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Evidence-based Series 6-16 Version 2 – EDUCATION AND INFORMATION 2016

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 November 2016 put Evidence-based Series (EBS) 6-16 Version 2 in the Education and Information Section. This means that the recommendation will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized 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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Alemtuzumab in Chronic Lymphocytic Leukemia

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

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version June 2006	1966-2005	Full Report	Web publication Journal publication	NA
Current Version 2 Oct 2012	2005- 2012	New data found in Section 4: Document Summary and Review Tool	Updated Web publication	2006 recommendations is **ENDORSED**

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Evidence-based Series #6-16 Version 2: Section 1

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:
    - 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.
    - Thrombocytopenia and neutropenia (grade III/IV) were each observed in approximately one third of patients.
    - 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*.

Funding

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REFERENCES

1. Wendtner CM, Ritgen M, Schweighofer CD, Ringerle-Rowson G, Campe H, Jager G, et al.; the German CLL Study Group (GCLLSG). Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission – experience on the safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GSCCSG). Leukemia. 2004;18:1093-1101.
2. Hillmen P, Skotnicki AB, Robak T, Mayer J, Jaksic B, Vukovic V, et al. Preliminary safety and efficacy report of a randomized trial of alemtuzumab vs chlorambucil as front-line therapy in 297 patients with progressive B-cell chronic lymphocytic leukemia (abstract 2505). Blood. 2004;104(11).

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Evidence-based Series #6-16 Version 2: Section 2

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

Alemtuzumab in Chronic Lymphocytic Leukemia: A Systematic Review

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

Report Date: June 14, 2006

QUESTIONS

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?

CHOICE OF TOPIC AND RATIONALE

Chronic lymphocytic leukemia is the most common form of adult leukemia in the Western hemisphere, with an incidence rate of 4 out of 100,000; in patients over age 70, the incidence approaches 50 out of 100,000. Established diagnostic criteria allow CLL to be differentiated from related subtypes of indolent non-Hodgkin lymphomas (1). Patients requiring therapy are usually treated either with systemic alkylator-based chemotherapy or with a purine analogue (fludarabine). Unfortunately, CLL remains incurable with conventional chemotherapeutic approaches, and patients will relapse even after a favourable response to front-line therapy. Several randomized, controlled trials (RCTs) in patients with untreated, advanced stage CLL have documented superior response rates and response duration in patients randomized to fludarabine in comparison with alkylator-based chemotherapy (2-4). Despite those encouraging results, an improvement in overall survival has not been shown. Patients with disease refractory to standard chemotherapy have a particularly poor prognosis, and there is currently no accepted standard treatment. In order to improve outcomes for patients with CLL, new therapies and treatment approaches are needed.

Monoclonal antibodies are an emerging class of drugs with a unique mechanism of action that represents a novel approach to cancer treatment; rituximab, a humanized anti-CD 20 monoclonal

antibody, has proven to be particularly effective for patients with B-cell lymphomas. Alemtuzumab, a humanized anti-CD52 monoclonal antibody, was the first of this class of drugs to receive U.S. Food and Drug Administration (FDA) approval for the treatment of patients with CLL relapsed or refractory to fludarabine; it is currently under review for approval in Canada. Although the function of CD52 is not known, this antigen is expressed on a variety of hematopoietic cells, including normal and malignant T- and B-lymphocytes; CD52 is not expressed on hematopoietic stem cells. Once bound to CD52, alemtuzumab induces cell death by one or more of three mechanisms: (i) complement-dependent cellular cytotoxicity (CDCC), (ii) antibody-dependent cellular cytotoxicity (ADCC), and (iii) induction of apoptosis. Clinical activity has been demonstrated in heavily pre-treated patients, including those with disease progression following treatment with fludarabine. However, the benefits of alemtuzumab are offset by potential toxicities, including infection-related morbidity and mortality.

As licensing approval may precede the publication of phase III studies, the Hematology Disease Site Group (DSG) felt a systematic overview of the current literature was needed. This systematic review will inform further recommendations on this topic when updated with relevant, high-quality evidence in the future.

METHODS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by one member of the PEBC Hematology DSG and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on alemtuzumab in CLL. The body of evidence in this review is primarily comprised of mature RCT data, where available. This evidence is the basis for clinical recommendations developed by the Hematology DSG and presented in a practice guideline as part of this evidence-based series (Section 1). The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

A systematic search of the published literature identified all reports relating to the use of alemtuzumab for the treatment of patients with CLL. The MEDLINE (1966 to July 2005), CINAHL (1982 to July 2005), Healthstar (1975 to July 2005), CANCERLIT (1975 to July 2005), PREMEDLINE (July 2005), Cochrane Controlled Trials Register (July 2005), and Cochrane Database of Systematic Reviews (July 2005) databases were searched according to the strategy shown in Appendix A. In addition, abstracts from the American Society of Hematology (ASH) (1995-2004) and the American Society of Clinical Oncology (ASCO) (1995-2005) annual conference proceedings were searched. Our search strategy included only studies published in English. Publications evaluating alemtuzumab in non-human subjects and those that were categorized as "published comments," "letters," and "editorials" were excluded. The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) Register, Physician Data Query (PDQ), National Institute of Health (NIH) Clinical Trials, and the European Organization for Research and Treatment of Cancer (EORTC) databases were searched to identify ongoing clinical trials. The National Guidelines Clearinghouse was searched for clinical practice guidelines. The references for each selected article were also reviewed. Where it was deemed necessary, the authors of included publications were contacted to obtain missing or additional data. It should be noted that a preliminary literature search was performed in November 2002 and subsequently updated in November 2004 and July 2005. After the preliminary literature search, the study selection criteria were amended to exclude studies with fewer than 20 evaluable patients. As a result, studies in the preliminary literature search that had fewer than 20 evaluable patients were later removed from the report. The data from those small studies, had they been included, would not have significantly affected the results or the DSG recommendations. For the

sake of clarity, results from the preliminary and updated searches for this systematic review are presented together.

Study Inclusion Criteria

Articles were selected for inclusion in this systematic review if they met the following criteria:

1. Studies included patients with CLL.
2. Studies tested the role of alemtuzumab as either induction or consolidation therapy, and either as a single agent or in combination with other therapy.
3. Results were reported for any of the following outcomes: survival, quality of life, time-to-progression, response duration, response rate, or adverse effects.
4. Trials had a minimum sample size of 20 evaluable patients.

Two independent observers reviewed the title and abstract of each citation. They were blinded to author name, institution, name of journal, nature of the paper (full paper or abstract), and results. The blinded observers scored each abstract as follows: "yes" if it met inclusion criteria, "no" if it did not meet inclusion criteria, or "maybe" if there was uncertainty. If both observers agreed that the abstract met the inclusion criteria, the complete document, if available, was retrieved for further analysis. In cases of disagreement, both observers reassessed the blinded abstracts together to achieve consensus. Where consensus could not be reached, or in cases where both observers gave a score of "maybe," the full document was retrieved and assessed by both reviewers to achieve consensus regarding eligibility. The reasons for excluding retrieved articles were documented.

Synthesizing the Evidence

Due to a lack of adequately designed RCTs in our sample, a formal meta-analysis was deemed inappropriate. Where possible, response rates from single-arm studies evaluating similar patient groups were calculated. Data were pooled using intention-to-treat groups, and response proportions computed.

RESULTS

Literature Search Results

A total of 527 citations were found with the original and updated searches; 40 citations met the inclusion criteria. Eighteen of the 40 citations were subsequently excluded from analysis for the following reasons:

- One publication was a duplicate,
- Three were anecdotal case reports (one report of severe immune thrombocytopenic purpura following a 10-week course of alemtuzumab, one report of gas gangrene six weeks after an eight-week course of alemtuzumab, and one report of a patient with CLL treated with three courses of alemtuzumab over a three-year period),
- One evaluated patients with Sezary syndrome,
- One evaluated non-clinical outcomes (T-cell subset recovery post-treatment with alemtuzumab—the clinical outcomes were reported in a separate publication that was included in this systematic review), and
- Eleven were abstracts subsequently published as full papers (all met the inclusion criteria for this systematic review).

The 22 publications eligible for review (Table 1) are summarized below:

- Nine single-arm studies (four full papers, five abstracts) evaluated alemtuzumab as a single agent in patients with relapsed or refractory CLL.
- Three studies (two full papers, one abstract) evaluated alemtuzumab as a single agent in newly diagnosed patients with previously untreated CLL. One abstract publication reported only

preliminary toxicity data from a RCT comparing alemtuzumab with chlorambucil as a first-line treatment of CLL.

- Three single-arm studies (two full papers, one abstract) evaluated alemtuzumab in combination with additional agents for patients with refractory CLL.
- Six studies (one full paper, five abstracts) evaluated alemtuzumab as consolidation therapy in CLL patients with a 'response' to previous-line therapy. One citation, published as a full paper, reported results from an RCT comparing alemtuzumab maintenance therapy to observation alone in patients with a response to first-line fludarabine. The trial was stopped early due to severe infection-related complications in patients randomized to the alemtuzumab arm. The remaining citations reported results from single-arm studies.
- One publication reported a pooled analysis for the risk of cytomegalovirus (CMV) reactivation, CMV pneumonia, and CMV-related deaths in patients with lymphoid malignancies treated with alemtuzumab.

Table 1: Characteristics of included citations.

Regimen Type	CLL Population	Trial Design	Citations			
			# Full	Refs	# Abs	Refs
Monotherapy	Relapsed / refractory	9 single-arm	4	Keating 2002 (5) Rai 2002 (13) Ferrajoli 2003 (7) Moreton 2005 (11)	5	Rai 2001 (6) Fiegl 2003 (14) Stilgenbauer 2004 (8) Osterborg 1997 (9) Osuji 2004 (10)
	Previously untreated	1 RCT 2 single-arm	2	Lundin 2002 (15) Karlsson 2005 (16)	1	Hillman 2004 (25)[1]
Combination Therapy	Relapsed / refractory	3 single arm	2	Faderl 2003 (17) Elter 2005 (19)	1	Wierda 2004 (18)
Consolidation Therapy	Response to prior line	1 RCT 5 single arm	1	Wendtner 2003 (20)[2]	5	Montillo 2004 (21) Rai 2002 (22) O'Brien 2003 (23) Liggett 2005 (24) Rossi 2004 (26)

Abbreviations: Abs, abstracts; CLL, chronic lymphocytic leukemia; Refs, references;
[1] Abstract reporting preliminary toxicity data from a RCT comparing alemtuzumab against chlorambucil for first-line treatment of CLL (response data not yet reported).
[2] Trial stopped early due to excessive infection-related toxicity in patients randomized to Alemtuzumab.

