ANTITUMOUR TREATMENT

Rituximab in lymphoma: A systematic review and consensus practice guideline from Cancer Care Ontario

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Rituximab; Non-Hodgkin’s lymphoma; Systematic review; Practice guidelines

Summary Rituximab is the first antibody-based therapy approved in cancer. The role of this treatment for non-Hodgkin’s lymphoma has evolved significantly since its introduction. We aimed to systematically review the literature on rituximab in non-Hodgkin’s lymphoma and provide consensus guidelines as to the rational use of this agent. Validated methodology from the Cancer Care Ontario Program in Evidence-Based Care was applied. A comprehensive literature search was completed by reviewers from the Hematology Disease Site Group of Cancer Care Ontario. Data were abstracted from randomized controlled trials of rituximab-containing regimens for patients with non-Hodgkin’s lymphoma. Twenty-three randomized controlled trials (RCTs) of rituximab-based therapy were analyzed. Consistent and clinically important benefits in progression-free and overall survival and were seen in the following settings: (1) addition of rituximab to combination chemotherapy for initial treatment of diffuse large B-cell lymphoma...
and other aggressive B-cell lymphomas; (2) addition of rituximab to combination chemotherapy for initial and subsequent treatment of follicular lymphoma and other indolent B-cell lymphomas; and (3) use of rituximab alone as extended maintenance therapy in patients with indolent B-cell lymphomas who have responded to initial treatment. The consensus opinion of the Hematology Disease Site Group is that rituximab is recommended for these indications.

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Introduction

Non-Hodgkin’s lymphomas (NHL) comprise a heterogeneous group of malignances with variable presentations that range from indolent to aggressive.1 Diffuse large B-cell lymphoma (DLBCL) is the most common histology, and although considered aggressive in nature, can be treated with curative intent with anthracycline-containing combination chemotherapy.1 Unfortunately, relapse is still common.2 In contrast, follicular (FL) and other indolent lymphomas are considered incurable with standard chemotherapies and current treatment paradigms are focused on palliation of symptoms and minimizing toxicity. Individuals can sustain prolonged remissions, but inevitably relapse and require subsequent courses of therapy that lead to fewer and shorter remissions.3 While superior overall survival has been observed in a large meta-analysis of trials testing interferon, other previous therapies tested have failed to detect survival advantages and no therapy has yet demonstrated curative potential.4,5

Rituximab (Mabthera/Rituxan, Roche, Basel, Switzerland) is a chimeric IgG1 monoclonal antibody directed against the CD20 surface antigen found on most normal and neoplastic B lymphocytes.6 The agent is the first antibody-based therapy approved in cancer and is thought to mediate its anti-lymphoma effect through antibody- and complement-dependent cytotoxicity and induction of apoptosis.7 Since this initial demonstration of benefit with rituximab monotherapy, there has been an explosion of research detailing the use of rituximab in combination with initial combination chemotherapy, in the relapsed setting, and most recently, as maintenance therapy to sustain patients in remission. A systematic summary of the existing evidence would be helpful to facilitate treatment decisions.

The Cancer Care Ontario Program in Evidence-Based Care (CCO-PEBC) is a state-funded organization that aims to assist physicians and patients in making appropriate decisions through a practice guidelines initiative.8 In this process, a group comprising physicians with content expertise, epidemiologists, and consumers, develops a guideline through a systematic process that involves assessment of the best available evidence, consensus interpretation of the evidence, and a validation process involving practitioners across the province. The CCO-PEBC has prioritized the development of this guideline to rationalize the emerging role for rituximab in lymphoma.

Methods

Guideline development and intent

The systematic review process was developed by the CCO-PEBC, using the validated methodology of the Practice Guideline Development Cycle.8 The CCO-PEBC is supported by, but editorially independent of, the Ontario Ministry of Health and Long-Term Care. The core activity of the Program is the development of practice guidelines through systematic review, evidence synthesis, and input from practitioners.

Evidence for this guideline was selected and reviewed by members of the Hematology Disease Site Group (DSG) of CCO (n = 25), which comprises hematologists, medical and radiation oncologists, an epidemiologist, and lay representatives.

Literature search strategy


Study selection criteria

English language articles were selected for inclusion if they met the following criteria: randomized controlled trial (RCT) comparing a rituximab-containing regimen with non-rituximab regimen; inclusion of adult patients with lymphoma of any type, at any stage, and any histology; and evaluation of overall survival, disease control, response rate, quality of life, or toxicity. Meta-analyses and systematic reviews were also included in the search strategy. Studies exclusively of patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) were not included.

Article selection and analysis

Citations obtained from the literature search were screened by two reviewers for inclusion. Study quality was assessed according to criteria established by Jadad et al.9 Briefly, this is a 3-item instrument with points awarded for the descriptive quality in reporting of (1) the method of randomization (0–2 points), (2) the use of double-blinding (0–2 points), and (3) study withdrawals (0–1 point). Because of the reliance on adequate methodologic descriptions, only full publication reports were scored (and not abstract reports). Data were extracted as guided by the following question: In patients with lymphoma, is the addition of rituximab more effective than non-rituximab containing regimens for improving overall survival, disease control, or quality of life? Outcomes of interest included response rates to therapy, disease control as
measured by event-free survival, time-to-treatment failure, or response duration, quality of life, and overall survival. Toxicity related to single-agent rituximab has been previously documented by the Hematology DSG and was not further reviewed in this document. Because the goal of systemic therapy in lymphoma differs according to histology, the data were presented according to lymphoma subtypes; aggressive histology B-cell lymphomas are initially treated with curative intent whereas indolent histology B-cell and mantle cell lymphomas (MCL) are treated to extend disease control and palliative symptoms. Studies of MCL were summarized in the same section as other indolent lymphomas. However, given the distinct clinical and pathologic features that distinguish this histology from other indolent lymphomas, the evidence was discussed separately where relevant.

Consensus development and practitioner feedback

The Hematology DSG participated in quarterly meetings to define the questions guiding data abstraction, summarize and interpret the data, and prepare the consensus document. Initial consensus was obtained after presentation of the systematic review results to the DSG members. A draft guideline was then circulated and revised in an iterative process until consensus. When consensus was not possible, minority opinions were recorded. The draft guideline was sent with a structured questionnaire using formal survey methodology to Ontario practitioners. Based on responses obtained, the Hematology DSG instituted modifications and submitted the guideline to the PEBC Report Approval Panel for final approval.

Results

Literature search results

Twenty-three randomized controlled trials (RCTs) of rituximab-based therapy were retrievable and met all inclusion criteria. Many studies were reported in more than one abstract or publication; for those trials, only the most recent citation was referenced. The trials were comprised of 14 full publications and 9 abstract reports. Details of the treatment regimens in all trials are found in Appendix II.

Nine trials studied patients with aggressive histology B-cell lymphomas (all with diffuse large B-cell lymphoma). Of those reports, six were in previously-untreated patients and compared a standard chemotherapy regimen with the same regimen with the addition of rituximab. The remaining three trials were in patients with relapsed disease and studied rituximab in the context of high-dose chemotherapy and autologous stem cell transplantation.

