ORIGINAL ARTICLE

Anti-lymphocyte Globulin Therapy in Aplastic Anaemia – A University Hospital Experience

K W Leong, MRCP*
A Teh, MRCP*
J J Bosco, FRACP*
S Jayaranee, MPath**
U Sadat, MBBS*
* *Division of Haematology, Department of Medicine*
** *Department of Pathology,*
Faculty of Medicine, University of Malaya, 59100 Kuala Lumpur

Summary

Antilymphocyte globulin (ALG) was given every other day for 5 doses with platelet transfusions immediately following ALG administration in 6 patients with aplastic anaemia. Four patients responded and 3 durable remissions were achieved. One patient relapsed and further treatment with anti-thymocyte globulin and cyclosporin also failed. One patient died of *Flavobacterium* septicaemia 6 days after completion of ALG. Our data suggests that using an alternate day regimen, a response rate similar to a daily regimen can be obtained.

Key Words: Aplastic anaemia, Alternate day anti-lymphocyte globulin, Flavibacterium septicaemia, Antithymocyte globulin, Cyclosporin

Introduction

Aplastic anaemia is an uncommon problem in Malaysia. Only 3-4 cases are seen in the University Hospital annually.

In its mild form, no treatment may be needed at all. When symptomatic anaemia, bleeding and infections occur, corticosteroids, androgens and anti-lymphocyte globulin (ALG) /anti-thymocyte globulin may be used[1].

In severe aplastic anaemia, the treatment of choice is allogeneic bone marrow transplantation (BMT)[2,3]. This is only possible if there is a compatible donor. In Malaysia, BMT is only beginning and therefore this option may not be feasible in all patients. In this situation, ALG therapy may produce good results[4] and would be cheaper, easier and faster. The major drawbacks are continued persistence of mild aplasia and the risk of progression to leukaemia, paroxysmal nocturnal haemoglobinuria and myelodysplasia.

In this paper, we describe our experience with ALG for severe aplastic anaemia in the University Hospital.

Patients and methods

In 1993, six patients (aged 13-36 years) were given ALG using an alternate day protocol. These patients were considered to have severe aplastic anaemia based on accepted criteria[5] (Patient 1, 2, 3) or if they had required extensive blood transfusion support and had either serious haemorrhages or infections (Patient 4, 5, 6).

ALG (Lymphoglobulin from Rhone-Poulenc Rorer) was given at a dose of 15 mg/kg/dose infusion over 6 hours on alternate days for 5 doses, after a test dose was given subcutaneously. If a reaction occurred, the infusion was slowed to be completed over 24 hours.

Promethazine 50 mg iv and hydrocortisone 200 mg iv were given just prior to every ALG administration. Prednisolone 2 mg/kg/day was given for 2 weeks and

then tailed to 1 mg/kg/day for another 1 week before tailing off. Prophylactic ranitidine 150 mg twice a day and co-trimoxazole 960 mg twice per week were used.

Six units of platelet concentrate were given prophylactically prior to the first ALG administration in all patients. Subsequently, immediately after completion of each ALG infusion, another 6 units of platelets were given prophylactically to prevent haemorrhage. All blood products were given through leucocyte filters. Venous access was secured via a central venous catheter inserted in the cubital vein.

Results

Of the 6 patients, 3 had sustained responses to ALG and are transfusion-free. Mean time to transfusion independence was 50 days. The increase in cell counts is shown in Table I.

Patient 4 responded to ALG but the response was not sustained. Seven months after ALG therapy, he was again transfusion dependent. Further treatment with cyclosporin and anti-thymocyte globulin was unsuccessful.

Patient 5 did not show any response at all and was still transfusion dependent after 6 months. He had been previously treated with steroids and androgens without any response and had been diagnosed for 1 year prior to ALG therapy.

Patient 6 died of *Flavobacterium* septicaemia despite appropriate antibiotics 6 days after completion of ALG. He had had several febrile episodes prior to ALG therapy which had required prolonged antibiotic therapy.

Adverse reactions were seen in 3 patients. Fever with chills and rigors were observed. One patient developed an anaphylactic reaction with swelling of the face and upper part of his trunk. He responded to increased intravenous hydrocortisone and promethazine, together with prolongation of the infusion to 24 hours.

