NHS England

Evidence review: Bendamustine-based chemotherapy for first-line treatment of Mantle Cell lymphoma (MCL)

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Contents

1. Introduction

Lymphomas are cancers of the lymphatic system, which is a part of the body's immune system (NICE 2012). Traditionally, lymphomas are divided into Hodgkin's disease (now known as Hodgkin's lymphoma) and non-Hodgkin's lymphoma. Non-Hodgkin's lymphomas are a diverse group of conditions which are categorised according to the cell type affected (B-cell or T-cell), as well as the clinical features and rate of progression of the disease. Mantle cell lymphoma (MCL) is a rare type of non-Hodgkin's lymphoma affecting the B-cells. Lymphomas are graded according to the rate at which the abnormal lymphocyte cells divide. They are termed 'high-grade' (or aggressive) when they divide quickly and 'indolent' (or low-grade) when they divide slowly. MCL exhibits a moderately aggressive course; it is rarely curable with currently available standard treatment.

The registered annual incidence of non-Hodgkin's lymphoma in England and Wales is around 10,400. Of these mantle cell lymphoma accounts for around 5 to 8%, equivalent to around 670 new diagnoses per year (NICE 2012).

MCL usually occurs in older adults (the median age of presentation is 60 years) and has a male predominance. Despite response rates of 50-70% with many regimens, MCL typically progresses after chemotherapy. The median survival time is approximately 3 years; the 10-year survival rate is 5 to 10%.(NICE 2012)

Currently treatment is based on an assessment of the patient's ability to tolerate intensive treatment (Nazeef M, 2015). Younger fit patients presenting with MCL and without significant co-morbidities are generally treated with a chemoimmunotherapy regimen and consolidation of response with high dose chemotherapy and autologous stem cell transplantation (Dreyling M, 2014).There are a number of induction regimens available but no universally accepted standard of care and prospective studies that compare intensified regimens have not been performed (McKay 2012, Cheah, 2016).

The European Society for Medical Oncology (ESMO) support the use of a rituximab containing induction regimen of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) and high-dose cytarabine followed by high dose consolidation and autologous stem cell transplant (ASCT) (Dreyling M, 2014). The largest cohort study assessing this regimen (n=455) reported an OR rate of 99%, a CR of 61%, a median PFS of 7.3 years and a treatment related mortality rate of 4% (Cheah, 2016).

However up to 50% of patients that present with MCL are not considered candidates for intensive treatment (Nazeef, 2014). Where chemotherapy is considered appropriate the most widely used treatment options for the first-line treatment of mantle cell lymphoma are cyclophosphamide, doxorubicin, vincristine and prednisolone in combination with rituximab (R-CHOP) and fludarabine and cyclophosphamide in combination with rituximab (R-FC). Other treatment options may include; cyclophosphamide, vincristine and prednisolone in combination with rituximab (R-CVP) and rituximab with chlorambucil. In their clinical guideline ESMO state that rituximab in combination with chemotherapy such as CHOP or bendamustine should be used and R-CVP is associated with inferior response rates and progression free survival rates (Dreyling M, 2014). They also discourage the use of purine analogue-based regimens such as R-FC (rituximab with fludarabine and cyclophosphamide) or R-FM (rituximab with fludarabine and mitozantrone) due to early failures and prolonged myelosuppression.

In 2012, the British Society for Haematology Committee (BHSC) recommend that first line chemotherapy regimens should contain rituximab and that older, less fit patients should receive R-chemotherapy regimens such as R-FC, R-CVP, R-CHOP, R-bendamustine, or R-chlorambucil but do not provide any advice on differentiating between these regimens (McKay 2012).

NICE has also approved the use of bortezomib plus rituximab as an option for previously untreated mantle cell lymphoma in adults for whom haematopoietic stem cell transplantation is unsuitable (NICE, 2015). Within that appraisal NICE state that rituximab in combination with cyclophosphamide, doxorubicin, prednisone and vincristine (R-CHOP) is the current standard of care for those who could tolerate it, and should be considered the main comparator for regimens

used in people with untreated mantle cell lymphoma for whom haematopoietic stem cell transplant is unsuitable.

As stated above bendamustine-based regimens are considered to be an option for this patient group although it is not licensed for use in this population. Bendamustine (Levact, Napp Pharmaceuticals) is an alkylating antitumour agent (NICE, 2012). The antineoplastic and cytocidal effect of bendamustine hydrochloride is based on a cross -linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired.