Fourteen trials studied patients with indolent histology B-cell and mantle cell lymphomas; nine trials compared a standard chemotherapy with or without the addition of rituximab. Six trials reported the use of rituximab compared with observation in patients who had achieved remission to initial therapy. One report compared rituximab monotherapy to the novel radioimmunotherapy yttrium-90 ibritumomab tiuxetan in patients with relapsed or refractory low-grade or transformed lymphoma.

Aggressive histology B-cell lymphomas

Table 1 summarizes the response rate, disease control, and overall survival data abstracted from the studies of rituximab for aggressive B-cell lymphomas. Five full publications were evaluated for RCT quality (Table 1).

Use of rituximab in initial therapy in aggressive histology lymphoma

The first RCT to study the addition of rituximab to a standard chemotherapy combination was completed by a French group in 2002. Patients aged 60–80 years with diffuse large B-cell lymphoma were treated with chemotherapy (CHOP; cyclophosphamide, doxorubicin, vincristine, prednisone) for eight cycles with or without rituximab (R). The complete response (CR) rate and overall survival were superior in patients allocated to CHOP-R (Table 1). In longer term follow-up, both five-year overall survival and event-free survival continued to be superior in the rituximab arm.

Four subsequent RCTs have studied the addition of rituximab to anthracycline-based (CHOP-like) chemotherapy regimens in older (age > 60 years) and younger patients with DLBCL. All studies reported superior disease control (failure-free or event-free survival) with the addition of rituximab. Overall survival benefits were documented in two trials, including a study by Pfreundschuh et al. in younger patients (age 18–60 years) with good-prognosis DLBCL.

Habermann et al. did not detect a difference in overall survival in their study of older patients with DLBCL. The design and analysis of that trial was complex because it included a second randomization to maintenance therapy with rituximab versus observation. An interaction between the induction and maintenance randomizations may have limited the ability to detect a survival advantage with initial rituximab. Furthermore, no survival benefit was detected between use of maintenance rituximab and observation. In a subset analysis, any benefit in disease control with maintenance therapy was limited to patients who did not receive rituximab with initial therapy.

An additional RCT comparing CHOP with or without rituximab was completed in patients with acquired immunodeficiency syndrome (AIDS)-related aggressive histology B-cell lymphomas. A difference in overall survival was not detected between the treatment arms. Secondary analyses revealed a statistically insignificant trend towards decreased mortality from lymphoma in patients who received rituximab. However, this potential benefit appeared to be offset by an increased risk of treatment-related infectious death. Of these deaths, 60% were in patients with CD4 counts <50/mm.3

Consensus interpretation. The DSG interpreted these results as strongly indicating a role for rituximab when added to combination chemotherapy for the initial treatment of adult patients with DLBCL. Rituximab should be administered at a dose of 375 mg/m² and given at the beginning of each treatment cycle of chemotherapy. The DSG deliberated about the role of maintenance rituximab. The single trial that addressed this question did not document a benefit for maintenance rituximab in those who have already received the agent in combination with upfront chemotherapy.
<table>
<thead>
<tr>
<th>Author, study</th>
<th>N rand</th>
<th>Patients</th>
<th>Treatment</th>
<th>Follow-up time of study</th>
<th>RR</th>
<th>Disease control</th>
<th>OS</th>
<th>Jadad Score</th>
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<tr>
<td>Coiffier, full</td>
<td>399</td>
<td>Untreated DLBCL, age 60–80y</td>
<td>CHOP-R vs. CHOP</td>
<td>Median 24 mo</td>
<td>76% vs. 63%; p = 0.005</td>
<td>At 2y: 70% vs. 57%; p = 0.007</td>
<td>2 points</td>
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<tr>
<td>Feugier, full, update</td>
<td>632</td>
<td>DLBCL, age ≥ 60y</td>
<td>CHOP-R vs. CHOP</td>
<td>Median 5 y</td>
<td>77% vs. 76%; p = 0.92</td>
<td>5 y EFS: 47% vs. 29%; p = 0.00002</td>
<td>1 point</td>
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<tr>
<td>Habermann, full, induction randomization</td>
<td>250</td>
<td>Untreated DLBCL, mantle cell lymphoma, FL grade III, intermediate/high-risk IPI, age ≥ 65</td>
<td>R-CHOP-14 vs. CHOP</td>
<td>Median 4 mo</td>
<td>EFS superior in R-CHOP-14; p-value NR</td>
<td>2 points</td>
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<td>Sonneveld, abst</td>
<td>1300</td>
<td>Untreated DLBCL, age 61–80 y</td>
<td>R-CHOP-14 vs. CHOP</td>
<td>Median 26 mo</td>
<td>FFTF superior in R-CHOP-14; p = 0.000025</td>
<td>2 points</td>
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<tr>
<td>Pfreundschuh, abst</td>
<td>824</td>
<td>Untreated DLBCL, IPI 0–1, age 18–60y</td>
<td>CTk + R vs. CTk</td>
<td>Median 26 mo</td>
<td>OS superior in R-CHOP-14; p = 0.000025</td>
<td>2 points</td>
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<tr>
<td>Kaplan, full</td>
<td>150</td>
<td>Untreated HIV lymphoma (aggressive B-cell)</td>
<td>CHOP-R (+R maint for pts with CR or PR) vs. CHOP</td>
<td>Median 137 wk</td>
<td>Median PFS: 45 vs. 38 wk (p = 0.67)</td>
<td>1 point</td>
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<tr>
<td>Van Heeckeren, full</td>
<td>34</td>
<td>B-cell NHL — high-risk, relapsed, or transformed disease undergoing HDC and ASCT (aggressive histology, n = 17; indolent histology, n = 10)</td>
<td>In vivo purge with pre-mobilisation rituximab vs. ex vivo CD34+ cell enrichment using immuno-magnetic beads</td>
<td>Median 796 days</td>
<td>2y EFS: 81% vs. 76% (p = 0.66)</td>
<td>1 point</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Patient Details</td>
<td>Treatment</td>
<td>Follow-up</td>
<td>PFS at 39 mo (p-value)</td>
<td>OS at 39 mo (p-value)</td>
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<td>Pohlman, 18 abst 76</td>
<td>B-cell NHL eligible for ASCT</td>
<td>Pre-mobilisation rituximab vs. no rituximab pre-mobilisation</td>
<td>Median 39 mo N/A</td>
<td>No difference in PFS at 39 mo (p-value NR)</td>
<td>No difference in OS at 39 mo (p-value NR)</td>
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<tr>
<td>Habermann, 12 full, maintenance randomization</td>
<td>DLBCL, age ≥ 60 y</td>
<td>CHOP-R vs. CHOP R</td>
<td>Median 3.5 y 77% vs. 76%; p = 0.92</td>
<td>3 y FFS: 53% vs. 46%, p = 0.04</td>
<td>p = 0.18</td>
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<tr>
<td>Haioun, 19 abst 269</td>
<td>DLBCL, 2 mo post-ASCT (+HDC), age &lt; 60 y</td>
<td>R vs. obs post ASCT</td>
<td>Median 3 y N/A</td>
<td>3 y EFS: 80% vs. 72% (p = 0.10)</td>
<td>NR</td>
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**Note:** aIPI: adverse age-adjusted International Prognostic Index factors; abst: abstract; ASCT: autologous stem cell transplantation; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOP-14: CHOP administered every 14 days; CR: complete response; CRu: unconfirmed CR; CT: chemotherapy; DLBCL: diffuse large B-cell lymphoma; EFS: event-free survival; eval: evaluable; HDC: high-dose consolidative chemotherapy; HIV: human immunodeficiency virus; ITT: intention-to-treat; maint: maintenance; mo: month; MR: maintenance rituximab; N: number; N/A: not applicable; NR: not reported; NS: not significant; obs: observation; OS: overall survival; PFS: progression-free survival; pts: patients; rand: randomized; R: rituximab; RR: response rate; TTF: time-to-treatment failure; FFTF: freedom from treatment failure; FFS: failure-free survival; vs.: versus; wk: week; y: year.

