High-dose cyclophosphamide for refractory autoimmune hemolytic anemia

Victor M. Moyo, Douglas Smith, Isadore Brodsky, Pamela Crilley, Richard J. Jones, and Robert A. Brodsky

High-dose cyclophosphamide, without stem cell rescue, has been used successfully to treat aplastic anemia and other autoimmune disorders. To determine the safety and efficacy of high-dose cyclophosphamide among patients with severe refractory autoimmune hemolytic anemia, we treated 9 patients with cyclophosphamide (50 mg · kg⁻¹ · d⁻¹ for 4 days) who had failed a median of 3 (range, 1-7) other treatments. The median hemoglobin before treatment was 6.7 g/dL (range, 5-10 g/dL). The median time to reach an absolute neutrophil count of 500/μL or greater was 16 days (range, 12-18 days). Six patients achieved complete remission (normal untransfused hemoglobin for age and sex), and none have relapsed after a median follow-up of 15 months (range, 4-29 months). Three patients achieved and continue in partial remission (hemoglobin at least 10 g/dL without transfusion support). High-dose cyclophosphamide was well tolerated and induced durable remissions in patients with severe refractory autoimmune hemolytic anemia. (Blood. 2002;100:704-706)

Introduction

High-dose cyclophosphamide was initially chosen as conditioning for allogeneic bone marrow transplantation because of its potent immunosuppressive properties. Lymphocytes are highly sensitive to cyclophosphamide, but primitive hematopoietic progenitors are resistant to its cytotoxic effects because they contain high levels of aldehyde dehydrogenase, an enzyme that confers resistance to cyclophosphamide. We and others showed that high-dose cyclophosphamide without stem cell transplantation induces durable treatment-free remissions in patients with severe aplastic anemia. This approach also has activity in a variety of other refractory autoimmune conditions and can eliminate alloantibodies. Moreover, it avoids the risk of reinfusing autoreactive effector cells with the autograft during stem cell transplantation, a potential source of relapse. Autoimmune hemolytic anemia (AIHA) has a prevalence of 1 per 100,000 and may be life-threatening. The disease is classified as primary (idiopathic) or secondary if there is an underlying disorder. The associated antibody that causes hemolysis is either a warm antibody or a cold agglutinin. Treatment with glucocorticoids results in improvement in the majority of cases, but relapse is common. For patients whose disease becomes refractory or who do not respond to glucocorticoids, splenectomy is often employed as a second-line treatment. Subsequent salvage treatments include intravenous immunoglobulin, danazol, and a variety of immunomodulating agents including low-dose cyclophosphamide, azathioprine, cyclosporine, and vincristine. Unfortunately, many patients become refractory to multiple therapeutic approaches and develop complications of chronic high-dose steroid therapy. Cold agglutinin autoimmune hemolytic anemia is particularly refractory to treatment. Because of its success in other severe autoimmune disorders, high-dose cyclophosphamide was studied in patients with severe AIHA that was refractory to standard therapies.

Study design

All patients gave informed consent for study participation as approved by the institutional review boards at Johns Hopkins Hospital and Johns Hopkins University (JHH) and at Medical College of Pennsylvania, Hahnemann University (MCPH). Between November 1998 and June 2001, 9 patients (JHH 6; MCPH 3) with severe refractory AIHA were treated with high-dose cyclophosphamide (50 mg/kg ideal body weight per day) intravenously for 4 consecutive days. Mesna (sodium 2-mercaptoethanesulfonate) 10 mg/kg was given at 3, 6, and 8 hours following each cyclophosphamide dose. Granulocyte colony-stimulating factor at 5 μg/kg was initiated 6 days after the completion of treatment with high-dose cyclophosphamide and continued until an absolute neutrophil count of 1000/μL or greater was attained. Patients had to be 70 years of age or younger and were required to have severe AIHA that had failed standard therapy (at least 2 standard therapies for primary AIHA and at least 1 standard therapy for secondary AIHA). Patients were also required to be steroid dependent by the criterion of inability to taper the prednisone dose to less than 10 mg/d. Other inclusion criteria were cardiac ejection fraction greater than 40%, serum creatinine value less than 2.5 mg/dL, and pulmonary function tests showing forced vital capacity, forced expiratory volume, and carbon monoxide diffusion in the lung at least 50% of predicted values.

