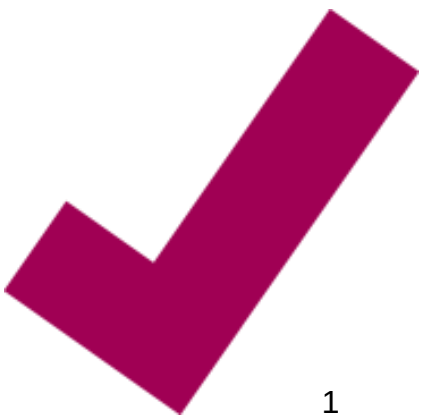
Clinical Commissioning Policy Proposition: Bendamustine with rituximab for relapsed indolent non-Hodgkin's lymphoma (all ages)

Reference: NHS England 1607



First published: TBC

Prepared by NHS England Specialised Services Clinical Reference Group for Chemotherapy

Published by NHS England, in electronic format only.

Contents

1 Executive Summary

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

Non-Hodgkin's lymphoma is a type of cancer that affects the lymphatic system, which is part of the body's immune system. It is the sixth most common cancer in the United Kingdom and is generally associated with older age, although it can develop at any age. People with this condition can experience a large number of symptoms, including frequent temperatures, heavy sweating at night, weight loss, unexplained itching, enlarged lymph nodes, bleeding problems and breathlessness.

It is difficult to cure non-Hodgkin's lymphoma completely and people with the condition will usually experience multiple episodes of treatment, remission and relapse. With effective management and treatment, it is possible to keep the disease and its symptoms under control for several years. However, as the disease continues to develop, people tend to experience a progressively lower rate of both remission and duration of remission.

Non-Hodgkin's lymphoma can be categorised in a number of different ways, including by how quickly abnormal cells divide, the stage/grade of disease and the

type of cells that are affected. This policy proposition relates to relapsed disease which is slow growing (indolent).

About current treatments

Chemotherapy is the main treatment option for non-Hodgkin's lymphoma, both in the first-line and in cases of disease relapse. Stem cell transplantation can also be an option for some forms of non-Hodgkin's lymphoma, where the treatment can be tolerated.

There are a number of different chemotherapy medicines available to treat relapsed, indolent non-Hodgkin's lymphoma, these are usually given in combination. Treatment choice is highly individualised and depends on many factors including age, health status, response to previous treatments, the time from the end of the treatment to relapse and the grade / stage of disease.

About the new treatment

Bendamustine given in combination with rituximab is another potential treatment option for relapsed, indolent NHL. Bendamustine works by binding to DNA in cancer cells to prevent them from multiplying. Rituximab is a biological medicine that works by targeting specific proteins (receptors) on the surface of cells relevant to the cause of the disease.

What we have decided

NHS England has carefully reviewed the evidence to treat relapsed indolent non-Hodgkin's lymphoma with bendamustine and rituximab (all ages). We have concluded that there is not enough evidence to make the treatment available at this time.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission bendamustine with rituximab (BR) for relapsed indolent non-Hodgkin's lymphoma (NHL) (all ages).

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether BR for relapsed indolent non-Hodgkin's lymphoma (all ages) will be not routinely commissioned is planned to be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Lymphoma is a cancer of the white blood 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 sixty different types of NHL and they can behave in very different ways which means that treatment is highly individualised. NHL can be classified in several different ways. One way is by the type of cell affected. NHL affects certain white blood cells called lymphocytes. Two types of lymphocyte can be affected – B cells and T cells. B-cell lymphomas are more common.

People with indolent NHL may not need to start treatment when it is first diagnosed, they are followed closely, and treatment is only started when they develop symptoms or the disease begins to change. This is called active surveillance. Most patients with indolent NHL have later-stage disease, stage III or IV, at the time of diagnosis. There are several effective chemotherapy treatments for the first line treatment of indolent NHL, however, it may relapse months or years after first line

treatment has finished, requiring further treatment. Stem cell transplantation is also an option for patients with a good functional status.

The most common chemotherapy treatment combination for relapsed, indolent NHL usually involves rituximab, which is given in combination with other medicines. The most common combination regimen is called R-CHOP (rituximab with cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisolone) and R-CVP (rituximab with cyclophosphamide, vincristine and prednisolone). If a previous therapy has induced remission of over two years' duration, this treatment will often be repeated until it fails.