- a Treatment details are provided in Appendix II.
- b Data provided in order of intervention versus control.
- c Of patients with central pathologic review (n = 385), 87% had confirmed DLBCL.
- d Some patients with T-cell lymphoma (exclusion criterion) were discovered on central pathologic review.
- e No difference between groups for baseline/clinical characteristics.
- f Log-rank.
- g In a secondary analysis of the effects of induction R-CHOP vs. CHOP excluding patients who received maintenance rituximab, R-CHOP was associated with improved 3-year OS (67% vs. 58%, p = 0.05) compared to CHOP induction alone.
- h Overall RR including CR and PR.
- i Data in each arm not provided.
- j Randomized in 2:1 ratio in favour of rituximab.
- k CT included CHOP-21, CHOEP-21, MACOP-B, or PMitCEBO; doses and schedules not reported.
- l Authors did not indicate whether groups similar at baseline.
- m 1300 patients recruited. Authors did not indicate number of patients randomized.
- n Jadad quality score: based on a 3-item instrument that awards points for reporting of method of randomization (R; 0–2 points); use of concealment (C; 0–2 points); and study withdrawals (W; 0–1 point).
- o Median time off protocol.
The evaluation in patients with AIDS-related lymphoma demonstrated an increased risk of infectious deaths with rituximab and no benefit in overall survival was detected. The trial results may have differed due to higher dosing of rituximab compared with other studies or differences in the disease process in the context of human immunodeficiency virus infection. Until further clarification of the risk in this setting, the DSG concluded that the evidence is currently insufficient to support recommending rituximab for these patients.

The Hematology DSG recognized that the majority of patients studied were diagnosed with DLBCL. Variants of this histology, including primary mediastinal B-cell lymphoma, T-cell-rich B-cell lymphoma, Burkitt-like lymphoma, or B-cell lymphoma transformed from an indolent histology are uncommon and consequently difficult to study in separate trials. Due to similarities in disease biology and the universal presence of the CD20 surface antigen targeted by rituximab, the DSG concluded that the recommendations could be extrapolated to these histologic variants.

**Evidence-based recommendations**

- Previously untreated patients with diffuse large B-cell lymphoma (DLBCL) or a variant of DLBCL (such as primary mediastinal B-cell lymphoma, T-cell-rich B-cell lymphoma, Burkitt-like lymphoma, transformed lymphoma from an indolent histology, or intravascular lymphoma), who are candidates for treatment with curative intent with combination chemotherapy, should receive rituximab with this therapy.
- There is currently insufficient evidence to support the use of rituximab as a maintenance therapy in patients with aggressive histology B-cell lymphoma who have completed initial chemotherapy that includes rituximab.
- There is insufficient evidence to support combining rituximab with chemotherapy when treating patients with HIV-related lymphoma.

**Use of rituximab in patients eligible for high-dose therapy and autologous stem cell transplantation (ASCT)**

Treatment of patients with high-risk or relapsed aggressive histology B-cell lymphoma might include the use of high-dose (myeloablative) chemo-radiotherapy followed by autologous stem cell transplantation (ASCT).\(^{20,21}\) Two RCTs have studied rituximab prior to stem cell mobilization\(^ {17,18}\) while another trial reported the use of rituximab following ASCT.\(^ {19}\)

When used prior to ASCT, rituximab was a component of the strategy to mobilize stem cells for collection prior to transplantation. The two studies were not powered to detect differences in disease control or survival. The third report compared maintenance rituximab with observation for patients with high-risk DLBCL who had completed high-dose chemotherapy and ASCT.\(^ {19}\) No difference in event-free survival was detected between treatment arms; overall survival was not reported in the abstract publication.

**Consensus interpretation.** The studies of rituximab use in patients eligible for high-dose therapy and ASCT were underpowered to detect differences in disease control or overall survival, and no differences were found in the reporting of these outcomes. Given these limitations, the DSG considered the data too preliminary to form conclusions.

**Evidence-based recommendation**

- The DSG concluded that there is currently insufficient evidence to support the use of rituximab as part of a pre-mobilisation strategy prior to, or maintenance therapy following completion of, autologous stem cell transplantation.

**Indolent histology B-cell and mantle cell lymphomas**

Table 2 summarizes the response rate, disease control, and overall survival data abstracted from the studies testing rituximab for indolent B-cell and mantle cell lymphomas (MCL). Eight full publications were evaluated for RCT quality (Table 2).\(^ {20,21,26,27,30–33}\) Five studies included patients with follicular lymphoma, six included patients with follicular and other histologies, and three included patients with only other indolent histologies (including two studies on MCL). A single published literature-based meta-analysis of RCTs studying the use of rituximab with or without chemotherapy in patients with indolent or mantle cell lymphoma was included in the data abstraction.\(^ {38}\)

**Use of rituximab in first-line and subsequent therapy in indolent B-cell or mantle cell lymphoma**

Seven RCTs have studied the use of rituximab in combination.\(^ {20–26}\) Other than for an interim analysis of one trial\(^ {22}\) that has not completed enrollment, all other RCTs have demonstrated improvements in disease control favouring patients who received rituximab. In addition, two studies\(^ {21,24}\) have shown statistically significant improvements in OS and a third, that showed substantial improvement in the disease control outcome, suggested a trend to a survival benefit that did not achieve statistical significance (\(p = 0.07\)).\(^ {20,39}\)

