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OFF-LABEL USE OF RITUXIMAB IN HOSPITALS

A position statement of the NSW Therapeutic Advisory Group (NSW TAG) March 2007

SCOPE

The purpose of this position statement is to assist hospital Drug and Therapeutics Committees to develop local hospital policy in this therapeutic area.

This position statement examines the current evidence for haematological and non-haematological off-label indications for rituximab in hospitals.

Evidence that has only been published in abstract form has not been included in this review.

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Key messages

1. At this time there are no published systematic reviews of randomised controlled trials (RCTs) of rituximab in any off-label indication in adults or children.
2. Based on results from randomised controlled trials (RCTs), rituximab currently cannot be supported in patients with the following conditions:
 - HIV-associated non-Hodgkins lymphoma
 - Mantle cell lymphoma (MCL)
3. The remainder of the evidence concerning use of rituximab in off-label conditions consists of uncontrolled trials, case series and case reports. In a number of cases, this evidence has been synthesised into guidelines and reviews. On the basis of this synthesised evidence:

Rituximab could be considered on an individual basis for patients with a number of conditions:

- Waldenstrom's macroglobulinaemia
- Acquired haemophilia (second line therapy)
- Adults with chronic, refractory immune thrombocytopenic purpura (ITP)
- Multifocal motor neuropathy
- Persistent or progressive post transplant lymphoproliferative disorder (PTLD) without evidence of allograft rejection

Use of rituximab currently cannot be supported in patients for:

- First-line therapy for patients with haemophilia A who develop inhibitors
- Chronic inflammatory demyelinating polyradiculoneuropathy

The role of rituximab remains unclear in the following conditions until the completion of RCTs:

- Chronic lymphocytic leukaemia (CLL)
- Children with ITP
- Acquired haemophilia (first line therapy)

4. For other conditions, there is currently insufficient evidence to define the role of rituximab. It is recommended that approval for use of rituximab in these conditions be assessed according to underlying disease and disease severity, potential benefits, adverse events (some of which are severe) and response to standard therapy. Guidance for decision making in off-label conditions can be found in the NSW TAG discussion paper regarding off-label use of registered medicines available on the NSW TAG website – www.nswtag.org.au.

5. Patients with a high tumour burden such as CLL or MCL may be at higher risk of severe infusion-related reactions; the product information advises that these patients should only be treated with extreme caution and when other therapeutic alternatives have been exhausted.

6. Hepatitis B screening is recommended for all patients receiving rituximab. Adult carriers should receive lamivudine in a dose of 100mg/day starting a minimum of 2 weeks before chemotherapy and continuing for 8 weeks following cessation of chemotherapy.

7. There is currently insufficient information to determine if the side effect profile of rituximab is different in children and adults. There is some evidence that serum sickness reactions may occur more commonly in children, particularly when treated for ITP.

8. In light of the evolving efficacy and adverse drug event profile of rituximab, NSW TAG recommends that Drug and Therapeutics Committees (DTCs) request follow-up reports from clinicians regarding safety and effectiveness of rituximab therapy for all patients for whom off-label use has been approved. NSW TAG recommends that effectiveness be monitored by DTCs at 3 to 6 monthly intervals and that all adverse events be reported to and reviewed by DTCs in a timely manner.

9. At this point in time, no cost-effectiveness data are available for off-label use of rituximab.

Summary of evidence of efficacy and adverse event profile

1. Current evidence for use of rituximab in off-label malignant haematological conditions can be summarised as follows:

1.1 *Chronic lymphocytic leukaemia (CLL):*

1.1.1 There are no completed randomised controlled trials (RCTs) for the use of rituximab (with or without chemotherapy) in patients with previously treated and previously untreated CLL. Consensus guidelines state that until the completion of randomised controlled trials (RCTs) there is inadequate evidence to support or refute rituximab as an appropriate therapy for CLL.¹

1.1.2 There is evidence from uncontrolled trials supporting the use of rituximab in combination with chemotherapy in previously treated and previously untreated patients with CLL.

1.1.3 There is little evidence supporting the use of rituximab as monotherapy.

1.1.4 The Cancer Institute NSW Standard Cancer Treatments has a protocol for use of fludarabine, cyclophosphamide and rituximab in CLL, but states this is an off-label indication and does not specify a patient group.²

1.2 *HIV-associated non-Hodgkin's lymphoma (NHL):*

1.2.1 There is evidence from case reports and uncontrolled trials of efficacy for rituximab in HIV-associated NHL.

1.2.2 Only one RCT has been identified to date; it does not support use of rituximab in this indication and shows a marked increase in infectious deaths in patients treated with rituximab.³

1.3 *Mantle cell lymphoma (MCL):*

1.3.1 There is evidence of efficacy of rituximab in mantle cell lymphoma based on case reports.

1.3.2 RCTs show there is no strong evidence that rituximab prolongs event-free survival⁴,⁵ whether used as standard or prolonged therapy⁶ in patients with MCL.

1.4 *Waldenstrom's macroglobulinaemia (WM):*

1.4.1 There are consensus guidelines recommending rituximab as a therapeutic option in WM^{7,8}.

1.4.2 The Cancer Institute NSW Standard Cancer Treatments⁹ has a protocol for use of cladribine, cyclophosphamide and rituximab for patients with WM.

1.4.3 Rituximab should be used cautiously in patients with WM due to the risk of transient exacerbation in patients with hyperviscosity and/or IgM levels >40 g/L.⁷

2. The current evidence for use of rituximab in non-malignant haematological off-label conditions can be summarised as follows:

2.1 *Acquired haemophilia*

A guideline¹⁰ recommends that rituximab could be considered for second line therapy for acquired haemophilia. The authors of the guideline recommend that further studies are required before rituximab could be considered as a first line therapy in acquired haemophilia and rituximab should not be considered a first-line therapy for patients with haemophilia A who develop inhibitors.