There is some evidence to suggest that bendamustine has a favourable side effect profile compared to other anthracycline-based regimens and thus may be the preferred agent in some patients presenting with MCL. When used in this indication it is administered by intravenous infusion at a dose of 90mg/m2 on two days every 28 days for up to 6 cycles

Three specific questions are addressed in this review.

What evidence is available to assess how bendamustine-based regimens compare with other regimens used in the treatment of patients with MCL receiving non-intensive, first-line, treatment in terms of efficacy, safety, quality of life and cost-effectiveness

What evidence is available to assess how bendamustine-based regimens compare with other regimens used in the treatment of patients receiving intensive first-line treatment prior to consolidation with high-dose chemotherapy and autologous stem cell transplant?

Is there any evidence available to guide selection of patients that will benefit from a bendamustine-based regimen instead of an alternative regimen in patients with MCL being treated with first-line chemotherapy

2. Summary of results

The findings of this review are mainly based on two randomised Phase III studies that compared B-R to R-CHOP or R-CVP in patients with indolent Non-Hodgkin's Lymphoma or MCL.

One of the studies (based on subgroup analysis of results in 94 patients with MCL) showed that B-R treated patients have a significantly longer period of progression free survival; B-R treated patients had a median PFS of 35.4 months compared to 22.1 months for R-CHOP.

The second study (based on results in 74 enrolled patients) showed that the complete response (CR) rate for B-R treatment was higher than that seen with R-CHOP/R-CVP; CR was 50% in the B-R treatment group and 27% in the standard therapy group.

There are insufficient data at this time to identify any difference between the treatments in overall survival. Neither study evaluated any differences in the ongoing response to rituximab maintenance therapy.

There are insufficient data to make a full assessment of any differences in the quality of life of patients who receive B-R compared to R-CHOP/R-CVP.

B-R appears to cause less alopecia and paraesthesia than the standard treatment in patients with either indolent NHL or MCL but is more likely to cause allergic reactions and skin rashes

One very small uncontrolled study (n=23) was identified in which a bendamustine-based regimen was used in patients receiving intensive first-line treatment prior to consolidation with high-dose chemotherapy and autologous stem cell transplant. The regimen tested achieved complete response rates in 96% of patients treated but without a control group or longer-term follow up it is not possible to set these results into any clinical context.

3. Methodology

Scoping. A PICO was prepared by the Clinical and Public Health Leads for this policy area at NHS England (see section 10 below)

Appraisal. The following databases/sites were searched for relevant publications: NHS Evidence, The Cochrane Library, EMBASE, MEDLINE, National Guideline Clearinghouse (USA), UK National Library for Health guidelines database, the New Zealand Guidelines Group, the Australian National Health & Medical Research Council Guidelines Portal, the UK National Institute of Health and Care Excellence. (see section for search terms)

The titles and abstracts of the results from the literature searches were examined using the criteria from the PICO. Full text versions of papers that were deemed to be useful or potentially useful were obtained and a decision made on the appropriateness of including their findings in this review.

Generally, where reasonable or good quality phase 3 studies were available, they were used in preference to earlier phase 1 and 2 studies. One study on cost-effectiveness was identified as being potentially relevant to the NHS in England.

Major, authoritative guidelines and reviews were examined and included where relevant. All papers included in this evaluation were assessed as to their quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria, the applicability of the results.

The evidence to support individual findings was graded.

4. Results

What evidence is available to assess how bendamustine-based regimens compare with other regimens used in the treatment of patients with MCL receiving non-intensive, first-line, treatment in terms of efficacy, safety and cost-effectiveness

Two fully published RCTs were identified from a search of the literature databases cited and a search of bibliographic references indicate that these were the only two randomised studies available that compare bendamustine and rituximab (B-R) with standard rituximab-containing treatment regimens in untreated patients with MCL that are .not considered suitable for more intensive treatment. In both cases the trials were powered to demonstrate that B-R was non-inferior to standard treatments (R-CHOP or R-CVP) in a population that comprised patients with either indolent NHL or MCL and although results are broken down for the subgroup with MCL in terms of effectiveness, the adverse event data are only presented in terms of incidence for the whole trial population.

Effectiveness

The Study Group for Indolent Lymphomas (StiL) study (Rummel, 2013) included 46 patients with MCL that were assigned to B-R and 48 to R-CHOP. The primary outcome measure for the whole trial population was progression free survival (PFS). After a median follow-up period of 45 months it was reported that patients treated with B-R had a longer median PFS (35.4 months) compared to R-CHOP (22.1 months). The secondary outcome measures included overall response (OR, no significant difference shown – 93% vs 91% respectively). There did not appear to be any significant difference in overall survival (OS) but insufficient time had elapsed to assess this properly at publication.