Two RCTs studied chemotherapy with or without rituximab in patients with resistant or relapsed indolent lymphoma. Forstpointner et al.\(^ {27}\) reported a comparison of fludarabine, cyclophosphamide and mitoxantrone (FCM) plus rituximab (FCM-R) with FCM alone in patients with relapsed follicular, mantle cell, and other indolent lymphomas. Progression-free and overall survival were superior in patients allocated to FCM-R. Van Oers et al.\(^ {28}\) reported the results of a RCT comparing CHOP-R with CHOP in patients with follicular NHL who had relapsed from or were resistant to a maximum of two non-anthracycline chemotherapies. The complete response rate was higher for patients that received CHOP-R which translated into an improvement in progression-free survival. Overall survival was not significantly different between the two groups. Responding patients in both studies underwent a second randomization comparing rituximab maintenance with observation (described below). A third study in relapsed patients with low-grade or transformed B-cell non-Hodgkin’s lymphoma compared rituximab monotherapy to a novel radioimmununconjugate agent, yttrium-90 ibritumomab tiuxetan.\(^ {32}\) Despite observing a higher response rate with radioimmunonotherapy, no evidence of improvement in progression-free survival, quality of life, or overall survival was detected.
<table>
<thead>
<tr>
<th>Author, study</th>
<th>N rand</th>
<th>Patients</th>
<th>Treatment</th>
<th>Follow-up time of study</th>
<th>RR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Disease control&lt;sup&gt;b&lt;/sup&gt;</th>
<th>OS&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Jadad Score&lt;sup&gt;u&lt;/sup&gt;</th>
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<tr>
<td><strong>First-line therapy</strong></td>
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<tr>
<td>Marcus, Solal-Celigny</td>
<td>321</td>
<td>First-line follicular (stg III,IV)</td>
<td>CVP-R vs. CVP&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Median 42 mo</td>
<td>81% vs. 57%; &lt;i&gt;p&lt;/i&gt; &lt; 0.0001</td>
<td>Median TTP, 34 vs. 15 mo; &lt;i&gt;p&lt;/i&gt; &lt; 0.0001&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Median OS: 89% vs. 81%; &lt;i&gt;p&lt;/i&gt; = 0.07&lt;sup&gt;e&lt;/sup&gt;</td>
<td>R: 1 point C: 0 points W: 1 point</td>
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<tr>
<td>Hiddemann</td>
<td>428</td>
<td>First-line follicular</td>
<td>CHOP-R&lt;sup&gt;h&lt;/sup&gt; vs. CHOP&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Median 18 mo</td>
<td>96% vs. 90%; &lt;i&gt;p&lt;/i&gt; = 0.011</td>
<td>Median TTF, not reached in either group; TTF superior in R-CHOP group (relative risk 0.40); &lt;i&gt;p&lt;/i&gt; &lt; 0.0001</td>
<td>Median OS not reached in either group; estimated probability of survival at 2 y, 95% vs. 90%; &lt;i&gt;p&lt;/i&gt; = 0.016</td>
<td>R: 2 points C: 0 points W: 0 points</td>
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<tr>
<td>Rivas-Vera</td>
<td>195</td>
<td>First-line indolent</td>
<td>CNOP vs. CNOP-R vs. R&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NR</td>
<td>83% vs. 90% vs. 85%; &lt;i&gt;p&lt;/i&gt; = 0.545</td>
<td>2 y DFS: 65% vs. 70% vs. 68%; &lt;i&gt;p&lt;/i&gt; = 0.93</td>
<td>2 y OS: 84% vs. 78% vs. 87%; &lt;i&gt;p&lt;/i&gt; = 0.016</td>
<td>R: 1 point C: 0 points W: 1 point</td>
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<td>Herold</td>
<td>358&lt;sup&gt;f,g&lt;/sup&gt;</td>
<td>First-line indolent NHL (follicular, mantle cell, and immunocytoma) (all stg III,IV)</td>
<td>MCP-R vs. MCP&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Accrual: 10/98 to 09/03</td>
<td>86% vs. 66%; &lt;i&gt;p&lt;/i&gt; &lt; 0.0001 (CR + PR)</td>
<td>2 y EFS, 69% vs. 44%; &lt;i&gt;p&lt;/i&gt; &lt; 0.001</td>
<td>NR</td>
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<tr>
<td>Foussard</td>
<td>358</td>
<td>First-line follicular NHL (stage II-IV)</td>
<td>ψIFN + CHVP-R vs. ψIFN + CHVP</td>
<td>Median 3.5 y</td>
<td>At 18 mo: 81% vs. 72%; &lt;i&gt;p&lt;/i&gt; = 0.0046 (CR + PR)</td>
<td>42 mo EFS, 67% vs. 46%; &lt;i&gt;p&lt;/i&gt; &lt; 0.0001</td>
<td>42 mo OS, 91% vs. 84%; &lt;i&gt;p&lt;/i&gt; = 0.029</td>
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<td>Buske</td>
<td>72&lt;sup&gt;f&lt;/sup&gt;</td>
<td>First-line lymphoplasmocytoid/ic immunocytoma</td>
<td>R-CHOP vs. CHOP&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Maximum 4 y</td>
<td>94% vs. 69%; &lt;i&gt;p&lt;/i&gt; = 0.012 (CR + PR)</td>
<td>Median TTF, not reached vs. 22 mo; &lt;i&gt;p&lt;/i&gt; = 0.0057</td>
<td>NR</td>
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<tr>
<td>Lenz</td>
<td>128</td>
<td>First-line mantle cell lymphoma (stg III or IV)</td>
<td>R-CHOP vs. CHOP</td>
<td>Median 18 mo</td>
<td>94% vs. 75%; &lt;i&gt;p&lt;/i&gt; = 0.0054 (CR + PR)</td>
<td>Median TTF, 21 mo vs. 14 mo; &lt;i&gt;p&lt;/i&gt; = 0.0131</td>
<td>2 y: 76% (both arms, &lt;i&gt;p&lt;/i&gt; = 0.93)</td>
<td>R: 1 point C: 0 points W: 1 point</td>
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<td><strong>Second-line or later therapy</strong></td>
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<tr>
<td>Forstpointner, Dreyling</td>
<td>147</td>
<td>Relapsed follicular and mantle cell lymphoma</td>
<td>FCM-R vs. FCM</td>
<td>Median 18 mo</td>
<td>79% vs. 58%; &lt;i&gt;p&lt;/i&gt; = 0.01 (CR + PR)</td>
<td>Median PFS, 16 vs. 10 mo; &lt;i&gt;p&lt;/i&gt; = 0.0381</td>
<td>Median, not reached vs. 24 mo (i.e. 0.0030)</td>
<td>R: 2 points C: 0 points W: 1 point</td>
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<table>
<thead>
<tr>
<th>Author, study</th>
<th>N rand</th>
<th>Patients</th>
<th>Treatmenta</th>
<th>Follow-up time of study</th>
<th>RRb</th>
<th>Disease controlb</th>
<th>OSb</th>
<th>Jadad Scoreu</th>
</tr>
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<tbody>
<tr>
<td>Van Oers,28 full 465</td>
<td>Relapsed/ Resistant follicular NHL (stg III or IV)</td>
<td>CHOP-R vs. CHOP</td>
<td>Median 39 mo</td>
<td>CR after induction: 30% vs. 16%; ( p &lt; 0.0001 )</td>
<td>Median PFS 33 vs. 20 mo (HR 0.65; ( p = 0.0003 ))</td>
<td>3 y OS, 83% vs. 72% (HR 0.74; ( p = 0.096 ))</td>
<td>R: 1 point C: 0 points W: 1 point</td>
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<tr>
<td>Witzig,33 full 143</td>
<td>Relapsed/ Resistant low-grade, follicular, or transformed NHL</td>
<td>Rituximab monotherapy vs. yttrium-90 ibritumomab tiuxetan</td>
<td>NR</td>
<td>CR: 34% vs. 20%; ( p = 0.063 )</td>
<td>Median TTP 11 vs. 10 mo (( p = 0.173 ))</td>
<td>NR</td>
<td>R: 1 point C: 0 points W: 0 points</td>
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<tr>
<td>Hochster,29 abst 304</td>
<td>Untreated, advanced indolent NHL (stg III–IV follicular grades 1–2 and SLL)</td>
<td>CVP</td>
<td>R maint vs. Obs1,</td>
<td>Median 3 y</td>
<td>PFS superior in R maint group (HR 0.38, ( p = 3 \times 10^{-8} )); FL only: 4 y PFS, 56% vs. 33% = NR</td>
<td>OS superior in R maint group (HR 0.66, ( p = 0.09 )); FL only: 4 y PFS, 88% vs. 72%, ( p = 0.03 )</td>
<td>R: 1 point C: 0 points W: 1 point</td>
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<tr>
<td>Ghielmini,30 full 202</td>
<td>Untreated and relapsed follicular lymphoma</td>
<td>Rituximab</td>
<td>R maint vs. Obs1</td>
<td>Median 35 mo</td>
<td>Median EFSa 23 vs. 12 mo (( p = 0.024 )); Response durationa at 24 mo, 58% vs. 35% (( p = 0.022 ))</td>
<td>NR</td>
<td>R: 1 point C: 0 points W: 1 point</td>
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<tr>
<td>Ghielmini,31 full 61</td>
<td>Untreated and relapsed mantle cell lymphoma</td>
<td>Rituximab</td>
<td>R maint vs. Obs</td>
<td>Median 29 mo</td>
<td>Median EFSa 12 mo vs. 6 mo (( p = 0.45 ))</td>
<td>NR</td>
<td>R: 1 point C: 0 points W: 1 point</td>
<td></td>
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<tr>
<td>Hainsworth,32 full 90f, i</td>
<td>Relapsed indolent NHL (grade 1 or 2 follicular, or SLL)</td>
<td>Rituximab</td>
<td>R maint vs. Obsa</td>
<td>Median 41 mo</td>
<td>Median PFS, 32 vs. 7 mo (( p = 0.007 )); median duration of rituximab benefit 31 vs. 27 mo; ( p = 0.94^m )</td>
<td>3 y, 72% vs. 68%, ( p = NS )</td>
<td>R: 1 point C: 0 points W: 1 point</td>
<td></td>
</tr>
<tr>
<td>Author, study</td>
<td>N rand</td>
<td>Patients Treatment</td>
<td>Follow-up time of study</td>
<td>RRb Disease controlb OSb Jadad Scoreu</td>
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<tr>
<td>Dreyling,34</td>
<td>abst</td>
<td>Relapsed follicular or mantle cell lymphoma</td>
<td>FCN or R-FCM (first random-ization)</td>
<td>Median response duration, not reached vs. 17 mo; ( p = 0.001 )</td>
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<tr>
<td>Van Oers,28</td>
<td>full</td>
<td>Relapsed/ Resistant follicular NHL (stg III or IV)</td>
<td>CHOP-R vs. CHOP (first randomization)</td>
<td>Median response duration, not reached vs. 17 mo; ( p = 0.001 )</td>
<td></td>
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</tbody>
</table>

