RAPID REVIEW

Bendamustine

for treatment of relapsed or refractory non-Hodgkin's lymphoma (NHL) or Chronic lymphocytic leukaemia (CLL)

South Australian Medicines Evaluation Panel

Government of South Australia
SA Health

Summary of SAMEP review

Date of SAMEP meeting:	11th September 2013

Name of medicine

Bendamustine

Dosage form

Injection, concentrated

Indication(s)

- Relapsed and/or refractory non-Hodgkin's lymphoma (NHL) as a single agent; or
- Relapsed and/or refractory chronic lymphocytic leukemia (CLL) in combination with rituximab +/- cytarabine

It is noted that in Europe bendamustine is used to treat other patient populations, including multiple myeloma, however this review is limited to the above populations (that is, the population groups currently accessing the drug in South Australia)

TGA registration status

Bendamustine is not registered by the Therapeutic Goods Administration for use within Australia.

Cost

Bendamustine costs $373 per 100mg vial and $95 per 25mg vial.

The doses currently used in South Australian hospitals are:

NHL: 120mg/m^2 on day 1 & day 2 , per 3 weekly (21 day) cycle for 6 cycles

CLL: 70mg/m^2 on day 1 & day 2 (+other agents), per 4 weekly (28 day) cycle for 4-6 cycles

Bendamustine dose and acquisition costs over a course of treatment for NHL, for varying patient BMI.

BSA m^2	NHL Dose: 120mg /m^2	Vials required per dose		Cost of vials per dose		Total drug cost per dose	Total # of doses	Total Cost/ Complete Treatment
		100mg	25mg	100mg vials @ $373ea	25mg vials @ $95ea			
1.33	160	1	3	$373	$285	$658	x2 doses /cycle x6 cycles /course ***= x12***	$7,896
1.60	192	2	0	$746	$0	$746		$8,952
1.87	224	2	1	$746	$95	$841		$10,092
2.0	240	2	2	$746	$190	$936		$11,232

Bendamustine dose and acquisition costs over a course of treatment for CLL, for varying patient BMI.

BSA m^2	CLL Dose: 70mg /m^2	Vials required per dose		Cost of vials per dose		Total drug cost per dose	Total # of doses	Total Cost/ Complete Treatment
		100mg	25mg	100mg vials @ $373ea	25mg vials @ $95ea			
1.33	93	1	0	$373	$0	$373	x2 doses /cycle x 4 to 6 cycles /course ***= x8 to 12***	$2,984 - $4,476
1.60	112	1	1	$373	$95	$468		$3,744 - $5,616
1.87	131	1	2	$373	$190	$563		$4,520 - $6,756
2.0	140	1	2	$373	$190	$563		

Note: No formulary application was received for this medicine. This is a SAMEP-initiated 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.

Summary of current usage in South Australia

- The ROBIN trial is currently enrolling patients at The Queen Elizabeth Hospital (TQEH), Flinders Medical Centre (FMC) and the Royal Adelaide Hospital (RAH). The ROBIN trial is a randomised, open-label, multi-centre, phase III study to investigate the efficacy of bendamustine compared to treatment of physicians choice in the treatment of subjects with indolent non-Hodgkin's lymphoma (NHL), refractory to rituximab. (http://clinicaltrials.gov/show/NCT01289223).

- Outside of clinical trials, the usage of bendamustine in South Australia is predominantly at one public hospital via the Special Access Scheme (SAS) for unregistered drugs.

- Data provided to SAMEP regarding individual patients who have received funding approval from hospital drug committees for treatment with bendamustine shows that usage to date is in patients who:

    - Were heavily pre-treated, often with multiple courses of chemotherapy prior to treatment with bendamustine; and
    - Were ineligible for inclusion in the ROBIN trial (follicular lymphoma, transformed aggressive lymphoma, poor performance status); and
    - Unable to have fludarabine, or failed various regimens including rituximab and/or fludarabine; and
    - Splenectomy was considered inappropriate or had failed.

Evidence to support current usage in South Australia

- No trials published to date exactly reflect current usage in South Australia (via SAS)
- A summary of the SAMEP review of the evidence in included in appendix 1

Areas of uncertainty

- There are differing protocols used at different SA public hospitals, for the first-line, second-line and salvage management of NHL and CLL. There is no agreed clinical pathway in the state for the possible role (if any) of bendamustine in the treatment of these diseases.
- There is no local outcome data available for the patients who have received bendamustine in SA to date.
- No trials published to date exactly reflect current usage in South Australia (via SAS). The actual size of any benefit in terms of survival or progression-free survival (PFS) is highly uncertain as there is no direct evidence reflective of current use.
- There is no evidence from clinical trials regarding the quality of life in this patient population who are treated with bendamustine.
- Because of uncertainty regarding the size of any benefits (including PFS), in this patient population, the cost-effectiveness of bendamustine is high and uncertain.

Consideration of further IPU requests

Based on the limited published evidence in this patient group (appendix 1), the uncertainty with regards to outcomes including progression free survival or quality of life, and the high cost, SAMEP recommend that drug committees consider the following points when assessing requests for funding of bendamustine for individual patient use:

- In heavily pre-treated relapsed/refractory NHL or CLL patients, there is no published evidence to indicate that bendamustine increases progression-free survival.
- Quality of life is extremely important with salvage therapy in heavily pre-treated patients. There is a lack of data regarding quality of life in refractory/relapsed patients receiving bendamustine. From the patient's perspective, it has to be questioned whether spending the money on best supportive care would provide better quality of life at this stage in their disease. Why does the clinician believe that best supportive care is less desirable than treatment with bendamustine?
- When bendamustine is used in combination with rituximab, the rituximab is also non-PBS.
- Due to the high cost and the lack of efficacy data in heavily pre-treated patients with relapsed or refractory NHL or CLL, the cost-effectiveness of bendamustine as salvage therapy in this population is uncertain.

Appendix 1 Review of the evidence

Evaluation by other jurisdictions:

Pharmaceutical Benefits Advisory Committee (PBAC)	Bendamustine has *not* been evaluated by the PBAC for the indications of NHL or CLL (or other indications) to date.
Canadian Agency for Drugs and Technologies in Health (CADTH)	Bendamustine has *not* been evaluated by the CADTH for the indications of NHL or CLL (or other indications) to date.
Scottish Medicines Consortium (SMC)	Bendamustine *has* been evaluated by the SMC for:[1] • First-line treatment of chronic lymphocytic leukaemia (CLL, Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. *Status: Recommended (April 2011);* • Front-line treatment of multiple myeloma *Status: Not recommended (April 2011);* • Treatment of indolent non-Hodgkin's lymphomas as monotherapy following progression during or within 6 months following a rituximab (containing) treatment *Status: Not recommended (April 2011).*
National Institute for Health and Clinical Excellence (NICE)	Bendamustine *has* been evaluated by NICE[2] for: • Chronic lymphocytic leukaemia of Binet stage B or C in untreated patients who cannot have fludarabine. *Guidance: Recommended (Feb 2011)* • Treatment of indolent (low grade) non-Hodgkin's lymphoma that is refractory to rituximab or a rituximab-containing regimen. *Appraisal terminated due to lack of evidence from sponsor. Guidance: Not able to be recommended (Oct 2010)* In addition, evaluations of bendamustine are *in progress* for: • First-line treatment of advanced indolent non-Hodgkin's lymphoma in combination with rituximab. *(Due July 2014)* • First-line treatment of lymphoma (mantle cell), in

[1] http://www.scottishmedicines.org.uk (Search 'Bendamustine'; Accessed 22/08/2013)
[2] http://www.nice.org.uk (Search 'Bendamustine'; Accessed 22/08/2013)

	combination with rituximab. *(Due date – to be confirmed)*
Cochrane Collaboration	The Cochrane Collaboration *has* published one systematic review on bendamustine titled; • Bendamustine for patients with slow-growing lymphoma *(Published online Sept 2012)*
EviQ – Cancer Institute of NSW (www.eviq.org.au)	Bendamustine has *not* been evaluated by eviQ for the indications of CLL or NHL (or other indications) to date.

