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CED-CCO Advice Report 6-22

Alemtuzumab for the Treatment of T-cell Prolymphocytic Leukemia

G. Fraser, A.E. Haynes, C.T. Kouroukis, and K. Imrie

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

Report Date: January 2007

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SUMMARY

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 T-cell prolymphocytic leukemia (T-PLL)?
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

These recommendations apply to adult patients with T-PLL.

Recommendations

With the recognition that evidence from randomized controlled trials (RCTs) is unlikely to become available in the future, owing to disease rarity, the authors offer the following recommendations:

- For patients with previously untreated T-PLL who are candidates to receive therapy, treatment with alemtuzumab is recommended as the preferred treatment option.

- For patients with relapsed/refractory T-PLL who are candidates for further therapy, alemtuzumab should be considered.

Qualifying Statements

- The evidence supporting treatment with alemtuzumab comes 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 remain speculative.
- The authors recommend the use of appropriate premedications, dose escalation, and antimicrobial prophylaxis as outlined in the product monograph. The recommended target

dose is 30mg administered three times per week to a maximum of 12 weeks. Subcutaneous administration is associated with reduced infusion related toxicity and may be preferred over the intravenous route.

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 T-PLL.

- Eight single-arm studies evaluated disease response for alemtuzumab as a single agent in the treatment of patients with relapsed/refractory T-PLL. The pooled overall response rate was 57% (complete response [CR] 43%, partial response [PR] 14%). Median time-to-progression was reported in four of those trials and ranged from three to 24 months.

- In a subset of previously untreated patients, complete remission rate was 95%.

- Five studies evaluated the toxicities associated with alemtuzumab as a single agent for the treatment of relapsed/refractory T-PLL:
  - The most common adverse events were mild infusion-related side effects (e.g., fever, rigours, rash, nausea), which occurred in the majority of patients; serious infusion-related toxicities were uncommon
  - Grade III/IV neutropenia and thrombocytopenia occurred in approximately 17% and 32% of patients, respectively.
  - Infections occurred in approximately one quarter of patients receiving alemtuzumab for T-PLL; the risk of cytomegalovirus (CMV) reactivation is not well described.

Future Research

Future studies should focus on evaluating alemtuzumab in combination with other active agents in first line, and consolidation/maintenance strategies. The German Chronic Lymphocytic Leukemia (CLL) Study Group is conducting a Phase II study investigating alemtuzumab consolidation following fludarabine/cyclophosphamide/mitoxantrone induction for patients with newly diagnosed or relapsed T-PLL. No other pending or active protocols were found.

Related Guidelines

- Evidence-based Series #6-16: *Alemtuzumab in Chronic Lymphocytic Leukemia*.

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FULL REPORT

I. 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 T-cell prolymphocytic leukemia (T-PLL)?
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?

II. CHOICE OF TOPIC AND RATIONALE

T-cell prolymphocytic leukemia is an extremely rare, aggressive malignancy of post-thymic T lymphocytes with characteristic clinical, immunophenotypic, and molecular features. Disease incidence is estimated to be less than 1 per million; thus, only a few cases are diagnosed each year in Ontario. Disease hallmarks include rapidly progressive leukocytosis, lymphadenopathy, marked splenomegaly, and a predilection for effusions and cutaneous tropism. Resistance to conventional chemotherapy is common, and median overall survival is approximately six to eight months (1). Drugs that interfere with nucleoside metabolism (2'deoxycoformycin (pentostatin), fludarabine) are generally regarded as the most active chemotherapeutic agents in this disease. In a large, retrospective study, Mercieca et al described outcomes in 55 patients treated with 2'deoxycoformycin; 15 patients in this cohort had previously untreated T-PLL, while 40 had received prior chemotherapy, most commonly an alkylator-based regimen (2). Overall response (RR) and complete response rates (CR) were reported in 45% and 9%, respectively, and were similar across the previously untreated and relapsed/refractory cohorts (RR 46% versus [vs.] 45%, respectively). Alkylator-based regimens commonly used to treat aggressive histology non-Hodgkin's lymphoma (e.g., cyclophosphamide, vincristine, doxorubicin, prednisone [CHOP]) have shown similarly disappointing results.