Note: abst: abstract; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CNOP: cyclophosphamide, mitoxantrone, vincristine, prednisone; CR: complete response; CVP: cyclophosphamide, vincristine, prednisone; EFS: event-free survival; DFS: disease-free survival; est: estimated; eval: evaluable; FCM: fludarabine, cyclophosphamide, mitoxantrone; IFN-alpha: interferon-alpha; ITT: intention to treat; maint: maintenance; max: maximum; MCP: mitoxantrone, chlorambucil, prednisone; mo: month; N: number; NHL: non-Hodgkin’s lymphoma; NR: not reported; NS: not significant; obs: observation; OS: overall survival; PFS: progression-free survival; PR: partial response; prelim: preliminary; pts: patients; rand: randomized; R: rituximab; RR: response rate; SD: stable disease; SLL: small lymphocytic lymphoma; stg: stage; TTF: time-to-treatment failure; vs.: versus; y: year.

a Treatment details are provided in Appendix II.
b Data provided in order of intervention versus control.
c Authors did not indicate whether groups similar at baseline.
d Overall RR; no definition provided.
e Log-rank.
f Number of patients in each group not given.
g Number of patients in analysis unknown.
h Responders in this trial received IFN-alpha maintenance or received myeloablative consolidation plus autologous stem cell transplant.
i 13 patients randomized to maintenance rituximab progressed before starting treatment.
j No previous treatment with rituximab.
k Obs = retreatment at progression.
l Authors indicate groups balanced for characteristics or for a list of characteristics.
m Duration of rituximab benefit = date of documented remission until date of other treatment necessary.
n Newly diagnosed or relapsed/refractory.
o EFS measured from start of induction.
p Among those responding with induction.
q Resistant to a maximum of 2 nonanthracycline regimens.
r First randomization stopped after 147 patients; all subsequent patients received induction R-FCM (136 of 174 evaluable patients for the second randomization received R-FCM).
s Median response duration reported for patients who received R-FCM and subsequent randomization to maintenance rituximab versus observation; median follow-up not reported.
t Results of the maintenance randomization were not provided in the conference abstract but presented at the 2005 American Society of Hematology meeting (Atlanta, Georgia) and available on the EORTC website.46
u Jadad quality score: based on a three-item instrument that awards points for reporting of method of randomization (R; 0–2 points); use of concealment (C; 0–2 points); and study withdrawals (W; 0–1 point).
The Cochrane Haematological Malignancies Group reported a literature-based meta-analysis of the reports of six RCTs of chemotherapy with or without rituximab in newly diagnosed or relapsed patients with indolent or mantle cell lymphoma. Five trials with 994 randomized patients were analyzed for the primary outcome of overall survival. Overall survival of these patients was significantly improved with the addition of rituximab to chemotherapy compared with chemotherapy alone (HR 0.61; 95% CI: 0.47–0.80). No statistically significant heterogeneity of trial results was evident despite clear differences in study inclusion criteria, chemotherapy regimens, and rituximab administration.