Practice Guidelines for CLL

Seven published practice guidelines on the management of CLL were retrieved. Two of those were excluded from our report because they were not published in English. The European Society for Medical Oncology (ESMO), the German CLL Study Group, and the Guidelines Working Group of the UK CLL Forum published separate guidelines for the diagnosis, staging, and treatment of patients with CLL that included reference to alemtuzumab therapy. One practice guideline was published specifically on the use of alemtuzumab in CLL by Keating et al. (2004).

The ESMO guideline did not include a description of the methods used to develop its recommendations; did not provide response rates, response durations, or associated toxicities of the studies included; and did not indicate explicitly which studies informed which recommendations.

The guideline published by German CLL group was described as a review article that stated it was a consensus document of the German CLL Study Group (with the membership listed). No description of the methods used to produce the guidelines were provided. Two studies on the outcomes of alemtuzumab therapy were cited as evidence for the German CLL group's recommendations, and were also retrieved in the literature search for our report (one was excluded because of our sample size criteria).

The UK CLL Forum guideline described the methods used to develop their recommendations and indicated explicitly which studies informed which recommendations. Outcome data, including response rates, durations of response, and median survival rates observed in trials were reported. Nine single-arm studies of alemtuzumab in patients with CLL informed their guideline. Of those studies, six are included in our report, and three were excluded in our search strategy because they did not meet our minimum sample-size criteria.

The practice guideline that addressed alemtuzumab use specifically indicated that it was developed out of an expert-opinion roundtable on the topic (held August 8-9, 2004). No description of methods are provided beyond that information. The Keating et al. guideline was informed by evidence from eight trials of alemtuzumab in CLL, all of which were included in our report.

The recommendations of these practice guidelines, which concern alemtuzumab use in patients with CLL, are addressed in the discussion.

Outcomes

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?

For this question, no studies reported quality-of-life outcome data.

(i) Single agent alemtuzumab for relapsed/refractory CLL

Response Rates

The overall response (RR), complete response (CR), and partial response (PR) rates associated with single-agent alemtuzumab for patients with relapsed or refractory CLL are summarized in Table 2 and include data from nine single-arm studies; there were no comparative or randomized studies available for analysis. Six trials each evaluated a standard 12-week course of alemtuzumab in patients with relapsed or refractory disease post-fludarabine therapy (5-10). The combined RR rate across those six trials was 38% (range 31-41%); combined CR and PR rates were 6% (range 1-10%) and 32% (range 26-38%), respectively. One study (8) evaluated alemtuzumab administered subcutaneously and reported RR and CR rates similar to studies with intravenous administration; no trials directly compared subcutaneous with intravenous administration.

Three studies administered alemtuzumab for longer than 12 weeks. A single-arm study by Moreton et al. (11) evaluated the treatment with alemtuzumab until a maximal clinical response was achieved in patients with relapsed or refractory disease post-fludarabine therapy. RR, CR, and PR rates of 54%, 35%, and 19%, respectively, were reported for 91 patients treated for a median of nine weeks (range 1-16 weeks). Peripheral blood and bone marrow samples were obtained from all patients before, during, and after alemtuzumab therapy to evaluate minimal residual disease (MRD) status. A highly sensitive and validated four-colour flow cytometry-based assay was used to define MRD status; the limit of detection for that assay was approximately one CLL cell in 104 to 105 leukocytes (12). Twenty percent of patients achieved an MRD-negative remission in the bone marrow and peripheral blood. However, those patients had a median treatment-free period, prior to initiating alemtuzumab, of 10 months (range 4-43 months), and most patients (72%) had no evidence of

lymphadenopathy or splenomegaly prior to alemtuzumab treatment. No trials have directly compared different alemtuzumab regimens.

The remaining two studies (13,14) administered therapy to 16 and 30 weeks, respectively, had smaller sample sizes (24 and 27 patients), and reported response rates similar to the other studies in that group.

Table 2: Responses to mono-therapy and combination therapy: single-arm trials of alemtuzumab for B-CLL.

Trial (ref)	Intervention[1] Prior / Current	N[2]	Response % RR	CR	PR	TTP (mo) All	TTP (mo) CR pts	OS (mo) All	OS (mo) CR pts
Mono-therapy: Relapsed/Refractory CLL									
Osterborg 1997 (9)	F[3] / A	29	41	4	38	NR	NR	NR	NR
Rai 2001 (6)a	F / A	136	40	7	32	3.9	7.3	7.6	13.4
Keating 2002 (5)a	F / A	93	33	2	31	4.7	9.5	16	32
Rai 2002 (13)	F / A to 16wks	24	33	0	33	7.1	19.6	27.5	35.8
Ferrajoli 2003 (7)	F / A	42	31	5	26	NR	NR	NR	NR
Fiegl 2003 (14)	F / A to max 30wks	27	41	4	37	NR	NR	NR	NR
Osuji 2004 (10)a	F / A[5]	26 (23)	52	22	30	NR	NR	NR	NR
Stilgenbauer 2004 (8)a	F / A via sc	50 (44)	36	2	34	9.7	NR	13.1	NR
Moreton 2005 (11)	F / A to max response	91	54	35	19	NR	20[4]	NR	41[4]
Mono-therapy: Previously Untreated									
Lundin 2002 (15); Karlsson 2005 (16)a	A via sc, 18wks	41 (38)	87	19	68	18+	35+	NR	NR
Hillmen 2004 (25)a	A vs.	149	NR	NR	NR	NR	NR	NR	NR
	C	148	NR	NR	NR	NR	NR	NR	NR
Combination Therapy									
Faderl 2003 (17)	A+R[6]	32	63	6	56	NR	NR	NR	NR
Wierda 2004 (18)a	C,F,A,R/CFAR	31 (21)	52	14	38	NR	NR	NR	NR
Elter 2005 (19)	F,A,R / A+F	36	83	31	53	13	22	36	nr

[1] Unless indicated otherwise, intervention was 30 mg Alemtuzumab administered intravenously three times per week for 12 weeks.
[2] Evaluable patients are given in parenthesis, if less than total number of patients.
[3] Only 3 patients received prior treatment (fludarabine).
[4] Complete remission not reached in MRD-ve pts. Numbers are for MRD+ve patients with complete remission.
[5] Regimen details not reported.
[6] Alemtuzumab administered intravenously bi-weekly for 8 weeks + rituximab (375mg/m^2) administered weekly for 4 weeks.
Notes: a = abstract; A = alemtuzumab; alk = alkylating agents; B-CLL = B-cell chronic lymphocytic leukemia; BIW = bi-weekly; C = chlorambucil; CFAR = cyclophosphamide 250mg/m2 d3-5, fludarabine 25mg/m2 d3-5, alemtuzumab 30mg d1,3,5, rituximab 375-500mg/m2 d2; CR = complete remission; d = day; eval = evaluable; F = fludarabine; iv = intravenous; mo = median months; MRD = minimal residual disease; N = number; nr = not reached; NR = not reported; OS = overall survival; PR = partial remission; pts = patients; q = every; R = rituximab; Rai = Rai 4-stage system; ref = reference; RR = response rate; sc = subcutaneous; TTP = time- to-progression; via = route of administration; vs., versus; wks = weeks.

Response Duration

Data on median time-to-progression (TTP) were reported in five single-arm studies evaluating alemtuzumab in patients with disease that had relapsed after or was refractory to fludarabine (Table 2) (5,6,8,11,13). Fludarabine-refractory disease was usually defined as either no response to fludarabine or relapse within six months following a response to fludarabine. The median TTP ranged from four to 10 months.

Moreton et al. (11) compared the median treatment-free-survival (TFS) according to the response to alemtuzumab (MRD–negative CR, MRD-positive CR, PR, or non-responders). Patients achieving MRD-negative CR had a significantly prolonged TFS compared to MRD-positive CR, PR, or non-responders (median TFS not reached, 20 months, 13 months, and six months, respectively, $p<0.0001$). The median TFS for the entire cohort was not reported.

Survival

Survival data were reported in 4 single-arm studies evaluating alemtuzumab in patients with relapsed or refractory disease post-fludarabine (Table 2) (5,6,8,13). Median overall survival (OS) ranged from 8 months to more than 2 years.

Moreton et al. (11) compared OS according to response to alemtuzumab. Patients achieving MRD-negative CR had a significantly prolonged OS compared to MRD-positive CR, PR, or non-responders (median OS not reached, 60 months, 70 months, and 15 months respectively, $p<0.0007$). Median OS for the entire cohort was not reported.

(ii) Single-agent alemtuzumab for previously untreated CLL

Response Rates

Two studies investigated the RR, CR, and PR rates associated with a trial of single-agent alemtuzumab for patients with previously untreated CLL (15,16). Lundin et al. (15) reported an RR rate of 87% for 38 evaluable patients treated with subcutaneous alemtuzumab for 18 weeks; the CR and PR rates were 19% and 68%, respectively. Most patients were at the advanced disease stage (69% Rai III/IV).

Response Duration

In the trial by Lundin et al. (15), median time-to-treatment-failure (TTF) had not been reached at 18 months. In an update of that trial, reported in abstract form, median TTF in responders had not been reached at 35 months (16). No other trials reported data pertaining to response duration.

Survival

No studies reported OS rates associated with alemtuzumab therapy for previously untreated patients with CLL.

(iii) Alemtuzumab in combination with additional agents for relapsed/refractory CLL

Response Rates

Three single-arm studies evaluated alemtuzumab-containing combination regimens for the treatment of relapsed or refractory CLL (Table 2) (17-19). No trials directly compared different combination regimens. One trial (19) evaluated alemtuzumab in combination with fludarabine. Elter et al. (19) reported an RR rate of 83% for 36 evaluable patients; the CR and PR rates were 31% and 53%, respectively.

Faderl et al. (17) reported a 63% RR rate (6% CR, 57% PR) for 32 patients treated with alemtuzumab in combination with rituximab. Wierda et al. (18) evaluated a regimen consisting of cyclophosphamide, fludarabine, alemtuzumab, and rituximab administered over six 28-day cycles; the overall response rate was 52% (14% CR, 38% PR).

Response Duration

Elter et al. (19) reported a median TTP of 13.0 months for the entire patient cohort; for patients who achieved a CR, median TTP was 21.9 months. No other studies reported data for response duration associated with alemtuzumab-containing combination regimens for patients with relapsed/refractory CLL.

Survival

Elter et al. (19) reported a median OS of 35.6 months; for patients who achieved CR, median OS was not reached. No other studies reported survival data.

