NHS England

Evidence review: Bendamustine-based chemotherapy for treatment of relapsed or refractory 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)

First-line treatment/treatment- naïve patients

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 (BSHC) recommended 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.

Treatments for patients with relapsed/refractory disease

For patients that relapse following chemotherapy or have refractory disease there is no agreed standard therapy (Cheah, 2016). ESMO state that the selection of a salvage regime depends on the efficacy of prior regimens. In early relapses (<12-24 months) they state a non-cross-resistant scheme should be preferred (e.g. R-BAC [i.e. rituximab with bendamustine and cytarabine] after CHOP or vice versa) and that rituximab should be added if the previous antibody-containing scheme achieved >6-12 months duration of remission). In cases of earlier relapse or refractory disease they state that the newer targeted approaches (temsirolimus, bortezomib, ibrutinib, lenalidomide) should be strongly considered (Dreyling M, 2014). They also note that high dose chemotherapy with ASCT may be considered in patients that relapse after conventional first-line therapy. However they note that the benefit seems to be minor in this setting and that there is no role for a second autograft at relapse

The BCSH also state that there is no gold standard therapy for relapsed MCL and that the choice of therapy at relapse should be determined by patient age, performance status, bone marrow reserve and initial therapy (McKie 2012). They recommend that options for consideration at relapse should include rituximab, bortezomib and combination chemotherapy and that temsirolimus should be considered as a possible option. BCSH do not address the management of refractory disease in their Guideline.

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.

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

Two 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 relapsed or refractory MCL in terms of efficacy, safety, quality of life and cost-effectiveness?

Is there any evidence to guide the placement of bendamustine-based chemotherapy either in sequence or as an alternative to the approaches described above?

2. Summary of results

The findings of this review are mainly based on one Phase III study that compared bendamustine plus rituximab (B-R) with rituximab plus fludarabine (R-F) in patients with relapsed indolent non-Hodgkin's lymphoma (NHL) or MCL. However as this trial only involved a very small number of patients with MCL and as R-F is not widely used in practice the results of a number of 7 uncontrolled Phase II studies are also described.

In the RCT there was a subgroup of 47 patients with MCL and it was shown that the median PFS was 17.6 months in the group that received B-R compared with 4.7 months in the group that received R-F – a difference of 13.3 months. Similarly an analysis of OS showed that patients that received B-R lived for a median of 35.3 months compared with 20.9 months in the control arm. Overall response rates and complete response rates were also significantly higher in the experimental arm (70.8% and 37.5% vs. 26.1% and 13% respectively). Of the Phase II studies identified, only one reported on overall survival and stated that 55% of patients treated with B-R were alive after 3 years follow up. In terms of median PFS, values varied between 17.2 months and >26months and in two studies it was reported that 2 year PFS was 47% and 70%. It should be noted that the Phase II studies included a range of patients that differed in terms of numbers of lines of previous treatment, prior exposure to rituximab, use of maintenance rituximab and mix of refractory and relapsed disease.

The Grade 3/4 adverse effects reported in two Phase II studies that were reported in more than 5% of patients treated with B-R in at least one of those studies included leucopenia (30% and 44%), neutropenia (37% and 44%), febrile neutropenia (7% and NR), thrombocytopenia (10% and 7%), infection (10% and NR collectively), fatigue (5% and NR), lymphopenia (89% and NR) and hypokalaemia (7% and NR).

No studies were identified that assessed impact of B-R on quality of life and no relevant health economic studies were identified assessing the use of B-R in this population.

No evidence was identified which helps further clarify how treatment with regimens such as B-R should be sequenced in patients with relapsed or refractory disease

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. Only fully published studies are included in this review and retrospective analyses of patient outcomes were excluded on the basis that prospective studies available. .

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 relapsed or refractory MCL in terms of efficacy, safety, quality of life and cost-effectiveness?

Only one fully published RCT was identified from a search of the literature databases cited and a search of bibliographic references indicate that this is the only randomised study available that compares bendamustine and rituximab with another rituximab-containing treatment regimen in patients with relapsed or refractory Mantle Cell Lymphoma that are .not considered suitable for more intensive treatment (Rummel, 2016). However as the comparator regimen in this RCT is not commonly used in practice the results from 7 uncontrolled single-arm unblinded studies that assessed a variety of bendamustine-containing regimens in this population are also presented. Retrospective studies and Phase 1 studies were excluded from this review.

