MEDICAL ONCOLOGY (1997) **14**, 43–46

Therapeutic effect of cyclosporine A in thrombocytopenia after myeloablative chemotherapy in acute myeloid leukaemia

YELENA NOVIK*, LESLIE OLEKSOWICZ and PETER H. WIERNIK

Albert Einstein Cancer Center, Department of Oncology, Montefiore Medical Center, 111 E. 210th street, Bronx, New York 10467, USA

Four patients with acute myelogenous leukaemia (AML), who developed isolated thrombocytopenia after anti-leukaemic chemotherapy, were treated with cyclosporine A and showed significantly enhanced platelet recovery. All four patients demonstrated decreased bone marrow megakaryocytes without dysplastic features, absence of identifiable peripheral autoimmune platelet destruction or cytogenetic evidence of secondary myelodysplasia. The duration of response to cyclosporine A ranged from 6 days to 40 months. The mechanism of cyclosporine A-induced platelet recovery may include inhibition of negative modulators and induction of thrombopoietic cytokines mediated by bone marrow regulatory cells.

Keywords: cyclosporine A; thrombocytopenia; myeloablative chemotherapy; acute leukaemia.

INTRODUCTION

Cyclosporine A(CSA) is a fungus metabolite widely utilized as an important immunosuppressive agent in transplantation medicine. Additionally, CSA has been shown to be effective in controlling immune-mediated thrombocytopenia associated with autoimmune diseases [1], 'autoimmune' myelodysplastic syndrome [2] and idiopathic thrombocytopenic purpura [3]. Other applications of CSA have been extended to the treatment of thrombocytopenias with decreased megakaryocytes seen in aplastic anaemia (AA) [4], paroxysmal nocturnal haemoglobinuria/AA [5] and acquired amegakaryocytic thrombocytopenia (AAMT) [6]. In this report, we demonstrate the effectiveness of CSA in four patients displaying prolonged thrombocytopenia associated with anti-leukaemic chemotherapy.

*To whom correspondence should be addressed at: Tel: 718-920-6639. Fax: 718-798-7474.

CASE REPORTS

Patient 1

A 65-year old female with AML (FAB M2) received treatment with idarubicine (Ida) and cytosine arabinoside (ARA-C) (see Table 1) and achieved complete remission (CR). Subsequently she received consolidation therapy with high-dose ARA-C (1500 mg/m^2 for 12 doses). Six weeks after high dose ARA-C she remained thrombocytopenic with a platelet count of $18-25\times10^9$/l and required platelet transfusions. Bone marrow biopsy at that time demonstrated no evidence of leukaemia, decreased marrow cellularity and the presence of all morphologically normal haematopoietic cell lines. The patient was started on CSA orally at a dose 100 mg/day. She was able to maintain a

platelet count at $70-80 \times 10^9$/l without requiring platelet transfusions for 6 months.

Patient 2

A 49-year old male with AML (M4) was treated with Ida and ARA-C (Table 1). Consolidation with high dose ARA-C at 3000 mg/m^2 for 12 doses was administered after achievement of CR. He remained thrombocytopenic (30×10^9/l for 6 weeks after the last consolidation treatment with high dose ARA-C. Bone marrow biopsy confirmed absence of leukaemia, the presence of all three haematopoietic cell lines, hypocellularity, and decreased megakaryocytes. CSA was started at 100 mg/day orally. In 7 days, the platelet count rose to 77×10^9/l, and in 8 weeks reached 120×10^9/l. The dose of CSA was escalated to 200 mg/day after 4 months of CSA treatment when the platelet count dropped to 67×10^9/l and an increase in platelet count to 101×10^9/l was documented. CSA was tapered to 100 mg/day in 2 weeks when the platelet count averaged $> 100 \times 10^9$/l. The dose of CSA was subsequently tapered to 50 mg every other day with every dose reduction accompanied with an initial decrease in platelet count and further stabilization at $> 120 \times 10^9$/l for a total of 40 months.

Patient 3

An 82-year old female with AML (M4) was induced with Ida and ARA-C (Table 1). Thrombocytopenia was noted 3 months after initial treatment, and bone marrow biopsy performed at that time revealed hypocellularity (10%), decreased megakaryocytes and no evidence of leukaemia. Cytogenetics were repeatedly normal. CSA was started 12 weeks after induction therapy. At that time the patient had peripheral platelet counts of 23×10^9/l. CSA was administered at a dose of 100 mg every other day in view of preexisting mild renal insufficiency attributed to a history of hypertension and prior use of nephrotoxic antibiotics. Within 7 days of CSA treatment, an increase in the platelet count to 80×10^9/l was noted. The CSA dose required escalation in the following 2 weeks due to a falling platelet count (20×10^9/l, and with a CSA dose of 300 mg/day^{-1} the platelet count increased to 114×10^9/l in the following 4 weeks. The patient maintained the response to CSA for 12 months when she experienced a relapse of AML, was reinduced with Ida and ARA-C (same doses) and achieved a second CR. CSA at a dose 100 mg/day was reinstituted 6 weeks after the second induction therapy due to a prolonged thrombocytopenia (platelet count 16×10^9/l), and the platelet count

Table 1. Effect of cyclosporine A on peripheral platelet counts in thrombocytopenic patients carrying the diagnosis of AML.