Monoclonal antibodies are an emerging class of drugs with a unique mechanism of action. Alemtuzumab, a humanized anti-CD52 monoclonal antibody, was the first of this class of drugs to receive the United States Food and Drug Administration (FDA) approval for the treatment of patients with chronic lymphocytic leukemia (CLL) as relapsed or refractory to fludarabine; it has recently been approved in Canada for the same indication. 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. Recently, alemtuzumab has been evaluated in patients with T-PLL because CD52 is densely expressed on the cell membrane of the malignant clone. Preliminary results suggest alemtuzumab is an active agent in T-PLL; objective clinical responses are obtained in many patients, including a substantial number of complete responses in patients refractory to standard first-line regimens. Based upon these reports, the desire to use alemtuzumab in this select group of patients is likely to be high among physicians in Ontario. However, the benefits of alemtuzumab are offset by potential toxicities, including infection-related morbidity and mortality. Therefore, the authors felt a systematic review of available literature was needed.

III. METHODS

This advice report, produced by the Program in Evidence-based Care (PEBC), is a convenient and up-to-date source of the best available evidence on the role of alemtuzumab in the treatment of T-PLL developed through systematic reviews of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

The PEBC has a formal standardized process to ensure the currency of each clinical guidance report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original clinical guidance report information.

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 November 2006), EMBASE (1980 to November 2006) and the Cochrane Library (November 2006) databases were searched according to the strategy shown in Table 1. This search strategy includes terms for CLL as the current advice report was initially planned to be part of an update for Evidence-Based Series (EBS) #6-16 *Alemtuzumab in Chronic Lymphocytic Leukemia*. However, the Hematology Disease Site Group (DSG) decided that the use of alemtuzumab in patients with T-PLL should be addressed in a separate document from EBS #6-16. Abstracts from the American Society of Hematology (ASH) (1996-2006) and the American Society of Clinical Oncology (ASCO) (1995-2006) annual conference proceedings were also 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.

Relevant articles and abstracts were selected and reviewed by one reviewer (GF), and the reference lists from those sources were searched for additional trials.

Table 1. Literature search strategy

Search date	Database	Search terms used
November 2006	MEDLINE	Text words: campath, alemtuzumab, cd52, anti-cd52, PLL, T-PLL, prolymphocytic leukemia MeSH terms: lymphoproliferative disorders
November 2006	EMBASE	Text words: campath, alemtuzumab, PLL, prolymphocytic leukemia EMTREE terms: alemtuzumab, lymphatic leukemia, t cell leukemia, prolymphocytic leukemia
November 2006	Cochrane Library	alemtuzumab, campath, PLL, prolymphocytic leukemia
November 2006	ASCO Abstracts ASH Abstracts	campath, campath-1H, alemtuzumab, PLL, T-PLL, prolymphocytic leukemia

Note: MeSH=Medical Subject Heading, EMTREE=Excerpta Medica Tree term.

Inclusion Criteria

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

1. Studies included patients with T-PLL.
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 for the treatment of T-PLL.
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 10 evaluable patients.

Exclusion Criteria

1. Letters and editorials were not eligible.
2. Reports were published in a language other than English.

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.

IV. RESULTS

Literature Search Results

A total of 698 citations were retrieved from the MEDLINE, EMBASE, and Cochrane Library databases and the conference proceedings of ASCO and ASH. Upon removal of duplicates, nine citations met the inclusion criteria. No evidence-based guideline documents or systematic reviews were found. Eligible publications were all single-arm studies or retrospective studies (five full papers, four abstracts) that evaluated alemtuzumab as a single agent in patients with previously untreated or relapsed/refractory T-PLL (Table 2).

