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CED-CCO Special Advice Report 15 EDUCATION AND INFORMATION 2013

Rituximab in Chronic Lymphocytic Leukemia

M. Cheung, R. Tey, and A. Haynes

Report Date: November 18, 2009

This CED-CCO Special Advice Report 15 was put in the Education and Information section in 2013. This means that the recommendations 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).

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SUMMARY

QUESTIONS

1. How does rituximab in combination with fludarabine and cyclophosphamide compare with fludarabine-cyclophosphamide and other standard of care regimens (e.g., chlorambucil) for first-line or greater treatment of patients with chronic lymphocytic leukemia (CLL)?

2. Which patients are most likely or less likely to benefit from rituximab?

3. What evidence is available to support the use of rituximab with other agents in CLL?

4. List the toxicities expected from treatment.

TARGET POPULATION

Patients with CLL.

RECOMMENDATIONS

The following recommendations reflect the opinions of the authors of this special advice report:

- In patients with previously untreated CLL who are being considered for fludarabine-based chemotherapy, it is recommended that this treatment be given in combination with rituximab.

- In patients with relapsed or refractory CLL who are being considered for fludarabine-based chemotherapy, it is recommended that this treatment be given in combination with rituximab.

QUALIFYING STATEMENTS

- In patients with CLL, rituximab should be administered at an initial dose of 375 mg/m^2 with the first cycle of fludarabine-based chemotherapy, and at a dose of 500 mg/m^2 with subsequent cycles of chemotherapy.

KEY EVIDENCE

- Two phase III randomized controlled trials (RCTs), reported in abstract form, compared fludarabine and cyclophosphamide chemotherapy with and without rituximab in patients with CLL (1, 2). Both studies showed that rituximab-containing chemotherapy led to a benefit in progression-free survival, overall response rate, and complete response rate, but not overall survival.
- One phase II RCT, reported in abstract form, compared fludarabine, cyclophosphamide, and mitoxantrone chemotherapy with and without rituximab (3). This study reported a higher overall response rate and complete response rate with rituximab-containing chemotherapy.
- The addition of rituximab to fludarabine-based chemotherapy did not appear to add significant incremental toxicity to the baseline toxicity.
- These recommendations are based on the assumption that the final reported data will be very similar to that reported in the conference abstracts.

FUTURE RESEARCH

One ongoing open-label, phase III RCT was identified that compares rituximab added to fludarabine and cyclophosphamide chemotherapy with alemtuzumab added to fludarabine and cyclophosphamide (4).

IMPLICATIONS FOR POLICY

In August 2009, Health Canada approved the use of rituximab in combination with fludarabine and cyclophosphamide in previously untreated CLL, based on an improvement in progression-free survival in a large phase III randomized-controlled trial (RCT) (5). In Ontario, the age-adjusted annual incidence rate for CLL is five per 100 000 people, with the incidence increasing to 22 per 100 000 after 65 years of age, based on 2005 data (6). Because current treatment options are not very effective, chemotherapy in combination with rituximab presents a new strategy for treating patients with CLL.

RELATED PROGRAM IN EVIDENCE-BASED CARE GUIDELINES

Evidence-based Series

- #6-8: *Rituximab in Lymphoma and Chronic Lymphocytic Leukemia*.
  Available at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34317

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FULL REPORT

QUESTIONS

1. How does rituximab in combination with fludarabine and cyclophosphamide compare with fludarabine-cyclophosphamide and other standard of care regimens (e.g., chlorambucil) for first-line or greater treatment of patients with chronic lymphocytic leukemia (CLL)?