2.2 *Chronic inflammatory demyelinating polyradiculoneuropathy*.

A systematic review of descriptive studies shows there is inadequate evidence for efficacy of rituximab in this condition¹¹

2.3 *Idiopathic thrombocytopenic purpura (ITP)*

2.3.1 One guideline recommends that rituximab has a potential role in therapy for adults with chronic, refractory ITP. According to this guideline, there is no place for rituximab in treating children with ITP.¹²

2.3.2 Systematic reviews of descriptive studies show overall data quality is poor and there is only preliminary evidence for efficacy of rituximab in adults with ITP, with or

without prior splenectomy.^{13,14} Authors of one review recommend that indiscriminate use of rituximab in adults with ITP should be avoided.¹⁴

2.3.3 Two studies involving rituximab use in children with ITP report serum sickness as an adverse event.^{15, 16}

2.3.4 There are currently no RCTs or systematic reviews of evidence for rituximab in treatment of ITP in paediatric patients.

2.4 One guideline recommends that rituximab could be considered for multifocal motor neuropathy¹⁷

2.5 One guideline recommends that rituximab could be considered for persistent or progressive post-transplant lymphoproliferative disorder (PTLD) without evidence of allograft rejection¹⁸

3. Potential benefits of rituximab need to be weighed against potential adverse events, some of which are severe. The adverse event profile of rituximab can be summarised as follows:

3.1 There have been 9 deaths in Australia reported to the Adverse Drug Reactions Advisory Committee (ADRAC),¹⁹ although there is difficulty in attributing causality of death directly to use of rituximab.

3.2 Examples of severe adverse events include²⁰⁻²⁶:

- Fatal infusion reactions
- Pulmonary events (hypoxia, pulmonary infiltrates and acute respiratory failure)
- Hepatitis B reactivation
- Tumour lysis syndrome
- Severe mucocutaneous reactions
- Abdominal pain, bowel obstruction, and perforation
- Neutropenia and thrombocytopenia
- Reactivation of JC virus resulting in progressive multifocal leukoencephalopathy

3.3 There is currently insufficient information to determine if the side effect profile of rituximab is different in children and adults. There is some evidence that serum sickness reactions may occur more commonly in children, particularly when treated for ITP.^{15, 16}

3.4 Progressive Multifocal Leucoencephalopathy (PML) has occurred following off-label use of rituximab in treating systemic lupus erythematosus. According to the product information, "The efficacy and safety of [rituximab] for the treatment of SLE has not been established."²⁶

3.5 Hepatitis B screening is recommended for all patients receiving rituximab. Adult carriers should receive lamivudine in a dose of 100mg/day starting a minimum of 2 weeks before chemotherapy and continuing for 8 weeks following cessation of chemotherapy.²⁷

3.6 Patients with a high tumour burden such as CLL or MCL may be at higher risk of severe infusion-related reactions; the product information advises that these patients should only be treated with extreme caution and when other therapeutic alternatives have been exhausted.²⁶

Introduction

Drug and Therapeutics Committees in NSW public hospitals have requested guidance about use of rituximab for a variety of “off-label” indications which are not approved by the Therapeutic Goods Administration (TGA). The term “off-label” refers to prescription of registered medicines for a use that is not included in the approved product information.²⁸

Australian TGA approved indications

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. It is currently approved by the TGA for²⁹:

- CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma (NHL), in combination with chemotherapy,
- CD20 positive, relapsed or refractory low grade or follicular, B-cell NHL,
- CD20 positive, diffuse large B-cell NHL, in combination with chemotherapy.

It is also approved “in combination with methotrexate...to reduce the signs and symptoms in adult patients with severe active rheumatoid arthritis who have had inadequate response or intolerance to at least one tumour necrosis factor (TNF) antagonist therapy.”²⁶

As for any TGA approved medication, these indications are based on the patient profiles in the clinical trials. It should be noted that use of rituximab for indications that approximate these indications, but are not specifically included (eg other CD20 positive B-cell NHL such as mantle cell, Burkitt's and mucosa-associated lymphoid tissue (MALT) lymphomas) are technically off-label uses of rituximab.

Methodology

A number of searches of The Cochrane Database of Systematic Reviews and MEDLINE databases were run using the term "Rituximab" combined with the following terms: "therapy (optimized)", "case report", "clinical trial", "clinical trial, phase i", "clinical trial, phase ii", "clinical trial, phase iii", "clinical trial, phase iv", "comment", "comparative study", "controlled clinical trial", "editorial", "guideline", "journal article", "meta analysis", "practice guideline", "randomized controlled trial", "review", "review literature", "adverse events".

Guideline Clearing Houses and organisations that produce peer reviewed guidelines were searched for guidelines regarding off-label use of rituximab.

The Adverse Drug Reaction Advisory Committee was asked to provide relevant information on rituximab.

Roche Products was approached to provide additional information regarding use of rituximab in a number of off-label conditions.

All randomised controlled trials have been critically appraised and a summary of this appraisal is included in appendix one.

To aid interpretation of the evidence, the NHMRC levels of evidence³⁰ for interventions are presented as follows:

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly-designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test/post-test.

It should be noted that expert opinion and/or expert consensus is not included as evidence in this framework.

Appraisal of evidence of efficacy

Where available we report preferentially on the highest levels of evidence from systematic reviews and randomised controlled trials (RCTs) and systematically developed guidelines. We also report on consensus guidelines where they are available.