Table 2: Characteristics of included studies.

Citation	T-PLL Population (N)	Study Design	Median # lines prior therapy (range)	Best Response to Prior Therapy	Citation Type
Ravandi, 2005 (3)	Relapsed/ Refractory (33) Previously Untreated (23)	Single-centre, retrospective	2 (1-6)	NR	Full paper
†Dearden, 2002 (4)	Relapsed/ Refractory (39) Previously untreated (5)	Multi-centre, prospective, single-arm	NR	NR	Abstract
Dearden, 2001 (5)	Relapsed/ Refractory (37) Previously Untreated (2)	Multi-centre, prospective, single-arm	2 (0-4)	CR=0% PR=33%	Full paper
‡Keating, 2002 (6)	Relapsed/ Refractory (72) Previously Untreated (4)	Multi-centre, retrospective	2 (0-5)	CR=6% PR=26%	Full paper
Coutre, 2001 (7)	Relapsed/ Refractory (38)	Multi-centre, single arm	3 (1-7)	NR	Abstract
Rai, 2002 (8)	Relapsed/ Refractory (36)	Multi-centre, single arm	NR	NR	Abstract
Ferrajoli 2003 (9)	Relapsed/ Refractory (18)	Single-centre, single arm	NR (≥ 1)	NR	Full paper
Pawson 1997 (10)	Relapsed/ Refractory (15)	Single-centre, retrospective	2 (1-4)	CR=0% PR=47%	Full paper
Dearden 2003 (11) abstract	Previously Untreated (11)	Single-centre, single arm	0	N/A	Abstract

Note: N=number of patients, NR=not reported, CR=complete remission, PR=partial remission, T-PLL=T-cell prolymphocytic leukemia.
†Update of data contained in Dearden et al, 2001 (5); includes data on five additional patients.
‡Includes data on 18 patients included in Dearden et al, 2001 (5).

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 T-cell prolymphocytic leukemia?

Response Rate

The overall response (RR), complete response (CR), and partial response (PR) rates associated with alemtuzumab for the treatment of T-PLL are summarized in Table 3 and include data from nine studies (N=268). Most trials evaluated a standard 12-week course of alemtuzumab administered intravenously three times per week. The combined response rate across studies was 57% (range 24-77%) in patients with relapsed/refractory disease (N=248); combined CR and PR rates were 43% (14-60%) and 14% (10-17%), respectively.

Response to previous therapy was described in two studies (5,6). Dearden et al (5) reported a best response to prior therapy of 33% (0% CR, 33% PR); previous therapies included fludarabine and/or pentostatin (85%), and alkylator-based regimens (35%). Keating et al (6) reported a 32% response rate to first-line therapy (6% CR, 26% PR) in a similarly treated group of patients (fludarabine and/or pentostatin in 84%). Two additional studies compared patients treated with alemtuzumab with a historical cohort of patients treated with conventional

chemotherapy (3,10). An increased frequency of complete and overall responses was observed following treatment with alemtuzumab in both studies.

Three studies (4,6,11) included previously untreated patients and reported their response to alemtuzumab separately (combined N=20). Complete remission was reported in 19 of 20 patients (95%) receiving first-line treatment with alemtuzumab.

Response Duration

Data on median time-to-progression in patients with relapsed/refractory disease were reported in four studies and ranged from 3.3 to 10 months. One study (6) reported an improvement in median time to progression following alemtuzumab for relapsed/refractory disease (4.5 months) compared with previous first-line therapy (2.3 months); in this instance, first-line therapy most often consisted of pentostatin (41%) or a nucleoside analogue (24%).

One study (11) reported median time-to-progression greater than 10 months in a previously untreated cohort of patients.

