Clinical commissioning policy: Bendamustine with rituximab for first line treatment of advanced indolent non-Hodgkin's lymphoma (all ages)

NHS England Reference: 170055P

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

Publications Gateway Reference:	**07603**
Document Purpose	Policy
Document Name	Clinical commissioning policy: Bendamustine with rituximab for first line treatment of advanced indolent non-Hodgkin's 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Superseded Docs (if applicable)	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

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Clinical Commissioning Policy: Bendamustine with rituximab for first line treatment of advanced indolent non-Hodgkin's 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.

Policy Statement

NHS England will commission bendamustine with rituximab for first line treatment of advanced indolent non-Hodgkin's lymphoma (all ages) 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 non-Hodgkin's lymphoma (all ages)

Non-Hodgkin's lymphoma (NHL) is a cancer that starts in cells called lymphocytes, which are part of the body's immune system and there are more than sixty different

sub-types. NHL can be grouped by how quickly the cancer is growing; it can be slow growing (indolent or low grade), or fast growing (aggressive or high grade). Most cases of indolent NHL are diagnosed at a late stage (advanced) of disease.

This policy covers the first line treatment of indolent, advanced cases of a number of NHL sub-types: follicular NHL, marginal zone NHL, small lymphocytic lymphoma and lymphoplasmacytic NHL.

About current treatments

In most cases, treatment will only be started when symptoms develop or the disease begins to change, usually this is where the cancer is at an advanced stage. Where treatment is required, chemotherapy is the main option and there are a number of different chemotherapy treatments currently available in the first line setting. The choice of chemotherapy treatment is highly individualised and is based on a number of clinical factors including health status of the patient, grade and stage of the cancer and tolerability.

Chemotherapy for this condition is usually given in ‘combination’, which means that two or more cancer medicines are administered to the same patient in the same cycle of treatment. Most combination chemotherapy for this condition involves a medicine called rituximab, which is usually administered with a number of other cancer medicines, for example, R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone and rituximab), R-CVP (cyclophosphamide, vincristine, prednisolone and rituximab), and chlorambucil ± rituximab for patients that cannot have either R-CHOP or R-CVP.

Because there is no one standard of care in the management of NHL, it is important to maintain a range of treatment choices in order to maximise clinical effectiveness and minimise drug associated toxicities, giving a greater choice to patients and clinicians.

About the new treatment

The new treatment is a combination chemotherapy regimen involving bendamustine and rituximab (BR) and is delivered in up to six cycles with each cycle last for four weeks.

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 administered as an intravenous (into the vein) infusion 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 infusion on the first day of each 4 week cycle, when given in combination with bendamustine.

What we have decided

NHS England has carefully reviewed the evidence to treat advanced, indolent NHL with BR. We have concluded that there is enough evidence to make the treatment available.

1 Introduction

Clinical Indication

Lymphoma is a cancer of the white cells, namely lymphocytes that constitute the lymphatic system. It is the most common 'blood' cancer and it occurs when lymphocytes grow abnormally. The two main types of lymphoma are Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL).

There are more than 60 different types of NHL and they can behave in very different ways which means that treatment is highly individualised. The clinical assessment of NHL will usually involve an assessment of:

- Grade of disease – either low (indolent) or high (aggressive);
- Type of lymphoma cell affected – either B or T cell (B cell is more common);
- Microscopic assessment of the cells – either tightly grouped (follicular) or spread out (diffuse);
- Whether there are any surface protein markers; and
- Whether there are any specific genetic changes to the cells.
- Stage of disease, with late or advanced stage being typically defined as Stage III and IV.

The policy relates to advanced, indolent NHL, specifically follicular NHL, marginal zone NHL, small lymphocytic lymphoma and lymphoplasmacytic NHL. Mantle cell lymphoma (MCL) is sometimes classed as an indolent lymphoma but its biology is generally different and requires different treatment strategies. The use of bendamustine plus rituximab in MCL is subject to different NHS England clinical commissioning policy.

Whilst indolent NHL grows slowly, it is usual for such cases to present at a late, or advanced, stage. People with advanced, indolent NHL may not need to start treatment when it is first diagnosed; instead they are followed closely and treatment is only started when they develop symptoms or the disease begins to change. This is sometimes called surveillance or watchful waiting.

There are several effective treatments currently available to treat advanced, indolent NHL. The current most commonly used first line treatment involves rituximab given in combination with other drugs, for example R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone and rituximab) or R-CVP (cyclophosphamide, vincristine, prednisolone and rituximab). Chlorambucil ± rituximab may be given to people who are unsuitable for R-CHOP/R-CVP regimens.

