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Rituximab in B-cell disorders other than non-Hodgkin's lymphoma

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Rituximab is a human/mouse chimeric monoclonal antibody that binds to the CD20 antigen and is expressed at all stages of B-cell development. Rituximab has demonstrated efficacy as monotherapy and in combination with chemotherapy in the treatment of both indolent and aggressive non-Hodgkin's lymphoma (NHL). Rituximab treatment results in rapid depletion of B-cells and this has led to the consideration of other B-cell disorders as candidates for rituximab therapy. Recent studies have demonstrated the efficacy of rituximab in a variety of such disorders, including chronic lymphocytic leukemia (CLL), post-transplant lymphoproliferative disorder (PTLD), Waldenström's macroglobulinemia (WM), multiple myeloma (MM), idiopathic thrombocytopenic purpura (ITP), hairy-cell leukemia (HCL) and cold agglutinin disease (CAD). In patients with CLL, increasing the dose and/or frequency of rituximab treatment has given improved response rates compared with the standard dose schedule used in NHL, and combination immunochemotherapy has yielded an overall response rate of 92% (with a 60% complete response rate). Clinical trials have also demonstrated evidence of efficacy for rituximab in PTLD, WM and relapsed or refractory ITP. Efficacy of rituximab in CAD and relapsed or refractory HCL has also been demonstrated in small studies and case reports. Available data thus indicate that rituximab can be an effective therapy in a wide range of CD20$^+$ lymphoid disorders. [© 2002 Lippincott Williams & Wilkins.]

Key words: rituximab, chronic lymphocytic leukemia, idiopathic thrombocytopenic purpura, Waldenström's macroglobulinemia, cold agglutinin disease.

Introduction

Rituximab, a human/mouse chimeric monoclonal antibody to CD20, is expressed exclusively on B-cells from the early stages of their development beyond pre–B cells, but not on stem cells. Rituximab has multiple mechanisms of action that bring about the destruction of CD20$^+$ B-cells, including complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity,[1] as well as direct effects on growth and apoptosis,[2] and synergy with chemotherapy.[3]

The clinical efficacy of rituximab, both as monotherapy and in combination with chemotherapy, has been established in both indolent non-Hodgkin's lymphoma (NHL)[4,5] and aggressive NHL.[6–8] Rituximab has also been shown to be of value in stem-cell transplantation in NHL, both in *in vivo* purging[9] and as post-transplant salvage and maintenance therapy.[10]

There are several disorders other than NHL that have a pathological B-cell involvement and in which the efficacy of rituximab has been investigated. These include B-cell lymphoproliferative diseases such as B-cell chronic lymphocytic leukemia (CLL), post-transplant lymphoproliferative disorder (PTLD) and hairy-cell leukemia (HCL), plasma cell disorders such as Waldenström's macroglobulinemia (WM) and multiple myeloma (MM), and autoimmune diseases such as idiopathic thrombocytopenic purpura (ITP) and cold agglutinin disease (CAD). In PTLD, proliferation of B-cells occurs after organ transplant, often as a result of transformation with Epstein–Barr virus (EBV). In other disorders, a disproportionate proliferation of B-cells takes place, resulting in the formation of autoantibodies that lead to the destruction of platelets (ITP) or red blood cells (CAD).

Chronic lymphocytic leukemia

CLL is an incurable lymphoproliferative disorder related to diminished or disordered apoptosis and is the most common leukemia in Western countries. CLL is characterized by the clonal proliferation of B-lymphocytes, arrested in an early stage of development.[11] The CD20 antigen is expressed on almost all

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B-cells in patients with CLL, but the intensity of expression appears to be lower than in patients with NHL.[12] Whether this reduced expression affects the efficacy of rituximab therapy is unclear.

Treatment options for CLL are limited and existing strategies are largely palliative. Although standard treatments such as alkylating agents, corticosteroids and purine analogs can reduce the leukemic burden and symptoms, they have not been shown to produce any significant effect on survival. Two monoclonal antibodies, rituximab and alemtuzumab (Campath-1 H), have become available for clinical use and research. Alemtuzumab is active as a single agent and is being recommended for treatment for patients with fludarabine-refractory disease.[13]