2. Which patients are most likely or less likely to benefit from rituximab?

3. What evidence is available to support the use of rituximab with other agents in CLL?

4. List the toxicities expected from treatment.

INTRODUCTION

CLL is the most common form of leukemia that affects adults. In 2005, the age-adjusted annual incidence rate for CLL was five per 100 000 people in Ontario, with the incidence increasing to 22 per 100 000 after 65 years of age and with men twice more likely than women to develop CLL (1). Conventional chemotherapy remains ineffective for CLL, and current treatment options include alkylators or purine analogues (2). Unfortunately, it is not uncommon for patients to relapse after first-line therapy, and, therefore, new treatment strategies are needed for treating patients with CLL.

Rituximab is a humanized anti-CD20 monoclonal antibody already shown to be effective in treating B-cell lymphoma (3). In August 2009, Health Canada approved the use of rituximab in combination with fludarabine and cyclophosphamide in previously untreated CLL, based on an improvement in progression-free survival in a large phase III randomized-controlled trial (RCT) (4). The Committee to Evaluate Drugs - Cancer Care Ontario (CED-CCO) has requested advice on the role of rituximab in CLL, based on evidence from RCTs and a systematic review was conducted to address this.

METHODS

This advice report, produced by the CCO Program in Evidence-based Care (PEBC), is a convenient and up-to-date source of the best available evidence on the role of rituximab in the treatment of patients with CLL, developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of 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

The MEDLINE (Ovid) (1966 to April Week 3 [April 23] 2009), EMBASE (Ovid) (1980 to Week 16 [April 23], 2009), and the Cochrane Library (2006 to 2009) databases were searched. The search strategies are available from the CCO practice guideline #6-8: *Rituximab in Lymphoma and Chronic Lymphocytic Leukemia*.

In addition, conference proceedings of the American Society of Hematology (ASH) (1998-2008) and the American Society of Clinical Oncology (ASCO) (1997 to 2009) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp), and the National Institute for Clinical Excellence

(http://www.nice.org.uk/) were also searched for existing evidence-based practice guidelines.

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

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were published full report articles or published meeting abstracts involving:

1. RCTs, systematic reviews, meta-analyses, or evidence-based practice guidelines of patients with CLL;
2. Studies comparing rituximab, alone or in combination with other agents, to non-rituximab containing regimens; and
3. Studies evaluating any of the following outcomes: progression-free survival (PFS), overall survival (OS), time-to-progression, time-to-next treatment, complete response rate (CRR), overall response rate (ORR), time-to-response, duration of response, quality of life, or adverse events.

Exclusion Criteria

Studies were excluded if they were:

1. Letters, comments, books, notes, or editorial publication types.
2. Articles published in a language other than English, because of financial considerations for translation.
3. Studies of patients undergoing stem cell transplantation.
4. Studies with fewer than ten patients.

Synthesizing the Evidence

Data appropriate for meta-analysis were not identified.