The analysis showing a statistically significant increase in PFS in the subgroup of patients with MCL was exploratory and could therefore be viewed as only being hypothesis generating.

Follow up results have since been published in abstract form (Rummel, 2015). The authors state

that after 7 years of follow up there are no significant differences in overall survival seen between patients with MCL in the two arms of the study (n= 95; HR = 1.28, 95% CI: 0.69–2.39; p = 0.429). There is an unexplained 1 patient discrepancy between the original study (n=94) and the 7-year follow up results presented at conference (n=95)

The BRIGHT study (Flinn I, 2014) included 74 patients with MCL of whom 36 were randomized to receive B-R and 38 to standard therapy (R-CHOP or R-CVP depending on clinical assessment). The primary outcome was Complete Response (CR) rate and a rate of 50% was reported for BR compared to 27% for standard treatment. The overall response (OR) rates recorded were 94% for BR compared to 85% for standard treatment. Again these results are based on a subgroup analysis so it could be argued that the trial was not adequately powered to support a suggestion that B-R is non-inferior to standard treatment in patients with MCL in terms of this outcome measure. This trial did not assess more patient-orientated outcomes such as progression-free survival or time to next treatment and follow up was limited to completion of the treatment regimen.

Safety and quality of life

There is no specific information available which supports a comparison of relative safety of B-R and standard treatments in patients with MCL. The two RCTs discussed above provide an overview of safety data in a cohort of patients with indolent NHL or MCL and key findings are outlined below:

- Compared with standard treatment B-R is associated with significantly lower incidences of peripheral neuropathy/parasthesiae, alopecia and stomatitis
- Compared with standard treatment B-R is associated with less Grade 3-4 leukocytopenia and neutropenia than R-CHOP There was no significant difference in these parameters between B-R and R-CVP in the BRIGHT study. In both trials it was noted that B-R patients were less likely to require G-CSF treatment to maintain neutrophil counts.
- Compared with standard treatment B-R is associated with significantly higher incidences of vomiting, skin reactions and lymphocytopenia.

It is reported that 20 of the 261 patients that received B-R have developed secondary cancers compared with 23 of the 253 that received R-CHOP and these numbers remained unchanged over 7 years of follow up (Rummel, 2015)

In a Quality of Life assessment that was conducted as part of the BRIGHT study it was reported that patients treated with B-R reported improvements in cognitive functioning, physical functioning, social functioning, emotional functioning and global health status and a reduction in dyspnoea, constipation and fatigue at some but not all time points compared with standard treatment (Burke 2016). Patients treated with standard treatment reported less nausea or vomiting and appetite loss at several time points.

Health economics

No relevant evidence was identified to quantify the incremental cost effectiveness of using B-R instead of standard treatment in patients with MCL. An economic modelling study based on the results of the RCT comparing B-R with R-CHOP in patients with either indolent NHL or MCL (the STiL study discussed above) was considered to be out of scope on the basis that patients with MCL were explicitly excluded from this analysis (Dewilde 2014)

What evidence is available to assess how bendamustine-based regimens compare with other regimens used in the treatment of patients receiving intensive first-line treatment prior to consolidation with high-dose chemotherapy and autologous stem cell transplant?

Only one small open-label single arm study was identified which assessed outcomes in 23 patients with newly diagnosed MCL and considered eligible for transplant (Armand 2016). These patients were treated with 3 cycles of B-R followed by 3 cycles of rituximab with high-dose cytarabine. It is reported that 96% of patients treated achieved a complete response (CR). It is also noted that only 1 out of 15 patients tested had measurable residual disease at the end of the treatment regimen and that 21/22 proceeded to ASCT with one patient declining. The adverse effects seen during the B-R phase were similar to those described above with Grade 3/4 leucopenia seen in over 30% of cycles administered.

No further data were identified to support an analysis of impact on quality of life or cost effectiveness.

