Clinical Commissioning Policy: Bortezomib for relapsed/refractory mantle cell lymphoma (all ages)

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Clinical Commissioning Policy: Bortezomib for relapsed/refractory mantle cell lymphoma (all ages)

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Policy Statement

NHS England will not routinely commission bortezomib for relapsed/refractory 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.

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 (MCL) 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 develops when the body makes abnormal white cells – these are cells in the lymph nodes and blood. The abnormal white cells don't work properly and grow in an uncontrolled way. Typically this leads to the condition affecting many 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 and its symptoms following a period of treatment and improvement. Sometimes patients do not respond to a particular chemotherapy treatment and when this happens it is called refractory disease.

This policy covers both relapsed and refractory disease, which means that each patient has had at least one prior treatment.

About current treatments

The treatment of MCL is highly individualised and based on a number of factors, including disease biology, overall patient health and fitness (functional status). Chemotherapy is the mainstay treatment for patients with MCL.

The preferred first line treatment for MCL is an intensive course of chemo-immunotherapy, usually followed by a very intensive programme of high-dose chemotherapy, and autologous stem-cell transplantation (autologous meaning donor and recipient are the same person). However, this treatment is only tolerated in patients with very good overall health and fitness.

For patients that are unable to tolerate such an intensive sequence of treatments, a range of alternative combination chemotherapy, where two or more medicines are given in the same treatment cycle, treatments are available. Each combination chemotherapy treatment varies in its side-effects, contraindications and tolerability.

In cases of relapsed and refractory MCL, treatment remains highly individualised with treatment choice also determined by each patient’s prior treatment(s), together with their response to prior treatment(s). Dependent on previous treatments, the chemotherapy options currently available include all those that are routinely available

in the first line setting. Autologous stem cell transplantation is generally not recommended for the treatment of relapsed and refractory MCL.

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 through 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/refractory mantle cell lymphoma with bortezomib. We have concluded that there is not enough evidence to make the treatment available at this time.

1 Introduction

MCL is rare and is one of the most challenging haematological malignancies, owing to an aggressive disease course, a high rate of relapse, and lack of standard of care. The clinical management of MCL is highly individualised and based on a number of factors, including disease biology, overall patient health and fitness (functional status). As a result, there is no single standard of care. In cases of relapsed and refractory MCL, both prior treatment(s) and treatment response are also important factors in determining the best treatment options.

Most cases of MCL are initially diagnosed at an advanced-stage of disease and patients are usually symptomatic at presentation. Common clinical 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.

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 routinely available treatment options in the first line setting for less fit patients include rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), cyclophosphamide, doxorubicin and, prednisone (VR-CAP), and rituximab, cyclophosphamide, vincristine, prednisone (R-CVP).

As with the management of MCL in the first line setting, at present, there is no single standard of care for the treatment of relapsed and refractory MCL and treatment remains highly individualised and determined in part by the prior treatment(s) that a patient has had together with their response to treatment(s). The available options, subject to prior treatment(s), include all of the routinely available regimens in the first line setting. Autologous stem cell transplantation is generally not recommended for the treatment of relapsed and refractory MCL.

Bortezomib, which is not licensed to treat relapsed and refractory MCL, 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.

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.

Complete response – this means that there is no detectable disease following a course of treatment.

Complete response unconfirmed (Cru) – is intended to designate patients with curable histologies that had a large mass prior to therapy, and for whom treatment eradicated all but the single persistent mass, which had shrunk by ≥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.

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

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

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

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.

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

3 Aims and Objectives

This policy considers: bortezomib for treatment of relapsed and refractory MCL (all ages).

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?

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 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).

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). However, there is no reliable source of data in relation to the number of relapsed and refractory cases. Because of this, the Cancer Drugs Fund (CDF) activity data is the best source for the needs assessment. Therefore, based on CDF data, it is estimated that approximately 250 cases of relapsed and refractory MCL would be eligible for treatment with bortezomib, were the treatment to be commissioned.

5 Evidence Base

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

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.

Overall response rate

The main efficacy outcome of all four trials was overall response rate (ORR), a composite of CR, CRu and PR. ORR was 32% (95% CI 24 – 40) in the updated report of PINNACLE (2009), 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 ≥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 and 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.

While bortezomib may be a useful treatment option for relapsed and 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.

6 Documents which have informed this Policy

- 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

7 Date of Review

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

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