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

September 2020

ONE WALES INTERIM COMMISSIONING DECISION

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

Date of original advice: April 2017
Date of review: September 2020

The following Interim Pathways Commissioning Group (IPCG) 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.

Bendamustine in combination with rituximab is not a licensed regimen to treat this indication and is therefore 'off-label'. Each provider organisation must ensure all internal governance arrangements are completed before these medicines are prescribed in combination.

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

Providers should consult the General Medical Council 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 Interim Commissioning decision.

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

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.

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[1,2]. 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[3].

A cohort of patients had been identified through data from individual patient funding request panels and clinicians in Wales considered 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.

Current One Wales Interim Commissioning Decision
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. July 2019.

Licence status
Bendamustine in combination with rituximab for the treatment of mantle cell lymphoma is off-label.

Guidelines
COVID-19: Interim NICE guidance relating to systematic anticancer treatments has been issued to reduce risk to patients and alleviate the impact on service capacity during the COVID-19 pandemic (NG161)[4]. Interim treatment changes are for an initial three-month period. These treatments will be implemented in NHS Wales subject to an interim submission and review process[5]. Treatment regimens will revert to the standard treatment protocol after this period unless the guideline is updated. Ibrutinib (with or without rituximab) is currently included as a first-line treatment option to be used instead of intravenous chemotherapy in patients with mantle cell lymphoma[4].

Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines
NICE ID1221: Ibrutinib for untreated mantle cell lymphoma[6]. Expected publication date: TBC. This treatment is currently on the Cancer Drugs Fund list as an interim treatment option during COVID-19 pandemic (see above)[7].

NICE ID1313: KTE-X19 for treating relapsed or refractory mantle cell lymphoma[8]. Expected publication date: 06 January 2021. This medicine is an advanced therapy medicinal product (ATMP).

Efficacy/Effectiveness
A repeat literature search conducted by AWTTC identified two retrospective studies.

A published conference abstract assessed the efficacy of bendamustine plus rituximab as an induction regimen for the treatment of mantle cell lymphoma (n = 190) in patients (median age = 66) treated in British Columbia[9]. Patients 65 years and under would have been eligible for high-dose BEAM and autologous stem cell transplantation (ASCT) and these patients were compared to historical control patients treated with R-CHOP. In this subgroup of patients aged ≤ 65 years (n = 89), there was no statistically significant improvement for progression free survival (PFS) or overall survival (OS) with benadmustine plus rituximab versus R-CHOP. This persisted for those patients who underwent ASCT. In the full cohort of 190 patients, 23 (12%) patients progressed during or within three months after bendamustine plus rituximab treatment, and all had highly proliferative disease or blastoid/pleomorphic histology. Authors conclude that longer term follow up is required to fully understand the impact of bendamustine plus rituximab in the frontline setting.

They also raise concerns that bendamustine plus rituximab may not be an optimal treatment across all patients with mantle cell lymphoma, particularly for those with aggressive or highly proliferative disease[9].

A peer-reviewed study, using data from a Medicare database linked to the Surveillance Epidemiology and End Results registry, compared real-life outcomes of older patients with either follicular lymphoma, mantle cell lymphoma or marginal zone/lymphoplasmacytic lymphoma treated with first-line bendamustine plus rituximab or cyclophosphamide-based regimens (RCHOP/RCVP)[10]. Median age of the patients in the analytic cohort (n = 3,491) was 75 years. In the analytic cohort, 1,368 patients who received bendamustine plus rituximab were matched to patients who received RCHOP/RCVP in a 1:1 ratio (n = 2,736). In this cohort, event-free survival (EFS) was statistically significantly better for all patients receiving bendamustine plus rituximab (hazard ratio [HR], 0.78; 95% confidence interval [CI]: 0.70 – 0.87) but there was no such difference for OS (HR 1.03, 95% CI: 0.91 – 1.17). Bendamustine plus rituximab was associated with statistically significantly fewer hospitalisations, infections, transfusions and cardiovascular events than RCHOP/RCVP. In histology-specific subcohorts separately matched in a 1:1 ratio, mantle cell lymphoma patients (n = 690) benefited most from bendamustine plus rituximab treatment in relation to EFS (HR 0.64; 95% CI: 0.54 – 0.76), with less benefit observed for follicular lymphoma patients (n = 1,330; HR 0.83; 95% CI: 0.69 – 0.98) and no significant benefit seen for marginal zone/lymphoplasmacytic lymphoma patients (n = 574; HR 0.92; 95% CI: 0.73 – 1.17)[10].

Safety
No new safety issues were identified.

Cost effectiveness
No relevant cost-effectiveness analyses were identified in the repeat literature search.

Budget impact
No information on patient numbers has been received.

Impact on health and social care services
The impact on the service remains minimal.

Patient outcome data
No patient outcome data have been provided.

References

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10. Olszewski AJ, Butera JN, Reagan JL et al. Outcomes of bendamustine- or cyclophosphamide-based first-line chemotherapy in older patients with indolent B-cell lymphoma. *American Journal of Hematology.* 2019;95:354-361. Available at: https://doi.org/10.1002/ajh.25707. Accessed May 2020.