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 indolent lymphomas (OW08)

September 2021

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Date of original advice 2017
Date of review: September 2021

The following One Wales 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 follicular lymphoma, marginal zone lymphoma and Waldenstrom's macroglobulinaemia under the following circumstances:

- In the first-line setting, for use in fit patients with aggressive follicular lymphoma and marginal zone lymphoma where other licensed and health technology appraisal-approved regimens are unsuitable.
- In the relapsed setting, for use in patients with follicular lymphoma and marginal zone lymphoma where other licensed and health technology appraisal-approved regimens are unsuitable.
- For the treatment of Waldenstrom's macroglobulinaemia for first-line and relapsed disease in patients deemed unsuitable for anthracycline-based regimens and/or where other licensed and health technology appraisal-approved regimens are unsuitable.

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 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 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.

One Wales advice assists consistency of access across NHS Wales and will be disseminated to the service following agreement of Health Board Chief Executives.

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 first-line treatment of advanced, indolent non-Hodgkin's lymphoma[1]. Bendamustine is available through NHS England's Cancer Drugs Fund for use in relapsed low grade lymphoma, in people for whom standard treatment is unsuitable[2]. According to the NHS England Cancer Drugs Fund criteria, bendamustine may be used in combination with rituximab, which is commissioned by NHS England for this indication[2].

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: young and fit people with aggressive, untreated and relapsed follicular lymphoma and marginal zone lymphoma, and Waldenström's macroglobulinaemia for whom standard therapy is unsuitable. Based on this unmet need, this medicine combination was considered suitable for assessment via the One Wales process.

Current One Wales Decision

Bendamustine in combination with rituximab can continue to be made available within NHS Wales for the treatment of previously untreated and relapsed follicular lymphoma, marginal zone lymphoma and Waldenström's macroglobulinaemia under the following circumstances (September 2020):

- In the first-line setting, for use in fit patients with aggressive follicular lymphoma and marginal zone lymphoma where other licensed and health technology appraisal-approved regimens are unsuitable.
- In the relapsed setting, for use in patients with follicular lymphoma and marginal zone lymphoma where other licensed and health technology appraisal-approved regimens are unsuitable.
- For the treatment of Waldenström's macroglobulinaemia for first-line and relapsed disease in patients deemed unsuitable for anthracycline-based regimens and/or where other licensed and health technology appraisal-approved regimens are unsuitable.

Licence status

Bendamustine in combination with rituximab for the treatment of follicular lymphoma, marginal zone lymphoma and Waldenström's macroglobulinaemia remains off-label.

Guidelines

There have been no new relevant guidelines or updates to existing guidelines identified.

Interim NICE guidance issued in April 2020 relating to systemic anticancer treatments (NG161) during COVID-19 is still in place[3].

Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines
There are no relevant new medicines or health technology appraisal advice.

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

A published conference abstract examined survival and toxicity of patients with previously untreated indolent lymphoma treated with bendamustine plus rituximab compared with rituximab in combination with cyclophosphamide, vincristine and prednisolone (R-CVP) or rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) in Ontario[4]. This retrospective cohort study included patients with a diagnosis of indolent lymphoma, excluding mantle cell lymphoma, who were treated with R-CVP/CHOP from 2005 to 2012 or with bendamustine plus rituximab from 2013 to 2018. A propensity-matched cohort of 2,029 patients treated with bendamustine plus rituximab and 2,029 patients treated with R-CVP/CHOP were analysed. The majority of patients had a diagnosis of follicular lymphoma (59%). The median age of patients was 64 years. Bendamustine plus rituximab was associated with a significant improvement in survival compared to R-CVP/CHOP (Hazard Ratio [HR] 0.76, 95% Confidence Interval [CI] 0.67–0.88, $p < 0.01$). Five-year overall survival (OS) was 80% and 75% for patients treated with bendamustine plus rituximab and R-CVP/CHOP respectively[4].

A second published conference abstract included patients with extranodal marginal zone lymphoma (EMZL) treated with frontline bendamustine plus rituximab (n = 118) in a retrospective analysis which involved 11 cancer centres from the US and Italy[5]. Median age was 61.5 years (range: 21–85). The response to treatment was as follows: complete response (CR): 96 (81.4%), partial response (PR): 13 (11%), stable disease (SD): 2 (1.7%), progressive disease (PD): 4 (3.4%), and unknown: 3 (2.5%) patients. With a median follow up of 2.85 (range 0.08 to 9.45) years, the estimated 5-years progression free survival (PFS) was 72.3% (95% CI 59.3-81.8%) and OS was 85.6% (95%CI 75.0-92.0%)[5].

A third published conference abstract reported on a retrospective, multicentre cohort analysis of consecutive Waldenström's macroglobulinaemia patients treated with bendamustine plus rituximab in the frontline or relapsed settings[6]. Data were collected for 250 matched frontline (n = 139) and relapsed (n = 111) patients from 17 sites across 4 countries, including UK centres. The overall response rate (ORR) (≥ PR on International Workshops on Waldenstrom's Macroglobulinaemia criteria) differed significantly between frontline and relapsed cohorts (91.4% versus 73.9%, respectively; $p < 0.001$). PFS was significantly longer in the frontline cohort compared with recipients of ≥ 2 prior lines of treatment, but not between frontline versus after 1 prior therapy line. Rates of toxicity-related treatment truncation were significantly lower in the frontline setting (17.3% versus 35.1%; $p < 0.001$). Frontline patients received higher total bendamustine doses than relapsed patients (median total dose 1,080 mg/m^2 versus 720 mg/m^2; $p < 0.001$). In the frontline setting, two-year predicted PFS was superior in the group receiving ≥ 1,000 mg/m^2

(i.e. 90 mg/m^2 on days 1 and 2 for 6 cycles) compared with those receiving 800-999 mg/m^2 (95% versus 89%; p = 0.04). In the relapsed cohort, by contrast, there was no PFS difference between the ≥ 800 mg/m^2 and the 600-799 mg/m^2 dose groups (p = 0.19). Those who received doses of < 600 mg/m^2 had significantly poorer two-year predicted PFS outcomes compared with those who received ≥ 600 mg/m^2 (75% versus 46%, p = 0.01). Older age significantly affected tolerated dose in the relapsed but not the frontline cohort[6].