Intervention

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.

Bendamustine-based regimens, such as BR, are considered to be an option in the management of advanced, indolent NHL because standard therapies, such as R-CHOP and R-CVP, are associated with toxicities such as peripheral neuropathy/paresthesias, cardiac toxicities, myelosuppression and alopecia which potentially restrict treatment options for patients.

The addition of bendamustine in combination with rituximab as a treatment option in the management of advanced, indolent NHL will offer greater patient and clinician choice because the regimen has a different toxicity and side-effect profile. BR is not licensed for use in the first line treatment of advanced, indolent NHL.

2 Definitions

Aggressive NHL – fast growing disease that is referred to as high grade.

Cancer staging – indicates whether the NHL is in one area of the body or has spread. There are 4 stages for NHL:

- Stage 1 (or ‘I’): is lymphoma in one group of lymph nodes or lymphoma in just one organ or area of the body outside the lymphatic system (extranodal lymphoma);

- Stage 2 (or ‘II’): is lymphoma in 2 or more groups of lymph nodes on the same side of your diaphragm or lymphoma in 1 or more groups of lymph nodes and also one nearby organ or area of body, all on the same side of the diaphragm;
- Stage 3 (or ‘III’): is lymphoma in lymph nodes on both sides of the diaphragm or lymphoma in lymph nodes on both sides of the diaphragm, and a nearby organ or area of your body is also affected; and
- Stage 4 (or ‘IV’): is lymphoma throughout one or more organs that are not part of the lymphatic system or lymphoma in an organ that is not part of the lymphatic system, and also in organs or lymph nodes far away from that organ or lymphoma in your liver, bone marrow, cerebrospinal fluid or lung (unless it has spread to your lung from nearby lymph nodes).

Complete Response (CR) – No detectable disease following a course of treatment.

Induction therapy – the first in a series of therapeutic measures taken to treat a disease, typically a cancer and that is designed to bring about a remission.

Indolent NHL – slow growing disease that is referred to as low grade (see above).

Maintenance therapy – a treatment that is designed to help a primary treatment succeed. For example, maintenance chemotherapy may be given to people who have a cancer in remission in an attempt to prevent or delay a relapse.

Non-Hodgkin’s Lymphoma (NHL) – a cancer that starts in white cells called lymphocytes which are part of the body’s immune system.

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

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

Partial Response (PR) - A decrease in tumour size or the amount of cancer detected in the body following treatment.

Performance status - a recognised system developed by the World Health Organisation and other bodies to describe the general health and daily activity status of patients.

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

3 Aims and Objectives

This policy considers: BR for first line treatment of advanced, indolent NHL.
The objectives are to: establish, through an evidence review, the following information:

- Safety and efficacy of the treatment compared with other treatment regimens;
- Quality of life (QOL) benefit of the treatment compared with other treatment regimens;
- Cost effectiveness of the treatment; and
- Identification of appropriate sub-groups (if any) and clinical criteria.

4 Epidemiology and Needs Assessment

The policy relates to a number of specific NHL sub-types, specifically: follicular, lymphoplasmacytic, small lymphocytic and marginal zone (gastric mucosa associated lymphoid tissue (MALT), non- gastric MALT, splenic, nodal). These comprise approximately 40% of NHL cases. Mantle cell lymphoma (MCL) and chronic lymphocytic leukaemia (CLL) are excluded from this list as they have different tumour biologies and have separate treatment strategies.

The incidence of NHL in the UK in 2014 was 13,605 cases and there were 4,801 deaths (Cancer Research UK 2016). Age-specific incidence is seen to rise from 50-54 years onwards and median age at diagnosis is 70+ years. Five year survival trends for both men and women have doubled since the mid 70's to two thirds and ten year survival has increased three-fold (Cancer Research UK 2016).

The needs assessment for advanced, indolent NHL is based on an assessment of Cancer Drugs Fund (CDF) activity. This reflects the lack of granularity in disease registry data.

5 Evidence Base

NHS England has concluded that there is sufficient evidence to support the routine commissioning of this treatment for the indication in systemic treatment-naïve (i.e. first-line) patients with advanced, indolent NHL.

Summary of Evidence

The efficacy of bendamustine with rituximab (BR) compared to R-CHOP or R-CVP.