Literature Search Results

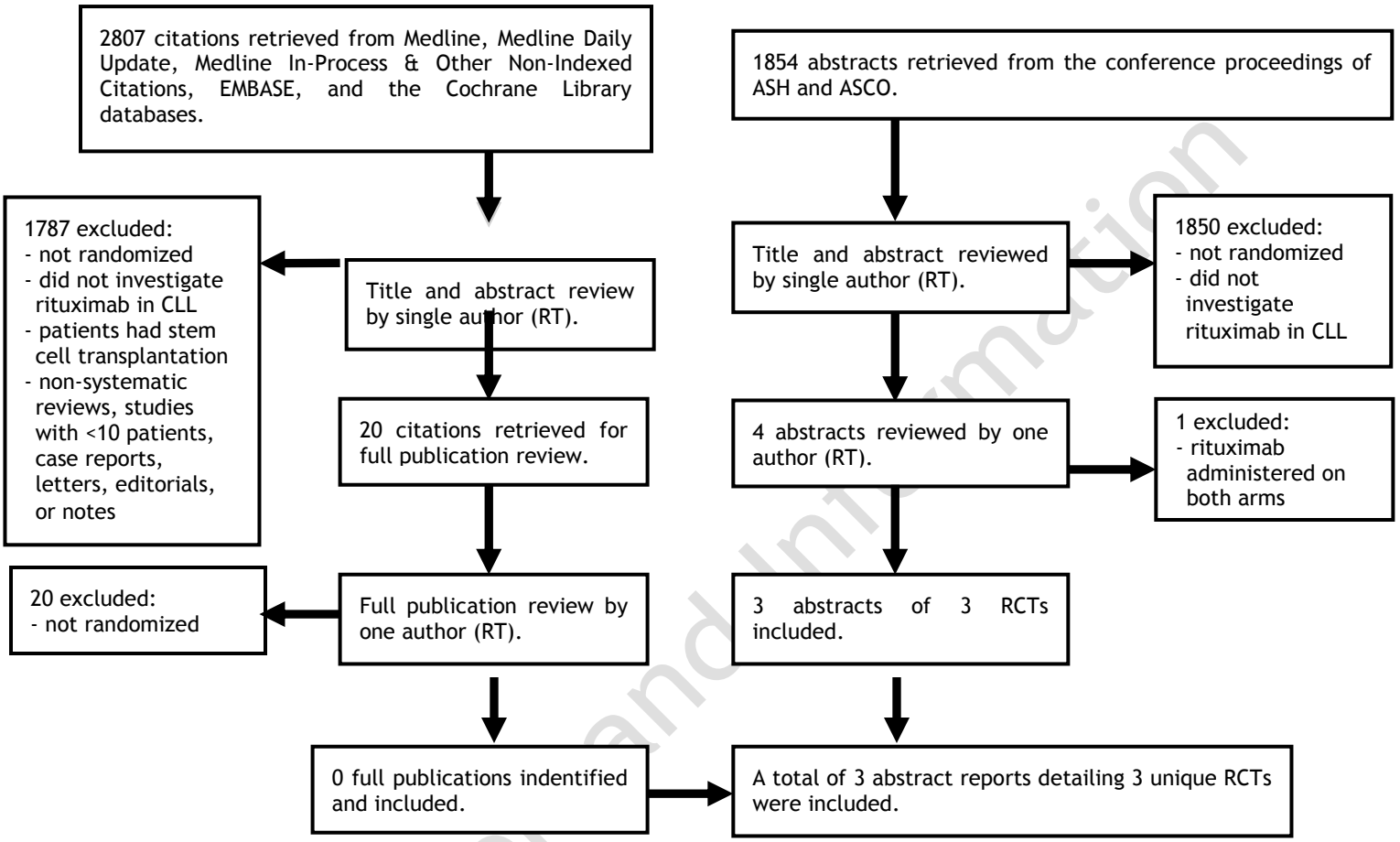
A total of 2807 citations of studies from the MEDLINE, EMBASE, and Cochrane Library databases and 1854 abstracts from the conference proceedings of ASH and ASCO were identified (Figure 1). From these citations, three abstracts representing three unique RCTs met the eligibility criteria and were included (5-7), and additional information was obtained from their trial registration reports (Table 1). Two RCTs reported PFS as the primary outcome and evaluated the same secondary outcomes; the third RCT evaluated PFS as a secondary outcome.

Table 1. Identified publications of RCTs of rituximab for CLL.

Trial	Phase	Primary publication/type	Primary outcome	Secondary outcomes	Additional sources of information
CLL8	3	Hallek et al, 2008 (5) abstract	PFS	EFS, DFS, OS, ORR, DoR, CRR, PR, TTNT, QoL, Tox	ClinicalTrials.gov NCT00281918 (8); ISRCTN Register 02757147 (9)
REACH	3	Robak et al, 2008 (6) abstract	PFS	EFS, DFS, OS, ORR, DoR, CRR, PR, TTNT, QoL, Tox	ClinicalTrials.gov NCT00090051 (10)
NCRI CLL201	2	Hillmen et al, 2007 (7) abstract	ORR	PFS, OS, CRR, MRD, Tox	ClinicalTrials.gov NCT00337246 (11); ISRCTN Register 77546448 (12)

Notes: ISRCTN=International Standard Randomised Controlled Trial Number, CRR=complete response rate; DoR=duration of response; EFS=event-free survival; ITT=intention to treat; MRD=minimal residual disease; NR=not reported; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; QoL=quality of life; ref=reference; TTNT=time to new treatment; Tox=toxicity.