Overall Survival

Data on median overall survival in patients with relapsed/refractory disease were reported in four studies and ranged from 5.8 months to 24 months. In a retrospective analysis, Ravandi et al (3) reported improved survival in patients treated with alemtuzumab compared with a historical cohort of patients treated with conventional chemotherapy (24 months vs. six months, P=0.002). Baseline characteristics of patients included in the alemtuzumab cohort are not well described; however, it is likely that some patients were treated with alemtuzumab in first line. Dearden et al (5) reported a median overall survival of 16 months in patients achieving a CR compared with nine months and four months for patients achieving a PR and no response, respectively (p=0.0007).

In one study (11) evaluating alemtuzumab as first-line therapy for previously untreated patients, median overall survival had not been reached at 12 months.

Table 3. Responses to alemtuzumab for T-PLL.

Trial (ref)	Intervention	Prior therapy	N (evaluable)	% Response			TTP (mo)	OS (mo)
				RR	CR	PR		
Ravandi 2005 (3)[†]	A: NR	Relapsed/ refractory	19 (19)	47	42	5	NR	24 (p=0.002)
	Other[†]		38 (30)	17	10	7	NR	6
Dearden 2002 (4) abstract	A: 30mg IV TIW to max response	Relapsed/ refractory	39 (38)	74	59	15	10	NR
		Previously untreated	5 (5)	100	100	0		
Dearden 2001 (5)	A: 30mg IV TIW to max response	Relapsed/ refractory	37 (36)	75	58	17	7	10
		Previously untreated	2 (2)	100	100	0		
Keating 2002 (6)	A: 30mg IV TIWx12 wk	Relapsed/ refractory	72 (72)	50	38	12	4.5	7.5
		Previously untreated	4 (4)	75	75	0		
Coutre 2001 (7) abstract	A: 30mg IV TIWx12 wk	Relapsed/ refractory	39 (38)	32	16	16	3.3	5.8
Rai 2002 (8) abstract	A: 30mg IV TIWx12 wk	Relapsed/ refractory	36 (29)	24	14	10	NR	NR
Ferrajoli 2003 (9)	A: 30mg IV TIWx12 wk	Relapsed/ refractory	18 (18)	55	44	11	NR	NR
Pawson 1997 (10) [‡]	A: 30mg IV TIWx6 wk	Relapsed/ refractory	15 (15)	73	60	13	NR	NR
	DCF: 4mg/m^2 q1-2 wk		25 (25)	40	12	28		
Dearden 2003 (11) abstract	A: 30mg IV TIW to max. response	Previously untreated	11 (11)	100	100	0	10+ (range 2-25 mo)	12+

Note: A=alemtuzumab, CLL=chronic lymphocytic leukemia, CR=complete response rate, DCF=2'deoxycoformycin, IV=intravenously, NR=not reported, OS=overall survival, PR=partial remission rate, RR=overall response rate, TIW=three times per week, TTP=time to progression, T-PLL=T-cell prolymphocytic leukemia.

[†]Non-randomized, retrospective report of patients treated at a single institution over an 18-year period. Details of treatment were not provided. 'Other' regimens included fludarabine (N=8), 2-CdA (N=6), Nelarabine (N=9), BCX-1777 (N=2), Ifosfamide (N=1), and Hyper-CVAD (N=1).

[‡]Non-randomized, retrospective cohort study.

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

Toxicities associated with the administration of alemtuzumab were reported in four studies and included data from 168 patients (Table 4). In general, toxicities were poorly described. The most common adverse events can be broadly grouped into: (i) infusion-related side effects, (ii) myelosuppression, and (iii) infection-related toxicities.

Infusion Related Toxicity

Infusion-related adverse events were reported in four studies (5-7,10). They were common, usually grade I/II in severity, and manageable with appropriate supportive care. Alemtuzumab was administered intravenously in all studies; pre-treatment with acetaminophen and antihistamines to reduce the incidence and severity of infusion-related side effects was described in two studies (5,6).