Search strategy for additional evidence

Population	Patients with relapsed or refractory NHL or relapsed or refractory CLL.
Intervention	Bendamustine treatment (with or without rituximab or cytarabine)
Comparator	Not specified (Many salvage chemotherapy regimens have been studied for recurrent NHL and SLL. Any of the first-line therapies may be used as salvage therapy as well. Treatment options tend to be tailored to individual circumstances. In anticipation of limited comparative information following scoping searches it was decided not to limit the search as any published comparison may potentially be informative.)
Outcome(s)	Not specified (any reported outcomes considered potentially patient relevant) eg survival, relapse, immune response.

Databases Searched (Refer To Appendix 2 For Search Terms)

- Cochrane Database of Systematic Reviews
- Medline
- Embase
- Current Controlled Trials *meta*Register

Selection criteria: Human, Clinical trials (various)[3], Systematic reviews.
Details of search strategy are attached in the Appendix.

Brief Overview of Evidence

Systematic Reviews And Clinical Trials

[3]The initial search criteria was restricted to 'randomised clinical trials' however given the lack of directly applicable high level evidence the search was broadened to include all 'clinical trials'.

Two systematic reviews/meta-analyses which considered bendamustine use in patients with indolent B cell lymphoid malignancies, including CLL, were identified:

- One Cochrane systematic review of bendamustine use in patients with indolent B cell lymphoid malignancies, including CLL, was identified (Vidal, Gafter-Gvili et al. 2012). However this analysis was not restricted to relapsed or refractory patients only. The included trials were considered too heterogenous to combine the results in a meta-analysis. Nevertheless, the analysis provides some relevant information and a summary of the findings are presented on pages 16-17.
- One mixed treatment comparison (MTC) meta-analysis of *first-line* therapies for advanced CLL (Terasawa, Trikalinos et al. 2013). The study identified significant progression free survival (PFS) benefit associated with single agent bendamustine treatment in the first-line (HR = 0.23, 95%CI 0.13, 0.42). The data associated with bendamustine was solely from Knauf *et al* (2009), which is detailed later in this report. Given that the analysis focused on the first-line use of bendamustine and did not contain additional bendamustine trials, this MTC is not reported further.

The search also identified four randomised controlled trials (RCTs, plus a results update) of bendamustine use in NHL and/or CLL. All of these trials were included in the Cochrane systematic review.

- Only one (Niederle, Megdenberg et al. 2013) was specifically in pre-treated relapsed or refractory patients as per recent SAS/IPU requests from The Royal Adelaide Hospital and Flinders Medical Centre. Niederle et al is summarised in the Cochrane review data (pages 16-17) and detailed individually on pages 18-19.
- The other three RCTs (Herold, Schulze et al. 2006; Knauf, Lissichkov et al. 2009; Rummel, Kaiser et al. 2010) report on bendamustine use as a first-line therapy and are presented in the Cochrane review summary. However, they are not detailed further given their limited applicability. Updated results to the Knauf 2009 publication (Knauf, Lissitchkov et al. 2012) were also identified in the search.

Given the few RCTs in the specific patient population where bendamustine use is occurring in South Australia, the search was extended further to identify 36 non-comparative studies which studied bendamustine in the correct population (i.e. as salvage therapy in relapsed/refractory disease). Of these;

- 12 studied bendamustine as a single-agent therapy. A tabulated summary of the 6 largest studies (*n >50*) is presented on pages 21-24.
- 7 studied bendamustine in combination with rituximab. A summary of the largest 3 studies (where *n >50*) is presented on pages 25-26.
- 2 studies included mixed regimens of bendamustine with and without rituximab (Iannitto, Morabito et al. 2011) and *(Sanchez-Gonzalez, Penalver et al. 2012),* respectively) and one study was identified that added cytarabine to bendamustine and rituximab (Visco, Finotto et al. 2013). These studies are presented on pages 27-28.
- The remaining 15 studies of bendamustine use in NHL/CLL were not considered particularly informative for the purposes of this review as they were all concerned with bendamustine use in combination with other therapies (mitoxantrone, bortezomide, vincristine+prednisolone and fludarabine *etc*) or high-dose bendamustine plus etoposide prior to autologous stem cell transfer. There is no

evidence that bendamustine is currently used in this manner in South Australian public hospitals.

CLINICAL PATHWAY

There is no single treatment pathway for NHL or CLL. Treatment options are complex with multiple options and recommendations vary depending on the more specific diagnosis of lymphoma or leukaemia type and the genetic information available. Furthermore the patient's overall health status (co-morbidities *etc*) and age and ability to tolerate treatment are considered and affect the clinical pathway offered.

SUMMARY OF EVIDENCE

***Systematic Review* – CLL and NHL**

Citation	Vidal, L, Gafter-Gvili, A, Gurion, R, Raanani, P, Dreyling, M & Shpilberg, O 2012, 'Bendamustine for patients with indolent B cell lymphoid malignancies including chronic lymphocytic leukaemia', Cochrane Database Syst Rev, vol. 9, p. CD009045.
Funding of study	Not stated
Design	Systematic review of randomised controlled trials that compared a bendamustine-containing regimen to other chemotherapy with or without immunotherapy. Electronic search of the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 2), MEDLINE (1966 to May 2012), EMBASE (1974 to November 2011), LILACS (1982 to May 2012), databases of ongoing trials (accessed 30 April 2012) and relevant conference proceedings.
Number of studies identified:	K=5 RCTs, N=1343 adult patients
Duration of treatment	24 weeks (8 x 3-weekly cycles or 6 x 4-weekly cycles) *or not described.*
Patient population	Patients with histologically confirmed indolent B cell lymphoid malignancies, i.e. SLL/CLL, follicular lymphoma, mantle cell lymphoma, lymphoplasmocytic lymphoma, marginal zone lymphoma. • All five eligible trials included adult patients with indolent B cell lymphoid malignancies requiring chemotherapy. Three trials (Herold 2006; Rummel 2009; Rummel 2010) included patients with follicular lymphoma, mantle cell lymphoma, lymphoplasmocytic lymphoma and other indolent lymphomas. The percentage of patients with follicular lymphoma ranged from 40% to 52% and the percentage of patients with mantle cell lymphoma was about 20%. Two trials included only patients with CLL (Knauf 2009; Niederle 2012). Patients receiving bendamustine as first-line therapy and patients with relapsed or refractory disease receiving it as salvage therapy. Patients might have received high-dose chemotherapy following first-line or salvage therapy. • Three trials (Herold 2006; Knauf 2009; Rummel 2009) included previously untreated patients and two trials included previously treated patients (Niederle 2012; Rummel 2010). Patients of any age.

