Clinical Commissioning Policy: Bendamustine with rituximab for relapsed and refractory mantle cell lymphoma (all ages)

NHS England Reference: 170054P

NHS England INFORMATION READER BOX		
Directorate		
Medical	Operations and Information	**Specialised Commissioning**
Nursing	Trans. & Corp. Ops.	Commissioning Strategy
Finance		

Publications Gateway Reference:	**07603**
Document Purpose	Policy
Document Name	Bendamustine with rituximab for relapsed and refractory mantle cell lymphoma (all ages)
Author	Specialised Commissioning Team
Publication Date	29 June 2018
Target Audience	CCG Clinical Leaders, Care Trust CEs, Foundation Trust CEs , Medical Directors, Directors of PH, Directors of Nursing, NHS England Regional Directors, NHS England Directors of Commissioning Operations, Directors of Finance, NHS Trust CEs
Additional Circulation List	
Description	Routinely Commissioned - NHS England will routinely commission this specialised treatment in accordance with the criteria described in this policy.
Cross Reference	
Superseded Docs (if applicable)	
Action Required	
Timing / Deadlines (if applicable)	
Contact Details for further information	england.specialisedcommissioning@nhs.net

Document Status

This is a controlled document. Whilst this document may be printed, the electronic version posted on the intranet is the controlled copy. Any printed copies of this document are not controlled. As a controlled document, this document should not be saved onto local or network drives but should always be accessed from the intranet.

Clinical Commissioning Policy: Bendamustine with rituximab for relapsed and refractory mantle cell lymphoma (all ages)

First published: June 2018

Prepared by NHS England Specialised Services Clinical Reference Group for Chemotherapy

Published by NHS England, in electronic format only.

CONTENTS

Policy Statement

NHS England will commission bendamustine with rituximab for patients with relapsed and refractory mantle cell lymphoma in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain Language Summary

About relapsed and refractory mantle cell lymphoma

Mantle cell lymphoma (MCL) is a rare form of a type of blood cancer called non-Hodgkin's lymphoma (NHL). The condition is more commonly diagnosed in older

adults (≥60 years) and whilst the condition can affect both males and females, it predominantly affects males.

MCL develops when the body makes abnormal white cells – these are cells in the lymph nodes and blood. The abnormal white cells don't work properly and grow in an uncontrolled way, typically this leads to the condition affecting lymph nodes and other parts of the body, such as the spleen, blood and marrow. It is a condition that is characterised by episodes of treatment followed by periods of remission, and then commonly by subsequent relapse. Relapse means the return of the disease and its symptoms following a period of treatment and improvement. In some cases, cancers do not respond to a particular chemotherapy treatment and when this happens it is called ‘refractory disease’.

This policy covers both relapsed and refractory disease, which means that each patient has had at least one prior treatment.

About current treatments

The treatment of MCL is highly individualised and based on a number of factors, including disease biology, overall patient health and fitness (functional status).

Chemotherapy is the main treatment option for patients with MCL. The preferred first line treatment for MCL is an intensive course of chemo-immunotherapy, followed by a high-dose chemotherapy treatment using a medicine called cytarabine (ARA-C) and autologous stem-cell transplantation. However, this treatment is only tolerated in patients with a very good functional status.

For patients that are unable to tolerate such an intensive sequence of treatments, a range of alternative combination, where two or more medicines are given in the same treatment cycle, chemotherapy treatments are available. These include rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), bortezomib with rituximab, cyclophosphamide, doxorubicin and, prednisone (VR-CAP), rituximab, cyclophosphamide, vincristine, prednisone (R-CVP) and bendamustine with rituximab (BR). Each of these combinations varies in their side-effects, contraindications and tolerability.

In cases of relapsed and refractory MCL, treatment remains highly individualised with treatment choice also determined by each patient's prior treatment(s), together with their response to treatment. Autologous stem cell transplantation is generally not recommended for the treatment of relapsed and refractory MCL.

