Safety of bendamustine for the treatment of indolent non-Hodgkin lymphoma: a UK real-world experience

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Abstract:
Introduction: Bendamustine is among the most effective chemotherapeutics for indolent B-cell non-Hodgkin lymphomas (iNHL), but trial reports of significant toxicity, including opportunistic infections and excess deaths, led to prescriber warnings. We conducted a multicentre observational study evaluating bendamustine toxicity in real-world practice. Methods: Patients receiving at least one dose of bendamustine (B) +/- rituximab (R) for iNHL were included. Demographics, lymphoma and treatment details and grade 3-5 adverse events (AEs) were analysed. Results: 323 patients were enrolled from 9 NHS hospitals. Most patients (96%) received BR and 46% R maintenance. 21.7% experienced serious AEs (SAE) related to treatment, including infections in 12%, with absolute risk highest during induction (63%), maintenance (20%), and follow-up (17%), and the relative risk highest during maintenance (54%), induction (34%) and follow-up (28%). Toxicity led to permanent treatment discontinuation in 13% of patients, and 2.8% died of bendamustine-related infections (n=5), myelodysplastic syndrome (n=3), and cardiac disease (n=1). More SAEs per patient were reported in patients with mantle cell lymphoma, poor pre-induction PS, poor pre-maintenance PS, abnormal pre-induction total globulins and in those receiving growth factors. Use of antimicrobial prophylaxis was variable, and 3/10 opportunistic infections occurred despite prophylaxis. Conclusion: In this real-world analysis, bendamustine-related deaths and treatment discontinuation were similar to trial populations of younger, fitter patients. Poor PS, mantle cell histology and maintenance rituximab were potential risk factors. Infections, including late onset events, were the most common treatment-related SAE and cause of death warranting extended antimicrobial prophylaxis and infectious surveillance, especially in maintenance-treated patients.

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Abstract (250 words)

Bendamustine is among the most effective chemotherapeutics for indolent B-cell non-Hodgkin lymphomas (iNHL), but trial reports of significant toxicity, including opportunistic infections and excess deaths, led to prescriber warnings. We conducted a multi-centre observational study evaluating bendamustine toxicity in real-world practice.

Patients receiving at least one dose of bendamustine (B) +/- rituximab (R) for iNHL were included. Demographics, lymphoma and treatment details and grade 3-5 adverse events (AEs) were analysed and correlated.

323 patients were enrolled from 9 NHS hospitals. Most patients (96%) received BR and 46% R maintenance. 21.7% experienced serious AEs (SAE) related to treatment, including infections in 12%, with absolute risk highest during induction (63%), maintenance (20%), and follow-up (17%), and the relative risk highest during maintenance (54%), induction (34%) and follow-up (28%). Toxicity led to permanent treatment discontinuation in 13% of patients, and 2.8% died of bendamustine-related infections (n=5), myelodysplastic syndrome (n=3), and cardiac disease (n=1). More SAEs per patient were reported in patients with mantle cell lymphoma, poor pre-induction PS, poor pre-maintenance PS, abnormal pre-induction total globulins and in those receiving growth factors. Use of antimicrobial prophylaxis was variable, and 3/10 opportunistic infections occurred despite prophylaxis.

In this real-world analysis, bendamustine-related deaths and treatment discontinuation were similar to trial populations of younger, fitter patients. Poor PS, mantle cell histology and maintenance rituximab were potential risk factors. Infections, including late onset events, were the most common treatment-related SAE and cause of death warranting extended antimicrobial prophylaxis and infectious surveillance, especially in maintenance-treated patients.

Key points (1-2, max 140 characters each including spaces)

Rates of bendamustine-related deaths and treatment discontinuation were similar to those reported in clinical trials.

Infections and opportunistic infections were common and often occurred long after completion of treatment.

Introduction

Bendamustine is a bi-functional chemotherapeutic agent with broad clinical activity in the treatment of indolent B-cell non-Hodgkin lymphomas (iNHL), including follicular (FL), lymphoplasmacytic (LPL), marginal zone (MZL) and mantle cell lymphomas (MCL) (1).

Early trials in iNHL demonstrated superior clinical outcomes for bendamustine compared to other chemotherapy, including superior progression-free survival (PFS) for bendamustine and rituximab (BR) compared to RCHOP/CVP (2), better tolerance than R-CHOP(3) and higher quality of life scores than RCHOP/RCVP (4). Although highly effective, recent large randomised trials flagged a high rate of infectious complications for bendamustine-treated patients compared to other chemotherapies (5), especially during an anti-CD20 antibody maintenance phase that was notably not part of treatment in earlier trials. In the GALLIUM trial comparing any chemotherapy in combination with rituximab vs. obinutuzumab followed by antibody maintenance (5), a *post hoc* analysis reported a two-fold increase in fatal AEs for bendamustine-treated patients who had not commenced a new anticancer treatment compared to CHOP or CVP (4% vs 2%) treated patients, with a remarkably higher event rate (13%) in patients aged ≥70 years. Long-term safety data for this trial reported a fatal AE event rate of ~6% for bendamustine-treated patients at a median follow-up of 7.9 years (6). Another trial comparing obinutuzumab-bendamustine and single agent bendamustine in rituximab-refractory relapsed iNHL reported high overall rates of grade 3-5 AEs (73% and 66% in the combined and monotherapy arms respectively) (7). The overall rate of treatment-related deaths was similar (~2%) in both arms, suggesting that most toxicity was due to bendamustine (8).