Studies	Herold 2006*	Knauf 2009*	Rummel 2009*	Niederle (unpublished 2012)#	Rummel 2010#
	* previously untreated patients			# previously treated patients	
Treatment arms	BOP vs COP	Bendamustine vs chlorambucil	B+R vs CHOP+R	Bendamustine vs fludarabine	B+R vs F+R
No. of patients in treatment group	164	319	549 (513 eval)	92	219 (208 eval)
Withdrawals from treatment group (overall)	1%	0	7%	0	5%
Blinding of patients	No	No	No	No	No
Blinding of outcome assessors	No	Yes	No	No	No
Allocation concealment	Unclear	Yes	Unclear	Yes	Not Reported

Outcomes:	Herold 2006*	Knauf 2009*	Rummel 2009*	Niederle 2012#	Rummel 2010#
Overall survival, HR (95%CI)	0.93 (0.61, 1.44)	0.69 (0.43, 1.11)	na	0.82 (0.47, 1.42)	na
All-cause mortality, RR (95% CI)	0.73 (0.52, 1.02)	0.86 (0.66, 1.12)	1.00 (0.64, 1.57)	0.81 (0.56, 1.18)	0.83 (0.60, 1.14)
Progression-free survival	na	0.28 (0.19, 0.42)	0.58 (0.43, 0.77)	0.90 (0.50, 1.63)	0.51 (0.37, 0.71)
Adverse Events: Treatment –related mortality	BOP: 2 patients vs COP: 0				
Discontinuation of treatment		B: 11% vs C: 3%			
Infection related		B: 8% vs C:3%	B+R: 37% vs CHOP-R: 48%		
	The differing comparators made the studies too heterogeneous to pool comparative adverse event data. Overall the authors conclude that, with respect to the risk of grade 3 or 4 adverse events, bendamustine has more risk than chlorambucil, is similar in risk to fludarabine and has lower risk than CHOP.				

BOP = Bendamustine + vincristine + prednisolone
COP = Cyclophsophamide + vincristine + prednisolone
B+R = Bendamustine + rituximab
CHOP + R = Cyclophosphamide + doxorubicin +vincristine + prednisolone
F+R = fludarabine + rituximab

Discussion re systematic review

While the systematic review suggests that bendamustine is an active treatment (or component of treatment) in indolent B cell lymphoid malignancies, with respect to prolonging progression-free survival, there is no evidence of increased overall survival and the relative toxicity of treatment needs to be considered.

The analysis and results from trials in populations where bendamustine is used as a first-line treatment are unlikely to be applicable to the more selective population of pre-treated

refractory or relapsed patients – these patients are, by definition, likely to be less responsive to chemotherapy treatments (see sub-group analysis in case series below).

Therefore, other than being broadly suggestive of having some stabilisation activity although not survival gain, the Cochrane analysis provides limited information to assess the value of bendamustine as it is being used in South Australia ie as a last-line salvage therapy (alone or in combination with rituximab or cytarabine) for resistant or refractory disease.

Nevertheless, more detailed information on the individual trials in pre-treated patients is provided below. The updated results of Niederle et al are presented, together with the Rummel 2010 study (only the abstract was available for the latter).

Randomised controlled trials (in correct population)

Citation	**Niederle**, N, Megdenberg, D, Balleisen, L, et al 2013, 'Bendamustine compared to fludarabine as second-line treatment in chronic lymphocytic leukemia', *Ann Hematol*, vol. 92, no. 5, May, pp. 653-660.		**Rummel** MJ, Kaiser U, Balser C, et al. 2010. Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas - Final results of the randomized phase III study NHL 2 - 2003 on behalf of the stil (study group indolent lymphomas, Germany) *Blood* 116:21	
Funding of study	In part by unrestricted research grants from Mundipharma GmbH, Germany, and Ribosepharm GmbH, Germany.			
Design	The study was designed as an open-label, multi-centre, randomised phase III trial.		Multicentre, randomised phase III study	
Duration of treatment	Treatment was administered in 28 day cycles (or extended if required for resolution of neutropenia/ thrombocytopenia) which were repeated until confirmation of best response to treatment, to a maximum of eight cycles. Median follow-up 34 months.		Treatment was administered in 28 day cycles to a maximum of six cycles.	
Patient population	Patients with histologically or immunologically confirmed chronic B cell leukaemia in refractory (i.e., no response or progression during initial chemotherapy) or relapsed situation after first-line treatment regimen, exhibiting disease status II–IV according to Rai or B/C according to Binet staging system, respectively, were enrolled. Further selection criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 3 or better and at least 18 years of age.		Relapsed follicular (FL), indolent or mantle cell lymphoma (MCL). Median patient age: 68 yrs (38 -87). Patients had received a median of 1 prior therapy (range 1 -7). Histological subtypes were distributed equally between the B -R and F -R arms: follicular 45.9 % and 47.5%, respectively; immunocytoma 11.9% and 11.1%; MCL 20.2% and 21.2%; other indolent lymphomas 23% and 20.2%	
Treatment group	**Bendamustine** 100mg/m^2 on days 1 and 2	Fludarabine 25mg/m^2 on days 1 to 5	Rituximab 375 mg/m^2 day 1 + **bendamustine** 90mg/m^2 days 1+2	Rituximab 375 mg/m^2 day 1 + fludarabine 25mg/m^2 days 1 -3
No. of patients in treatment group (n)	49 (modified ITT)	43 (modified ITT)	109	99
Withdrawals from treatment group	1 (incorrectly treated with fludarabine)	1 (incorrectly treated with bendamustine)	11 (data on treatment allocation not available in abstract)	
Blinding of patients	None		None	
Blinding of outcome assessors	None described		None described	
Allocation concealment	Computer-generated randomisation lists, created by a block randomisation method		Not reported	

		with variable block size. Patients stratified according to Binet stage B or C and study centre.			
Outcomes:		B	F	B+R	F+R
1'	PFS (months)	20.1	14.8	30	11
		HR = 0.87 (95% CI; 0.60, 1.27) Cochran–Armitage trend test across response categories, p=0.11, no significant difference.		HR = 0.51, (95 % CI 0.34, 0.67) p<0.0001	
2'	OS (months)	43.8	41.0	Trial end not reached (B+R: 42 deaths vs F+R: 46 deaths) No difference/ immature data	
		HR=0.82 (95% CI 0.47, 1.43)			
Res-ponse:	Complete	27%	9%	38.5%	16.2% (p=0.0004)
	Partial	49%	53%		
	Complete or Partial	76%	62%		
	Stable Disease	8%	16%		

