



Evidence-based Series #6-8 Version 2.2005: Section 1

**Rituximab in Lymphoma and Chronic Lymphocytic Leukemia:
A Clinical Practice Guideline**

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Developed by the Hematology Disease Site Group

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Questions

Lymphoma

1. In patients with lymphoma of any type or stage, is rituximab used alone or in combination with chemotherapy more effective than non-rituximab-containing regimens for improving overall survival, disease control (as assessed by measures such as progression-free survival, event-free survival, time-to-treatment failure, or response duration), response rate, or quality of life?
2. What is the toxicity associated with the use of rituximab used alone or in combination with chemotherapy compared with non-rituximab-containing regimens?
3. Which patients with lymphoma are more or less likely to benefit from treatment with rituximab compared with those treated with non-rituximab-containing regimens?

Chronic Lymphocytic Leukemia

1. What beneficial outcomes are associated with the use of rituximab for the treatment of patients with chronic lymphocytic leukemia (CLL)? Outcomes of interest are overall survival, disease control (as assessed by measures such as progression-free survival, event-free survival, time-to-treatment failure, or response duration), and response rate.
2. What is the toxicity associated with the use of rituximab?
3. Which patients are more or less likely to benefit from treatment with rituximab?

Target Population

Lymphoma

These recommendations apply to adult patients with lymphoma of any type, at any stage, and any histology.

Chronic Lymphocytic Leukemia

These recommendations apply to adult patients with CLL at any stage.

Recommendations

Lymphoma

- Previously untreated patients with diffuse large B-cell lymphoma (DLBCL), or a variant of DLBCL (such as mediastinal sclerosing B-cell lymphoma, T-cell-rich B-cell lymphoma, Burkitt-like lymphoma, or intravascular lymphoma), who are candidates for treatment with curative intent and will receive cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), should receive this therapy in combination with rituximab. This grouping includes patients with untreated DLBCL that has transformed from follicular or other indolent lymphoma.
- There is insufficient evidence at this time to support or refute treatment with a rituximab-containing chemotherapy regimen in patients who have been previously treated for diffuse DLBCL or a variant of DLBCL.
- There is insufficient evidence to support combining rituximab with chemotherapy when treating patients with human immunodeficiency virus (HIV)-related lymphoma. These patients may be at an increased risk for life-threatening infections when rituximab is combined with CHOP.
- Previously untreated patients with follicular or other indolent B-cell-histology lymphoma (such as mantle cell lymphoma, marginal zone lymphoma, and lymphoplasmacytoid lymphoma), excluding small lymphocytic lymphoma (SLL), who are appropriate candidates for chemotherapy, should receive this chemotherapy in combination with rituximab.
- 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.
- For previously treated patients with follicular or other indolent B-cell-histology lymphoma (such as mantle cell lymphoma, marginal zone lymphoma, and lymphoplasmacytoid lymphoma), excluding SLL:
 - Patients who have not previously received rituximab and who are appropriate candidates for chemotherapy should receive this chemotherapy in combination with rituximab.
 - Patients who have previously received rituximab (including combination rituximab-chemotherapy, rituximab monotherapy, or maintenance rituximab) and who have achieved a response of at least one year's duration to the last rituximab administration and who are appropriate candidates for chemotherapy should receive this chemotherapy in combination with rituximab.

Chronic Lymphocytic Leukemia

- 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.

Qualifying Statements

- Rituximab has a favourable single-agent toxicity profile. The addition of rituximab to chemotherapeutic regimens such as cyclophosphamide, vincristine, and prednisone (CVP),

CHOP, and fludarabine, cyclophosphamide, and mitoxantrone (FCM) does not appear to significantly alter the toxicity of these regimens in lymphoma.

- Rituximab should be administered at a dose of 375 mg/m² and given at the beginning of each treatment cycle of chemotherapy.
- There is significant variability in the published administration schedules for rituximab maintenance. The DSG felt that the regimen studied by the EORTC/Intergroup (rituximab 375mg/m² every 3 months until relapse or 2 years) was a reasonable and convenient option. Maintenance rituximab should be initiated within 8 weeks of completion of the induction regimen.
- Prolonged rituximab therapy may be associated with hypogammaglobulinemia. Immunoglobulin quantitation was a common monitoring strategy in the pivotal clinical trials and should be considered for patients receiving maintenance therapy.
- In the absence of randomized data evaluating the role of rituximab re-treatment, the recommendation that rituximab be reused in combination with chemotherapy is based on the consensus opinion of the Hematology Disease Site Group.
- There is a rapid availability of new data regarding the role of rituximab in treating these diseases. Practitioners and patients are advised to review the Web site of Cancer Care Ontario's Program in Evidence-based Care (PEBC) to learn the status of this practice guideline.