The published evidence raised concerns among clinicians about the safety of bendamustine for treating iNHL in routine practice. We performed a retrospective, multi-centre, observational study to evaluate this question and identify potential risk factors for toxicity.

Methods

Patient selection and data collection

Eligible patients received at least one dose of bendamustine +/- rituximab induction +/- rituximab maintenance for untreated or relapsed/refractory iNHL (FL, MCL, LPL and MZL). Patients treated between 1st January 2013 and 31st December 2016 were identified from nine NHS centres in the UK. Every effort was made to collect consecutively treated patients to avoid selection bias. Patients with CLL/SLL, transformed lymphoma or enrolled on a clinical trial were excluded. Data for obinutuzumab-bendamustine treated patients were not collected as this option was not funded by the NHS during the study period. This was a fully anonymised, non-consent, retrospective research study approved by The Christie NHS Foundation Trust and abiding to the Declaration of Helsinki.

Data collection included patient demographics, European Cooperative Oncology Group performance status (ECOG), histological diagnosis, past medical history, previous lymphoma treatment, current lymphoma induction and maintenance treatment, dose reductions and delays, prophylactic anti-microbial and supportive medication, blood results prior to induction and maintenance therapy and worse grade during grade 3-5 adverse events; including full blood count, serum biochemistry, immunoglobulins, treatment response data, and grade 3-5 adverse events (AEs). Data were collected from the first dose of bendamustine until the start of the next systemic anti-lymphoma treatment, death or date of last follow-up at the time of analysis. Baseline co-morbidity was assessed according to the Adult Comorbidity Evaluation 27 (ACE-27) index (9).

Treatment

Bendamustine was given according to local institutional standards at a recommended full dose of 90mg/m^2 in combination with rituximab (375mg/m^2) or 120mg/m^2 as monotherapy, for a total of 6-8 three to four weekly cycles, followed by maintenance rituximab, consolidation treatment or no further therapy at the discretion of the treating physician. Rituximab maintenance was delivered by

intravenous or subcutaneous injection once every 2 or 3 months for up to 2 years in patients with iNHL, and for up to 3 years after transplant in MCL patients. Dose reductions and the use of primary granulocyte colony stimulating factor (G-CSF) prophylaxis, antimicrobial prophylaxis and other supportive medications were discretionary.

Outcomes

The primary endpoint of the study was the rate of treatment-related grade 3-5 serious adverse events (SAE). AE causality was assessed by investigators and graded according to CTCAE v4.3. Serious adverse events were defined as fatal, life-threatening, causing or prolonging hospital admission, or leading to significant disability. Other outcomes of interest included grade 3-5 AE frequency by treatment phase (induction, maintenance, follow-up), grade 3-5 infections, opportunistic infections, second cancers, impact of AEs on dose reductions, delays and treatment discontinuation, and deaths related to bendamustine. The induction period was measured from the start of bendamustine +/- rituximab to three months after completion of the final induction cycle. The maintenance phase was measured from the start of the first cycle of *rituximab* maintenance until 3 months after the last maintenance cycle; the follow-up period was measured from the end of the induction or maintenance period, whichever occurred later, until the date of death, last follow-up or start of next anti-lymphoma treatment. Patients were followed from the start date of bendamustine to the date of death or last hospital visit.

Safety risk factors

Potential risk factors were examined for an association with the number (1-6) of treatment-related SAEs and the proportion of patients experiencing ≥1 treatment-related SAE, evaluated against: patient age (≤65 vs >65, ≤70 vs >70 or ≤80 or >80), gender, ACE-27 score (0-1 vs 2-3), ECOG score prior to induction and prior to maintenance, histology (MCL vs FL vs other iNHL), disease stage, FLIPI score, simplified MIPI score, prior fludarabine treatment, prolonged steroid use (defined as ≥20mg prednisolone for >2 weeks), antibiotic prophylaxis, G-CSF prophylaxis, line of treatment, starting

dose of bendamustine (100% vs 75-99% vs 50-74%), lymphocyte count (normal vs abnormal) and total globulin count (normal vs abnormal). Outcomes were compared for patients receiving first line vs later lines of treatment.