Rituximab monotherapy in CLL

In the pivotal study of rituximab in relapsed or refractory follicular (FL) and low-grade lymphoma, the subset of patients with small lymphocytic lymphoma (SLL) showed an overall response (OR) rate of only 13% compared with 58% for FL.[4] One possibility considered was that this low response rate might be due to the lower density of CD20 on the lymphoma cells in these patients, which are closely analogous phenotypically to CLL cells. However, further studies do not appear to support this hypothesis. Byrd *et al.*[14] reported that there was no relationship between the density of CD20 and response to rituximab, and in a study carried out in patients with CLL, a standard dose of rituximab (375 mg/m^2) once-weekly for 4 weeks produced an OR rate of 25%, with a trend towards higher response rates in patients with lower CD20 expression.[15] McLaughlin *et al.*[4] reported that the half-life of rituximab in CLL patients was shorter than that seen in patients with follicular lymphoma, and suggested that rapid clearance of rituximab might prevent adequate accumulation of the antibody. There is also some evidence that patients with CLL may have some degree of circulating CD20 antigen, although the origin of this is unclear (Keating, unpublished data).

In order to overcome possible effects of antibody clearance and/or low CD20 expression, the use of higher or more frequent doses of rituximab has been evaluated in CLL. In a dose–response study, patients were treated with an initial dose of 375 mg/m^2, which was then increased to a fixed dose of between 500 and 2250 mg/m^2 once-weekly for 4 weeks. The response rate ranged between 22% and 75%, with clear evidence that higher doses induced better responses (Table 1).[16] In a different study, increased frequency of dosing was investigated.[14] An initial dose of 100 mg/m^2 was administered on day 1, followed by doses of either 250 or 375 mg/m^2 on day 3 and thereafter thrice-weekly for 4 weeks.

A selection of response rates according to clinical features is shown in Table 2. It has been demonstrated that non-responding patients have significantly lower plasma trough concentrations of rituximab at most time points examined, and it may be that higher concentrations of rituximab mediates more effective tumor regression.[17] In the study of thrice-weekly dosing by Byrd *et al.*,[14] rapid clearance of antibodies and subsequent low serum trough levels of rituximab were not observed, suggesting that this treatment schedule may be pharmacokinetically superior. These data suggest that the standard dose of a once-weekly schedule of rituximab may not be optimal in CLL (Table 2). The tolerability profile of rituximab in CLL in both the dose-escalation study[16] and the thrice-weekly dosing study[14] was acceptable. The most serious adverse events were infusion-related reactions, which had resolved by the third infusion. In the former study, infusion–related reactions (grade 1 or 2) with the first dose were

Table 1. Response rates to rituximab by dose level in patients with chronic lymphocytic leukemia. Reproduced with permission from O'Brien *et al.*[16]

Dose (mg/m^2)	No. of patients	Response (%)
500	17	5 (PR)
650	4	0
825	3	0
1000	4	2 (PR)
1500	3	1 (PR)
2250	8	6 (PR)

PR, partial response.

Table 2. Response rates for patients with chronic lymphocytic leukemia after thrice-weekly treatments with rituximab monotherapy. Adapted with permission from Byrd *et al.*[14]

Disease characteristic	No. of patients	Response (%)
Stage (Rai)		
I–II	9	56
III–IV	24	42
Nodes (cm)		
<5	21	48
5–9	10	40
$\geqslant 16$	2	50
CD20 antigen density		
High	10	50
Low	10	40

noted in 94% of patients. However, on subsequent doses, reactions were minimal, with 67% of patients presenting with grade 2 reactions. No patient had a grade 3 or 4 reaction.[16]

Immunochemotherapy in CLL

The combination of rituximab with chemotherapy has proven highly effective in both indolent and aggressive NHL.[5,7,8] A recent study has evaluated the combination of fludarabine (F) and cyclophosphamide (C) with rituximab in CLL. Patients with previously untreated advanced or progressive CLL were given six courses of rituximab plus FC (375 mg/m^2 rituximab in course 1; 500 mg/m^2 rituximab in courses 2–6; fludarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2 daily for 3 days in all courses). Courses were repeated every 4 weeks. This combination was highly active, with an OR rate of 92% and a complete response (CR) rate of 60%. Although the OR rate for F and FC regimens is similar to that seen with FC plus rituximab, CR rates are higher with the latter treatment regimen (Table 3). In addition, although follow-up was short, the time to treatment failure in this study appears longer than previously seen with FC or other chemotherapeutic regimens. (Figure 1).[18] Apart from the occurrence of tumor lysis syndrome in one patient, the combination of FC plus rituximab was shown to be no more toxic than FC alone.

