Autoimmune Cytopenias

Rituximab in the treatment of refractory autoimmune cytopenias in adults

We report the results of four cycles of rituximab therapy in eleven patients with chronic warm antibody type autoimmune hemolytic anemia (AIHA) and six patients with chronic idiopathic thrombocytopoena (ITP). The overall response rate was 64% in the AIHA group (3 complete responses and 4 partial responses) and 83% in the ITP group (4 complete responses, 1 partial response). Responses in AIHA patients with underlying lymphoproliferative disorders receiving rituximab with chemotherapy were generally better sustained, whereas responses in ITP were often transient.

Rituximab, a chimeric monoclonal antibody against the CD20 antigen on B lymphocytes has a significant role in the management of B-cell lymphoproliferative disorders and is beneficial in autoimmune cytopenias. We report a retrospective analysis of 17 adult patients treated with rituximab for autoimmune hemolytic anemia (AIHA, n = 11, mean age 52 years; range 26-81, males = 5, females = 6) or immune thrombocytopeina (ITP, n = 6 mean age 51 years; range 28-89, males = 4, females = 2). Criteria for rituximab therapy for AIHA were evidence of hemolysis (anemia, raised reticulocyte count, elevated indirect bilirubin and lactate dehydrogenase), positive direct antiglobin test (DAT) and failure of first line therapy (Table 1); the criteria for ITP were symptomatic thrombocytopeina with platelet counts < 100x10^9/L for 3 months, a normal bone marrow and refractoriness to at least two lines of treatment (Table 2). All patients received four cycles of rituximab (375 mg/m^2 weekly for 4 weeks). No acute adverse reactions were observed. Responses were evaluated clinically and by full blood count weekly for 1 month and monthly for a minimum of 6 months. Criteria for complete response (CR) for AIHA were resolution of both anemia (Hb ≥ 13g/dL [males], ≥ 12g/dL [females]) and signs of hemolysis off all therapy for at least 4 weeks after rituximab treatment. A partial response (PR) was defined as a stable increase in hemoglobin level of at least 2 g/dL and discontinuation of concomitant therapy. CR and PR in ITP were defined as resolution of bleeding with a platelet count of >150x10^9/L and >50x10^9/L, respectively, on two consecutive occasions off all concomitant therapy 4 weeks after completion of rituximab.

All patients with AIHA had the warm antibody form. Five of the 11 patients had undergone prior splenectomy. Responses were observed in seven of the 11 (63.6%) patients (CR = 3, PR = 4). Two patients continue in CR at 13 and 20 months post-therapy. One patient died of sepsis 10 weeks after treatment while in CR. The median duration of response was 11 months (range 2.5-20). Reticulocyte count remained raised and the DAT persisted in positive partial responders. Four of the five patients with underlying lymphoproliferative disorder responded to rituximab therapy for AIHA were evidence of hemolysis (anemia, raised reticulocyte count, elevated indirect bilirubin and lactate dehydrogenase), positive direct antiglobin test (DAT) and failure of first line therapy (Table 1); the criteria for ITP were symptomatic thrombocytopoena with platelet counts < 100x10^9/L for 3 months, a normal bone marrow and refractoriness to at least two lines of treatment (Table 2). All patients received four cycles of rituximab (375 mg/m^2 weekly for 4 weeks). No acute adverse reactions were observed. Responses were evaluated clinically and by full blood count weekly for 1 month and monthly for a minimum of 6 months. Criteria for complete response (CR) for AIHA were resolution of both anemia (Hb ≥ 13g/dL [males], ≥ 12g/dL [females]) and signs of hemolysis off all therapy for at least 4 weeks after rituximab treatment. A partial response (PR) was defined as a stable increase in hemoglobin level of at least 2 g/dL and discontinuation of concomitant therapy. CR and PR in ITP were defined as resolution of bleeding with a platelet count of >150x10^9/L and >50x10^9/L, respectively, on two consecutive occasions off all concomitant therapy 4 weeks after completion of rituximab.

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Responses were observed in five of the six patients with ITP (83%, CR = 4) and were maintained at 18.5 and 7 months in two, although two others relapsed within 2 months; one patient had a PR that persisted at 9 months after completion of therapy. All five responders in the ITP group achieved a normal platelet count before the fourth dose (week 4) of rituximab. The median duration of response was 7 months (range 2-18.5).

Rituximab has been increasingly used in the treatments of refractory AIHA and ITP. Favorable responses were noted in children with AIHA among adults, our 64% response rate in AIHA is comparable to that in previous reports. Likewise, our overall response rate in ITP is similar to that in previous studies. The mechanism of action of rituximab may be related to depletion of auto-reactive B cells. However, the response in ITP preceded completion of the planned four infusions of rituximab, suggesting saturation of Fc receptors of the monocyte-macrophage system by opsonized B cells as an additional mechanism. Four responding patients with AIHA and lymphoproliferative malignancy received chemotherapy with rituximab and this may have improved their responses. Rituximab was well tolerated by all patients with no significant acute side effects. One infection-related death occurred in a patient with chronic lymphocytic leukemia and AIHA who had been heavily pre-treated and was severely immunocompromised. All the other responders in the AIHA group remain in remission. One non-responder in the AIHA group had a further course of rituximab without any response. Although five out of the six patients (83%) with ITP responded, only two patients remained in remission beyond 6 months. In conclusion, rituximab is a relatively safe and effective treatment option in patients with refractory AIHA and ITP in whom conventional treatments, including splenectomy, have failed. Adjunctive chemotherapy should be considered with rituximab, particularly for those patients with refractory AIHA and ITP who have an underlying lymphoproliferative disorder.

### Table 2. ITP patients and results.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Co-morbid conditions</th>
<th>Treatment pre-rituximab</th>
<th>Pre-rituximab platelets (10/L)</th>
<th>Post-rituximab platelets (10/L)</th>
<th>Treatment during and after rituximab</th>
<th>Response</th>
<th>Time to maximum response (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>F</td>
<td>None</td>
<td>P, IVIg, A, CSA, MMF</td>
<td>8</td>
<td>209</td>
<td>Vincristine</td>
<td>Prednisolone</td>
<td>CR</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>M</td>
<td>Fas ligand deficiency</td>
<td>P, D, CSA, Splenectomy, MMF</td>
<td>15</td>
<td>448</td>
<td>None</td>
<td>Prednisolone</td>
<td>CR</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>M</td>
<td>Ulcerative colitis</td>
<td>P, IVIg</td>
<td>19</td>
<td>488</td>
<td>None</td>
<td>Prednisolone</td>
<td>CR</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>F</td>
<td>None</td>
<td>P, IVIg</td>
<td>47</td>
<td>357</td>
<td>None</td>
<td>Prednisolone</td>
<td>CR</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>M</td>
<td>Hypertension</td>
<td>D, IVIg, MMF, CSA</td>
<td>10</td>
<td>97</td>
<td>None</td>
<td>Prednisolone</td>
<td>CR</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>M</td>
<td>Recurrent deep vein thrombosis, osteoporosis, gastrointestinal bleeding</td>
<td>P, IVIg, A, CSA</td>
<td>89</td>
<td>74</td>
<td>Prednisolone</td>
<td>NR</td>
<td>–</td>
</tr>
</tbody>
</table>

A: azathioprine; C: cyclophosphamide; CR: complete response; CSA: cyclosporine; D: dexamethasone; IVIg: intravenous immunoglobulin; MMF: mycophenolate mofetil, NR: no response; P: prednisolone; PR: partial response.

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Key words: autoimmune hemolytic anemia, idiopathic thrombocytopenia, rituximab, autoimmune cytopenia.

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### References