Is there any evidence available to guide selection of patients that will benefit from a bendamustine-based regimen instead of an alternative regimen in patients with MCL being treated with first-line chemotherapy

The most recently published Clinical Guideline from ESMO states that patients that are not considered suitable for dose-intensified regimens should be treated with rituximab in combination with chemotherapy such as CHOP or bendamustine (Dreyling M, 2014). They state that R-CVP is associated with inferior response rates and durations of PFS and that purine analogue based schemes (i.e. those containing fludarabine) should also be discouraged due to early failures and long-term immunosuppression. However ESMO do not provide any advice on potential criteria to be considered when choosing between B-R and R-CHOP. BSHC support the use of rituximab-containing regimens such as R-FC, R-CVP, R-CHOP, R-bendamustine or R-chlorambucil and do not differentiate between them (McKie 2012)

In terms of contra-indications listed in the relevant SPCs for patients not previously exposed to chemotherapy doxorubicin should not be used in patients with a history of heart disease (specifically severe arrhythmias, heart failure, previous myocardial infarction, acute inflammatory heart disease) and vincristine should not be used in patients with the demyelinating form of Charcot-Marie-Tooth syndrome (Summaries of Product Characteristics for doxorubicin and vincristine).

5. Discussion

What evidence is available to assess how bendamustine-based regimens compare with other regimens used in the treatment of patients with MCL receiving non-intensive, first-line, treatment in terms of efficacy, safety and cost-effectiveness

The evidence provided from small subgroup analyses of two randomised controlled clinical trials of B-R compared to R-CHOP/R-CVP in treatment naïve MCL is generally supportive of the comparative effectiveness of B-R compared to R-CHOP or R-CVP. The StiL study demonstrated improved progress free survival which would have clinical advantages given the size of the difference between the medians of 13.3 months. However this remains the only evidence derived from a controlled study that demonstrates a difference in this outcome and it is based on an unspecified subgroup analysis. The BRIGHT study showed that B-R was non-inferior to R-

CHOP/R-CVP based on the primary outcome measure of complete response (CR) but did not provide any data in terms of impact on PFS.

Neither RCT however showed any treatment differences in overall survival.

The conclusion that B-R and R-CHOP are similarly effective in terms of impact on overall survival is supported by an unpublished meta-analysis (Stradwick S 2015)

The StiL study was liable to a degree of bias as patients, investigators and assessors were unblinded to which treatment was being used. The BRIGHT study addressed this by using two blinded assessors from an Independent Review Committee (IRC) to assess images and clinical data for the assessment of the primary outcome measure of complete response (CR). There is some evidence from BRIGHT that unblinded assessors may have judged complete response rate to be greater for B-R treated patients than the ICR. This may explain the difference between the CR rates between the two studies.

The other limitations from both studies relate to the non-availability of longer term, time-dependent outcomes (e.g. overall survival) and the fact that neither study included the option of continued maintenance therapy with rituximab as advocated by ESMO (Dreyling, 2014). Hence there is no data on how B-R treated patients respond to rituximab maintenance compared to those treated with R-CHOP.

There are limited data on differences in quality of life in B-R treated patients. The data available are limited to assessments made during induction treatment; the clinical significance of the benefits was small, and the differences between the groups were not statistically significant at all points in time.

The side effect profile of B-R is qualitatively different to that of R-CHOP/R-CVP in some respects. Some individual drug specific side effects seen with CHOP and CVP are less likely with bendamustine. These include alopecia, peripheral neuropathy/parasthesia and stomatitis. Whilst being associated with less leukopenia and neutropenia than R-CHOP and R-CVP, B-R is associated with more lymphocytopenia.

B-R is associated with a higher incidence of drug hypersensitivity and skin rashes than R-CHOP or R-CVP.

Some areas of uncertainty exist about

- longer term, time dependent outcomes (for example overall survival)
- longer-term adverse effects including impact on developing secondary tumours
- possible bias arising from unblinded assessment of primary outcomes in one of the major RCTs
- how B-R treated patients respond after rituximab maintenance therapy compared to those treated with R-CHOP/R-CVP
- How B-R compares with bortezomib-rituximab which is licensed and approved by NICE for use in this patient population
- How cost effective B-R is compared to standard treatments in patients with MCL

There is however some evidence that, compared to R-CHOP/R-CVP, B-R

- B-R is non-inferior in its effect on complete response rates

- B-R has a superior effect to R-CHOP on progression free survival
- Is relatively safe
- Has a different side effect profile particularly for alopecia and peripheral neuropathy

On that basis B-R has potential as an alternative treatment regimen for the initial therapy of patients with MCL in patients for whom standard treatment with R-CHOP is considered inappropriate.

What evidence is available to assess how bendamustine-based regimens compare with other regimens used in the treatment of patients receiving intensive first-line treatment prior to consolidation with high-dose chemotherapy and autologous stem cell transplant?