- An evidence review was undertaken which found two randomised controlled clinical trials that examine the effectiveness of BR compared to R-CHOP or R-CVP in patients with indolent non-Hodgkin's lymphoma.
- The Study Group for indolent lymphomas (StiL) study (Rummel 2013) included 274 patients that were assigned to BR (261 assessed) and 275 to R-CHOP (253 assessed). These figures included 46 and 48 patients in each treatment group respectively with mantle cell lymphoma (most of the bendamustine studies have been performed in Germany and the German classification of indolent NHL includes mantle cell lymphoma). The primary outcome measure was progression free survival (PFS). Patients treated with BR had a significantly longer median PFS (69.5 months) compared to R-CHOP (31.2 months) ($p<0.0001$). The secondary outcome measures included overall response (OR), no difference being shown between the treatment groups, and complete response (CR), there being a significant increase seen for BR, 40% compared to R-CHOP 30% ($p=0.021$). There did not appear to be any difference in overall survival (OS) but insufficient time had elapsed to assess this properly at the time of publication of the study.
- The BRIGHT study (Flinn 2014) included 447 patients of which 224 were randomised to receive BR and 223 to standard therapy (R-CHOP or R-CVP depending on clinical assessment). These included 36 and 38

patients in each treatment group respectively with mantle cell lymphoma. The primary outcome was CR rate and BR (31%) demonstrated non-inferiority to standard treatment (25%) (p=0.0225 for non-inferiority). The OR rate did not differ significantly between the groups. Other secondary, time to event results (PFS, OS etc. based on 5 year minimum follow up specified in protocol) were not sufficiently mature to report at the time of publication.

- A meta-analysis of treatments for newly diagnosed follicular NHL included data from StiL (Messori 2015). Data from BRIGHT was excluded due to the absence of PFS data. This analysis found no efficacy difference between BR and R-CHOP.

The Quality of Life (QoL) of bendamustine with rituximab (BR) compared to R-CHOP or R-CVP.

- The BRIGHT study (Flinn 2014) included an assessment of the impact on quality of life of BR compared to R-CHOP/R-CVP. These results were published in a separate paper (Burke 2016). BR treated patients reported a better quality of life in some areas assessed (cognitive, physical, emotional and social functioning) and some symptoms (constipation, dyspnoea and fatigue). Overall, despite reaching statistical significance in some cases, the clinical benefits of the differences were small.
- A small study (Zimmer 2015) looked at cognitive performance within three months of BR or R-CHOP induction therapy for patients with treatment naïve B-cell NHL. Compared to healthy controls, treated patients, particularly those treated with BR demonstrated a degree of cognitive impairment.
- This parity in overall quality of life occurs despite the fact that BR has to be administered on 2 successive days of each chemotherapy cycle whereas R-CHOP and R-CVP are administered on one day of each chemotherapy cycle.

The cost-effectiveness of Bendamustine-Rituximab (BR) compared to R-CHOP or R-CVP.

- A cost-utility analysis (Dewilde 2014) used data from StiL (Rummel 2013) as well as other modelling from the Sheffield School of Health and Related Research (ScHARR) to develop a model that included BR, R-CHOP, R-CVP as first line treatment of indolent NHL and maintenance rituximab for responders. BR had the highest patient costs but due to better PFS, produced incremental cost-effectiveness ratios (ICERs) of £5249 per quality-adjusted life year (QALY) and £8092 per QALY compared to R-CHOP and R-CVP respectively.

Note: Generic bendamustine, at a much lower drug cost, has become available since this analysis, and so it would be expected that the ICERs would be significantly lower if re-calculated using the generic price.

To assess whether BR has consistency of overall treatment effect across all indolent NHL histological sub-types.

- Sub-group analysis in the StiL study (Rummel 2013) looked at the progression-free survival (PFS) in four histological subtypes. The median PFS for BR treated follicular lymphoma, mantle cell lymphoma and Waldenstrom's macroglobulinaemia were all significantly higher than with R-CHOP. The median PFS for marginal-zone lymphoma was not significantly different.
- The BRIGHT study (Flinn 2014) showed that complete response (CR) in patients treated with BR was non-inferior to R-CHOP/R-CVP based on the whole study population results. In the sub-group analysis of patients with follicular lymphoma, BR did not reach statistical significance for non-inferiority with R-CHOP/R-CVP (p=0.057). For mantle cell lymphoma, BR was superior to R-CHOP/R-CVP (p=0.018).