However, for some rare disorders there will never be RCTs because of the small numbers of patients and the likelihood of heterogeneity in patient cohorts. Accordingly, we note case reports, case series and phase 1/2 studies for a number of conditions to aid clinicians and DTCs in their decision making. In general, these reports and studies are not presented in detail due to the extensive number of immune mediated medical conditions, in addition to B-cell malignancies, for which rituximab has been used. There are also many other variables that make systematic interpretation of the evidence difficult. These include:

- Variations in the exact rituximab regimen used – even for the same conditions - eg, rituximab may have been used alone or in combination with other medications, rituximab may have been used in different doses for differing numbers of cycles
- Variations in stage of illness eg, rituximab has been used variably in acute refractory conditions and chronic relapsing conditions and patients may have had varied treatments prior to trials of therapy with rituximab
- Variations in methods for assessing and classifying clinical response eg, differing definitions for partial or complete response
- Variation in follow-up periods
- Adverse events with differing levels of severity are often reported with these reports and studies and these need to be weighed against potential benefits
- Many of the phase 1/2 trials are industry sponsored.

Thus, although reports showing some benefits with rituximab are numerous, it is currently not possible to systematically establish the efficacy or risk-benefit ratio for use of rituximab in these conditions.

Clinicians considering use of rituximab for non-approved (off-label) conditions should review the available evidence in light of the clinical circumstances for individual patients. As evidence continues to evolve, new literature reviews for individual conditions may need to be conducted. NSW TAG has produced guidance which can aid in decision making for off-label conditions.²⁸

The following list of conditions is arranged alphabetically:

Chronic inflammatory demyelinating polyradiculopathy

Systematic reviews:

A Cochrane review¹¹ concluded there is inadequate evidence to decide whether any immunosuppressive drug, including rituximab, is beneficial in chronic inflammatory demyelinating polyradiculopathy.

Case reports, case series and uncontrolled trials:

At least one case report showing some evidence of benefit has been reported for chronic inflammatory demyelinating polyradiculopathy.³¹

Chronic lymphocytic leukaemia (CLL)

Guidelines:

A guideline produced by the *program in evidence-based care – a cancer care Ontario program* states: “there is insufficient evidence at this time to support or refute the use of single-agent rituximab or a rituximab containing chemotherapy regimen in patients with CLL.”¹

Authors of a previous guideline, based on a literature review up to 2003 by the British Society for Haematology,³² said, "Rituximab monotherapy is not recommended in untreated CLL." This recommendation is based on evidence obtained from well-designed, non-experimental, descriptive studies. Additionally the authors said, "Rituximab combined with fludarabine (with or without cyclophosphamide) requires further evaluation in untreated CLL." This recommendation is based on at least one randomised controlled trial. Further, this guideline did not support the use of rituximab monotherapy in previously treated patients, as even with very high doses all responses are partial. However, the authors said the response rate of rituximab in combination with fludarabine (with or without cyclophosphamide) was superior to standard second line therapies.

The Cancer Institute NSW has listed a protocol for CLL (Fludarabine, Cyclophosphamide and Rituximab)² in their standard cancer protocols (CI-SCaT) - see www.treatment.cancerinstitute.org.au. The protocol does not specify whether it applies to previously treated or previously untreated patients with CLL. The protocol states: "Rituximab is not registered for this indication, use in CLL is off label." The Cancer Institute NSW has used 3 uncontrolled studies³³⁻³⁵ to support the use of rituximab in CLL (outlined below).

Uncontrolled trials

The most recent uncontrolled trial³³ involved 77 patients with CLL or follicular lymphoma treated with rituximab, fludarabine and cyclophosphamide. Results of this study showed the complete response rate was 67% in previously untreated patients with CLL and 14% in previously treated patients with CLL.

Another single-arm study³⁴ of rituximab, fludarabine and cyclophosphamide as initial therapy in 224 patients with progressive or advanced CLL has been conducted. Early results showed the complete response rate was 70%.

One study³⁵ reporting 28 month (mean) follow-up of 177 previously treated CLL patients treated with rituximab, fludarabine and cyclophosphamide showed complete response (CR), nodular partial remission and partial remission was achieved in 25%, 16% and 32% of patients respectively. The authors commented that this was the "highest CR rate reported in a clinical trial of previously treated patients with CLL." Myelosuppression was the most common toxicity.

One phase 2 study³⁶ (sponsored by Roche) of 28 patients with previously treated CLL showed 7 had a partial remission lasting for 20 weeks. There was one rituximab related death.

Another randomised phase 2 study³⁷ compared fludarabine with concurrent or sequential rituximab in 104 patients with previously untreated CLL. Complete response rate was 47% in the concurrent regimen arm compared with 28% in the sequential regimen.

Other studies and reports:

A case series of 32 patients with previously treated CLL retreated with pentostatin, cyclophosphamide and rituximab showed 25% had a complete response. The authors said toxicity was acceptable with infections occurring in 28%.³⁸

In a dose-escalation trial of rituximab monotherapy in 50 patients with CLL, all responses (36%) in patients with CLL were described as partial remission, regardless of the dose.³⁹

Numerous other reports show some evidence of benefit for rituximab in CLL / small lymphocytic lymphoma.³⁸⁻⁴¹

Factor VIII and IX inhibitors

Guidelines:

A guideline from the United Kingdom Haemophilia Centre Doctors Organisation recommends that rituximab can be considered as a second-line therapy for acquired haemophilia (based on evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities). The authors of the guideline said that further studies are required before rituximab could be considered as a first-line therapy in acquired haemophilia and rituximab should not be considered a first-line therapy for patients with haemophilia A who develop inhibitors.¹⁰

Case reports, case series and uncontrolled trials:

A number of these, showing some evidence of benefit, have been reported for acquired and congenital haemophilia in adolescents and adults,⁴²⁻⁴⁹ and autoimmune haemolytic anaemia (warm or cold antibody types),⁵⁰⁻⁵³

HIV Associated NHL

Randomised controlled trials:

One RCT of patients with HIV-associated NHL found no differences in response rate between those on chemotherapy with or without additional rituximab³. Also, infectious deaths were significantly more common in the rituximab group. See Appendix 1 for appraisal of trial.