Figure 1. Selection of studies investigating rituximab in CLL from the search results of MEDLINE, EMBASE, and the Cochrane Library databases and the conference proceedings of ASH and ASCO.



Trial Quality

All three RCTs were published as abstracts, were open-label studies, and were funded by the drug manufacturer. Their quality characteristics are in Table 2. None of the three reported on the required sample size, randomization method, allocation concealment, intention to treat analysis, or ethical approval. The two RCTs that did report on follow-up had rates of losses to follow-up below 20%.

Table 2. Quality characteristics of identified RCTs.

Trial (ref)	Required sample size	Randomization method	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Losses to follow-up	Ethical Approval
CLL8 (5, 8, 9)	NR	NR – stratified by Binet stage and study centre	NR	Open-label	NR	Yes	No	7%	NR
REACH (6, 10)	NR	NR	NR	Open-label	NR	Yes	No	NR	NR
NCRI CLL201 (7, 11, 12)	NR	NR – stratified by prior fludarabine treatment	NR	Open-label	NR	Yes	No	12%	NR

Trial and Patient Characteristics

The patient and intervention details of the three included RCTs are in Table 3. One RCT evaluated rituximab as first-line therapy for CLL, whereas the other two RCTs evaluated rituximab in patients who received previous chemotherapy. All three evaluated rituximab in combination with fludarabine and cyclophosphamide, and one also evaluated mitoxantrone in the combination therapy. Two RCTs enrolled over 500 patients and evaluated nearly identical treatment regimens, with treatment groups well balanced for baseline characteristics.

Table 3. Patient and intervention details for RCTs of rituximab in CLL.

Trial (ref)	Patient characteristics	Treatment	Differences between groups at baseline
First-line therapy			
CLL8 (5, 8, 9)	817 patients with CLL who had no previous treatment; median age (range) = 61 y (30-81 y)	FDB 25 mg/m^2 iv d1-3 + CPA 250 mg/m^2 iv d1-3 + RTX 375 mg/m^2 iv d0 for cycle 1 and 500 mg/m^2 d1 for subsequent cycles; q28d FDB + CPA	Balanced

Second-line or greater therapy			
REACH (6, 10)	552 patients with CD20-positive CLL who received ≤1 previous chemotherapy regimen, except for RTX or combination FDB + CPA therapy; median age 63 y	RTX 375 mg/m^2 iv for cycle 1 and 500 mg/m^2 iv for cycles 2-6, q28d + FDB 25 mg/m^2/d iv for 3d for 6 cycles + CPA 250 mg/m^2/d iv for 3d for 6 cycles FDB + CPA	Balanced
NCRI CLL201 (7, 11, 12)	52 patients with CLL who received ≥1 previous chemotherapy regimen, except for RTX or combination FDB + CPA + MXT therapy; median age (range) = 65 y (32-79 y); 79% men	FDB 24 mg/m^2 for 5d + CPA 150 mg/m^2 for 5d + MXT 6 mg/m^2 iv on d1 of each cycle + RTX 375 mg/m^2 for cycle 1 and 500 mg/m^2 for cycles 2-6 FDB + CPA + MXT	NR

Notes: CPA=cyclophosphamide; FDB=fludarabine; MXT=mitoxantrone; RTX=rituximab; d=day(s); iv=intravenous; NR=not reported; q=every; ref=reference.

Efficacy Outcomes

The data on the efficacy outcomes of PFS, OS, ORR, and CRR from the RCTs of rituximab in CLL are in Table 4.