Statistical analysis

This was a descriptive analysis with no formal power calculations. Frequency tables were provided for categorical demographic variables. Summary statistics together with boxplots and histograms were provided for continuous demographic variables. Descriptive analyses were applied to summarise AE data. Fisher's Exact tests were applied to assess the association between the number of AEs patients had and a series of factors. Proportion tests were applied to assess the difference in proportions of patients with ≥1 AE in subgroups of relevant factors. All presented P values are two-sided. Statistical analyses were performed with R v3.5.3 (2019 The R Foundation for Statistical Computing).

Results

Patient characteristics

The study enrolled 323 patients from nine participating UK centres treated with bendamustine between 1 January 2013 and 31 December 2016. The median age of patients at iNHL diagnosis was 65 years (range 20-92). FL was the most common histology (54%).

150 patients (46%) had no co-morbidities (ACE-27 score 0), and 86 (27%) had moderate to severe comorbidities (ACE-27 score 2-3). Cardiovascular disease, respiratory disease and diabetes mellitus were the most common co-morbidities reported in 24%, 9% and 6% of patients, respectively. Baseline characteristics are summarised in Table 1.

Treatment details

The vast majority of participants (96%) received bendamustine in combination with rituximab; the remainder received bendamustine monotherapy. Sixty percent were treated in the first line setting for iNHL. In patients receiving bendamustine for relapsed/refractory iNHL (40%), the median number of prior treatment lines was 2 (1 – >5) and the most common therapy prior to bendamustine was R-CHOP or R-CVP (64%).

Most patients (86%) initiated bendamustine at full dose, and 79% of patients completed planned induction treatment, with a median of 6 bendamustine cycles delivered (range 1-8; 3 patients received 7 cycles of bendamustine, and 1 received 8 cycles). Following induction treatment, 147 patients (46%) commenced maintenance rituximab treatment and 88 (60%) completed planned maintenance. The median number of maintenance cycles delivered was 8 (range 1-12).

Primary G-CSF prophylaxis was administered to 65 patients (20.1%) during induction; 72% received primary anti-viral prophylaxis, 57% against PJP (co-trimoxazole, 55%; nebulised pentamidine, 2%) and 21% against fungal infections. Patients receiving primary G-CSF prophylaxis were significantly more heavily pre-treated (mean 1.806 prior lines of therapy (G-CSF group) versus 1.648 (no G-CSF); p=0.0130; 95% CI -0.4528 – 0.1363) but not significantly older (mean age 63.0 versus 63.9 years). Very few patients (6%) received high dose steroids (prednisolone ≥20mg within 2 weeks) prior to starting induction therapy.

Clinical outcomes

The median follow-up was 38.9 months (range 36.3-40.7 months). Median progression-free survival for patients treated in the first-line or relapsed/refractory settings were 181 months and 114 months respectively. Median overall and progression-free survival across all histologies were 153 months and 133 months respectively. Kaplan Meier curves for overall and progression free survival are shown in the online supplementary appendix.

Safety analysis

All 323 patients in the study were included in the safety analysis. One hundred and fifty-six patients (48%) experienced 248 grade 3-5 adverse events (AE) of any cause, of which 163 (66%) occurred during induction, 33 (13%) during maintenance and 52 (21%) during follow up. Of the AEs occurring during induction and maintenance, 25/163 and 19/33 led to treatment discontinuation respectively. There was no difference in the rate of grade 3-5 AEs between patients treated in first versus subsequent line settings (45.9% vs 51.9% respectively; p=0.31).

Grade 3-5 serious adverse events (SAEs) related to treatment: A total of 70/323 patients (21.7%) experienced 89 SAEs related to treatment, the primary endpoint of the study, accounting for the majority (87%) of the 102 reported SAEs. Most events occurred during induction (56/89; 63%), followed by maintenance (18/89; 20%) and follow-up (15/89; 17%). When considered in relation to the number of patients per treatment phase, the highest proportion of SAEs occurred during maintenance (18 events/33 patients; 54%) followed by induction (56/163; 34%) and follow-up (15/53; 28%). There was no difference in incidence of grade 3-5 serious treatment-related AEs between patients receiving bendamustine as first versus subsequent line of treatment (20.1% vs 21.7% respectively; p=0.78). AEs and SAEs stratified by treatment phase are summarised in Table 2 and AEs by category are shown in Table 3.

Infections: Seventy-seven patients (24%) experienced 91 grade 3-5 infections of which 44% were treatment-related SAEs, affecting 39 patients (12%). The majority of infections occurred during induction (49% of all infections and 53% of treatment related SAEs) followed by maintenance (21% and 30%) and follow-up (30% and 18%). Most infections were non-neutropenic, with neutropenic sepsis accounting for only 4.8% and 9.0% of all grade 3-5 AEs and all grade 3-5 SAEs, respectively. Fifty patients (15%) experienced at least one episode of grade 3-5 neutropenia (40 patients, 12%) or febrile neutropenia (12 patients, 4%). Grade 3-5 neutropenic episodes mostly occurred during induction (Induction: 42 events, 83%; Maintenance: 6 events, 12%; Follow-up: 3 events (6%).