Only one small uncontrolled study was identified from a search of the literature. Although the results described are impressive in terms of reported rates of CR and proceeding to ASCT, the lack of a control arm limits the ability to compare this regimen with more widely used regimens in terms of safety and efficacy. No data were identified which supported an assessment of impact on quality of life or cost-effectiveness. Without evidence from appropriately designed RCTs it would not seem appropriate to support the use of this regimen at this time.

Is there any evidence available to guide selection of patients that will benefit from a bendamustine-based regimen instead of an alternative regimen in patients with MCL being treated with first-line chemotherapy

ESMO support the use of either R-CHOP or B-R and do not provide any guidance on choosing between these regimens. Similarly BCSH do not differentiate between R-FC, R-CVP, R-CHOP, R-bendamustine and R-chlorambucil.

R-CHOP is contraindicated in patients with a history of specific forms of heart disease due to the doxorubicin component and in patients with the demyelinating form of Charcot-Marie-Tooth syndrome due to the vincristine. As bendamustine is not contraindicated in either of these conditions it would seem to be an appropriate choice of regimen for this subgroup of patients.

6. Conclusion

The available data indicate that in patients with treatment naïve MCL that are not considered suitable for intensive therapy

- B-R has a superior effect on progression free survival than R-CHOP and is associated higher rates of complete response than R-CHOP/ RCVP.
- B-R is relatively safe with a different side effect profile particularly with reduced risk of alopecia and peripheral neuropathy and increased risk of skin rash
- There are insufficient data to make a full assessment of any differences in the quality of life of patients who receive B-R compared to R-CHOP/R-CVP

B-R has potential as an alternative treatment regimen for the initial therapy of patients with MCL that are not considered to be suitable candidates for intensive treatment but there are some areas on uncertainty because of the lack of data on longer term, time dependent outcomes (for example overall survival). There is possible bias arising from the unblinded assessment of progression free survival in one of the major RCTs. Neither of the two phase three studies assessed how B-R treated patients respond after rituximab maintenance therapy compared to those treated with R-CHOP/R-CVP

7. Evidence Summary Tables

Use of bendamustine plus rituximab (BR) Vs. CHOP plus rituximab or CVP plus rituximab as a first line treatment to treat mantle cell lymphoma									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Rummel MJ et al 2013	*P1-Randomised control trial powered to demonstrate that BR was non-inferior to R-CHOP in terms of PFS in the overall trial population*	*261 previously untreated patients with Stage III or IV disease due to indolent or mantle cell lymphomas randomised to receive BR (of whom 46 had MCL) and 253 randomised to receive R-CHOP (of whom 48 had MCL)*	*Pts randomised to BR received intravenous bendamustine 90mg/m2 on days 1 and 2 of a 4 week cycle for up to 6 cycles.* *Pts randomised to R-CHOP received chemotherapy every 3 weeks for up to 6 cycles with rituximab given on day 1 of each cycle*	*Primary/*	*Progression free survival*	*At a median follow up of 45 months median PFS was longer in the subgroup of patients with MCL that received BR vs. R-CHOP (35.4 months vs. 22.1 months)* *HR 0.49 (95% CI: 0.28 – 0.79) p= 0.0044*	*7*	*The efficacy data are derived from studies which are directly applicable however the adverse event data are based on a mixture of direct and indirect data.*	*The study was powered to assess impact on PFS to show that BR was non-inferior to R-CHOP in a population of patients with indolent and mantle cell lymphomas. The analysis showing a statistically significant reduction in PFS in the subgroup of patients with MCL was exploratory and not prospectively defined and could therefore be viewed as only being hypothesis generating. The effect seen in MCL was consistent with effects reported for subgroups presenting with follicular lymphoma, marginal-zone lymphoma and Waldenstrom's macroglobulinaemia.* *Randomisation produced two groups who appear well balanced at baseline.* *Results were analysed using the per-protocol population as is appropriate when conducting non-inferiority studies although it would have been helpful to see the intention-to-treat results for comparison.* *The study was not blinded although that is unlikely to have had a significant impact in terms of assessment of primary outcome and should not have impacted on assessment of overall survival.* *There are clear differences in the toxicity profile seen between the two regimens and although these data*
				Secondary	*Overall survival*	*Results for overall survival not broken down by histological subtype but no significant difference between the two arms and median overall survival not reached in either group after 45 months follow up.* *In an unpublished analysis of follow up at 7 years (Rummell*			

