Approach to Aplastic Anemia- An Overview and Practical Approach

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Abstract: Despite the fact that cytopenia has been a common hematological entity seen in clinical practice for decades, the understanding of its etiopathogenesis has been changing, which in turn impacts on the management strategies. The current review focuses on the understanding of the current concepts and a brief overview of the management of aplastic anemia. As the spectrum of stem cell biology, etiology, and treatment from transplantation to graft-versus-host disease cannot be covered in few paragraphs, the most concise form is presented here.

Keywords: Aplastic anemia, Etiology, Transplant, Cytopenia, Management.

INTRODUCTION

Aplastic anemia is a syndrome, characterized by peripheral blood cytopenia and reduced marrow cellularity, resulting from various etiologies. Thus In contrast to conventional reasoning, where any peripheral cytopenia with marrow aplasia is considered as Aplastic Anemia, currently it is recommended to exclude similar disease entities such as MDS, PNH etc before concluding it is AA. This disease in majority of cases is acquired, though occasionally it may be congenital. In the presence of aplastic marrow, grading of the severity of the disease is based on absolute neutrophil count [ANC] [1]:

1. Non severe AA (nSAA; PMN > 0.5 × 109/L)

2. severe AA (SAA; PMN 0.2–0.5 × 109/L), and

3. very severe AA (vSAA; PMN < 0.2 × 109/L).

However, the above classification/ staging may no longer be relevant with current treatment strategies.

PATHOGENESIS

The etiopathogenesis is very complex and here we are presenting the two commonly accepted models.

Soil, Seed and Fertilizer Hypothesis

[1-3]- One of the old and widely accepted hypotheses relies predominantly on few observations. Laboratory evidence that suggests majority of cases of idiopathic AA are due to immune suppression of the hematopoietic stem cell arose from observations of

a) After BMT unexpected improvement of pancytopenia in some patients after allogeneic graft failure

b) Successful BMT of identical twins generally requires some sort of immunosuppressive conditioning regimen.

This further presumes that Normal hematopoiesis depends on a complex interaction of several cell types, including hemopoietic stem cells (HSC; the seed) and cells from the microenvironment (the soil), the T cells and growth factors [fertilizers].

STEM CELL DEFECT (SEED)

Evidence for stem cells (seed) as targets came from the observations that:

I. *in vitro* colony forming assays used to define the stem cell compartment showed that they were defective in cases

II. two papers in 1996 showed profound deficits in the stem cell population in patients with AA

III. at the time of clinical presentation the absolute number of stem cells is < 1% of normal population

This is further augmented by the etiological agents that damage stem cells leading to AA like radiation, chemotherapy, Benzene and few drug metabolites.

Soil and Fertilizer

The concept of Stromal cell defect (soil) and Growth Factor defect (fertilizer) came from the observation that

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A.   Mononuclear cells from blood and marrow of AA patients suppress hematopoietic colony formation by normal marrow stem cells

B.   Laboratory studies have shown the stroma of AA patients is able to support normal stem cell growth and successful BMT implies intact stroma since it is not replaced in the transplant

C.   Stromal cells of AA patients tend to make increased levels of several growth factors (EPO, TPO, G-CSF)

D.   Selectively removing T cells from the sample, apparently improve *in vitro* colony formation

E.   Direct cellular cytotoxicity by T cells as evidenced by:

   a.   blood and marrow of AA patients contain increased numbers of activated cytotoxic lymphocytes

   b.   the numbers and activities of these cells decrease after ATG.

F.   And lastly the effect of Cytokines:

   a)   T cells of AA patients overproduce both IFN-gamma and TNF-alpha

   b)   both of these cytokines inhibit colony formation *in vitro*

   c)   IFN-gamma induces nitric oxide synthase (NOS) and production of nitric oxide (NO)

   d)   both induce expression of Fas receptor on CD34+ cells and activation of this receptor by its ligand induces apoptosis

   e)   both appear to inhibit mitosis

   f)   IFN-gamma increases IFN regulatory factor 1 which inhibits transcription of cellular genes and entry into the cell cycle.

This supports the etio-pathogenesis of the following agents drug metabolites, transfusion associated AA, post hepatitis associated and few idiopathic cases.

While this explains the difficulty in deciding (1) which comes first and (2) whether there is a causal relationship between the two lead to the alternate hypothesis.

ALTERNATE HYPOTHESIS [4]

The hypothesis is very similar to filed cancerization effect, where a damage in the marrow such as genetic predesposition/toxins, leads to a trigger. This damaged stem cell may in turn trigger immune reaction to reject the "All the existing Marrow stem cell" resulting in Aplastic anemia, or may propogate in defective manner leading to Myelo Dysplatic Syndrome [ineffective meylo/erytropoeisis]. This therapy explains the PNH/MDS and AA together. This also explains high success rates of BMT as well as supports use of ATG in the conditioning regimens.

DIAGNOSIS

The work up includes a complete physical examination, and detailed history, peripheral blood examination, bone marrow aspiration, biopsy and flow cytometry with stress cytogeneitcs and FISH panel to rule out other causes.