Adverse Events: (% patients)	**CTC grade**	Bendamustine					Fludarabine					B+ R	F+R
		0	1	2	3	4	0	1	2	3	4		
Anaemia		45	33	18	2	2	43	34	15	3	5		
Leukopenia		44	15	23	15	3	60	17	10	11	2	11.8% grade 3/4	12.4%
Neutropenia		46	19	15	14	6	59	11	13	11	6	8.9% grade 3/4	9.1%
Thrombocyto-penia		36	41	16	5	2	54	30	9	4	2		
Fever		63	11	26	–	–	66	10	22	–	2		
Infection		54	11	22	13	–	56	2	27	10	5	No significant difference	
Nausea		30	46	22	2	–	63	27	10	–	–		
Vomiting		65	20	15	–	–	80	20	–	–	–		
Diarrhoea		80	11	9	–	–	90	5	2	2	–		
Constipation		78	15	7	–	–	78	12	7	2	–		
Mucositis		87	9	2	2	–	90	–	10	–	–		
Allergic reaction		87	9	4	–	–	98	–	2	–	–	No significant difference	
Alopecia		80	17	2	–	–	90	10	–	–	–	No significant difference	
Sensory		98	2	2	–	–	95	5	–	–	–	No significant difference	
Creatinine		78	17	–	–	4	88	10	2	–	–		
Skin		93	7	–	–	–	95	5	–	–	–	No significant difference	
Tumor lysis syndrome		96	–	–	–	4	100	–	–	–	–	Similar overall incidence of serious adverse events: B+R: 17.4% vs F+R: 22.2%	

B=bendamustine, B+R=bendamustine + rituximab, CTC=Common Toxicity Critera, F=fludarabine, F+R=fludarabine + rituximab, HR=hazard ratio, ITT=intention to treat, MCL=mantle cell lymphoma.

A further RCT of bendamustine versus chlorambucil is ongoing (see Table following) which includes patients with lower performance status (both first and second-line). The dosage of bendamustine used in second-line patients in this trial is consistent with the dose used in

combination therapy in South Australia. Given the trial is on-going, the interim results should be interpreted with caution.

Additional randomised controlled trial (mixed population) – Interim results

Citation	Leblond, V. Laribi, K. Ilhan, O. 2012, 'Rituximab in combination with bendamustine or chlorambucil for treating patients with chronic lymphocytic leukemia: Interim results of a phase IIIB study (mable), *Blood*, vol. 120, no. 21.		
Funding of study	None described (abstract reviewed only)		
Design	Randomised phase III trial.		
Patient population	Patients aged >18 years who were ineligible for fludarabine treatment, as a result of age or a greater number of comorbidities. Either 1st or 2nd line, where relapse had occurred no earlier than 12 months since their last dose of first line treatment. At time of interim analysis: 85 (67%) of patients were previously untreated, with the remaining 41 (33%) having received at least 1 line of previous treatment.		
Treatment group	Bendamustine 90 mg/m^2 (or, if 2nd line: 70mg/m^2) on days 1 and 2; + Rituximab 375 mg/m^2 on day 1 of cycle 1 and 500 mg/m^2 for cycles 2-6. Six 28-day cycles	Chlorambucil 10 mg/m^2 days 1-7 + Rituximab 375 mg/m^2 on day 1 of cycle 1 and 500 mg/m^2 for cycles 2-6. Six 28-day cycles If no CR after 6 cycles: continue Chlorambucil monotherapy up to 6 further cycles	
No. of patients in treatment group	339 to date, but enrolment ongoing. 126 in interim analysis		
Interim analysis	58	68	
Primary efficacy outcome(s)	Confirmed complete response rate		
Blinding of patients/ outcome assessors, Allocation concealment	None described (abstract reviewed only)		
Interim Outcomes:	R+B	R+chlorambucil	
Response:	14/58 (24%)	7/68 (10%)	p = 0.033
Complete	88%	81%	p = 0.404
Overall	30%	13%	p = 0.054
1st line patients :	88%	80%	no difference
Complete	11%	4%	0.413
Overall	89%	83%	no difference
2nd line patients:			
Complete			
Overall			

Non-comparative studies: Bendamustine (single agent use) in recurrent/relapsed CLL/NHL (6 single arm studies where n>50). Page 1 of 2

Citation	Bremer, K 2002, 'High rates of long-lasting remissions after 5-day bendamustine chemotherapy cycles in pre-treated low-grade non-Hodgkin's-lymphomas', *J Cancer Res Clin Oncol*, vol. 128, no. 11, Nov, pp. 603-609.	Damaj, G, Gressin, R, Bouabdallah, K, et al. 2013, 'Results from a prospective, open-label, phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: the BENTLY trial', *J Clin Oncol*, vol. 31, no. 1, Jan 1, pp. 104-110.	Friedberg, JW, Cohen, P, Chen, L et al 2008, 'Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study', *J Clin Oncol*, vol. 26, no. 2, Jan 10, pp. 204-210.
Funding of study	*NR*	*NR*	Research support provided by Cephalon Inc. J.W.F. is supported in part by Grant No. CA-102216 from National Cancer Institute.
Design	*NR*	*NR*	Multi-centre
Duration of treatment	Patients received a median of 4 cycles (range 1-11)	6 cycles	*NR*
Patient population	Patients with pre-treated low-grade NHL Histologic subtypes: CLL n=15, immunocytic n=46, multiple myeloma: n=25, others: n=16.	Patients with histologically confirmed peripheral T-cell lymphoma (PTCL) or cutaneous T-cell lymphoma who progressed after ≥1 lines of chemotherapy (45% refractory). Median previous chemotherapies: 1 (range 1-3) Histology was predominantly angioimmunoblastic lymphadenopathy and PTCL NOS. Disseminated disease: 87%.	Ages 38 to 84 years, with predominantly stage III/IV indolent (80%) or transformed (20%) disease. Twenty-four (32%) were refractory to chemotherapy. Patients received a median of 2 prior regimens.
Treatment protocol (summary)	5-day cycles of bendamustine 60mg/m^2 (short iv infusion) daily, at intervals of 4-6 weeks.	Bendamustine at 120mg/m^2 per day on days 1 and 2, every 3 weeks for six cycles.	Bendamustine 120mg/m^2 intravenously on days 1 and 2 of each 21 day cycle
No. of patients registered	102	60	76
No. of patients in analysis	*NR*	*NR*	*74*