Infections are summarised in Table 4 by anatomical site and microbiological cause. The most common sites were respiratory (n=54) and urinary tract (n=11). The clinical source of infection was not identifiable in 14 cases. There was no significant difference in rates of grade 3-5 AE and treatment-related grade 3-5 SAE infections between first and subsequent line treatments (21.2% vs 24.8% (p=0.50) and 11.3% vs 12.4% (p=0.86), respectively).

Ten patients (3%) had grade 3-5 opportunistic infections during the study, including 8 non-fatal infections (5 *pneumocystis jirovecii* (PJP; 3 despite prophylaxis), 2 varicella zoster virus (VZV) and 1 aspergillosis) and 2 fatal infections (a case of JC virus leading to progressive multifocal leukoencephalopathy during follow up after first line bendamustine and maintenance, and a case of metapneumovirus infection during second line bendamustine induction). Median lowest lymphocyte and neutrophil count at the time of these infections were 0.21 and 1.6 respectively. Three of the opportunistic infections were considered related to bendamustine and the remainder related to rituximab. The 3 opportunistic infections related to bendamustine were metapneumonvirus grade 5 after cycle 2 full dose bendamustine with rituximab as 2nd line therapy for follicular lymphoma, varicella zoster virus grade 3, 19 days after cycle 6 full dose bendamustine with rituximab as 1st line therapy for marginal zone lymphoma, and neutropenic aspergillosis grade 4 in follow-up, 13 months after cycle 6 rituximab wit bendamustine as 4th line therapy for follicular lymphoma. Half of the 8 non-fatal opportunistic infections led to treatment discontinuation. There were 3 other grade 3-5 non-opportunistic viral infections that did not affect treatment (2 influenza A, 1 rhinovirus). There were no cases of CMV or hepatitis B reactivation.

Second cancers: There were 10 second cancers in the cohort (3% of all patients): a non-fatal case of non-melanocytic skin cancer 20 months after treatment initiation, and 5 cases of myelodysplastic syndrome (MDS) (3 fatal) occurring at 15, 16, 44 and 51 months after starting treatment; time to

onset was not available for the remaining case. Bendamustine was first line therapy in 1 of these patients, and third and fourth line in 2 patients each. Of the 5 cases of MDS, 4 had received prior alkylating agents or autologous stem cell transplant, and there was no risk factor other than age (80 years) in the remaining case. A further 4 patients died of second cancers (1 case each of metastatic squamous cell carcinoma, myeloma, transitional cell carcinoma of the kidney and metastatic non-small cell lung cancer).

Deaths: At the time of analysis, 91 of 323 patients (28%) had died, most commonly in the context of active lymphoma (n=54, 59%), including progressive disease (n=43, 47%) and any treatment-related death (n=11, 12%). Within these groups, 12 patients (13%) died of infections related to treatment or underlying lymphoma. Seven deaths (8%) occurred due to unrelated causes at the time of progressive disease and 31 deaths (34%) were unrelated to lymphoma or treatment. Most deaths occurred during follow-up (78%), followed by induction (14%) and maintenance (8%). Patients receiving bendamustine at second or later lines were more likely to die from any cause than those receiving first line treatment (19.6% vs 41.1%; p<0.0001).

Treatment-related events (n=11) included 6 definite and 3 possible deaths related to bendamustine (2.8% of all patients) and 2 related to rituximab (0.6%). The bendamustine related deaths were 6 deaths during induction (4 non-neutropenic infections including an opportunistic metapneumovirus; 1 neutropenic sepsis; 1 cardiac disease) and 3 deaths from MDS, all during follow-up, considered at least possibly related to bendamustine, however one patient had also had a prior autologous stem cell transplant. Two deaths related to rituximab (0.6% of all patients) included 1 case of progressive multifocal encephalopathy due to JC virus during follow up after first line bendamustine and maintenance, and 1 case of *Pneumocystis jirovecii* pneumonia in a neutropenic patient after one dose of maintenance rituximab in the first line setting. Additionally, 6 patients died of toxicity relating to subsequent lymphoma therapy after bendamustine (excluding maintenance rituximab),

including 3 infections complicating allogeneic stem cell transplant. A full breakdown of deaths is shown in Table 2.

Dose reductions, delays and treatment discontinuation: Of the 196 AEs reported during induction and maintenance, 25 (13% of AEs) resulted in a dose reduction, including 17 (9%) leading to dose delay. A further 43 (22% of all AEs) led to permanent discontinuation of treatment in 13% of patients. Infection, neutropenia and infusion related reactions were the most common AEs leading to treatment discontinuation (n=18, 8 and 5, respectively), followed by gastrointestinal symptoms (n=3), thrombocytopenia (n=3), respiratory symptoms (n=2), cardiac event, rash, MDS, hypomagnesaemia (n=1 each). According to investigator assessment, 49% of the events leading to treatment discontinuation (21/43) were related to bendamustine treatment.

