Clinical Commissioning Policy Proposition: Bendamustine with rituximab for first line treatment of mantle cell lymphoma

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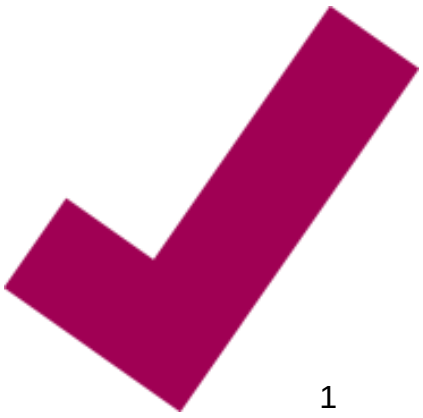

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1 Executive Summary

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 mantle cell lymphoma

Mantle cell lymphoma (MCL) is a rare form of a type of cancer called non-Hodgkin's lymphoma. It happens when the body makes abnormal white blood cells – these are cells in the blood that fight infection. The abnormal white blood cells don't work properly, so they can't fight infection like normal white blood cells do. It is a condition that is characterised by episodes of treatment followed by periods of remission, and then commonly by subsequent relapse.

About current treatments

There are existing routinely commissioned first line chemotherapy treatments for mantle cell lymphoma available in the NHS. These include rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), bortezomib with rituximab, cyclophosphamide, doxorubicin and, prednisone (VR-CAP) or rituximab, cyclophosphamide, vincristine, prednisone (R-CVP). These combinations vary in their side-effects, contraindications and tolerability. For patients with MCL a choice of treatment regimens will be necessary in order for oncologists to select an

individualised treatment regimen that maximises clinical effectiveness and minimises drug associated toxicities and is cost effective to the NHS.

About the new treatment

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 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.

What we have decided

NHS England has carefully reviewed the evidence to treat first line mantle cell lymphoma with bendamustine and rituximab in combination. We have concluded that there is sufficient evidence to consider making the treatment available.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission Bendamustine and Rituximab in combination for first line treatment of mantle cell lymphoma (MCL).

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

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 bendamustine with rituximab for untreated patients with mantle cell lymphoma will be 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

Mantle cell lymphoma (MCL) is rare and one of the most challenging haematological malignancies, owing to an aggressive disease course, a high rate of relapse, and lack of standard of care.

Most patients are initially diagnosed with advanced-stage disease. They are often symptomatic at presentation. Common features include widespread lymphadenopathy and splenomegaly, as well as bone marrow infiltration. Leukemic 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. There is no consensus on first line or relapsed treatments.

First Line Treatment

Although mantle cell lymphoma often responds well to frontline chemo-immunotherapy with high overall response rates, the responses may not be durable and sequential therapies may be necessary.

In the first line setting, up-front consolidation of chemo-immunotherapy with cytarabine (ARA-C), high-dose therapy and autologous stem cell transplant remains an attractive option for those young, fit patients with chemosensitive disease, regardless of the induction regimen chosen. Effective treatment options in the frontline setting for less fit and older patients have included the addition of rituximab to bendamustine, or rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). The latter with maintenance rituximab following induction therapy.

Proposed Intervention

Bendamustine is an alkylating antitumour 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 is not licensed for treatment of relapsed mantle cell lymphoma, and therefore will not be considered for NICE appraisal.

As stated above bendamustine-based regimens are considered to be an option for this patient group although it is not licensed for use in this population. When used in this indication it 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.

4 Definitions

Mantle cell lymphoma (MCL) - a rare form of a type of cancer called non-Hodgkin's lymphoma. It happens when the body makes abnormal white blood cells

White blood cells – these are cells in the blood that fight infection. The abnormal white blood cells don't work properly, so they can't fight infection like normal white blood cells do.

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.

First line therapy- describes treatment regimen or regimens that are generally accepted for initial treatment of a given type and stage of cancer. It is also called primary treatment or therapy. It is often part of a standard set of treatments, e.g. surgery followed by chemotherapy and radiation. First-line therapy is the one accepted as the best 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.

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

5 Aims and Objectives

This policy proposition considered: Bendamustine with rituximab in combination for the first line treatment of mantle cell lymphoma.