			Randomisation was conducted centrally and stratified by histological subtype.			*2014) it was reported that No difference in OS was found in the subgroup of patients with MCL (n = 95; HR = 1.28, 95% CI: 0.69–2.39; p = 0.429)*			*are not broken down in terms of disease subgroup it is unlikely that they would differ significantly.*
				Secondary	*Overall response rate (ORR)*	*For the subgroup of patients with MCL the recorded ORR rates were 93% vs. 91% for BR and R-CHOP respectively*			
				Secondary	*Acute and late toxic effects*	*Overall it is reported that 19% of patients exposed to BR and 29% exposed to R-CHOP experienced serious adverse effects. In patients receiving 3 or more cycles of treatment. Lower rates of alopecia (0 vs. 100%), haematological toxicity (30% vs. 68%), infections (37% vs. 50%), parasthesia/ peripheral neuropathy (7% vs. 29%) and stomatitis (6% vs. 19%) were seen in patients treated with BR. However BR was*			

						associated with higher rates of skin reactions (16% vs. 9%). In terms of haematological toxicity BR was associated with lower rates of Grade 3 or 4 leucocytopenia (37% vs. 72%), and neutropenia (29% vs. 69%), but higher rates of lymphocytopenia (74% vs. 43%). It is also noted that G-CSF was used in 4% of BR cycles compared with 20% of R-CHOP cycles.			
Flinn IW et al 2014 *Burke JM et al. 2016*	*Randomised control trial powered to demonstrate that BR was non-*	*224 previously untreated patients with Stage III or IV disease due to indolent or mantle cell lymphomas randomised to*	*Pts randomised to BR received intravenous bendamustine 90mg/m2 on days 1 and 2 of a*	*Primary*	*Complete response rate (CR) following completion of the treatment regimen*	*A CR of 50% (17 out of 34) was recorded for BR compared with 27% (9 out of 33) in patients randomised to R-CHOP or R-CVP (22 and 11 respectively).*	8	*The efficacy data are derived from studies which are directly applicable however the adverse event data are based on a*	*The study was powered to assess impact on CR to show that BR was non-inferior to R-CHOP/ R-CVP in a population of patients with indolent and mantle cell lymphomas. The subgroup analysis comparing response rates in patients with MCL was exploratory and not prospectively defined and could therefore be viewed as only being hypothesis generating. The differences in effect seen in MCL were more marked than the effects reported for subgroups presenting with follicular lymphoma, marginal-zone lymphoma*

	inferior to R-CHOP or R-CVP in terms of CR in the overall trial population	*receive BR (of whom 36 had MCL) and 223 randomised to receive R-CHOP or R-CVP (of whom 38 had MCL)*	*4 week cycle for up to 8 cycles* *Pts randomised to R-CHOP or R-CVP received chemotherapy every 3 weeks for up to 8 cycles with rituximab given on day 1 of each cycle.* *Pts were screened and pre-assigned to the most standard treatment (R-CHOP or R-CVP) and then centrally randomised to either BR or their pre-assigned regimen. Randomisation was stratified by pre-assigned*	*Secondary*	*Overall Response Rate (OR) defined as CR + partial response*	*An OR of 94% (32 out of 34) was recorded for BR compared with 85% (28 out of 33) in patients randomised to R-CHOP or R-CVP (22 and 11 respectively).*		*mixture of direct and indirect data.*	*and lymphoplasmacytic disease.* *The study only followed patients up until they stopped treatment – it provides no insight into impact on progression-free survival or overall survival.* *Randomisation produced two groups who appear well balanced at baseline.* *Results were analysed using the per-protocol population as is appropriate when conducting non-inferiority studies although it would have been helpful to see the intention-to-treat results for comparison. Only one patient (randomised to R_CHOP/R-CVP was lost to follow up)* *The study was not blinded however assessment of response rates were undertaken by an independent review committee blinded to patient allocation.* *There are clear differences in the acute toxicity profile seen between the two regimens and although these data are not broken down in terms of disease subgroup it is unlikely that they would differ significantly due to disease subtype. This study provides no evidence on longer term toxicities.* *There was a high level of compliance with completing the assessment form (> 89% except for patients that did not complete 3, 6 or 8 cycles). The quality of life assessment was based on a tool not used in clinical practice and perhaps limited in its ability to provide a comprehensive overview of health-related quality of life. It was also only applied during treatment and therefore only likely to measure the impact of acute events. The patients and clinicians were aware of the treatment being received and therefore results may be distorted by patients reporting on the toxicities they had been told to expect. The differences in QoL benefits observed were small and were not statistically significant at all*
				Secondary	*Incidence of adverse effects and impact on health-related quality of life*	*Overall it is noted that BR was associated with lower incidences of peripheral neuropathy/ parasthesia than R-CHOP/ R-CVP (9 /14% vs. 44/ 47% respectively). Similarly BR was associated with lower rates of alopecia (4/3 % vs. 51/21%). However BR was associated with higher levels of vomiting (29/25% vs. 13/13%) and higher levels of nausea than R-CVP (63 vs. 39%), higher levels of drug*			

