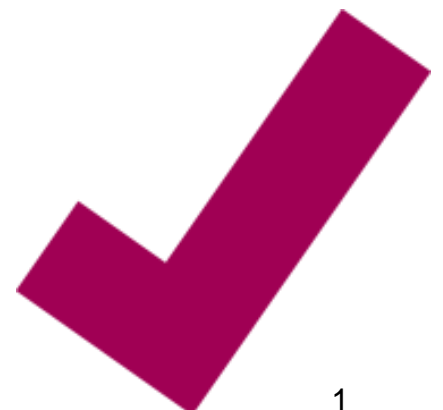


Clinical Commissioning Policy Proposition: Bortezomib for relapsed/refractory mantle cell lymphoma

Reference: NHS England **xxxxx**



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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 relapsed mantle cell lymphoma

Mantle cell lymphoma is a rare form of a type of blood cancer called non-Hodgkin's lymphoma. The condition is more commonly diagnosed in older adults (≥ 60 years) and whilst the condition can affect both males and females, it predominantly affects males.

MCL 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. Typically this leads to the condition affecting lymph nodes and other sites in 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 its symptoms following a period of treatment and improvement. Sometimes patients do not respond to particular chemotherapy treatment, when this happens it is called 'refractory disease'. This policy proposition covers both relapsed and refractory disease.

About current treatments

Chemotherapy is the main treatment option for patients with MCL, though some patients may also receive autologous stem cell transplantation, which is type of high-dose chemotherapy. Treatment of MCL is highly individualised and based on a number of factors, including functional status, prior treatments and response to them, and disease biology.

A number of chemotherapy medicines, which are given in different combinations (or 'regimens'), are available to treat MCL initially, this is called 'first line treatment'. In cases of relapsed MCL, chemotherapy continues to be the main treatment option, however, at present there are no routinely available chemotherapy regimens and autologous stem cell transplantation is generally not recommended.

About the new treatment

Bortezomib belongs to the group of drugs known as proteasome inhibitors, and is a drug that stops cancer cells from growing and causes them to die. It is administered as either a subcutaneous (under the skin) or intravenous (into the vein) injection.

What we have decided

NHS England has carefully reviewed the evidence to treat relapsed and refractory mantle cell lymphoma with bortezomib. We have concluded that there is not enough evidence to make the treatment available at this time.

Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission bortezomib for relapsed and refractory mantle cell lymphoma (MCL).

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 bortezomib for relapsed and refractory mantle cell lymphoma will be not routinely commissioned is planned to be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

2 Proposed Intervention and Clinical Indication

Mantle cell lymphoma 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. Management of relapsed and refractory mantle cell lymphoma requires an individualised treatment approach, incorporating factors such as: functional status, prior treatments and response to them, and disease biology.

Most cases of MCL are initially diagnosed at an advanced-stage of disease and patients 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.

A number of first line chemotherapy treatments are currently available to treat mantle cell lymphoma in the NHS, usually involving rituximab in combination with other drugs. However, there is no consensus on the standard of care and treatment is highly individualised (Cheah, 2016). Whilst there are at present no routinely

available chemotherapy drugs to treat relapsed and refractory disease, a number of chemotherapy drugs can be used. As in the first line setting, there is no agreed standard of care for relapsed MCL.

Bortezomib belongs to the group of drugs known as proteasome inhibitors. It is administered as either a subcutaneous or intravenous injection twice a week for the first two weeks of every three week cycle. Commonly reported adverse reactions during treatment with bortezomib are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.

Bortezomib is not licensed for treatment of relapsed mantle cell lymphoma, and therefore will not be considered for NICE appraisal.

3 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

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

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

Overall survival (OS) – is 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

4 Aims and Objectives

This policy proposition considered: Bortezomib for treatment of relapsed and refractory mantle cell lymphoma (MCL).

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

- What is the activity of Bortezomib in relapsed MCL?
- What is its efficacy, safety and toxicity profile?
- What is its optimal place of treatment?
- What is its relative clinical effectiveness and cost effectiveness against other alternatives in this setting?

5 Epidemiology and Needs Assessment

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

The estimated number of cases of MCL in the United Kingdom was 510 (Haematological Malignancy Research Network (HMRN) data, 2004-2014). Based on CDF applications, it is estimated that approximately 250 cases of relapsed MCL would be eligible for treatment with bortezomib.