**Consensus interpretation.** Multiple RCTs have demonstrated a survival advantage and prolonged disease control when rituximab is added to initial or subsequent chemotherapy in patients with indolent B-cell or mantle cell lymphoma. Given the inclusion of a number of non-follicular indolent histologies in four of the nine trials (representing 432 of 2468 total patients; 18%) and the comparable activity of rituximab in follicular lymphoma and other non-follicular indolent histologies, the DSG recommended that data from follicular lymphoma be generalized to these histologies (such as mantle cell lymphoma, marginal zone lymphoma, and lymphoplasmacytoid lymphoma). The consensus was that previously-un-treated patients with follicular, mantle cell or other indolent lymphomas who are appropriate candidates for chemotherapy, should receive this chemotherapy in combination with rituximab. Previously-treated patients who are appropriate candidates for further chemotherapy and who have not previously received rituximab, should also receive treatment in combination with rituximab.

**Evidence-based recommendations**
- Previously untreated patients with follicular or other indolent B-cell-histology lymphoma (such as mantle cell lymphoma, marginal zone lymphoma, and lymphoplasmacytoid lymphoma), who are appropriate candidates for chemotherapy, should receive this chemotherapy in combination with rituximab.
- Previously treated patients with follicular or other indolent B-cell-histology lymphoma (such as mantle cell lymphoma, marginal zone lymphoma, and lymphoplasmacytoid lymphoma) who have not previously received rituximab and who are appropriate candidates for chemotherapy should receive this chemotherapy in combination with rituximab.

**Maintenance rituximab in indolent B-cell or mantle cell lymphoma**

The role of rituximab as maintenance therapy for patients with indolent B-cell lymphomas has been tested in six randomized trials. The use of maintenance rituximab (MR) has been studied in the following contexts: (1) following rituximab monotherapy; (2) following initial combination chemotherapy; and (3) following second-line or subsequent combination chemotherapy.

Three RCTs studied the role of maintenance rituximab (MR) following treatment with rituximab monotherapy. Two of those reports included patients with both previously-un-treated and relapsed disease, whereas a third trial was specific to second-line or subsequent therapy. Ghielmini et al. published two similarly designed trials of MR versus observation in patients with follicular lymphoma and mantle cell lymphoma who attained at least stable disease with single-agent rituximab. In follicular lymphoma patients, MR was associated with prolonged response duration and event-free survival compared with patients who were observed. In the smaller trial that included mantle cell lymphoma patients, no significant benefit in event-free survival was detected. Overall survival was not reported in either study. Hainsworth et al. studied MR in patients with relapsed follicular or small lymphocytic lymphoma who had achieved at least stable disease with single-agent rituximab. Median progression-free survival was longer in patients allocated to MR. There was no significant difference in overall survival. Only one trial has studied the use of MR following initial combination chemotherapy. Hochster et al. studied MR in previously-un-treated patients with follicular or small lymphocytic lymphoma who had received CVP alone as induction chemotherapy and achieved at least stable disease. In the subgroup of patients with follicular lymphoma, progression-free survival and overall survival were significantly improved in patients receiving MR. No studies have addressed the use of MR following initial combination chemotherapy that includes rituximab. Two trials studied the use of MR in the setting of relapsed or refractory indolent disease. Both trials incorporated initial randomizations to combination chemotherapy with or without rituximab prior to second randomizations comparing MR to observation. Dreyling et al. studied patients with relapsed or refractory follicular or mantle cell lymphoma who underwent initial induction with FCM versus FCM-R prior to a second randomization to MR versus observation. With regards to the maintenance question, MR was associated with a prolonged response duration and a statistically insignificant trend toward improved overall survival ($p = 0.0562$). The improvement in response duration (in patients responding to FCM-R therapy) was significant in patients with follicular ($p = 0.0346$) and mantle cell lymphoma ($p = 0.0489$). Van Oers et al. studied patients with relapsed or refractory follicular lymphoma who had responded to a first randomization to CHOP chemotherapy with or without rituximab. MR was associated with a significant improvement in progression-free survival and overall survival compared to observation. In the subgroup of patients who had received rituximab with CHOP as induction therapy, MR continued to demonstrate an improvement in progression-free survival and statistically insignificant improvement in overall survival ($p = 0.059$).

**Consensus interpretation.** There are now six RCTs of maintenance rituximab (MR) in patients with indolent B-cell lymphoma; five studies have demonstrated clinically important improvements in disease control and two trials have shown prolongation of survival.

In patients receiving therapy for relapsed follicular lymphoma, there are clear benefits of disease control and survival attained with the use of MR. The benefit in disease control is preserved even in patients who have received combination chemotherapy that includes rituximab.

Following initial therapy, MR has similarly resulted in prolonged progression-free and overall survival. However, this strategy has only been studied following combination che-
Rituximab in lymphoma: A systematic review and consensus practice guideline from Cancer Care Ontario

Evidence-based recommendation

- For patients with follicular lymphoma or other indolent B-cell lymphomas who respond to treatment with combination chemotherapy and/or rituximab, this treatment should be followed by the use of maintenance rituximab.

Rituximab retreatment

Consensus interpretation

The role of rituximab in combination with chemotherapy for patients previously treated with a rituximab-based combination was not addressed in any of the available randomized trials. The DSG was unable to offer definitive recommendations where no direct evidence exists; however, following external review of the document, the DSG was requested by practitioners and provincial policy makers to provide guidance on this issue. Therefore, members of the DSG were compelled to rely on other sources of evidence to guide the decision process. Firstly, non-RCT data from trials of rituximab monotherapy suggested that rituximab-sensitive patients could attain response rates comparable to those observed with initial treatment. Secondly, the reuse of previously effective therapies is a common and effective strategy when managing patients with indolent lymphomas. Finally, cumulative toxicity from retreatment with rituximab is not expected, given the lack of myelosuppression observed with this agent. Based upon these data, the consensus opinion of the Hematology DSG was that patients previously treated with rituximab who remain sensitive to this agent should receive subsequent chemotherapy in combination with rituximab. While no evidence-based definition of rituximab sensitivity exists, the DSG considered relapse one year or more after treatment with rituximab to be a reasonable threshold. The group also considered patients who remained stable for one year following the last dose of maintenance rituximab to be rituximab-sensitive.

Consensus opinion-based recommendation

- Patients who have previously received rituximab (including combination rituximab-chemotherapy, rituximab monotherapy, or maintenance rituximab) and who have achieved a complete or partial response and have remained treatment free for at least one year's duration following the last rituximab administration and who become candidates for chemotherapy should receive this chemotherapy in combination with rituximab.

Practitioner feedback

Practitioner feedback on a draft version of the recommendations was obtained through a mailed survey of 120 practitioners in Ontario (60 hematologists, 30 academic medical oncologists, and 30 community medical oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations. The survey was mailed in August 2004 with follow-up reminders sent at two and four weeks. Forty-six responses were received out of the 120 surveys sent (38% response rate). Of the responders, 32 indicated that the report was relevant to their clinical practice and completed the survey. A majority of practitioners (97%) felt that there was a need for a clinical practice guideline on this topic. Most also felt that the interpretation of the results was consistent with their own understanding of the data (94%). Eighty-eight percent (88%) recommended that the report be approved as a practice guideline for Ontario physicians. The current guideline incorporates feedback received through the external review process. The DSG was asked to address the role of rituximab re-treatment in patients who had previously responded to rituximab-based therapy and the document was amended to include this discussion.

