AWTTC
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Evidence Status Report: Bendamustine plus rituximab (MabThera®) for treating mantle cell lymphoma

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KEY FINDINGS

Report 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. According to the Cancer Drugs Fund criteria, bendamustine may be used in combination with rituximab, which is commissioned by NHS England for this indication[1]. Although rituximab is not licensed for treating mantle cell lymphoma, the National Institute for Health and Care Excellence (NICE) mantle cell pathway recommends it in combination with chemotherapy as first-line treatment of advanced-stage mantle cell lymphoma[2].

A cohort of patients has been identified through data from individual patient funding request (IPFR) panels and clinicians in Wales consider there is an unmet need within the service. This cohort includes people with untreated and relapsed mantle cell lymphoma for whom anthracycline-based chemotherapy is unsuitable. Based on this unmet need this medicine combination was therefore considered suitable for assessment via the One Wales process.

Efficacy/Effectiveness

Data from a phase III study showed that bendamustine plus rituximab was more effective and less toxic than rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) in first-line treatment of mantle cell lymphoma[3]. Data from a second phase III study showed that bendamustine plus rituximab was superior to rituximab plus CHOP/CVP (cyclophosphamide, vincristine and prednisolone)[4].

Data from a phase III study showed that bendamustine plus rituximab was more effective than fludarabine plus rituximab in treating relapsed mantle cell lymphomas, giving a longer progression-free survival and median overall survival[5].

Further evidence considers bendamustine plus rituximab plus cytarabine for first-line and following first relapse. Overall response rates and progression-free survival were higher than those reported in the phase III bendamustine with rituximab studies, however, these studies did not include a comparator arm and patient numbers were small[6,7].

Safety

Bendamustine plus rituximab is associated with high incidences of serious haematological toxicities, in common with other chemotherapy regimens used to treat mantle cell lymphoma. The phase III studies showed that bendamustine plus rituximab has a safety profile that is distinct from those of the standard chemotherapy regimens, and has some favourable aspects[4]. In the first-line treatment of mantle cell lymphoma bendamustine plus rituximab showed a generally lower incidence of neutropenia, leukopenia, alopecia and neuropathy than was seen in patients treated with rituximab plus CHOP, with a higher incidence of skin reactions and drug sensitivity[3]. A Cochrane review of bendamustine in treating indolent B cell lymphoid malignancies concluded that the risk of grade 3–4 adverse events was similar when bendamustine was compared with CHOP and fludarabine[8]. Clinical expert opinion suggests that haematological toxicity is higher when adding cytarabine to the bendamustine plus rituximab combination.

Patient factors

Health-related quality of life data showed that first-line treatment with bendamustine plus rituximab was associated with small improvements in functioning compared with standard therapy[9]. No data were identified for assessing the health-related quality of life in the relapsed setting.

Cost effectiveness
No cost-effectiveness analyses were identified for bendamustine plus rituximab for the treatment of mantle cell lymphoma.

Budget impact
Based on an estimated 12 patients with mantle cell lymphoma eligible for treatment the annual budget impact is £6,864. This analysis focuses on bendamustine acquisition costs only because patients would receive rituximab as part of an alternative regimen so rituximab does not represent an additional cost. Additional resource costs for one extra day of medicine administration per cycle for bendamustine will be dependent upon current service capacity. Some patients are already receiving this regimen through IPFR and local applications though accurate figures were not available from the health boards. In addition, alternative regimens are similarly priced and therefore the true net cost is likely to be lower than £6,684.

Welsh commercial access agreement
These medicines are currently not licensed for the indication being considered (i.e. off-label). Therefore a commercial agreement cannot be offered by the relevant companies because the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine.

Impact on health and social care services
Using bendamustine plus rituximab to treat mantle cell lymphoma, including newly diagnosed and relapsed disease, is expected to have minimal impact on existing services.

Innovation and/or advantages
Bendamustine plus rituximab offers an anthracycline-free regimen for the treatment of mantle cell lymphoma. It therefore may be suitable for people who are unable to tolerate or who have a contra-indication to an anthracycline-based regimen, or who may have reached the maximum cumulative dose of anthracycline at which the risk of chronic cardiotoxicity increases.

BACKGROUND

Target group

The indication being considered is mantle cell lymphoma, including newly diagnosed and relapsed disease.
First line: for patients not deemed suitable for anthracycline-based therapy. This will include (but is not limited to) patients unsuitable for stem cell transplant.
Second line (and beyond): as an anthracycline-sparing option, assuming other licensed and health technology appraisal approved regimens are unsuitable.

Technology

Bendamustine is an alkylating antitumor agent[10]. Its antineoplastic activity is based on cross-linking of DNA single and double strands by alkylation, which impairs DNA matrix functions and DNA synthesis and repair[10].

Rituximab (MabThera®) is a genetically engineered chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20 on pre-B and mature B lymphocytes[11]. This binding mediates B-cell lysis by complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and also induces cell death by apoptosis[11].