Effectiveness

Rummel et al conducted a Phase III non-inferiority RCT designed to demonstrate that bendamustine plus rituximab was non-inferior to rituximab plus fludarabine (R-F) in terms of median PFS in a cohort of patients with relapsed indolent non-Hodgkin's lymphoma or MCL (Rummel, 2016). In the subgroup of 47 patients with MCL it was shown that the median PFS was 17.6 months in the group that received B-R compared with 4.7 months in the group that received R-F – a difference of 13.3 months. Similarly an analysis of OS showed that patients that received B-R lived for a median of 35.3 months compared with 20.9 months in the control arm. Overall response rates and complete response rates were also significantly higher in the experimental arm (70.8% and 37.5% vs. 26.1% and 13% respectively).

Of the Phase II studies identified, only one reported on overall survival and stated that 55% of patients treated were alive after 3 years follow up. In terms of median PFS, values varied between 17.2 months and >26months and in two studies it was reported that 2 year PFS was 47% and 70%. Overall response rates of between 71 and 100% and complete response rates of between 33% and 70% were described. However it should be noted that a variety of bendamustine-based regimens were tested and there were differences in trial populations in terms of factors such as previous number of lines of treatment, prior exposure to rituximab, use of maintenance rituximab and mix of refractory and relapsed disease.

Safety and quality of life

In the Phase III RCT, it is reported that the following Grade 3/4 adverse effects were seen in patients treated with bendamustine and rituximab: leucocytopenia (18% vs. 12% in the control group), neutropenia (9% vs. 9%), thrombocytopenia (3% vs. 2%), anaemia (2% vs. 2%), nausea/vomiting (4% vs. 1%), fatigue (1% vs. 0) and alopecia (0 vs. 2%).

In the Phase II studies identified, the incidence is reported either in terms of the percentage patients affected or in terms of percentage cycles seen. Two studies reported the incidence of Grade 3/4 effects seen in patients treated with bendamustine and rituximab as follows: leucopenia (30% and 44%), neutropenia (37% and 44%), febrile neutropenia (7% and NR), thrombocytopenia (10% and 7%), anaemia (2% and 4%), infection (10% and NR collectively), fatigue (5% and NR), diarrhoea (3% and NR), infusion reactions (3% and NR), lymphopenia (89% and NR), hypokalaemia (7% and NR), pneumonia (4% + 1 fatal case and NR), back pain (4% and NR), device infection (4% and NR), hyponatraemia (4% and NR), pleural effusion (4% and NR), syncope 4% ad NR and weight loss (4% and NR).

No studies assessing impact on quality of life were identified from the literature

Cost effectiveness

No studies assessing the incremental cost effectiveness of using bendamustine-based chemotherapy regimens instead of other treatment regimens in patients with relapsed or refractory MCL were identified in the literature.

Is there any evidence to guide the placement of bendamustine-based chemotherapy either in sequence or as an alternative to the approaches described above?

ESMO state that the selection of a salvage regime depends on the efficacy of prior regimens (Dreyling, 2014). In early relapses (<12-24 months) they state a non-cross-resistant scheme should be preferred (e.g. R-BAC [i.e. rituximab with bendamustine and cytarabine] after CHOP or vice versa) and that rituximab should be added if the previous antibody-containing scheme achieved >6-12 months duration of remission). In cases of earlier relapse or refractory disease they state that the newer targeted approaches (temsirolimus, bortezomib, ibrutinib, lenalidomide) should be strongly considered.

BCSH that the choice of therapy at relapse should be determined by patient age, performance status, bone marrow reserve and initial therapy (McKie 2012). They recommend that options for consideration at relapse should include rituximab, bortezomib and combination chemotherapy and that temsirolimus should be considered as a possible option. BCSH do not address the management of refractory disease in their Guideline

No evidence was identified which helps further clarify how treatment should be sequenced in patients with relapsed or refractory disease

5. Discussion

What evidence is available to assess how bendamustine-based regimens compare with other regimens used in the treatment of patients with relapsed or refractory MCL in terms of efficacy, safety, quality of life and cost-effectiveness?