Myelosuppression

The combined incidence of grade III/IV neutropenia and thrombocytopenia reported across studies was 17% (range 8-20) and 41% (15-41), respectively. In general, myelosuppression related to alemtuzumab was transient; however, four cases (3.4%) of prolonged pancytopenia, possibly related to alemtuzumab treatment and requiring discontinuation of treatment, were reported. The use of hematopoietic growth factors was not described.

Table 4: Toxicities associated with alemtuzumab for T-PLL.

Trial (ref)	N (evaluable)	Prophylactic Antimicrobials	Infusion-Related (Grade III/IV%)	Cytopenias, Grade III/IV %		Infections % (Grade III/IV%)	CMV %[1] (Disease %)
				Neutropenia	Thrombo-cytopenia		
Ravandi 2005 (3)	57 (49)	NR	NR	NR	NR	NR	NR
Dearden 2002 (4) abstract	44 (44)	Cotrimoxazole Acyclovir	NR	NR	NR	NR	NR
Dearden 2001 (5)	39 (39)	Cotrimoxazole Acyclovir	Grade I/II: 100 (0)	8	15	21 (NR)	3 (0)
Keating 2002 (6)	76 (76)	Septra Famciclovir	Fever 62 (1) Rigor 54 (5) Rash 21 (4) Hypotension (1) Dyspnea (1)	20	41	13 (3)	4(NR)
Coutre 2001 (7) abstract	38 (38)	Septra Famciclovir	Rigor 74 Fever 55 Nausea 42	18	26	34 (18)	NR
Rai 2002 (8) abstract	187 CLL (152) 36 T-PLL (29)	NR	NR	NR	NR	NR	NR
Ferrajoli 2003 (9)	18 (18)	Septra Valacyclovir	NR	NR	NR	NR	NR
Pawson 1997 (10)	15 (15)	Cotrimoxazole Acyclovir	Fever 100 Rigor 100	NR	NR	33 (NR)	7 (0)
Dearden 2003 (11) abstract	11 (11)	NR	NR	NR	NR	NR	NR

Note: CLL=chronic lymphocytic leukemia, CMV=cytomegalovirus, N=number of patients, NR=not reported, ref=reference, T-PLL=T-cell prolymphocytic leukemia.

[1] Routine CMV monitoring was not reported in any study.

Infectious complications

Six studies (4-7) reported routine administration of antimicrobial prophylaxis against *Pneumocystis carinii* pneumonia (Cotrimoxazole) and herpes virus infections (acyclovir or famciclovir). The per capita incidence of all infections during alemtuzumab therapy was 23 per 100 patients across studies (range 13 to 34 per 100 patients). The incidence of Grade III/IV infections was reported in two studies and ranged from three to 18 per 100 patients; one infection-related death was reported across studies. Reported infections included five cases of pneumonia, four cases of CMV reactivation, two cases each of *Pneumocystis* pneumonia and *Varicella zoster* infection, and one case each of cryptococcal meningitis and *Legionella* pneumonia. CMV reactivation was not routinely monitored for in any study. Five cases of CMV reactivation were reported across studies; there were no reports of CMV pneumonitis or CMV-related deaths.

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. Dearden et al (5) noted that patients with bulky lymphadenopathy, effusions, or central nervous system (CNS) involvement tended to have a poor response to therapy. No statistical difference in response according to patient age, sex, baseline white blood cell (WBC) count, baseline immunophenotype, or karyotype was found, although specific inferences were limited by sample size.

V. INTERPRETIVE SUMMARY

In their deliberations, the authors placed 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 the quality of life, and (c) the potential toxicities associated with treatment, with particular emphasis on those toxicities seen in patients most likely to make up the eventual population treated. In developing this Advice Document, the authors are aware that available evidence is of lower methodologic quality and recognize that this is principally related to disease incidence/prevalence. Furthermore, data from large RCTs are not expected, owing to disease rarity.