			regimen and by histological subtype *Analysis of impact of quality was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. This was administered at end of Cycles 1, 3, 6 and 8 (if applicable)*			*hypersensitivity than R-CHOP/ R-CVP (17/13% vs. 6/3%). In terms of haematological toxicity BR was associated with lower rates of Grade3/4 drops in WBC vs. R-CHOP (32/% vs. 72%) and drops in neutrophil count (39% vs. 87%) but higher incidences of Grade 3/4 drops in lymphocyte count than either R-CHOP or R-CVP (61/63% vs. 33/28%). It is also reported that 29% of cycles of BR required GCSF support compared with 43% of cycles of R-CHOP/ R-CVP.* *Patients treated with BR reported improvements in cognitive functioning, physical functioning, social functioning, emotional functioning and global health status and a reduction in dyspnoea, constipation and fatigue at some but not all time points compared with*			*points in time.*

						standard treatment. Patients treated with standard treatment reported less nausea and vomiting and appetite loss at several time points.			

Use of bendamustine-based regimens compare with other regimens in the treatment of patients receiving intensive first-line treatment prior to consolidation with high-dose chemotherapy and autologous stem cell transplant									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Armand et al 2016	*P1-open-label single arm trial*	*23 patients with newly diagnosed MCL and considered eligible for transplant were recruited*	*In this non-randomised study all patients received three cycles of rituximab/ cytarabine/*	*Primary*	*The primary endpoint was rate of confirmed and unconfirmed CR*	*22 patients achieved a CR equating to a response rate of 96% (90% CI: 81-100%)*	*6*	*This study is directly applicable to the population in question.*	*This is a very small open-label single arm study and as such is limited by the fact there is no control arm and can only be regarded as hypothesis generating. The data available would support suggestions that this regimen warrants further investigation within a randomised controlled trial that compares outcomes with a suitable control regimen such as R-CHOP. There are no follow up data available as yet to enable any assessment of PFS or longer term*
				Secondary	*Numerous measures of effectiveness including:*	*Results were as follows*			

			bendamustine followed by three cycles of rituximab/ high-dose cytarabine provided there was evidence of stable disease or improvement		*Overall response arte* *Rate of successful stem cell mobilisation* *Proportion of patients that successfully completed entire treatment course and proceeded to ASCT* *The rate of minimal residual disease (MRD)*	*96%* *21/21 (one declined)* *21/22 (one declined)* *1/15 had detectable disease at the end of treatment*			*adverse events.*
				Secondary	*Toxicity* *.*	*Overall in 69 cycles of B-R administered there was 29 cases of Grade 3/4 leucopenia, 1 Grade 3 thrombocytopenia, 3 Grade 3 anaemia, 1 Grade 4 neutropenia, 1 Grade 4 lymphopenia and 1 Grade 3 sepsis*			

8. Grade of evidence tables

Use of bendamustine plus rituximab (BR) Vs. CHOP plus rituximab or CVP plus rituximab as a first line treatment to treat mantle cell lymphoma					
Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Progression-free survival	**Rummel (2013)**	**7**	**Directly applicable**	**B**	*At a median follow up of 45 months median PFS was longer in the subgroup of patients with MCL that received BR vs. R-CHOP (35.4 months vs. 22.1 months) equating to a difference of 13.3 months.* *Progression free survival was defined as the time between first treatment and one of the following events: progressive disease, relapse after response or death from any cause.* *This is a subgroup analysis and therefore could be viewed as being hypothesis generating. Overall the trial was designed to demonstrate that B-R was non-inferior to R-CHOP* *The trial was conducted before the use of maintenance rituximab became standard clinical practice and therefore this may limit the generalisability of the results described*
Overall response rate	**Rummel (2013)**	**7**	**Directly applicable**	**B**	*For the subgroup of patients with MCL the recorded ORR rates were 93% vs. 91% for BR and R-CHOP respectively* *Response rates were defined as being*