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

- Compare the efficacy and safety (non–inferiority / superiority), tolerability, side-effect profile and cost-effectiveness, for bendamustine with rituximab with current first line. treatment regimen options i.e. rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), bortezomib with rituximab, cyclophosphamide, doxorubicin and, prednisone (VR-CAP)
- Consider the applicability/suitability of the intervention for both young fit (as part of intensive treatment approach) and elderly age groups.
- Identify any selection criteria for which patients will benefit from bendamustine with rituximab vs R-CHOP/R-CVP/ Rituximab with bortezomib in first line use.

6 Epidemiology and Needs Assessment

Mantle cell lymphoma (MCL) is a distinct non-Hodgkin's lymphoma (NHL) sub-type that accounts for 6% of patients with non-Hodgkin's Lymphoma. In 2013 there were 13,400 cases of NHL in the UK (Cancer Research UK 2015). In England, there were 11,392 (6186 males, 5206 females) cases of NHL (Cancer Registration Statistics England 2013). The estimated number of UK cases of MCL was 510 (Haematological Malignancy Research Network data, 2004-2014). The European age standardised incidence rate is 0.9/100k.

Of the 510 estimated cases, it is expected that 75% of these would present at an advanced and late stage and would be eligible for first line treatment; of which 50% of these would not be suitable for intensive treatment (Nazeef 2014). Therefore, the needs assessment indicates that approximately 192 patients would be eligible for treatment.

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal

for the routine commissioning of this treatment for the indication

Rationale for supporting policy proposition

This recommendation is supported by the evidence review and in particular two recent randomised controlled trials (RCT) designed to demonstrate non-inferiority against contemporary chemotherapy (R-CHOP, R-CVP) but have resulted in showing superiority in both response rates and median progression free survival gain of a year. Bendamustine with rituximab (BR) is additionally cited as an established treatment in European and British Guidelines, the European Society of Medical Oncology (ESMO) (Dreyling M, 2014) and British Society of Haematology Guidelines (BSHC) (McKay 2012). The cost–effectiveness of BR will increase further following the availability of generic bio equivalents and emerging, preliminary evidence of lack of additional benefit (vis-à-vis R-CHOP) with maintenance rituximab (Rummel 2016). Mantle cell lymphoma (MCL) is an aggressive non-Hodgkin's lymphoma (NHL) sub-type that presents in older people. It has a poor prognosis which is improving with the advent of newer and novel treatments. Choice of first-line treatment in MCL is individualised to take account of age, fitness and comorbidities, anticipated drug toxicities and patient tolerability. BR is an important alternative drug option with at least equivalent/non- inferior effectiveness to bortezomib and R-CHOP but with a different and unique safety/ toxicity profile which assists patient selection. The side-effects of R-CHOP/R-CVP are cardiac, peripheral neuropathy, paraesthesias and alopecia whereas bendamustine with rituximab is associated with nausea, vomiting and hypersensitivity. Bortezomib also has a side effect profile characterised by peripheral neuropathy / paraesthesias, hypersensitivity and oedema. There are also differences in haematological toxicities with a lesser documented use of colony- stimulating factors with bortezomib.

Summary of Evidence Review

What evidence is available to assess how bendamustine-based regimens compare with other regimens used in the treatment of patients with MCL receiving non-intensive, first-line, treatment in terms of efficacy, safety and cost-effectiveness?

Two fully published RCT's were identified from a search of the literature databases

cited and a search of bibliographic references indicate that these were the only two randomised studies available that compare BR with standard rituximab-containing treatment regimens in untreated patients with MCL that are not considered suitable for more intensive treatment. In both cases the trials were powered to demonstrate that BR was non-inferior to standard treatments (R-CHOP or R-CVP) in a population that comprised patients with either indolent NHL or MCL and although results are broken down for the subgroup with MCL in terms of effectiveness, the adverse event data are only presented in terms of incidence for the whole trial population.