Diagnosis	Patient 1 AML M2	Patient 2 AML M4	Patient 3 AML M4	Patient 4 AML M2, MM
Bone marrow status prior to CSA initiation	CR, decreased megakaryocytes	CR, decreased megakaryocytes	CR, decreased megakaryocytes	Hypoplastic, increased plasma cells, decreased megakaryocytes, blasts by flow cytometry
Induction chemotherapy	Idarubicin: 12 mg/m^2/day IVP for 3 days; ARA-C: 100 mg/m^2/day IVCI for 7 days	Idarubicin: 12 mg/m^{-2}/day IVP for 3 days; ARA-C: 100 mg/m^2/day IVCI for 7 days	Idarubicin: 12 mg/m^2/day^{-1} IVP for 3 days; ARA-C: 100 mg /m^2/day IVCI for 7 days	ARA-C: 30 mg s.q. every 12 hours for 12 days; Hydroxyurea: 3 g/m^2/day P.O. daily for 7 days
Platelet count prior to CSF (cells/l)	19×10^9	30×10^9	23×10^9	25×10^9
Maximum platelet count on CSA (cells/l)	78×10^9	176×10^9	114×10^9	62×10^9
Minimum dose of CSA	100 mg/day	50 mg every other day	100 mg every other day	100 mg/day^{-1}
Maximum dose of CSA	100 mg/day	200 mg/day	300 mg/day	100 mg/day
Bone marrow status while on CSA	CR, decreased megakaryocytes	CR, decreased megakaryocytes	CR, decreased megakaryocytes	Hypercellular and consistent with AML
Duration of response with platelet count $>50 \times 10^9$/l	6 months +	40 months	12 months	4 days
Survival after CSA	13 months +	40 months +	18 months	6 days

Description of peripheral platelet counts, bone marrow morphology, and doses of cyclosporine A in four patients carrying the diagnosis of AML. CSA: cyclosporine A; IVP: intravenous push; IVCI: intravenous continuous infusion; s.q.: subcutaneously.

increased to 70×10^9/l. However, a second relapse was diagnosed 4 months after the second remission and despite aggressive reinduction therapy, the patient expired from neutropenic sepsis.

Patient 4

A 74-year old male diagnosed with AML (M2) received low dose subcutanously administered ARA-C and hydroxyurea in view of serious comorbidities including congestive heart failure, renal insufficiency, and organic brain syndrome. Four weeks later the patient was severely thrombocytopenic and refractory to platelet transfusions. A bone marrow biopsy demonstrated a severely hypoplastic marrow with no morphological evidence of acute leukaemia. Immunophenotype studies revealed the presence of blasts, consistent with M2 differentiated leukaemia. Additional studies determined a pre-existing plasma cell dyscrasia with a monoclonal IgG kappa spike and lytic bone lesions. The patient was given CSA at a dose of 100 mg/day and had a significant response in platelet count from 25 to 62×10^9/l. However, the patient expired on day 6 of CSA treatment due to progressive pulmonary oedema.

None of these patients had clinical, serological or radiological evidence of splenomegaly, B12 deficiency, documentation of autoimmune peripheral destruction of platelets or exposure to known thrombotoxic agents. All patients received support with granulocyte-colony-stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) and demonstrated neutrophil and erythrocyte recovery prior to initiation of CSA Cytogenetic analysis performed on all bone marrow aspirates revealed no chromosomal abnormalities. The starting CSA dose was empirically set at 100 mg/day and was adjusted to achieve maximum increment in platelet counts. No patients experienced CSA toxicity during the period of observation.

DISCUSSION

Although CSA has shown clinical utility in the treatment of thrombocytopenia associated with disorders of haematopoietic progenitor cells, its value in the treatment of prolonged thrombocytopenia following myeloablative chemotherapy has yet to be investigated. In this report, we demonstrate a prompt and significant 2.5–5.8 fold increase in the maximum peripheral platelet counts of four thrombocytopenic post-myeloablated patients treated with CSA. Further, the CSA-enhanced platelet responses appeared to be durable and devoid of significant CSA-induced toxicity. The observation that dose escalation of CSA positively correlated with increase in the patients' platelet counts is strongly supportive of a dose response effect of CSA.

The pathophysiologic mechanism of CSA's observed effect is unclear. Delayed unilineage recovery is frequently recognized in patients after chemotherapy and may precede bone marrow failure[7]. Other conditions associated with ineffective haematopoiesis, such as AA and AAMT are pathogenetically related to negative regulators such as TNFα, IFNγ, cytotoxic antibodies against bone marrow progenitor cells and aberrant interactions between the bone marrow progenitor cells and their microenvironment involving regulatory cytokines [8]. With both AA and AAMT, treatment with CSA with and without anti-lymphocyte globulin and steroids has been shown to be effective in increasing the peripheral platelet counts.

