Supportive Care and Newer Therapies in Aplastic Anaemia

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Introduction

The prognosis of patients with aplastic anaemia (AA) has improved in the last few years.¹-⁴ This improvement has occurred not only because of immunosuppressive therapy (IST) and stem cell transplantation (SCT) in increasing number of patients but also contributed by improvement in supportive care.⁵-⁸ The supportive care in AA consists of treatment and prevention of infections and bleeding, the two main complications which are responsible for mortality in patients with AA.

1. Management of Infections⁹,¹⁰:
AA patients are at risk of getting infections because of their low absolute neutrophil count (ANC).¹¹ As the ANC goes down, the risk of bacterial, fungal and viral infections increases. Hence the highest risk is in patients who suffer from very severe AA (ANC < 200/ml).

a. General recommendations
i. For patients: The general advice given to patients with severe and very severe AA are that they should preferably stay in protective environment, avoid going to crowded places, eat cooked food (or avoid raw food).¹² However, the evidence for all these recommendations is weak. Nevertheless, these suggestions are given to all patients of AA as most patients belong to low and middle socioeconomic status in India and general hygienic conditions and living environment is poor. If patients are capable of self care then they should themselves maintain personal hygiene as much as possible in the form of daily bath, changing clothes daily, brushing teeth after every meal with soft brush (however, if there is gum or dental bleeding then brushing could be avoided temporarily). Antiseptic mouth wash (e.g. Hexidine) should be done daily after meals to take care of oral hygiene. If patients have constipation, liberal laxatives should be used. Seitz bath is a good practice in neutropenic patients to reduce perianal infections. Patients should also be physically active and should not confine themselves to bed unless they have Fever and severe anaemia.

ii. General instructions to hospital staff handling the patients:
Patients with AA are at high risk of acquiring infections hence use of alcohol based hand rub or soap water hand washing before touching these patients is recommended. Physicians, nursing staff and other ancillary staff including relatives taking care of patients must follow these simple but effective anti infective measures. Isolation during admission is preferable. Although HEPA filter rooms with positive pressure are ideal for managing such patients; in resource constraints setting it may not be possible. Physicians and more importantly administrative staff of hospital should be sensitised to the need of neutropenic ward in the hospitals where not only patients with aplastic anaemia but also chemotherapy induced febrile neutropenia should be cared. Relatives and people visiting these patients and ward should be kept to minimum to prevent occurrence of cross infections. Staff who has cough and cold or symptoms of upper respiratory tract infections should also avoid exposing themselves to these patients. Visitors are also instructed not to bring live flowers...

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in these wards as live flowers carry fungal spores. The intravenous lines and catheters should be handled very carefully in these patients because of two main reasons. Firstly, these patients require repeated venepuncture for blood and blood product transfusions and intravenous antibiotics. Hence preservation of intravenous lines should be maintained. Second and more importantly the intravenous lines are important source of infections if not handled carefully.

b. Medical management: The medical supportive care consists of red blood cell transfusion, platelet transfusion and rarely granulocyte transfusions. Haematopoietic growth factors, prophylactic antibiotics and antifungals are used in special circumstances.

i. Prophylactic use of antibiotics: The practice of using prophylactic antibiotics in patients with severe and very severe AA varies from centre to centre. Most centres use prophylactic antibiotics in patients who receive IST with ATG and cyclosporin or are undergoing allogeneic SCT till recovery of ANC is above 500/ml. Centres treating these patients should evolve their own hospital antibiotic policies based on the prevailing infection rate in their hospital. Prophylactic antibiotics choice depends upon the prevailing bacterial flora and antibiotic policy of the hospital. The disadvantage of use of prophylactic antibiotics is development of resistance and increased incidence of some other bacterial infections (e.g. patients on prophylactic quinolones are at a higher risk of getting Staphylococcal infections).

