Original Articles

TREATMENT OF APLASTIC ANEMIA IN CHILDREN WITH HIGH DOSE METHYL PREDNISOLONE

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ABSTRACT

Severe aplastic anemia (SAA) in children has been previously treated with high dose methyl prednisolone (HDMP) with favorable results. We reviewed our experience with intravenous HDMP. Seven children with a diagnosis of SAA confirmed on bone marrow biopsy were treated with 300 mg/kg total dose of intravenous HDMP over a 4 week period. Patients were closely monitored for response and side effects. HDMP was well tolerated except for hyperglycemia in one case. Six of the seven patients showed no response to HDMP. This observation is in stark contrast ^ with previous trials on use of HDMP in SAA. It is concluded that HDMP should be reserved only for patients with milder bone marrow hypoplasia.

Keywords: *Aplastic anemia. High dose methyl prednisolone, Treatment.*

Aplastic anemia (AA) is characterized by peripheral blood pancytopenia, variable bone marrow hypocellulariry and absence of underlying malignant or myeloproliferative disease. Various autoimmune phenomena play a role as primary or perpetuating factors in AA. This has led to numerous trials with immunosuppressive agents like antilymphocyte globulin (ALG), methylprednisolone, cyclosporine, cyclophosphamide, monoclonal anti-T cell antibody(l). In this communications, we review our experience with intravenous high dose methyl prednisolone (HDMP).

Material and Methods

Seven children in the age group of 3-11 years were admitted in the pediatric wards of Bai Jerbai Wadia Hospital for children, Parel, Bombay with a clinical diagnosis of AA. Initial workup showed a pancytopenia with a low reticulocyte count. Bone marrow aspiration (BMA) and biopsy confirmed the diagnosis of severe AA (SAA). Patients were graded on the basis of criteria for defining severity based on International Aplastic Anemia Study Group(2,3) (*Table* I).

On diagnosis of SAA, Patients were supported with packed red cell transfu-

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TABLE I—*Criteria for Defining Severe Aplastic Anemia : International Aplastic Anemia Study Group(2).*

A.	Peripheral blood criteria :	2/3 required
	Neutrophils	$<0.5 \times 10^6/l$
	Platelets	$<20 \times 10^9/l$
	Reticulocytes	<1% (corrected for hematocrit)
B.	Bone marrow criteria :	1 required
	Severe hypocellularity	< 25% of normal
	Moderate hypocellularity	25-50% of normal and < 30% residual hematopoietic cells.

* VSAA—Those patients fulfilling Camitta's criteria for SAA and in addition having $< 0.2 \times 10^9/l$ peripheral blood neutrophils(3).

sion, platelet transfusion, antibiotics and general hygiene. Subjects were started on intravenous methylprednisolone to receive a total dosage of 300 mg/kg over a period of 28 days. Regimen used was : 30 mg/kg/day for 4 days, 20 mg/kg/day for 3 days, 10 mg/kg/day for 7 days, 5 mg/kg/day for 7 days and 2.5 mg/kg/day for 7 days. Patients were monitored clinically and by laboratory parameters to check for any response and side effects.

Response was judged by a rise in reticulocyte count (expected on D6), rise in neutrophil count (expected on Dll) or a rise in platelet count (expected on D39) and reduction in transfusion requirement, bleeding episodes or temperature abating to normal(4).

Results

Of the 7 patients reviewed, 4 had SAA, 2 had VSAA and 1 had moderately SAA (MSAA) *(Table II)*. These patients were symptomatic for a duration lasting from 12 days to 2 months prior to their admission to this hospital. Cases 1 and 2 received in addition to HDMP, oral androgenic steroids oxymetholone for 17 and 21 days, respectively. Case 6 received cyclosporine A and testosterone enanthate for 3 days and 1 day, respectively. Except Case 5 who received HDMP for 6 days, others received it for 2 or more weeks. HDMP was tolerated well by these patients. Hyperglycmia (blood sugar = 252 mg/dl) developed in Case 3 on 30 mg/kg/day. Cases 4,6 and 7 developed steroid facies. No patient had hypertension or serum electrolyte changes.