(iv) Alemtuzumab consolidation for patients with a response to previous-line therapy

Response Rates

One RCT (20) and four single-arm studies (32,33,35,37) reported response rates for alemtuzumab consolidation therapy; results are summarized in Table 3. The German CLL Study Group (Wendtner et al.) published results from an open-label, multicentre, randomized phase III trial comparing 12 weeks of alemtuzumab consolidation with observation in patients achieving at least a PR following six cycles of first-line fludarabine-containing chemotherapy (20). The study's sample size of 90 patients was designed to have an 80% statistical power to detect a 25% improvement in progression-free survival (PFS) at two years. The trial was stopped after the accrual of 21 patients due to the occurrence of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 2.0 grade III/IV infections in seven of the first 11 patients randomized to alemtuzumab consolidation. Two of eleven patients (18%) randomized to alemtuzumab consolidation improved upon their response to first-line therapy; both patients achieved a PR following first-line fludarabine-containing chemotherapy and improved to CR following consolidation with alemtuzumab.

The four single-arm studies evaluating alemtuzumab-consolidation therapy were reported in abstract form only (21-24). All studies evaluated a four- to eight-week course of alemtuzumab in patients who had stable disease (SD) or better following first- or second-line chemotherapy. Response to alemtuzumab consolidation was generally defined as an improvement in 'post-induction' response status according to National Cancer Institute-Working Group (NCI-WG) criteria. Overall, response status improved following alemtuzumab consolidation. Two studies (21,23) documented an MRD-negative remission status in 38% to 51% of patients, based on clonality of the IgH gene rearrangement by polymerase chain reaction (PCR) analysis of peripheral blood and/or bone marrow samples.

Table 3: Responses to maintenance/consolidation therapy: randomized and single-arm trials of alemtuzumab for CLL.

				Post-induction		Post-alemtuzumab			
Trial (ref)	**Population**	**Intervention[1]**	**N[2]**	**RR**	**CR**	**RR**	**CR**	**TTP (mo)**	**OS (mo)**
RCTs of Alemtuzumab Consolidation Following First-Line Chemotherapy									
Wendtner, 2004 (20)	PR+ resp F,F+C	A vs. Obs	11 10	100 100	9 20	100 70	27 20	nr 24.7[3]	nr nr
Single-Arm Studies of Alemtuzumab Maintenance/Consolidation Therapy in Patients with CLL									
Rai, 2002 (22)a	SD+ fl F	A 6 wks	56 (36)	55	4	92	27 (42)	NR	NR
O'Brien, 2003 (23)[a]	PR+ post-chemo	A 10-30mg 4-8 wks	58 (49)	100	12	100	28 (33)	24+ in resp	NR
Montillo, 2004 (21)[a]	PR+ post-fl F	A 10mg sc 6 wks	35	100	29	100	83	NR	NR
Liggett, 2005 (24)[a]	resp fl F+R	A 4 wks	29 (21)	100	NR	83	34	NR	NR

[1] Unless indicated otherwise, intervention was 30 mg Alemtuzumab administered intravenously three times per week for 12 weeks.
[2] Number of patients that were assigned a treatment at the start of the trial. Numbers in parenthesis indicate evaluable patients at follow-up period, where the number of evaluable patients differs from the number assigned therapy.
[3] p=0.036.
Note: a = abstract; A = alemtuzumab; C = cyclophosphamide; chemo = chemotherapy; CR = complete remission; fl = first-line; mc = monoclonal; med = median; mo = median months; n = near; N = number; nr = no response; NR = not reported; OS = overall survival; pc = polyclonal; PR = partial remission; PR+ = partial remission or better; ref = reference; resp = response to; RR = response rate; SD+ = stable disease or better; TTP = time-to-progression; vs. = versus, w = with; wks = weeks.

Response Duration

Two studies reported data for response duration associated with alemtuzumab consolidation following a response to first- or second-line chemotherapy (20, 23). In the RCT published by the German CLL Study Group (20), no progression occurred in the 11 patients randomized to alemtuzumab consolidation compared with a 24.7 months mean PFS in the 10 patients randomized to observation (p=0.036). O'Brien et al. (23) reported a median TTP of greater than 24 months in patients who demonstrated a response to alemtuzumab consolidation.

Survival

Survival data associated with the use of alemtuzumab-consolidation therapy were reported in the RCT published by the German CLL Study Group (20); median OS had not been reached in either the alemtuzumab arm or the observation arm. No other studies reported survival data.

Question 2: What toxicities are associated with the use of alemtuzumab?

Toxicities associated with the administration of alemtuzumab were reported in most studies (Table 4). The most common adverse events can be broadly grouped into: (i) infusion-related side effects, (ii) myelosuppression, and (iii) infection-related toxicities.

Table 4: Toxicities associated with Alemtuzumab for CLL.

Trial (ref)	Prophylactic Antimicrobials	Pre-medications	Infusion-related toxicity % (Grade I/II, III/IV)	Cytopenias % (Grade III/IV)	Infections N (%)	AE (%)
Single-Arm Studies of Alemtuzumab Monotherapy in Relapsed/Refractory CLL						
Osterborg 1997 (9)	Optional	Clemastine, Pethidine, Acetaminophen	Fever (97,0) Rash (65,0) Nausea (69,0) Diarrhea (17,0) Hypotension (17,3)	Anemia - 28 Neutropenia - 31 Thrombocytopenia - 28	Grade I/II HSV - 11 (38) Grade I/II thrush - 4 (14) Grade I/II pneumonia - 5 (17) Grade III/IV pneumonia - 1 (3) Grade III/IV septicaemia - 4 (14) PCP pneumonia - 2 (7) Infection-related deaths: 0	NR
Rai 2001 (6)a	Famciclovir, Septra	NR	Fever - 65 Rigors - 71 Nausea - 45 (Grades NR)	Anemia - 11 Neutropenia - 22 Thrombocytopenia - 23	Total infections - 44 (32): Candida - 7 (1% grade III) Pneumonia - 7 (3% grade III/IV) HSV - 6 (1% grade III) VZV - 2 (1.5) CMV reactivation - 2 (1.5) Pseudomonal sepsis - 1 (0.7) Infection-related deaths: 3 (2)	19
Williams 2001 (27)a	NR	NR	NR	NR	CMV reactivation - 3.6 CMV pneumonia - 0.6 CMV deaths - 0.2 Note: CMV reactivation not routinely evaluated in these studies	NR
Keating 2002 (5)	Famciclovir, Septra	Diphenhydramine, Acetaminophen	Fever (85,20) Rigors (90,14) Vomiting (38,1) Rash (33,0) Dyspnea (28,12) Hypotension (17,2) Hypoxia (3,2)	NR	Total infections - 51 (55): Grade III/IV - 25 (27) Sepsis - 14 (15) CMV reactivation - 7 (8) PCP pneumonia - 1 (1) Aspergillus pneumonia - 1 (2) Rhinocerebral Mucormycosis - 1 (1) Systemic candidiasis - 1 (1) Cryptococcal pneumonia - 1 (1) VZV - 4 (4) Listeria meningitis - 1 (1)	24

Trial (ref)		Prophylactic Antimicrobials	Pre-medications	Infusion-related toxicity % (Grade I/II, III/IV)	Cytopenias % (Grade III/IV)	Infections N (%)	AE (%)
						HSV reactivation - 6 (6.5) Infection-related deaths: 5 (5.4)	
Rai (13)	2002	Optional	Diphenhydramine, Acetaminophen	Fever (100,17) Rigors (92,17) Vomiting (54,17) Dyspnea (17,4)	Neutropenia - 59 Thrombocytopenia - NR	Total infections - 10 (42): PCP pneumonia - 4 (17) Candida/aspergillus pneumonia - 1 (4) Invasive aspergillosis -1 (4) Disseminated VZV - 1 (4) CMV / mycobacterial pneumonitis - 1 (4) Klebsiella pneumonia - 1 (4) Infection-related deaths: 2 (9)	37
Ferrajoli 2003 (7)		Cotrimoxazole, Valacyclovir	Diphenhydramine, Acetaminophen	Fever (83, 2) Rigors (72, 1) Rash (42, 0) Nausea (35, 0) Dyspnea (19, 12) Hypotension (22, 1) Headache (8, 1)	Anemia - 0 Neutropenia - 35 Thrombocytopenia - 41	Total infection - (71): CMV reactivation - 12 (29) (in CLL and non-CLL pts) Disseminated VZV - 1 (1) PCP -1 (1) (S noncompliance) Invasive aspergillosis - 1 (1) Bacteremia -17 (22) Sinus zygomycosis - 1 (1) Cutaneous mycobacterial - 2 (3) Infection-related deaths: 4 (5)	NR
Fiegl (14)a	2003	NR	NR	NR	NR	CMV reactivation - 4 (15) Tuberculosis reactivation - 2 (7) Grade IV infections - 2 (7) Infection-related deaths: 1 (4)	NR
Moreton 2004 (11)		Cotrimoxazole, Acyclovir, G-CSF, Ganciclovir	Paracetamol, Chlorpheniramine	Fever (63, 13) Urticaria (27, 1), Nausea/vomiting (31, 0), Hypotension (13, 4), Hypoxia (3, 3)	Grade III Neutropenia - 48% Grade IV Neutropenia - 30% Thrombocytopenia - 46%	Total infections - 39 (43): Grade III/IV infections - 33 episodes in 22 patients (24) Septicemia - 11 (12) CMV reactivation - 8 (9) CMV pneumonitis - 1 (1) Proven/probable invasive fungal infections - 5 (5) Infection-related death: 4 (4)	11