These results demonstrate that it is possible to improve the response rates of patients with CLL by increasing the dose intensity, increasing the frequency of rituximab infusion and/or by combining rituximab with other treatment options.

Post-transplant lymphoproliferative disorder

A B-cell lymphoma (often transformed by EBV) known as PTLD may develop in patients who are immunosuppressed following allogeneic organ transplantation. Treatment of this disorder usually

Table 3. Response rates for patients with chronic lymphocytic leukemia who received rituximab combination therapy. Reproduced with permission from Keating *et al.*[43]

Regimen	No. of patients	CR (%)	PR (%)	OR (%)
Fludarabine[a]	82	35	50	85
Fludarabine and cyclophosphamide (FC)[a]	53	43	48	91
Rituximab plus FC	79	66	29	95

[a]Historical controls.
CR, complete response; PR, partial response; OR, overall response.

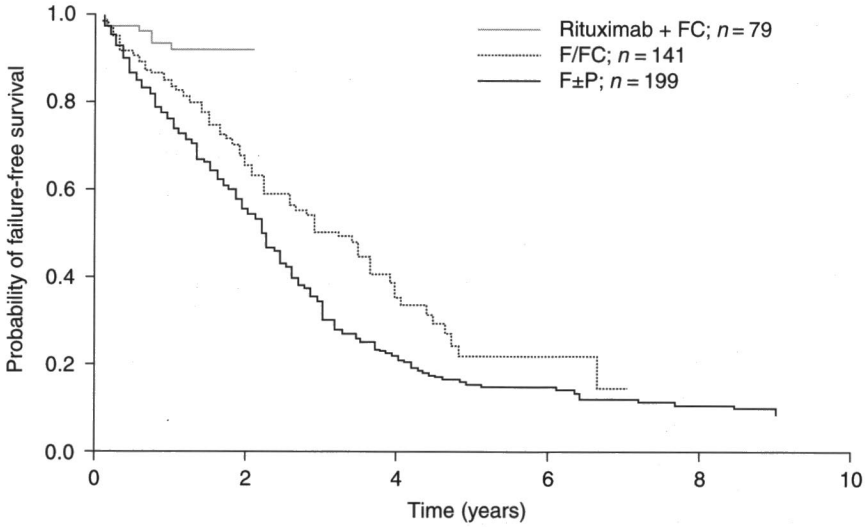

Figure 1. Probability of failure-free survival for fludarabine (F) and cyclophosphamide (C) plus rituximab compared with chemotherapy alone in patients with chronic lymphocytic leukemia. P, prednisone.

involves reduction or discontinuation of immunosuppressive treatment, although this invariably increases the probability of graft rejection. A number of recent studies have demonstrated that rituximab is a safe and effective treatment for patients with PTLD. Rituximab was first used to treat PTLD in three patients following lung transplantation. Treatment resulted in two complete remissions and one non-response.[19] Zilz *et al.*[20] described a case of complete remission from PTLD in a heart transplant recipient. The patient had been in remission during 10 months' clinical follow-up. In another study, two of three patients who developed PTLD following liver transplantation achieved rapid complete remission following the administration of four doses of 375 mg/m^2 rituximab.[21] Rituximab therapy has also been given to a patient who developed PTLD following a kidney/pancreas transplant. Despite subsequent re-intensification of immunosuppression, rituximab induced complete disappearance of lymphoproliferative lesions within five months of treatment.[22]

In a study in 32 patients with PTLD (26 post-solid organ transplant, six post-bone marrow transplant), rituximab was used as either first-line therapy (30 patients) or salvage therapy (two patients). Treatment resulted in an OR rate of 69%, with 20 CRs and two partial responses (PRs).[23] Recently rituximab has been used as first-line treatment in 12 children with PTLD; 66% responded to the treatment and went into complete remission, and a rapid decrease in fever (within 1 week) was observed in all responders.[24]

Idiopathic thrombocytopenic purpura

ITP is a B-cell-mediated disorder, characterized by the formation of anti-platelet autoantibodies, and the consequent premature destruction of platelets by the reticuloendothelial system. Standard treatment for ITP includes corticosteroids, high-dose intravenous gamma globulin, anti-D gamma globulin (RhoGam) and splenectomy, but 25–30% of adult patients with ITP develop disease that is refractory to these treatments. These patients have a 10-year mortality rate of between 10% and 20%.[25] Prognosis in children with ITP is much better, with far fewer cases of chronic ITP reported. As rituximab is highly effective in depleting B-cells, it has the potential to eliminate the B-cell clones that form the anti-platelet autoantibodies in ITP.