About the new treatment

BR is a combination chemotherapy treatment which is delivered in up to six cycles with each cycle lasting four weeks. The treatment has a different side-effect and toxicity profile which means that it expands the choice of treatments for patients and clinicians to manage relapsed and refractory MCL.

Bendamustine is an anticancer drug belonging to a group of drugs called alkylating agents, which work by binding to DNA in cancer cells to prevent them from multiplying. It is adminstered as an intravenous (into the vein) injection on the first two days of a 4-week cycle of treatment.

Rituximab belongs to a group of drugs known as 'monoclonal anti-bodies'. It is a biological medicine that works by 'targeting' specific proteins (receptors) on the surface of cells relevant to the cause of the disease. It is administered as an intravenous injection on the first day of each 4 week cycle when given with bendamustine.

What we have decided

NHS England has carefully reviewed the evidence to treat relapsed and refractory MCL with BR. We have concluded that there is enough evidence to make the treatment available.

1 Introduction

Clinical Indication

Mantle cell lymphoma (MCL) is rare and is one of the most challenging haematological malignancies, owing to an aggressive disease course, a high rate of relapse, and lack of standard of care. The clinical management of MCL is highly individualised and based on a number of factors, including disease biology, overall patient health and fitness (functional status). As a result, there is no single standard of care. In cases of relapsed and refractory MCL, both prior treatment(s) and treatment response are also important factors in determining the best treatment options.

Most cases of MCL are initially diagnosed at an advanced-stage of disease and patients are usually symptomatic at presentation. Common clinical features include widespread lymphadenopathy and splenomegaly, as well as bone marrow infiltration. Leukaemic involvement is found in 20% to 30% of patients. The disease course can be highly variable. Some patients may have very aggressive disease, whereas others may have a much more indolent course.

In the first line setting, up-front consolidation of chemo-immunotherapy with cytarabine (ARA-C), a high-dose chemotherapy, and autologous stem cell transplant remains an attractive option for fit patients with chemosensitive disease, regardless of the induction regimen chosen. Effective treatment options in the first line setting for less fit patients include rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), bortezomib with rituximab, cyclophosphamide, doxorubicin and, prednisone (VR-CAP), rituximab, cyclophosphamide, vincristine, prednisone (R-CVP) and bendamustine with rituximab.

As with the management of MCL in the first line setting, at present, there is no single standard of care for the treatment of relapsed and refractory MCL and treatment is highly individualised and determined in part by the prior treatment(s) that a patient has had and their response to that treatment.

Intervention

BR is a combination chemotherapy regimen involving the administration of bendamustine and rituximab. Bendamustine is an alkylating anti-tumour agent. The antineoplastic and cytocidal effect of bendamustine hydrochloride is based on a cross -linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired. Rituximab belongs to a group of drugs known as ‘monoclonal anti-bodies’. It is a biological medicine that works by ‘targeting’ specific proteins (receptors) on the surface of cells relevant to the cause of the disease.

Bendamustine-based regimens, such as BR, are considered to be an important option in the management of MCL, including relapsed and refractory MCL, because standard therapies, such as R-CHOP and R-CVP, are associated with toxicities such as peripheral neuropathy/paraesthesias, cardiac toxicities, myelosuppression and alopecia which potentially restrict treatment options for patients. As such, BR is considered to offer greater patient and clinician choice.

2 Definitions

White cells – these are cells in the lymph nodes and blood that fight infection. The abnormal white blood cells in MCL grow in an uncontrolled way and don't work properly.

Advanced disease – describes when there is disease in lymph nodes above and below the patients diaphragm, with or without disease in organs outside of the lymph nodes e.g. bone marrow.

Relapsed disease – describes when a condition has recurred following response to previous treatment, this may occur at any time following completion of treatment.

Refractory disease – means that there has been no response to the immediately preceding treatment, patients have either progressed during treatment or have stable disease whenever treatment has been stopped.