Trial (ref)	Prophylactic Antimicrobials	Pre-medications	Infusion-related toxicity % (Grade I/II, III/IV)	Cytopenias % (Grade III/IV)	Infections N (%)	AE (%)
Osuji 2004 (10)a	NR	NR	NR	NR	CMV reactivation - 4 (17) CMV pneumonitis - 1 (4) Infection related death - 1 (4) (CMV pneumonitis)	NR
Stilgenbauer 2004 (8)a	NR	Paracetamol, Antihistamines	NR	Anemia - 14 Neutropenia - 66 Thrombocytopenia - 34	Grade III/IV infections - 11 (24) CMV reactivation - 6 (14) Infection related death - 3 (7) (sepsis)	30
RCTs of Alemtuzumab in Previously Untreated CLL						
Hillman 2004 (25)a	NR	Cotrimoxazole, Famciclovir	Fevers Rigors Dermatitis Urticaria Headache Hypertension Hypotension Nausea (Grades NR)	NR	CMV reactivation - 22 (15) CMV pneumonitis - 0 (0)	10+
Single-Arm Studies of Alemtuzumab Monotherapy in Previously Untreated CLL						
Lundin 2002 (15); Karlsson 2005 (16)a	Valacyclovir, Fluconazole, Cotrimoxazole to 8wks post-A	Paracetamol, Antihistamines	Injection site rxn (88, 2) Fever (68, 2) Rigor (15, 2) Rash (0,0) Dyspnea (0, 0) Hypotension (0, 0) Fatigue (5,2)	(Grades II-IV) Anemia - 39 Neutropenia - 74 Thrombocytopenia - 16	CMV reactivation - 4 (11) PCP pneumonia - 1 (3) Grade II-IV febrile neutropenia / bacterial infections - 0 (0) EBV infection at 21 months, histologically confirmed. Richter's trans in 12%	16
Single-Arm Studies of Alemtuzumab Combination Therapy in Relapsed/Refractory CLL						
Faderl 2003 (17)	Valacyclovir, Cotrimoxazole	NR	Fever 75 Rigor 67 Rash 38 Fatigue 33 Dyspnea 25 Nausea/vomiting 27 (Grade NR)	NR	Total infections - 27 (52): CMV reactivation - 13 (27) FUO - 6 (13) Pneumonia - 5 (10) Sinusitis - 3 (6) Infection-related death: 0	NR
Wierda 2004 (18)a	Valacyclovir, Cotrimoxazole	Corticosteroids	Grade I/II "common": Fatigue Fever Rash/hives Nausea	Grade III Neutropenia - 23 Thrombocytopenia - 23 Grade IV Neutropenia - 39	CMV reactivation - 5 (24)	NR

Trial (ref)	Prophylactic Antimicrobials	Pre-medications	Infusion-related toxicity % (Grade I/II, III/IV)	Cytopenias % (Grade III/IV)	Infections N (%)	AE (%)
			Grade III/IV "uncommon": Nausea/vomiting Fever/chills Fatigue Constipation Dyspnea, Arthralgias	Thrombocytopenia - 16		
Elter 2005 (19)	Septra, Valacyclovir	Clemastine, Acetaminophen, Prednisone, Allopurinal	Grade III/IV (% out of 140 total cycles of therapy): Chills - 1 Fever - 1 Edema - 4 Dyspnea - 3	(% out of 140 total cycles of therapy): Neutropenia - 26 Thrombocytopenia - 30	CMV reactivation - 2 (6) Fungal pneumonia - 2(6) E. coli sepsis - 1 (3) Infection-related death: 1 (3) (from E. coli sepsis)	NR
Single-Arm Studies of Alemtuzumab Maintenance/Consolidation Therapy in Patients in Patients with CLL						
Rai 2002 (22)a	Acyclovir, Cotrimoxazole to 6 mos post-A	NR	"Infusion reactions occurred in most patients" usually grade I/II	NR	Grade III/IV infections - 12 (33): CMV infection - 8 (22) Infection-related death: 1 (3) (CMV infection)	NR
O'Brien 2003 (23)a	Valacyclovir, Cotrimoxazole	NR	Fever/Chills (100,0) Rash/nausea (50,0)	NR	Pneumonia - 1 (3) Staph sepsis - 1 (3) Listeria sepsis - 1 (3) Viral myocarditis - 1 (3) CMV reactivation - 6 (21) EBV +ve large cell lymphoma - 2 (6)	NR
Rossi 2004 (26)a	NR	NR	NR	NR	CMV reactivation - 20 (57) Median time to CMV reactivation 43 days (23-61); treatment with oral ganciclovir for CMV Ag > 10 +ve cells No cases of CMV pneumonitis, enteritis.	NR
Liggett 2005 (24)a			Grade III/IV : F+R - 6 A - 38	F+R: Neutropenia – 26 Thrombocytopenia – 6 A: Neutropenia – 14 Thrombocytopenia – 7	F+R: Febrile neutropenia - 2 (8) A: Opportunistic infections - 6 (27) Infection related deaths - 2 (7) Febrile neutropenia - 2 (7)	24

Trial (ref)	Prophylactic Antimicrobials	Pre-medications	Infusion-related toxicity % (Grade I/II, III/IV)	Cytopenias % (Grade III/IV)	Infections N (%)	AE (%)
RCTs of Alemtuzumab Consolidation in CLL Patients with a Response to First-Line Chemotherapy						
Wendtner 2003 (20)	Cotrimoxazole, Famciclovir	Paracetamol, Antihistamines, Prednisone	Fever (64, 0) Chills (27, 0) Rash (36, 0) Nausea/vomiting (9,0) Dyspnea (9, 0) Hypotension (0,0) Myalgias (27, 0) Diarrhea (18, 0)	Anemia – 18 Neutropenia – 64 Thrombocytopenia - 36	Trial stopped early due to grade III/IV infections in 7 of 11 patients randomized to A. CMV reactivation - 4 (36) CMV pneumonitis - 2 (18) Pulmonary aspergillosis - 1 (9) HSV/HHV-6 infection - 1 (9) Pulmonary TB - 1 (9) VZV reactivation - 1 (9) Pneumonia - 1 (9) Observation arm: VZV reactivation (grade II) Sinusitis (grade I)	82

Note: a = abstract; A = alemtuzumab; AE = patients experiencing adverse events; Ag = antigenemia; CLL = chronic lymphocytic leukemia; CMV = cytomegalovirus; EBV = Epstein-Barr virus; F = fludarabine; FUO = Fever of unknown origin; HSV = herpes simplex virus; N = number; NR = not reported; PCP = pneumocystis carinii pneumonia; R = rituximab; ref = reference; rxn = reaction; VZV = varicella-zoster virus.

(i) Infusion-related side effects

Infusion-related side effects were reported in 17 studies (5-7,9,11,13,15-25). They occurred in most patients treated with intravenous alemtuzumab, were usually grade I/II in severity, and were manageable with appropriate supportive care. The prophylactic use of pre-medications was reported in about one third of the studies and usually consisted of orally administered acetaminophen and antihistamines; corticosteroids were generally reserved for more severe reactions. Grade III/IV fever, rigor, and nausea were reported in up to 20% of patients, while other serious infusion-related toxicities were less common. The incidence of infusion-related side effects was similar regardless of the population evaluated, tended to be higher and more severe with the first infusion, and improved with subsequent courses of treatment.

The subcutaneous administration of alemtuzumab was reported in three trials (8,15,21) and was generally much better tolerated compared to similar patients treated intravenously (Table 4). Grade I/II fever (68%) and local injection site reactions (88%) were reported; grade III/IV reactions of any kind were rarely reported (≥ 2% of patients) (15).

(ii) Myelosuppression

Data regarding myelosuppression associated with the use of alemtuzumab were reported in 10 trials (6-9,11,13,15,18-20). Results for studies evaluating different disease populations were analyzed separately.

Grade III/IV myelosuppression was common in studies evaluating alemtuzumab monotherapy for patients with relapsed/refractory disease (6-9,11,13); the pooled estimates (range) for grade III/IV neutropenia, thrombocytopenia, and anemia were 39% (22-66%), 31% (23-46%), and 8% (0-28%), respectively. Similar rates of grade III/IV myelosuppression were reported for studies evaluating alemtuzumab in combination and maintenance/consolidation regimens. Data regarding the co-administration of hematopoietic growth factors were not well reported.

(iii) Infection-related toxicity

Data regarding the incidence of infections in patients treated with alemtuzumab were reported in 21 publications (5-11,13-20,22-27). In 13 studies, antimicrobial prophylaxis was administered during alemtuzumab therapy; cotrimoxazole in combination with antiviral therapy (acyclovir, valacyclovir, famciclovir), for the prevention of pneumocystis carinii pneumonia (PCP) and herpes virus infections, respectively, were most frequently cited. For this systematic review, data relating to infection-related toxicity were analyzed and reported separately for different study populations.

(a) *Single agent alemtuzumab for relapsed/refractory CLL*

Data pertaining to infection-related morbidity in that patient population were reported in eight studies (5-9,11,13,14). The per capita incidence of all infections ranged from 30 to 93 per 100 patients (46 per 100 patients across studies). The incidence of Grade III/IV infections was 7 to 36 per 100 patients (18 per 100 across), and infection-related mortality ranged from 0 to 10 per 100 patients (4.5 per 100 across). Grade III/IV infections included disseminated viral infections (e.g., Varicella zoster virus and herpes simplex virus [HSV]), systemic candidal infections, mycobacterial reactivation, and invasive fungal infections (e.g., pulmonary aspergillosis, rhinocerebral mucormycosis, and cryptococcal meningitis/pneumonia). PCP was reported but generally occurred in patients not receiving prophylaxis.

The incidence of CMV reactivation was reported in seven of the above-mentioned trials (5-8,10,11,14) and ranged from 1% to 29% (9% across); CMV pneumonitis was reported in four patients (0.8% across). The actual risk of CMV reactivation in that patient population was not clear because most studies did not prospectively screen all patients.

Williams et al. (27) retrospectively reported pooled safety data—3.6% of patients experienced 'symptomatic' CMV reactivation, CMV pneumonitis (0.8%), and CMV related-deaths (0.2%) in 1,538 patients with lymphoid malignancies treated with alemtuzumab in five single-arm trials—the routine screening of all patients for CMV reactivation was not performed in those studies. Patients who developed CMV reactivation were usually treated with intravenous ganciclovir until evidence of viremia resolved. Ganciclovir therapy was highly effective for treating CMV reactivation, but, because ganciclovir-induced neutropenia was common, treatment with myeloid growth factors (G-CSF) was often co-administered.

Rates of adverse events ranged from 11 to 82% in those studies. Overall, alemtuzumab therapy was prematurely discontinued in approximately 20% of patients due to an adverse event, most often due to infection-related complications and/or myelosuppression.

(b) *Single-agent alemtuzumab for previously untreated CLL*

In an RCT comparing alemtuzumab to chlorambucil for newly diagnosed patients with CLL, Hillmen et al. (25) reported a CMV-reactivation rate of 15% for all patients randomized to receive alemtuzumab. All patients with detectable CMV reactivation were treated with ganciclovir; no cases of CMV pneumonitis occurred. Other infection-related toxicities have not yet been reported. Lundin et al. (15) reported CMV reactivation in four (11%) patients treated with subcutaneous alemtuzumab. One case of PCP occurred in a patient not receiving prophylaxis. An update describing the long-term follow-up for that patient cohort documented one episode of symptomatic Epstein-Barr virus (EBV infection 21 months post-alemtuzumab therapy (16). No other serious infections occurred.