The efficacy and safety of rituximab in ITP has been evaluated in a phase I/II trial of patients with chronic ITP.[26] Twenty-eight patients who had received at least two previous therapies received once-weekly infusions of rituximab (375 mg/m^2) for a total of 4 weeks. Patient response rates were measured in terms of a rise in the platelet count. Patient characteristics and response rates are presented in Figure 2 and Table 4. The latest data available from this trial showed six patients with a CR (platelet count $>100 \times 10^9$/l) and six patients with a PR (platelet count between 50 and 100×10^9/l). Three additional patients developed a minor response (MR) (platelet count below 50×10^9/l with no need for further treatment). Seven patients from this trial developed a sustained response that lasted 6 months or more. Rituximab was well tolerated, with the majority of adverse events being of grade 1 severity, with only one grade 3 event. Although randomized clinical trials are necessary, these results suggest that rituximab may be an effective and safe treatment option for patients with chronic ITP that is refractory to standard treatments.

Plasma cell dyscrasias

Plasma cell dyscrasias (PCDs) are a group of clinically and biochemically diverse disorders of unknown etiology. They are characterized by the disproportionate proliferation of a single clone of B-cells, resulting in excessive production of a monoclonal immunoglobulin (IgM, often referred to as the M protein).[27] The two most common PCDs are WM and MM.[28,29] Some patients may be cured by allogeneic transplantation, but no other curative treatment is available. For patients with MM, alkylating agents are the standard treatment, and purine analogs are generally used for patients with WM. Although these treatments can achieve clinical response rates up to 90%, patients eventually become refractory.

The plasma cells of normal individuals do not usually express CD20. However, up to 20% of MM patients express CD20 on their plasma cells, although in most cases expression is either weak or is heterogeneous, with a proportion of CD20$^-$ cells. In contrast, between 75% and 100% of patients with WM have plasma cells that express CD20.[30]

Rituximab in WM

Several studies have indicated that rituximab can induce an objective response in patients with WM and is able to alleviate the polyneuropathy commonly associated with this disease. Byrd *et al.*[31]

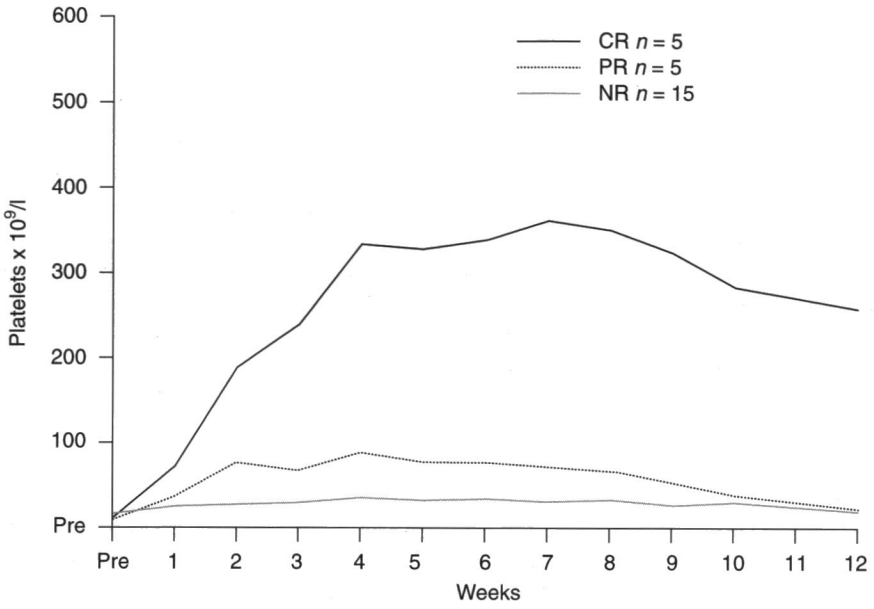

Figure 2. Patient response rates over time in terms of platelet counts for patients with idiopathic thrombocytopenic purpura. CR, complete response; PR, partial response; NR, no response.