Safety risk analysis

Results of univariate analysis for risk factors associated with the incidence of ≥1 treatment-related SAE are shown in Table 5. The following risk factors were significantly associated with increased risk: mantle cell vs follicular histology (p=0.015), mantle cell vs other non-follicular iNHL (p=0.0036), pre-induction ECOG 2 vs ECOG 0 (p=0.0154), pre-maintenance ECOG 1 or 2 vs ECOG 0 (p=0.0021 and p=0.0053 respectively), receipt of primary G-CSF prophylaxis (p=0.02847), and abnormal total globulins prior to induction (p=0.0274). The paradoxical association between G-CSF and treatment-related SAEs likely reflects the preferential use of GCSF in patients at heightened risk of any serious toxicity. Since the rate of neutropenic sepsis was very low, overall SAE event rates were not impacted by GCSF use and it was not possible to specifically examine the association between GCSF use and neutropenic sepsis.

None of the other analysed risk factors were associated with adverse safety outcomes, including age, gender, ACE-27 score, disease stage, FLIPI/sMIPI score, prior fludarabine treatment, prolonged

steroid use, antibiotic prophylaxis, line of treatment, starting dose of bendamustine, lymphocyte count and total globulin count.

Discussion

This multi-centre, retrospective, observational study is one of the largest studies to date evaluating the safety and toxicity profile of bendamustine in patients with iNHL treated outside of a clinical trial setting. We evaluated 323 previously treated and untreated patients receiving bendamustine-rituximab (96%) or bendamustine monotherapy in routine practice for common iNHL lymphomas: follicular (54%), lymphoplasmacytic (17%), mantle cell (10%) and marginal zone (10%). Patients were followed during induction, maintenance and post-treatment for a median of 34 months.

Grade 3-5 serious adverse events (SAEs) related to bendamustine were reported in 21.7% of participants, approximately half due to infections most commonly of respiratory and urinary tract origin. Thirteen percent of patients stopped treatment due to bendamustine-related toxicity, most commonly infection, and 2.8% of patients died of causes deemed by investigators to be related to bendamustine. The most common causes of bendamustine-related deaths were non-neutropenic infections during induction and myelodysplastic syndrome during follow-up. Neutropenic sepsis events were rare.

AEs occurred during all treatment phases, however the relative risk of experiencing a treatment-related grade 3-5 SAE was highest during the maintenance phase, with events reported in 54% of patients compared to 34% during induction and 28% during follow-up prior to initiating next anti-lymphoma treatment.

A high rate of infections during maintenance and follow-up (21% and 30% of all grade 3-5 infections, respectively, and 23% of all deaths) is one of the most important observations of the current study, mirroring data from the GALLIUM trial in previously untreated FL where a higher frequency of grade

3-5 infections in bendamustine-treated patients was shown to be driven by events during the maintenance phase (5). The added risk of maintenance is further inferred by findings from a meta-analysis of 9 randomised-controlled trials where no association between bendamustine and higher rates of any grade infection was reported, presumably because the study had very few maintenance-treated patients (10).

In the current study we did not observe a significant effect of increasing age on the risk of infectious complications or death, however our analysis was limited by a small number of patients in a heterogenous population. Very large population-based studies including two Surveillance, Epidemiology, and End Results (SEER) database studies have shown a clear association with increasing age. The first study, involving 9395 patients aged ≥65 receiving chemotherapy from 2006 to 2013 for iNHL (follicular, marginal zone, lymphoplasmacytic lymphoma), showed higher rates of bacterial pneumonia, other unspecified bacterial infections, viral infections and opportunistic infections, reaching statistical significance for cytomegalovirus (CMV), varicella zoster virus (VZV), and histoplasmosis. The hazard ratio for *Pneumocystis jirovecii* pneumonia (PJP) infection was 3.26, but this was not statistically significant (11). The second study reported outcomes for 1791 previously untreated iNHL patients aged >65 receiving bendamustine (12). Compared with R-CHOP/R-CVP, bendamustine-treated patients had significantly higher rates of hospitalisation, infection and pneumonia extending into the second year of follow-up (22). Persisting risk fits with results of the current study where almost one third of all grade 3-5 infections occurred during follow-up, supported by studies showing delayed T cell reconstitution for up to 25 months after bendamustine(13,14) and sustained reductions in $CD3^+CD4^+$ cells (5). Lymphopenia is commonly seen during treatment with rituximab and CD4+ lymphopenia has been reported to continue throughout maintenance rituximab, with gradual recovery after stopping (15). Thus, the widely reported and prolonged risk of infection is most likely related to the T-cell depleting effect of bendamustine. Most patients in our current study became lymphopenic during induction treatment,

however CD4/8 levels were not routinely or consistently recorded in our cohort making it impossible to draw correlations in this study.