Table 4. Efficacy outcomes for RCTs of rituximab in CLL.

Trial (ref)	Treatment	N	FU (y)	PFS			OS			ORR (%)	P-val	CRR (%)	P-val
				%	P-val	HR (95% CI)	%	P-val	HR				
First-line therapy													
CLL8 (5)	FDB + CPA + RTX	408	2	77	<0.0001	0.59	91	NS	0.76	95	0.001	52	<0.0001
	FDB + CPA	409		62			88			88		27	
				Mdn (mo)			Mdn (mo)						
Second-line or greater therapy													
REACH (6)	RTX + FDB + CPA	276	NR	30.6	0.0002	0.65 (0.51-0.82)	NYR	NS	0.83	70	0.003	24	0.0007
	FDB + CPA	276		20.6			53			58		13	
NCRI CLL201 (7)	FDB + CPA + MXT + RTX	26	NR	NR	NR	NR	NR	NR	NR	70	NR	43	NR
	FDB + CPA + MXT	26								57		13	

Notes: CPA=cyclophosphamide; CI=confidence interval; CRR=complete response rate; FDB=fludarabine; FU=follow-up; HR=hazard ratio; mdn=median; MXT=mitoxantrone; mo=month(s); N=number of patients; NR=not reported; NS=not significant; NYR=not yet reached; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; ref=reference; RTX=rituximab; val=value; y=year(s).

Disease Control

The CLL8 and REACH trials reported greater PFS with rituximab in combination with fludarabine and cyclophosphamide than in the non-rituximab-containing group (Table 4). The CLL8 trial showed that subgroups of patients with Binet stages A ($p=0.01$) and B ($p<0.0001$) received the largest benefit from rituximab chemotherapy for PFS. Multivariate analysis in the REACH trial showed that incremental benefits in PFS with rituximab chemotherapy were similar across subgroups of patients with Binet stages A (hazard ratio [HR], 0.75), B (HR, 0.65), and C (HR, 0.61).

The NCRI CLL201 trial reported that more patients receiving rituximab chemotherapy achieved minimal residual disease (MRD) negativity compared with those who received non-rituximab chemotherapy (22% versus [vs.] 9%). The results for PFS were not reported for the NCRI CLL201 trial.

Survival

The CLL8 and REACH trials reported no difference in OS between the rituximab-containing and non-rituximab-containing chemotherapy groups (Table 4); results for event-free survival were not reported. The NCRI CLL201 trial did not report results for OS.

Response

All three RCTs reported a higher ORR and CRR with rituximab-containing chemotherapy regimens than with non-rituximab-containing regimens (Table 4). Two reported the difference was significant, and the third did not report statistical level. The NCRI CLL201 trial reported that adding rituximab to fludarabine, cyclophosphamide, and mitoxantrone led to a lower rate of partial response (26% vs. 43%) compared with chemotherapy without rituximab. The CLL8 and REACH trials did not report results for partial response or time to new treatment.

Quality of life

Although quality of life was assessed as an outcome in the CLL8 and REACH trials, the results were not reported.

Adverse Events

The CLL8 trial reported higher rates of neutropenia (34% vs 21%, $p=0.0001$) and leukocytopenia (24% vs 12%, $p<0.0001$) in patients who received rituximab-containing chemotherapy compared with non-rituximab chemotherapy, but groups did not differ for anemia, thrombocytopenia, infections, or treatment-related mortality.

The REACH trial reported higher rates of grade 3/4 adverse events (80% vs. 74%) and fatal adverse events (13% vs. 10%) because of infections, secondary cancers, and cardiac disorders in patients who received rituximab-containing chemotherapy compared with non-rituximab chemotherapy, but no difference between groups for serious adverse events, neutropenia, thrombocytopenia, and infections.