Effectiveness

The Study Group for Indolent Lymphomas (Stil) study (Rummel, 2013) included 46 patients with MCL that were assigned to bendamustine with rituximab and 48 to R-CHOP. The primary outcome measure for the whole trial population was progression free survival (PFS). After a median follow-up period of 45 months it was reported that patients treated with BR had a longer median PFS (35.4 months) compared to R-CHOP (22.1 months). The secondary outcome measures included overall response rate (ORR), no significant difference shown – 93% vs 91% respectively. There did not appear to be any significant difference in overall survival (OS) but insufficient time had elapsed to assess this properly at publication.
The analysis showing a statistically significant increase in PFS in the subgroup of patients with MCL was exploratory and could therefore be viewed as only being hypothesis generating.

Follow up results have since been published in abstract form (Rummel, 2015). The authors state that after 7 years of follow up there are no significant differences in overall survival seen between patients with MCL in the two arms of the study (n= 95; HR = 1.28, 95% CI: 0.69–2.39; p = 0.429). There is an unexplained 1 patient discrepancy between the original study (n=94) and the 7-year follow up results presented at conference (n=95).

The BRIGHT study (Flinn I, 2014) included 74 patients with MCL of whom 36 were randomized to receive bendamustine with rituximab and 38 to standard therapy (R-CHOP or R-CVP depending on clinical assessment). The primary outcome was

complete response (CR) rate and a rate of 50% was reported for BR compared to 27% for standard treatment. The overall response (OR) rates recorded were 94% for BR compared to 85% for standard treatment. Again these results are based on a subgroup analysis so it could be argued that the trial was not adequately powered to support a suggestion that BR is non-inferior to standard treatment in patients with MCL in terms of this outcome measure. This trial did not assess more patient-orientated outcomes such as PFS or time to next treatment and follow up was limited to completion of the treatment regimen.

Safety and quality of life

There is no specific information available which supports a comparison of relative safety of BR and standard treatments in patients with MCL. The two RCT's discussed above provide an overview of safety data in a cohort of patients with indolent NHL or MCL and key findings are outlined below:

- Compared with standard treatment BR is associated with significantly lower incidences of peripheral neuropathy / parasthesiae, alopecia and stomatitis
- Compared with standard treatment BR is associated with less Grade 3-4 leukocytopenia and neutropenia than R-CHOP. There was no significant difference in these parameters between BR and R-CVP in the BRIGHT study. In both trials it was noted that BR patients were less likely to require granulocyte-colony stimulating factor (G-CSF) treatment to maintain neutrophil counts.
- Compared with standard treatment BR is associated with significantly higher incidences of vomiting, skin reactions and lymphocytopenia.

It is reported that 20 of the 261 patients that received BR have developed secondary cancers compared with 23 of the 253 that received R-CHOP and these numbers remained unchanged over 7 years of follow up (Rummel, 2015).

In a Quality of Life assessment that was conducted as part of the BRIGHT study it was reported that patients treated with BR reported improvements in cognitive functioning, physical functioning, social functioning, emotional functioning and global health status and a reduction in dyspnoea, constipation and fatigue at some but not

all time points compared with standard treatment (Burke 2016). Patients treated with standard treatment reported less nausea or vomiting and appetite loss at several time points.

Health economics

No relevant evidence was identified to quantify the incremental cost effectiveness of using BR instead of standard treatment in patients with MCL. An economic modelling study based on the results of the RCT comparing BR with R-CHOP in patients with either indolent NHL or MCL (the STiL study discussed above) was considered to be out of scope on the basis that patients with MCL were explicitly excluded from this analysis (Dewilde 2014).

What evidence is available to assess how bendamustine-based regimens compare with other regimens used in the treatment of patients receiving intensive first-line treatment prior to consolidation with high-dose chemotherapy and autologous stem cell transplant?

Only one small open-label single arm study was identified which assessed outcomes in 23 patients with newly diagnosed MCL and considered eligible for transplant (Armand 2016). These patients were treated with 3 cycles of BR followed by 3 cycles of rituximab with high-dose cytarabine (ARA-C). It is reported that 96% of patients treated achieved a complete response (CR). It is also noted that only 1 out of 15 patients tested had measurable residual disease at the end of the treatment regimen and that 21/22 proceeded to ASCT with one patient declining. The adverse effects seen during the BR phase were similar to those described above with Grade 3/4 leucopenia seen in over 30% of cycles administered.