Marketing authorisation date: Not applicable, off-label

Bendamustine is indicated as monotherapy for indolent non-Hodgkin's lymphomas in patients who have progressed during or within six months of treatment with rituximab or a regimen containing rituximab[10].

The use of rituximab in combination with bendamustine for mantle cell lymphoma is therefore off-label.

The European patent for rituximab (MabThera®) expired in 2013 and the US patent in 2016[12]. Biosimilars are now becoming available.

Dosing

Bendamustine is given by intravenous infusion over 30–60 minutes and administration must be supervised by a physician qualified and experienced in the use of chemotherapeutic agents[10]. In clinical studies it was given at a dose of 90 mg/m^2/day on days 1 and 2 of a four-week cycle, for up to six cycles[3-5].

The recommended dose of intravenous rituximab for treating non-Hodgkin's lymphoma is 375 mg/m^2 body surface area per cycle, for up to eight cycles, which is the dose used in clinical studies[11].

Clinical background

Mantle cell lymphoma is a rare form of non-Hodgkin's lymphoma, a cancer that affects the lymphocytes in the blood[13]. It represents about 6% of non-Hodgkin's lymphoma cases and it affects mainly men aged over 50[13,14].

Symptoms of mantle cell lymphoma are similar to other types of non-Hodgkin's lymphoma[14]. The most common symptom is one or more painless swellings (enlarged lymph nodes) in the neck, armpit or groin[14]. Mantle cell lymphoma is a quickly growing lymphoma, which may have spread from the lymph nodes to the spleen and bone marrow by the time it is diagnosed[14]. It has one of the poorest outcomes among the B-cell lymphomas: median overall survival with immunochemotherapy is between 3 and 4 years[13].

Incidence/prevalence

Mantle cell lymphoma has an estimated incidence of 510 cases per year in the UK[13]. In Wales in 2014 there were 595 cases of non-Hodgkin's lymphoma reported; assuming 6% of these are mantle cell lymphoma gives an incidence of 36 cases per year in Wales[15]. The annual incidence is 1–2 cases per 100,000[16]. Of these, 75% of patients would present with advanced or late-stage disease and would be eligible for first-line treatment. Assuming 75% of cases are diagnosed at an advanced or late stage, an incidence of 36 cases per year in Wales equates to 27 patients eligible for first-line treatment. Intensive treatment would not be suitable for around 50% of patients[17], which equates to 10–14 patients in Wales. No incidence data were available on the number of relapsed mantle cell patients that may be eligible for treatment in Wales.

Current treatment options

There is no accepted standard of care for mantle cell lymphoma[13]. Radiotherapy is a treatment option for people with localised stage I or II mantle cell lymphoma[2]. For advanced stage disease, the choice of therapy often depends on the person's fitness for high-dose

chemotherapy and autologous stem cell transplantation[13].

For advanced stage disease, NICE recommends offering chemotherapy with rituximab as first-line treatment for people who are symptomatic[2]. The intensity of the chemotherapy depends on the person's fitness; for fitter people a cytarabine-containing immunochemotherapy may be considered for an intensive approach (Nordic protocol)[2]. If people have at least a partial response to induction chemotherapy, NICE recommends consolidation with autologous stem cell transplantation for people who are fit enough[2]. For adults who are not fit enough for stem cell transplantation, NICE recommends, as an option, bortezomib (Velcade®) in combination with rituximab, cyclophosphamide, doxorubicin and prednisone[18].

The European Society for Medical Oncology (ESMO) notes that with a median age of 65 years at first diagnosis, dose-intensified chemotherapy regimens are not suitable for most people[16]. ESMO recommends first-line treatment with rituximab plus chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine in patients aged over 65, and dose-intensified immunochemotherapy with rituximab plus CHOP and rituximab plus high-dose cytarabine followed by autologous stem cell transplantation for younger patients (under 65 years)[16]. ESMO guidelines discourage the use of purine analogue-based schemes such as rituximab plus fludarabine and cyclophosphamide and rituximab plus fludarabine and mitoxantrone because of early failures and long-lasting myelosuppression[16]. A clinical expert in North Wales has indicated that within their health board rituximab with bendamustine and cytarabine is used as the main regimen for first-line treatment of patients not fit for autologous stem cell transplant. They follow the Thames Valley Strategic Clinical Network protocol that specifies two regimens for patients unfit for anthracycline based chemotherapy. The two regimens differ in the dose of cytarabine with a lower dose option for patients considered unfit for the higher dose; these regimens are also used for relapsed/refractory patients[19,20].

For treating relapsed disease ESMO guidelines state that selection of treatment depends on the efficacy of prior regimens[16]. In early relapses (< 12–24 months) they state that a non-cross resistant should be preferred (e.g. rituximab with bendamustine and cytarabine after rituximab plus CHOP or vice versa). Rituximab should be added if the previous antibody-containing regimen achieved > 6–12 months remission. They state that in early relapse or refractory cases newer targeted approaches (e.g. temsirolimus, bortezomib, ibrutinib or lenalidomide) should be strongly considered[16].