Discussion

Using androgens or high dose methylprednisolone to treat aplastic anaemia, a response rate of 10-30% is possible[6]. Using anti-lymphocyte globulin or anti-thymocyte globulin, with or without cyclosporin, a 40-60 % response rate has been reported [4,7,8] . Up to 80% long term remissions can be achieved using BMT[2].

In Malaysia, the option of BMT is limited and most patients have been frequently transfused before a firm diagnosis is made. This would affect the outcome of transplantation[4]. Preparation of the patient and the waiting list may result in a transplant being done months after diagnosis.

ALG appears to be an alternative[9] and it can be administered readily soon after a diagnosis of aplastic anaemia is established.

An alternate day protocol has produced comparable results to other larger series using a daily administration protocol[2,4,7,9,10]. An alternate day protocol has several advantages. If a reaction occurs, the infusion can easily be prolonged to 24 hours and still allow the patient to rest till the following infusion. Prophylactic platelet transfusions are easier to arrange in a setting where transfusion resources are limited.

A shorter duration of illness appears to be associated with more durable responses. The patient who did not respond at all had been ill for more than 1 year. This observation is consistent with that of published series[4,11].

Adverse reactions[12] were manageable and all patients were able to complete the protocol. The use of prophylactic prednisolone, hydrocortisone and promethazine has made its administration safer. Bleeding did not occur in any patient. Prophylactic platelet transfusions were used to prevent bleeding that might have resulted from worsening thrombocytopenia during ALG infusion. Leucocyte filters[13] were used to minimise sensitisation and platelet refractoriness.

ALG therapy is an immunosuppressive therapy and predisposes the patient to infections. In aplastic anaemia, infection is a major problem. Using ALG increases the risk of infection, especially when combined with high dose steroids[14].

Table I

Patient Number	1	2	3	4	5	6
Age (yrs)	15	35	16	14	13	31
Sex	Male	Male	Male	Male	Male	Male
Race	Malay	Chinese	Chinese	Chinese	Chinese	Malay
Duration of illness prior to ALG	5 weeks	3 weeks	30 weeks	30 weeks	70 weeks	8 weeks
Number of transfusions prior to ALG	6 pack cells 9 platelet concentrates	3 pack cells 5 platelet concentrates	3 pack cells 10 platelet concentrates	>5pack cells >12 platelet concentrates	>15 pack cells 30 platelet concentrates	10 pack cell 30 platelet concentrates
Haemorrhage just before ALG therapy	Yes	Yes	No	Yes	No	Yes
Infection just before ALG therapy	No	No	No	Yes	No	Yes
Prior treatment	None	None	Steroids Androgens	Steroids Androgens	Steroids Androgens	None
Total platelet concentrates used during ALG therapy	30	21	25	19	24	33
Peripheral counts prior to ALG						
Reticulocyte*	0.19	0.18	0.72	NA	NA	NA
Haemoglobin#	34	66	86	45	60	57
Platelets"	11	9	16	21	10	34
TWBC"	3.0	2.8	2.4	2.8	2.1	1.5
Neutrophils"	0.1	1.0	0.6	0.54	0.5	0.2
Peripheral counts post ALG therapy						
Days post ALG	28	45	70	60	90	NA
Haemoglobin#	138	119	153	123	61	NA
Platelets"	88	144	65	53	10	NA
TWBC"	7.5	5.5	6.0	3.6	1.4	NA
Neutrophils"	3.1	2.5	2.0	1.5	0.63	NA
Outcome	Responded	Responded	Responded	Response not sustained	No	Died during therapy
Duration of follow up	18 months	13 months	14 months	18 months	20 months	NA

* *reticulocyte index in %;*
\# *Haemoglobin in g/l;*
" *cell counts in x 10^9/l.*
NA = not available or not applicable.

Recent reports have indicated a possibility of developing clonal haematological disorders long after anti-lymphocyte globulin therapy ie the development of myelodysplastic syndrome, paroxysmal nocturnal haemoglobinuria and acute myeloid leukaemia[15,16] Other authors did not make this observation in their patients over long term follow up[11]. ALG should be reserved for symptomatic or severe aplastic anaemia patients, when BMT is not feasible.

Conclusion

ALG therapy is a safe option and yields good results[9] and similar response to a daily protocol is observed using an alternate day protocol and prophylactic filtered platelet transfusions.

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