Proposed intervention

Indolent non-Hodgkin's lymphomas are generally incurable. Although initially responsive to therapy, they rarely show complete or sustained remissions to conventional chemotherapy. Therefore, active, effective and tolerable treatments for patients with relapsed disease are needed.

Bendamustine works by binding to DNA in cancer cells to prevent them from multiplying. Rituximab is a biological medicine that works by 'targeting' specific proteins (receptors) on the surface of cells relevant to the cause of the disease.

Bendamustine has become an important agent for the treatment of lymphoid malignancies. Standard therapies e.g., R-CHOP and R-CVP used in both the first line and relapsed settings are associated with peripheral neuropathy/paraesthesias, cardiac toxicities, myelosuppression and alopecia. BR has a different side-effect profile, and may offer an alternative treatment option.

4 Definitions

Indolent – this term refers to slow-growing disease which worsens over time.

Non-Hodgkin's Lymphoma (NHL) – a type of cancer of the lymphatic system that affects all ages. It comprises a group of lymphomas except for Hodgkin's

lymphomas. Risk factors include age, autoimmune diseases, reduced immunity, viral infections, obesity, radiotherapy etc. Following diagnosis NHL is staged and graded and this determines treatment strategy, response and prognosis. Whilst prognosis and outcomes including survival has improved (with better diagnosis, chemotherapy and immunotherapy treatments), NHL remains incurable.

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

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.

5 Aims and Objectives

This policy proposition considered bendamustine given in combination with rituximab for the treatment of relapsed, indolent NHL (all ages).

The objectives were to establish, via an evidence review, the following:

- The evidence on clinical effectiveness of using bendamustine with rituximab for bendamustine naive individuals with relapsed low-grade non-Hodgkin's lymphoma who are chemotherapy-refractory or unsuitable for R-CHOP.
- The evidence relating to the safety of bendamustine with rituximab for bendamustine naive individuals with relapsed low-grade non-Hodgkin's lymphoma who are chemotherapy-refractory or unsuitable for R-CHOP.
- The evidence on the cost effectiveness of bendamustine with rituximab for bendamustine naive individuals with relapsed low-grade non-Hodgkin's lymphoma who are chemotherapy-refractory or unsuitable for R-CHOP
- If the evidence of clinical and cost-effectiveness identifies any subgroups of bendamustine naive patients with relapsed low-grade non-Hodgkin's

lymphoma who are chemotherapy-refractory or unsuitable for R-CHOP who would gain greater benefit from using bendamustine with rituximab:

1. Follicular lymphoma;
2. Marginal zone lymphoma;
3. Lymphoplasmacytoid lymphoma;
4. Stage on treatment pathway / line of treatment;
5. Other.

6 Epidemiology and Needs Assessment

Low grade, indolent or slow – growing NHL includes the following lymphomas: follicular, lymphoplasmacytic, small lymphocytic, marginal zone (gastric mucosa associated lymphoid tissue (MALT), non- gastric MALT, splenic, nodal). These comprise 40% of NHL cases.

The incidence of NHL in the UK in 2015 was 13,682 cases. For both men and women NHL is the 7th most common cancer (7,500 and 6,200 new cases respectively in 2015). Rates are significantly higher in males than females in most age groups. NHL incidence is strongly related to age, with the highest incidence rates being in older people. Age-specific incidence rates rise steadily from around age 45-49 years and more steeply from around age 55-59 years. On average more than a third (35%) of new cases were in people aged 75 years and over, with the highest rates in people aged 80 to 84 years. NHL is as common in White, Asian and Black people (Cancer Research UK 2018).

Since the early 1990s, non-Hodgkin lymphoma incidence rates have increased by almost two-fifths (39%) in the UK. Rates in males have increased by more than a third (36%), and rates in females have increased by two-fifths (40%). Incidence rates for non-Hodgkin lymphoma are projected to fall by 2% in the UK between 2014 and 2035, to 26 cases per 100,000 people by 2035.