Case reports, case series and uncontrolled trials:

In contrast to the RCT above, other reports do show some evidence of benefit for HIV-associated NHL.⁵⁴⁻⁵⁶

Immune Thrombocytopenic Purpura (ITP)

Guidelines

A guideline¹² by the British Committee for Standards in Haematology, General Haematology Task Force regarding investigation and management of ITP in adults, children and in pregnancy recommends in adults, "rituximab...may be of value for patients in whom there is no response to other therapies and in whom there is a definite requirement to elevate the platelet count (e.g. active bleeding)." In the guideline there is no recommendation for rituximab in children as the authors state: "Children with chronic ITP usually do not need active therapy but should be followed up regularly". The guideline was literature and evidence-based, although there are no details given on how evidence was appraised for the production of this guideline.

Systematic reviews:

A recent systematic review¹⁴ of efficacy and safety of rituximab for the treatment of adults with ITP recommended avoiding "indiscriminate use of rituximab" in treating ITP. Descriptive and comparative studies were selected for inclusion in the review if they fulfilled all of the following criteria: prospective data collection; consecutive patient enrolment; a clearly stated duration of follow-up; and description of losses to follow-up. Approximately 46% (CI, 29.5%-57.7%) of patients had a complete response (platelet count $>150 \times 10^9$ cells/L) and approximately 24% (CI, 15.2%-32.7%) had a partial response to rituximab therapy. Median response duration was 10.5 months, and thrombocytopenia recurred in 10.5% of patients. Overall, 62.5% of patients treated with rituximab had a favourable platelet count response. Mortality was "surprisingly high" with 9 deaths reported after use of rituximab. However, the authors note it is not possible to attribute causation of death from the available data. The authors felt overall the quality of data was "poor" and that there are relatively few reports of use of rituximab treatment in patients with ITP.

A previous systematic review¹³ of case series found minimal evidence for effectiveness of any treatment (including rituximab) for adult patients with ITP and persistent severe thrombocytopenia following splenectomy as no RCTs have been completed. However, the authors note rituximab looks promising for further study, as do cyclophosphamide and azathioprine.

Case reports, case series and uncontrolled trials:

A prospective phase 1/2 study¹⁶ of rituximab in 36 children and adolescents with chronic ITP showed 31% of patients achieved the primary outcome (platelet count above $50 \times 10^9/L$). Serum sickness occurred in 2 (6%) of patients.

A retrospective multicentre study⁵⁷ of rituximab in 35 adults with refractory ITP showed complete response occurred in 7 (18%).

A case series⁵⁸ of 57 adults with chronic ITP treated with rituximab showed 18 achieved a complete response. Rituximab was well tolerated.

A retrospective study of rituximab in 19 paediatric patients with chronic refractory ITP showed the overall response rate was 68%.⁵⁹

A case series¹⁵ of 24 children with chronic ITP showed 63% achieved a complete response lasting 4-30 months. Three patients developed serum sickness.

A retrospective study⁶⁰ of rituximab in the treatment of 89 patients with chronic refractory ITP showed 46% achieved a complete response. "Heavily treated patients (more than three different previous treatments, including any corticosteroids) and those with longer ITP duration (>10 years from diagnosis) had a worse response."

Other case reports and smaller case series showing some evidence of benefit are also reported in the literature.⁶¹⁻⁶⁶

Mantle Cell Lymphoma (MCL)

Randomised controlled trials**Comparison of rituximab versus control**

Two RCTs showed little additional benefit of rituximab over chemotherapy in treatment of MCL.^{4, 5} One showed the addition of rituximab to fludarabine-based therapy in patients with relapsed or refractory MCL was promising with improvements in overall response rates and progression-free survival. However, these improvements were not statistically significant.⁴ Another showed, among previously untreated patients with MCL, that adding rituximab to chemotherapy resulted in improved overall response rates but had no impact on progression-free or overall survival.⁵ See Appendix 1 for appraisal of these trials.

Comparison of differing rituximab regimens

One RCT of different rituximab-dosing regimens for treatment of MCL showed little difference between groups except for apparent increased event-free survival in those receiving prolonged rituximab therapy who had been previously treated for MCL.⁶ See Appendix 1 for appraisal of this trial. The adverse event profile from this trial has been reported in combination with a related sub-study of rituximab in follicular lymphoma (FL). In 306 patients with FL or MCL who received standard or prolonged therapy with rituximab, there were a number of serious adverse events including 13 infections, 6 cardiac events and 5 intestinal complications resulting in 7 deaths.⁶⁷

Case reports, case series and uncontrolled trials:

A number of these showing some evidence of benefit have been reported for MCL.⁶⁸⁻⁷³

Multifocal motor neuropathy

Guidelines

A guideline produced by the European Federation of Neurological Societies and Peripheral Nerve Society states: "if intravenous immunoglobulin is not or not sufficiently effective then immunosuppressive treatment may be considered. Cyclophosphamide, cyclosporine, azathioprine, interferon beta1a or rituximab are possible agents." This is a "good practice point" reached by consensus of the task force members based on evidence from uncontrolled studies, case series, case reports or expert opinion.¹⁷

