Immunosuppressive Therapy for Aplastic Anaemia

S Damodar*

Abstract

Immunosuppressive therapy is the standard of care in aplastic anaemia in younger patients who do not have a matched sibling donor, and also in adults and older patients. Hence, a large population of patients with aplastic anaemia undergo this treatment. In patients who have responded to the first course of ATG, and have had a relapse, a second course of ATG can be administered with reasonable response rates. Response rates to first course of ATG vary from 50-85% in both children and adult. Indian data also suggests similar response rates.

Introduction

Therapy for aplastic anaemia (AA) essentially consists of 3 modalities – stem cell transplant (SCT), immunosuppressive therapy (IST) and supportive care only. Supportive care is the bare minimum, which is the common factor to any treatment. We will discuss the option of immunosuppressive therapy in relation to its feasibility in our country.

History of IST for Aplastic Anemia

The first reports of IST working in AA came from patients who received conditioning therapy for stem cell transplant but failed donor engraftment and had autologous recovery of hematopoiesis.1,2 This leads to the theory that immunosuppression itself may be sufficient in some patients to allow hematopoietic recovery. Subsequent studies then showed that the infusion of Anti-lymphocyte globulin (ALG) alone lead to hematopoietic recovery and based on the results of a prospective randomised trial,3 IST became the standard of care for AA patients in whom transplant was not a feasible option. This study clearly demonstrated that antithymocyte globulin (ATG) was superior to best supportive care (response rates were 52% and 0% respectively with an additional 50% response after crossover), even if a complete normalisation of blood counts was not achieved in many responders. Response rates using ATG or ALG ranged between 30% and 70% in larger series from other groups, which also pointed out the risk of late treatment failure due to disease relapse.4,5 Thus, the subsequent aim for investigators was to increase the response rate and sustain such responses for longer, preventing subsequent relapses. A number of immunosuppresssive agents were initially combined with ATG or ALG, including corticosteroids (i.e. methylprednisolone),6 androgens7,8 and Cyclosporin A (CyA). Only CyA, a calcineurin inhibitor (CNI) that impairs interleukin (IL)-2-dependent T cell activation and differentiation, has proven effective in increasing the response rate, as initially demonstrated by the German Aplastic Anaemia Group in a randomised trial9. In fact, the addition of CyA to ATG and high dose steroids (utilised as prophylaxis of serum-sickness) increased the 6-month overall response rate from 46% to 70% in all AA patients (from 31% to 65% in severe or very severe forms only), possibly impacting long term survival (even if no statistically significant difference was shown in this initial cohort). This study leads us to the present day; in fact, based on these results, ATG + CyA has been the most utilised IST for AA patients in the past two decades in Western countries. Unfortunately, the access to such treatment still represents a problem in developing countries, mainly due to economic reasons.10

When and Whom to Treat

Patients who are transfusion independent or moderate aplastic anaemia, observation would be the appropriate treatment. Many patients with AA may present stable blood counts for years, but pancytopenia may worsen over time in some.11 Patients who progress to severe pancytopenia and meet the criteria for SAA or become transfusion-dependent, can then be treated according to current algorithms (Figure 1). Elderly, feeble, or patients experiencing severe comorbidities might not benefit from more aggressive treatment approaches,
particularly if they are not bleeding and have neutrophil counts (generally between >200-400/L) that defend them from serious infections.

**Standard Immunosuppression**

Since the early 1990s, ATG + CyA has been considered the standard IST for AA patients, with an expected 50–60% probability of response and 60% overall survival at 1 year. A heterogeneous definition of clinical response may account for differences in response rates in distinct studies, thus the use of common response criteria is encouraged, even more so because such criteria clearly predict the long-term survival of AA patients. Most studies reported a response rate (complete response (CR) + partial response (PR)) ranging from 50% to 70%, without any improvement in the past two decades. However, most recent studies have shown improved overall survival (above 80% at 1 year), regardless of the initial response to IST, probably due to better supportive care and salvage treatment (mainly HSCT).

**ATG Preparations**

ATG is a heterologous anti-serum obtained by injecting human lymphocytes in animals; various ATG preparations exist, which differ in stimulating antigens (peripheral lymphocytes, thymocytes or even T cell lines), and/or in the host animal (either horse or rabbit). In the last two decades physicians have utilised any commercially available ATG preparation without distinction. Most available data from large randomised clinical trials refer to polyclonal ATGs obtained from horse (h), which have to be considered the gold standard for AA treatment. Of note, U.S. and Japanese investigators utilised hATG (40 mg/kg per day for 4 days, ATGAM; Pharmacia and Upjohn, New York, NY, U.S.) which is different from the hATG preparation used in Europe (15 mg/kg per day for 5 days, Lymphoglobuline; Genzyme, Cambridge, MA, U.S.; Fresenius Biotech, Munich, Germany). Thus, both preparations can be considered equivalent as standard IST for AA; however, Lymphoglobuline is no longer available. Alternative polyclonal ATGs may be obtained from rabbits (r); two rATGs are currently available (Thymoglobuline, Genzyme; ATG-Fresenius), but to date the clinical results with these agents are less robust for the lack of large randomised trials. However, hATG (ATGAM) is the recommended first line IST for patients ineligible for HLA identical sibling haemopoietic stem cell transplantation (HSCT) as stated by the British Committee for Standards in Haematology (BCSH) guidance following the results obtained from a prospective randomised trial comparing hATG versus rATG for the treatment of AA. rATG is more immunosuppressive than hATG but does not improve haematological recovery as compared to hATG. rATG is used successfully to salvage patients with refractory or relapsed SAA following initial hATG.

