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 relapsed mantle cell lymphoma

May 2018

ONE WALES INTERIM COMMISSIONING DECISION

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

Date of original advice: April 2017
Date of review: May 2018

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 is available through NHS England's Cancer Drugs Fund for off-label use in the first-line treatment of mantle cell lymphoma, in people for whom standard treatment is unsuitable[1]. According to the Cancer Drugs Fund criteria, bendamustine may be used in combination with rituximab, which is commissioned by NHS England for this indication. 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[2]. In April 2018 NHS England reviewed bendamustine plus rituximab for relapsed and refractory mantle cell lymphoma[3]. NHS England recognised that there is some clinical evidence to support the use of this treatment for this condition, however, balanced against other relative priorities that were also considered, NHS England decided not to fund this treatment[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 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. April 2017.

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

Guidelines
In the updated European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment and follow-up in newly diagnosed and relapsed mantle cell lymphoma (2017) bendamustine and rituximab remains a first-line option for patients over the age of 65 and for patients with early relapse disease[4].

Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines
NICE TA502: ibrutinib (Imbruvica®▼) is recommended, within its marketing authorisation, as an option for treating relapsed or refractory mantle cell lymphoma[5]. Guidance states that ibrutinib can only be used in people who have had no more than one previous line of therapy[5].

In progress with NICE: ibrutinib (Imbruvica®▼) for untreated mantle cell lymphoma[6].

Efficacy/Effectiveness
A five-year follow-up (presented as a conference abstract) to the BRIGHT study which was described in the original evidence status report has been published[7]. BRIGHT was conducted in patients with treatment naive indolent non-Hodgkin's lymphoma or mantle cell lymphoma. Patients were monitored for at least five years to assess the effect of bendamustine plus rituximab compared to rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) or rituximab plus cyclophosphamide, vincristine and prednisone (R-CVP) on progression-free survival, event-free survival, duration of response and overall survival. Of the 447 patients enrolled in the BRIGHT study, 419 entered the five-year follow-up study. The median follow-up time was 65.0 months for the bendamustine plus rituximab group and 64.1 months for the R-CHOP/R-CVP group. The results showed that progression-free survival, event-free survival and duration of response were significantly better for the bendamustine and rituximab group compared with the R-CHOP/R-CVP group (Table 1). Similar results for progression-free survival were found in patients with mantle cell lymphoma (hazard ratio 0.40; 95% confidence interval 0.21 to 0.75; p = 0.0035). Overall survival was not statistically different between the two groups (Table 1). The safety profile was as previously reported[7].

Table 1. Results from the BRIGHT five-year follow up study[7]

	Bendamustine plus rituximab	R-CHOP/R-CVP	Hazard ratio (95% CI) p value
Progression-free survival	65.5%	55.8%	0.61 (0.45–0.85) p = 0.0025
Overall survival	81.7%	85%	1.15 (0.72–1.84) p = 0.5461
Event-free survival	NR	NR	0.63 (0.46–0.84) p = 0.0020
Duration of response	NR	NR	0.66 (0.47–0.92) p = 0.0134
CI: confidence interval; NR: not reported; R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP: rituximab plus cyclophosphamide, vincristine and prednisone.			

Safety

In July 2017, the Medicines and Healthcare products Regulatory Agency published a Drug Safety Update article highlighting new safety information regarding a risk of increased mortality associated with the use of bendamustine when used in non-approved combination treatment or outside approved indications[8]. Fatal toxicities were mainly due to opportunistic infections[8]. An accompanying letter sent to healthcare professionals providing the background to this safety concern refers to results from the BRIGHT and GALLIUM studies and also included unpublished post marketing safety data[9]. In the BRIGHT study mortality rates were 12 (5%) in the bendamustine plus rituximab arm and 9 (4%) in the R-CHOP group. The GALLIUM study compared safety of obinutuzumab versus rituximab in combination with CHOP, CVP or bendamustine in patients with previously untreated follicular lymphoma[10]. At a mean follow up of 34.5 months fatal adverse events were reported in 4% of patients on obinutuzumab and 3.4% of patients on rituximab. When analysed by chemotherapy used in induction, bendamustine was associated with the highest mortality rates: 5.6% (n = 19) for obinutuzumab-bendamustine and 4.4% (n = 15) for rituximab-bendamustine. Fatalities occurred in nine patients across all other arms[10]. The post marketing data showed a signal of increased frequency of opportunistic infections after treatment with bendamustine[9]. Such infections may be linked to lymphocytopenia and low CD4-positive T-cell counts which have been reported in patients for at least 7–9 months after the end of treatment[9]. The summary of product characteristics has been updated to reflect these findings[11].

A repeat literature search identified three papers with long term safety results[12-14]. Median follow up ranged from 31.2 months to 8.9 years and the indication, place in therapy and dose varied within and between studies. Across the three reports a total of 930 patients received bendamustine plus rituximab. No new safety signals arose from these studies, infection rates and secondary malignancies were in line with those previously reported[12-15].

Cost effectiveness

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

Budget impact

Based on the small numbr of patients who received bendamustine plus rituximab for the treatment of relapsed mantle cell lymphoma across NHS Wales since April 2017, it is likely that the actual budget impact is minimal.

Rituximab biosimilars are now available[16,17]; however they will not directly affect the original budget impact as this was based on generic bendamustine costs alone as patients with mantle cell lymphoma would receive rituximab as part of any alternative regimen.

Impact on health and social care services

The impact on the service remains minimal.

Patient outcome data

[Confidential data removed.]

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