Case reports, case series and uncontrolled trials:

A number of these showing some evidence of benefit have been reported for the following neurological conditions: monoclonal IgM related neuropathies,⁷⁴ paraneoplastic neurological syndromes,⁷⁵ peripheral neuropathy,^{76, 77} polyneuropathies,⁷⁸ refractory myopathy,⁷⁹ transverse myelitis⁸⁰

Post transplant lymphoproliferative disorder (PTLD)

Guidelines

A guideline from Cincinnati Children's Hospital Medical Centre states: "In patients with evidence of persistent or progressive PTLD, without evidence of allograft rejection, despite reduced immunosuppression, it is recommended that treatment with anti-CD 20 monoclonal antibody (Rituximab) be considered".¹⁸ This recommendation is based on 3 retrospective analysis studies. The use of rituximab for pre-emptive therapy after Epstein Barr virus (EBV) reactivation is not mentioned in the guideline. At this time, evidence for this indication is based on observational data.⁸¹⁻⁸⁶

Case reports, case series and uncontrolled trials:

A number of these showing some evidence of benefit have been reported for post-transplant lymphoproliferative disorder (PTLD) including pre-emptive therapy for EBV reactivation prior to development of PTLD,⁸¹⁻⁹⁶ and steroid-refractory chronic graft-versus-host disease⁹⁷

Waldenstrom's macroglobulinaemia (WM)

Guidelines

A guideline by the Haemato-Oncology Task Force of the British Committee for Standards in Haematology⁷ notes response rates of WM to rituximab vary from 20-50% whether or not patients have been previously exposed to chemotherapy. However, the guideline cautions there is a risk of transient exacerbation of clinical effects of WM, thus rituximab should be used cautiously in patients with symptoms of hyperviscosity and/or IgM levels >40 g/L. This recommendation is based on evidence from at least 1 well-designed quasi-experimental study.

Updated consensus recommendations from the third International Workshop on Waldenstrom's Macroglobulinemia have been recently published.⁸ Options for frontline and salvage therapy include rituximab (standard or extended schedule), fludarabine plus rituximab, nucleoside analogues plus alkylators and rituximab, combination chemotherapy and rituximab. These recommendations are based on evidence obtained from at least 1 well-designed controlled study without randomisation or evidence obtained from well-designed, non-experimental descriptive studies such as comparative studies, correlation studies, and case-controlled studies.

The Cancer Institute NSW has listed a protocol for use of rituximab in WM (Cladaribine, Cyclophosphamide and Rituximab)⁹ in their standard cancer protocols (CI-SCaT) - see www.treatment.cancerinstitute.org.au.

Case reports, case series and uncontrolled trials:

A number of these showing some evidence of benefit have been reported for WM.⁹⁸⁻¹⁰¹

Other conditions

Some benefits with the use of rituximab +/- chemotherapy have been reported in case reports, case series or uncontrolled trials for conditions listed below:

- Dermatological disorders: autoimmune bullous disease,¹⁰² pemphigus vulgaris^{103, 104}
- Haematological oncology disorders: acute lymphoblastic leukemia,¹⁰⁵⁻¹⁰⁷ Burkitt's lymphoma (including paediatric patients),^{70, 106-112} NHL with acute haemolysis,¹¹³ MALT lymphoma,¹¹⁴⁻¹²³ pure red cell aplasia associated with lymphoproliferative disorders (not de novo),^{124, 125}
- Other haematological disorders: cold agglutinin disease,¹²⁶ mixed cryoglobulinemia,¹²⁷ TTP¹²⁸⁻¹³⁵
- Rheumatologic disorders/autoimmune diseases: acquired angioedema,¹³⁶ antiphospholipid syndrome,¹³⁷ Churg-Strauss syndrome,¹³⁸ polymyositis and dermatomyositis,¹³⁹⁻¹⁴³ Sjogren's syndrome,¹⁴⁴ systemic lupus erythematosus in children and adults,¹⁴⁵⁻¹⁵¹ vasculitis,¹⁵² Wegener's granulomatosis,¹⁵³ other disorders¹⁵⁴⁻¹⁵⁶
- Renal disorders: glomerulonephritis in HCV-associated mixed cryoglobulinemia,^{157, 158} refractory membranous glomerulonephritis,¹⁵⁹ lupus nephritis^{160, 161}
- Other: hepatitis C related cryoglobulinaemic vasculitis,¹⁶²

The following conditions have case reports showing no benefit with the use of rituximab therapy:

- Relapsed myeloma¹⁶³
- Childhood Burkitt's Lymphoma¹⁶⁴
- Autoimmune neutropenia and de novo pure red-cell aplasia.¹⁶⁵

Note that the listing above is necessarily incomplete due to the large number of conditions in which rituximab has been used. Clinicians considering use of rituximab in these conditions are advised to conduct a focussed literature review on each topic.

Ongoing RCTs

As at 10 August 2006, numerous clinical trials involving rituximab had been registered on one or more of the following registers: metaRegister of Controlled Trials (mRCT) <http://www.controlled-trials.com/mrct/>; the International Standard Randomised Controlled Trial Number (ISRCTN) Register <http://www.controlled-trials.com/isrctn/>; and the Australian Clinical Trials Registry (ACTR) <http://www.actr.org.au/>.