Interestingly, although neutropenia was relatively common, the overall rate of febrile neutropenia for bendamustine-treated patients was low in the current study (4.8% and 7.8% of all grade 3-5 AEs and SAEs, respectively) and most infections related to bendamustine, including fatal events, were non-neutropenic in nature. This is consistent with other studies showing lower rates of neutropenia and febrile neutropenia for bendamustine compared to CHOP(2,3,16).

The rate of opportunistic infection of any grade was 3.1% in the current study. A Medicines and Healthcare products Regulatory Agency (MHRA) Drug Safety Update published in 2017 recommended prophylaxis and monitoring for opportunistic infections and Hepatitis B reactivation in bendamustine-treated patients based on observations of higher rates of PJP, VZV, CMV and hepatitis B reactivation (17). This report was published after the recruitment period for this study, which may explain why almost half of the patients in our study did not receive primary prophylaxis against PJP and viral infections. It is also pertinent to note that 3 of 5 patients in the current study developed PJP infections despite prophylaxis, underscoring the importance of clinical suspicion and surveillance for opportunistic infections even when prophylaxis is given. Instances of PJP can lead to treatment discontinuation – as in our study – or death, as in the GADOLIN study where 1% of patients treated with bendamustine monotherapy died of treatment-related PJP(18).

In terms of non-infectious adverse events such as gastrointestinal and dermatological toxicities and infusion reactions, the rates recorded in our study broadly reflect the literature. Second cancers, including myelodysplastic syndrome (MDS) (19), have been reported but registry study data suggest that patients treated with bendamustine are no more likely to develop a second cancer than those treated with R-CHOP or R-CVP (rates 4% versus 6%, p=0.6) (20). The rate of MDS in this study (1.5%) is lower than reported by Martin *et al*(19) (4%) but follow-up time was shorter.

Mantle cell histology, abnormal total globulins and poor performance status were associated with an increased risk of treatment related grade 3-5 AEs in the current study. A larger sample size may have resulted in statistically significant associations for other patient and treatment related factors reported in the literature.

The findings of this study are limited by the retrospective nature of data collection, thus adverse events may have been under-reported and there may have been investigator bias in assigning causality. In addition, the study population did not include patients treated with bendamustine combined with obinutuzumab as this was not funded during the study period. Whilst obinutuzumab and rituximab have similar mechanisms of action and toxicity profiles, safety data from this study cannot be extrapolated to patients receiving obinutuzumab and bendamustine.

Conclusion

This multi-centre, retrospective observational study of bendamustine treatment for iNHL in routine practice demonstrates rates of bendamustine-related treatment discontinuation, dose delays and reductions, haematological toxicity and grade 5 events that are comparable to trial population outcomes, despite including previously treated and untreated patients as well as older, frailer and more comorbid participants. Notably, the rate of fatal AEs related to bendamustine (2.8%) is similar to the rituximab-chemotherapy arm of the GALLIUM trial (3.4%), which included bendamustine, CVP and CHOP in an exclusive first line FL population.

This study highlights important safety considerations when administering bendamustine including vigilant monitoring and long-term surveillance for infection, especially in patients receiving maintenance rituximab, and for opportunistic infection despite the use of antimicrobial prophylaxis. Patients with mantle cell lymphoma, poor baseline performance status and weakened immunity (evidenced by low total globulins), as demonstrated in this study, and older age, as demonstrated

elsewhere, are at heightened risk of treatment related AEs. These patients should therefore be considered for treatment modifications and increased supportive care in line with published practice guidelines (21–23).

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Tables

Table 1: Demographics and disease characteristics of patients included in the analysis (n=323)

	Number (%)		
	All pts	1st line	2nd line or greater
Total	323	194 (60)	129 (40)
Age (median years, range)	65 (20-92)	66 (20-88)	62 (31-92)
Gender Male Female Missing data	161 (50) 160 (50) 2 (0.7)	93 (48) 101 (52) 0	68 (53) 59 (46) 2 (2)
ACE-27 score 0 (none) 1 (mild) 2 (moderate) 3 (severe) Missing data	150 (46) 86 (26) 54 (17) 32 (10) 1 (<1)	81 (42) 60 (31) 34 (18) 19 (10) 0	69 (53) 26 (20) 20 (16) 13 (10) 1 (<1)

