

RAPID REVIEW

Alemtuzumab

for treatment of B-cell
chronic lymphocytic leukaemia

South Australian Medicines Evaluation Panel



Government
of South Australia

SA Health

Summary of SAMEP review

Date of SAMEP meeting:

11th July 2012

Name of medicine	Alemtuzumab (Tradename: MabCampath®)
Dosage form	Concentrated solution for infusion
Indication	B-cell chronic lymphocytic leukaemia (B-CLL)
Cost	<p>Alemtuzumab costs \$1000 per 30mg vial. At the recommended maintenance dose of 30mg three times weekly, a 12 week course costs \$36,000.</p> <p>Additional costs of anti-infective prophylaxis (or treatment) need to be considered, including against cytomegalovirus.</p>

Note: No formulary application was received for this medicine. This is a SAMEP-initiated rapid review due to the number of Individual Patient Use (IPU) requests for this medicine exceeding the threshold for review as directed under SA Health policy.

SAMEP recommendations

Following the review of the current available evidence (appendix 1), SAMEP recommend rejecting further IPU requests for alemtuzumab for the treatment of B-CLL for the following reasons:

- A 2012 Cochrane review, included five trials of moderate quality comparing alemtuzumab to a number of different comparators. The review suggested that:
 - Alemtuzumab is superior to chlorambucil (in terms of progression-free survival)
 - Alemtuzumab may offer some better outcomes than fludarabine alone especially in the setting of relapse but there is no direct comparative trial
 - Alemtuzumab does not appear superior to rituximab with current data
- Trials included in the Cochrane review did not provide health-related quality of life data. Given that CLL is a common and usually slowly-progressing disease, it was the opinion of SAMEP that progression-free-survival as an outcome measure may be less relevant.
- Safety → The Cochrane review concluded that from the available evidence, treatment with alemtuzumab is associated with an increased risk of opportunistic infections and viral reactivation, in particular a statistically increased cytomegalovirus (CMV) reactivation rate and symptomatic CMV infection rate.
- Cost-effectiveness → As the effect size of treatment with alemtuzumab is uncertain due to a lack of direct comparator trials, it is not possible to determine the cost-effectiveness compared to current recommended treatment.

- SAMEP members noted that alemtuzumab is available in Scotland for B-CLL, restricted to patients with the cytogenetic abnormality 17p-deletion. It was noted however that the cost for alemtuzumab in Scotland appears to be considerably less than in Australia. The cost of a 30mg vial in the UK is £264.11 (BNF No. 63., March 2012) compared to AUS\$3,000 in Australia.
- It appears internationally that there is a lack of consensus regarding the definitive role of alemtuzumab in the treatment of B-CLL:
 - There are currently no current protocols for treatment of B-CLL that include alemtuzumab on EviQ – Cancer treatments on-line (as of July 2012).
 - *UpToDate* lists two options for initial treatment of CLL when patients become symptomatic: Fludarabine plus rituximab, or fludarabine plus cyclophosphamide plus rituximab. Alemtuzumab is not recommended for initial treatment of CLL. (In Australia, fludarabine is authority-listed on the PBS for CLL).
 - National Comprehensive Cancer Network (NCCN) guidelines for CLL:
 - does not recommend alemtuzumab for frail patients with significant co-morbidity
 - alemtuzumab is recommended as 3rd-line in patients ≥70yrs or younger patients with co-morbidity, *without* the cytogenetic abnormalities 11q or 17p-deletion (del 11q or del 17p)
 - alemtuzumab is not recommended in <70yrs or older patients without co-morbidity and *without* del 11q or 17p
 - alemtuzumab 4th preference in patients ≥ 70yrs or younger patients with co-morbidity *with* del 11q
 - alemtuzumab is not recommended in patients < 70yrs or older patients without significant co-morbidity and *with* del 11q
 - alemtuzumab 4th preference in patients *with* del 17p (regardless of age or co-morbidity)
- There is already one monoclonal antibody, rituximab, which is listed on the PBS for used in CLL. Rituximab targets CD20 which is only present on B-lymphocytes. Alemtuzumab targets CD52 which is found on all mature lymphocytes so is potentially likely to be more immunosuppressive than rituximab.
- Without a statewide consensus on a clinical pathway with clear inclusion and exclusion criteria, SAMEP did not feel there is enough evidence to endorse the approval of further IPU.

Evaluation by other jurisdictions:

Pharmaceutical Benefits Advisory Committee (PBAC)	Alemtuzumab has not been evaluated by PBAC
Canadian Agency for Drugs and Technologies in Health (CADTH)	Evaluated by CADTH in 2005 for the treatment of B-cell Chronic Lymphocytic Leukemia (CADTH 2005)
Scottish Medicines Consortium (SMC)	Evaluated by SMC in September 2008 – Accepted for restricted use in Scotland for B-CLL when fludarabine combination therapy not appropriate. Restricted to patients with previously untreated B-CLL with the cytogenetic abnormality 17p-deletion (Scottish Medicines Consortium 2008).
National Institute for Health and Clinical Excellence (NICE)	NICE have not issued guidance on the use of alemtuzumab in CLL.
Cochrane Collaboration	Alemtuzumab for patients with chronic lymphocytic leukaemia (Review) (Skoetz, Bauer et al. 2012)

Search strategy for additional evidence

Refer to appendix 2 for search strategy for additional recent randomised controlled trials. (The Cochrane review published this year included RCT up to and including November 2011)

A Medline search for 2011-2012 (search strategy in appendix 1) identified one phase III clinical trial published subsequent to the inclusion dates for the Cochrane review (Elter, Gercheva-Kyuchukova et al. 2011). This trial however was published on-line in October 2011 ahead of print and was included in the Cochrane review.

