“Efficacy of 2-Chlorodeoxyadenosine in Refractory Factor VIII Inhibitors in Non-Hemophilic Persons

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Abstract

The authors examined the efficacy of 2-chlorodeoxyadenosine (2-CDA) in the treatment of refractory inhibitors to factor VIII in non-hemophilic persons. The drug was administered to 6 patients at a dose of 0.1 mg/kg as a 24-hour continuous infusion for a total of 7 days each cycle. An average of 3 immunosuppressive regimens per patient was administered prior to enrollment in this study.

The median inhibitor titer against human and porcine factor VIII before treatment with 2-CDA was 31 Bethesda Units (BU) and 9BU, respectively. The median inhibitor titer against human and porcine factor VIII after treatment was 3.5 BU and 1.5 BU, respectively. The median time to reach nadir inhibitor titer in this study was 137 days while the median time to reach 50% increase in factor VIII was 117 days. No major toxicity was observed in any patient in this study. Patients with acquired inhibitors to factor VIII refractory to conventional immunosuppressive therapy may respond favorably to 2-CDA.
The spontaneous formation of inhibitors against clotting factors is a rare event. The most common inhibitors are those directed against factor VIII$^{1-4}$. This condition is also referred to as acquired hemophilia. The resulting bleeding episodes are usually more serious than those encountered in hemophilic persons. A mortality rate of 22% secondary to uncontrolled hemorrhages was reported in one survey of patients with acquired inhibitors$^3$. The increased awareness of this condition and the availability of more products to manage this condition have improved the outcome of these patients in recent years$^{4-6}$. Nevertheless, patients with bleedings secondary to spontaneous inhibitors to factor VIII should be approached with great caution because of the seriousness of these episodes.

In the present investigation, we report on the use of 2-chlorodeoxyadenosine (2-CDA) in the treatment of patients with acquired inhibitors to factor VIII. The inhibitor titer declined in all 6 patients with virtually no serious toxicity. The study demonstrates that 2-CDA is an effective and safe immunosuppressent in patients with inhibitors to factor VIII refractory to conventional treatment.
Patients and Methods

Between 1997 and 2001, six patients with acquired inhibitors to factor VIII were enrolled in a prospective study. The criteria for enrollment included patients with confirmed diagnosis of inhibitor against factor VIII measured by the Bethesda assay, prior treatment with conventional immunosuppressents and age above 18 years. Patients were considered candidates for the study if they had experienced bleeding or increase in inhibitor titer while receiving immunosuppressive therapy. Patients positive for the human immunodeficiency virus were excluded. All patients gave written informed consent.

Complete blood count was obtained at baseline and repeated at the end of chemotherapy and at least monthly during the follow-up period. Liver functions tests, blood urea nitrogen and creatinine were available in all patients prior to treatment and at frequent intervals thereafter.

The patients received 2-CDA at a dose of 0.1 mg/kg/24 hours as a continuous infusion for a total of 7 days per cycle. The inhibitor titer against human and porcine factor VIII was measured at the end of treatment and once at least every 2-3 months for a year after treatment. A second cycle of treatment was administered if the inhibitor titer was not reduced by at least 25% of the baseline value by the eighth week post therapy. If no response had been detected after the second cycle, further treatment with 2-CDA was discontinued. The end points of the study included increase in factor VIII level above 50% and the absence of further bleeding episodes during this period.
Results and Discussion

The median age of the 4 men and 2 women in this study was 67 years. Table 1 depicts the characteristics of the patients treated with 2-CDA. Serial inhibitor titers, response and toxicity data were available for all patients. The median time between the diagnosis of inhibitors and treatment with 2-CDA was 14.3 months (range, 11.5 – 19.5 months). The number of 2-CDA treatments was one per patient with the exception of a single patient who received two cycles. The median time between the last dose of concentrates used for acute bleeding episodes and receiving 2-CDA was 2.7 days (range, 2.5 – 3 days). The median inhibitor titer against human and porcine factor VIII prior to 2-CDA was 31 Bethesda Units (BU) and 9 BU, respectively.

An average of 3 immunosuppressive regimens per patient was administered prior to enrollment on the current study. The median time between the diagnosis of inhibitor and initiating immunosuppression was 8.6 days (range, 6 – 34 days). These agents included prednisone alone at a dose of 1-2 mg/kg/day for a median of 58 days in all patients, prednisone 1-2 mg/kg/day in combination with cyclophosphamide 2 mg/kg/day for a median of 48 days in five patients, intravenous immunoglobulin 0.5 – 2 mg/kg in four patients and cyclosporin 200 mg daily for a median of 74 days in three patients. The median time between last day of immunosuppressive therapy and 2-CDA was 79 days (range, 66 – 94 days). Treatments aimed at controlling the acute bleeding episodes included porcine factor VIII in three patients, activated prothrombin complex concentrates (FEIBA) in two patients and activated recombinant factor VII in one patient.
These concentrates were administrated for a median of 3 days prior to 2-CDA and for a median of 2 days, thereafter.

The course of treatment in each individual in this study is depicted in figure 1. The median time to reach 50% increase in factor VIII level was 117 days. The median time to 50% reduction in human inhibitor titer was 81.5 days. The median nadir inhibitor titer against human and porcine factor VIII was 3.5 BU and 1.5 BU, respectively. The median time to reach nadir inhibitor titer in this study was 137 days. The median maximum factor VIII level achieved was 70%.