(c) *Alemtuzumab in combination with additional agents for relapsed/refractory CLL*

Faderl et al. (17) documented infections in 52% of patients with lymphoid malignancies treated with alemtuzumab in combination with rituximab; CMV reactivation occurred in 27%. Infections in CLL patients were not reported separately. Elter (19) reported data on 36 patients treated with alemtuzumab in combination with fludarabine; fungal pneumonia (n=2), CMV reactivation (n=2), and one infection-related death (E. coli sepsis) were the only reported infection-related complications.

Wierda et al. (18) reported CMV reactivation in 24% of patients (n=21) treated with alemtuzumab in combination with cyclophosphamide, rituximab, and fludarabine.

(d) *Alemtuzumab consolidation for patients with a response to previous-line therapy*

Wendtner et al. randomized patients with a response to first-line fludarabine containing chemotherapy to consolidation with alemtuzumab (30mg intravenously three times per week [TIW] for 12 weeks) or observation (20). Explicit stopping rules were determined a priori and included grade III/IV infections occurring in five of the first 10 patients accrued to the alemtuzumab arm. The study was stopped early due to severe infections in seven of 11 patients randomized to alemtuzumab consolidation. Grade III/IV infections included CMV reactivation (n=2), CMV pneumonitis (n=2), pulmonary aspergillosis and HSV/human herpes virus (HHV)-6 (n=1), pulmonary tuberculosis (n=1), and herpes zoster reactivation (n=1). An additional two patients developed grade II CMV reactivation. Overall, nine of 11 patients (82%) randomized to alemtuzumab consolidation discontinued therapy due to an adverse event (severe infection in five patients and severe myelosuppression in four patients).

Four additional single-arm studies reported infection-related toxicity for alemtuzumab consolidation therapy (22-24,26). CMV reactivation was common, occurring in 21-57% of patients; the one reported case of CMV pneumonitis (22) contributed to patient death. The studies evaluated either 10mg or 30mg doses of alemtuzumab administered over six to eight weeks; there was no apparent difference in the rate or severity of infections according to treatment regimen.

Question 3: Which patients are more likely, or less likely, to benefit from treatment with alemtuzumab?

Statistical evaluations for independent predictors of response, response duration, or survival were not reported in any study included in this systematic review. However, several publications reported subgroup analyses and clinical observations for patients who were more or less likely to respond to alemtuzumab. Several authors noted that patients with lymphadenopathy, particularly bulky lymph nodes (> 5cm), were less likely to achieve a clinical response to alemtuzumab-containing therapy (5,9,11,13,15,20,23). Keating et al. (5) reported that patients less likely to respond included those with Rai stage IV disease, at least one lymph node greater than 5cm in diameter, or a World Health Organization (WHO) performance status of two. Moreton et al. (11) evaluated alemtuzumab monotherapy administered to maximal response in patients relapsed or refractory to fludarabine and reported that patients were significantly less likely to respond if they had lymph nodes larger than 5cm ($p<0.0001$), had received three or more previous lines of therapy ($p=0.0005$), or had a pre-treatment WHO performance status greater than one. The RCT published by the German CLL study group (20) failed to find a correlation between response status and age, disease stage, response to previous-line fludarabine-containing chemotherapy, cumulative alemtuzumab dose, duration of alemtuzumab therapy, IgH mutational status, or cytogenetic aberrations; however, the analysis was limited to only 11 patients, because the trial was stopped early due to excessive severe infections in the alemtuzumab-consolidation arm.

DISCUSSION

In its deliberations, the Hematology DSG places particular emphasis on the following: (a) results from published RCTs (where available), (b) the recognition of a hierarchy of outcomes that should influence treatment decisions, with priority given to therapies found to extend life or improve quality of life, and (c) the potential toxicities associated with treatment, with particular emphasis on those toxicities seen in the patients most likely to make up the eventual population treated. The members of the Hematology DSG had considerable difficulty reaching consensus on the appropriate wording of the recommendation for a potential indication for alemtuzumab in patients with CLL; the recommendation went through multiple iterations (see section 3, Guideline Development and External

Review—Methods and Results). Based on their review of the evidence provided in this systematic review, the DSG considered several interpretations for the use of alemtuzumab in patients with CLL.

The DSG regards alemtuzumab as an active agent for the treatment of patients with relapsed or chemotherapy-refractory CLL. This conclusion is based on response data from single-arm studies that report partial responses in approximately one third of patients and recognizes that complete remissions are uncommon. From a perspective of drug and/or multi-agent regimen development, these data are extremely promising and warrant further testing of alemtuzumab.

In their deliberations, the DSG cited the following factors leading to the above recommendation: (a) a lack of data from properly designed RCTs, (b) a paucity of comparative data suggesting improved response duration, quality of life, or improved overall survival compared with alternative treatment approaches, and (c) significant potential toxicity, particularly infection-related morbidity and mortality. Given the anticipated toxicity, data from RCTs demonstrating improvement in clinically meaningful outcome measures (e.g., time-to-progression, quality of life, or overall survival) are required before recommendations permitting the routine use of alemtuzumab in this patient population can be made.

The practice guidelines published by ESMO (28) and the UK CLL Forum (29) made recommendations regarding the use of alemtuzumab in previously treated patients. The ESMO guideline recommended alemtuzumab as an option for patients with refractory disease following first-line therapy, based on the lowest level evidence (ASCO level V evidence: small case-series). In addition, the UK CLL Forum guideline recommended alemtuzumab for use in patients without bulky lymphadenopathy (<5cm), who were previously treated with alkylating agents and refractory to fludarabine. The evidence informing the UK CLL Forum recommendation was similar to the evidence contained in this report and was comprised of data from a smaller selection of single-arm studies. The German CLL Study Group determined that definitive recommendations could not be made regarding alemtuzumab use and indicated that further testing in clinical trials would be preferred (30). The Keating et al. guideline (31) did not make explicit recommendations regarding the appropriateness of alemtuzumab use in CLL patients, but implied that alemtuzumab is appropriate in fludarabine-refractory patients. Keating et al. also stated that advanced age should not be a contraindication for alemtuzumab use.

The DSG considered the above recommendations to be based on low levels of evidence and, initially, was not convinced that these recommendations would inform the basis of a best clinical practice. Instead, the DSG initially concluded that potential benefits (response rates in a minority of patients, uncertain benefit in terms of response duration, overall survival, and quality of life) were offset by the potential for significant toxicity. Therefore, an initial recommendation was developed to indicate that there were insufficient data to support the routine use of alemtuzumab in patients with CLL. The DSG acknowledged the potential controversy that could result from issuing a "non–permissive" recommendation regarding alemtuzumab use and the potential implications such a recommendation might have for drug availability. The DSG was aware that its recommendations differed from those of other existing practice recommendations, including those published by ESMO and the UK CLL Forum.

The DSG was also aware that within the response data described from the literature reviewed were responses of a magnitude that reporting authors, and members of the DSG, considered to be clinically important. While the precise frequency of these responses were uncertain, and the best estimate was that they would be infrequent, the DSG acknowledged that an opportunity for such a response, even with substantial risks of toxicity, may be highly desired by some patients. The DSG attempted to reflect this sentiment by indicating that, after balancing the benefits and risks of treatment, certain patients may wish to consider a trial of therapy. While the DSG had concerns with issuing an unclear and potentially conflicting set of recommendations, it initially considered this option to represent the best available alternative and offered the following guidance: For patients with CLL, there is insufficient evidence to recommend the use of alemtuzumab outside of clinical trials. The DSG recognizes that, in highly selected cases, after thorough consideration of the risks and benefits,

a trial of alemtuzumab might be considered. Section 3 details the subsequent Practitioner Feedback and notes that responding clinicians were generally in agreement with the synthesis and interpretation of the available literature and the resulting recommendation. However, a small number of respondents commented on the lack of clarity associated with the recommendations. As a result, the DSG continued its consensus process in an effort to develop a clearer statement and issued a new set of recommendations. The redeveloped recommendation states, "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." In order to account for the continued concern about the level of evidence supporting this recommendation and the potential adverse risk-benefit profiles of this therapy, a detailed set of Qualifying Statements were also developed.

ONGOING TRIALS

The NCI, UKCCCCR, PDQ, NIH Clinical Trials, and EORTC databases were searched for any ongoing clinical trials. Alemtuzumab in combination with fludarabine is being compared with fludarabine alone for patients with relapsed CLL in one 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). Alemtuzumab is also being compared with chlorambucil in a large, multicentre RCT of the first-line treatment of newly diagnosed patients with CLL (25).

CONCLUSIONS

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.

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.

CONFLICT OF INTEREST

None reported.

JOURNAL REFERENCE

Fraser G, Smith CA, Imrie K, Meyer R; Hematology Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. Alemtuzumab in chronic lymphocytic leukemia. Curr Oncol. 2007;14(3):96-109.

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For a complete list of the Hematology DSG members and the Report Approval Panel members, please visit the CCO Web site at http://www.cancercare.on.ca/

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The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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REFERENCES

