Clinical Commissioning Policy: Bendamustine for relapsed multiple myeloma (all ages)

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Executive Summary

Policy Statement

NHS England will not routinely commission bendamustine for the treatment of relapsed multiple myeloma.

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 multiple myeloma

Multiple myeloma is an uncommon form of blood cancer which affects a type of white blood cell called a plasma cells. The condition develops when abnormal plasma cells build up in the bone marrow and release a type of protein into the blood called paraprotein. Multiple myeloma can develop at any age, but it is most common in

males and adults aged over 60 years, with the majority of cases diagnosed at around the age of 70 years.

Plasma cells play an important role in helping to fight infection by making antibodies that recognise and attack germs. In the early stages, the condition may not cause any symptoms and is often only suspected or diagnosed after a routine blood or urine test. However, it will eventually cause a wide range of problems, including a persistent dull ache or specific areas of tenderness in bones, weak bones that break or fracture easily, tiredness, weakness, shortness of breath (caused by anaemia) and repeated infections.

Multiple myeloma is an incurable cancer, however, treatment can control the disease, relieving symptoms and complications and prolonging life. Most people with the condition will usually experience multiple episides of treatment, remission and relapse. This policy relates to relapsed multiple myeloma, this means that at least one prior treatment will have been given.

About current treatments

Chemotherapy is the main treatment for multiple myeloma and there are a number of different chemotherapy medicines available, either given individually or in combination. Treatments are usually given sequentially and are continued until either the disease progresses or the side-effects of the chemotherapy treatment can no longer be tolerated. Stem cell transplantation may also be considered, however, the treatment is very intensive and requires a good level of fitness.

About the new treatment

Bendamustine is a chemotherapy medicine which has a different side-effect and toxicity profile to other chemotherapy medicines. It belongs 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.

What we have decided

NHS England has carefully reviewed the evidence to treat relapsed multiple myeloma with bendamustine. It has been concluded that there is not sufficient evidence to consider making the treatment routinely available at this time.

1 Introduction

Multiple myeloma (MM) is a malignant proliferation of plasma cells which are present in the bone marrow and circulation. It is an incurable disease and the main aims of therapy are to prolong survival and maintain quality of life by controlling the disease and relieving symptoms.

Clinical complications related to MM include bone pain, bony fractures, spinal collapse and compression, renal failure, hypercalcemia, infection, bone marrow failure, neuropathy, retinal bleeds, heart failure and cerebral ischaemia.

Current treatments recommended by the National Insitute of Health and Care Excellence (NICE) for use in the first line setting (where patients that are not suitable for high dose chemotherapy and stem cell transplantation) include thalidomide and bortezomib in combination with steroid and alkylating agents.

For relapsed patients NICE has recommended:

- bortezomib at first relapse (NICE TA 129, 2007);
- carfilzomib in relapsed patients who have had one previous non-Bortezomib therapy (NICE TA 457, 2017);
- lenalidomide (at ≥2 relapses) (NICE TA 171, 2014);
- panobinostat (with bortezomib and dexamethasone) in patients who have had at least two prior regimens (NICE NG35, 2016); and
- pomalidomide as an option for treating MM in adults at third or subsequent relapse (NICE TA427, 2017).

Allogeneic and autologous stem cell transplantation are also options for people that are fit enough for intensive treatment, either in the first line or relapsed settings.

Chemotherapy treatments for MM are usually given sequentially and continued until either disease progression or intolerable toxicity or patient choice to discontinue treatment. Although MM is incurable, there are some patients that exhaust the available treatment options, but who are still fit enough to benefit from further treatment.

Proposed intervention

Bendamustine is an alkylating anti-tumour agent and is administered by intravenous infusion, over 30-60 minutes on days 1 and 2, every 4 weeks for a maximum of 6 cycles.

Bendamustine is not licensed for the treatment of relapsed MM. However, bendamustine is licensed for the first line treatment of MM in patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at the time of diagnosis precluding the use of thalidomide or bortezomib containing treatment.

2 Definitions

Allogenic stem cell transplantation – stem cells are collected from a matching donor and transplanted into the patient to restore the patient's immune system following intensive treatment. Unlike autologous stem cell transplantation, no cells are taken from a patient's own body.

Autologous stem cell transplantation – 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.

Bendamustine (B) - a chemotherapy drug. It is used to treat chronic lymphocytic leukaemia (CLL), non-Hodgkin lymphoma (NHL) and myeloma.

Multiple Myeloma (MM) – a type of bone marrow cancer that affects the plasma cells. These cells multiply abnormally and cease to fulfil their usual function, instead producing only one type of antibody known as a paraprotein.

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 – is a recognised system developed by the World Health Organisation and other groups to describe the general health 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 – this term refers to a disease which has recurred after treatment and a period of remission

3 Aims and Objectives

This policy aims to: consider the use of bendamustine in the treatment of relapsed multiple myeloma.

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

- The evidence on clinical effectiveness of using bendamustine +/- steroid compared with best supportive care for individuals with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant;
- The evidence relating to the safety of bendamustine +/- steroid compared with best supportive care for individuals with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant;
- The evidence on the cost effectiveness of bendamustine +/- steroid compared with best supportive care for individuals with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant;
- If the evidence of clinical and cost-effectiveness identifies any subgroups of patients with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant who would gain greater benefit from using bendamustine +/- steroid compared with best supportive care.