Outcomes:	*Response*	Remission (CR/PR): 76.5% Disease stabilisation: 19.6% PD: 3.9%	ORR: 50% (ITT) CR: 17 (28%) PR: 13 (22%)	ORR: 77% CR: 15% Unconfirmed CR: 19% PR: 43%
	Median duration of response	39 months for the NHL patients	*Not reported*	6.7 months (95% CI, 5.1, 9.9) 36% of responses were >1 year.
	Median PFS		3.6 months	*Not reported*
	Median OS	CLL patients: 32 months NHL patients: 31.5 months	6.2 months	*Not reported*
	Other (eg sub-group analysis etc)		Bendamustine showed consistent efficacy, independent of major disease characteristics. 20 patients (33%) received <3 cycles of bendamustine, mostly because of disease progression	Patients with indolent disease; median DOR was 9.0 months (95% CI 5.8, 16.7) Patients with transformed disease; median DOR was 2.3 months (95% CI 1.7, 5.1)
Adverse events:	*Grade 3/4 Haematologic*	Anaemia: 6.9%, thrombocytopenia: 11.8% and leukocytopenia: 24.5%	Neutropenia (30%) and thrombocytopenia (24%)	Neutropenia (54%), thrombocytopenia (25%), and anaemia (12%)
	Grade 3/4 Non-haematologic	Reversible reduction of performance status, loss of appetite, and nausea/vomiting and diarrhoea: <5%	Infections (20%)	Nausea and vomiting, fatigue, constipation, anorexia, fever, cough, and diarrhoea.
	Other	Bendamustine induced profound and long-lasting lymphocytopenias, including CD4+-, CD8+-, CD19+-, B-lymphocytes, and NK-cells		

ORR = Overall response rate (= CR+PR); CR = complete response; PR = partial response; PD = Progressive disease; ITT=intention to treat; DOR = duration of response; NOS=not otherwise specified; PFS=progression free survival; OS=overall survival; CLL=chronic lymphocytic leukaemia; NHL=non-Hodgkin lymphoma; NR = Not reported (for some studies the abstract only was sighted – additional information may be in full text publication).

Non-comparative studies: Bendamustine (single agent use) in recurrent/relapsed CLL/NHL (6 single arm studies where n>50). Page 2 of 2

Citation	Heider, A & Niederle, N 2001, 'Efficacy and toxicity of bendamustine in patients with relapsed low-grade non-Hodgkin's lymphomas', *Anticancer Drugs*, vol. 12, no. 9, Oct, pp. 725-729.	Kahl, BS, Bartlett, NL, Leonard, JP, et al. 2010, 'Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a Multicenter Study', *Cancer*, vol. 116, no. 1, Jan 1, pp. 106-114.	Ohmachi, K, Ando, K, Ogura, M, et al 2010, 'Multicenter phase II study of bendamustine for relapsed or refractory indolent B-cell non-Hodgkin lymphoma and mantle cell lymphoma', *Cancer Sci*, vol. 101, no. 9, Sep, pp. 2059-2064.
Funding of study	*NR*	*NR*	*NR*
Design	Single-institution trial	Multicentre	Multicentre phase II trial
Duration of treatment	Until CR/PR/SD confirmed on 2 consecutive cycles	6-8 cycles	Up to 6 cycles
Patient population	Low-grade NHL patients pre-treated with different cytostatic regimens	Rituximab-refractory, indolent B-cell lymphoma patients aged 31-84 years. Histologies include follicular (62%), small lymphocytic (21%), and marginal zone (16%) lymphomas. Patients received a median of 2 previous regimens (range, 0-6 previous regimens), and 36% were refractory to their most recent chemotherapy.	Japanese patients with relapsed or refractory indolent B-NHL or mantle-cell lymphoma (MCL).
Treatment protocol (summary)	Bendamustine 120mg/m^2 as a 1 hour infusion on 2 consecutive days. The treatment was repeated every 3 weeks	Bendamustine 120mg/m^2 by intravenous infusion on Days 1 and 2, every 21 days for 6 to 8 cycles.	Bendamustine 120mg/m^2 on days 1-2 of a 21-day cycle, for up to six cycles.
No. of patients registered	58	100	58
No. of patients in analysis	52	*NR*	*NR*

Outcomes:	*Response rates:*	CR: 11% PR: 62% SD: 10% No response: 17%	ORR: 75% CR: 14% Unconfirmed CR: 3% PR: 58%	ORR:* 91% (95% CI 82%, 97%) CR: 67% (95% CI 54%, 78%) ORR:** 93% (95% CI 84%, 98%) CR: 57% (95% CI 44%, 68%)
	Median DOR	16 months	9.2 months	*Not reported*
	Median PFS	*Not reported*	9.3 months	Not reached (at median follow-up 12.6 months)
	Median OS	36 months	*Not reported*	Not reached
	Other			Indolent B-NHL ORR: 90%, PFS at 1 year: 70% MCL ORR: 100%, PFS at 1 year: 90%
Adverse events:	*Grade 3/4 haematological*	Myelosuppression	Neutropenia (61%), thrombocytopenia (25%), and anaemia (10%).	
	Grade 3/4 Non haematological	Any grade: gastrointestinal toxicity and allergic reactions	Any grade: nausea (77%), infection (69%), fatigue (64%), diarrhoea (42%), vomiting (40%), pyrexia (36%), constipation (31%), and anorexia (24%).	
	Other	Side effects were generally mild	Six deaths were considered to be possibly treatment related.	

ORR = Overall response rate (= CR+PR); CR = complete response; PR = partial response; PD = Progressive disease; ITT=intention to treat; DOR = duration of response; NOS=not otherwise specified; PFS=progression free survival; OS=overall survival; CLL=chronic lymphocytic leukaemia; NHL=non-Hodgkin lymphoma; NR = Not reported (for some studies the abstract only was sighted – additional information may be in full text publication)

* IWRC=International Workshop Response Criteria; **revised RC=revised Response Criteria.

Non-comparative studies: Bendamustine + rituximab for refractory/relapsed CLL (3 single arm studies where n>50)

Citation	Fischer, K, Cramer, P, Busch, R, et al 2011, 'Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group', *J Clin Oncol,* vol. 29, no. 26, Sep 10, pp. 3559-3566.	Robinson, KS, Williams, ME, van der Jagt, RH, et al 2008, 'Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma', *J Clin Oncol*, vol. 26, no. 27, Sep 20, pp. 4473-4479.	Rummel, MJ, Al-Batran, SE, Kim, SZ, et al 2005, 'Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma', *J Clin Oncol*, vol. 23, no. 15, May 20, pp. 3383-3389.
Funding of study	Research grants from F. Hoffmann-La Roche and Mundipharma. The German Chronic Lymphocytic Leukemia Study Group receives financial support from German Cancer Aid.	Supported by Cephalon, Inc.	*NR*
Design	Prospective, multicentre (32, all in Germany), nonrandomised, phase II study	Multicentre (22 sites in the United States, Canada, and Australia), open-label, single-arm, phase II clinical trial.	Open label, phase II, multicentre trial (12 German centres).
Duration of treatment	Up to 6 courses Median follow-up time of 24 months,	4 to 6 courses	Median of 4 courses per patient
Patient population	Median age of 66.5 years (range 42-86yrs) Median of 2 previous therapies. 22 patients with fludarabine-refractory disease (28.2%) and 14 patients (17.9%) with deletion of 17p.	Median age of 60 years (range 40-84 yrs). Male 59% Median 3.4 years since diagnosis. Median prior chemotherapy regimens: 1 (range 1-4). Histology: Indolent 82% (FCC: 61%, SLL: 15%)	Median age: 64 years (range 40-81 yrs). Male: 63%. Stage IV disease: 79%, All pre-treated, 30% refractory to their last treatment. Histology: 24 follicular, 16 mantle cell, 17 lymphoplasmacytoid, and six marginal zone lymphoma.
Treatment protocol (summary)	Bendamustine 70mg/m^2 on days 1 and 2 combined with rituximab 375 mg/m^2 on day 0 of the 1st course and 500mg/m^2 on day 1 during subsequent courses.	Rituximab 375mg/m^2 IV on day 1 and bendamustine 90mg/m^2 IV on days 2 and 3 of each 28-day cycle for 4-6 cycles. An additional dose of rituximab was administered 1 week before the 1st cycle and 4 weeks after the last cycle.	Bendamustine was given at a dose of 90mg/m^2 as a 30-minute infusion on days 1 and 2, combined with rituximab 375mg/m^2 on day 1, for a maximum of four cycles every 4 weeks