1. Cheson BD, Bennett JM, Grever M, Kay N, Keating MJ, O'Brien S, et al. National Cancer Institute-Sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood. 1996;87:4990.
2. Rai KR, Peterson BL, Appelbaum FR, Kolitz J, Elias L, Shepherd L, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Engl J Med. 2000;343:1750-7.
3. Johnson S, Smith AG, Loffler H, Osby E, Juliusson G, Emmerich B, et al. Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia. The French Cooperative Group on CLL. Lancet. 1996;347:1432-8.
4. Leporrier M, Chevret S, Cazin B, Boudjerra N, Feugier P, Desablens B, et al; French Cooperative Group on Chronic Lymphocytic Leukemia. Randomized comparison of fludarabine, CAP, and ChOP in 938 previously untreated stage B and C chronic lymphocytic leukemia patients. Blood. 2001;98:2319-25.
5. Keating MJ, Flinn I, Jain V, Binet J, Hillmen P, Byrd J, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. Blood. 2002;99:3554-3561.
6. Rai KR, Coutre S, Rizzieri D, Gribben JG, Flinn I, Rabinowe S, et al. Efficacy and safety of alemtuzumab (Campath-1H) in refractory B-CLL patients treated on a compassionate basis. [abstract]. Blood. 2001;98(11 Suppl): A1538.
7. Ferrajoli A, O'Brien SM, Cortes JE, Giles FJ, Thomas DA, Faderl S, et al. Phase II study of alemtuzumab in chronic lymphoproliferative disorders. Cancer. 2003;98:773-8.
8. Stilgenbauer S, Winkler D, Krober A, Kienle D, Hallek M, Hensel M, et al. Subcutaneous campath-1H (alemtuzumab) in fludarabine-refractory CLL: interim analysis of the CLL2h study of the German CLL Study Group (GCLLSG). [abstract]. Blood. 2004;104(11): A487.
9. Osterborg A, Dyer MJS, Bunjes D, Pangalis GA, Bastian Y, Catovsky D, et al. Phase II multicentre study of human CD52 antibody in previously treated chronic lymphocytic leukemia. J Clin Oncol. 1997;15:1567-74.
10. Osuji N, Del Giudice I, Matutes E, Dearden C, Catovsky D. Alemtuzumab for chronic lymphocytic leukemia with and without p53 deletions. [abstract]. Blood. 2004;104(11): A2510.
11. Moreton P, Kennedy B, Lucas G, Rassam SMB, Haynes A, Tighe J, et al. Eradication of Minimal Residual Disease in B-cell Chronic Lymphocytic Leukemia after Alemtuzumab Therapy Is Associated with Prolonged Survival. Journal of Clinical Oncology. 2005;23(13):1-9.
12. Rawstron AC, Kennedy B, Evans PAS, Davies FE, Richards SJ, Haynes AP, et al. Quantitation of minimal disease levels in chronic lymphocytic leukemia using a sensitive flow cytometric assay improves the prediction of outcome and can be used to optimize therapy. Blood. 2001;98:29-35.
13. Rai K, Freter CE, Mercier RJ, Cooper MR, Mitchell BS, Stadtmauer EA, et al. Alemtuzumab in previously treated Chronic Lymphocytic Leukemia Patients who had also received fludarabine. Journal of Clinical Oncology. 2002;20:3891-3897.
14. Fiegl M, Hopfinger G, Jaeger G, Fridrik M, Zojer N, Walla B, et al. Alemtuzumab is Effective in the Treatment of Patients with Advanced, Heavily Pretreated B-Cell Chronic Lymphocytic Leukemia. [abstract]. Blood. 2003;102(11): A5157.
15. Lundin J, Kimby E, Bjorkholm M, Broliden P, Celsing F, Hjalmar V, et al. Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). Blood. 2002;100:768-773.
16. Karlsson C, Norin S, Lundin J, Kimby E, Mellstedt H, Sander B, et al. Alemtuzumab as first-line therapy in B-cell chronic lymphocytic leukemia (B-CLL): Long term follow-up of clinical effects, infectious complications, and risk of Richter transformation (RT). [abstract]. EHA 2001-2005:083.

17. Faderl S, Thomas DA, O'Brien S, Garcia-Manero G, Kantarjian HM, Giles FJ, et al. Experience with Alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. Blood. 2003;101:3413-3415.
18. Wierda W, Faderl S, O'Brien S, Cortes J, Ferrajoli A, Giles F, et al. Combined Cyclophosphamide, Fludarabine, Alemtuzumab, and Rituximab (CFAR) is Active for Relapsed and Refractory Patients with CLL. [abstract]. Blood. 2004;104(11): A340.
19. Elter T, Bochmann P, Schulz H, Reiser M, Trelle S, Schnell R, et al. Fludarabine in combination with alemtuzumab is effective and feasible in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: results of a phase II trial. J Clin Oncol. 2005;23(10):7024-7031.
20. Wendtner CM, Ritgen M, Schweighofer CD, Ringerle-Rowson G, Campe H, Jager G, et al. Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission – experience on the safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GSCCSG). Leukemia. 2004;18:1093-1101.
21. Montillo M, Tedeschi A, Rossi V, Cafro AM, Cairoli R, Veronese S, et al. Alemtuzumab as Consolidation after a Response to Fludarabine is Effective to Purge Residual Disease in Patients with Chronic Lymphocytic Leukemia. [abstract]. Blood. 2004;104(11): A479.
22. Rai KR, Bryd JC, Peterson BL, Larson RA. A Phase II Trial of Fludarabine Followed by Alemtuzumab (Campath-1H) in Previously Untreated Chronic Lymphocytic Leukemia (CLL) Patients with Active Disease: Cancer and Leukemia Group B (CALGB) Study 19901. [abstract]. Blood. 2002;100(11): A772.
23. O'Brien SM, Gribben JG, Thomas DA, Albitar M, Wierda W, Ferrajoli A, et al. Alemtuzumab for Minimal Residual Disease in CLL. [abstract]. Blood. 2003;102(11): A371.
24. Liggett WH, Hainsworth JD, Spigel DR, Meluch AA, Raefsky EL, Kennedy S, et al. Fludarabine/rituximab (FR) followed by alemtuzumab as first-line treatment for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic/lymphoma: A Minnie Pearl Cancer Research Network phase II trial. [abstract]. J Clin Oncol (Meeting Abstracts) 2005 23: A6556.
25. Hillmen P, Skotnicki AB, Robak T, Mayer J, Jaksic B, Vukovic V, et al. Preliminary Safety and Efficacy Report of a Randomized Trial of Alemtuzumab vs Chlorambucil as Front-Line Therapy in 297 Patients with Progressive B-cell Chronic Lymphocytic Leukemia. [abstract]. Blood. 2004;104(11): A2505.
26. Rossi V, Montillo M, Tedeschi A, Cafto AM, Morra E. Management of Cytomegalovirus (CMV) Reactivation in B-CLL Patients Receiving Sequential Treatment with Fludarabine (FAMP) Including Regimens and Alemtuzumab. [abstract]. Blood. 2004;104(11): A2521.
27. Williams TE, Roach J, Rugg T, Brettman L. Frequency of Cytomegalovirus Pneumonia Following Alemtuzumab (Campath®) Treatment in Lymphoid Malignancies: Review of 1538 Patients. [abstract]. Blood. 2001;98(Suppl): A4923.
28. Hallek M, Stahel RA, Greil R; ESMO Guidelines Task Force. ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of chronic lymphocytic leukemia. Ann Oncol. 2005;16 Suppl 1:i50-1.
29. Oscier D, Fegan C, Hillmen P, Illidge T, Johnson S, Maguire P, et al. British Committee for Standards in Haematology. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. Br J Haematol. 2004 May;125(3):294-317.
30. Hallek M, Bergmann M, Emmerich B. Chronic lymphocytic leukaemia: up-dated recommendations on diagnosis and treatment. Onkologie. 2004;27(1):97-104.
31. Keating M, Coutre S, Rai K, Osterborg A, Faderl S, Kennedy B, et al. Management guidelines for use of alemtuzumab in B-cell chronic lymphocytic leukemia. Clinical Lymphoma 4(4):220-7.

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Evidence-based Series #6-16 Version 2: Section 3

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

Alemtuzumab in Chronic Lymphocytic Leukemia: Guideline Development and External Review—Methods and Results

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

Report Date: June 14, 2006

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series: A New Look to the PEBC Practice Guidelines

Each evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline*. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Hematology DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on alemtuzumab in chronic lymphocytic leukemia (CLL), developed through systematic review, evidence synthesis, and input from practitioners in Ontario. This document was reviewed and approved by the Hematology DSG in June 2006.

An earlier version of this draft evidence-based series was reviewed and discussed by the Hematology DSG on October 25, 2005 and again by teleconference on March 7, 2006. As indicated in the Discussion of Section 2, the DSG concluded that there was insufficient evidence to support the routine use of alemtuzumab but that, in highly selected cases, and after thorough consideration of the risks and benefits, a trial of alemtuzumab might be considered.

Report Approval Panel

The final evidence-based series report was reviewed and approved by the PEBC Report Approval Panel (RAP) in April 2006. The panel normally consists of two members, including an oncologist, with expertise in clinical and methodological issues. However, in this case, the oncologist member did not participate in the RAP review process because they were one of the authors of the report. No significant issues were raised by the other panel member, and the report was approved for distribution.

External Review by Ontario Clinicians

Following approval by DSG members, the systematic review (Section 2) and recommendations (Section 1) were circulated to Ontario practitioners for feedback. Section 3 of this evidence-based series details the results from this practitioner feedback, and any changes made to the draft report. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the DSG.

Box 1: DRAFT RECOMMENDATIONS (approved for external review April, 2006)
Target Population • This evidence summary applies to adult patients with CLL.
Recommendations In the absence of evidence from randomized controlled trials (RCTs), the Hematology DSG offers the following recommendation: • For patients with CLL, there is insufficient evidence to recommend the use of alemtuzumab outside of clinical trials. The DSG recognizes that in highly selected cases,

after thorough consideration of the risks and benefits, a trial of alemtuzumab might be considered.

Key Evidence

- Currently, there are no published RCTs evaluating alemtuzumab alone or in combination with other chemotherapeutic agents for the treatment of relapsed/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 NCI-CTC v2.0 grade III/IV infection-related toxicity in 7 of the first 11 patients randomized to the alemtuzumab arm. Patients in this arm had a significantly improved progression-free-survival (PFS) compared to observation (no progression vs. mean PFS 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% (CR 6%, PR 32%). Median time-to-progression was reported in three of these trials and ranged from 4 to 10 months.
- Seventeen studies evaluated the toxicities associated with alemtuzumab as a single-agent for the treatment of relapsed/refractory CLL:
    - 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.
    - Thrombocytopenia and neutropenia (grade III/IV) were each observed in approximately one third of patients.
    - Infections were common (46% overall), often severe (18% overall grade III/IV), and included opportunistic, systemic viral, and invasive fungal diseases despite antimicrobial prophylaxis. Cytomegalovirus 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 was observed in approximately 4-5% of patients.

Methods

The above recommendations (Section 1) were submitted with the systematic review (Section 2) to a sample of 95 hematologists in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on April 13, 2006, and a complete repeat mailing was sent thereafter.

Results

The response rate for the survey was 63 responses out of 95 questionnaires mailed (66%). Of the 63 respondents, 30 (48%) indicated they cared for patients for whom the guideline is relevant and completed the survey.

Overall, respondents showed support for the guideline (selected response data is presented in Table 1). For questions that addressed issues such as the rationale for the guideline, the quality of the guideline, and the clarity of the recommendations, a substantial majority of respondents (range 87% to 100%) expressed modest to “strong” support (1 or 2) for

the report (Scale 1 to 5, 1 = “strongly agree,” 3 = “neither agree or disagree,” 5 = “strongly disagree”).

With respect to the appropriateness of the recommendations, a majority of respondents agreed with the draft recommendations as stated (70%) and their appropriateness for the specified target population (73%). Some respondents (20%) felt that the recommendations were excessively rigid and could not be applied to individual patients.