6 Evidence Base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

Rationale for policy proposition

Relevant research studies highlighted by the evidence review of bortezomib in the relapsed / refractory mantle cell lymphoma (MCL) setting are all observational with heterogeneous results and variation in outcomes such as overall response rates (ORR). The predominant response to treatment appeared to be partial response/stable disease, associated with modest progression free survival (PFS) durations and a significant haematological and non-haematological toxicity profile e.g. paraesthesias/peripheral neuropathy similar to cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)-like regimens and also oedema. Whilst bortezomib appears to be an active drug (and in combination with chemotherapy) in this group of patients, its degree of effectiveness and direct comparison with other possible treatments cannot be accurately and reliably established. Further robust comparative evidence of non-inferiority/superiority against existing treatments in the relapsed setting will be required for policy recommendation. It is expected that there may be renewed interest in its use combined with chemotherapy once the drug becomes generic and cost effectiveness increases (Furtado 2014).

Five papers matching the Population Intervention Comparator and Outcomes (PICO) document were identified, which reported the results of four trials of bortezomib for treatment of MCL (Fisher et al., 2006, Goy et al., 2009, O'Connor et al., 2009, Belch et al., 2007, Zinzani et al., 2013). All of the trials were early-phase, single-arm studies, which ranged in size from 30 to 155 participants. There was no randomisation or blinding in any trial, and no comparison with any other treatment for MCL. No cost-effectiveness studies or evidence on health-related quality of life were located.

Patients were adults with relapsed or refractory MCL despite ≥ 1 prior treatment. Bortezomib was administered at a dose of 1.3 mg/m^2 on days 1, 4, 8 & 11 of a 21 day cycle, but the number of cycles varied between trials.

Outcomes assessed included overall survival (OS), progression-free survival (PFS), treatment response, disease progression and adverse events. Treatment response or remission was the most common measure of efficacy reported. All trials used

definitions of treatment response as set out by the International Workshop for Response Criteria (Cheson et al., 1999). These criteria require several conditions to be met for each category of complete remission (CR), unconfirmed complete remission (CRu), partial response (PR), stable disease (SD) and progressive disease (PD). For example, CR requires resolution of symptoms, normalisation of blood and biochemical markers, reduction in lymph node masses, resolution of any spleen enlargement, and normalised bone marrow histology. Full definitions are listed in the appendix, below.

Overall response rate

The main efficacy outcome of all four trials was overall response rate (ORR), a composite of CR, CRu and PR (see appendix for definitions of CR, CRu and PR). ORR was 32% (95% CI 24 – 40) in the updated report of PINNACLE, which was the largest trial and also had the longest reported follow-up. (Goy et al., 2009). The other three studies all reported ORR in the region of 50%, however these are smaller trials and generally of lower quality. (Belch et al., 2007, O'Connor et al., 2009, Zinzani et al., 2013).

Complete remission of disease, either confirmed or unconfirmed, was not common. CR was reported for 6% of patients in the updated PINNACLE trial, while CR or CRu was reported for 8%. CRu is intended to designate patients with curable histology's who have a large mass prior to therapy, and for whom treatment eradicated all but the single persistent mass, which had shrunk by $\geq 75\%$. This acknowledges that in most cases the remaining mass represents scar tissue or fibrosis. It should not be applied to patients with multiple masses which have decreased by 75% in total; this is more correctly a partial response (Cheson, 2008). CRu can also apply to patients with indeterminate bone marrow biopsy post-treatment, and should not be applied to patients who have not had repeated biopsy.

PR was the most common response type in all of the published trials. It was not specifically reported by Goy et al, but given an ORR (CR + CRu + PR) of 32% and reported CR+CRu of 8% (95% CI 4-14), it can be inferred that the majority

of treatment responses were defined as partial. The remaining trials all reported PR in 25-40% of patients.

Stable disease (SD) is also an important outcome; while not as desirable as full or partial treatment response, the absence of disease progression in this aggressive disease is still positive. SD was reported by three of the published trials (Fisher et al., 2006, Belch et al., 2007, O'Connor et al., 2009), and was 30-40% in each case. One trial (n=15) reported that stable disease was achieved by 6 patients (40%) and maintained for a median of 7.7 months (range 1.2 to 26.1).

Progressive disease (PD) despite treatment is the least desirable outcome, but unfortunately still common in the published trials. Fisher et al (n=155) reported PD in 26% of patients (95% CI), while O'Connor et al (n=40) reported the incidence as 8%.