A diagnosis of AIHA was made on the basis of severe anemia, a positive direct antiglobulin test (DAT for IgG and C3b), or the presence of cold agglutinin in the serum, and corroborating evidence of hemolysis (unconjugated hyperbilirubinemia, elevated lactate dehydrogenase, low serum haptoglobin levels). Following treatment with high-dose cyclophosphamide, patients were provided with supportive care as described previously. A complete remission (CR) was defined as achieving a normal untransfused hemoglobin for age and sex while taking less than or equal to 10 mg/d prednisone and the resolution of hemolysis: partial response (PR) was defined as achieving a hemoglobin of 10 g/dL or greater following treatment and transfusion independence.
Results and discussion

The patient characteristics and response to treatment are shown in Table 1. There were 5 males and 4 females with a median age of 52 years (range, 7-64 years). Of the 9 patients, 7 had the warm-antibody variety of hemolytic anemia, 1 patient had a combination of both warm and cold antibodies, and 1 patient had purely cold-agglutinin disease. Six patients had primary AIHA and 3 patients had secondary AIHA. The underlying diseases in patients with secondary AIHA included chronic lymphocytic leukemia, Castleman disease, and graft-versus-host disease following allogeneic transplantation. The patients had received a median of 3 (range, 1-7) treatment modalities; splenectomy was performed in 3 patients. The median hemoglobin at the time of treatment was 6.7 g/dL (range, 5-10 g/dL), and 8 patients were erythrocyte transfusion dependent.

High-dose cyclophosphamide was well tolerated. Common side effects included nausea, vomiting, transient alopecia, and neutropenic fever. There were no deaths or documented fungal infections, although one patient was treated empirically with amphotericin B for persistent neutropenic fever. The median number of hospital days was 21 (range, 15-25 days); however, 4 of the patients were hospitalized for complications of their AIHA before treatment with high-dose cyclophosphamide. The median times to an ANC of 500/µL or greater and to platelet-transfusion independence were 16 days (range, 12-18 days) and 15 days (range, 0-27 days), respectively. Patients became independent of packed red blood cell transfusion after a median of 19 days (range, 15-25 days); however, 4 of the patients were hospitalized for complications of their AIHA before treatment with high-dose cyclophosphamide.

Table 1. Patient characteristics and response to treatment

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Antibody type</th>
<th>Associated disease</th>
<th>Prior therapy</th>
<th>Pretreatment status</th>
<th>Status at discharge</th>
<th>Current status</th>
<th>Months of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56; F</td>
<td>Warm DAT (+); cold agg. (+) (9 y)</td>
<td>None</td>
<td>Glucocorticoids, splenectomy, oral cyclophosphamide, cyclosporine</td>
<td>HB 5 g/dL; DAT (+); cold agg (+)</td>
<td>HB 9.9 g/dL; DAT (+); cold agg (+)</td>
<td>PR HB 11.1 g/dL; DAT (+); cold agg (+); off therapy</td>
<td>CR HB 13.7 g/dL; DAT (-); off therapy</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>52; M</td>
<td>Warm DAT (+) (4 mo)</td>
<td>None</td>
<td>Glucocorticoids, splenectomy, azathioprine, hydroxychloroquine, ascorbic acid, intravenous immunoglobulin</td>
<td>HB 6 g/dL; DAT (+); prednisone 30 mg</td>
<td>HB 9.0 g/dL; DAT (+); prednisone 30 mg</td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>55; F</td>
<td>Warm DAT (+) (18 mo)</td>
<td>None</td>
<td>Glucocorticoids, cyclophosphamide, intravenous immunoglobulin</td>
<td>HB 6.8 g/dL; DAT (+); prednisone 40 mg</td>
<td>HB 9.0 g/dL; DAT (+); prednisone 40 mg</td>
<td>CR HB 14.7 g/dL; DAT (-); off therapy</td>
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<tr>
<td>4</td>
<td>64; M</td>
<td>Cold agg (+) (40 mo)</td>
<td>None</td>
<td>Glucocorticoids, chlorambucil</td>
<td>HB 10 g/dL; cold agg (+); prednisone 40 mg</td>
<td>HB 9.0 g/dL; cold agg (+); prednisone 40 mg</td>
<td>CR HB 15 g/dL; cold agg (+); off therapy</td>
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<td>5</td>
<td>39; M</td>
<td>Warm DAT (+) (12 mo)</td>
<td>None</td>
<td>Glucocorticoids, intravenous immunoglobulin, oral cyclophosphamide</td>
<td>HB 5 g/dL; DAT (+); prednisone 60 mg</td>
<td>HB 9.6 g/dL; DAT (+); prednisone 40 mg</td>
<td>CR HB 14 g/dL; DAT (+); off therapy</td>
<td></td>
<td>18</td>
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<td>6</td>
<td>7; M</td>
<td>Warm DAT (+) (46 mo)</td>
<td>GVHD following allogeneic BMT at age 2 y for Hurler syndrome</td>
<td>Glucocorticoids, azathioprine, mycophenolate mofetil, FK 506, intravenous immunoglobulin</td>
<td>HB 6.5 g/dL; DAT (+); prednisolone 35 mg, FK 506 (3 mg)</td>
<td>HB 7.1 g/dL; DAT (+); prednisolone 35 mg, FK 506 (0.4 mg)</td>
<td>PR HB 13.8 g/dL; DAT (+); dexamethasone 1.75 mg; QOD† rituximab</td>
<td>PR HB 14 g/dL; rituximab</td>
<td>15</td>
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<td>7</td>
<td>45; F</td>
<td>Warm DAT (+) (23 mo)</td>
<td>Castleman disease</td>
<td>Glucocorticoids, rituximab</td>
<td>HB 6.5 g/dL; DAT (+); no therapy</td>
<td>HB 10.4 g/dL; DAT (+); no steroids</td>
<td>PR HB 14 g/dL; rituximab</td>
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<td>15</td>
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<td>8</td>
<td>55; M</td>
<td>Warm DAT (+) (3 mo)</td>
<td>Chronic lymphocytic leukemia</td>
<td>Glucocorticoids</td>
<td>HB 6.9 g/dL; DAT (+); prednisone 50 mg</td>
<td>HB 14.3 g/dL; DAT (+); prednisone 20 mg</td>
<td>CR HB 14.9 g/dL; DAT (+); off therapy</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>48; F</td>
<td>Warm DAT (+) (on and off 30 y)</td>
<td>None</td>
<td>Glucocorticoids, splenectomy, vincristine, intravenous immunoglobulin, danazol, plasmapheresis, ascorbic acid</td>
<td>HB 6.7 g/dL; DAT (+); prednisone 60 mg</td>
<td>HB 8.4 g/dL; DAT (+); prednisone 40 mg</td>
<td>CR HB 13.7 g/dL; DAT (+); prednisone 5 mg QOD†</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