Diseases currently being investigated by one or more investigator groups include: acute lymphoblastic leukaemia; anti-neutrophilic cytoplasmic antibodies associated vasculitis; atopic dermatitis; chronic graft vs host disease; chronic lymphocytic leukaemia in combination with chemotherapy; dermatomyositis; immune thrombocytopenic purpura; kidney transplantation; lupus nephritis; MCL multiple sclerosis; polymyositis; polyneuropathy associated with anti-MAG IgM monoclonal gammopathy; rheumatoid arthritis; Sjogren's syndrome; stiff person syndrome; systemic lupus erythematosus; systemic necrotising vasculitides; type 1 diabetes; ulcerative colitis; Wegener's granulomatosis and microscopic polyangiitis.

Cost-effectiveness

There are no published data regarding cost-effectiveness of rituximab in off-label conditions.

Adverse effects

Current product information warnings

The product information (PI) for rituximab was last amended on 20 December 2006.²⁶ The most recent version of the PI cautions about the following adverse events with rituximab (in alphabetical order):

- Cardiac events: Angina pectoris, atrial flutter and atrial fibrillation have been reported. Severe cardiac events including heart failure and myocardial infarction in patients with prior cardiac conditions have also been reported. The PI says, “there are no data on the safety of [rituximab] in patients with moderate heart failure... or severe, uncontrolled cardiovascular disease.”
- Cranial neuropathy +/- peripheral neuropathy: These have been reported rarely and may occur at various times up to several months after completion of rituximab therapy
- Gastrointestinal perforation: this may be fatal and has been reported in patients receiving rituximab for NHL.
- Infections: Very rare cases of hepatitis B reactivation have been reported in people receiving rituximab in combination with cytotoxic chemotherapy. Other serious, sometimes fatal, viral infections (new, reactivation, exacerbation) have been reported rarely; the majority of patients received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant. These infections include cytomegalovirus, varicella zoster virus, herpes simplex virus, JC virus and hepatitis C virus. Caution should be exercised when using rituximab in patients with chronic infections or with underlying conditions that predispose to infections. Rituximab should not be administered to patients with an active infection or in those who are severely immunocompromised.
- Leucocytoclastic vasulitis: This has been reported very rarely.
- Malignancy: There is a potential risk that rituximab therapy may lead to development of solid tumours, especially in patients treated for rheumatoid arthritis.
- Pancytopenia and neutropenia: These occur rarely, but sometimes the onset of neutropenia may occur up to 4 weeks after the last infusion of rituximab.
- Progressive Multifocal Leucoencephalopathy (PML): This has occurred following off-label use of rituximab in treatment of systemic lupus erythematosus. “The efficacy and safety of [rituximab] for the treatment of SLE has not been established.”
- Pulmonary events: These include hypoxia, pulmonary infiltrates and acute respiratory failure. These may be preceded by severe bronchospasm and dyspnoea and usually occur in the context of infusion related reactions. Interstitial pneumonitis has been reported unrelated to infusion reactions
- Rapid tumour lysis and tumour lysis syndrome: Patients especially at risk have high numbers of circulating malignant lymphocytes. Prophylaxis should be considered.
- Serum-sickness like reactions: These have been reported rarely
- Severe bullous skin reactions including fatal toxic epidermal necrolysis: These has occurred rarely
- Severe infusion related reactions: These might be clinically indistinguishable from hypersensitivity reactions or cytokine release syndrome. Hypotension, fever, chills, rigors, urticaria, bronchospasm, and angio-oedema have occurred as part of an infusion related symptom complex. ***Patients with a high tumour burden such as CLL or MCL may be at higher risk of “especially severe” infusion-related reactions and these patients “should only be treated with extreme caution and when other therapeutic alternatives have been exhausted.*** Withholding antihypertensive medications from 12 hours before and during rituximab infusions should be considered due to the risk of hypotension. In patients with rheumatoid arthritis, premedication with intravenous glucocorticoid reduces the incidence and severity of infusion reactions. The PI states, “Most patients who have experienced non-life threatening infusion-related reactions have been able to complete the full course of... therapy.”

- **Transient increases in IgM levels:** This occurs in patients with treated with rituximab for Waldenstrom's macroglobulinaemia and is associated with hyperviscosity.

The PI also contains the following cautions about the safe use of rituximab:²⁶

- Rituximab should be “administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced oncologist/haematologist”.
- “Adrenalin, antihistamines and corticosteroids should be available for immediate use in the event of a hypersensitivity reaction”
- “Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy.”

For further information about adverse events please refer to full product information.

International black box labels and other warnings

US rituximab product information includes the following black box warning.²²

“WARNINGS

Fatal Infusion Reactions: Deaths within 24 hours of RITUXAN [rituximab] infusion have been reported. These fatal reactions followed an infusion reaction complex, which included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. (See WARNINGS and ADVERSE REACTIONS.)

Patients who develop severe infusion reactions should have RITUXAN [rituximab] infusion discontinued and receive medical treatment.

Tumor Lysis Syndrome (TLS): Acute renal failure requiring dialysis with instances of fatal outcome has been reported in the setting of TLS following treatment of non-Hodgkin's lymphoma (NHL) patients with RITUXAN [rituximab]. (See WARNINGS.)

Severe Mucocutaneous Reactions: Severe mucocutaneous reactions, some with fatal outcome, have been reported in association with RITUXAN [rituximab] treatment. (See WARNINGS and ADVERSE REACTIONS.)

The US Food and Drug Administration has also recently warned that rituximab may cause reactivation of JC virus which can lead to progressive multifocal leukoencephalopathy which is usually fatal.²⁵

Health Canada warnings

In May 2001, Health Canada issued an important drug warning regarding 20 post-marketing reports of severe mucocutaneous reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, paraneoplastic pemphigus,²⁰ lichenoid dermatitis, vesiculobullous dermatitis) associated with rituximab – of which 8 were fatal.