No further data were identified to support an analysis of impact on quality of life or cost effectiveness.

Is there any evidence available to guide selection of patients that will benefit from a bendamustine-based regimen instead of an alternative regimen in patients with MCL being treated with first-line chemotherapy?

The most recently published Clinical Guideline from ESMO states that patients that

are not considered suitable for dose-intensified regimens should be treated with rituximab in combination with chemotherapy such as CHOP or bendamustine (Dreyling M, 2014). They state that R-CVP is associated with inferior response rates and durations of PFS and that purine analogue based schemes (i.e. those containing fludarabine) should also be discouraged due to early failures and long-term immunosuppression. However ESMO do not provide any advice on potential criteria to be considered when choosing between BR and R-CHOP. BSHC support the use of rituximab-containing regimens such as rituximab with fludarabine and cyclophosphamide (R-FC), R-CVP, R-CHOP, R-bendamustine (BR) or R-chlorambucil and do not differentiate between them (McKay 2012).

In terms of contra-indications listed in the relevant SPCs for patients not previously exposed to chemotherapy doxorubicin should not be used in patients with a history of heart disease (specifically severe arrhythmias, heart failure, previous myocardial infarction, acute inflammatory heart disease) and vincristine should not be used in patients with the demyelinating form of Charcot-Marie-Tooth syndrome (Summaries of Product Characteristics for doxorubicin and vincristine).

<u>Conclusion of Evidence Review:</u>

The available data indicate that in patients with treatment naïve MCL that are not considered suitable for intensive therapy:

- BR has a superior effect on progression free survival than R-CHOP and is associated with higher rates of complete response than R-CHOP/ R-CVP.
- BR is relatively safe with a different side effect profile particularly with reduced risk of alopecia and peripheral neuropathy and increased risk of skin rash
- There are insufficient data to make a full assessment of any differences in the quality of life of patients who receive BR compared to R-CHOP/R-CVP

BR has potential as an alternative treatment regimen for the initial therapy of patients with MCL that are not considered to be suitable candidates for intensive treatment but there may be some areas of uncertainty because of the lack of data on longer term, time dependent outcomes (for example overall survival). 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 three studies assessed how BR treated patients respond after rituximab maintenance therapy compared to those treated with R-CHOP/R-CVP.

8 Proposed Criteria for Commissioning

Bendamustine with rituximab should be considered as first line treatment for patients with mantle cell lymphoma who may not be suitable for intensive or other alternative first line chemotherapy treatments with a performance status 0-1.

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

9 Proposed Patient Pathway

Bendamustine with rituximab should be considered as a first line treatment for patients diagnosed with mantle cell lymphoma alongside other commissioned treatments for this indication.

Followed by maintenance rituximab schedule in patients who respond to standard first line chemotherapy to a maximum of 2 years treatment (until more definitive evidence is available).

10 Proposed Governance Arrangements

Any provider organisation treating patients with this intervention 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 may ask for

assurance of this process.

11 Proposed Mechanism for Funding

Routine Commissioning.

12 Proposed Audit Requirements

Chemotherapy (Systemic Anti-Cancer Therapy Dataset).

13 Documents That Have Informed This Policy Proposition

The following documents have informed this policy proposition:

- National CDF: https://www.england.nhs.uk/cancer/cdf/
- CDF Drugs Fund List: https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/
- 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. Ann Oncol 2014,25 (Suppl 3): iii83-iii92
- British Committee for Standards in Haematology Guidelines: McKay P, Leach M. Jackson R, Cook G, Rule S. Guidelines for the investigation and management of mantle cell lymphoma. Br J Haematol, 159**,** 405-26. 2012
- PICO 1604, NHS England, Bortezomib for relapse Mantle Cell Lymphoma
- Evidence Review 1604, UKMI/NHS England, Bortezomib for relapse Mantle Cell Lymphoma
- Preliminary Policy Proposal, NHS England, Bendamustine (+ Rituximab) for first line treatment of Mantle Cell

14 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.

15 References

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