Overall survival (OS) – the length of time from either diagnosis or start of treatment that the patient is still alive.

Progression-free survival (PFS) – the length of time from either diagnosis or start of treatment to disease progression or patient death from any cause.

Overall response rate (ORR) – the ratio or percentage of patients who have achieved a complete or partial response at a designated time point.

Autologous stem cell transplantation – is the harvest of the patient's stem cells prior to treatment with high-dose chemotherapy. The harvesting of stem cells enables treatment with much higher doses of chemotherapy than would normally be the case. Stem cells are replaced following completion of the chemotherapy treatment.

Performance status – is a recognised system developed by the World Health Organisation and other groups to describe the general health of patients.

3 Aims and Objectives

This policy considers: BR given in combination for treatment of relapsed and refractory MCL.

The objectives are to: stablish via an evidence review the following:

- Efficacy, safety, toxicity profile, cost-effectiveness of BR in the relapsed and refractory MCL setting:
- Comparison of above with other treatment regimens e.g. ibrutinib, temsirolimus, bortezomib and other conventional combination regimens: and
- Whether bendamustine plus rituximab achieved improved/equivalent outcomes in comparison with other current therapies/novel therapies.

4 Epidemiology and Needs Assessment

MCL is a distinct non-Hodgkin's lymphoma (NHL) sub-type that accounts for between 5-10% of all cases of NHL (CRUK, 2016). The condition usually occurs in older adults (the median age of presentation is 60 years) and has a male predominance. The median survival time is approximately 3 years; the 10-year survival rate is 5-10% (NICE, 2012).

In England there were 11,392 (6186 males; 5206 females) cases of NHL (Cancer Registration Statistics England, 2013). This would, based on MCL constituting between 5-10% of all NHL cases, equate to between 570-1,140 cases of MCL annually. This is a relatively wide range, however, the lower end accords reasonably well with Haematological Malignancy Research Network data. This estimates that there were 510 cases of MCL in the United Kingdom (Haematological Malignancy Research Network data, 2004-2014). However, there is no reliable source of data in relation to the number of relapsed and refractory cases. Because of this, Cancer Drug Fund (CDF) activity data is the best source for the needs assessment. Therefore, based on CDF data, it is estimated that approximately 250 cases of relapsed and refractory MCL would be eligible for treatment with BR.

5 Evidence Base

NHS England has concluded that there is sufficient evidence to support the routine commissioning of this treatment for the indication.

Summary of evidence

An evidence review was undertaken to establish the clinical effectiveness, safety and cost-effectiveness of bendamustine and rituximab used in combination to treat relapsed and refractory mantle cell lymphoma. The data available to assess the safety and effectiveness of bendamustine and rituximab in combination in patients is limited to a subgroup analysis of an Randomised Control Trial (RCT) in which it was compared with fludarabine and rituximab and there was supporting data from seven Phase II studies.

The results of the subgroup analysis of the RCT indicate BR is superior to fludarabine with rituximab in terms of both progression-free and overall survival (Rummel et al, 2016). The Phase II studies indicate that its use is associated with significant periods of progression-free survival and that the majority of patients achieve some level of response to treatment. The outcomes data available are limited by the fact that the studies were largely conducted before rituximab became established as a first-line treatment and before rituximab maintenance treatment became routinely available.

The safety data available indicate that BR is associated with significant adverse effects largely involving bone marrow suppression but there was no evidence identified to suggest that the overall tolerability of this regimen is significantly worse from other regimens that may be used in this population.

Further details of the evidence are provided below.

What evidence is available to assess how bendamustine-based regimens compare with other regimens used in the treatment of patients with relapsed mantle cell lymphoma in terms of efficacy, safety, quality of life and cost-effectiveness?