**Immunosuppression Administration**

**ATG**

During the administration of ATG, referral to hospitals with experience in treating SAA or enrolment into research trials should be encouraged, owing to the unfamiliarity of the administration of polyclonal antibodies and its immediate toxicities, such as ATG, amongst inexperienced nurses and physicians. To test for hypersensitivity to horse serum an ATG skin test should be performed. Furthermore, ease of drug delivery and transfusions can be improved with the use of a double lumen central line. Scheinberg and Young recommend maintaining platelets at more than 20000/L during the ATG administration period. In cases of platelet refractoriness, they recommend testing for alloantibodies to determine the need for best matched platelet products and using universal filtration of blood products to prevent alloantibody formation. While there is no formal recommendation regarding the use of irradiated products after hATG in SAA patients, their practice has been to apply universal irradiation in their protocols, in accordance with recommendations from a European study survey. Establishing responsiveness to antibiotic therapy for bacterial infections is preferred, even though patients need not be free of infection before

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**Fig. 1 : Algorithm for approach to aplastic Anaemia**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Sibling donor</th>
<th>Response</th>
<th>IST</th>
<th>Response</th>
<th>IST</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 years</td>
<td>No sibling donor</td>
<td>H-ATG + CSA</td>
<td>No response</td>
<td>HSCT</td>
<td>3rd IST MUD HALPLO CORD</td>
</tr>
<tr>
<td>40-60 years</td>
<td>H-ATG + CSA</td>
<td>No response</td>
<td>HSCT</td>
<td>3rd IST MUD HALPLO CORD</td>
<td></td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>H-ATG + CSA</td>
<td>No response</td>
<td>HSCT</td>
<td>3rd IST MUD HALPLO CORD</td>
<td></td>
</tr>
</tbody>
</table>

MUD - matched unrelated donor, EXP –experimental therapy, IST – immunosuppressive therapy, BST –best supportive care
starting ATG. However, it is important to note that prolonged attempts to clear fungal infections or extensive bacterial infections can defer definitive IST or HSCT therapies. β-blockers may be withheld before ATG to evade suppression of physiologic compensatory responses to anaphylaxis. It is also advisable to not initiate ATG late in the day or on weekends when hospitals may be understaffed.

The normal daily dose of ATG is 40mg/kg over 4 hours, for 4 days. Prophylactic treatment for serum sickness may be initiated on day 1 with Prednisone 1 mg/kg, which may be continued for 2 weeks. Conventional premedication prior to every ATG dose involves acetaminophen and diphenhydramine. Furthermore, symptomatic management of common infusion reactions may comprise of meperidine (rigors), acetaminophen (fevers), diphenhydramine (rash), intravenous hydration (hypotension), and supplemental oxygen (hypoxaemia). Haemodynamic and/or respiratory compromise can result in admittances to the intensive care unit, vasopressor support, and even, although infrequently, intubation. Under life-threatening circumstances, it is recommended that the ATG infusion is slowed or briefly stopped till severe signs and symptoms recede. ATG may be reintroduced at a normal or slower infusion rate in a monitored setting, occasionally over a 24 hour period, subject to the severity of the reactions. ATG may be infused even if patients experience mild to moderate elevation in transaminases, and increased liver enzymes tend to normalise over several days. Management of infusion related toxicities should not comprise of switching ATG formulations, for example, from horse to rabbit. Moreover, to manage rising creatinine, CsA can be withheld in the short term until renal function recovers.

Cyclosporine

CsA may be initiated on day 1 at a daily dose of 10 mg/kg (15 mg/kg per day in children) to a target trough level between 200 and 400 ng/mL. Patient frequently develop hypertension during CsA treatment, and management with amlodipine is recommended owing to minimal overlap with CsA related toxicities. A short course of azithromycin is recommended to improve gingival hyperplasia. It is important to note that calcium channel blockers have been associated with worsening gingival hyperplasia when combined with CsA. CsA may be continued despite modest increases in creatinine, with careful monitoring of the patient’s renal function and dose modifications to attain the desired CsA levels. Sustained CsA use requires dose adjustment of the CsA to the lower end of the therapeutic range, optimized blood pressure control, adequate hydration and the avoidance of other nephrotoxic agents to allow for improved tolerability. Temporary cessation of CsA is advised in patients with severe compromise of kidney function from baseline (creatinine >2mg/ mL). Low doses of CsA may be reintroduced at a later stage, with gradual increases proportionate to the patient’s tolerability.

