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Cyclosporin A in myelodysplastic syndrome: a preliminary report

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Abstract Therapeutic approaches are not well established in patients with myelodysplastic syndrome (MDS). We evaluated response to cyclosporin A (CyA) in 19 cases with MDS who were enrolled for the study [13 refractory anemia (RA), 5 refractory anemia with excess of blasts (RAEB), and 1 refractory anemia with ringed sideroblasts (RARS)]. Bone marrow was normocellular in ten, hypercellular in five, and hypocellular in four cases. Fifteen patients were transfusion dependent and the rest were not transfusion dependent but with a hemoglobin range of 6.4–8.8 g% with a mean of 7.4 g%. CyA was given at a dose of 3–5 mg/kg per day. A major response was observed in seven patients with RA, which was sustained on follow-up. Four cases of RA showed minor response and two cases of RA did not respond to CyA therapy. A minor response was also seen in one RAEB and one RARS case, while one RAEB case that initially showed a major response relapsed on therapy. The first effect of therapy was evident after a mean period of 2.5 months. A rise in platelets and leukocyte count was seen in three and two cases, respectively. One case developed renal failure on therapy and later died of septicemia. Response to CyA was independent of bone marrow cellularity. CyA could be an effective mode of therapy in patients with MDS especially those having RA.

Keywords Myelodysplastic syndrome · Cyclosporin A · Hypoplastic MDS · Immunosuppressive therapy · MDS

Introduction

Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disorder characterized by anemia, neutropenia, or associated thrombocytopenia in various combinations with usually cellular marrow and a risk for leukemic transformation [1]. The therapeutic approach is not well established and the only curative therapy available is bone marrow transplantation with its inherent morbidity and limitations with regard to donor availability. Most of these patients receive supportive care only.

About 15% of MDS patients exhibit hypoplastic marrow [2, 3]. Immunosuppressive therapy such as cyclosporin A (CyA) and antithymocyte globulin (ATG) is being used successfully in aplastic anemia cases suggesting that immune dysregulation plays a role in the pathogenesis of cytopenia [4, 5]. Based on these observations, immunosuppressive therapy has been evaluated in a limited number of cases with MDS either alone [6–12] or in combination with cytokines [13]. We hereby present our experience with cyclosporin A (CyA) in 19 patients with MDS from this region.

Patients and methods

Nineteen consecutive cases of MDS (12 males and 7 females) attending the hematology clinic of All India Institute of Medical Sciences with normal renal and hepatic functions were selected for the study. Written informed consent was obtained before the enrollment. Patient characteristics are summarized in Table 1. The median time from the diagnosis of MDS to the start of therapy was 2 months (range: 1–12 months), and the mean age of the patients was 47.5 years (range: 20–77 years).

Diagnosis of MDS was based on clinical and hematological criteria including morphological examination of bone marrow. Pancytopenia was present in nine patients. Five patients had bicytopenia in the form of anemia and thrombocytopenia while five patients had anemia alone at the time of presentation. Bone marrow cellularity was assessed by examination of marrow biopsies taken from the posterior iliac crest. Patients were classified as per the French-American-British (FAB) criteria [12]. Thirteen patients had refractory anemia (RA), five patients refractory anemia with excess of blasts (RAEB), and one patient had

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Table 1 Patient characteristics