					based on standard WHO criteria *This is a subgroup analysis and therefore could be viewed as being hypothesis generating. Overall the trial was designed to demonstrate that B-R was non-inferior to R-CHOP*
	Flinn (2013)	**8**	**Directly applicable**	**B**	*For the subgroup of patients with MCL the recorded ORR rates were 94% vs. 85% for BR vs. R-CHOP or R-CVP respectively* *Response rates were defined as being based on standard WHO criteria* *This is a subgroup analysis and therefore could be viewed as being hypothesis generating. Overall the trial was designed to demonstrate that B-R was non-inferior to R-CHOP*
Safety	**Rummel (2013)**	**7**	**Mixture of directly and indirectly applicable**	**B**	*B-R has a different side effect profile to R-CHOP/R-CVP greatly reducing the incidence of alopecia and peripheral neuropathy.* *It caused less leukopenia and neutropenia but more lymphocytopenia.* *B-R has a higher risk of drug hypersensitivity and skin rash* *The risk of secondary malignancies for B-R and R-CHOP/R-CVP does not.appear to be different.*
	Flinn (2013)	**8**	**Mixture of directly and indirectly applicable**		

Impact on quality of life	**Burke (2016) Flinn (2013)**	**8**	**Mixture of directly and indirectly applicable**	**B**	*B-R showed some advantages in QoL compared to R-CHOP/R-CVP but the clinical significance of the benefits was small, and the differences between the groups were not statistically significant at all points in time*

Use of bendamustine-based regimens compare with other regimens in the treatment of patients receiving intensive first-line treatment prior to consolidation with high-dose chemotherapy and autologous stem cell transplant					
Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Rate of confirmed and unconfirmed CR	**Armand 2016**	**6**	**Direct**	**C**	*22 patients achieved a CR equating to a response rate of 96% (90% CI: 81-100%).* *This is a very small open-label single arm study and as such is limited by the fact there is no control arm and can only be regarded as hypothesis generating. There are no follow up data available as yet to enable any assessment of PFS or longer term adverse events.*

9. Fact Sheet (to be completed)

Intervention Fact Sheet	
What is the intervention for?	
Who might consider taking it?	
Who should not take it?	
Other things to consider	

	Placebo/comparator	Intervention
Benefits **What difference did the intervention make?** *Include questions based on outcomes measures report* • ***For. e.g. What was the change in pulmonary vascular resistance?*** •	*Present results from studies*	
Harms **Did the intervention have side effects?** *Include questions based on outcomes measures report* • ***For. e.g. Were there life-threatening side effects?*** •	*Present results from studies*	

10. Literature Search Terms

Search strategy *Indicate all terms to be used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Mantle cell lymphoma (as a thesaurus term) and as freetext. **Restricted to patients receiving chemotherapy for the first time**
I – Intervention Which intervention, treatment or approach should be used?	Bendamustine (as a thesaurus term) and as freetext
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Not restricted
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	**Critical to decision-making:** Not restricted **Important to decision-making:** Not restricted
Assumptions / limits applied to search	
Inclusion Criteria	Any articles that were fully published including guidelines, meta-analyses, reviews, controlled trials (randomised or non-randomised) or Phase II clinical trials
Exclusion Criteria	Non-English publications and research not conducted in humans

11. Search Strategy

Embase:

1. *BENDAMUSTINE/; 1170 RESULTS
2. *MANTLE CELL LYMPHOMA/; 3490 RESULTS
3. 1 AND 2; 104 RESULTS

Medline

1 *BENDAMUSTINE HYDROCHLORIDE/; 29 results.
2. bendamustine.ti,ab; 659 results.
3. 1 OR 2; 661 results.
4.*LYMPHOMA, MANTLE-CELL/; 1904 results.
5. 3 AND 4; 65 results.

NHS Evidence: bendamustine mantle cell lymphoma

The Cochrane library: bendamustine mantle cell lymphoma

NICE: mantle cell lymphoma

ClinicalTrials.gov: bendamustine AND mantle cell lymphoma

NIHR Horizon Scanning Centre: bendamustine

The New Zealand Guidelines Group: bendamustine;

The Australian National Health & Medical Research Council Guidelines Portal: bendamustine;

The National Guideline Clearinghouse: bendamustine

12. Evidence selection

- Total number of publications reviewed: 53
- Total number of publications considered relevant: 39
- Total number of publications selected for inclusion in this briefing: 12

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Rummel M, Maschmeyer G et al. Bendamustine plus Rituximab (B-R) versus CHOP plus Rituximab (CHOP-R) as first-line treatment in patients with indolent lymphomas or mantle cell lymphomas (MCL)- 7 year updated results from StiL NHL1 study. Oncol Research and Treatment, 2015; 38: 118 (unpublished abstract)