The British Society for Haematology and the US National Comprehensive Cancer Network guidelines recommend bendamustine plus rituximab as a treatment option for first line and relapsed or refractory disease disease[21 22]. NICE suspended an appraisal of bendamustine, in combination with rituximab, for the first-line treatment of mantle cell lymphoma after the manufacturer said it would no longer pursue a licensing application for this indication[23]. Bendamustine is available through the Cancer Drugs Fund for off-label use in the first-line treatment of mantle cell lymphoma[1].

Guidance and related advice

- NICE Guideline NG52 (2016): Non-Hodgkin's lymphoma: diagnosis and management[13]
- NICE Pathway (2016): Non-Hodgkin's lymphoma[2]
- NICE Technology Appraisal TA370 (2015): Bortezomib for previously untreated mantle cell lymphoma[18]
- European Society for Medical Oncology (2014): Newly diagnosed and relapsed mantle cell lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up[16]
- National Comprehensive Cancer Network (2014): Clinical practice guidelines in

oncology: non-Hodgkin's lymphomas[22]
- British Society for Haematology (2012): Guidelines for the investigation and management of mantle cell lymphoma[21]

Guidance in progress:
- NICE: ibrutinib (Imbruvica®) for the treatment of relapsed or refractory mantle cell lymphoma. The expected publication date was December 2016[24], however, this guidance is not yet published.

NICE: lenalidomide (Revlimid®) and temsirolimus (Torisel®) for the treatment of relapsed or refractory mantle cell lymphoma; these appraisals are suspended and terminated respectively[25,26].

SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

A comprehensive literature search conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC), and information from the manufacturer of rituximab, identified two phase III studies comparing bendamustine plus rituximab with standard chemotherapy plus rituximab for treating newly diagnosed indolent and mantle cell lymphomas, and a phase III trial comparing bendamustine plus rituximab with fludarabine plus rituximab for treating relapsed or refractory indolent and mantle cell lymphomas. These studies are described below.

One open-label phase II study and two retrospective studies were also identified which evaluated bendamustine plus rituximab in treating relapsed or refractory mantle cell lymphoma. Two phase II trials were identified which evaluated bendamustine with rituximab and cytarabine for first line and relapsed/refractory mantle cell lymphoma[6,7]. These studies are briefly described below. Other phase II studies of bendamustine in mantle cell lymphoma were identified but have not been included here because of differences in the treatment regimen or very small patient numbers.

Efficacy

First-line treatment: STiL NHL1 and BRIGHT studies
Two open-label phase III studies aimed to demonstrate non-inferiority of bendamustine plus rituximab compared with rituximab plus CHOP, CVP (cyclophosphamide, vincristine, prednisone) or fludarabine. The dosing regimens, for a maximum of six cycles, were:
- bendamustine 90 mg/m^2 on days 1 and 2 plus rituximab 375 mg/m^2 on day 1 of a four-week cycle
- rituximab 375 mg/m^2 on day 1 plus cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 and vincristine 1.4 mg/m^2 on day 1 and prednisone 100 mg/day for 5 days of a three-week cycle
- rituximab 375 mg/m^2 on day 1 plus cyclophosphamide 750 mg/m^2 on day 1, vincristine at 1.4 mg/m^2 on day 1 and prednisone 100 mg/day for 5 days of a three-week cycle.

Eligibility criteria included age over 18 years and a World Health Organization or an Eastern Cooperative Oncology Group performance status score of two or less.

STiL NHL1: Bendamustine plus rituximab versus CHOP plus rituximab
This study was conducted in Germany in 549 patients with treatment-naive newly diagnosed stage III or IV indolent or mantle cell lymphoma [3].

Patients were stratified by lymphoma subtype then randomised 1:1 to receive rituximab plus either bendamustine or CHOP. The primary endpoint was progression-free survival, with a non-inferiority margin of 10%. Analysis was per-protocol; 35 patients were excluded therefore

261 were treated with bendamustine plus rituximab and 253 with rituximab plus CHOP. Of the patients included in the analysis, 94 had mantle cell lymphoma; they had a median age of 70 years and 46 were treated with bendamustine plus rituximab and 48 with rituximab plus CHOP[3].

In the whole study population, at a median follow-up of 45 months, progression-free survival was significantly longer for patients treated with bendamustine plus rituximab than in those treated with rituximab plus CHOP (Table 1)[3]. This significant benefit was also seen in the sub-group of patients with mantle cell lymphoma (Table 1) and was independent of age (≤ 60 years: HR 0.52; 95% CI 0.33 to 0.79; p = 0.002; > 60 years: HR 0.62; 95% CI 0.45 to 0.84; p = 0.002). In multivariate analysis with backward selection, mantle cell histology was identified as an independent negative predictor of poor outcome (HR 1.84; 95% CI 1.37 to 2.48; p < 0.0001), whereas bendamustine plus rituximab treatment showed a similar benefit to that in the unadjusted analysis (HR 0.56; 95% CI 0.43 to 0.72; p < 0.0001).

