AA, i.e., Acquired Aplastic Anemia and Inherited Aplastic Anemia, but according to blood count these are divided in three types

1) Non severe Aplastic Anemia (nSAA)
2) Server Aplastic Anemia (SAA)
3) Very severe Aplastic Anemia (vSAA)

The required criteria for the incidence are given in Table 1. [7],[8]

	nSAA	SAA	vSAA
Reticulocytes	<20 G/L	<20 G/L	<20 G/L
Platelets	<50 G/L	<20 G/L	<20 G/L

Neutrophilic granulocytes	<1 G/L	<0.5 G/L	<0.2 G/L

Table 1

Causes

The AA conditions onset of occurrence either acquired during the life period or inherited. In acquired condition of AA developed after birth can be caused by damaging of the bone marrow which is further unable to proceed with the production of new blood cells due to the exposure to radiation, [10][11] chemicals i.e. Benzene,[12][13] consumption of chloramphenicol,[14] Hepatitis Associated Aplastic Anemia (HAAA) [15] or viral infection along with other unknown. infections which lead to the destruction of blood forming cells by lymphocytes. [9]

In inherited condition of AA, the anemia is passed through the genes from the parent to offsprings some inherited conditions lead to cause serious damage to bone marrow e.g. Fanconi Anemia is included with progressive bone marrow failure and increased risk of malignancy. [16]

Dyskeratosis congenita (DC) is a bone marrow failure and cancer predisposition syndrome mainly caused by defect in telomere biology. [17]

Shwachman Diamond syndrome is an autosomal recessive disorder which proceed with inherited bones marrow failure.[18]

Diamond Blackfan anemia is due to the genetic mutation in the ribosomal protein on chromosome. It is associated with congenital bone abnormalities. [19]

Symptoms

Symptoms seem to be equally distributed among the gender and age criteria which are related to pancytopenia (including weakness, fatigue, skin rashes, rapid heart rate, shortness of breath, bleeding problems, infections). [1],[20]

Diagnosis

The most preferable assessment in bone marrow biopsy is done by taking a small sample of bone marrow from the pelvis. Further the analysis of sample is done. In AA condition the count of the blood cells determined less than usual. Gives the confirmation of the Aplastic Anemia.[4],[21]

Treatment

The treatment of AA is given with respect to the age of patients, type of AA, donor availability and performance status. The initial treatment for this condition is blood transfusion and medication. For young patients who are below 50 years allogeneic hematopoietic cell transplant (HCT) is suggested. And for older patients above 50 years immunosuppressive therapy is preferred. [1] Aplastic Anemia can be treated by various therapies and transfusion of bone marrow.

• Blood transfusion

It is a temporary solution for the condition which prevent symptoms occurring due to the AA But it may lead to other problems like transfused red blood cells containing iron can further damage organs know as hemochromatosis; consulting physician can provide treatment for removal of excessive irons as well as after some period body develop antibodies which destroys transfused blood cells but can be prevented by the medication provided by physician. [22], [24]

• Immunosuppressive therapy (IST)

It is frequently preferred for older patients (above 50 years), generally used for patients who cannot undergo bone marrow transplantation. Anti thymocyte globulin (ATG) Cyclosporine is the agent majorly used to suppress the immune system and prevent the damage of bone marrow. [22]

It is especially used in Acquired Aplastic Anemia conditions. Between 2012 to 2015 study was performed separately on Childrens and adults, where 99 AA patients including 4 patients of nSAA, 57 patients of SAA and 30 patients VSAA are treated with IST. Within 2 years the response is observed in 23.5% adults and 39.1% Childrens, overall observation is 68.1%. The results show the effectiveness of IST. [23]

• Bone marrow transplant

Bone marrow transplant is also called stem cell transplant or hematopoietic stem cell transplant. It includes transfer of healthy stem cells to the patient's body and replacing the damaged stem cell, but the limitation is the donor's cells must be closely matched to the patient's cell. Siblings' cells are preferred firstly but in circumstances like if there is no match in family searching of donor is done through National Marrow Donor Program. Though it consists of risks, still it is the only possible cure till this date. [22]

Before the transplant the abnormal cell present in the bone marrow of patients is destroyed and the immunosuppressive agents are given. By this patient body can efficiently adapt the transplanted cells. The transplantation is done by the intravenous catheter. The cells reach bone marrow with the help of blood. Furthermore, the patient is kept under the observation of respective Physican. [24] Bone marrow transplants occur in different types i.e.

Autologous bone marrow transplant

This transplant is often known as rescue than transplant because in this the doner cells are collected from patients by bone marrow harvest or apheresis.

Allogeneic bone marrow transplant

The doner must be genetically similar to the patient, usually siblings. But it May includes other donors i.e., a parent or unrelated bone marrow transplant.

Umbilical cord blood transplant

The stem cells are taken right after the delivery of a child. The cells are tested, typed, counted, and Frozen and used when they are needed. [24] [25]

• Medicine

Medicine is not the accurate cure, but it helps to proceed the treatment and minimize the risk. Medicine leads to the improvement in a patient's condition. There are some medicines which are preferably used and frequently prescribed by physician in AA condition e.g. Erythropoietin is used as bone marrow stimulator Azacitidine or decitabine as hypomethylating agents, Lenalidomide as an immune modulator and other antibiotics to provide protection against infections. [22]

Conclusion

AA is a serious condition in which the survival rate depends upon the severity, patients age and patients' response to the treatment. In the past 30 years the study reported that the increase in the survival rate for AA patients is due to immunosuppressive agents and hematopoietic stem cell transplantation. 5-year survival is 75% for the patients with HCT. The reason for the demise of the untreated AA patients is majorly found to be infections, bleeding or lymphoproliferative disorders. Patients with transplantation may face graft failure. [1]

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