Extensive clinical experience with CSA in the setting of solid organ transplantation as well as allogeneic bone marrow transplantation failed to demonstrate any myelotoxicity of this agent *in vivo*. The majority of *in vitro* studies have shown no CSA-induced inhibition of haematopoietic progenitors [10,11], and some studies demonstrated a stimulatory effect of CSA on haematopoiesis [13]. The *in vitro* effect of CSA on megakaryocyte colony-forming units has yet to be investigated. The effect of CSA on the cells constituting the bone marrow microenvironment is more complicated. While CSA has been shown to inhibit T-lymphocytes proliferation at the level of transcription of regulatory cytokines (IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, TNFα, IFNγ) [13,14], CSA increased IL-6 transcription by mitogen-stimulated mononuclear cells *in vitro* [15].

Taken together, these findings suggest that the efficacy of CSA in upregulating platelet production is determined by multiple factors including the status of the effector cells, possible inhibition of negative modulators, and the induction of cytokines with thrombopoietic properties. In summary we have empirically identified a therapy which was observed to be beneficial in maintaining adequate peripheral platelet counts in our patients after anti-leukaemic therapy. Future investigation will be necessary to understand the complex cytokine-cellular regulatory interactions involved in the platelet enhancing effect of CSA following myeloablative chemotherapy.

REFERENCES

1 Matsumara, O., Kawashima, Y., Kato, S., Sanaka, T., Teraoka, S., Kawai, T., Honda, H., Fichinoue, S., Takahashi, K., Toma, H., Ota, K. and Sugino, N. (1988) Therapeutic effect of cyclosporine in thrombocytopenia associated with autoimmune disease. *Transplantation Proceedings* XX, (3), suppl. 4, 317–22.

2 Miesher, P.A., Favre, H. and Beris, P. (1991) Autoimmune myelodysplasias. *Seminars in Hematology* 28, 45, 322–30.
3 Kelsey, P.R., Schofield, K.P. and Geary, C.G. (1985) Refractory idiopathic thrombocytopenic purpura (ITP) treated with cyclosporine. *British Journal of Haematology* 60, 197–8.
4 Young, N.S. (1992) The problem of clonality in aplastic anemia: Dr Dameshek's riddle, restated. *Blood* 79, (6), 1385–92.
5 Van Kamp, H., Van Imhoff, G. W., De Wolf, J.T.M., Smit, J., Halie, M.R. and Vellenga, E. (1995) The effect of cyclosporine on haematological parameters in patients with paroxysmal nocturnal haemoglobinuria. *British Journal of Haematology* 89, 79–82.
6 Hill, W. and Landgraf, R. (1985) Successful treatment of amegakaryocytic thrombocytopenic purpura with cyclosporine. *New England Journal of Medicine*, 312, 1612 (letter).
7 Jacobs, P. Bone marrow failure: pathophysiology and management. (1995) *Disease-a-month* XLI, 4, 203–89.
8 Nagasawa, T., Sakurai, T., Kashiwagi, H., Abe, T. (1986) Cell-mediated amegakaryocytic thrombocytopenia associated with systemic *lupus erythematosus*. *Blood* 67, 479–83.
9 Slater, L., Katz, J., Walter, B. and Armentrout, S. (1985) Aplastic anemia occurring as amegakaryocytic thrombocytopenia with and without an inhibitor of granulopoiesis. *American Journal of Hematology* 18, 251–4.
10 Berger, R., Majdic, O., Meingassner, J.G. and Knapp, W. (1982) *In vitro* effect of Cyclosporine A (CSA) on human hemopoietic cell lines. *Immunopharmacology* 5, 123–7.
11 Gordon, M.Y. and Singer, J.W. (1979) Selective effects of cyclosporine A on colony-forming lymphoid and myeloid cells in man. *Nature* 279, 433–4.
12 Hirao, A., Kawano, Y. and Takaue, Y. (1993) Effects of immunosuppressants FK 506, deoxypergualin, and cyclosporine A on immature human hamatopoiesis. *Blood* 81, (5), 1179–83.
13 Quesniaux, V.F.J. (1993) Immunosuppressants: Tools to investigate the physiological role of cytokines. *BioEssays* 15, (11), 731–9.
14 Cockerill, P.N., Shannon, M.F., Bert, A.G., Ryan, G.R. and Vadas, M.V. (1993) The granulocyte-macrophage colony-stimulating factor/ interleukin 3 locus is regulated by an inducible cyclosporine A-sensitive enhancer. *Proceedings of National Academy of Science USA*, 90, 2466–70.
15 Walz, G., Zanker, B., Melton L., Suthatiran, M., Strom, T. (1990) Possible association of the immunosuppressive and B-cell lymphoma-promoting properties of cyclosporine. *Transplantation* 49, (1), 191–4.