Respondents varied in their views regarding the clinical utility of the recommendations: approximately half responded ambivalently when asked if the recommendations would produce more benefit than harm (Q11); responses varied widely on whether the recommendations provided options that would be acceptable to patients (31% agreed, 38% ambivalent, and 31% disagreed; Q12). The vast majority (69%) responded ambivalently when asked if the effect of these recommendations on patient outcomes would be obvious (Q17). When asked to compare these recommendations with current practice, approximately half of respondents felt those questions were not applicable. A majority of respondents (57%) would be comfortable with their patients receiving the care recommended in the draft document (Q20), and a sizable majority (70%) felt the draft report should be approved as a practice guideline.

Most respondents felt that implementing these recommendations would not require reorganization of their practices nor be technically challenging or expensive (67,57,62%, Q13,14,15). A majority of respondents felt the recommendations would be supported by a majority of their colleagues (52%), although many responded ambivalently (34%) (Q16).

A strong majority of respondents (79%) indicated they would use this guideline in their own practice (Q22) and apply it to their patients (83%, Q23).

Table 1. Responses to selected items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
Q2: The rationale for developing a guideline, as stated in the “Introduction” section of the report, is clear.	29 (100)		
Q3: There is a need for a guideline on this topic.	26 (87)	3 (10)	1 (3)
Q4: The literature search is relevant and complete.	28 (93)	2 (7)	
Q6: The results of the trials described in the report are interpreted according to my understanding of the data.	28 (93)		2 (7)
Q7: The draft recommendations in the report are clear.	29 (97)		1 (3)
Q8: I agree with the draft recommendations as stated.	21 (70)	4 (13)	5 (17)
Q13: To apply the draft recommendations will require reorganization of services/care in my practice setting.	1 (3)	9 (30)	20 (67)
Q14: To apply the draft recommendations will be technically challenging.	4 (13)	9 (30)	17 (57)
Q15: The draft recommendations are too expensive to apply.	2 (7)	9 (31)	18 (62)
Q19: When applied, the draft recommendations will result in better use of resources than current usual practice. *	5 (17)	9 (30)	
Q21: This report should be approved as a practice guideline.	21 (70)	3 (10)	6 (20)
	Very likely or likely	**Unsure**	**Not at all likely or unlikely**
Q22: If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	1 (4)	5 (17)	21 (79)

* 16 people (53%) responded “not applicable” to this question.

Summary of Written Comments and DSG Responses
The DSG reviewed and addressed the written feedback as follows:

- Two reviewers felt the drug should be made available to select patients. One reviewer felt that alemtuzumab should be recommended for use in patients with CLL who are resistant to fludarabine-containing combination regiments with marrow infiltration as a primary treatment indication. This reviewer noted that a response rate of 38% was observed in this sub-population in a phase II trial, and that treatment options for these patients are extremely limited.

  In its deliberations, the members of the Hematology DSG were unanimous in their view that the data included in this evidence summary were generally of low methodologic quality and were characterized by a lack of prospective comparative trials, thereby precluding the development of a definitive recommendation to use alemtuzumab in patients with CLL. However, members of the DSG acknowledged that there may be instances where patients and physicians who are well informed of the risks and uncertain net clinical benefit might prefer treatment with alemtuzumab. In addition, individual members of the DSG shared anecdotal experiences involving carefully selected patients who derived benefit from treatment with alemtuzumab. The DSG is fully aware that anecdotal clinical experience is not a basis for informing a guideline recommendation but acknowledged that such experience was consistent with available data and contributed to the general support of alemtuzumab as a reasonable option for select patients that may have few available alternatives.

- Two reviewers commented that the wording of the recommendation was unusual. One suggested specific criteria be given for the highly specific circumstances referred to in the recommendation.

  In its deliberations, the Hematology DSG acknowledged that the current wording of the draft recommendation might be viewed as contradictory and should be revised.

- Two reviewers agreed that the current recommendation was appropriate and that alemtuzumab should only be used in a clinical trial situation.

  In its deliberations, the members of the Hematology DSG felt strongly that alemtuzumab is an active agent in CLL and merits continued testing in well-designed clinical trials. The DSG felt that a recommendation for the use of alemtuzumab only in the setting of a clinical trial was too restrictive and did not take into consideration clinician or patient preferences to use alemtuzumab in selected circumstances.

Discussion

The DSG discussed the practitioner feedback and reviewed the draft recommendation at its bi-annual meeting of May 16, 2006. Feedback for this report was uniformly positive for those questions related to the report development process. In contrast, feedback relating to several aspects of clinical care were generally less positive. Some commentators noted that the initial draft recommendation could be perceived as contradictory in nature. Based upon these concerns, members of the DSG felt that the draft recommendation required revision. Following a detailed discussion, the DSG reached consensus on a revised recommendation and issued the three the qualifying statements now found in Sections 1 and 2.

The DSG remained unanimous in their view that the data for use of alemtuzumab in CLL were limited and of low methodologic quality. Therefore, the decision to revise the draft recommendation was not due to an alternate interpretation of the available data. Instead, the major basis for revision included: (1) the appreciation of DSG members that, despite no clear evidence for the inducement of durable periods of disease control or improvements in quality of life, or overall survival, patients and/or clinicians may prefer to use alemtuzumab in selected instances; inherent in this decision is an understanding that the potential risks could be substantial and the potential for benefit uncertain, and (2) the notion that some patients with few available treatment alternatives may derive benefit from treatment with alemtuzumab; this potential benefit was supported anecdotally by members of the DSG who cited specific examples of carefully selected patients who derived benefit following treatment with alemtuzumab.

In summary, the DSG has reframed the recommendation to consider alemtuzumab as a potential option for patients whose CLL is refractory to current standard options (alkylator–based therapy and fludarabine). The limitations and risks of this option are addressed in a series of Qualifying Statements.

Implications for Policy

Approximately 450 patients are diagnosed with CLL annually in Ontario. Since the natural history of CLL follows a chronic relapsing course, the disease prevalence exceeds the disease incidence. Most patients requiring therapy will eventually relapse or become refractory to currently available chemotherapeutic regimens and would be potential candidates for alemtuzumab at some point during their disease course. The introduction of alemtuzumab for the treatment of relapsed/refractory CLL could have a significant impact on cancer drug funding in Ontario. Results from RCTs demonstrating improvement in important clinical outcome measures such as response duration, survival, or quality of life are lacking.

Funding

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REFERENCES

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.

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Evidence-based Series 6-16 Version 2: Section 4

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

Alemtuzumab in Chronic Lymphocytic Leukemia

Guideline Summary Review

G. Fraser, C. Agbassi, and the Hematology Disease Site Group

The 2006 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

Review Date: November 7, 2013

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2006. In September 2011, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (GF) reviewed and interpreted the new eligible evidence and proposed the existing recommendations be endorsed. The Hematology Cancer Disease Site Group (DSG) endorsed the recommendations found in Section 1 (Clinical Practice Guideline) in November 2013.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

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?

Literature Search and New Evidence

The new search (July 2005 to July 2013) yielded nine relevant publications of one meta-analysis comparing alemtuzumab with anti-leukemic therapy and seven RCTs comparing adjuvant radiotherapy to either no adjuvant radiotherapy or to another form of adjuvant radiotherapy. An additional search for ongoing studies on Clinicaltrials.gov yielded three potentially relevant ongoing RCTs. Brief results of these searches are shown in the Document Review Tool.

Impact on Guidelines and Its Recommendations

The new data supports existing recommendations and also shows a survival benefit in patients on fludarabine plus alemtuzumab compared to fludarabine alone. Since this regimen has not evolved to become a standard of care in patients with relapsed/refractory CLL, the Hematology Cancer DSG decided to endorse the 2006 recommendations on Alemtuzumab in Chronic Lymphocytic Leukemia. This guideline will be updated to reflect the new regimen when more evidence becomes available.

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Document Review Tool

Number and title of document under review	6-16 **Alemtuzumab in Chronic Lymphocytic Leukemia**
Current Report Date	**June 14, 2006**
Clinical Expert	Dr. Graeme Fraser
Research Coordinator	Chika Agbassi
Assessment Date	Sept 2011
Approval Date and Review Outcome (once completed)	ENDORSED- November 7, 2013

Original Question(s):

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

Study Section Criteria:

Articles were selected for inclusion in this systematic review if they met the following criteria:

1. Studies included patients with CLL.
2. Studies tested the role of alemtuzumab as either induction or consolidation therapy, and either as a single agent or in combination with other therapy.
3. Results were reported for any of the following outcomes: survival, quality of life, time-to-progression, response duration, response rate, or adverse effects.
4. Trials had a minimum sample size of 20 evaluable patients.

Search Details:

- July 2005 to July 2013 (Medline week 2 and Embase week 42)
- July 2005 to July 2013 (ASCO Annual Meeting)
- July 2005 to July 2013 (ASH annual Meeting)
- July 2005 to July 2013 (Clinicaltrial.gov)

Brief Summary/Discussion of New Evidence:

Of 286 total hits from Medline + Embase and 28 total hits from ASCO + ASH conference abstract searches, 10 references representing one meta-analysis and seven RCTs comparing alemtuzumab with anti-leukemic therapy were found.

Interventions	Name of RCT (med F/U)	Population (n)	Outcomes	Brief results	References
Alemtuzumab + Anti-leukemic therapy vs. identical Anti-leukemic therapy and Alemtuzumab + Anti-leukemic therapy vs. different anti-leukemic therapy	Meta-analysis of 5 RCTs	Histologically confirmed B-cell CLL (845)	OS, PFS TTT, TRM, CRR, ORR, MRD,AE	Addition of alemtuzumab.to anti-leukemic therapy significantly improved the following: PSF (HR 0.58; 95%CI 0.44 to 0.76; p<0.0001) CRR (RR 2.61; 95%CI 1.26 to 5.42; p=0.01) However, the rates of CMV reactivation (RR 10.52; 95%CI 1.42 to 77.68; p=0.02) and all grade infection (RR 1.32; 95%CI 1.01 to 1.74; p= 0.04) were shown to be significantly higher in alemtuzumab arm. The TRM were not significantly different between arms. There was no significant difference between arms when alemtuzumab is added to a different anti-leukemic therapy.	Skoetz N. et al 2012
Alemtuzumab 10mg & 20mg two days in week 1 30mg twice a week in weeks 2 & 3, 30 mg biweekly in weeks 4-12 and monthly from week 16-52	(27mos)	Relapsed/refractory CLL Age ≥ 18 yrs ECOG PS <3 (n=62)	OS, ORR Toxicity	OS was 46% at 3 years and ORR was shown to be 95% with 51% CR.	Bezares R. et al 2011
HDMP-R. →Alemtuzumab(3 doses/W for 8W)	(46mos)	Evidence of MRD after induction Med Age= 60yrs 81% in Rai stage III-IV (n=21)	PFS CRR, toxicity	81% achieved CR and no evidence of MRD was found in 71% of those that achieved CR. Median PFS was 63 mos (range 6-84mos) for all patients	Castro J.E et al 2011 [ABSTRACT]