In July 2004, Health Canada issued safety information to health care professionals as follows:²¹

Based upon review of recent post marketing and clinical safety reports:

- Hepatitis B virus (HBV) reactivation, occasionally with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with RITUXAN [rituximab], mostly in combination with chemotherapy.
- Persons at high risk of HBV infection should be screened before initiation of RITUXAN [rituximab].
- Carriers of hepatitis B and patients with evidence of having recovered from hepatitis B infection should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and up to one year following RITUXAN [rituximab] therapy.

The health warning also states the median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately 1 month after the last dose. Health Canada recommends people at high risk of HBV infection should be screened before initiation of rituximab. Additionally, carriers of hepatitis B, and patients who have recovered from hepatitis B infection should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and up to 1 year following rituximab therapy.

In November 2006, Hoffmann-La Roche Limited wrote to health professionals warning of abdominal pain, bowel obstruction, and perforation, in some cases leading to death, mostly in patients receiving rituximab in combination with chemotherapy for NHL.²⁴

The letter notes the mean time to onset of symptoms was 6 days from the start of therapy (range 1 day to 77 days) for documented gastrointestinal perforation and recommends prompt evaluation of complaints of abdominal pain. The full text of the letter is available from http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/rituxan_3_hpc-cps_e.html

Adverse Drug Reactions Advisory Committee (ADRAC) reports

As at 28 September 2006, ADRAC had 191 reports of rituximab associated reactions, including 9 deaths,¹⁹ although there is difficulty in attributing causality of death directly to use of rituximab.

These 9 patients were:

- 86-year old female who developed respiratory failure and tumour lysis syndrome
- 84-year old female who developed pulmonary oedema, oedema and rash
- Male of unknown age who developed hepatic failure and dyspnoea
- Male of unknown age who developed hepatic failure
- 49-year old male who developed anaemia, gastric ulcer, cytomegalovirus infection and pneumocystis jiroveci pneumonia
- 75-year old male who developed staphylococcal sepsis
- 64-year old female who developed cytomegalovirus (CMV) infection and pneumonia
- 79-year old male who developed neutropenia and acute respiratory distress syndrome
- 80-year old female who developed squamous cell carcinoma of the skin.

Of all rituximab related reports to ADRAC where age was recorded only 1 involved a child less than 18 years.¹⁹

In June 2006, ADRAC warned of the possibility of HBV reactivation following cytotoxic or immunosuppressant therapy.²³ ADRAC recommends screening all patients undergoing cytotoxic or immunosuppressant therapy for HBsAg and considering oral prophylaxis with an oral agent for HBV carriers. No particular agent is recommended in this bulletin. However, a systematic review of lamivudine prophylaxis for chemotherapy-induced reactivation of chronic HBV showed lamivudine prophylaxis reduced the rate of HBV reactivation 4 to 7 fold compared with controls.¹⁶⁶ The authors recommend continuing lamivudine prophylaxis for at least 1 year following completion of chemotherapy as delayed HBV reactivation has been reported.¹⁶⁷ The Cancer

Institute NSW standard cancer treatment protocols (CI-SCaT) recommends all patients treated with rituximab be screened for HBV. Lamivudine is recommended for adults in a dose of 100mg/day starting a minimum of 2 weeks before chemotherapy and continuing for 8 weeks following cessation of chemotherapy.²⁷

Other adverse events reported in the literature

- Cardiovascular problems: acute coronary syndrome,¹⁶⁸ cardiogenic shock,¹⁶⁹ collapse and severe drop in systolic blood pressure,¹⁷⁰ reduction in cardiac function,¹⁷¹ severe refractory shock,¹⁷² ventricular tachycardia.
- Dermatological problems: Merkel cell carcinoma,¹⁷⁴⁻¹⁷⁷ cutaneous squamous cell carcinoma,¹⁷⁸ leukocytoclastic vasculitis,¹⁷⁹ necrotic skin ulceration,¹⁸⁰ oedema of eyelids and sclera,¹⁸¹ vasculitis.¹⁸² These cases all involved adults aged 44 to 80 years.
- Haematological problems: acute thrombocytopenia,¹⁸³⁻¹⁸⁵ agranulocytosis,¹⁸⁶ delayed onset peripheral blood cytopenia,¹⁸⁷ dysimmune cytopenia,¹⁸⁸ late-onset neutropenia,¹⁸⁹⁻¹⁹⁴ neutropenic fever and sepsis,⁶⁹ progression of multiple myeloma,¹⁹⁵ prolonged hypogammaglobulinemia,^{196, 197} transformation to large cell tumour during treatment for indolent lymphoproliferative disease,¹⁹⁸ transformation of MALT lymphoma to pure plasma cell tumour,¹⁹⁹ transformation to T-cell lymphoma after treatment for B-cell lymphoma.²⁰⁰
- Hepatitis B reactivation/liver failure including a number of fatal events.²⁰¹⁻²¹⁴ Some hepatitis B reactivation occurred after withdrawal of prophylactic lamivudine.¹⁶⁷ Acute fatal liver failure without HBV reactivation.²¹⁵ Where age is reported these involved adults with ages ranging from 21 to 73 years.
- Other infectious complications and reactivations, some of which were fatal, include: central nervous system EBV,²¹⁶ CMV,^{69, 106, 217-219} enteroviral meningoencephalitis,^{220, 221} infective endocarditis,²²² pure red cell aplasia due to parvovirus B19,^{223, 224} parvovirus,^{225, 226} *Pneumocystis carinii* pneumonia,¹⁶⁵ varicella-zoster (fatal),²²⁷ other viral problems.²¹⁶ The majority of these occurred in adults aged 26 to 75. However, 2 children aged 2.5 and 10 years have been reported with infectious complications – EBV and enteroviral meningoencephalitis respectively.
- Neurological problems: flare in neuropathy,²²⁸ worsening of chronic sensorimotor demyelinating polyneuropathy,²²⁹ reversible posterior leukoencephalopathy.²³⁰ These cases all involved adults aged 38 to 75 years.
- Respiratory problems: acute respiratory distress syndrome,^{231, 232} haemoptysis (fatal),²³³ interstitial pneumonitis,²³⁴⁻²³⁶ pulmonary fibrosis.²³⁷ These cases all involved adults aged 33 to 82 years.
- Serum sickness.^{16, 238-241} There is some evidence, albeit from an uncontrolled phase 1/2 study, that serum sickness reactions may be more common in the paediatric population (approximately 12%) than in the adult population.¹⁶
- Stevens-Johnson syndrome.²⁴²
- Other: fatal systemic inflammatory response syndrome,²⁴³ acute tumour lysis syndrome,²⁴⁴⁻²⁴⁷ intestinal perforations,²⁴⁸ recurrent psychosis.²⁴⁹