Both the patients with VSAA (Case 1 and 5) did not show any response to HDMP. Subjects with SAA (Cases 2,3,6 and 7) also did not show any response. Only case 4 showed a response who had MSAA. A rise in the reticulocyte count was seen on D15 which was sustained till the time patient was on HDMP. Platelet counts remained in the range of 30-60 x 10^9/l. The child was readmitted 5 days following the completion of HDMP therapy with no platelets and a reticulocyte count of 0.1%. This indi-

TABLE II—*Clinical Details of Children With SAA Treated With HDMP*

Case No.	Age/ Sex (Years)	Parameters at diagnosis					Severity	Therapy with HDMP		Side Effects	Response	Outcome (Number of days after treatment)
		Hb (g/dl)	Retic. (%)	Total Count ($\times 10^9$/1)	ANC	Platelet ($\times 10^9$/1)		Total dose (mg)	Duration (days)			
1.	7/M	2.4	0.3	2.4	48	Absent	VSAA	245	17	None	–	Expired (D18)
2.	7/M	3.4	0.6	3.4	952	Absent	SAA	150	21	None	–	LTFU+ (D22)
3.	6/M	3.8	0.8	5.0	650	Absent	SAA	210	14	Hyper-glycemia	–	LTFU (D14)
4.	3/F	6.6	0.2	4.8	1536	40	MSAA	255	28	Steroid facies	PR*	LTFU (D30)
5.	11/F	1.6	0.2	3.5	200	Occasional	VSAA	150	6	None	–	Expired (D7)
6.	3/M	7.7	0.5	15.9	400	8	SAA	157	23	Steroid facies	–	Expired (D24)
7.	9/F	3.5	0.3	5.0	60	10	SAA	300	28	Steroid facies	–	Expired (D29)

* PR=Partial Response, + = Lost to follow-up.

cated that she had a temporary response. She was started on oral prednisolone and androgenic steroids; however, the patient was lost to follow up.

Discussion

All children with SAA are best treated with bone marrow transplantation (BMT). Since BMT is not available in our setup, patients are treated with immunsuppressive agents where there is only 20-30% chance of survival.

HDMP has been used in previous trials to treat SAA with favorable results. Ozsoylu *et al* reported 18 responses in 28 children(4) *(Table III)*. The average time for elevation of reticulocytes was 6 days, neutrophils 11 days and platelets 39 days. Survival at 1 year was 57% and at 3 years 54%. In various European centres trials with HDMP showed a 2 years survival of 50%(6,7). When a slightly lower initial dose was used, the response rate (7 out of 29) and rate of 1 year survival (25%) was lower than those of other trials(8).

Since the above trials showed benefit in SAA, we chose to treat our patient with HDMP. However, 6 out of 7 subjects had a very poor response with no rise in reticulocytes, neutrophils or platelets. Transfusion requirements did not reduce and patients continued to remain symptomatic. There was however, a very low incidence of side effects inspite of the high dose. Other studies were associated with a number of side effects which included hypertension,

TABLE III—*Trials of HDMP in Treatment of AA*

Authorss (Reference)	Regimen	Total No.	Severe	Response	Survival	Time (Yr.)
Ozsoylu *et al.*(4)	30 mg/kg/day D1-3, 20 mg/kg/day D4-7, 10-5-2 mg/kg × 7 days each	28	7	17 Cr* 1PR+	16/28 (57%)	1
					15/28 (53%)	3
Marmont *et al.*(6)	100 mg/kg week 1, 50 mg/kg week 2. then taper.	39	39	13 CR 2 PR	60%	5
Gluckman *et al.*(7)	100 mg/kg week 1, 50 mg/kg week 2, then taper.	46	46	Not reported	50%	2
Issaragrisil *et al.*(8)	1 gm on D 1-3, then 60 mg on alternate days.	29	16	7 PR	25%	1
Present trial	30 mg/kg/day × 4 days, 20 mg/kg/day × 3 days, 10-5-2.5 mg/kg/day × 7 days each.	7	6	1 PR	—	—

+ PR = Partial response, * CR = Complete response.

gastritis, hyperglycemia, depression ache, aspetic necrosis of femoral head and cushingoid habitus(6-9).

HDMP was bebeficial in only one patient with MSAA. Similar effects were seen in another study where milder cases had long term improvement(7). Thus response to HDMP can be obtained in a few selected cases only. We suggest that mehtylprednisolone should be reserved only for patients with MSAA or for those awaiting a BMT who otherwise have a stable course, since the response is temporary. It can be combined with other immunosuppressive treatment like ALG(6).

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