Evidence-based Series 6-16 Version 2

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Alemtuzumab in Chronic Lymphocytic Leukemia

G. Fraser, C.A. Smith, K. Imrie, R. Meyer, and the Hematology Disease Site Group

Report Date: January 16, 2014

An assessment conducted in October 2015 deferred the review of Evidence-based Series 6-16 Version 2. This means the document remains current until it is assessed again next year. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol).

The reviewed EBS report, which is available on the CCO web site consists of the following four sections:
Section 1: Clinical Practice Guideline (ENDORSED)
Section 2: Systematic Review
Section 3: Guideline Development and External Review
Section 4: Guideline Review Summary & Tool

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Guideline Report History

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A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Alemtuzumab in Chronic Lymphocytic Leukemia: A Clinical Practice Guideline

G. Fraser, C.A. Smith, K. Imrie, R. Meyer, and the Hematology Disease Site Group

Report Date: June 14, 2006

Question
1. Is alemtuzumab a beneficial treatment option, with respect to outcomes such as survival, response rate, response duration, time-to-progression, and quality of life, for patients with B-cell chronic lymphocytic leukemia (CLL)?
2. What toxicities are associated with the use of alemtuzumab?
3. Which patients are more likely, or less likely, to benefit from treatment with alemtuzumab?

Target Population
This evidence summary applies to adult patients with CLL.

Recommendation
- Treatment with alemtuzumab is a reasonable option for patients with progressive and symptomatic CLL that is refractory to both alkylator-based and fludarabine-based regimens.

Qualifying Statements
- The evidence supporting treatment with alemtuzumab comes principally from case-series studies that evaluate disease response as the primary outcome measure. Patients should be informed that any possible beneficial effect of alemtuzumab on other outcome measures such as duration of response, quality of life, and overall survival are not supported in evidence and remain speculative at this time.
- Treatment with alemtuzumab is associated with significant and potentially serious adverse treatment-related toxicities. Patients must be carefully informed of the uncertain balance between potential risks of harm and the chance for benefit reported in studies. Given the current substantial uncertainty in this balance, patient preferences will likely play a large role in determining the appropriate treatment choice.
• Given the potential toxicities associated with alemtuzumab, and given the limited nature of the clinical trials testing its use in broad populations of patients with CLL, the use of alemtuzumab in patients with important co-morbidities may be associated with excessive risks.

**Key Evidence**
• Currently, there are no published randomized controlled trials (RCTs) evaluating alemtuzumab alone or in combination with other chemotherapeutic agents for the treatment of relapsed or refractory CLL.
• One RCT evaluated alemtuzumab administered to consolidate a complete or partial response to first-line fludarabine-containing chemotherapy in patients with CLL (1). The study was stopped early due to the occurrence of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 2.0 grade III/IV infection-related toxicity in seven of the first 11 patients randomized to the alemtuzumab arm. Patients in that arm had a significantly improved progression-free survival (PFS) compared to observation (no progression versus [vs.] a mean PFS of 24.7 months, p=0.036).
• Six single-arm studies evaluated disease response for alemtuzumab as a single agent in the treatment of patients with relapsed/refractory CLL post-fludarabine. The pooled overall response rate was 38% (complete response [CR] 6%, partial response [PR] 32%). Median time-to-progression was reported in three of those trials and ranged from four to 10 months.
• Seventeen studies evaluated the toxicities associated with alemtuzumab as a single agent for the treatment of relapsed/refractory CLL:
  o Mild infusion-related side effects (e.g., grade I/II fever, rigors, vomiting, rash, dyspnea, and hypotension) were observed in most patients treated with intravenous alemtuzumab. Severe reactions (grade III/IV) were observed in up to 20% of patients treated with intravenous alemtuzumab; subcutaneous administration was rarely associated with severe infusion-related toxicity.
  o Thrombocytopenia and neutropenia (grade III/IV) were each observed in approximately one third of patients.
  o Infections were common (46% overall), often severe (18% grade III/IV), and included opportunistic, systemic viral, and invasive fungal diseases, despite antimicrobial prophylaxis. Cytomegalovirus (CMV) reactivation was commonly reported but effectively managed with adequate surveillance and treatment (usually intravenous ganciclovir); invasive CMV disease was rarely reported. Death due to infection occurred in approximately 4-5% of patients.

**Future Research**
• Alemtuzumab is being compared to chlorambucil for first-line treatment of newly diagnosed patients with CLL in a large, multicentre, phase III RCT (2).
• Alemtuzumab in combination with fludarabine is being compared to fludarabine alone for patients with relapsed CLL in a large, multicentre, phase III industry-sponsored study.
• Alemtuzumab continues to be investigated in phase II studies as consolidation therapy for both newly diagnosed patients (fludarabine/rituximab/alemtuzumab) and patients with relapsed/refractory CLL (Pentostatin/cyclophosphamide/rituximab/alemtuzumab).

**Related Guidelines**
• Practice Guideline Report #6-1 Fludarabine in Intermediate and High-Risk Chronic Lymphocytic Leukemia.
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REFERENCES