DAT indicates direct antiglobulin (Coombs) test; cold agg, cold-agglutinin screen; HB, hemoglobin in g/dL; PR, partial response; CR, complete response; GVHD, graft-versus-host disease; and BMT, bone marrow transplantation.

* g/dL represents the hemoglobin with packed red blood cell transfusion; all other hemoglobin values represent nontransfused values.
†QOD indicates every other day; prednisone doses reflect daily dosage unless stated otherwise.
All patients became transfusion independent in response to treatment. Six patients went into CR, including 5 of 6 patients with primary AIHA, and 1 patient with secondary AIHA. The remaining 3 patients achieved a partial remission, including patient no. 1, who had both cold and warm antibodies and in whom the warm antibody was eliminated. The DAT became negative in 2 of the patients who achieved a CR. At the time of treatment, patients required a median of 40 mg/d (range, 0-60 mg/d) of prednisone. At last follow-up, only one of the patients in CR (patient no. 9) was receiving tapering doses of prednisone (5 mg every other day) and one other patient in PR (patient no. 6) was still taking dexamethasone at a low maintenance dose. All others had discontinued steroids. None of the patients had experienced relapse at a median follow-up of 15 months (range, 4-29 months).

For patients with AIHA in whom glucocorticoid treatment fails, splenectomy is frequently offered as second-line treatment. However, this approach is limited because splenectomy is generally ineffective for cold-agglutinin disease and may be less effective and have a higher complication rate in secondary AIHA. Of the 6 patients with primary AIHA, 3 had splenectomy, 2 refused the procedure, and 1 patient with cold-agglutinin disease was not offered the procedure. Splenectomy was not performed in any of the patients with secondary AIHA. There is little consensus on how to manage AIHA when corticosteroid therapy fails and when splenectomy is ineffective or is not an option. Treatments for these patients include low-dose cyclotoxic therapy, danazol, and intravenous immunoglobulin. Most of these treatments are only partially successful, with many patients becoming dependent on glucocorticoid maintenance therapy and eventually suffering the consequences of chronic steroid administration.

This small study suggests that treatment with “transplant doses” of cyclophosphamide without stem cell rescue is well tolerated and effective in patients with refractory AIHA. The majority of patients achieved a durable CR, including 5 of 6 with primary AIHA and 2 of 3 who failed splenectomy. Although this approach is associated with prolonged aplasia in patients with severe aplastic anemia, hematopoietic reconstitution is rapid in patients with autoimmune disorders and normal bone marrow function. Because autografting is not required, the potential risk of relapse from reinforcing autoimmune effectors is avoided. Thus, further study of this approach as treatment for refractory AIHA is warranted.

References

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