Clinical Commissioning Policy: Bendamustine with rituximab for first line treatment of mantle cell lymphoma (all ages)

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Clinical Commissioning Policy: Bendamustine with rituximab for first line treatment of mantle cell lymphoma (all ages)

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Policy Statement

NHS England will commission bendamustine with rituximab for first line treatment of 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 mantle cell lymphoma

Mantle cell lymphoma (MCL) is a rare form of a type of cancer called non-Hodgkin's lymphoma (NHL). The condition is more commonly diagnosed in older adults (≥60

years) but it can affect people of any age and whilst the condition can affect both males and females, it predominantly affects males.

MCL happens when the body makes abnormal, growing white cells in the blood and lymph nodes. The abnormal white cells don't work properly, so they can't fight infection like normal white cells do and they continue to grow in an uncontrolled way. Typically this leads to the condition affecting many 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 or it’s symptoms following a period of treatment and improvement. This policy applies to initial (first line) chemotherapy treatments for MCL.

About current treatments

Chemotherapy is the main treatment option for patients with MCL 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 factors including disease biology and patient health and fitness (functional status).

The preferred first-line chemotherapy treatment for MCL is an intensive course of chemo-immunotherapy for people with a very good functional status and this will usually involve treatment with chemo-immunotherapy followed by a high-dose chemotherapy treatment using a medicine called cytarabine (ARA-C) and autologous stem-cell transplantation.

For patients that are unable to tolerate such an intensive sequence of treatments, a range of alternative treatments are available, including 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 also vary in their side-effects, contraindications and tolerability.

Because there is no one standard of care in the management of MCL, 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). Combination chemotherapy is where two or more chemotherapy medicines are administered in combination. BR is delivered in up to six cycles and 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 adminstered 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 first line MCL with BR. We have concluded that there is enough evidence to make the treatment available.

1 Introduction

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 and are often symptomatic at presentation. Common 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. As a result, treatment choice is highly-individualised and based on a range of factors including disease biology and functional status of the patient.

First Line Treatment

Although MCL 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), 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 have included the addition of rituximab to bendamustine, or rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). The latter having evidence of improved benefit with maintenance rituximab following induction therapy. R-CHOP is considered as the most common alternative treatment used other than BR.

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 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.

The addition of bendamustine in combination with rituximab as a treatment option in the management of MCL will offer greater patient and clinician choice because the regimen has a different toxicity and side-effect profile to other standard treatments

2 Definitions

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.

Autologous stem cell transplant – 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.

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. initial (induction) chemotherapy followed by consolidation chemotherapy or induction chemotherapy followed by maintenance immunotherapy. First-line therapy is the one accepted as the best treatment for a particular type of patient.

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.

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

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

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

Performance status - a recognised system developed by the World Health Organisation and others 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.

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

Stem cells – are very early blood cells in the bone marrow that develop into red blood cells, white blood cells and platelets.

White cells – these are cells in the blood and lymph nodes that fight infection. The abnormal white cells do not work properly, so they cannot fight infection like normal white cells do.

3 Aims and Objectives

This policy considered: BR for the first line treatment of MCL.

The objectives were to: establishthe following via an evidence review:

- Compare the efficacy and safety (non–inferiority / superiority), tolerability, side-effect profile and cost-effectiveness, of bendamustine in combination with

rituximab with current first line treatment regimen options such as rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), bortezomib with rituximab, cyclophosphamide, doxorubicin and, prednisone (VR-CAP) and rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP).

- Consider the applicability/suitability of the intervention for patients with different functional status, including as part of intensive treatment approach for patients with a good functional status.
- Identify any selection criteria for which patients will benefit from bendamustine with rituximab vs R-CHOP/R-CVP/VR-CAP in first line use where an intensive treatment approach is not possible.

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 on NHL (CRUK, 2016). The condition usually occurs in older adults and has a median age at presentation of sixty years. The condition can affect both males and females but does have a male predominance. The median survival time is approximately three years; the ten 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).

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 approximately 50% of these would not be suitable for a very intensive sequence of treatment (Nazeef, 2014), such as chemo-immunotherapy followed by ARA-C, a high-dose chemotherapy, and autologous stem cell transplantation. Therefore, the

needs assessment indicates that approximately 192 patients would be eligible for treatment with combination chemotherapy, such as 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 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 randomised controlled trials (RCTs) 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. Although efficacy results were reported separately for MCL, this was not the case for the reporting of toxicities, the latter described 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) and 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 and the MCL part of the study would have been underpowered for survival in any case. 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 for MCL patients 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.

<u>Safety and quality of life</u>

There is no specific information available which supports a comparison of relative safety of BR and standard treatments in patients with MCL. The two RCTs 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 in these trials, 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 leucopoenia 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 the European Society for Medical Oncology (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. The British Society for Haematology (BSH) supports 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 does 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).

Conclusion of Evidence Review:

The available data indicate that in patients with treatment naïve (i.e. first line setting) MCL that are not considered suitable for intensive therapy, such as induction chemo-immunotherapy followed by ARA-C, a high-dose chemotherapy, and autologous stem cell transplantation:

- 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; and
- 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.

6 Criteria for Commissioning

BR is an additional, alternative treatment choice for patients with MCL that are unable to tolerate more intensive treatment options, such as induction chemo-immunotherapy followed by ARA-C, a high-dose chemotherapy, and autologous stem cell transplantation. BR is a suitable alternative to combination chemotherapies such as R-CHOP and R-CVP. Patients must have a performance status of 0-1.

When used in this indication, bendamustine in combination with rituximab should be given for up to six cycles. Bendamustine should be administered by intravenous infusion at a dose of 90mg/m2 on two days every 28 days, concurrently with Rituximab 375 mg/ sq. m^2 on day 1.

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. The first cycle must be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy.

7 Patient Pathway

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

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 Therapy Dataset.

11 Documents which have informed this Policy

The following documents 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/;
- 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; and
- 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.

12 Date of Review

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

References

Armand P, Redd R et al. A phase II study of rituximab-bendamustine and rituximab-cytarabine for transplant-eligible patients with mantle cell lymphoma. Br J Haematol 2016; 173: 89-95

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

Burke JM, van der Jagt R et al. Differences in quality of life between bendamustine-rituximab and R-CHOP/ R-CVP in patients with previously untreated advanced indolent non-Hodgkin lymphoma or mantle cell lymphoma. Clin Lymphoma, Myeloma & Leukaemia 2016; 16: 182-90

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. http://www.cancerresearchuk.org/health-professional/cancer-statistics

DeWilde S, Woods B et al. Bendamustine-rituximab: a cost-utility analysis in first-line treatment of indolent non-Hodgkin's lymphoma in England and Wales. J Medical Economics 2014; 17: 111-24

European Society for Medical Oncology 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

Flinn IW, van der Jagt R et al. Randomised trial of bendamustine-rituximab or R-CHOP/ R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood 2014; 123: 2944-52

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

National Institute for Health and Care Excellence (NICE) 2015. Bortezomib for previously untreated mantle cell lymphoma NICE technology appraisal guidance [TA370]. Available: https://www.nice.org.uk/guidance/ta370

National Institute for 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/guidance /GID-TAG321/documents/lymphoma-mantle-cell-bendamustine-1st-line-with-rituximab-final-scope2 Accessed 05/09/16

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

Rummel MJ, Niederle N et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013; 381: 1203-10.

Vose JM. Mantle Cell Lymphoma: Update on Diagnosis, Risk-Stratification and Clinical Management. *Am J Hematol* 2015.