The single RCT identified provides good quality evidence that using bendamustine plus rituximab instead of fludarabine plus rituximab results in significant improvements in median PFS and this also results in improvements in OS. The trial methodology appears to be robust although it could be argued that as the results described are based on a subgroup analysis they may be viewed as hypothesis generating. This trial is also limited by the fact that the control regimen selected does not reflect current clinical practice. Also there may be concerns that the results are not necessarily generalisable to current practice in that that when the trial was started rituximab was not routinely accepted as a standard treatment and so only 42% of patients recruited had been exposed to rituximab prior to recruitment to this study. Similarly a protocol amendment was required during the study to allow the use of rituximab maintenance treatment in patients that responded to their allocated treatment. However this is the only RCT available and it only included a relatively small number of patients with MCL and given the limitations outlined above there may be some concerns about basing any recommendations about it being the regimen of choice on such a limited set of evidence.

The Phase 2 data available support the results outlined above and indicate that this regimen is associated with high overall response rates and that if patients respond then they remain free from disease progression for a median period of 17+ months. These data are derived from uncontrolled studies and as such it is not possible to compare these outcomes with those that might be expected in similar patients treated with different chemotherapy regimens.

The safety data available indicate that this regimen is associated with high incidences of serious haematological toxicities and has the potential to cause a wide range of other debilitating adverse

effects when used to treat patients with either relapsed refractory indolent NHL or MCL. However it is not possible to ascertain whether this regimen differs significantly from other regimens that would be used in this indication.

No evidence was identified to support an assessment of the impact of using a bendamustine-based regimen on the quality of life of patients with relapsed or refractory MCL and how this compares to treatment with other regimens. Similarly no evidence was identified to support an assessment of the relative cost effectiveness of this intervention compared to the use of other regimens.

Is there any evidence to guide the placement of bendamustine-based chemotherapy either in sequence or as an alternative to the approaches described above?

No evidence was identified to guide practice on how bendamustine-based regimens should be used in treatment pathways for patients with relapsed or refractory MCL. Existing guidance from ESMO and BCSH does not offer much differentiation between regimens in terms of effectiveness and both state that choice of regimen is dependent on factors such as patient age, performance status, bone marrow reserve and initial therapy. The evidence identified in this review is not robust enough to impact on this approach.

6. Conclusion

The data available to assess the safety and effectiveness of B-R in patients is limited to a small subgroup analysis of an RCT in which it was compared with fludarabine and rituximab and seven Phase II studies. The data that are available support existing clinical guidelines which suggest that B-R is one of a number of regimens which could be considered in this patient cohort. The results of the subgroup analysis of the RCT indicate that B-R is superior to fludarabine plus rituximab in terms of both progression-free and overall survival. The Phase II studies indicate that its use is associated with significant periods of progression-free survival and that the majority of patients achieve some level of response to treatment. The data available are limited by the fact that the studies were largely conducted before rituximab became established as a first-line treatment and before rituximab maintenance treatment became routinely available.

The safety data available indicate that B-R is associated with significant adverse effects largely involving bone marrow suppression but there was no evidence identified to suggest that the overall tolerability of this regimen is significantly different from other regimens that may be used in this population. Unfortunately no data were identified which helped clarify the impact of B-R on quality of life and no relevant health economic studies were identified.

7. Evidence Summary Table

Study reference	Study Design	Population characteristic	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Rummel et al 2016	P1 open label, non-inferiority randomised study	219 patients with relapsed indolent (n=162) or MCL (n= 47)	Patients received rituximab (375mg/m2 on Day 1) and either bendamustine (90mg/m2 on Days 1 and 2) or fludarabine (25mg/m2 on days 1-3) every 4 weeks for a maximum of 6 cycles.	Primary	Median PFS	17.6 months (7.9 to 30.4) vs. 4.7 months (2.3 to 11.2)	7	The efficacy data are directly applicable however the adverse event data are 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-F in a population of patients with indolent and mantle cell lymphomas. The analysis showing a statistically significant increase 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 and small lymphocytic lymphoma.* *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 are not broken down in terms of disease subgroup it is unlikely that they would differ*
				Secondary	Overall response (OR) CR Median OS	70.8% vs. 26.1% 37.5% vs. 13% 35.3 months (14.9 to not yet reached) vs. 20.9 (10.6 to 56.7)			
				Secondary	Adverse events	Grade 3/4 events reported as follows: Leucocytopenia (18% vs. 12%) Neutropenia (9% vs. 9%) Thrombocytopenia (3% vs. 2%) Anaemia (2% vs 2%) Nausea/vomiting (4%			