MANAGEMENT

The target is to restore the normal counts, avoid long and short term side effects of drugs and cytopenia. Patients with moderate cytopenia, not requiring transfusions, can be offered outpatient treatment with anabolic steroids and cyclosporine (CsA), which were shown to be effective [5]. Patients with cytopenia requiring transfusions should be treated as in-patients, with either immunosuppressive therapy or bone marrow transplantation (BMT). It is important to understand that early treatment had long term better outcomes and the decision to start treatment should be as early as possible after confirmation of diagnosis. The choice between these two treatments is still debated and the discussion below will give an overview of the literature.

SUPPORTIVE MEDICATIONS

Growth Factors

The literature does not support the use of G-CSF as an adjunt or alone in the management of AA. The potential advantages of using G-CSF for faster neutrophil recovery and the prediction to test for white blood cell (WBC) increments/ failures is not substantiated in log term trails [6-8]. Similarly Anemia does not respond to erythropoietin and their use is strongly discouraged. However multiple trials of thrombopoietin mimetics, eltrombopag, and romiplostim

are in progress, which in early phases are promising for platelet series [9].

Immunosuppressive Treatment

Despite being a gold standard for ages, it is recommended only in a subset of patients in whom transplant is not an option. Treatment with antithymocyte globulin (ATG) yields superior survival when compared with supportive care alone. Horse ATG combined with cyclosporine remains standard as first-line immunosuppressive therapy, based on a prospective randomized comparison with rabbit ATG and confirmed in several retrospective studies [10]. Although 66% responses are seen promptly after therapy, only 60% of such population shall be in true remission. Remaining patients eventually either relapse (defined by the need for renewed immune therapy) or blood counts are dependent on cyclosporine administration. Rabbit ATG at standard dosage is a more potent immunosuppressant than is horse ATG, but does not improve the rate of hematologic recovery in aplastic anemia. Other attempts to increase response rates by intensifying immunosuppression have failed, including the addition of high-dose corticosteroids, mycophenolate mofetil, or rapamycin. At present either horse or rabit ATG is considered standard.

Cyclosporin

A dose of 5 mg/kg orally per day for 6 months is considered as standard followed by taperin. Though various protocols are available, it is unclear exactly (1) when and (2) how fast this should be done. It is usually practiced and agreed that it is safe to start tapering CsA at 12 months of treatment (rather than 6 months) and tapering should be very slow (less than 10% of the dose/month) for at least 1 year, to minimize the risk of relapse. However it should be kept in mind that the risk of relapse is in the order of 30% and is not easily predicted [11, 12].

IST FOR SPECIAL POPULATION

Pregnancy

There is no data except for few case reports on how to manage AA in pregnancy. Hence the standard adult protocol are applied and it is always advisable to postpone therapy and consider supportive care only [transfusions]. Regarding second pregnancy, its is worth noting that it is possible but at the expense of a risk of relapse of the aplasia (approximately 20%) [13].

Elderly

Although response rates and survival are lower compared with young patients, [projected 10 Yr survival of 45% for patients aged 51 to 70 years and 25% for patients over the age of 70 years], the current data suggest the use of the ATG, if there are no contraindications [14].

HEPATIC AND RENAL FAILURE PATIENTS

There is no published literature in this group and the decision of treatment needs to be individualized.

BONE MARROW TRANSPLANTATION [1, 10, 15]

BMT is still the gold standard for newly diagnosed cases of AA, whenever feasible. With a success rate of over 90%, and EBMT/IBMTR study suggests that Peripheral Blood transplantations actually reduce survival compared with marrow transplantations, in patients with AA younger than 20 years, the first option should always be a bone marrow rather than peripheral blood stem cells. With standardized protocols of RIC/myeloablative regimens, and GVHD prophylaxis the outcomes are promising.

HLA IDENTICAL BMT FOR PATIENTS OLDER THAN 30 YEARS [15]

The effect of age cannot be underestimated: overall survival in the last decade for HLA-identical sibling transplantations at 10 years is, respectively, 83%, 73%, 68% and 51% for patients age ranges 1–20, 21–30, 31–40 and ≥40 years; EBMT data). The age effect has remained significant over time, with survival in the range of 50% for patients over the age of 40 years. The EBMT is exploring the use of low-dose CY (300 mg/m2 × 4) in combination with low-dose fludarabine (FLU; 30 mg/m2 × 4) and ATG in patients older than 30 years: the initial results are encouraging, with transplantation mortality of 30%, rather than the expected 50%, but more patients need to be accrued (EBMT, unpublished data). Interestingly, a recent report has confirmed that the combination of FLU-CY and ATG may reduce the transplantation-related toxicity.

UNRELATED DONOR TRANSPLANTS/ HALPO TRANSPLANTS [1, 10, 15]

Significant progress has been made in the past few years, and at least three studies have addressed the issue of the conditioning regimen. The first of these studies tested de-escalating doses of radiation, those undergoing an unrelated donor (UD) transplantation

and various reduced intensity conditioning regimen which is very similar to the Japanese regimen: FLU-CY-ATG and low-dose TBI (2 Gy) (unpublished). The overall data confirm that haemopoietic stem cells obtained from matched unrelated or haploidentical donors have a curative potential.

CONCLUSIONS

The practical approach in patients with Aplastic Anemia includes early institution of treatment in AA patients will improve overall outcomes and they require continuation of immunospression for minimum of 6 months. Whenever possible transplant should be the first choice in these cases and in case of transplant ineligible patients, they should be offered to be entered into well-designed prospective clinical trials.

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CONFLICTS OF INTEREST

None

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