There were 4,920 deaths in 2016. Non-Hodgkin lymphoma survival is improving and has tripled in the last 40 years in the UK. Almost two-thirds (63%) of people

diagnosed with NHL survive their disease for ten years or more. Survival is similar in both men and women.

Utilising the figures above, approximately 5,500 cases of indolent NHL will be expected in a given year. It is not possible to quantify the number of patients that would be likely to have BR as a treatment option because each patient will have a number of treatments over the course of the disease, based on a highly individual assessment. However, it is estimated by the Chemotherapy Clinical Reference Group that approximately 500 patients would be likely to be eligible for BR per year.

7 Evidence Base

NHS England has concluded that there is insufficient evidence to support a proposal for the routine commissioning of this treatment for relapsed indolent non-Hodgkin's lymphoma (all ages).

Summary of evidence review

No studies that compared B-R with fludarabine, cyclophosphamide and rituximab (FCR) or any other regimen specified in the Population, Intervention, Comparison and Outcomes (PICO) template were identified. One randomised, non-inferiority, open-label, phase 3 trial (StiL NHL 2–2003; n=230) that compared the efficacy and safety of bendamustine plus rituximab (B-R) with fludarabine plus rituximab (F-R) in patients with relapsed or refractory indolent, non-Hodgkin lymphoma and Mantle-cell lymphoma (MCL) was identified (Rummel et al 2016). It was not clear if the MCL patients included in the study had indolent disease.

1. **What is the evidence on clinical effectiveness of using bendamustine with rituximab for bendamustine naive individuals with relapsed low-grade non-Hodgkin's lymphoma who are chemotherapy-refractory or unsuitable for R-CHOP?**

- **Progression free survival (PFS)**

Median PFS was longer for patients treated with bendamustine plus rituximab

(B-R) compared to fludarabine plus rituximab (F-R): 34.2 months (95% CI 23.5 to 52.7) vs. 11.7 months (8.0 to 16.1) (HR 0.54 [95% CI 0.38 to 0.72], p<0.0001). The median follow-up was 96 months (interquartile range (IQR)[1] 73.2 to 112.9).

At one year, a greater proportion of patients in the B-R group (76%) compared with the F-R group (48%) remained progression free (B-R vs. F-R: 0.76 (95% CI 0.68 to 0.84) vs. 0.48 (0.39 to 0.58), non-inferiority[2] p<0.0001).

152 patients responded to treatment with either B-R or F-R. Of these, 44 patients with follicular lymphoma (25 in the B-R arm, 19 in the F-R arm) also received rituximab maintenance therapy. The other 108 responders did not receive rituximab maintenance therapy (69 in the B-R arm, 39 in the F-R arm).The median PFS was significantly longer for patients who received rituximab maintenance than those who did not: 72.1 months [95% CI 54.1 to not reached] vs. 30.4 months [24.7 to 36.5], (HR 0.52 [95% CI 0.37 to 0.86], p=0.01).

Among those 44 patients who received rituximab maintenance in addition to B-R or F-R , there was no difference in median PFS between those who received B-R (72.1 months [95% CI 52.7 to not reached]) and those who had F-R (93.6 months [45.0 to not reached], (HR 1.02 [95% CI 0.42 to 2.50], p=0.96).

By contrast, patients who did not receive rituximab maintenance had significantly longer PFS if they were treated with B-R than with F-R: 25.0 months [95% CI 15.2 to 34.8] vs. 8.6 months [5.8 to 12.2], (HR 0.49 [95% CI 0.33 to 0.65], p<0.0001).

- **Overall survival (OS)**

Of all the study participants, those receiving B-R had longer median overall survival than those receiving F-R (109.7 months [95% CI 50.2 to not reached] vs. 49.1 months [36.2 to 59.0]; HR 0.64, 95% CI 0.45 to 0.91, p=0.012). There were fewer deaths in the B-R group compared to the F-R group (55 deaths vs 71

[1] A measure of statistical dispersion; equal to the difference between 75th and 25th percentiles

[2] Non-inferiority trials test whether a new experimental treatment (B-R in this case) is not unacceptably less efficacious than an active control treatment (F-R) already in use.

deaths).

