AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Bendamustine in combination with rituximab for the treatment of previously untreated and relapsed mantle cell lymphoma (OW09)

December 2022

ONE WALES INTERIM DECISION

Bendamustine in combination with rituximab for the treatment of previously untreated and relapsed mantle cell lymphoma

Date of original advice: Monday 27th March 2017
Date of review: December 2022

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been endorsed by health board Chief Executives.

Bendamustine in combination with rituximab can continue to be made available within NHS Wales for the treatment of previously untreated and relapsed mantle cell lymphoma in patients currently deemed unsuitable for anthracycline-based therapy or other health technology appraisal-approved regimens.

The risks and benefits of the off-label use of bendamustine plus rituximab for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment Group decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

One Wales advice promotes consistency of access across NHS Wales.

This is a summary of new evidence available and patient outcome data collected, to inform the review.

Bendamustine in combination with rituximab for the treatment of previously untreated and relapsed mantle cell lymphoma

This report was prepared by the All Wales Therapeutics and Toxicology Centre in September 2022. It summarises any new evidence available and patient outcome data collected since the last review in September 2021.

Background: Bendamustine with rituximab is available in NHS England through clinical commissioning for the treatment of previously untreated and relapsed and refractory mantle cell lymphoma. Although rituximab is not licensed for treating mantle cell lymphoma, the National Institute for Health and Care Excellence (NICE) mantle cell lymphoma treatment pathway recommends it in combination with chemotherapy as first-line treatment of advanced-stage mantle cell lymphoma.

A cohort of patients, identified through data from individual patient funding request panels, and clinicians in Wales, have confirmed there to be an unmet need within the service. This cohort includes people with untreated and relapsed mantle cell lymphoma for whom anthracycline-based therapy is unsuitable. Based on this unmet need, this medicine combination was considered suitable for assessment via the One Wales process. Clinical experts consulted for this review supported the ongoing need for the option for use in NHS Wales for this cohort of patients.

Current One Wales Decision: Supported with restrictions.

Licence status: Off-label use for this licensed medicine combination.

Guidelines: No change to guidelines of note.

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines: NICE ID1221: Ibrutinib for untreated mantle cell lymphoma. This STA appraisal has been suspended, August 2022.

Effectiveness: A systematic literature search identified four retrospective studies examining the use of bendamustine plus rituximab to treat mantle cell lymphoma (See Appendix 1). One of the retrospective studies featured in last year's review as a conference abstract (Villa et al. 2022). The updated study reported a decline in the complete response (CR) for bendamustine plus rituximab compared to the earlier study report (Villa et al. 2021). The authors concluded that bendamustine plus rituximab with autologous stem cell transplant (ASCT) and maintenance rituximab is a feasible and effective first line treatment with outcomes comparable to alternating rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) with rituximab in combination with dexamethasone, high dose cytarabine and cisplatin (R-DHAP). There was no change from the other previously reported results.

Safety: No new safety concerns or other relevant safety analyses have been identified in the repeat literature search.

Cost-effectiveness: No relevant cost-effectiveness analyses have been identified.

Budget impact: No information on patient numbers has been provided.

Impact on health and social care services: Minimal.

Patient outcome data: No patient outcome data have been received.

Evaluation of evidence

The clinical evidence presented supports the current use of bendamustine with rituximab as a treatment option in line with the current One Wales advice. Bendamustine in combination with rituximab for the treatment of mantle cell lymphoma should only be used in circumstances where other licensed and health technology appraisal-approved regimens are unsuitable.

Next review date: 12 months

References: A full reference list is available on request.

This document includes evidence published since the last review or full assessment of this medicine for the indication under consideration. It does not replace the original full evidence status report. Any previous reviews and the original full evidence status report are available on request by email to AWTTC@wales.nhs.uk.

Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

Information presented in this document can be reproduced using the following citation: One Wales Interim Decision. Bendamustine in combination with rituximab for the treatment of mantle cell lymphoma (OW09). December 2022.

Appendix 1

Reference	Study details	Main results
Villa et al. 2022 Villa et al. 2021	Retrospective Untreated MCL (n = 97) treated with bendamustine plus rituximab Six cycles according to methods Compared to historical control cohort of 232 patients randomised to R-CHOP or R-DHAP (European MCL Younger trial)	The ORR was 90% for bendamustine plus rituximab (CR rate was 54%, previously reported as 77%) and 94% for R-CHOP/R-DHAP (54% CR). With no change from last year's results, the percentage of patients who proceeded to ASCT was 77% and 78% respectively, while 78% and 2% of patients received RM. There remained no statistically significant improvement for PFS, EFS or OS for bendamustine plus rituximab with ASCT and RM versus R-CHOP/R-DHAP with ASCT.
Karadurmus et al. 2021	Retrospective Relapsed/refractory MCL (n = 18) treated with bendamustine plus rituximab Bendamustine 90 mg/m^2 received by 88.9% and 100 mg/m^2 received by 11.1% Median six cycles (range 2 – 38)	The ORR was 72.2% (95% CI: 46.5 – 90.3), two-year PFS was 53.3% (95% CI: 24.3 – 75.6) and two-year OS was 74.9% (95% CI: 45.6 – 89.9). The most common adverse events across the entire population were lymphopenia (74.7%), anaemia (64.6%) and neutropenia (61.6%).
Visco et al. 2021	Retrospective Relapsed/refractory MCL (n = 261), 54 treated with bendamustine 90 mg/m^2 days one to two plus rituximab 375 mg/m^2 on day one	When adjusted for age and early/late POD in a logistic regression model, CR was 43% for bendamustine plus rituximab versus 63% for R-BAC (OR 0.43; 95% CI: 0.20 – 0.93). Median PFS was 13 months (95% CI: 3 – 26); it was approximately two years for ibrutinib and for R-BAC. For the entire cohort, median early POD OS was 14.3 months (95% CI: 10.9 – 17), for ibrutinib it was 29.7 months (95% CI: 15.7 – not reported), for R-BAC it was 10.3 months (95% CI: 7.7 – 22.1) and for bendamustine plus rituximab it was 11.9 months (95% CI: 5.3 – 28.7).
Bega et al. 2021	Retrospective Untreated MCL (n = 156) treated with bendamustine plus rituximab (n=53) or R-BAC (n=103)	According to International Working Group Criteria, CR rate was 76% and 47% for R-BAC and for bendamustine plus rituximab respectively (p = 0.0004). Median follow-up was 46 months (range: 12 – 135); 49 patients died during the study, 65% from progressive disease. Two-year PFS was 87% and 64% for R-BAC and for bendamustine plus rituximab respectively (p = 0.001). Median OS was 121 months and 78 months for R-BAC and for bendamustine plus rituximab respectively (p = 0.08). R-BAC was associated with significantly more pronounced grade 3 – 4 thrombocytopenia (50%) than bendamustine plus rituximab (17%).

ASCT: autologous stem cell transplant; CI: confidence interval; CR: complete response; EFS: event free survival; MCL: mantle cell lymphoma; OD: odds ratio; ORR: overall response rate; OS: overall survival; PFS: progression free survival; POD: progression of disease; R-BAC: rituximab, bendamustine and cytarabine; R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-DHAP: rituximab with dexamethasone, high dose cytarabine and cisplatin; RM: rituximab maintenance