No. of patients registered		83	67	63
No. of patients excluded from analysis		5 (missing consent x3, wrong diagnosis x2)	1 (withdrew consent)	*NR*
No. of patients in analysis		78	66	*NR*
Outcomes:	*Response rates*	ORR: 59.0% (95%CI 47.3%, 70.0%) CR: 9.0% PR: 47.4% Nodular PR: 2.6%	ORR: 92% CR: 41% Unconfirmed CR: 14% PR: 38%	ORR: 57/63 (90%) (95% CI 80%, 96%) CR: 60% (95% CI 47%, 72%) PR: 30% (95% CI 19%, 43%)
	Median DOR	*Not reported*	21 months (95% CI 18, 24 months)	*Not reported*
	Median PFS	Median event-free survival: 14.7 months.	23 months (95% CI 20, 26 months)	24 months (range, 5 to 44+ months)
	Median OS	*Not reported*	*Not reported*	Not yet reached
	Subgroup analyses	ORR was 45.5% in fludarabine-refractory patients and 60.5% in fludarabine-sensitive patients. Among genetic subgroups: 92.3% of patients with del(11q), 100% with trisomy 12, 7.1% with del(17p), and 58.7% with unmutated IGHV status responded to treatment.	Outcomes were similar for patients with indolent or mantle cell histologies.	In mantle cell lymphomas: ORR= 75% (95% CI 48%, 93%) with a CR: 50%. Median PFS for MCL patients was 18 months, whereas the median PFS for patients with follicular and lymphoplasmacytoid lymphomas has not yet been reached.
Adverse events:	*Grade 3/4 haem/ myelosuppression:*	Neutropenia: 23.1%, Thrombocytopenia: 28.2%, Anaemia: 16.6%	Neutropenia: 36%, Thrombocytopenia: 9%	Leukocytopenia: 16% Thrombocytopenia: 3%
	Grade 3/4 non-heam toxicities:	Severe infections occurred in 12.8% of patients	10 infections/6 patients, compartment syndrome, pulmonary edema, and toxic epidermal necrolysis (1 patient each).	
	Other		Events commonly attributed to rituximab included fatigue (45%) and nausea (30%).	

CLL=chronic lymphocytic leukaemia; CR = complete response; DOR = duration of response; FCC = Follicular Cell Centre; IGHV=. immunoglobulin heavy variable (gene), ITT=intention to treat; NHL=non-Hodgkin lymphoma; NOS=not otherwise specified; PD = Progressive disease; PFS=progression free survival; PR = partial response; OS=overall survival; ORR = Overall response rate (= CR+PR); SLL=small lymphocytic lymphoma.
NR = Not reported (for some studies the abstract only was sighted – additional information may be in full text publication)

Non-comparative studies: Bendamustine (mixed regimens, including cytarabine) in recurrent/relapsed CLL/NHL (n>50 or including cytarabine).

Citation	Iannitto, E, Morabito, F, Mancuso, S, et al, L 2011, 'Bendamustine with or without rituximab in the treatment of relapsed chronic lymphocytic leukaemia: an Italian retrospective study', *Br J Haematol*, vol. 153, no. 3, May, pp. 351-357.	Sanchez-Gonzalez, B, Penalver, FJ, Medina, A, et al. 2012, 'Clinical experience of bendamustine treatment for non-Hodgkin lymphoma and chronic lymphocytic leukemia in Spain', *Leuk Res*, vol. 36, no. 6, Jun, pp. 709-714.	Visco, C, Finotto, S, Zambello, R, et al 2013, 'Combination of rituximab, bendamustine, and cytarabine for patients with mantle-cell non-Hodgkin lymphoma ineligible for intensive regimens or autologous transplantation', *J Clin Oncol*, vol. 31, no. 11, Apr 10, pp. 1442-1449.
Funding of study	Grants from the Associazione Italiana Ricerca sul Cancro cofinanced by CARICAL, Fondazione 'Amelia Scorza' ONLUS, and Provincia di Cosenza		
Design	Two-arm retrospective multi-centre (24 Italian centres) study	Retrospective questionnaire to 22 Spanish centres who had used bendamustine, to include all patients with use	Phase II study
Patient population	Median age 66 years (range 39-85 yrs). CLL: 43% relapsed and 57% were resistant. Median previous therapies = 3; range 1-8.	Patients with relapsed/refractory NHL or CLL were eligible 49 patients had indolent NHL, 18 aggressive NHL and 42 CLL. 40% were refractory to previous treatment Median age; in NHL: 67 (range 37–87 yrs) in CLL: 65 (range 35–82 yrs)	Patients with Mantle Cell Lymphoma (NHL) age ≥ 65 years (median age 70) who were previously untreated or relapsed or refractory (R/R) after one prior immunochemotherapy treatment. (35% refractory, 20 previously untreated patients).
Treatment protocol (summary)	Arm 1: Bendamustine alone: 70–130mg/m^2, delivered in two consecutive days in a 28-d cycle Arm 2: Bendamustine (as above) combined with rituximab 375mg/m^2 on day 1. (Median bendamustine dosage given: 100 mg/m^2 per day, range 90-130 mg/m^2 per day).	All types of bendamustine-containing regimens were acceptable. Most frequently used was bendamustine + rituximab, independent of histology. Median daily dose of bendamustine was 90mg/m^2 for NHL and 70mg/m^2 for CLL patients for 2 days of a 28 day cycle. Patients received a median of 4 cycles of bendamustine (range 1–8). A total of 443 cycles of bendamustine-containing chemotherapy was administered.	Stage one: established the maximum-tolerated dose (MTD) of cytarabine in R-BAC. Stage two: patients received R 375 mg/m^2 intravenously [IV] on day 1, B 70 mg/m^2 IV on days 2 and 3, and **cytarabine** MTD IV on days 2 to 4 every 28 days for four to six cycles.