For the whole study population the rate of complete response was significantly higher in the bendamustine plus rituximab-treated patients (Table 1), and time to next anti-lymphoma treatment was significantly longer with bendamustine plus rituximab than with rituximab plus CHOP (HR 0.52; 95% CI 0.39 to 0.69; p < 0.0001)[3]. Because of the immaturity of the data, and the use of salvage therapies (including bendamustine-based regimens and stem cell transplantation) for patients who had disease progression on rituximab plus CHOP, this study did not show any difference between treatments in overall survival[3].

Results from follow-up after 87 months confirmed no difference in overall survival in the subgroup of 95 patients with mantle cell lymphoma (HR 1.28; 95% CI 0.69 to 2.39; p = 0.429), and no significant difference in overall survival in the whole study population[27]. The estimated 10-year survival rates were 67.4% for bendamustine plus rituximab group and 60.1% for rituximab plus CHOP group (HR 0.70; 95% CI 0.48 to 1.04; p = 0.076)[27].

BRIGHT study: bendamustine plus rituximab versus rituximab plus CHOP or rituximab plus CVP

This study was conducted in 447 patients with treatment-naive CD-20 positive indolent non-Hodgkin's lymphoma or mantle cell lymphoma who had an estimated life expectancy of at least six months[4].

In total, 447 patients were enrolled; 74 had mantle cell lymphoma. Patients were preassigned to the most appropriate standard chemotherapy regimen, either rituximab plus CHOP or rituximab plus CVP, based on their performance status, co-morbidities and general health. They were then randomised in a 1:1 ratio to receive either bendamustine plus rituximab (n = 224) or the standard chemotherapy (rituximab plus CHOP: n = 104; rituximab plus CVP: n = 119). Randomisation was stratified by the pre-determined chemotherapy and by lymphoma type[4].

No patients received rituximab maintenance treatment. The primary endpoint was complete response rate, with a non-inferiority threshold of 22%. Complete response was defined by International Working Group criteria as disappearance of all evidence of disease[28], and was evaluated by an independent review committee (IRC) in a blinded manner[4]. The analyses were conducted for evaluable patients in each treatment group: 213 patients who received bendamustine plus rituximab; 206 who received rituximab plus either CHOP or CVP[4].

Overall, the results showed that the bendamustine plus rituximab combination was statistically non-inferior to rituximab plus CHOP or rituximab plus CVP, in the evaluable population, as assessed by complete response rate (Table 1)[4]. In mantle cell lymphoma, bendamustine plus rituximab showed superiority over standard chemotherapy regimens (22 had rituximab plus CHOP and 11 had rituximab plus CVP), with a complete response rate ratio of 1.95 (95% CI 1.01 to 3.77; p = 0.018)[4]. For mantle cell lymphoma, the IRC assessment of histologic subtypes showed a complete response rate of 50% in the

bendamustine plus rituximab group compared with 27% in the standard chemotherapy groups; overall response rates were 94% in the bendamustine plus rituximab group and 85% in the standard chemotherapy groups[4].

Health-related quality of life data were collected during treatment using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)[9]. Results showed that treatment with bendamustine plus rituximab was associated with improved functioning scores at several time points. Scores for Cognitive Functioning, Physical Functioning, Social Functioning, Emotional Functioning and Global Health Status, measured at various time points, were the same or improved with bendamustine plus rituximab compared with standard therapy[9] However, the clinical significance of the benefits was small and differences were not statistically significant at all time points[9].

Table 1. The results from the phase III studies

	STiL NHL1[3]		BRIGHT[4]	
Overall population	**BR (n = 261)**	**R-CHOP (n = 253)**	**BR (n = 213)**	**R-CHOP/R-CVP (n = 206)**
Progression free survival (months)	69.5	31.2	NR	
Hazard ratio (95% CI)	0.58 (0.44–0.74)			
p value	p < 0.0001			
Complete response	40%*	30%*	67%†	52%†
Complete response ratio (95% CI)	NR		1.26 (0.93–1.73)	
p value	p = 0.021		p = 0.0225	
Mantle cell lymphoma population§	**BR (n = 46)**	**R-CHOP (n = 48)**	**BR (n = 34)**	**R-CHOP/R-CVP (n = 33)**
Progression free survival (months)	35.4	22.1	NR	
Hazard ratio (95% CI)	0.49 (0.28–0.79)			
p value	p = 0.0044			
Complete response	NR		50%†	27%†**
Complete response ratio (95% CI)			NR	
p value			NR	

BR: bendamustine plus rituximab; CI: confidence interval; R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP: rituximab plus cyclophosphamide, vincristine and prednisone; NR: not reported.
* Assessed by the World Health Organization response criteria
† Assessed by an independent review committee
§ Exploratory sub-analyses
** R-CHOP, n = 22