Table 4. Patient characteristics according to response for patients with idiopathic thrombocytopenic purpura receiving rituximab therapy

Patient characteristics	CR ($n = 5$)	PR ($n = 5$)	MR ($n = 3$)	NR ($n = 12$)
Sex (female/male)	5/0	3/2	7/5	7/5
Median age (years)	25	45	49.5	49.5
Median baseline platelet count ($\times 10^9$/l)	11	9	13.5	13.5
Median ITP duration before rituximab (months)	25	19	12	33.5
Prior splenectomy ($n = 8$)	1	2	0	5

reported a 57% OR rate in seven heavily pretreated patients with WM, with a median progression-free survival of 6.6 months. Treon *et al.*[32] described a patient with WM who responded to rituximab and who maintained a response for at least 24 months, suggesting that responses to rituximab can be durable. In a recent retrospective study, 80% of patients demonstrated a decrease in their IgM paraprotein level after rituximab therapy, with 27% of patients displaying a reduction in IgM >50%, and 33% and 30% of patients demonstrating reductions of ⩾25% and ⩽25%, respectively[33] (Figure 3).

Rituximab in MM

The use of rituximab in the treatment of MM has not been widely reported. In a recent phase II trial, $CD20^+$ plasma cells and B-cells were shown by flow cytometric analysis to have disappeared in response to rituximab therapy. However, residual $CD20^-$ tumor cells remained in the bone marrow of one patient, and after 6 months this patient progressed with $CD20^-$ myeloma cells.[34] Although the majority of plasma cells in patients with MM are $CD20^-$, it has been shown that interferon-γ (IFN-γ) is able to induce expression of CD20 on freshly isolated plasma cells from MM patients.[34] IFN-γ is also an activator of natural killer (NK) cells and monocytes. These properties of IFN-γ might therefore help render MM cells more susceptible to rituximab, and clinical studies of rituximab plus IFN-γ in MM patients are now being considered.[30] A schematic representation of the potential utility of IFN-γ to enhance CD20 expression on MM cells is depicted in Figure 4.

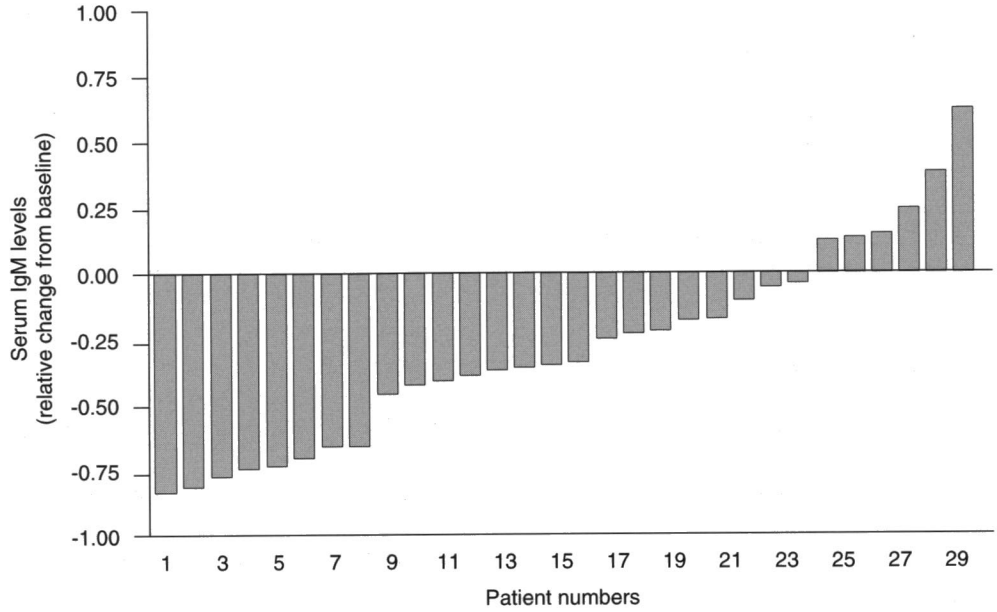

Figure 3. The effect of rituximab on IgM in patients with Waldenström's macroglobulinemia. Reproduced with permission from Treon *et al.*[33]