ii. Prophylactic use of antifungals: Primary antifungal prophylaxis is used frequently in patients with AA especially among patients on IST therapy or undergoing allogeneic SCT. The drugs used for primary antifungal therapy depends upon centre to centre but the drugs used should preferably be active against aspergillus or mould infections. This primary prophylaxis is continued till recovery of ANC to above 500/ul. The secondary antifungal prophylaxis (past evidence of invasive fungal infection) is continued till full recovery of neutrophil count (ANC >1500/ml). For prevention of Pneumocystis jirovecii infections, most centres do not use any prophylaxis. However some centres in the west do use prophylaxis with nebulised pentamidine. A very few centers use oral sulphamethoxazole and trimethoprim combination post IST for one month since in this period the risk of PCP is highest because of concomitant use of high dose corticosteroids for the prevention of serum sickness. However, sulphamethoxazole is myelosuppressive and hence should not be used beyond a certain period of time. PCP prophylaxis is routinely used in patients post allogeneic SCT.

Use of prophylactic antifungal in patients among patients who are only on supportive therapy is controversial. Surely antifungal prophylaxis is not to be used in patients with non-severe AA. Patients with VSAA and SAA, use of prophylactic antifungal therapy help in lowering their risk of getting fungal infections, however in absence of definitive therapy for AA, continuing antifungal indefinitely will be a challenge both from increased risk of resistant infection and costs involved.

iii. Antiviral prophylaxis: Patients who receive IST or allogeneic SCT receive antiviral prophylaxis with acyclovir or valacyclovir. Based on hospital policy, these are continued till 3-6 months post treatment. Patients who are only on supportive therapy are not candidates for receiving primary antiviral prophylaxis. Patients undergoing allogeneic SCT are monitored regularly for CMV infections and are candidates for pre emptive anti CMV therapy based on CMV copies in blood.

iv. Use of haematopoietic growth factors: G-CSF and erythropoietin are rarely used in patients with AA as there is insufficient haematopoietic tissue to be stimulated. Use of G CSF is perhaps in patients who have life threatening infections and severe neutropenia may be considered. But the use here is more as a desperate measure rather than for real benefit. Some trials have used G CSF when using IST, however, the results are equivocal. The use of newer thrombopoietin receptor agonist eltrombopag is increasing in patients with AA patients especially those who are refractory to multiple forms of therapy. This is discussed in more details in newer therapies (vide infra).

2. Transfusion therapy

a. Packed red blood cell (PRBC) transfusion: Even before the diagnosis of AA is made, most patients may have already received multiple red cell transfusions for anaemia. Although packed red blood transfusions (PRBC) are required to temporarily improve the symptoms, repeated PRBC transfusions result in increased risk of allo immunisation and iron overload. Both of these complications are major hindrances and are risk factors for morbidity and mortality for patients receiving IST therapy or allo SCT. Hence AA patients who are candidates for definitive therapy should be evaluated early for these complications and preventive measures should be taken. To reduce the risk of alloimmunisation, leucocyte filters should be used while transfusing blood. Most blood bank centres now have facility for PRBC units that are leucoreduced at source. PRBC
units should also be irradiated especially patients receiving IST therapy or allogeneic SCT.

i. Target Haemoglobin: Target haemoglobin in patients with AA may vary from patient to patient depending on his/her symptoms. Restrictive transfusion policy is what is recommended e.g. a young patient with no co-morbidities, may remain asymptomatic if his Hb is above 6 gm/dl. However, for an elderly patient or patient with co-morbidities (specifically underlying coronary heart disease), target haemoglobin may vary from 8-10 gm/dl depending upon at what level the patient feels comfortable or is asymptomatic. As mentioned previously, excess PRBC transfusion carries its own inherent risk of complications and hence a planned transfusion policy with periodic review is must in these patients.