Cyclophosphamide (250mg/m^2) + Fludarabin (25mg/m^2) + Rrituximab (375mg/m^2) →Alemtuzumab (30mg d1,3,5)		Relapsed/refractory CLL Age range 39-79yrs (n=80)	ORR, OS, PFS,	ORR was 65% including 29% complete response. The PFS was estimated to be 10.6 mos and the median OS was 16.7 mos	Badoux X. et al 2011
6 courses of CFAR: Fludarabin (20mg/m^2 d3-5q4W) + Cyclophosphamide (200mg/m^2 d3-5q4W) + Rrituximab (375mg/m^2 d2 or 500m/m^2 d2-6 q4W) + Alemtuzumab (30mg/m^2 d1,3,5 q4W)	(25mos)	Previously untreated CLL β2M ≥ 4mg/L ECOG PS = 0-2 Age range 42-69yrs (n=60)	PFS,OS	CFAR was shown to be an active frontline regimen for high risk CLL with a median PFS of 38mos and a median OS that was not reached.	Parikh S. et al 2011
Alentuzumab + Fludarabin (30/30mg/m^2 d1-3 q4W x6cycles) vs Fludarabin (25mg d1-5 q4W x6cycles)	Sub group analysis of those with Rai stage III-IV (21mos)	Relapsed/refractory CLL Rai stage III-IV Median age= 65yrs (n=123)	PFS, ORR, OS, CR, SAFETY	Alemtuzumab arm was significantly better in the ORR (77% vs 56%) p= 0.016 and CR (16% vs. 3%) p= 0.014; Alemtuzumab arm also showed a 56% reduction in risk of death. With a median f/u of 21mos OS was significantly better in the alemtuzumab arm; median not reached at f/u vs. 23.5mos in the fludarabin arm; p= 0.005; HR: 0.44; 95%CI 0.24-0.79. There was no significant difference in the AE profile between arms.	Engert et al 2010 [ABSTRACT]
	(29.5)	Relapsed/refractory CLL Binet stage A, B,C or Rai stage I-IV ECOG PS ≤ 1 Age≥ 18yrs (n=335)		Alamtuzumab arm significantly prolonged the PFS 23.7mos vs 16.5mos in the fludarabin arm. P= 0.0003; HR: 0.61 (95%CI 0.47-0.80). With a median f/u of 29.5mos for all enrolled patient, OS was significantly better in the alemtuzumab arm; median not reached at f/u vs. 52.9mos in the fludarabin arm; p= 0.02; HR: 0.65; 95%CI 0.45-0.94. Serious AE incidence was higher in the combination therapy group but death due to AE was similar between arms.	Elter T. et al 2011
Alentuzumab 30mg 3x/W for 12W vs. No treatment	CLL4B (48mos)	CLL in complete/partial remission Previous treatment with CF Age range 18-65yrs	PFS	The PFS was significantly better in those receiving alemtuzumab consolidation compared to those without further treatment. P=0.004	Shweighofer C. et al 2009
6 cycles of Fludarabin (25mg/m^2 d1-5) + Rituximab (50 mg/m^{2}d1; 325mg/m^2 d3; 375mg/m^2 d5 of cycle 1 and d1 of cycle 2-5) repeated q4W → 18 doses of Alemtuzumab (3mg d1, 10mg d3, 30mg d5, and then 3x/W x6W).	(34mos)	Median age= 61yrs (n=102)	PFS, ORR, CRR, PR	ORR, CRR and PR rates were 91%, 66% and 26% respectively with 50% achieving MRD negative 62% of patients in PR after FR attained CR with Alemtuzumab Median PFS was 37mos (95% CI, 33-43 mos) but 2 years PFS and OS were not significantly different between those who did and those who did not receive alemtuzumab after FR Alemtuzumab significantly resulted in significant infection	Lin TS. et al 2009 [ABSTRACT]
Alemtuzumab (30mg 3x/W) vs. Chlorambucil (40mg/m q4W x12mos)		(n=297)	PFS, ORR, OS, CRR, TTT, safety	Compared with chlorambucil, PFS was significantly better in the alemtuzumab arm with a 42% reduction in risk of progression or death. HR=0.58 P=0.00001 ORR was 83% with a 24% CR in alemtuzumab arm versus 55%with 2% CR in chlorambucil. P<0.0001 Serious AE were more common in the alemtuzumab arm.26.5% versus 6.8% in chlorambucil arm.	Hillmen P. et al 2007

On Going trials Retrieved from www.clinicaltrial.gov				
Interventions	**Official title**	**Status**	**Protocol ID**	**Last Updated**
Bendamustine Plus Alemtuzumab	A Phase I Trial of Bendamustine Plus Alemtuzumab for the Treatment of Fludarabine Refractory Chronic Lymphocytic Leukemia	ongoing, not recruiting	NCT00947388	January 22, 2013
Alemtuzumab-Ofatumumab	A Phase 2 Trial of Alemtuzumab-Ofatumumab Combination in Previously Untreated Symptomatic Chronic Lymphocytic Leukemia	recruiting	NCT01361711	August 11, 2011
Rituximab and Alemtuzumab	A Phase II Randomized Trial Comparing Standard and Low Dose Rituximab: Initial Treatment of Progressive Chronic Lymphocytic Leukemia in Elderly Patients Using Alemtuzumab, and Rituximab	recruiting	NCT01013961	December 4, 2012

→**=** followed b**y; AE=** adverse event; **C=** cyclophosphamide; **CLL=** Chronic Lymphocytic leukemia; **CRR** = complete response rate; **d**= days; **ECOG** = Eastern Cooperative Oncology Group; **F=** Fludarabine; **HDMP-R**= high-dose methylprednisolone with rituximab; **HR** = harzard ratio; **Med**= median; **Mos**= months; **MRD=** minimal residual disease; **n**= number enrolled; **ORR** = overall response rate; **OS** = overall survival; **PR** = partial response; **Prev**= Previous; **PFS** = progression free survival; **TTT** = time to treatment; **TRM =** Treatment related mortality; **W**= week(s); **Yrs**= Year(s)

Clinical Expert Interest Declaration:

No potential conflict of interest was declared by the clinical expert.

Instructions. Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?	NO
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?	a) YES b) The updated literature search contains a randomized controlled trial showing a survival benefit in patients with relapsed/refractory CLL randomized to fludarabine + alemtuzumab compared to fludarabine alone. This is not a regimen that has evolved to become a standard of care yet but it cannot be ignored. An evidence based guideline on alemtuzumab in CLL is probably not complete without this data explicitly addressed.
3. Is there a good reason (e.g., new stronger evidence	NO

will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	Not applicable.

Review Outcome	ENDORSED
DSG/GDG Approval Date	November 7, 2013
DSG/GDG Commentary	No Comments.

New References Identified (alphabetic order):

1. Badoux, X.C., et al., Cyclophosphamide, fludarabine, alemtuzumab, and rituximab as salvage therapy for heavily pretreated patients with chronic lymphocytic leukemia. Blood, 2011. 118(8): p. 2085-2093.
2. Bezares, R.F., et al., Multicenter study of subcutaneous alemtuzumab administered at reduced dose in patients with fludarabine-relapsed/refractory chronic lymphocytic leukemia: Final analysis. Leukemia and Lymphoma, 2011. 52(10): p. 1936-1941.
3. Castro, J.E., et al., Eradication of Minimal Residual Disease Using Alemtuzumab Consolidation After High-Dose Methyl-Prednisolone Plus Rituximab (HDMP-R) Is Safe, Effective and Induces Long Term Remission
4. Elter, T., et al., Fludarabine plus alemtuzumab versus fludarabine alone in patients with previously treated chronic lymphocytic leukaemia: a randomised phase 3 trial. Lancet Oncology, 2011. 12(13): p. 1204-13.
5. Hillmen, P., et al., Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. Journal of Clinical Oncology, 2007. 25(35): p. 5616-23.
6. Lin, T.S., et al., Consolidation Therapy with Subcutaneous (SC) Alemtuzumab After Fludarabine and Rituximab (FR) Induction Therapy Improves the Complete Response (CR) Rate in Chronic Lymphocytic Leukemia (CLL) and Eradicates Minimal Residual Disease (MRD) but Is Associated with Severe Infectious Toxicity: Final Analysis of CALGB Study 10101. ASH Annual Meeting Abstracts, 2009. 114(22): p. 210.
7. Parikh, S.A. and W.G. Wierda, Role of cd20 monoclonal antibodies in previously untreated chronic lymphocytic leukemia. Clinical Lymphoma, Myeloma and Leukemia, 2010. 10(SUPPL. 1): p. S27-S33.
8. Schweighofer, C.D., et al., Consolidation with alemtuzumab improves progression-free survival in patients with chronic lymphocytic leukaemia (CLL) in first remission: long-term follow-up of a

randomized phase III trial of the German CLL Study Group (GCLLSG). British Journal of Haematology, 2009. 144(1): p. 95-8.
9. Skoetz, N., et al., Alemtuzumab for patients with chronic lymphocytic leukaemia. Cochrane Database of Systematic Reviews, 2012. 2: p. CD008078.

Literature Search Strategy:

Medline

1. meta-Analysis as topic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/

26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.

27. (allocated adj2 random).tw.

28. or/23-27

29. practice guidelines/

30. practice guideline?.tw.

31. practice guideline.pt.

32. or/29-31

33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32

34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.

35. 33 not 34

36. exp chronic lymphocytic leukemia/

37. (alemtuzumab or lemtrade or compath).mp.

38. 36 and 37

39. 35 and 38

40. (200507$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or "201210").ed.

41. 39 and 40

42. limit 41 to humans

Embase

1. exp meta analysis/ or exp systematic review/

2. (meta analy$ or metaanaly$).tw.

3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.

4. (systematic adj (review$ or overview?)).tw.

5. exp review/ or review.pt.

6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.

7. (study adj selection).ab.

8. 5 and (6 or 7)

9. or/1-4,8

10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.

11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.

12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/

13. randomization/ or single blind procedure/ or double blind procedure/

14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
30. 28 not 29
31. exp chronic lymphocytic leukemia/
32. (alemtuzumab or lemtrade or compath).mp.
33. 31 and 32
34. 30 and 33
35. (200525$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or "201242").ew.
36. 34 and 35
37. limit 36 to human

OUTCOMES DEFINITION

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word “ARCHIVED”.

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DELAY –** A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.