						vs 1%) Fatigue (1% vs 0) Alopecia (0 vs 2%)			*significantly.* *The choice of R-F as a comparator regimen could be viewed as being a limitation. Although there is not an agreed gold standard treatment regimen this would no longer be considered to be a standard treatment.* *Similarly this study was started at a time when rituximab was not a standard treatment and therefore only 42% of all patients recruited had received it as part of their first-line regimen. Therefore there may be some concern that the results may not be fully generalisable to patients that receive rituximab as part of their first-line treatment regimen. Also rituximab maintenance treatment was only just gaining approval when this trial started and the protocol was amended to allow the use of rituximab maintenance in patients that responded to their allocated treatment – subgroup showed that patients that received rituximab maintenance had superior PFS and OS than those that did not.*
Visco 2013	P1 uncontrolled, unblinded, single arm study	40 patients with MCL of whom 20 had relapsed or were refractory following one previous rituximab containing regimen. The other 20 were previously untreated	Patients were treated with a regimen of rituximab (375mg/m2 IV on day 1), bendamustine (70mg/m2 on days 2 and 3) and cytarabine	Primary	Overall response rate	In the 20 patients with relapsed/ refractory disease an overall response rate of 80% was reported (70% CR and 10% PR)	7	The data are directly applicable	*This is a 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. A longer follow up period is required to quantify median PFS and OS.*
				Secondary	Progression-free survival (PFS)	Not reached after a median follow up of 26 months 2-year PFS – in 20 patients with relapsed refractory disease was 70%, similarly			

			(800mg/m2 on days 2,3,4) every 28 days for 4-6 cycles			the rate of 2-year duration of response was 87%.			
				Secondary	Adverse events	Overall 5/20 R/R patients discontinued treatment before receiving 4 cycles due to adverse events Grade 3/4 Adverse events in R/R patients Leucopenia – 67% cycles Neutropenia – 49% cycles Thrombocytopenia – 83% cycles Anaemia – 32% cycles Infection – 12% patients treated Fatigue – 5% patients treated Isolated gamma-GT elevation – 23 patients treated			

Rummel 2005	P1 uncontrolled, unblinded, single arm study	63 patients with MCL (n= 16) or low grade lymphoma (n= 47) in first to third relapse or refractory to previous treatment	Patients were treated with rituximab (375mg/m2) 1 week prior to treatment initiation then on Day 1 of a 28-day cycle. . Bendamustine (90mg/m2) was given on Days 2 and 3. Patients received four cycles of treatment followed by a final dose of rituximab after four weeks.	Primary	Progression free survival (PFS) which was then compared with patient's previous treatment.	Median PFS was 18 months (range 6 to 22+) – a comparison with the patients previous PFS was not provided for the MCL subgroup.	7	The PFS and ORR efficacy data are derived from patients which are directly applicable however overall OS and the adverse event data are based on a mixture of direct and indirect data	*This is a 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. A longer follow up period is required to quantify median OS.*
				Secondary	Overall response rate (ORR) Overall survival (OS)	ORR was 75% (CR was 50%) The median OS was not reached – an actuarial survival rate of 55% at 48 months was reported for the whole cohort but no data on the MCL subgroup are reported.			
				Secondary	Adverse events	No breakdown is available for the subgroup of patients with MCL but overall it is reported that Grade 3/4 leucopenia occurred in 16% cycles, thrombocytopenia in 3% cycles and anaemia in 1% cycles. Mild nausea was seen in 43% cycles.			