G-CSF

Use of G-CSF in combination with immunosuppression has not shown any benefits in terms of hematologic response or survival in SAA patients. Hence it is not recommended to use with ATG owing to the lack of benefit and the theoretical risk of harmful side-effects. In fact, some retrospective studies have reported an increased risk of clonal evolution with G-CSF use, but this remains to be confirmed. The decision to try to improve neutrophil with G-CSF in select patients who are actively infected or those that experience persistent severe neutropenia (< 200/ uL) should be based on clinical grounds. However, if there is no significant response, reassessment and discontinuation after no more than a few days or weeks is advised.

Antimicrobial prophylaxis

As prophylaxis for Pneumocystis carinii infections while patients are on therapeutic doses of CsA, monthly aerosolised pentamidine is suggested. The basis of this regimen follows the observation that several cases of P carinii pneumonia were reported by Scheinberg and Young at their institution in the late 1980s in AA patients who were treated with horse ATG and CsA. Treatment with dapsone or atovaquone may be used when aerosolised pentamidine cannot be tolerated or in very young children. However, sulfa drugs should be avoided because of their myelosuppressive properties. While antibacterial, antiviral, and antifungal prophylaxes are not routinely administered with standard horse ATG/CsA, they have been used in the context of investigational regimens that are more immunosuppressive.

Response and Follow-Up

Most AA patients achieve some clinical benefit from IST, but the quality of response is heterogeneous: with current regimens, the response rate is about 60–70%, equally distributed between CR and PR, but most patients cannot be considered cured. In fact, many of them require long-term maintenance IST by CyA to sustain their response: even in recent studies, CyA-dependency ranged between 25% and 50% of patients. Nevertheless, relapses after an initial response to IST are frequent: in about 30–50% of cases the disease reappears within months or years from IST discontinuation. In the most recent experiences, the extension of CyA therapy beyond 6 months resulted in a reduction of the relapse rate; the general recommendation is to taper CyA by 10% every month, starting at least 1 year from IST. Late relapses remain possible, maybe also due to a suboptimal therapeutic range of CyA in long-term responders (due to tolerability or scarce compliance). Treatment failure-free survival at 5 years may be estimated in the range of 30–50%, although overall survival remains significantly higher (55–85%), because of available salvage treatments (either further IST courses or HSCT). In relapsed patients, the expected response rate
to a second IST is 50–70%, proving the principle that standard IST may be insufficient in some patients. In case of further relapses, even a third course of ATG may be considered, although this strategy is usually useless in refractory patients. However, given the increased risk of systemic reactions, all these patients are seeming candidates for alternative experimental IST. Beside refractoriness and relapses, it has to be noted that clonal evolution accounts for about 10–15% of treatment-failures and solid tumours account for an additional 10%.  

### Indian Data

We have limited Indian data published on IST in AA summarized in Table 1. One of the largest adult studies conducted in 322 patients showed an overall response of 63% with an overall survival of 67% at a median follow up of 32 months. Data from another centre on 120 patients reported an overall response rate of 85% at 6 months with an overall survival of 83% at 76 months. Paediatric data on 40 patients is available from the same centre with an overall response rate of 87.9% and overall survival of 90% at 24 months and 85% at 5 years. However, data from other centres do not show such high response rates as in an Indian study in 70 children, which described a response rate of 43% and an overall survival of 37%. Another study on 35 children showed a response rate of 50% to first course of ATG, with the response going up to 57% when a second course was included.

### References


### Table 1: Indian data on IST

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient no.</th>
<th>OR</th>
<th>OS</th>
<th>f/u</th>
</tr>
</thead>
<tbody>
<tr>
<td>George et al</td>
<td>322 (Adults and children)</td>
<td>63%</td>
<td>67%</td>
<td>32 mths</td>
</tr>
<tr>
<td>Nair et al</td>
<td>120 adults</td>
<td>85%</td>
<td>83%</td>
<td>76 mths</td>
</tr>
<tr>
<td>Nair et al</td>
<td>40 children</td>
<td>87%</td>
<td>85%</td>
<td>5 years</td>
</tr>
<tr>
<td>George et al</td>
<td>70 children</td>
<td>43%</td>
<td>37%</td>
<td>38 mths</td>
</tr>
<tr>
<td>Sharma et al</td>
<td>35 children</td>
<td>50%</td>
<td>-</td>
<td>40 mths</td>
</tr>
</tbody>
</table>

OR-Overall Response; OS-Overall Survival; f/u-Follow up