Note that although many of these adverse reactions occurred in relation to use of rituximab, epidemiological causation cannot necessarily be established with evidence from case reports. Further post-marketing surveillance of rituximab is recommended.

APPENDIX 1: Appraisal of RCTs referred to in text

Authors	Design	Clinical endpoints	Results	Adverse events	Industry Involvement
AIDS-Malignancies Consortium Trial 010 ³	Multicentre phase 3 trial. 150 patients with HIV-associated NHL receiving chemotherapy were randomly assigned to also receive rituximab with each chemotherapy cycle.	Restaging of all sites of measurable or evaluable disease was carried out after every second cycle. Staging was performed by CT or MRI scans of chest, abdomen and pelvis, bone marrow biopsy and lumbar puncture. Standard International Workshop criteria were used to categorise responses	No significant differences between groups in: *complete response rate ($p=0.147$) *progression-free survival *time to progression *overall survival	Treatment-related infectious deaths occurred in 14% of those receiving rituximab compared to 2% only receiving chemotherapy ($p=0.035$)	None acknowledged
German Low-Grade Lymphoma Study Group ⁴	Randomised, open-label phase 3 trial of rituximab in combination with chemotherapy (fludarabine, cyclophosphamide, mitoxantrone) versus chemotherapy alone in 147 patients with relapsed or refractory follicular lymphoma (n=93) and MCL (n=40). All had been previously treated. Response to therapy was assessed after first 2 cycles and 4 weeks after completion of fourth cycle.	Remission was determined by physical examination, abdominal ultrasound, CT scan of involved areas and bone marrow biopsy. Response was defined by International Working Group criteria. Frequency and severity of side effects were recorded according to the National Cancer Institute of Canada Common Toxicity Criteria	57 patients in each arm were treated according to protocol. Patients in the rituximab arm had an overall response rate of 79% versus 58% in the chemotherapy alone arm ($p=0.01$). However, response was only significant for patients with follicular lymphoma ($p=0.011$) but not MCL ($p=0.282$).	Lymphocytopenia occurred more often in rituximab arm but was not associated with increased infectious complications. In 4 cases, rituximab therapy was stopped due to allergic reactions	None acknowledged
German Low-Grade Lymphoma Study Group ⁵	Prospective, randomised, open-label, multicentre trial of 122 previously untreated advanced-stage MCL patients. Patients were randomly assigned to 6 cycles of rituximab plus chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) or	Response to therapy was assessed after every 2 cycles of induction therapy and 4 weeks after completion of last cycle. Response evaluation included physical examination, blood count, biochemistry, abdominal ultrasound, CT of involved areas, bone marrow	Compared to chemotherapy alone, the rituximab plus chemotherapy group had significantly better: *overall response rate (94% vs 75%; $p=0.0054$)	Severe grade 3 and 4 granulocytopenia was significantly more frequent in rituximab arm, but there were no differences in infectious complications.	None acknowledged

	chemotherapy alone	<p>biopsy.</p> <p>Follow-up was performed every 3 months.</p> <p>Response was defined by International Working Group criteria.</p> <p>Frequency and severity of side effects were recorded according to WHO classification.</p>	<p>*complete remission rate (34% vs 7%; p=0.00024)</p> <p>*time to treatment failure (21 vs 14 months; p=0.0131).</p> <p>But there was no difference between groups for progression-free survival confirming “the favourable effect of rituximab is restricted to the period of induction therapy.”</p>		
Swiss Group for Clinical Cancer Research ²⁵⁰	<p>104 patients with newly diagnosed or refractory or relapsed MCL.</p> <p>All were given induction treatment with single agent rituximab. Those who were responding or who had stable disease at week 12 were randomly assigned to no further treatment or prolonged rituximab administration every 8 weeks for 4 cycles</p>	<p>Response evaluation included: Blood counts, biochemistry, serum immunoglobulin for 12-24 months.</p> <p>Event-free survival was defined as time from first induction infusion to progression, relapse, second tumour, or death from any cause.</p>	<p>27% responded to induction therapy. At 29 month follow-up, response rate and duration of response were not significantly different between the 2 dosing regimens. Prolonged treatment appeared to improve event free survival in patients who had previously received treatment for MCL (p=0.04)</p>	<p>The majority of toxicity was mild infusion-related symptoms during the first infusion. 17 cases of serious adverse events were documented during induction. One patient died of <i>Pneumocystis carinii</i> pneumonia and one patient died of a probable myocardial infarction.</p>	Supported in part by Roche

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Dr Lowinger is an employee of NSW TAG. She has no other interests to declare.

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