b. Platelet transfusion: It is expected that the platelet count of patients with AA will be low. The general guidelines in the west are to transfuse platelets if less than 10000/ml or < 20000/ml if patients are running fever or have sepsis. In addition platelet transfusion is given if there is evidence of bleeding from any site irrespective of platelet count. These policies are difficult to follow in our country because of scarcity of blood and blood products in smaller cities and towns. Hence, at many places in India, patients are transfused fresh blood instead of platelets. This may lead to more problems for the patients as discussed above. We suggest patients who are getting treatment at specialised centres should follow platelet transfusion policy as in the west. However, if a patient is on supportive care and at a place where the availability of platelet is a problem, we suggest following policy. These patients should be transfused platelets only if there is evidence of clinical bleeding irrespective of platelet count. e.g. if the platelet count is less than 10000/ml but patient is apparently asymptomatic, platelet transfusion should be avoided. In case of superficial bleed, patients can be managed with antifibrinolytic agents like tranexamic acid or epsilon amino caproic acid which can temporarily arrest bleeding in some situations. Moreover, accuracy of cell counters to predict the value of platelet count when they are below 20000/ml is controversial. Hence the treatment focus should be more on clinical bleeding rather than platelet count. These suggestions do not apply in patients who are actively bleeding or have sepsis. Platelet transfusion is necessary when patients are undergoing any invasive procedure or are expected to receive IST (Immunosuppressive Therapy) with ATG and cyclosporin therapy. For ATG cyclosporin based therapy, generally the platelets are maintained above 30000/ml. For invasive procedure, platelets are maintained above 50000/ml. Platelet transfusion should be given using leucocyte depletion filter or platelets product should be leucodepleted at source when separating at cell counter.

c. Granulocyte transfusion: Granulocyte transfusions are not routinely used in patients with AA because of multiple reasons. The only place where these may be helpful is in severely neutropenic patient with sepsis and the expected rise of blood counts is within days in case of post allogeneic stem cell transplant or IST.

3. Iron overload:15 One unit of PRBC contain approximately 200-250 mg of iron. Hence it is expected that after 10-15 PRBC transfusions, body iron stores will be more than 2 gm and excess iron would start depositing in vital organs of the body like heart and liver. Hence a patient who is expected to receive PRBC transfusion as a measure to maintain his/her life, iron chelation either with oral deferasirox or deferiprone could be started when the serum ferritin crosses 1000 ng/ml (some authors recommend when it crosses 500 ng/ml) Combination of deferasirox and deferiprone is considered best for iron chelation as both do iron chelation from different body organs. However, in India, because of resource constraints, majority of patients either do not receive any iron chelation therapy or receive one of the drugs (deferiprone or deferasirox).

4. Newer therapies

a. Eltrombopag:16,17 Eltrombopag is a thrombopoietin receptor agonist developed originally to stimulate platelet production in patients with immune thrombocytopenia. However, thrombopoietin receptors are known to be expressed on haematopoietic stem cells and progenitor cells. In a pilot study of use of eltrombopag in refractory AA patients, 44% patients responded.17 The haematopoiesis was sustained even after discontinuation of the drug. However the dose use in refractory AA is 3-4 times higher than what is used in ITP. The initial dose is 50 mg upto maximum of 150 mg per day. Clonal evolution is a concern and hence its use is still experimental till more data is available.

b. Arsenic therapy: Three papers from China18-20 reported use of Arsenic therapy in refractory AA. Interestingly the overall response rates of 100% were demonstrated in refractory AA. Following these reports, an investigator initiated study was conducted in six refractory AA patients at PGI, Chandigarh. However, the trial has to be terminated prematurely because of no response in any patients.21 Based on our data, we do not
recommend use of Arsenic therapy in any patients of AA.

c. Other IST (Immunosuppressive Therapy) medications: Other immunosuppressive medications like mycophenolate, tacrolimus, sirolimus, fludarabine, alemtuzumab have been used in refractory AA patients either alone or in combination with other medications. However, the response rates have been dismal though all of these medications have worked in an occasional patient.

d. Alternate donor transplant: In a young fit patient, matched unrelated donor if available is increasingly being considered as treatment of choice after failure of IST therapy. However, if unrelated match donor is not available, patients are then given 2nd line ATG therapy. As a third line option, patients are being considered for either cord blood transplant or haploidentical stem cell transplantation. The detailed description of these transplants is beyond the scope of this chapter.

References


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