Time to event outcomes

Time to event outcomes such as progression-free survival (PFS), duration of response (DOR) and time to next therapy (TTNT) are important in MCL, since they give information on how long a patient can expect to remain relatively well. DOR was the most commonly reported of these outcomes. The PINNACLE study found median DOR to be 9.2 months (95% CI 5.9-13.8). One other study found that DOR varied with response type (Belch et al., 2007). One patient had CR with response duration of 24 months. Six patients had PR and a median DOR of 9.8 months (range 2.1 to 25.1) and an additional six patients had stable disease and a DOR of 7.7 months (range 1.2 to 26.1). It should be noted that these data should be interpreted with caution, due to the very small sample size in this trial (n=15).

Progression-free survival was reported by two trials. In the PINNACLE study median PFS was 6.5 months (95% CI 4.0-7.2), while O'Connor et al reported a very similar PFS of 6.2 months in their smaller trial (n=40).

PINNACLE also reported several other time-to-event outcomes which were not

addressed by any other trial:

- Time to first response – median 1.4 months
- Time to progression – median 6.7 months (95% CI 4.0 – 7.3)
- Time to next therapy – median 7.4 months (95% CI 5.6 – 9.3)
- Overall survival – median 23.5 months (95% CI 20.3 – 27.9)

Safety

Safety events were reported in all four trials. The largest, PINNACLE, reported that 98% of patients experienced at least one adverse effect (AE) during treatment and 70% of patients experienced at least one AE of grade 3 (moderate) or higher. Commonly reported toxicities of grade ≥ 3 included peripheral neuropathy (13%), fatigue (12%) and thrombocytopenia (11%). In total 41 patients (26%) discontinued treatment due to an intolerable AE, most commonly peripheral neuropathy (10%) or fatigue (6%).

The updated PINNACLE data reported by Goy et al suggested that the median time to onset of peripheral neuropathy was 4 cycles (12 weeks). It also reported that 67% of patients experienced lymphopenia, and 34% experienced lymphopenia of grade ≥ 3 . There were four deaths considered to be treatment-related; three due to non-neutropenic sepsis, and one due to respiratory failure.

AEs reported by the other trials were in line with the pattern described above, with the most commonly reported events including fatigue, peripheral neuropathies, and haematological toxicities. One trial reported several serious AEs related to oedema or fluid retention, all of which occurred in patients known to have oedema or effusions at baseline. Oedema is a known common AE of bortezomib, and angioedema, lymphoedema, pulmonary oedema and brain oedema have all been reported (Janssen-Cilag Ltd).

In summary, the pattern of AEs reported in these trials is in line with the known AE profile of bortezomib. Given the lack of comparative trial data and the symptoms commonly reported with MCL, it is difficult to determine what proportion of AEs is attributable to bortezomib therapy, and what proportion may

be due to symptomatic disease.

Conclusion

The published evidence on bortezomib for treatment of relapsed/refractory MCL consists of several early-phase, non-randomised, non-comparative trials of variable quality. The literature appears to show that bortezomib is active to some extent in the treatment of relapsed mantle cell lymphoma. However, the published trials are very limited and there are no randomised controlled trials comparing bortezomib with other drugs or with standard care. It is therefore not clear whether bortezomib is any more or less effective than other drugs currently used for the treatment of relapsed/refractory disease. Similarly, adverse effects were common, but a lack of comparisons with other drugs or standard care means that it is not clear whether bortezomib is more or less safe than other regimens used in this indication.

In summary, while bortezomib may be a useful treatment option for relapsed/refractory MCL, there is insufficient evidence to make clear recommendations on factors such as patients most likely to benefit from treatment, or combinations with other drugs.

7 Proposed Criteria for Commissioning

Not applicable.

9 Proposed Patient Pathway

Not applicable.

10 Proposed Governance Arrangements

Not applicable.

11 Proposed Mechanism for Funding

Not applicable.

12 Proposed Audit Requirements

Not applicable.

13 Documents That Have Informed This Policy Proposition

- National Cancer Drug Fund (CDF): <https://www.england.nhs.uk/cancer/cdf/>
- CDF Drugs Fund List: <https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/>
- JANSSEN-CILAG LTD Summary of Product Characteristics Velcade 3.5 mg powder for solution for injection. Date of revision of the text 25/01/2016.
<https://www.medicines.org.uk/emc/medicine/17109>

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.

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