The authors are also aware that recommendations contained in this document differ from those offered in EBS #6-16: *Alemtuzumab in Chronic Lymphocytic Leukemia*. In contrast to T-PLL, B-cell CLL is a common disorder with a unique disease biology. Several effective treatment options have been clearly established based on meta-analysis data and large RCTs. In patients with heavily pretreated and refractory disease, alemtuzumab is associated with PRs in a minority of patients, few CRs, and the potential for significant toxicity. Several ongoing studies, including RCTs, offer the potential to better define the risks and benefits associated with alemtuzumab for the treatment of CLL. The authors judged the evidence contained in this report as sufficient to inform best practice and developed their recommendations based on the considerations outlined below.

The authors regard alemtuzumab to be an active agent in T-PLL. This conclusion is based primarily on response rates from single-arm studies that report responses in approximately half of heavily pretreated patients and recognizes that most responses are complete remissions. In formulating their recommendations, the authoring group also considered several other factors. First, treatment with alemtuzumab for relapsed/refractory disease was associated with higher response rates compared with responses to previous standard first-line therapy. Second, compared with historical controls treated with nucleoside

analogues, treatment with alemtuzumab is associated with improved rates of complete remission and potentially improved survival; the authors are aware of the limitations and inherent biases associated with interpreting data from historical cohort comparisons. Third, complete remissions were reported for 95% of previously untreated patients; these results suggest alemtuzumab to be the most active single agent for the treatment of T-PLL. Fourth, few effective alternative treatments are available to this patient population. The authors recognize that alemtuzumab as a single agent is not likely to be curative; however, the high rate of complete remissions, potential for improved response duration, and potential to facilitate definitive treatment (i.e., allogeneic stem cell transplantation) are likely to be of considerable benefit to this patient population.

VI. RECOMMENDATIONS AND EVIDENCE

Recommendations

With the recognition that evidence from randomized controlled trials (RCTs) is unlikely to become available in the future owing to disease rarity, the authors of this advice report offer the following recommendations:

- For patients with previously untreated T-PLL who are candidates to receive therapy, treatment with alemtuzumab is recommended as the preferred treatment option.

- For patients with relapsed/refractory T-PLL who are candidates for further therapy, alemtuzumab should be considered.

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 remain speculative.

- The authors recommend the use of appropriate premedications, dose escalation, and antimicrobial prophylaxis as outlined in the product monograph. The recommended target dose is 30mg administered three times per week to a maximum of 12 weeks. Subcutaneous administration is associated with reduced infusion related toxicity and may be preferred over the intravenous route.

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 T-PLL.

- Eight single-arm studies evaluated disease response for alemtuzumab as a single agent in the treatment of patients with relapsed/refractory T-PLL. The pooled overall response rate was 57% (complete response [CR] 43%, partial response [PR] 14%). Median time-to-progression was reported in four of those trials and ranged from three to 24 months.

- In a subset of previously untreated patients, complete remission rate was 95%.

- Five studies evaluated the toxicities associated with alemtuzumab as a single agent for the treatment of relapsed/refractory T-PLL:

- The most common adverse events were mild infusion related side-effects (fever, rigors, rash, nausea), which occurred in the majority of patients; serious infusion related toxicities were uncommon
- Grade III/IV neutropenia and thrombocytopenia occurred in approximately 17% and 32% of patients respectively.
- Infections occurred in approximately one quarter of patients receiving alemtuzumab for T-PLL; the risk of CMV reactivation is not well described.

Future Research

Future studies should focus on evaluating alemtuzumab in combination with other active agents in first line, and consolidation/maintenance strategies. The German CLL Study Group are conducting a Phase II study investigating alemtuzumab consolidation following fludarabine/cyclophosphamide/mitoxantrone induction for patients with newly diagnosed or relapsed T-PLL. No other pending or active protocols were found.

Related Guidelines

- EBS #6-16: *Alemtuzumab in Chronic Lymphocytic Leukemia*.

VII. CONFLICTS OF INTEREST

The authors of this report declared that there were no potential conflicts of interest related to the topic of this CED/CCO advice report.

VIII. ACKNOWLEDGEMENTS

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