The single RCT identified provides good quality evidence that using BR instead of fludarabine plus rituximab in patients with relapsed MCL results in significant improvements in median progression free survival (PFS) and this also results in improvements in overall survival (OS). In the RCT there was a subgroup of 47 patients with mantle cell lymphoma and it was shown that the median PFS was 17.6 months in the group that received BR compared with 4.7 months in the group that received fludarabine with rituximab, a difference of 13.3 months. Similarly an analysis of OS showed that patients that received BR lived for a median of 35.3 months compared with 20.9 months in the control arm. Overall response rates and complete response rates were also significantly higher in the experimental arm (70.8% and 37.5% vs. 26.1% and 13% respectively) (Rummel et. al 2016). The trial methodology appears to be robust although it could be argued that as the results described are based on a subgroup analysis they may be viewed as hypothesis

generating. This trial is also limited by the fact that the control regimen selected does not reflect current clinical practice. There may also be concerns that the results are not necessarily generalisable to current practice in that when the trial was started rituximab was not routinely accepted as a standard treatment and so only 42% of patients recruited had been exposed to rituximab prior to recruitment to this study. Similarly a protocol amendment was required during the study to allow the use of rituximab maintenance treatment in patients that responded to their allocated treatment. However this is the only RCT available and though it only included a relatively small number of patients with mantle cell lymphoma and its limitations are outlined above.

The phase II trial data available support the results outlined above and indicate that this regimen is associated with high overall response rates and that if patients respond then they remain free from disease progression for a median period of 17+ months. These data are derived from uncontrolled studies and as such it is not possible to compare these outcomes with those that might be expected in similar patients treated with different chemotherapy regimens (Czuzman et al 2015, Friedberg et al 2011, Robinson et al 2008, Rummel et al 2005, Visco et al 2013, Weide et al 2007).

The safety data available indicate that this regimen is associated with high incidences of serious haematological toxicities and has the potential to cause a wide range of other debilitating adverse effects when used to treat patients with relapsed indolent non-Hodgkin's lymphoma or mantle cell lymphoma. It is not possible though to ascertain whether this regimen differs definitively from other regimens that would be used in this indication.

No evidence was identified to support an assessment of the impact of using a bendamustine-based regimen on the quality of life of patients with relapsed mantle cell lymphoma and how this compares to treatment with other regimens. Similarly no evidence was identified to support an assessment of the relative cost effectiveness of this intervention compared to the use of other regimens.

Is there any evidence to guide the placement of bendamustine-based chemotherapy either in sequence or as an alternative to the approaches described above?

No evidence was identified to guide practice on how bendamustine-based regimens should be used in treatment pathways for patients with relapsed mantle cell lymphoma. Existing guidance from European Society for Medical Oncology (ESMO) Guidelines and the British Committee for Standards in Haematology (BCSH) Guidelines does not offer much differentiation between regimens in terms of effectiveness and both state that choice of regimen is dependent on factors such as patient age, performance status, bone marrow reserve and initial therapy. The evidence identified in this review is not robust enough to impact on this approach.

No data were identified which helped clarify the impact of BR on quality of life and no relevant health economic studies were identified.

6 Criteria for Commissioning

BR should be considered in patients with relapsed and refractory MCL where patients have been treated with one or more previous chemotherapies (excluding bendamustine-based regimens) or autologous stem cell transplantation, and have a performance status of 0-1. It must only be given to patients who have not previously been treated with bendamustine.

When used in this indication, BR is administered by intravenous infusion at a dose of 90mg/m2 on two days every 28 days for up to 6 cycles, concurrently with rituximab 375 mg/ sq. m^2 on day 1.

The decision to treat with BR must be made by either the haematology multi-disciplinary team or lymphoma multi-disciplinary team, and the patient. The first cycle must be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy. A decision to continue or stop treatment should be made by either the haematology multi-disciplinary team or lymphoma multi-disciplinary team, and the patient.

7 Patient Pathway

BR should be considered for all patients with confirmed MCL who have already undergone one or more prior chemotherapy treatments (excluding bendamustine-based regimens) or autologous stem cell transplantation.

