MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
05 02 2019

Agenda Item No	02.1
National Programme	Cancer
Clinical Reference Group	Chemotherapy
URN	1608

Title
Bendamustine for relapsed multiple myeloma (all ages)

Actions Requested	1. Support the adoption of the policy proposition.
	2. Recommend its approval as an IYSD.

Proposition
The policy proposition recommends that bendamustine, an off-label chemotherapy drug for this indication, should not be routinely available for patients with relapsed multiple myeloma. In developing the policy proposition, an evidence review was undertaken. This found a lack of evidence of net benefit to warrant making the treatment routinely available. At present, there is a wide range of routinely commissioned alternative treatments for this condition; if used to treat this indication, bendamustine would be a last line treatment and as an alternative to best supportive care / palliative care.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition was changed from a routine commissioning to a not for routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Cancer Programme confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.

3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

No	*Metric*	*Summary from evidence review*
1.	Survival	Overall Survival (OS) is a measure of how long following treatment patients are expected to live. It is not restricted to deaths that are disease-related; deaths of any cause are accounted for. The best quality study for this outcome measure (Stohr et al 2015) found a median OS of 17 months (n=58). No evidence was found for an association between the dose of bendamustine used (above or below 120mg/m2) and median overall survival (15 months vs 16.7 months) (p=0.58). There was also no significant difference observed in median OS when bendamustine was used alone (OS 17 months) compared to its use in conjunction with steroids (OS 13.5 months) (p=0.85). This result suggests that on average patients with relapsed or refractory multiple myeloma survived 17 months following commencement of bendamustine therapy. Because the study had no comparator group of patients receiving best supportive care without bendamustine, we do not know whether bendamustine is more or less effective in terms of overall survival than best supportive care. Additionally, the study had a relatively small sample size and was retrospective, with the possibility of bias in relation to which patients were and were not included.
2.	Progression free survival	Progression free survival (PFS) is the time between the first treatment and one of the following: progressive disease, relapse after response or death from any cause. PFS and event free survival (EFS) were both defined in the studies

		reviewed as the time from first bendamustine treatment to disease progression or death or relapse. The best quality study for this outcome measure (Stohr et al 2015) found a median EFS to be 7 months (n=58), and found no difference in EFS when bendamustine was used alone compared to its use in combination with steroids (EFS 7 months for both, p=0.6). Although reporting was unclear, Cox regression analysis suggested an association between EFS and calcium level (p=0.02, hazard ratio (HR) 1.6) and prior Autologous Stem Cell Transplantation (p=0.03, HR 3.9). This suggests that on average patients with relapsed or refractory multiple myeloma survive for 7 months following first bendamustine treatment before progression of disease, relapse or death, and that factors such as calcium level and prior treatment may affect survival. The implications of the results of the study are not entirely clear as there is no comparison made with patients who did not have the bendamustine treatment, and we do not know how long the latter group might survive without measurable disease progression. This is an uncontrolled retrospective study. The design of the study, i.e. looking back at case notes, introduces the possibility of selection bias in the selection of patients for the study and in the study population outcome information obtained, as it is possible that not all the relevant patients or information are included in the study.
3.	Mobility	Not directly assessed
4.	Self-care	Not directly assessed
5.	Usual activities	Not directly assessed
6.	Pain	Not directly assessed
7.	Anxiety / Depression	Not directly assessed
8.	Replacement of more toxic treatment	Not directly assessed
9.	Dependency on care giver /	Not directly assessed

	supporting independence	
10.	Safety	An adverse event (AE) is any untoward medical occurrence in a patient who has been given a treatment which does not necessarily have a causal relationship with this treatment. In the studies reviewed, adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, in which Grade 1 refers to mild AE, Grade 2 moderate AE, Grade 3 severe AE, Grade 4 life-threatening or disabling AE and Grade 5 refers to death related to AE. The best quality study for this outcome measure, Stohr et al (2015), found 71% of patients (n=41) experienced severe (grade 3 or 4) anaemia, 16% (n=9) severe leucopenia and 21% (n=12) severe thrombocytopenia. However, it is reported that of the 30 patients with grade 4 anaemia, this only developed during or after bendamustine treatment in 6 patients (ie 24 had grade 4 anaemia prior to bendamustine treatment). Bendamustine dosage and whether patients had concomitant steroids did not influence the severity of the anaemia (p values not provided). A small number of patients suffered a mild allergy to bendamustine. Other side effects included mild fatigue, nausea, and vomiting. This suggests that severe (grade 3) and life-threatening (grade 4) levels of haematological toxicity are not uncommon in patients who have had bendamustine treatment for late stage multiple myeloma. This is an uncontrolled retrospective study. The lack of comparator in the study limits the strength of conclusions that can be drawn because, for example, many of the reported side effects may have been due to the illness itself and without a comparator group, we do not know how many were due to the bendamustine treatment. This is indicated, for example, by the relatively large proportion of patients that had grade 4 anaemia prior to bendamustine treatment. Additionally, the retrospective design of the study introduces the possibility of bias in the selection of patients for the study and in the outcome information obtained, as it is possible that not all the relevant patients or information were included.
11.	Delivery of intervention	Not directly assessed

No	Metric	Summary from evidence review

1.	Overall Response rate (ORR)	The overall response rate (ORR) to bendamustine is the proportion of patients with either a complete response (CR) or partial response (PR) following treatment. CR is when there is no detectable disease following a course of treatment. It does not always mean the disease has been cured but is the best result that can be reported and means that there is no evidence of disease. PR is a decrease in tumour size or the amount of cancer detected in the body following treatment. The best quality study for this outcome measure, Stohr et al (2015), found an ORR of 59% among 58 patients with relapsed or refractory multiple myeloma, of whom 44 could be evaluated for response. No complete remission was observed. 20% (9 patients) had a partial response and a further 39% (17 patients) had a minimal response. No significant difference was found in ORR when groups who received bendamustine with and without a steroid were compared (59% in both groups), nor when a dose of bendamustine above and below 120mg/m^2 were compared (53% vs 64%) (p=1). This suggests that 59% of patients had some response to bendamustine treatment. However the response may have been small and short-lived. This is an uncontrolled retrospective study of a relatively small sample size (n=58). The lack of comparator in the study limits the strength of conclusions that can be drawn. Additionally, the impact, if any, of a minimal response on patients' quality of life or overall survival is not known. The retrospective design of the study introduces the possibility of bias in the selection of patients for the study and in the outcome information obtained, as it is possible that not all the relevant patients or information were included.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
This policy does not approve bendamustine for the treatment of patients with relapsed multiple myeloma. This would be an off label use of bendamustine. It is excluded from tariff.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Cancer PoC Board on 6th December 2018.