Robinson 2008	P1 uncontrolled, unblinded, single arm study	66 patients with MCL (n=12) or indolent lymphoma (n=54). Patients were eligible for inclusion as long as they have received no more than 3 previous lines of treatment and were not known to be refractory to rituximab.	Patients were treated with rituximab (375mg/m2) 1 week prior to treatment initiation then on Day 1 of a 28-day cycle. . Bendamustine (90mg/m2) was given on Days 2 and 3. Patients received four cycles of treatment followed by a final dose of rituximab after four weeks.	Primary	Overall response rate (ORR)	92% (42% CR, 17% unconfirmed CR, 33% PR and 8% SD)	7	The efficacy data are directly applicable however the adverse event data are a mixture of direct and indirect data	*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. A longer follow up period is required to quantify median PFS and OS.*
				Secondary	Median duration of response	19 months (95%CI: 12 to 24 months)			
				Secondary	Adverse effects	Overall 2 out of 66 patients treated discontinued treatment before they received 4 cycles due to adverse events. 30% patients experienced Grade 3/4 leucopenia, 37% neutropenia, 7% febrile neutropenia, 10% thrombocytopenia and 2% anaemia. In terms of non-haematological Grade 3/4 events 10% experienced infections, 5% fatigue, 3% diarrhoea, 3%			

						infusion reactions and 3% asthenia.			
Weide et al 2007	P1 uncontrolled, unblinded, single arm study	57 patients with relapsed or refractory MCL (n=18) or indolent lymphoma (n=39). There were no limits to numbers of lines of treatment prior to participation	Patients received bendamustine 90mg/m2 on Days 1 and 2, mitoxantrone 10mg/m2 on Day1 and rituximab 375mg/m2 on Day 8 of a 28-day cycle. Up to 4 cycles were given	Primary	Overall Response rate (ORR)	78% (33% CR and 44% PR)	7	The efficacy data are directly applicable however the adverse event data are a mixture of direct and indirect data	*This is a 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. A longer follow up period is required to quantify OS.*
				Secondary	Median PFS Estimated 2-year survival rate	21 months 60%			
				Secondary	Adverse effects	Overall the following Grade 3/4 adverse effects were reported Anaemia (10%), leucopenia (78%), granulocytopenia (46%), thrombocytopenia (16%), nausea/vomiting (5%), constipation (2%), alopecia (5%), infection (4%), cardiac dysfunction (5%), cardiac arrhythmias (2%),			

						neurotoxicity (2%).			
Czucz man (2015)	P1 uncontrol led, unblinde d, single arm study	45 patients with relapsed/refra ctory MCL. There were no limits to numbers of lines of treatment prior to participation (patients with up to 4 prior lines of chemotherapy were recruited)	Patients were treated with a regimen of rituximab (375mg/m2 IV on day 1), bendamusti ne (90mg/m2 on days 1 and 2) of a 28-day cycle. Patients were treated for 6 cycles but this could be increased to 8 if they had not achieved CR and did not have disease progression	Primary	Overall response rate (ORR) after 6 cycles	82% (CR 40% and PR 42%)	7	Directly applicable	*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. A longer follow up period is required to quantify median PFS and OS.*
				Secondary	Median PFS Median duration of response (DOR) OS Rate of conversion from Pet-CT +ve to –ve disease or complete metabolic response	17.2 months (range 0.03 to 45.37) 18.9 month (range 2.76 to 42.77) 55% alive at 3 year follow up 75% (n= 32)			
				Secondary	Adverse events	Grade3/4 advents reported were Lymphopenia (89%) Leucopenia (44%) Neutropenia (44%) Thrombocytopenia			

						7% Anaemia (4%) Hypokalaemia (7%) Hypotension (7%) Pneumonia (4%) + 1 fatal case Back pain 4% Decreased appetite (4%) Device-related infection (4%) Hyponatraemia (4%) Pleural effusion (4%) Syncope (4%) Weight loss (4%)			
Friedbergh 2011	P1 uncontrolled, unblinded, single arm study	30 patients with relapsed refractory indolent NHL or MCL (7 with MCL) There were no limits to	Patients were treated with bendamustine (90mg/m2) on Day 1 and 4,	Primary	Median PFS	At a median follow up of 2 years the 2-year PFS in the 29 evaluable patients was 47% (95%CI: 25 to 69%). No results for the subgroup with MCL are presented.	7	The only directly applicable data are those that describe the ORR, the rest are indirect data	*This is a 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. A longer follow up period is required to quantify OS.*