The NCRI CLL201 trial reported that treatment groups did not differ in the number of patients with serious adverse events and rates of early death.

DISCUSSION

The current evidence for the use of rituximab in treating patients with CLL consists of two large phase III RCTs and one phase II RCT. The two phase III RCTs showed that rituximab combined with fludarabine and cyclophosphamide increased PFS but not OS compared with chemotherapy without rituximab in first-line or second-line therapy (5, 6). The phase II RCT compared rituximab added to fludarabine, cyclophosphamide, and mitoxantrone

chemotherapy with the same chemotherapy without rituximab (7). All three RCTs showed that the rituximab chemotherapy regimen improved ORR and CRR compared with non-rituximab regimens. The two phase III RCTs also assessed PFS according to the Binet stage but showed inconsistent results. Therefore, it is unclear if certain subgroups of patients are more or less likely to benefit from rituximab therapy. Combination chemotherapy with rituximab did not increase infection-related toxicity compared with non-rituximab chemotherapy but may increase some grade 3/4 adverse events.

The Hematology Disease Site Group (DSG) noted that this new RCT evidence builds upon phase II historically controlled data that documented improvements in disease control and survival when rituximab was added to fludarabine alone. However, some members of the DSG expressed concerns regarding the clinical benefit attained by the improvement of PFS alone. In particular, lymphocyte count doubling was considered a progressive event, and a predominant reduction in this outcome may not have considerable value for individuals who are otherwise asymptomatic. A thorough understanding of the nature of disease control offered by the addition of rituximab will depend on the full publication of these studies. Finally, the DSG recognized that the RCTs studied the addition of rituximab to a fludarabine-based chemotherapy backbone. Fludarabine-based chemotherapy does not currently represent the sole standard of care in Ontario for the front-line treatment of CLL. The current standard of care in Ontario is chlorambucil, although the group acknowledges that fludarabine-based therapy is commonly used as an alternative. In the interim, the DSG recognizes the consistent and moderate benefit in PFS in the phase III setting and the acceptable toxicity profile of rituximab and feels that the addition of rituximab to fludarabine-based chemotherapy should be recommended in the treatment of CLL.

CONCLUSIONS

Rituximab in combination with fludarabine and cyclophosphamide increased PFS but not OS compared with fludarabine and cyclophosphamide without rituximab in first- and second-line therapy in patients with CLL. The addition of rituximab to fludarabine-based chemotherapy did not appear to add significant incremental toxicity to the baseline toxicity, but some adverse events may be increased. At this time, definitive conclusions cannot be made about which subgroups of patients would be more or less likely to benefit from rituximab therapy.

ONGOING TRIALS

On the Internet, the National Cancer Institute's clinical trials database (http://www.cancer.gov/search/clinical_trials/) and the National Institutes of Health Clinical Trials database (http://clinicaltrials.gov/) were searched for reports of new or ongoing phase III RCTs investigating the use of rituximab in patients with CLL that met our eligibility criteria. One ongoing phase III RCT was identified (13), and the details are in Appendix 1.

CONFLICT OF INTEREST

The authors of this special advice report disclosed potential conflicts of interest relating to the topic of this special advice report. MC is a principal investigator on a study in which Roche provided the drugs. RT reported no conflicts of interest.

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Appendix 1. Ongoing trial.

Phase III, Multicentre, European, Randomized Trial Comparing the Combination Fludarabine Phosphate-Cyclophosphamide-Rituximab (FCR) with the Combination Fludarabine Phosphate-Cyclophosphamide-Campath (FCCam) in Previously Untreated Adults with B and C Binet Stage B-Chronic Lymphoid Leukemia (B-CLL)

Protocol ID:	NCT00564512
Last date modified:	April 4, 2009
Trial type:	Randomized, open-label, phase III trial
Accrual:	310
Primary outcome:	Progression-free survival
Sponsorship:	Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang GOELAMS
Status:	Ongoing, not accruing