Histological subtype			
Follicular lymphoma	175 (54)	111 (57)	64 (50)
Lymphoplasmacytic lymphoma	54 (17)	32 (16)	22 (17)
Mantle cell lymphoma	34 (11)	19 (10)	15 (12)
Marginal zone lymphoma	33 (10)	22 (11)	11 (9)
Extranodal marginal zone (MALT)	11 (3)	5 (3)	6 (5)
Splenic marginal zone lymphoma	11 (3)	3 (2)	8 (6)
Indolent B-NHL other	5 (2)	2 (1)	3 (2)
Ann Arbor stage at diagnosis			
I	10 (3)	6 (3)	4 (3)
II	27 (8)	20 (10)	7 (5)
III	53 (16)	36 (19)	17 (13)
IV	217 (67)	127 (65)	90 (70)
NA	16 (5)	5 (3)	11 (9)
B symptoms			
Yes	79 (24)	44 (23)	35 (27)
No	210 (65)	128 (66)	82 (64)
Not known	34 (11)	22 (11)	12 (9)
Extra nodal disease			
Yes	142 (44)	81 (42)	61 (47)
No	155 (48)	93 (48)	62 (48)
Not known	26 (8)	20 (10)	6 (5)
Bone marrow involvement*			
Yes	176 (54)	99 (51)	77 (60)
No	102 (32)	68 (35)	34 (26)
Not known	45 (14)	27 (14)	18 (14)
Bulky disease**			
Yes	61 (19)	41 (21)	20 (16)
No	224 (69)	128 (66)	96 (74)
Not known	38 (12)	25 (13)	13 (10)
FLIPI score (in 175 patients with FL)***			
low	31 (18)	22 (20)	9 (14)
moderate	50 (29)	40 (36)	10 (16)
high	72 (41)	41 (37)	31 (8)
Missing	22 (13)	8 (6)	14 (22)
sMIPI score in 34 patients with MCL****			
low	5 (15)	3 (16)	2 (13)
intermediate	13 (38)	7 (37)	6 (40)
high	15 (44)	8 (42)	7 (47)
missing/inapplicable	1 (3)	1 (5)	0
Performance status at start of induction n=323 (N, %)			
0	123 (38)	87 (45)	36 (28)
1	151 (47)	82 (42)	69 (53)
2	30 (9)	11 (6)	19 (15)
3	10 (3)	6 (3)	4 (3)
4	1 (<1)	0 ()	1 (<1)
Missing data	8 (2)	8 (4)	0
Performance status at start of maintenance n=147 (N, %)			
0	66 (45)	53 (45)	13 (43)

1	63 (43)	48 (41)	15 (50)
2	9 (6)	7 (6)	2 (7)
Missing /inapplicable	9 (6)	9 (8)	0
Baseline lymphopenia			
At start of induction	89/295 (30)	45 (26)	44 (36)
At start of maintenance	103/132 (78)	79 (77)	24 (80)
Follow-up time from commencement of bendamustine; median (range)	34 months (0-62)	36.3	32.3
Prior treatments in 129 patients			
Median number of prior treatments	2		
R-CHOP/R-CVP	83 (64)		
Rituximab monotherapy	24 (19)		
Fludarabine-based	19 (15)		
HD chemotherapy/transplant	14 (11)		
Radiotherapy	9 (7)		
Platinum-based	4 (3)		
Splenectomy	4 (3)		
Ibrutinib	2 (2)		
*Patients with bone marrow involvement are classified as having extra nodal disease ** Bulky disease is defined as tumour that is 7cm or larger in greatest dimension *** FLIPI is follicular Lymphoma International Prognostic Index based on number of risk factors: zero or one risk factor indicates low risk, two risk factors indicates moderate risk and more than two indicates high risk **** Simplified Mantle cell International Prognostic index is based on calculation of risk factors: low risk (score 0–3); intermediate (score 4–5) or high-risk (score 6–11)			

Table 2: The number and proportion of ≥grade 3 adverse events by treatment phase

Number of events (number of patients)	Induction (n, %)	Maintenance (n, %)	Follow-up (n, %)
Grade ≥3 AEs			
N = 248 (156)	163 (66%)	33 (13%)	52 (21%)
Serious and treatment related – 89 (70)	56/163 (34%)	18/33 (54%)	15/53 (28%)
Grade ≥3 Infections			
N = 91 (77)	45/91 (49%)	19/91 (21%)	27/91 (30%)

Serious and treatment related – 40 (39)		21/91 (23%)	12/91 (13%)	7/91 (8%)
Grade 5 events (infections in brackets)				
N = 91 (infections in brackets)		**13**	**7**	**71**
Causality	Bendamustine	6 (5)	0	3
	Rituximab	0	1 (1)	1 (1)
	Lymphoma	7	5	31 (5)
	Unrelated	0	1	30 (10)
	Subsequent treatment	NA		6 (4)
Impact on treatment				
Dose reduction, no delay		8/196 (4%)		
Dose reduction and delay		17/196 (9%)		
Treatment stopped		43/196 (22%)		

*Adverse events of grade 3, 4, and 5 indicate severe, life threatening and fatal adverse events
**Serious adverse events include fatal or life threating events or events that caused (prolonged) hospital admission or substantial disability