Key Evidence

Lymphoma

- A total of 22 randomized controlled trials were identified: 9 trials assessed patients with aggressive histology and 13 assessed patients with indolent histology. Three trials in aggressive histology were published in article form, as were seven trials in indolent histology; all remaining reports were preliminary publications in abstract form. The Hematology DSG was compelled by these data despite the limitation of their being primarily in abstract form.
- In one randomized trial comparing CHOP plus rituximab (CHOP-rituximab) with CHOP alone in previously untreated patients with DLBCL (aged 60 to 80 years), complete response, disease control (event-free survival), and overall survival were superior in patients allocated to receive CHOP-rituximab. In another randomized (reported in abstract form) comparing CHOP-14 (administered every 14 days) plus rituximab with CHOP-14 alone in patients aged 65 and older with DLBCL, mantle cell lymphoma, or grade III follicular lymphoma, disease control (event-free survival) and overall survival were again superior in the R-CHOP-14 group. A third randomized trial in elderly patients (age 61 to 80 years) with DLBCL similarly randomized patients to R-CHOP-14 vs. CHOP-14 and demonstrated improved disease control (freedom from treatment failure). No difference in overall survival has been detected in the preliminary analysis of this trial (presented in abstract form).
- In one randomized trial comparing CHOP-rituximab with CHOP alone (reported in abstract form), in previously untreated patients with DLBCL (age 60 years and greater), disease control (time-to-treatment failure) was superior in patients allocated to receive CHOP-rituximab. No difference between randomized groups in overall survival was detected. In that trial, patients responding to induction therapy underwent a second randomization to receive maintenance therapy with rituximab or observation. Disease control (time-to-treatment failure) was superior in patients allocated to receive rituximab; no difference between randomized groups in overall survival was detected.
- In one randomized trial of younger patients (age 60 and younger) with low-risk DLBCL (reported in abstract form), patients received CHOP-like chemotherapy with or without rituximab. Disease control (time-to-treatment failure), and overall survival were superior in

patients that received rituximab in addition to chemotherapy compared to patients that received chemotherapy alone.

- In a randomized trial of CHOP-rituximab compared with CHOP alone in patients with previously untreated human immunodeficiency virus (HIV)-related lymphoma, no overall survival benefit was derived from the addition of rituximab therapy. Although there was a trend to improvement in the primary outcome of response rate for R-CHOP, this benefit was offset by a statistically significant increased risk of treatment-related infectious death.
- In three trials comparing chemotherapy with or without rituximab in previously untreated patients with advanced-stage follicular lymphoma, disease control (time-to-treatment failure, time to progression, or two-year event-free survival) was superior in patients allocated to receive rituximab. An overall survival benefit was demonstrated with rituximab-based therapy in one full publication report, despite a brief median follow-up period of only 18 months. In another study, a strong trend to improved overall survival in the rituximab arm has been reported. An aggregate-data meta-analysis including these data has also confirmed an overall survival benefit in patients treated with rituximab and chemotherapy.
- In one trial comparing FCM to FCM-R in previously treated patients with indolent lymphomas, response rate, disease control (progression-free survival) and overall survival were superior in patients allocated to receive FCM-R. In another trial comparing CHOP to CHOP-R in patients with follicular lymphoma relapsed or resistant to a maximum of two non-anthracycline regimens, complete response and disease control (three-year progression-free survival) were superior in patients allocated to receive CHOP-R compared to patients that received CHOP alone. In both trials, patients responding to induction therapy underwent a second randomization to receive maintenance therapy with rituximab or observation. Disease control (response duration or progression-free survival) was superior in patients allocated to receive maintenance rituximab; overall survival was not reported in the abstract reports of these studies.
- In one randomized trial comparing maintenance rituximab to observation in patients with untreated indolent lymphoma who initially responded to CVP induction, disease control (progression-free survival) and overall survival were superior in patients allocated to receive rituximab maintenance.
- There were no trials that compared chemotherapy to the same chemotherapy plus rituximab in patients who had previously received rituximab and achieved a response duration of at least one year. Two randomized trials comparing chemotherapy plus rituximab to chemotherapy alone in patients previously treated with rituximab alone showed improvement in survival or progression-free survival. One randomized trial that compared maintenance rituximab to re-treatment with rituximab at disease progression following induction treatment with rituximab monotherapy, reported a response rate for re-treatment that was comparable to first-line treatment.
- No important additional hematologic or non-hematologic toxicities were observed when rituximab was combined with chemotherapy.

Chronic Lymphocytic Leukemia

- No randomized controlled trials were located.

Related Guidelines

PEBC Evidence-Based Series:

- #6-1: *Fludarabine in Intermediate and High-Risk Chronic Lymphocytic Leukemia.*
- #6-7: *The Use of Chemotherapy and Growth Factors in Older Patients with Newly Diagnosed, Advanced-Stage, Aggressive Histology Non-Hodgkin's Lymphoma.*

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