Overall, treatment was well tolerated by all patients. Mild neutropenia with absolute neutrophil count of 655/mm$^3$ was observed in patient number 2 following the administration of a second cycle of 2-CDA. Atypical pneumonia was diagnosed in patient number 1 approximately 5 weeks following treatment. This patient has a lymphocyte count of 370/mm$^3$ at the time of diagnosis of pneumonia. The lymphopenia in this patient lasted approximately 9 weeks. No CD4 ratio was measured and no organism was isolated as an offending agent in this case. No grade 4 toxicity or death from treatment was observed during the study.

Spontaneous inhibitors against factor VIII in persons without history of bleeding tendency constitute the most common inhibitors against clotting factor. In general, management of patients with these inhibitors is based on a twofold principle; treatment of the acute hemorrhagic event and long-term control of the inhibitor.$^{1-6}$ Concentrates used for the treatment of bleeding episodes include porcine factor VIII, activated prothrombin complex concentrates, high-dose factor VIII and recombinant activated factor VII.$^{1,4-6}$
Prednisone alone or in combination with cyclophosphamide are considered standard immunosuppressive agents administered once the acute bleeding episode has been controlled. The reported response rate (disappearance of inhibitor) using these agents is approximately 70%. Patients with low inhibitor titer appear to achieve better response when using immunosuppressents, but the cut-off level between low and high inhibitor titer is not well defined. Other agents used in the treatment of acquired inhibitors to factor VIII include cyclosporin, azathioprine, immunoadsorption, vincristine, 6-mercaptopurine and intravenous immunoglobulin.

In the current investigation, 2-CDA was administered to 6 patients with inhibitors against factor VIII that failed to respond to other immunosuppressents. Although the exact mechanism of action of 2-CDA is not well characterized, its strong immunosuppressive properties are thought to be mediated through the Fas/Fas ligand pathway and subsequent activation of cellular apoptosis. Defects in this particular pathway appear to be important for the induction of some autoimmune disorders. Modulation of the Fas receptor and the Fas ligand by various pharmacologic agents may lead to suppression of autoimmune phenomena. The toxicity profile of 2-CDA includes neutropenic fever, atypical infections and prolonged but reversible immunosuppression and myelosuppression. Disorders where 2-CDA has shown high efficacy include hairy cell leukemia, chronic lymphocytic leukemia and angioimmunoblastic lymphadenopathy with dysproteinemia. All these disorders are thought to have strong autoimmune basis.

All patients in this study responded with long-term control of the inhibitor and bleeding episodes. Decline in inhibitor titer was achieved regardless of the level of inhibitor at the
onset of treatment and the primary therapy received by these patients. It is noteworthy that no hemorrhages were recorded after the administration of 2-CDA. The few patient series available in the literature on the long-term control of acquired inhibitors against factor VIII differ in the type of immunosuppression used, follow-up period and most importantly, the definition of response. One may argue whether continuing immunosuppression is essential in eradicating the inhibitor in our patients. It has been suggested that spontaneous resolution of inhibitors against factor VIII may occur in some patients. However, the severity of bleedings in such patients and the lack of sufficient supportive literature are two important issues to consider before adopting a strategy of “watch and wait”. Immunosuppression has been recommended even in post-partum inhibitors, which are considered by many as the most likely type of inhibitors to remit spontaneously. Remarkably, 5 patients in this series achieved sustained remission after only one course of treatment with 2-CDA. Equally important, is that all patients were heavily pretreated with a variety of agents prior to the administration of the study drug.

In summary, 2-CDA appears to be an effective agent for inhibitors to factor VIII. It provides long-term immunosuppression with an acceptable toxicity profile. It is our view that this agent may be administered after failure of other standard treatments used to reduce and eradicate the inhibitor. Further studies with larger number of patients and longer follow-up are needed before determining the best use of 2-CDA in patients with inhibitors against factor VIII.
Table 1. Characteristics of 6 patients with inhibitors against FVIII treated with 2-chlorodeoxyadenosine

<table>
<thead>
<tr>
<th>Pts</th>
<th>Age/Sex</th>
<th>Underlying Condition</th>
<th>Titer at time of Treatment (BU/ml)</th>
<th>Bleeding</th>
<th>Time to 50% increase in FVIII (day)</th>
<th>Time to 50% decline in inhibitor (day)</th>
<th>Time to nadir inhibitor (day)</th>
<th>Nadar inhibitor Titer (BU/ml)</th>
<th>Maximum FVIII(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72/M</td>
<td>Chronic lymphocytic leukemia</td>
<td>26</td>
<td>3</td>
<td>soft tissues</td>
<td>95</td>
<td>68</td>
<td>117</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>63/M</td>
<td>None</td>
<td>162</td>
<td>16</td>
<td>soft tissues, hematuria</td>
<td>265</td>
<td>124</td>
<td>280</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>67/F</td>
<td>Scleroderma</td>
<td>24</td>
<td>2</td>
<td>postoperative</td>
<td>105</td>
<td>79</td>
<td>145</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>59/F</td>
<td>Systemic lupus erythematosus</td>
<td>36</td>
<td>8</td>
<td>skin, hemarthrosis</td>
<td>128</td>
<td>84</td>
<td>129</td>
<td>4</td>
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<tr>
<td>5</td>
<td>78/M</td>
<td>Colon cancer resected 2 years prior inhibitor</td>
<td>18</td>
<td>10</td>
<td>soft tissues, intra-abdominal</td>
<td>86</td>
<td>54</td>
<td>102</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>68/M</td>
<td>None</td>
<td>54</td>
<td>14</td>
<td>soft tissues, epistaxis</td>
<td>94</td>
<td>87</td>
<td>218</td>
<td>4</td>
</tr>
</tbody>
</table>
Figure 1. The course of factor VIII inhibitor and factor VIII level in 6 patients with inhibitors against factor VIII. Day 0 corresponds to the first day of treatment with 2-chlorodeoxyadenosine
References


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