No. of patients registered		109 Bendamustine alone; n = 22, Rituximab+bendamustine; n = 87			109	40	
No. of patients in analysis		105			109	*Not reported*	
Outcomes:		Collapsed treatment arms	B single agent	B+R		Untreated patients	R/R patients
	Response rate	ORR: 69·6% CR: 28·6% PR: 41%	CR: 13.6% PR: 68.2 No Response: 18.2%	CR: 32.5%PR: 33.7% No response: 33.7%	ORR: 66% CR: 30%	ORR: 100% CR: 95% for	ORR: 80% CR: 70%
	Median DOR	13 months	Response was significantly higher in patients treated with B+R (p = 0·014) and in those responsive to the previous treatment (p=0·04).			2-year PFS rate(± standard deviation):	
	Median PFS	16.0 months			13 months	95% ± 5%	70% ± 10%
	Median OS	16·8 months					
	Other Analysis	In multivariate analysis, only resistant disease status at start of bendamustine treatment had an independent prognostic value for OS (HR 3·2, 95% CI 1·4, 7·3, p = 0·006). Response was significantly higher in patients responsive to previous treatment (P=0·04).			ORR observed in refractory patients was 45%. Outcome was influenced by histology, number of previous treatments, resistance to previous chemotherapy.		
Adverse events:	*Grade 3/4 Haematologic/ Myelosuppress'n*	Neutropenia 16.5%, Thrombocytopenia 17.5%, Anaemia 15.5%			Neutropenia: 53%, thrombocytopenia: 28%, anaemia: 20%. G-CSF was administered to 75 patients (69%) in 1 or more cycles	Thrombocytopenia: 87%; febrile neutropenia: 12%.	
	Grade 3/4 Non-	Infection 4.5%			Opportunistic infections: 14 patients (13%)		

Haematologic		(2 herpes zoster, 1 pulmonary aspergillosis, 2 reactivations of hepatitis B virus or hepatitis C virus and 5 severe bacteremias)	
Other	3 of 34 deaths (9%) were due to infections (1x herpes encephalitis; 1x bacterial pneumonia, 1x pulmonary aspergillosis) and were considered to be treatment-related.	Overall 63% of patients had adverse events grade 3-4 (mainly haematological).	

CLL=chronic lymphocytic leukaemia; NHL=non-Hodgkin lymphoma; R-BAC= rituximab + bendamustine + cytarabine; B=bendamustine; B+R=bendamustine + rituximab; G-CSF = Granulocyte colony-stimulating factor; R/R = refractory or relapsed; ORR=overall response rate; CR=complete response; PR=partial response; DOR = duration of response.

OVERVIEW OF EVIDENCE

Study Design and Quality

None of the high quality evidence (i.e. systematic reviews or randomised controlled trials) is directly applicable to the situation in South Australia.

Although the studies are in the correct population, there are limitations with respect to the applicability of their results to the population currently being treated in South Australian public hospitals ie those receiving bendamustine through special access scheme arrangements.

The interventions (specifically the bendamustine dose) used in the randomised trials with completed data are not the same as the doses used in South Australia; the bendamustine dose was lower in the monotherapy trial (Niederle, Megdenberg et al. 2013) (100mg in trial vs 120mg in SA), but higher than that used in South Australia in the combination therapy trial (Rummel, Kaiser et al. 2010) (90mg in trial vs 70mg in SA). Therefore, in terms of absolute activity/response the effects could under-estimate or over-estimate, respectively, the outcomes that would be achieved.

The comparator in these trials was fludarabine (with/without rituximab) – an active chemotherapy. However it is likely that patients receiving bendamustine in South Australia are likely to have already received fludarabine as first line treatment, given this is routinely available (and PBS listed). It is unclear whether patients would receive fludarabine second line in those patients who have refractory disease, although it may well be used in those patients who had an initial response but relapsed over time.

Other chemotherapy options are available for relapsed/refractory patients (see NCCN Clinical Pathways) but it is unclear exactly what mix of therapies are commonly given in current practice in South Australia. Relapsed patients may be re-treated with the initial therapy but different salvage treatments may be offered second line, while other refractory patients may receive supportive or palliative care only.

The randomised controlled trial evidence primarily relates to the use of bendamustine as a first-line treatment for CLL, and as such is the basis of the recommendations by NICE and the Scottish Medicines Consortium, that bendamustine use is an appropriate first-line treatment for chronic lymphocytic leukaemia (CLL, Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

There are numerous case series available which include the same patient population and dosage regimens as used in South Australian public hospitals. These are useful in that they confirm that the regimen is being used in clinical practice around the world.

Effectiveness

A statistically significant gain in progression free survival and response rates was observed when bendamustine was used in combination with rituximab, compared to fludarabine in combination with rituximab (Rummel, Kaiser et al. 2010). However, there was no difference in effect when bendamustine was used as monotherapy (Niederle, Megdenberg et al. 2013). The lack of effect in monotherapy may have been due to the low dose of bendamustine that was used, as well as the lack of statistical power in the trial. Data on overall survival for both trials (bendamustine monotherapy or bendamustine in combination with rituximab), while still immature does not look particularly promising with respect to overall survival gain relative to the comparators.

Given that the PFS gain was achieved in comparison to an active treatment in relapsed or refractory indolent lymphomas, it may be reasonable to expect that bendamustine would compare favourably against placebo (or no active treatment). However, it is unclear what proportion of the benefit could be attributed to relapsed or refractory status *ie* whether the PFS gain is more likely to occur in relapsed as opposed to refractory indolent lymphoma patients.

Treatment response was a primary or secondary outcome in most studies and varying degrees of treatment response (between 50% and 100%) were reported in many studies/series. However relapsed/refractory patients consistently achieved less response than patients receiving bendamustine treatment as a first-line option.

The numerous case series published appear to 'support' the treatment regimen, with some authors interpreting all positive treatment responses in case series as indications of treatment effectiveness. However without comparative data it is not possible to quantify the treatment effect attributable to bendamustine and separate this from placebo benefits and possible spontaneous disease improvements (although the grave nature of the natural history of NHL/CLL once patients have become refractory to/relapsed following treatments is acknowledged).

Safety

The primary treatment-limiting toxicities associated with bendamustine treatment are haematological. Studies commonly reported Grade 3 or 4 neutropenia, leukopenia and/or thrombocytopenia.

Treatment-associated infections were also often reported, including infections that led to fatalities in some studies. It is unclear what proportion of these infections were solely related to treatment in the studies as patients with NHL and CLL are immunocompromised as part of the normal disease process.

Despite the recommended 3-weekly dosing in the product information, promotional material for Levact also states:

> '*an international consensus panel… has recommended that bendamustine should be dosed every 4 weeks instead of every 3 weeks to reduce haematological toxicity, dose reductions or treatment delays.*' (Cheson BD, et al. *Clin Lymphoma Myeloma Leuk* 2010;10:21–7.)

With the exception of infection – which is associated with haematological toxicity and the underlying disease process - non-haematologic adverse events have rarely been dose limiting. The most common non-haematologic adverse events include fatigue, nausea, xerostomia, and pyrexia. Although reasonably common as low-grade events, few studies reported any grade 3 or 4 non-haematological events.