4 Epidemiology and Needs Assessment

There were 5,540 new cases of MM in the UK in 2015 and 3,079 deaths in 2016. Almost half (45%) of new cases were in people aged 75 years and over.

Over the last decade in the UK myeloma incidence rates for males and females combined increased by 17%. In males rates increased by 18%, and in females rates increased by 14%.

The incidence rate is projected to increase by 11% in the UK between 2014 and 2035 to 12 per 100,000 population. This includes a larger increase for males than for females.Based on this, the annual number of new cases of MM is expected to be 8,888 in the UK in 2035.

A third of patients survive MM for ten years or more and 50% survive for five years or more. Survival from MM is improving and over the last 40 years has quadrupled in the UK (Cancer Research UK 2018).

Based on CDF utilisation data from 2017/18, it is estimated that 118 patients would be eligible for this treatment.

5 Evidence Base

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

Summary of Evidence Review

The evidence review found four uncontrolled studies. These included a total of 272 patients who had relapsing multiple myeloma that had been heavily pre-treated. All four studies were retrospective using information retrieved from case notes. The proportion who were treated with concomitant steroids ranged from 38% to 100%. Outcomes reported include overall survival, progression free and event free survival, response rates and toxicity.

1. **What is the evidence on clinical effectiveness of using bendamustine +/- steroid compared with best supportive care for individuals with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant?**
    - **Overall survival (OS):** Four uncontrolled studies reported median overall survival between 5.5 months and 17 months. The lowest of these (Kim et al 2016) (n=65, OS 5.5 months, 95% confidence interval (CI) 3.5 to 7.5) showed the majority of patients experiencing early progression or treatment related adverse events. Damaj et al (2012) showed a median OS of 12.4 months (n=110, no CI provided). Stohr et al (2015) showed a median OS of 17 months (n=58, CI not provided), as did Michael et al (2010) (n=39).
    - **Progression free survival (PFS) / Event free survival (EFS):** Kim at al (2016) showed a median PFS of 3.1 months (95% CI 2.4 to 3.8), the majority of patients showing early progression. In the Damaj et al (2012) study the median PFS was 9.3 months and 66% of patients who responded to bendamustine remained in response for more than six months. Michael at al (2010) showed a median 7 months EFS, as did Stohr et al (2015) (CIs not provided).
    - **Overall response rate (ORR):**
      All four studies described ORR. The proportion of patients showing a response to bendamustine varied from 30% (Damaj et al 2012) to 59% (Stohr et al 2015). The proportion showing a complete response varied from 0% (Stohr et al 2015 and Michael et al 2010) to 2% (Damaj et al 2012 and Kim et al 2016), and the proportion showing a partial response varied from 20% (Stohr et al 2015) to 36% (Michael et al 2010).

2. **What is the evidence relating to the safety of bendamustine +/- steroid compared with best supportive care for individuals with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant?**

The extent of reporting of adverse events varied in these uncontrolled studies. Three studies reported toxicity related adverse events. Most frequently reported adverse effects were haematological. Severe (grade 3/4) anaemia was experienced by

between 10% (Michael et al 2010) and 71% (Stohr et al 2015). Severe neutropenia/leucopenia was experienced by between 16% (Stohr et al 2015) and 65% (Kim et al 2016), and severe thrombocytopenia was experienced by between 21% (Stohr et al 2015) and 46% (Kim et al 2016). Fifteen percent experienced severe infection in the Michael et al study (2010). There were five deaths from sepsis and five deaths from pneumonia in the Kim et al study (2016) (n=65).

3. **What is the evidence on the cost effectiveness of bendamustine +/- steroid compared with best supportive care for individuals with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant?**

No studies assessing the cost effectiveness of bendamustine with or without steroids for patients with refractory or relapsed multiple myeloma were identified.

4. **Does the evidence of clinical and cost-effectiveness identify any subgroups of patients with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant who would gain greater benefit from using bendamustine +/- steroid compared with best supportive care?**

Where a comparison was made between outcomes using bendamustine doses above and below 120mg/m2, no significant differences were found. The only significant difference found when comparing the use of concomitant steroids with treatment with bendamustine alone, was a higher rate of infections in patients who received steroids (33% vs 0%, p=0.04, n=39) (Michael et al 2010).

Regarding potentially prognostic subgroups, although not surprisingly some associations were found between relevant prognostic variables and OS or EFS, without a comparator group that did not receive bendamustine, it is not possible to assess whether there were any subgroup differences relating to the effectiveness or safety of bendamustine treatment.

Conclusion

Overall, the evidence base is limited to uncontrolled, retrospective studies, which are at risk of selection bias and which do not allow a comparison of outcomes with outcomes for patients treated with best supportive care without bendamustine. The limitations of the evidence base limit the strength of conclusions that can be drawn.

Thus although there is some weak evidence that bendamustine might help to slow progression for a short period of time in some patients, the types of studies found mean that it is not possible to have any level of confidence about either the effectiveness or the toxicity of bendamustine in this group of patients.

6 Documents which have informed this Policy

This documents that informed this policy include:

- National Cancer Drugs Fund (CDF) 2016. https://www.nice.org.uk/guidance/NG35
- Evidence Review, NHS England, Bendamustine for relapsed multiple myeloma. updates and replaces

7 Date of Review

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

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