		numbers of lines of treatment prior to participation (patients with a median of 4 prior lines of chemotherapy were recruited)	rituximab (375mg/m2) on Day 1 and bortezomib (1.3mg/m2 on Days 1, 4, 8 and 11 of a 28-day cycle. Patients received up to 6 cycles of treatment.	Secondary	Overall response rate	83% (95%CI: 65 to 92%) a ORR of 71% (95%CI: 36 to 92%) was reported for the subgroup of MCL patients		derived from the whole trial population of patients with indolent NHL and MCL	
				Secondary	Adverse events	26% patients treated experienced serious AE. One patient had Grade3/4 liver and renal failure and died of sepsis. In terms of other Grade 3 events there were 2 cases of peripheral neuropathy, 2 of fatigue, 1 of constipation, 2 of hypotension, 2 of herpes zoster and 1 of back pain			
Ohmachi 2010	P1 uncontrolled, unblinde	58 Japanese patients with relapsed/ refractory indolent NHL	Patients were treated with bendamustine	Primary	Overall response rate (ORR)	100% (72 -100) - CR 64%, CR unconfirmed 9%, PR 27%	7	The efficacy data are directly applicable however the	*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*

	d, single arm study	and 11 with MCL. There was no upper limit on number of prior regimens patients were exposed to and the subgroup with MCL had received a median of 4 (range 1 to 16).	120mg/m2 on Days 1 and 2 of a 21-day cycle. Patients received up to 6 cycles	Secondary	Adverse events	The following Grade 3/4 adverse events were reported Leucopenia: 65% Neutropenia 72% Thrombocytopenia 16% Anaemia 6% Anorexia 3% Rash 1% Vomiting 4% Weight loss 1% Phlebitis 3% Infections 7%		adverse event data are a mixture of direct and indirect data	*randomised controlled trial that compares outcomes with a suitable control regimen such as R-CHOP. A longer follow up period is required to quantify median PFS and OS.*

8. Grade of evidence tables

Use of bendamustine plus rituximab (BR) Vs. as a treatment for relapsed or refractory MCL					
Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Progression-free survival	**Rummel (2016)**	**7**	**Directly applicable**	**B**	Median PFS in the subgroup of patients with MCL was 17.6 months (7.9 to 30.4) in the group treated with bendamustine vs. 4.7 months (2.3 to 11.2) in the control group *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 fludarabine plus rituximab* *The trial was conducted before the use of maintenance rituximab became standard clinical practice. This required a protocol amendment during the trial and may limit the generalisability of the results described*
	Visco (2013)	**7**	**Directly applicable**		
	Rummel (2005)	**7**	**Directly applicable**		
	Weide (2007)	**7**	**Directly applicable**		
	Czuczman (2015)	**7**	**Directly applicable**		
	Friedbergh (2011)	**7**	**Directly applicable**		
Median overall survival	**Rummel (2016)**	**7**	**Directly applicable**	**B**	Median OS in the subgroup of patients with MCL was 35.3 months in the group treated with bendamustine vs. 20.9 months in the control group. Other
	Czuczman (2015)	**7**	**Directly applicable**		

					comments as above.
Overall response rate(OR) and Complete response rates	**Rummel (2016)**	**7**	**Directly applicable**	**B**	OR in the subgroup of patients with MCL was 70.8% in the group treated with bendamustine vs. 26.1% in the control group. The corresponding CR rates were 37.5% and 13% respectively. Other comments as above
	Visco (2013)	**7**	**Directly applicable**		
	Rummel (2005)	**7**	**Directly applicable**		
	Robinson (2008)	**7**	**Directly applicable**		
	Weide (2007)	**7**	**Directly applicable**		
	Czuczman (2015)	**7**	**Directly applicable**		
	Friedbergh (2011)	**7**	**Directly applicable**		
	Ohmachi (2010)	**7**	**Directly applicable**		
Safety	**Rummel (2016)**	**7**	**Directly applicable**	**B**	Grade 3/4 events reported as follows: Leucocytopenia (18% vs. 12% receiving fludarabine with rituximab) Neutropenia (9% vs. 9%) Thrombocytopenia (3% vs. 2%) Anaemia (2% vs 2%) Nausea/vomiting (4% vs 1%) Fatigue (1% vs. 0) Alopecia (0 vs. 2%) The other data from the Phase II trials is reported in Table 7 which supports the profile described above but is not reproduced here as it does not provide any additional contextual information.

9. 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 free text. **Restricted to patients receiving chemotherapy for relapsed or refractory disease**
I – Intervention Which intervention, treatment or approach should be used?	Bendamustine (as a thesaurus term) and as free text
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

10. 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

11. 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: 14

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