Discussion

This evidence-based summary and consensus process was guided by a number of principles. The group prioritized the use of comparative evidence in the exclusive form of randomized controlled trials to form the basis of these guidelines. In the consensus discussions, the group recognized a hierarchy of outcomes that influence therapeutic and policy decisions; changes in practice should be influenced primarily by evidence that a treatment extends life or improves quality of life. The group considered the provision of new or promising agents based solely on surrogate outcomes to be a lesser priority. The group did not consider the costs associated with rituximab in its evaluation. Finally, the DSG concluded that the evidence...
regarding the role of rituximab in lymphoma was fluid and evolving, and would require ongoing evaluation.

Under this framework, the DSG consensus process developed recommendations for the use of rituximab in lymphoma care. This document represents the first practice guideline addressing the role of rituximab in lymphoma care. We are aware of two systematic reviews that have studied rituximab in lymphoma. The previous systematic reviews addressed the cost-effectiveness of CHOP-R therapy in DLBCL and clinical effectiveness of rituximab in indolent lymphoma, respectively. Both literature reviews were completed prior to September 2002 and neither included searches of conference proceedings. The current Hematology DSG systematic review comprises 22 RCT publications; all but one of those reports were published after 2002. Therefore, the current summary represents the most comprehensive review of the RCT evidence for this first-in-class antibody therapy.

Additional strengths of this review include the use of validated methods to create the evidence-based summary and develop consensus guideline statements. The systematic review process relied on an extensive literature search that included conference abstracts to minimize publication bias and objective data abstraction according to pre-defined outcome questions. The guideline development process included an independent external review step to validate the final product. The process is unique in that the external review is completed by non-expert cancer practitioners “in-the-field”, the majority of whom are community and not academic physicians. The response rate in the review of this document was unfortunately low (<40%), and thus not necessarily representative of all oncologists-haematologists in the province. However, the external feedback was still an essential component of the guidelines process, resulting in the discussion surrounding rituximab retreatment.

This review had additional limitations. Quality of life outcomes were not reported in any of the included studies. The variability of study designs and patient populations was not conducive to pooling of results or use of meta-analytic summary techniques. Trial quality was assessed only in the subset of fully-published studies; consequently, quality scores did not weigh significantly in the consensus discussions. It is notable that the quality scores attained were generally poor-to-moderate, predominantly because none of the studies incorporated double-blinding, a rarity in phase III studies in hematologic malignancies. Finally, an important clinical problem, that of retreatment of patients with follicular and other indolent lymphomas, has not been addressed by any of the reported randomized trials. In considering the management of these patients, the DSG had to resort to a consensus opinion-based recommendation.

Despite these limitations, this evidence summary delineates a clear role for rituximab for the initial care of patients with B-cell NHL. As the evidence regarding the role of rituximab continues to mature and evolve, we invite practitioners and patients to review the website of the CCO-PEBC (http://www.cancercare.on.ca/index_practiceGuideline-andEvidencesummaries.htm) to remain abreast of the continued update process mandated for these guidelines.

Acknowledgements

The Hematology Disease Site Group thank Drs. Rena Buckstein and Eugenia Piliotis who assisted in scoring citations for inclusion. For the previous evidence summary version of this guideline, we thank Dr. Rena Buckstein and Dr. Neil Berinstein for their contributions and Ms. Manya Charette, Ms. Rosmin Esmail, and Ms. Julie Makarski for providing research support.

Appendix I: Literature search strategy

In MEDLINE, “Exp lymphoma/” (Medical subject heading [MeSH]) was combined with “exp lymphoma, large-cell/” (MeSH), “lymphoma.mp.” (textword), and each of the following phrases used as text words: “rituxan.mp.”, “rituximab.mp.”, “ritux:.mp.”, “idec.mp.” combined with “c2b8.mp.”, “anti-cd20.mp.”, “anticd-20.mp.”, “anticd20.mp.”, “mabthera.mp.”, and “rituxin.mp.”. These terms were then combined with the search terms for the following publication types and study designs: systematic reviews, meta-analyses, reviews, randomized controlled trials, controlled clinical trials, and clinical trials. Searches in the other bibliographic databases were similar.

Appendix II: Details of treatment administration

<table>
<thead>
<tr>
<th>Author, study</th>
<th>Protocol treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive histology lymphoma trials</td>
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<tr>
<td>Coiffier,11, full</td>
<td>CHOP-R vs. CHOP</td>
</tr>
<tr>
<td>Feugier,25, full</td>
<td>Groups treated with 3-week cycle for 8 cycles. R 375 mg/m² d1 each cycle</td>
</tr>
<tr>
<td>Habermann,12, abst</td>
<td>Randomization1: CHOP-R vs. CHOP Groups treated for 2 cycles after complete response for 6–8 cycles total. R 375 mg/m² d7 and d-3 before cycles 1 and 2 before cycles 3,5,7 Randomization2: R maint (R 375 mg/m² weekly ×4 repeated every 6 mo × 4) vs. observation</td>
</tr>
<tr>
<td>Sonneveld,13, abst</td>
<td>R-CHOP-14 vs. CHOP-14 Groups treated with 14-day cycle for 8 cycles. R × 6 doses (schedule and dose unspecified)</td>
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### Appendix II: (continued)

<table>
<thead>
<tr>
<th>Author, study</th>
<th>Protocol treatment</th>
</tr>
</thead>
</table>
| Pfrendschuh, 14 abst | Randomization1: R-CHOP-14 vs. CHOP-14  
Randomization2: 6 vs. 8 cycles of chemotherapy  
Patients randomized to rituximab all received 8 doses (375 mg/m²) given on days 1, 15, 29, 43, 57, 71, 85, 99 |
| Pfrendschuh, 15 full | Chemotherapy vs. R-Chemotherapy  
Groups treated with 6 cycles of either CHOP-21 d cycle, CHOEP-21d cycle, MACOP-B, or PMitCEBO regimen. R 375 mg/m² d 1, 22, 43, 64, 85, 106 |
| Kaplan, 16 full | CHOP-R (+R maint) vs. CHOP  
Groups treated with 3-week cycle for 8 cycles. R 375 mg/m² d-2 for all cycles  
R maint in pts with CR or PR = 3 monthly doses of 375 mg/m² |
| Haioun, 19 abst | R vs. observation 2 months post ASCT  
R 375 mg/m² weekly × 4 wk |
| van Heeckeren, 17 abst | in vivo purging with pre-mobilisation R 375 mg/m² 2 weeks, 1 week, and 1-2 d prior to mobilisation chemotherapy vs. ex vivo purging with positive CD34+ cell selection using immunomagnetic beads (no R therapy) |
| Pohlman, 18 abst | pre-mobilisation R 375 mg/m² 2 weeks, 1 week, and 1-2 days prior to VP16/GCSF mobilisation chemotherapy vs. VP16/GCSF alone |