A peer-reviewed, retrospective, monocentric study explored the clinical outcomes of patients with splenic marginal zone lymphoma (SMZL) and compared the effectiveness of different rituximab containing treatment options[7]. A total of 48 patients received rituximab, in 12 patients it was provided alone, in 23 patients in combination with bendamustine and in 13 patients with CHOP. The median time from diagnosis to therapy was 7 months. Median age of the patients receiving bendamustine plus rituximab was 70 years; the patients in the R-CHOP group presented more aggressive features at baseline (nodal involvement, lower platelets and haemoglobin, higher lactate dehydrogenase value). The 4-year OS was not significantly different between the different treatment groups (p = 0.09). The 4-year PFS was significantly lower in the group of patients treated with the R-CHOP regimen (30.8 ± 12%) in comparison with rituximab monotherapy (91.3 ± 9%) or in combination with bendamustine (75 ± 15%), p < 0.001[7].

A second peer-reviewed, retrospective, monocentric study analysed the effectiveness and safety of the use of bendamustine plus rituximab in marginal zone lymphoma patients in first line therapy in daily clinical practice[8]. The treatment schedule was rituximab at the dose of 375 mg/m^2 on day 1 of each cycle and bendamustine at the dose of 90 mg/m^2 on day 1 and 2, every 28 days for a maximum of 6 cycles. The study analysed 65 marginal zone lymphoma patients (28 extranodal [EMZL], 23 splenic [SMZL], and 14 nodal [NMZL]) who underwent bendamustine plus rituximab regimen as first line treatment. Median age at diagnosis was 66 years. At the end of treatment 38 patients achieved CR (58.5%) and 20 patients a PR (30.7%) leading to an ORR of 89.2%. The remaining seven patients had progressive disease. OS was 84.9% at 68 months. The estimated six-year PFS was 71.8% with 15 relapsed/progressed patients showing lymphoma recurrence within 48 months from end of treatment. With respect to the histology, no significant differences in ORR, CR or PFS were found[8].

A third peer-reviewed, retrospective, multicentre study examined treatment options for grade 3 follicular lymphoma, which frequently coexists with grades 1 and 2 (1-2-3A)[9]. The study included 95 grade 3A or 1-2-3A patients and also studies the outcomes of 203 grade1-2 patients treated first-line with either bendamustine plus rituximab or R-CHOP. In the 3A or 1-2-3A patient group a higher ORR was observed for R-CHOP (95% versus 76%) as well as longer OS (three-year OS: 89% versus 73%, p = 0.008). The difference in PFS did not reach statistical significance. While transformation rates into aggressive lymphoma were similar between both groups, there were more additional malignancies after bendamustine plus rituximab compared with R-CHOP (6 versus 2 cases). In the Grade 1-2 patients bendamustine plus rituximab achieved a higher three-year PFS in grade 1-2 patients (79% versus 47%, P < 0.01), no significant differences were found for

OS or transformation rates. In the Grade 1-2 patient group additional malignancies occurred with the same frequency in both treatment groups[9].

Safety
In March 2021, the Medicines and Healthcare products Regulatory Agency published a Drug Safety Update article highlighting new safety information regarding a risk of increased risk of non-melanoma skin cancer and progressive multifocal encephalopathy (PML) associated with the use of bendamustine[10]. The background to this safety concern refers to results from the BRIGHT and GALLIUM studies which show a higher number of cases of non-melanoma skin cancer with bendamustine containing regimens than with other treatments used for lymphoma. In the BRIGHT trial, 14 of 221 (6.3%) patients treated with bendamustine plus rituximab and 5 of 215 (2.3%) patients treated with R-CHOP/R-CVP were reported to develop squamous cell carcinoma or basal cell carcinoma. In the GALLIUM trial basal cell carcinoma was reported in 16 of 676 patients (2.4%) receiving bendamustine versus 1 of 513 patients receiving CHOP/CVP. There were also increases in the number of reports of squamous cell carcinoma in patients receiving bendamustine, while no cases were reported in patients receiving CHOP/CVP. In addition, very rare cases of PML have been reported in patients on bendamustine containing regimens. The European review of safety data also identified an increase in reporting of cases of PML when bendamustine containing therapy is used. During the period reviewed (7 January 2018 to 6 January 2020), 42 cases of PML worldwide were reported, 11 of which were fatal. This compared to 9 cases in the previous period (7 January 2017 to 6 January 2018). Although concomitant treatment was present in all cases where information was provided, a temporal relationship with bendamustine was evident in most cases. In 31 of the cases, bendamustine-containing therapy was the latest treatment before onset. The summary of product characteristics and patient information leaflet have been updated to reflect these findings[10].

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

Budget impact
No information on patient numbers has been received. Clinician indicates that with the availability of oral targeted agents bendamustine use is lower than before.

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

Patient outcome data
One clinician indicated that they use this regimen for front line Waldenstrom's macroglobulinaemia patients who have bulky nodal disease. They believe that bendamustine with or without rituximab remains a useful option for selected patients with indolent lymphomas. No patient numbers have been provided.

References

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