Patient	Age	Sex	BM cellularity	Transfusion dependent	MDS type	Length of treatment (months)	Months to first effect	Transfusion dependence on treatment	Previous Hb	Post CyA Hb	Effect
1	57	M	Normocellular	Yes	RA	6	3	Yes	7.0	8.1	Minor
2	54	M	Normocellular	Yes	RAEB	5	Nil	Yes	7.0	4.6	No
3	40	F	Hypercellular	Yes	RA	14	1	No	7.6	13.4	Major
4	60	F	Hypocellular	Yes	RARS	7	4	Yes	6.0	7.2	Minor
5	62	F	Normocellular	Yes	RAEB	5	Nil	Yes	6.4	3.8	No
6	36	M	Hypocellular	Yes	RA	11	2	No	7.0	10.1	Major
7	50	M	Normocellular	Yes	RA	5	1	No	8.3	12.4	Major
8	38	M	Hypocellular	No	RA	7	4	No	6.5	8.5	Major
9	28	F	Normocellular	Yes	RA	8	5	No	6.9	8.3	Minor
10	56	F	Hypocellular	Yes	RA	10	1	No	5.7	11.4	Major
11	58	F	Normocellular	Yes	RAEB	6	1	No	7.5	8.6	Minor
12	20	M	Normocellular	Yes	RA	6	1	No	6.4	7.5	Minor
13	77	M	Hypocellular	Yes	RA	4	Nil	Yes	7.0	7.7	No
14	43	F	Hypercellular	No	RA	26	3	No	6.4	7.9	Minor
15	67	F	Hypercellular	No	RAEB	26	Nil	Yes	8.8	9.5	No
16	43	M	Normocellular	Yes	RA	7	Nil	Yes	3.2	5.0	No
17	57	M	Normocellular	No	RA	26	4	No	7.9	10.3	Major
18	30	F	Hypocellular	Yes	RA	26	12	Yes	4.9	8.0	Major
19	28	M	Normocellular	Yes	RAEB	17	2	Yes	6.8	6.3	Initial major, relapsed

refractory anemia with ringed sideroblasts (RARS). Bone marrow was normocellular in ten, hypercellular in five, and hypocellular in four patients.

Fifteen patients were transfusion dependent at presentation and four were transfusion independent with a hemoglobin level of less than 8 g%. One of these patients (patient 15) became transfusion dependent on follow-up. None of the patients had serious bleeding manifestations or autoimmune manifestations.

Cyclosporin A (Sandimmune neoral, Novartis, Cambridge, Mass., USA) was used in doses of 3–5 mg/kg per day in two to three divided doses. Frequent monitoring of blood levels of CyA was performed to maintain the levels between 100 and 300 mg/ml. Blood counts were performed at 2- to 3-weekly intervals. Renal and hepatic function studies were done at 4- to 6-week intervals.

Response to therapy was assessed as per the international working group's criteria for hematological improvement in MDS [14]. Response was primarily assessed on the basis of erythroid response and interpreted as:

1. Major response: rise in hemoglobin level of more than 2 g/dl for those patients who were transfusion independent while for cases who were transfusion dependent, transfusion independence with hemoglobin above 8 g%.
2. Minor response: rise in hemoglobin between 1 and 2 g/dl for those who were transfusion independent and for patients who were transfusion dependent, 50% decrease in transfusion requirement.

Results

Thirteen patients were responders to CyA therapy. A major response was seen in eight patients (seven RA and one RAEB). All major responders with RA showed sustained response while the lone patient with RAEB showed a major response with transfusion independency for 5 months followed by a relapse to previous status despite continued therapy. Six patients (four RA, one RAEB, and one RARS) showed a minor response while five patients (two RA and three RAEB) were nonresponders. All of the responders were continued on CyA therapy. Two RAEB patients progressed to develop acute myeloid leukemia (AML) shortly after starting on therapy.

A rise in platelet count of more than 30×10^9/l was seen in three patients with thrombocytopenia, and two patients with neutropenia also showed a rise in total count of more than 1.5×10^9/l.

The effect of therapy was observed between 1 and 12 months with an average of 2.5 months. Interestingly, response to CyA therapy was independent of bone marrow cellularity and type of cytopenias in peripheral blood. Duration of therapy ranged from 4 to 26 months. Only one patient showed a significant side effect in the form of azotemia and later died of life-threatening infection. The rest of the patients tolerated the therapy well.