- **Response Rates**

Overall and complete response rates were greater for patients who received B-R compared to F-R: 82% vs. 51% ($p<0.0001$) and 40% vs.17% ($p=0.0002$) respectively.

Twenty seven out of 230 patients recruited to the study were not bendamustine naïve. Thirteen of these were randomised to the B-R group and 14 to the F-R group. Results were reported separately for patients who had received previous bendamustine therapy in the B-R group but not for the F-R group. It is not clear to what extent the inclusion of a small number of patients who were not bendamustine naïve (and out of scope of this review) might have had an impact on the apparent non-inferiority of B-R compared to F-R.

2. What is the evidence relating to the safety of bendamustine with rituximab for bendamustine naive individuals with relapsed low-grade non-Hodgkin's lymphoma who are chemotherapy-refractory or unsuitable for R-CHOP?

No significant differences in the occurrence of adverse events between the patients who received B-R or those who received F-R therapy were reported. Actual results and p-values were not provided.

The overall incidence of serious adverse events was similar for both treatment groups, with 23 events in the B-R group and 23 events in the F-R group. The most common adverse events were infections (B-R vs F-R: 11 vs 8) and myelosuppression (B-R vs F-R: 3 vs 2). Clinical definitions or significance details were not provided.

3. What is the evidence on the cost effectiveness of bendamustine with rituximab for bendamustine naive individuals with relapsed low-grade non-Hodgkin's lymphoma who are chemotherapy-refractory or

unsuitable for R-CHOP?

No studies that evaluated the cost-effectiveness of bendamustine with rituximab for bendamustine naive individuals with relapsed low-grade non-Hodgkin's lymphoma who are chemotherapy-refractory or unsuitable for R-CHOP were found.

4. **Does the evidence of clinical and cost-effectiveness identify any subgroups of bendamustine naive patients with relapsed low-grade non-Hodgkin's lymphoma who are chemotherapy-refractory or unsuitable for R-CHOP who would gain greater benefit from using bendamustine with rituximab?**

Limited sub-group testing showed that the increase in PFS associated with B-R compared to F-R was evident in patients with follicular lymphoma (n=111, HR 0.56, 95% CI 0.34 to 0.87), mantle-cell lymphoma (n=47, HR 0.45, 95% CI 0.22 to 0.76) and small lymphocytic lymphoma sub-entities (n=17, HR 0.28, 95% CI 0.07 to 0.62). It is not clear if the other 55 patients in the study who had different types of NHL experienced any improvement in PFS as no further information or data on the sub-group testing was provided.

Conclusion

There is moderate evidence to suggest that bendamustine plus rituximab in patients with relapsed and/or refractory low-grade NHL is safe, and may be as effective as fludarabine plus rituximab at improving progression free survival, overall survival, overall and complete response.

However, there is no published evidence for the unlicensed use of bendamustine plus rituximab compared with current standard treatments of interest:

- FCR (fludarabine, cyclophosphamide and rituximab);
- Rituximab + chlorambucil (RCbl);
- Rituximab + CVP (cyclophosphamide, vincristine and prednisolone);
- Cyclophosphamide and dexamethasone.

The effectiveness of bendamustine plus rituximab in bendamustine naïve patients is still uncertain, as is the comparative effectiveness for different subtypes of NHL. In addition, the study by Rummel et al 2016 introduces an important question about the extent to which improved outcomes might be achieved by rituximab maintenance therapy.

8 Documents That Have Informed This Policy Proposition

- 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/
- Evidence review, NHS England, Bendamustine-rituximab for relapsed Indolent/low grade Non-Hodgkin's lymphoma

9 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

10 References

Cancer Research UK. (2018). Non-Hodgkins lymphoma statistics. [online] Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma#heading-Zero [Accessed 22.6.2018].

NHS England. 2018 National Cancer Drugs Fund List ver. 1.80 May 2018.

Rummel M, Kaiser U, Balser C, Stauch M, Brugger W, Welslau M, Niederle N, Losem C, Boeck H, Weidmann E, von Gruenhagen U, Mueller L, Sandherr M, Hahn L, Vereshchagina J, Kauff F, Blau W, Hinke A. and Barth J. 2016. 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. The Lancet Oncology. 17(1): 57-66.