Clearly, any concerns regarding the safety of bendamustine and the effect of the adverse events on quality of life are substantially greater in patients that would otherwise be receiving no active treatment or relatively non-aggressive treatments. Given the lack of clear benefit and the side effect profile, the Cochrane review authors did not recommend bendamustine for indolent lymphoma patients where chlorambucil was still a treatment option; however, in other circumstances where toxicity was comparable to alternative treatments then the potential (but unknown) benefit of bendamustine treatment was acknowledged (Vidal, Gafter-Gvili et al. 2012).

Current usage

Between 1/7/2012 to 13/06/2013 (347 days), bendamustine was dispensed to 9 different patients (diagnoses not provided), ranging from 1 to 13 times per patient, for a total of 62 uses, at a total cost of ~$49,895.

Based on existing data, the median use per patient is 6 courses (average 6.9). However the expected quantity per person is likely to be underestimated if some patients included in the data set have not yet finished treatment.

Comparative Costs

Current prices for bendamustine are: $373 per 100mg vial and $95 per 25mg vial[d]

Based on the doses used in South Australian hospitals[e], the bendamustine acquisition cost per person for a complete course of treatment would be expected to be:

For NHL - approximately $9,564 per complete course per person (range $7,896 - $11,232)

For CLL - approximately $4,870 per complete course per person (range $2,984 - $6,756)

This is comparable to the existing average cost per person of ~$5,500. This is a likely underestimate of future costs given patients may not have completed treatments and some patients received product subsidised for clinical trial use.

In the context of the current SAS usage of bendamustine (with or without additional agents) the comparator is understood to most likely be usual care (including palliative care), as bendamustine is requested as a salvage therapy when all other therapies are exhausted. The costs of usual care are not estimated as it is common to both arms of the comparison (see cost-offsets).

Another potential comparator for refractory CLL patients is alemtuzumab. This product is registered in Australia but is not funded by the PBS. It is not routinely available across the public hospitals.

Cost offsets

Where bendamustine is being used as a last-line/salvage treatment it is reasonable to assume that there are no cost-offsets associated with treatment. Assuming on the available evidence that bendamustine treatment may be effective and extend PFS and perhaps OS, it is not suggested that the treatment will be curative. Therefore, standard care and palliative care costs might be delayed but not off-set

If bendamustine was to be used in place of an active treatment (such as fludarabine - as was done in the clinical trials, where usage was second-line or later, but not necessary last-line/salvage) then alternative chemotherapy costs would need to be considered.

Other costs

Use of bendamustine is associated with additional costs including:

[d]Price 22/08/2013 per email from Kailin Teh, Specialist Pharmacist - Haematology, FMC. Note:price is prone to varying depending on currency exchange rates.

[e] Based on clinical advice per email 13/06/13 from Kailin Teh, Specialist Pharmacist - Haematology, FMC

- Consumables for reconstitution and administration, eg, fluids, bags, needles etc
- Import duties/taxes and shipping costs
- Administration costs - medical/nursing and day centre/ward costs. These are estimated at $529 per day of administration as a public hospital outpatient (based on average cost for a non-admitted patient in medical oncology, excluding pharmacy costs; NHCDC Round 12 p.145.)
- Monitoring and managing side-effects. These would include blood tests ie blood counts (MBS Item 65070; $16.95), liver function tests (MBS Item 66512; $17.70), electrolytes etc, at least once each cycle, blood products and G-CSF for the management of febrile neutropenia and opportunistic infections.
- Concurrent medications - anti-emetic prophylaxis (eg a 5HT3 antagonist (Cheson, Friedberg et al. 2010)) and if used in a combination regimen; rituximab and cytarabine (and their respective associated costs).
- For simplicity, the costs of rituximab and cytarabine are not considered given that it would be assumed that use of these additional agents are active and would confer additional benefits and therefore should be considered as separate cost analyses.

Although many of the above costs have not been estimated, it is apparent that additional (non-drug procurement) costs for bendamustine treatment would be greater than $1,092[f] per cycle of treatment, which equates to >$6,555 per patient receiving 6 cycles (one complete course).

The total costs of treatment associated with bendamustine per patient would therefore be, on average, in excess of $16,110[g] for NHL or $11,425[h] for CLL treatment.

Effectiveness/Utility

Although the evidence would suggest that bendamustine does produce some treatment effect in NHL and CLL patients, any quantification of this is highly uncertain given the lack of comparative trials in the correct patient population and/or uncertainties regarding the clinical effectiveness of bendamustine relative to treatments used in South Australia for relapsed/refractory indolent lymphoma.

Furthermore, consideration of the side-effects of bendamustine and the impact that they would have on patient quality of life would need to be taken into account in an economic analysis attempting to estimate an incremental cost effectiveness ration, ICER ($/QALY).

On face value and given that the cost data are incomplete, it might be expected that to be broadly considered cost-effective in the Australian setting, bendamustine should demonstrate a gain of at least 2.5 quality-adjusted life months over alternative treatments i.e. this would correspond to ICERs of ~ $55,000-$77,000/QALY, depending on the dosing regimen used. It is highly uncertain whether bendamustine could achieve such an outcome.

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[f] One cycle would incur, at minimum; 2x administration costs (day 1 and day 2) at $529 each +1 FBC $16.95 + LFT $17.70) = $1,092.

[g] $16,110 = average drug acquisition costs per complete course (NHL) $9,564 + other costs (administration etc) >$6,555

[h] $11,425 = average drug acquisition costs per complete course (CLL) of $4,870 + other costs (administration etc) >$6,555

There are two published studies on the cost-effectiveness of bendamustine as first-line treatment in CLL – one in England and Wales (Woods, Hawkins et al. 2012) and one in the Netherlands (Vandekerckhove, Holtzer-Goor et al. 2012) These studies estimated ICERs of £11,960/QALY and € 7,374/LYG, respectively, and concluded treatment was cost-effective. However these findings may not be applicable in the salvage setting or in the Australian healthcare setting.

Appendix 2 Search strategy

Cochrane Database of Systematic Reviews

Search strategy: 1. bendamustine

Medline (PubMed)

Search strategy: 1. bendamustine OR sdx-105 OR sdx105 OR treakisym OR ribomustin OR levact OR treanda

2. leukaemia or leukemia or lymphoma or CLL or NHL
3. #1 AND #2
4. Filters: Systematic Reviews; Randomized controlled trial; Clinical trial; Humans

Citations returned: 55

Embase

Search strategy:

1. bendamustine OR sdx-105 OR sdx105 OR treakisym OR ribomustin OR levact OR treanda (all terms/exp and text)
2. leukaemia or leukemia or lymphoma or CLL or NHL (all terms/exp and text)
3. #1 AND #2
4. #3 and Limits: Humans and english
5. #$ and 'clinical study' OR 'clinical trial' OR 'controlled clinical trial' OR 'controlled study' OR 'dosage schedule comparison' OR 'drug dose comparison' OR 'major clinical study' OR 'multicentre study' OR 'phase 2 clinical trial' OR 'phase 3 clinical trial' OR 'randomized controlled trial'

Citations returned: 607

Clinical Trials Registry

Search terms: Bendamustine AND (leukaemia or leukemia or lymphoma or CLL or NHL), Trial Status: ongoing.

Listings returned: 128

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