The safety of bendamustine with rituximab (BR) compared to R-CHOP or R-CVP. To assess whether BR has a distinct safety and adverse event profile that is more favourable in comparison to R-CHOP and R-CVP

Both randomised controlled trials (RCT) (Rummel 2013, Flinn 2014) found that the incidence of the following side effects were less frequent with BR compared to R-CHOP/R-CVP

- Peripheral neuropathy/paraesthesia
- Alopecia
- Stomatitis

Patients treated with BR were more likely to suffer drug hypersensitivity and skin reactions (erythema or allergic reactions), nausea and vomiting.

A small case series from India (Malipatil 2011) describes a bendamustine associated rash as being erythematous and papular and that it resolves on completion of chemotherapy. In addition there are case reports of more serious rashes including fatal toxic epidermal necrolysis (Fallon 2015) and paraneoplastic pemphigus (Higo 2015).

BR was associated with less Grade 3-4 leukocytopenia and neutropenia than R-CHOP in both the StiL and BRIGHT studies ($p<0.0001$ vs R-CHOP). There were no differences in these parameters between BR and R-CVP. BR was associated with more grade 3-4 lymphopenia than R-CHOP and R-CVP ($p<0.0001$) in the BRIGHT study. In both studies the use of colony stimulating factors was higher in patients receiving R-CHOP than BR or R-CVP.

The incidence of infections was not statistically different between any of the groups in the BRIGHT study but BR was associated with significantly less infectious episodes than R-CHOP (37% vs 50% $p=0.0025$) in the StiL study. There is recent evidence that such immunosuppression with bendamustine results in a modest increase in opportunistic infections but this is a complication which is well known to the treating specialists and their teams (Drug Safety Update, July 2017).

Case reports have been published linking BR therapy with hepatitis B reactivation (Tsutsumi 2012), pneumocystis jirovecii pneumonia (Carter 2011), Epstein Barr virus (Muroi 2015), liver damage/non-allergic bronchitis and eosinophilia (Jo 2014) and progressive multifocal leukoencephalopathy (Warsch 2012). There are insufficient data to ascribe a level of risk to these side effects occurring with BR compared to other induction regimes.

The incidence of secondary malignancies was similar for BR (20/274) and R-CHOP (23/275) treated patients in the StiL study. Numbers have not been reported for BRIGHT.

Conclusion

The available data, based on the commissioned evidence review, indicates that in patients with treatment naïve indolent NHL, compared to R-CHOP and R-CVP regimes, that:

- BR is non-inferior in its effect on complete response to induction therapy and has a superior effect on progression free survival (69.5 months vs 31.2 months);
- BR is very cost-effective;
- BR is relatively safe with comparable haematological side effects (with lesser use of colony stimulating factor support) and a different and unique side effect profile, particularly with reduced risk of alopecia and peripheral neuropathy and increased risk of skin rash; and that
- BR has an overall treatment effect which was consistent across all histological sub-groups.

The differences between the two induction regimes in the various histological subtypes are inconsistent between the two main phase III studies.

There is insufficient data to make a full assessment of any significant differences in the quality of life of patients who receive BR compared to R-CHOP/R-CVP. However, there appears to be no deterioration of quality of life when compared with standard treatment.

BR has potential as an alternative treatment regimen for the initial therapy of patients with advanced, indolent NHL but there are some areas of uncertainty because of the lack of data on longer term, time dependent outcomes (for example overall survival but this would take many years for such data to be collected). There is possible bias arising from the un-blinded assessment of progression free survival in one of the major RCTs. Neither of the two phase III studies assessed how patients treated with

BR responded after rituximab maintenance therapy compared to those treated with R-CHOP/R-CVP.

6 Criteria for Commissioning

BR is an additional, alternative first-line treatment choice for cases of advanced, indolent NHL. BR is a suitable alternative to combination chemotherapies, such as R-CHOP and R-CVP. Patients must have a performance status of 0-2.

When used in this indication, BR should be given for up to six cycles (Bendamustine 90mg/m2 IV Day 1 and Day 2, with rituximab 375mg/m2 IV Day 1, of a 28 day cycle).

The decision to treat, or to stop treatment, with BR must be made by either the haematology multi-disciplinary team or lymphoma multi-disciplinary team, and the patient.

7 Patient Pathway

BR with rituximab should be considered as a first line treatment for patients diagnosed with advanced, indolent NHL alongside other commissioned treatments for this indication.

The decision to select the patient for treatment 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.

8 Governance Arrangements

BR is not a licensed medicine for this indication. Therefore, each provider organisation treating patients with a medicine approved under this policy will be required to assure itself 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 can ask for documented evidence that these processes are in place.

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

Documents that have informed this policy include:

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

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