Brief Overview of Evidence

Appropriate comparator

The Cochrane review published in 2012 included five trials (n=845) with a number of different comparator groups (Skoetz, Bauer et al. 2012):

- One trial compared alemtuzumab with no further therapy
- One trial compared alemtuzumab plus fludarabine versus fludarabine (as relapse therapy)
- Two trials compared alemtuzumab with rituximab
- One trial compared alemtuzumab with chlorambucil

Efficacy

Of the five randomised controlled trials included in the 2012 Cochrane review, only one compared alemtuzumab with chlorambucil. The CAM307 trial was a randomised, controlled open-label phase III study (n= 297) comparing alemtuzumab 30mg (IV) three times weekly for up to 12 weeks, to chlorambucil 40mg/m² (orally) every 28 days for a maximum of 12 months. The trial was funded by Genzyme Corporation, the manufacturers of alemtuzumab. No

difference in overall survival had been detected as median survival had not been reached when the trial was published (Hillmen, Skotnicki et al. 2007). Alemtuzumab statistically significantly improved progression-free survival compared to chlorambucil (HR 0.58; 95% CI 0.43-0.77; p=0.0001).

The quality of the five included trials in the Cochrane review was moderate, with unclear allocation concealment and possibility of selection, performance and reporting bias (Skoetz, Bauer et al. 2012).

Safety

Although alemtuzumab improved progression-free survival in three of the five studies included in the Cochrane review, all three studies also showed a statistically increased cytomegalovirus (CMV) reactivation rate and symptomatic CMV infection rates. In the CAM307 trial CMV viraemia occurred in 52% of alemtuzumab-treated patients, compared to 7.5% of patients in the chlorambucil group (Hillmen, Skotnicki et al. 2007).

Areas of uncertainty

- . The cost and duration of CMV prophylaxis and/or treatment required is variable depending upon the antiviral agent used.
- . Due to no formulary application being submitted, we have no proposed clinical pathway to review and assumptions must be made with regard to comparators.

Appendix 2 Search strategy

Cochrane Database of Systematic Reviews

- Search strategy:
1. alemtuzumab.mp. [mp=title, short title, abstract, full text, keywords, caption text]
 2. mabcampath.mp. [mp=title, short title, abstract, full text, keywords, caption text]
 3. 1 or 2
 4. chronic lymphocytic leukemia.mp. [mp=title, short title, abstract, full text, keywords, caption text]
 5. chronic lymphocytic leukaemia.mp. [mp=title, short title, abstract, full text, keywords, caption text]
 6. 4 or 5
 7. 3 and 6
 8. limit 7 to full systematic reviews

Returned 2 citations, of which only one was applicable

Medline

- Search strategy:
1. clinical trial.mp.
 2. clinical trial.pt.
 3. random\$.mp.
 4. tu.xs.
 5. 1 or 2 or 3 or 4
 6. randomised clinical trial.mp.
 7. randomized.ab.
 8. placebo.ab.
 9. 5 or 6 or 7 or 8
 10. alemtuzumab.mp.
 11. Mabcampath.mp.
 12. 10 or 11
 13. 9 and 12
 14. exp Leukemia, Lymphocytic, Chronic, B-Cell/
 15. 13 and 14
 16. limit 15 to yr="2011 - 2012"

Returned 36 citations, including one phase III clinical trial

REFERENCES

CADTH (2005). Alemtuzumab in chronic lymphocytic leukemia [Internet]. C. A. f. D. a. T. i. Health. Ottawa. [Available from: http://www.cadth.ca/media/pdf/281_alemtuzumab_cetap_e.pdf].

Elter, T., L. Gercheva-Kyuchukova, et al. (2011). "Fludarabine plus alemtuzumab versus fludarabine alone in patients with previously treated chronic lymphocytic leukaemia: a randomised phase 3 trial." *Lancet Oncology* **12**(13): 1204-1213.

Hillmen, P., A. B. Skotnicki, et al. (2007). "Alemtuzumab Compared With Chlorambucil As First-Line Therapy for Chronic Lymphocytic Leukemia." *Journal of Clinical Oncology* **25**(35): 5616-5623.

Scottish Medicines Consortium (2008). SMC advice: alemtuzumab (MabCampath) [Internet]. Glasgow, NHS Scotland. [Available from: http://www.scottishmedicines.org.uk/SMC_Advice/Advice/494_08_alemtuzumab_MabCampath_/alemtuzumab_MabCampath_].

Skoetz, N., K. Bauer, et al. (2012). "Alemtuzumab for patients with chronic lymphocytic leukaemia." *Cochrane Database of Systematic Reviews*(2).