Table 3: Adverse events during treatment according to category

	Grade ≥3 adverse events * Total number 248	Serious grade ≥3 adverse events** Total number 102
Infection	84	41
Febrile neutropenia	12	8
Neutropenia	40	6
Thrombocytopenia	8	2
Lymphopenia	32	1
Infusion related events [a]	11	8
Tumour lysis syndrome	4	3
Pyrexia	6	0
Anaemia	4	2
Constitutional /musculoskeletal	3	1
Cardiac event	5	4
CNS (CVA, TIA, syncope, etc)	2	1[b]
Myelodysplastic syndrome	5	4
Gastrointestinal symptoms	9	5
Gastrointestinal perforation	2	1
Respiratory (dyspnoea, cough, etc)	6	2
Haemorrhagic event	1	1
Non melanoma skin cancer	1	1
Skin rash	2	2
Hypogammaglobulinemia	3	3
Thrombo-embolic event	4	2
Progressive multifocal encephalopathy	1	1
Other	3	3
[a] infusion reactions were attributed to rituximab in 9 patients and to bendamustine in 2 patients (Grade 3 (1), grade 4 (1 – which resulted in treatment discontinuation). [b] 1 patient died from PML due to JC virus during follow-up		

*Adverse events of grade 3, 4, and 5 indicate severe, life threatening and fatal adverse events
**Serious adverse events include fatal or life threating events or events that caused (prolonged) hospital admission or substantial disability

Table 4: Anatomical sites and causative organisms of grade ≥3 infections (All 'infection' AEs, plus febrile neutropenia or hypogammoglobulinaemia if there was a clinical source). In addition, there was 1 case of fatal progressive multifocal leukoencephalopathy due to JC virus during follow-up.

Anatomical site	N	Organism	N
Not known	14	Not identified	68
Chest	54	E. coli	6
Urine	11	Klebsiella	1
Skin	4	Enterococcus	1
Blood	3	Vancomycin resistant enterococcus	1
Ear	1	Pseudomonas	1
Vulva	2	Gram positive cocci	1

Gallbladder	1	PJP	5
		Aspergillus	1
		Influenza A	2
		Metapneumovirus (grade 5)	1
		Rhinovirus	1
		VZV	2

Table 5: Univariate analysis for association with ≥1 serious, treatment-related adverse event

Univariate analysis for association with ≥1 serious, treatment-related adverse event				
Comparison	Odds ratio	95% confidence interval lower	95% confidence interval upper	Wald p value (bold if <0.05)
During any treatment phase				
Mantle cell histology vs follicular	**2.61**	**1.19**	**5.64**	**0.015**
Other B-NHL histology vs follicular	0.75	0.40	1.36	0.348
Other B-NHL histology vs mantle cell	**0.29**	**0.12**	**0.67**	**0.0036**
Age >65 vs ≤65	1.20	0.71	2.05	0.496
Age ≥70 vs <70	1.26	0.73	2.17	0.398
Age ≥80 vs <80	1.93	0.83	4.26	0.111
Male vs female gender	0.99	0.58	1.69	0.976
Bendamustine line of treatment 2-3 vs 1	1.17	0.65	2.07	0.602
Bendamustine line of treatment ≥4 vs 1	0.94	0.33	2.32	0.898
ACE27 2-3 vs 0-1	1.60	0.89	2.81	0.107
Pre-induction ECOG 1 vs 0	1.55	0.85	2.90	0.1568
Pre-induction ECOG 2 vs 0	**2.98**	**1.21**	**7.19**	**0.0154**
Pre-induction ECOG 3 vs 0	2.21	0.45	8.70	0.2795
Pre-maintenance ECOG 1 vs 0	**5.27**	**1.95**	**16.87**	**0.0021**
Pre-maintenance	**9.76**	**1.92**	**50.82**	**0.0053**

ECOG 2 vs 0				
Stage III vs II	2.34	0.66	11.03	0.2207
Stage IV vs II	2.65	0.88	11.46	0.1231
FLIPI score moderate vs low	1.97	0.60	7.71	0.2835
FLIPI score high vs low	2.16	0.72	8.06	0.2000
Simplified MIPi score moderate vs low	0.67	0.08	6.59	0.7110
Simplified MIPi score high vs low	1.31	0.17	12.27	0.7960
Simplified MIPi score=Not Applicable	0.36	0.06	2.80	0.2720
Gender male vs female	0.99	0.58	1.69	0.976
G-CSF prophylaxis yes vs no				**0.02847**
Prolonged steroid use yes vs no				0.2938
Prior fludarabine yes vs no				0.7243
Antibiotic prophylaxis yes vs no				0.9282
Induction phase				
Starting bendamustine dose 50-74% vs 100%	0.93	0.21	3.04	0.91
Starting bendamustine dose 75-99% vs 100%	1.35	0.54	3.08	0.494
Lymphocyte count normal vs abnormal	0.76	0.41	1.38	0.379

Total globulins normal vs abnormal	**2.43**	**1.11**	**5.40**	**0.0274**
Maintenance & follow-up phases				
Lymphocyte count normal vs abnormal	0.95	0.14	3.99	0.947
Total globulins normal vs abnormal	1.20	0.29	5.56	0.806