ORIGINAL ARTICLE

The Use of Mycophenolate Mofetil in Treating Patients with Non Responding Aplastic Anemia

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Summary

Aplastic anemia is a relatively uncommon disease and conventional management options include immunosuppressive drugs and/or haematopoeitic stem cell transplantation. It is now known that the pathogenesis of aplastic anemia is immune mediated. Mycophenolate mofetil is a common immunosuppressive drug now used mainly in prophylaxis of graft rejection in organ transplant and also for prevention/treatment for graft versus host disease in haemtopoeitic stem cell transplantation. It is thought that mycophenolate mofetil may be useful in this groups of patients. In this short report, mycophenolate mofetil was tried in 6 patients who had severe aplastic anemia with variable doses for a minimum duration of 9 months. The result has however not been encouraging.

Key Words: Aplastic anemia, Immunosuppressive, Mycophenolate mofetil

Introduction

Aplastic anemia (AA) is a relatively rare condition and was first described in the early 19th century. In aplastic anemia, there is a decrease in hematopoeisis where all the three cell lines fall and the bone marrow appears empty. It is currently agreed that the pathophysiology of AA is immune mediated with destruction of the hematopoeitic cells by T lymphocytes[1]. The severity of the disease is classified by the degree of cytopenia, whereby severe aplastic anemia (SAA) is defined by a reduction of two of the three lineages; neutrophil count of less than $0.5x10^9/l$, platelet counts less than $20x10^9/l$ and corrected reticulocyte counts less than 1%[2].

Management of aplastic anemia remains problematic although it has reached a milestone with the introduction of allogeneic bone marrow transplantation. For patients who are not eligible for bone marrow transplantation (BMT), immunosuppressive agents e.g. cyclosporin (CSA) and anti-thymocyte globulin (ATG) are used. The combination of ATG/CSA leads to a 5-year survival comparable to BMT[3]. However, there is no other convincing therapy for those who relapse or refractory to the conventional treatment.

Mycophenolate mofetil (MMF) is a pro-drug of mycophenolic acid: a fermentation product derived from several penicillium species. It is a potent inhibitor of inosine 5'-mono-phosphate dehydrogenase, a crucial enzyme in purine synthesis. Its principle mechanism of immunosuppression is inhibition of lymphocyte proliferation[4]. MMF has recently been shown to be effective as a possible second line therapy for autoimmune hemolytic anemia (AIHA) besides its use in graft versus host disease (GVHD) prophylaxis in the BMT patients[4]. In view of the mechanism of action, it is thought that perhaps MMF may be beneficial in patients with AA.

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Unfortunately, there is limited data in MMF usage in AA and the data available has not been very encouraging[5]. Currently, there is an ongoing study on MMF in this group of patients in United States. Here, we report on our experience of MMF in our aplastic anemia patients who had failed all other therapies.

Materials and Methods

Between January 2001 and March 2002, MMF was given to 6 patients with refractory /relapsed AA. MMF dose was started from 250mg twice daily for each patient and increased to a maximum dose of 2g daily of tolerated. The blood parameters (hemoglobin, total white cell counts and platelet counts) were documented on each visit. Blood transfusion requirement was recorded as total red cells and platelet concentrates used per visit if relevant. The blood parameters were then compared at the start and completion of MMF. The average blood products required for each patient were also compared before and after starting MMF.

Results

There were 4 males and 2 females with the median age of 22 years ranging from 20 - 49 years, Table I.

All of them have had at least 2 prior treatments before starting on MMF. Patient 1 had a non-myeloablative transplant prior to MMF. The remaining 5 patients have either no suitable sibling donor or refused BMT. The median duration to starting MMF from diagnosis was 5 years. MMF was commenced in most patients at a dosage of 500mg twice daily except for patient 5 and 6 in which MMF were started at 250mg BD. Maximum dosage of MMF achieved was 2 g daily. In all patients, there were no reduction of red cells and platelet transfusion requirement. Patient 2 and 3 had infections which required hospitalization after commencement of MMF. There was no significant side effect that requires withdrawal of the drug.

Table I: Patients details and results

Patient	Age (years)	Sex	Time from diagnosis to treatment with MMF	Rx before MMF	Maximum dosage of MMF used	Hb (g/dl) when MMF commenced	Hb (g/dl) when MMF was stopped	Plt (x10⁹/l) when MMF commenced	Plt (x10⁹/l) when MMF was stopped	Total duration of Rx	Transfusion requirement after MMF
1	20	M	11 months	CSA, BMT	1g BD	8.9	7.1	19	21	12 months	Yes
2	20	M	3 years	CSA,ATG, MP, Oxy	1g BD	6.2	7.7	6	6	9 months	Yes
3	22	M	13 years	CSA,ALG, Oxy	1g BD	5.1	7.3	23	5	12 months	Yes
4	24	M	4 years	CSA,ATG, Oxy	1 g BD	6.3	7.3	3	5	11 months	Yes
5	30	F	10 years	Pred,CSA, Oxy,ALG	1g OD	7.7	6.6	13	12	9 months	Yes
6	49	F	7 years	Pred,ALG, Oxy	1.5g OD	8.9	4.3	11	8	9 months	Yes

M-male, F-female, Rx-treatment,Hb-hemoglobin, Plt-platelet, CSA-cyclosporin, ATG-anti-thymocyte globulin, MP-methyprednisolone, Oxy-oxymethalone, ALG-anti-lymphocyte globulin, Pred-prednisolone, BD-twice daily, OD-once daily

Discussion

Acquired aplastic anemia is a relatively rare but potentially fatal hematological disorder. In acquired aplastic anemia, hematopoeisis is reduced and the bone marrow is replaced by fatty tissue. Recently, the pathophysiology of aplastic anemia is believed to be immune mediated, with active destruction of the hematopoeitic stem cells by lymphocytes. The abberant immune response may be triggered by environmental exposures, e.g chemicals, drugs or infections. Chemicals documented to cause AA are benzenes exposure and pesticides[1]. Drugs which have been reported to cause AA include chloramphenicol, sulphonamides, penicillamine etc. Infections such as Hepatitis A, C are also known to be associated with AA. There is also a close association between AA and paroxysmal nocturnal hemoglobinuria (PNH)[1,6]. In the West, the incidence of AA is approximately 2 per million per year,[7] and in Asia e.g. Bangkok, the overall incidence is 3.6 per million per year and this was thought to be related to the socio-economic status of the population[8].

The management of AA is difficult and challenging when patients do not respond to conventional treatment. There are few therapy options available. In patients who are relatively young and has a matched sibling donor, an allogeneic transplantation is recommended. The five year survival rates are about 70% to 80%[1,3]. Late complications of transplantation also occur, including lung diseases and secondary malignancies. A second established therapy is immunosuppression. The immunosuppression commonly used are ATG and CSA.ATG alone gives an overall 61% survival rate at 5 years and 40% to 50% of patients respond[1]. However, the response rate depends on the severity of AA. Combination of ATG and CSA has shown to be superior to just ATG or CSA alone with an approximate response rate of 78% and 5-year survival of 80% to 90%[1].

Relapse is not infrequent and refractory cases are difficult to treat. MMF, a drug which is cytotoxic to the circulating T cells was thought to be effective as another option for the treatment of AA. However, in our experience, this is not found to be so although side effects are minimal and none of the patients developed any major events from MMF. Although our case series did not show any encouraging results, this may be due to the relatively small numbers of patients. Further trials and perhaps combination therapy with MMF may be beneficial.

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