Treatment of relapsed or refractory disease:

Phase II study:
In an open-label single-arm study in the USA, 45 patients (median age 70 years) with relapsed or refractory non-blastoid mantle cell lymphoma were given bendamustine (90 mg/m^2 on days 1 and 2) plus rituximab (375 mg/m^2 on day 1) for six planned 28-day cycles[29]. All patients had been previously treated with rituximab; the median number of previous treatments was two. Functional imaging with 18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (18F-FDG PET/CT) was conducted at baseline and after cycle 6. Thirty-two patients had complete 18F-FDG PET/CT data: 75% achieved a complete metabolic response. The median follow up from last date of treatment was approximately 1.6 years, median progression-free survival was 17.2 months; one-year progression-free survival was 67% and three-year overall survival was 55%[29].

Phase III study:
This open-label study was conducted in Germany in 230 patients with relapsed indolent and mantle cell lymphomas, with the aim of establishing non-inferiority of bendamustine plus

rituximab compared with rituximab plus fludarabine[5].

Eligibility criteria included age over 18 years and a WHO performance status of 0–2, with relapsed or refractory stage III or IV indolent or mantle cell lymphoma[5]. Patients with lymphomas that were refractory to regimens that included rituximab, bendamustine or purine analogues were excluded. The median number of previous treatments was 1; 15% had received more than two previous treatments and over 50% of these were CHOP-based chemotherapy. Patients were stratified by lymphoma subtype then randomised 1:1 to receive rituximab 375 mg/m^2 on day 1 plus either bendamustine 90 mg/m^2 on days 1 and 2 (n = 116) or fludarabine 25 mg/m^2 on days 1–3 (n = 114) every four weeks for a maximum of six cycles.

The primary endpoint was progression-free survival for the per-protocol population, with a non-inferiority margin of 15%. Analysis was per-protocol: 11 patients were excluded, therefore the analysis included 114 patients treated with bendamustine plus rituximab and 105 treated with rituximab plus fludarabine. Of the 47 patients with mantle cell lymphoma, 24 were treated with bendamustine plus rituximab and 23 with rituximab plus fludarabine[5].

The median follow-up was 96 months. For the whole study population the median progression-free survival was 34.2 months for bendamustine plus rituximab-treated patients compared with 11.7 months for fludarabine plus rituximab-treated patients (HR 0.54, 95% CI 0.38 to 0.72; $p < 0.0001$)[5]. More patients did not respond to treatment and had progressive disease on fludarabine plus rituximab treatment than with bendamustine plus rituximab ($p < 0.0001$). Median overall survival was longer in patients treated with bendamustine plus rituximab than in those receiving fludarabine plus rituximab (109.7 versus 49.1 months; HR 0.64; 95% CI: 0.45 to 0.91; $p = 0.012$)[5]. Subgroup analysis showed that the 47 patients with mantle cell lymphoma had longer progression-free survival with bendamustine plus rituximab treatment compared with fludarabine plus rituximab (HR: 0.45; 95% CI: 0.22 to 0.76). Median progression-free survival was 17.6 months in patients with mantle cell lymphoma treated with bendamustine plus rituximab and 4.7 months in those treated with rituximab plus fludarabine. Additional subgroup analyses showed that progression-free survival and overall survival were longer in patients who received rituximab maintenance therapy than in those who did not receive maintenance treatment[5].

Retrospective studies:
A retrospective study was conducted in the USA of 30 patients with mantle cell lymphoma, 25 with relapsed disease, who were treated with bendamustine in combination with rituximab[30]. The median age at diagnosis was 58 years; most had advanced disease (28% with stage III and 69% with stage IV) at diagnosis. Of the patients with relapsed disease, 15 were being treated second-line and 10 as third-line or beyond, with a median of one previous chemotherapy regimen. Rituximab was administered at 375 mg/m^2 and the daily doses of bendamustine given were 100 mg/m^2, 90 mg/m^2 or 80 mg/m^2. Results for the whole study population showed that after a median follow-up of 12 months there were 15 complete responses and an overall response rate of 83% (95% confidence interval [CI] 70 to 97%)[30].

A retrospective study was conducted in Spain of 58 patients (median age 71 years) with relapsed or refractory mantle cell lymphoma (median of two previous treatments) who were given bendamustine either alone or in combination[31]. The 48 patients (83%) who were treated with rituximab plus bendamustine were given doses of rituximab 375 mg/m^2 and bendamustine 90 mg/m^2. Results for the whole study population showed that the overall response rate was 86%, with 55% having response or unconfirmed complete response. Median progression-free survival was 16 months (95% CI 13.3 to 18.8); in patients who achieved complete responses it was 33 months. Median overall survival was 32 months (95% CI 20.9 to 43.9)[31].