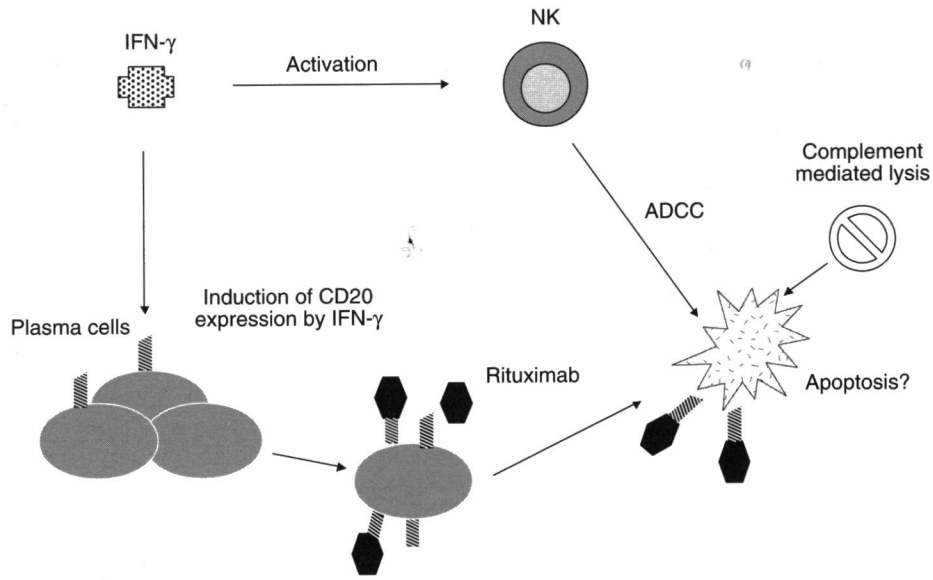

Figure 4. Targeting myeloma by serotherapy and the induction of tumor-selective antigens. ADCC, antibody-dependent cell cytotoxicity; IFN-γ, interferon-γ; NK, natural killer cell.

Other B-cell disorders

Cold agglutinin disease

CAD is an acquired autoimmune hemolytic anemia caused by an IgM autoantibody directed against the I antigen on red blood cells. Formation of these autoantibodies is thought to be associated with monoclonal B-cell proliferation,[35] providing the rationale for the use of rituximab in this disease. The course of CAD is chronic and most treatments are ineffective. The evidence for the efficacy of

rituximab in CAD comes from a series of case reports. Bauduer[36] reported that rituximab monotherapy brought about a complete and rapid hematologic response, with no evidence of relapse for at least nine months. Rituximab has also been used in combination with other agents for the treatment of CAD. In a 75 year old patient with unresponsive cold agglutinin-mediated hemolytic anemia, rituximab, in combination with cyclophosphamide and prednisone, induced a rapid clinical improvement with a sustained response.[37] In another case report, rituximab was used in combination with IFN-α, resulting in a complete hematologic response for at least 7 months.[38] CAD is a difficult disease to treat, and the use of rituximab may be an appealing treatment option for this complex disorder.

Hairy-cell leukemia

HCL is a chronic $CD20^+$ B-cell malignancy and has the highest level of CD20 expression of any of the lymphoproliferative diseases.[39] Standard treatments (IFN, pentostatin, cladribine and splenectomy) can result in long-lasting responses,[40] although a proportion of patients relapse or become refractory. These patients have a poor prognosis and alternative treatments are needed. A number of recent reports have demonstrated the efficacy of rituximab in HCL. Case studies have reported the induction of complete remission, with disappearance of hairy cells from the bone marrow and peripheral blood, in patients with HCL refractory to standard treatment regimens.[39,41] A phase I/II study, in which 11 patients with HCL (eight relapsing and three newly diagnosed) were treated with rituximab, resulted in an objective response in seven patients (CR in six), with a duration of response of 0–34 months and a median time to response of 14 months.[42]

Discussion

The efficacy of rituximab as monotherapy or in combination with chemotherapy has now been established in NHL. Rituximab acts on all $CD20^+$ cells and this has led to the expectation that it may produce equivalent results in other B-cell disorders. A variety of data are now available indicating that the efficacy of rituximab extends beyond NHL.

CLL appears not to respond as well as NHL to the standard dose of rituximab for reasons that may include the level of CD20 expression, or more rapid clearance of antibodies. However, higher responses have been obtained by increasing the frequency or intensity of dose, and by the use of immunochemotherapy with fludarabine and cyclophosphamide plus rituximab, yielding response rates among the highest seen for any regimen in CLL.

Some B-cell disorders, such as WM and CAD, are difficult to treat, and the introduction of new therapies is imperative. Although only preliminary case studies have been reported so far, these have presented interesting and encouraging data. Investigations into the effect of rituximab in MM are in the very early stages, but the potential for induction of CD20 antigens is evident. For incurable disorders such as CLL, PCD and CAD, rituximab has the potential for first-line use. For disorders such as ITP and HCL, rituximab offers an effective alternative after failure of standard treatment.

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