Discussion

Immune dysregulation has been proposed as the underlying mechanism in aplastic anemia (AA). Successful immunosuppressive treatment has been documented in AA [5]. Similarities in the profile of hypoplastic MDS and AA cases and occurrence of autoimmune manifestations in MDS cases prompted the use of immunosuppressive therapy in MDS [6]. Autoimmunity in MDS is considered to be a consequence of an abnormality of the immune system [17, 18]. It has been suggested that immune dysregulation may precede or predispose to the development of clonal hematological disorders and immune reaction against bone marrow stem cells may accompany or underline MDS [6]. Activated cytotoxic lymphocytes and abnormalities of T-cell function may play a role in development of MDS. Cytotoxic lymphocyte attack can induce aplastic as well as dysplastic marrow changes, can trigger apoptosis, and can induce chromosomal abnormalities as a consequence of DNA injury [15, 16].

The choice of CyA in our study was guided by its mechanism of action. CyA blocks synthesis and/or release of interleukin (IL)-2 from T-helper cells thereby inhibiting the expansion of unprimed T-helper cells, cytotoxic T-cell expansion, and T-cell-dependent B-cell activation [19]. CyA induces T-cell suppression, which may also affect production of several cytokines including interferons, tumor necrosis factors, and transforming growth factor-β that are capable of inhibiting hemopoiesis. Suppression of T-lymphocyte-facilitated antibody production by CyA may affect the potential pathogenic role of cytotoxic antibodies against hematopoietic precursors [20]. Moreover, CyA does not influence immunity mediated by polymorphonuclear cells and macrophages. The risk of secondary infections is lower than with other immunosuppressive drugs.

We observed a good response in cases of MDS with RA. A major response was seen in 7 of 13 cases (53.8%) while a minor response was present in 4 (30.7%) cases. Only one case of RA (patient 14) did not have any effect of CyA therapy. The response rate in RAEB was poor when compared to RA cases. Our observations are in conformity with other studies (Table 2).

Molldrem et al. [11] studied the response to single-dose ATG therapy in 25 MDS patients (14 RA, 6 RAEB, and 5 RARS cases). All of these cases were refractory to CyA, cyclophosphamide, and corticosteroids before ATG therapy. Eleven patients responded and became transfusion independent. Three cases (all RA) showed complete hematological recovery. Three responders relapsed later and again became transfusion dependent. The median response duration was 10 months (range: 3–38 months). Combination of ATG/antilymphocyte globulin (ALG) therapy with CyA may offer much more benefit than either drug alone and needs to be evaluated in larger studies.

Asano et al. [12] tried to correlate the response to immunosuppressive therapy (CyA and ATG) with HLA-DRB1*1501 and found a positive (but not statistically significant) association. Nand and Godwin [21] found a lower response rate in 11 patients with hypoplastic MDS to various immunosuppressive agents compared to normocellular and hypercellular MDS. In our study, however, the response was independent of bone marrow cellularity.

Table 2 Comparison of response to CyA in various studies

	Janasova et al. [9]	Shinamoto et al. [10]	Asano et al. [12]	Present study
Total subjects	17	4	8	19
RA	16	4	8	13
Marrow cellularity	Variable	Hypoplastic	Variable	Variable
Major response	14	4	4	7
Time to first effect (months)	3	1	1.5	2.5
Side effect	3	Nil	Nil	1

Both the present and the other studies did not show a significant benefit to patients with RAEB. The possibility that these patients may respond to a higher dose of CyA, either alone or in combination with ATG/ALG, needs to be explored.

In our series, one case suffered significant side effects requiring termination of therapy and later also died of serious infection. Other investigators [9–13] have also witnessed a similar side effect profile. The use of CyA in preleukemias raises the possibility of reducing the antitumor immunity thereby facilitating the transformation to acute leukemia. Two of our RAEB cases progressed to AML soon after starting CyA therapy, within 1 month, and thus CyA does not seem to have influenced the progression; however, the follow-up period was too short to address this issue convincingly.

We therefore believe that all patients with MDS-RA could be treated with CyA at least for 6 months and CyA should be continued in those patients who benefit from this therapy. However, there is need for a larger study so that response to CyA in various subtypes can be evaluated in an adequate number of cases.

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