Bendamustine in combination with rituximab and cytarabine

First line treatment

A multicentre phase II study was conducted in Italy of 57 previously untreated patients (median age 71 years, range 67–75) who were fit according to comprehensive geriatric assessment[6]. All patients received rituximab 375 mg/m^2 on day 1, bendamustine 70 mg/m^2 on days 2 and 3 and cytarabine 500 mg/m^2 on days 2–4 of a 4-week cycle. The primary endpoint was the proportion of patients achieving complete response defined according to 2007 International Working Group response criteria[6].

Of the 57 patients 54 received at least 4 cycles and 38 had six cycles with a median of 6 cycles per patient[6]. Complete response was achieved by 52 patients (91%, lower limit of one-sided 95% CI 85%), two patients had disease progression and three received fewer than four cycles and were considered non-responders. At median follow-up of 35 months (interquartile range [IQR] 30–41, range 28–52) 42 patients (74%) were alive and disease free; median progression-free survival and median duration of response was not reached. There were 12 deaths reported. Overall survival at 2 years was 86% (74–93); progression-free survival was 81% (68–89) and duration of response was 90% (85–94)[6].

First line and relapsed or refractory treatment

A two-stage multicentre phase II study was conducted in Italy of 40 patients (median age 70 years) 20 of whom had been previously untreated and 20 who had received one previous chemotherapy treatment (with or without prior stem cell transplant)[7]. Stage one of the study was a dose finding study; the maximum tolerated dose of cytarabine was established to be 800 mg/m^2 and this was the dose used in stage two. Stage two evaluated safety and efficacy and patients received rituximab 375 mg/m^2 on day 1, bendamustine 70 mg/m^2 on days 2 and 3 and cytarabine 800 mg/m^2 on days 2–4 of a 4–week cycle. All patients were intended to receive 4 cycles with previously untreated patients able to receive 6 cycles depending upon age, tolerance to treatment and if they had exhibited disease regression from cycles two to four [7].

The primary endpoint for stage two was overall response rate; 90% of patients achieved a response (83% complete response and 7% partial response)[7]. Overall response rate for previously untreated patients was 100% (95% complete response and 5 % partial response) and for relapsed or refractory patients 80% (70% complete response and 10% partial response). Three relapsed or refractory patients had no response and one had disease progression. After median follow up of 26 months (range 11–38) 31 patients (78%) were alive and disease free, median progression free survival and duration of response had not been reached. The 2–year progression-free survival was 95% (±95% CI, 5%) and 70% (±95% CI, 10%) for previously untreated and relapsed or refractory patients respectively and duration of response rate was 100% and 87% (±95% CI, 8%) respectively[7].

Safety

Bendamustine plus rituximab is associated with high incidences of serious haematological toxicities, in common with other chemotherapy regimens used to treat indolent non-Hodgkin's lymphoma.

In the STiL NHL1 study, patients treated with bendamustine plus rituximab had fewer toxic effects than those treated with rituximab plus CHOP; serious adverse events occurred in 49 patients (19%) treated with bendamustine plus rituximab and in 74 (29%) treated with rituximab plus CHOP[3]. Fewer incidences of grade 3–4 neutropenia and leukopenia were reported in patients treated with bendamustine plus rituximab than in those treated with rituximab plus CHOP ($p < 0.0001$)[3]. The use of granulocyte-colony stimulating factors was significantly reduced in the bendamustine plus rituximab group compared with the rituximab plus CHOP group (4% versus 20%; $p < 0.0001$). Infections were significantly less frequent in

patients treated with bendamustine plus rituximab and neurotoxic effects were less common[3]. No patients treated with bendamustine plus rituximab had alopecia, whereas all patients treated with rituximab plus CHOP did have alopecia[3]. Drug-associated erythematous skin reactions were more common in patients treated with bendamustine plus rituximab ($p = 0.024$)[3]. The adverse effects reported in this phase III study were similar to those reported in the retrospective study. Results from follow-up after 87 months showed that there were 20 cases of secondary malignancies in bendamustine plus rituximab group and 23 in the rituximab plus CHOP group[27].

In the BRIGHT study, patients treated with bendamustine plus rituximab had a higher incidence of nausea and vomiting, and drug hypersensitivity reactions than patients treated with the standard chemotherapy regimens[4]. Standard chemotherapy regimens plus rituximab were associated with a significantly higher incidence of peripheral neuropathy/paresthesia and alopecia than bendamustine plus rituximab[4].

In the study of bendamustine plus rituximab versus rituximab plus fludarabine in treating relapsed mantle cell lymphoma, no substantial differences were noted between treatment groups for the occurrence of adverse events such as alopecia, stomatitis, erythema and allergic reactions or infections[5]. Haematological toxicities were also similar between the treatment groups. The most common adverse events were infections and myelosuppression[5].

In a phase II single-arm study in 45 patients with mantle cell lymphoma treated with bendamustine plus rituximab, grade 3 or 4 neutropenia occurred in 44% of patients and lymphopenia in 89%. The main non-haematological adverse events were nausea (69%), fatigue (56%), decreased appetite (42%), constipation (38%), diarrhoea (36%), vomiting (36%) and decreased weight (31%) [29].