### Indolent histology lymphoma trials

| Marcus, 20 full | CVP-R vs. CVP  
Groups treated with 21-day cycle for 8 cycles. R 375 mg/m² on d1 of each cycle |
| Solal-Celigny, 39 abst | |

| Hiddemann, 21 full | CHOP-R vs. CHOP  
Groups given up to 6 courses (both arms assumed). R 375 mg/m² on d1  
Responders <60 were subsequently randomized to IFN-alpha maintenance or myeloablative consolidation plus autologous stem cell transplant. Responders ≥60 received IFN-alpha maintenance |
| Rivas-Vera, 22 abst | CNOP vs. CNOP-R vs. R  
CNOP: 21-day cycle × 6. R: 375 mg/m² weekly × 6. CNOP-R: × 6  
Radiotherapy allowed if needed |
| Herold, 23,45 prelim report/abst | MCP-R vs. MCP  
Groups treated with 28-day cycle for 8 cycles. R 375 mg/m² on d1. Minor response after first 2 cycles required to continue on study. Patients in CR or PR after first six cycles then receive 2 cycles consolidation (same as above)  
Patients in CR or PR then receive IFN-alpha maintenance |
| Foussard, 24 abst | CHVP + αIFN vs. CHVP-R + αIFN  
CHVP: 6 monthly courses + 6 courses every 2 months. αIFN: 4.5MU 3 times weekly for 18 months. R: 6 infusions of 375 mg/m² d1, 8 courses 3,4 and d1 courses 5,6 |
| Buske, 25 abst | CHOP vs. R-CHOP  
R 375 mg/m² d0–1. Number of cycles not reported |
| Lenz, 26 full | CHOP vs. R-CHOP  
Groups treated with 21-day cycle for six cycles. R 375 mg/m² d0 |
| Forstpointner, 27 full | Randomization 1: FCM-R vs. FCM  
28-day cycles for four cycles. R 375 mg/m² on d1 |

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Appendix II: (continued)

<table>
<thead>
<tr>
<th>Author, study</th>
<th>Protocol treatment</th>
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<tbody>
<tr>
<td>Dreyling, 34 abst</td>
<td>Randomization 2: R maint vs. obs</td>
</tr>
<tr>
<td></td>
<td>R maint 375 mg/m² weekly × 4 at 3 and 9 months</td>
</tr>
<tr>
<td></td>
<td>Patients with complete or partial remission from induction chemotherapy were randomized to maintenance R or to observation</td>
</tr>
<tr>
<td>Van Oers, 28 full</td>
<td>Randomization 1: CHOP vs. R-CHOP</td>
</tr>
<tr>
<td></td>
<td>Groups treated with 21-day cycle for six cycles. R 375 mg/m² d1</td>
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<tr>
<td></td>
<td>Randomization 2: R maint vs. obs</td>
</tr>
<tr>
<td></td>
<td>R maint 375 mg/m² every 12 weeks until relapse or maximum of 2 y</td>
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<tr>
<td>Witzig, 23 full</td>
<td>R vs. yttrium-90 ibritumomab tiuxetan</td>
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<td>R 375 mg/m² weekly × 4</td>
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<td>Yttrium-90 ibritumomab tiuxetan includes (1) a dose of rituximab 250 mg/m² followed by ¹¹¹In-ibritumomab tiuxetan (on day 0) for dosimetry and imaging and (2) rituximab 250 mg/m² followed by ⁹⁰Y-ibritumomab tiuxetan (on day 8). Rituximab is given to enable clearance of peripheral B-cells and maximize biodistribution prior to radioimmunotherapy</td>
</tr>
<tr>
<td>Hochster, 29 abst</td>
<td>R maint vs. obs</td>
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<tr>
<td></td>
<td>R maint 375 mg/m² weekly × 4 every 6 mo × 4 cycles</td>
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<tr>
<td></td>
<td>All pts initially received CVP or CF; those with objective response or stable disease were randomized to maintenance R or to observation</td>
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<tr>
<td>Ghielmini, 30 full</td>
<td>R maint vs. obs</td>
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<tr>
<td></td>
<td>R maint 375 mg/m² every 8 weeks × 4</td>
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<tr>
<td></td>
<td>All pts initially received standard induction 375 mg/m² weekly × 4; responders or stable disease at week 12 were randomized to maintenance or to observation</td>
</tr>
<tr>
<td>Ghielmini, 31 full</td>
<td>R maint vs. obs</td>
</tr>
<tr>
<td></td>
<td>R maint 375 mg/m² at wk 12, and mo 5,7</td>
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<tr>
<td></td>
<td>All pts initially received induction with R 375 mg/m² weekly × 4; those with objective response or stable disease at wk 12 were randomized to maintenance R or to observation</td>
</tr>
<tr>
<td>Hainsworth, 32 full</td>
<td>R vs. obs following R</td>
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<tr>
<td></td>
<td>R maint 375 mg/m² weekly × 4 every 6 mo × 4 courses</td>
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<td></td>
<td>Obs = standard 4-week rituximab course at progression</td>
</tr>
<tr>
<td></td>
<td>All pts initially received rituximab 375 mg/m² weekly × 4; those with objective response or stable disease were randomized to maintenance R or to observation</td>
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</tbody>
</table>

CHVP: cyclophosphamide, doxorubicin, etoposide, prednisone; CNOP: cyclophosphamide, mitoxantrone, vincristine, prednisone; CP: chlorambucil, prednisone; CR: complete response/remission; CVP: cyclophosphamide, vincristine, prednisone; d: day; FC: fludarabine, cyclophosphamide; FCM: fludarabine, cyclophosphamide, mitoxantrone; fludara: fludarabine; FR: fludarabine plus rituximab; IFN: interferon; intermed: intermediate; MACOP-B: methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisone; VP16: etoposide; GCSF: granulocyte colony stimulating factor; maint: maintenance; max: maximum; MCP: mitoxantrone, chlorambucil, prednisone; mo: month; n: number; obs: observation; PD: progressive disease; PR: partial response/remission; pts: patients; R: rituximab; refract: refractory; relap: relapsed; SD: stable disease; stg: stage; TIW: thrice weekly; vs.: versus; wk: week. 

A Administration schedule differed among patients; the study included three treated cohorts.

References


3. Hainsworth, 32 full | R vs. obs following R |
|                | R maint 375 mg/m² weekly × 4 every 6 mo × 4 courses |
|                | Obs = standard 4-week rituximab course at progression |
|                | All pts initially received rituximab 375 mg/m² weekly × 4; those with objective response or stable disease were randomized to maintenance R or to observation |

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References


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rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly \(x4\) schedule. *Blood* 2004;103(12):4416–23.