8 Governance Arrangements

As BR is unlicensed in the treatment of relapsed and refractory MCL, any provider organisation treating patients with this intervention will be required to provide assurance that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Providers will be expected to follow Trust and Cancer Network policies for the safe prescribing and monitoring of off-label licensed medications including compliance with the Medicines and Healthcare products Regulatory Agency (MHRA) safety alerts. Prescribers need to also be aware of their responsibilities as specified in MHRA Drug Safety Update volume 10 issue, 12 July 2017:2.

9 Mechanism for Funding

BR will be funded by local specialised commissioning teams, through established chemotherapy funding arrangements.

10 Audit Requirements

Systemic Anti-Cancer Treatment (SACT) dataset.

11 Documents which have informed this Policy

- National Cancer Drugs Fund (CDF): https://www.england.nhs.uk/cancer/**cdf**/
- CDF Drugs Fund List: https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/ .

12 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

References

British Committee for Standards in Haematology (BSCH) Guidelines: McKay P, Leach M. Jackson R, Cook G, Rule S. Guidelines for the investigation and management of mantle cell lymphoma. British Journal of Haematology, 159**,** 405-26. 2012

Cancer Research UK Non-Hodgkin lymphoma incidence statistics. February 2016. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma/incidence#heading-Zero Accessed 14/09/16.

Cheah YC, Seymour JF, Wang ML. Mantle Cell Lymphoma. Journal of Clinical Oncology 2016; 34:1256-69

Czuczman MS, Goy A et al. Phase II study of bendamustine combined with rituximab in relapsed/refractory mantle cell lymphoma: efficacy, tolerability, and safety findings. Annals of Haematology. 2015; 94: 2025-32

European Society for Medical Oncology (ESMO) Guidelines: Dreyling M, Geisler C et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2014, 25 (Suppl 3): iii83-iii92

Friedberg JW, Vose JM et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/ refractory indolent and mantle cell non-Hodgkin lymphoma. Blood 2011; 117: 2807-12

Haematology Malignancy Research Network Mantle Cell Lymphoma statistics. https://www.hmrn.org/statistics/incidence

Nazeef M, Kahl BS. 2015. Mantle Cell Lymphoma: First-line therapy in patients not eligible for stem cell transplantation. Curr. Treat. Options in Oncology (2015) 16:29

National Institute of Health and Care Excellence (NICE) 2012. Final scope for single technology appraisal of “Bendamustine in combination with rituximab for the first-line treatment of mantle cell lymphoma”. https://www.nice.org.uk/guidance/GID-TAG321/documents/lymphoma-mantle-cell-bendamustine-1st-line-with-rituximab-final-scope2 Accessed 05/09/16

Robinson KS, Williams ME et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin’s lymphoma. Journal of Clinical Oncology. 2008; 26: 4473-9

Rummel MJ, Al-Batran SE et al. Bendamustine plus rituximab is effective and has a favourable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin’s Lymphoma. Journal of Clinical Oncology 2005; 23: 3383-9

Rummel M, Kaiser U et al. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial. Lancet Oncology 2016; 17: 57-66

Visco C, Finotto S et al. Combination of rituximab, bendamustine, and cytarabine for patients with mantle cell non-Hodgkin Lymphoma ineligible for intensive regimens or autologous transplantation. Journal of Clinical Oncology 2013; 31: 1442-9

Vose JM**.** Mantle Cell Lymphoma: Update on Diagnosis, Risk-Stratification and Clinical Management. American Journal of Hematology 2015.

Weide R, Hess G et al. High anti-lymphoma activity of bendamustine/mitoxantrone/ rituximab in rituximab pre-treated relapsed or refractory indolent lymphomas and mantle cell lymphomas. A multicenter phase II study of the German Low grade Lymphoma Study Group (GLSG). Leukaemia & Lymphoma 2007; 48: 1299-1306