In 2012 a Cochrane review of bendamustine in treating indolent B-cell lymphoid malignancies based on five studies in 1,343 people (around 20% of whom had mantle cell lymphoma), concluded that the risk of grade 3 or 4 adverse events was similar when bendamustine was compared with CHOP and fludarabine, and higher when compared with chlorambucil[8].

In the phase II study which evaluated bendamustine with rituximab and cytarabine 500 mg/m^2 as first line treatment the primary toxicity was reversible myelosuppression, platelet transfusions were administered in 29% of delivered cycles[6]. Haematological toxicities were recorded per treatment cycle, a total of 304 cycles were given. Grade 3 or 4 toxicities were: leucopenia in 44%; neutropenia in 49%; febrile neutropenia in 5%; thrombocytopenia in 52% and anaemia in 13% of all cycles. Non-haematological grade 3 or 4 adverse events included: documented infections or viral reactivations (11%); infusion-related reactions (2%); fatigue (2%) and cardiac events (6%)[6].

In the study of bendamustine with rituximab and cytarabine 800 mg/m^2 in previously untreated and in relapsed/refractory patients thrombocytopenia required transfusions in 65% of cycles and 44% of patients received erythropoietin[7]. Thrombocytopenia and leukopenia was more common in the relapsed or refractory patients (83% and 49% respectively) than in the previously untreated patients (70% and 32% respectively). Grade 3 or 4 non-haematological adverse events were: infection (12%); gamma-GT elevation (23%); fatigue (5%) and cardiac events (4%)[7].

Clinical effectiveness issues

The three phase III studies were designed to demonstrate non-inferiority of bendamustine plus rituximab to the other treatments; any analyses for superiority were conducted *post hoc*. In all three, the analysis for the primary endpoint was per-protocol (evaluable patients only)

rather than intention-to-treat. This could have introduced bias. In addition all sub-group analyses conducted in the phase III studies were exploratory rather than prospectively defined. The results of the sub-analyses should be interpreted with caution.

All the studies reported are open label, which could potentially introduce bias. The lack of blinding in the BRIGHT study may have influenced the health-related quality of life results[9]. However, blinding was not possible because of the different treatment regimens. The BRIGHT study included a blinded independent review committee to assess the complete response rate, the primary endpoint.

The phase III study evaluating bendamustine plus rituximab versus rituximab plus fludarabine was conducted over a long period of time, and the study protocol was changed after 3 years to include rituximab maintenance therapy for those patients with follicular lymphoma (n = 111; 50%), which is standard treatment. This was likely to have increased median progression-free survival[5]. In addition, only 42% of patients recruited had previously been treated with rituximab; this is not representative of current practice in Wales.

The phase III studies included small numbers of patients with mantle cell lymphoma. These patients were broadly representative of those likely to be seen in clinical practice in Wales.

Clinical experts in Wales have identified the relevant comparators as rituximab plus CHOP or rituximab plus bortezomib plus CAP (cyclophosphamide, doxorubicin and prednisone) for treating newly diagnosed mantle cell lymphoma. No studies were identified that compared bendamustine plus rituximab with rituximab plus bortezomib plus CAP in the first-line treatment of mantle cell lymphoma.

For second-line treatment of mantle cell lymphoma, clinical experts identified comparators as: rituximab plus CHOP, rituximab plus CVP, rituximab plus bortezomib plus CAP, ibrutinib and lenalidomide. Thus, rituximab plus fludarabine may not be a relevant comparator. The ESMO guidelines discourage the use of rituximab plus fludarabine to treat mantle cell lymphoma. No studies were identified that compared rituximab plus bendamustine with rituximab plus bortezomib plus CAP, or with ibrutinib, or with lenalidomide.

The phase III studies showed that bendamustine plus rituximab has a safety profile that is distinct from those of the standard chemotherapy regimens, and has some favourable aspects[4]. In the first-line treatment of mantle cell lymphoma bendamustine plus rituximab showed a generally lower incidence of alopecia and neuropathy, with a higher incidence of skin reactions and drug sensitivity[3].

The phase II studies which evaluated the use of bendamustine with rituximab and cytarabine gave higher overall response rates and progression-free survival than those reported in the phase III bendamustine with rituximab studies[3,4,6,7]. A longer follow up period would allow median progression free survival to be quantified. The two studies did not include a comparator arm and patient numbers were small. Clinical expert opinion suggests that haematological toxicity is higher for this regimen than with bendamustine plus rituximab. Clinical expert opinion indicates that this regimen may be an option for patients unsuitable for consolidation stem cell transplant or whom do not want to receive maintenance rituximab treatment in the first-line setting. Secondly, in the relapse setting either following rituximab plus CHOP or after a good remission with the Nordic protocol – though patient numbers are likely to be small.

SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

Cost-effectiveness evidence

No cost-effectiveness analyses were identified in this patient population. Patients with mantle cell lymphoma were excluded from a cost-utility analysis comparing bendamustine plus rituximab, rituximab plus CHOP, and rituximab plus CVP[32]. These patients were excluded because mantle cell lymphoma is a more aggressive disease and treated differently.

BUDGET IMPACT

The budget impact focuses on the costs of bendamustine because patients with mantle cell lymphoma would receive rituximab as part of any alternative regimen and therefore the use of rituximab in combination does not represent a change in costs The list price of bendamustine is £6.85 for 25 mg and £27.77 for 100 mg[33]. The dose of bendamustine is 90 mg/m^2 body surface area on days 1 and 2 of a cycle. Clinical experts in Wales estimate that a cycle is 28 days in length and on average a patient will have six cycles.

Table 2. Estimated budget impact in Wales

	Year 1	Year 2	Data source
Bendamustine * † §	£572	£572	British National Formulary
Number of patients newly treated per annum	12	12	Cancer Research UK[14] ESMO Guidelines[16] Nazeef M and Kahl BS[17]
Net medicine cost	**£6,864**	**£6,864**	

* This assumes vial sharing and zero wastage.
† This assumes a body surface area of 1.91 m^2.
§ This assumes six cycles of treatment.

Bendamustine is administered by intravenous infusion on two days of a cycle, for other rituximab-containing regimens intravenous administration is on one day of a treatment cycle. One extra day of medicine administration per cycle may incur additional resource cost, this will depend upon current service capacity.

Budget impact issues

- The budget impact has only considered drug costs for induction therapy.
- The budget impact has not considered the discontinuation of therapy and mortality rates.
- The number of eligible patients is estimated and therefore subject to uncertainty.
- In current practice there are a proportion of patients already receiving bendamustine in combination with rituximab in these settings in the absence of a suitable alternative treatment. Bendamustine in combination with rituximab is accessed through local agreements and individual patient funding requests.

Welsh commercial access agreement

These medicines are currently not licensed for the indication under consideration (i.e. off-label). Therefore, because the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine, a commercial agreement cannot be offered by the relative companies.

Comparative unit costs

Table 3 provides the approximate cost per patient for medicines that could be used in patients with newly diagnosed or relapsed mantle cell lymphoma. Costs are based on an average body surface area of 1.91 m^2.

Table 3. Examples of medicine acquisition costs

Regimens	Example doses per 28-day or 21-day cycle	Cost per patient per cycle
Rituximab (MabThera®) plus bendamustine*†	Rituximab 375 mg/m^2 IV on day 1; bendamustine 90 mg/m^2 IV on days 1 and 2 of a 4-week cycle	£1,346
Rituximab (MabThera®) plus CHOP*†	Rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 (max dose 2 mg) IV all on day 1; oral prednisolone 100 mg on days 1–5, every 21 days	£1,486
Rituximab (MabThera®) plus bortezomib (Velcade®) plus CAP*†	Bortezomib 1.3 mg/m^2 IV or SC on days 1, 4, 8 and 11 of a 21-day cycle; rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV all on day 1;oral prednisone 100 mg/m^2 orally on days 1–5, of a 21 cycle	£3,668
Rituximab (MabThera®) plus CVP†	Rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, vincristine 1.4 mg/m^2 (max dose 2 mg) IV all on day 1; oral prednisolone 100 mg on days 1–5, every 21 days	£1,309
Rituximab (MabThera®) plus bendamustine plus cytarabine 500	Rituximab 375 mg/m^2 IV; bendamustine 70 mg/m^2 IV on days 1 and 2; cytarabine 500 mg/m^2 IV on days 1,2 and 3	£1,436
Rituximab (MabThera®) plus bendamustine plus cytarabine 800	Rituximab 375 mg/m^2 IV; bendamustine 70 mg/m^2 IV on days 1 and 2; cytarabine 800 mg/m^2 IV on days 1,2 and 3	£1,504
Ibrutinib (Imbruvica®)†	Ibrutinib 560 mg/day (four oral 140 mg capsules) every day	£5,723
Lenalidomide (Revlimid®)†	Lenalidomide 25 mg/day oral capsules every 21 days of a 28-day cycle	£4,368

*Newly diagnosed
† Relapsed
IV: intravenous; SC subcutaneous
Costs are based on British National Formulary list prices. Where generic medicines are available the lowest cost is used.
Intravenous doses are based on a body surface area of 1.91 m^2. Costs assume vial sharing and zero wastage.
Not all regimens may be licensed for use in this patient population. See relevant Summaries of Product Characteristics for full licensed indications and dosing details[10,11,34-40].
This table does not imply therapeutic equivalence of drugs or the stated doses.

ADDITIONAL FACTORS

Prescribing unlicensed medicines

Bendamustine plus rituximab is not licensed to treat this indication and is therefore 'off label'. Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

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