Clinical Commissioning Policy Statement:

Bendamustine for relapsed/refractory classical Hodgkin lymphoma (all ages) [1828] [Publication reference: 200701P]

Commissioning position

Summary

Bendamustine is not recommended as a treatment option for relapsed/refractory classical Hodgkin lymphoma.

Information about bendamustine

The intervention

Bendamustine is a chemotherapy medicine which interferes with the DNA in cancer cells to prevent their growth. It has demonstrated clinical efficacy in several lymphoid malignancies, however, its use in the treatment of relapsed/refractory classical Hodgkin lymphoma is outside the terms of its licence, i.e., it is off-label.

Committee discussion

See the committee papers (link) for full details of the evidence.

The condition

Classical Hodgkin lymphoma is a rare blood cancer in which white blood cells start to grow in an uncontrolled way and begin to collect in certain parts of the lymphatic system, such as the lymph nodes. The affected white blood cells lose their infection-fighting properties, making the body more vulnerable to infection. The condition can occur at any age but is more common in people aged between 15 and 30 years and those over 55 years (Cancer Research UK, 2018); it is also more common in males than females.

Current treatments

The main treatment is chemotherapy, however, some people will also have radiotherapy and/or steroid medication. In most cases, people respond well to treatment with a 5-year progression free survival rate of 75% (Zinzani et al, 2013). However, in a small number of cases, the condition doesn't respond to treatment (refractory disease) or returns following treatment (relapsed disease). In these cases, further treatment with chemotherapy is usually offered, though some people may instead undergo a stem cell transplant to replace cancer cells with healthy cells. It is estimated that 5 – 10% of people with CHL will have refractory disease and up to 30% will suffer from disease relapse (Zinzani et al, 2013).

Comparators

There have been no studies with treatment comparators.

Clinical trial evidence

NHS England has considered the evidence submitted as part of a Preliminary Policy Proposal to establish the Clinical Commissioning Policy Statementand have concluded that there is not enough evidence to make bendamustine available relapsed/refractory classical Hodgkin lymphoma the treatment available at this time. The evidence includes up to three of the most clinically impactful publications, identified using a literature search strategy defined by the clinical lead. These publications are summarised below.

Zinzani et al (2013) described two cases in a letter. The first was a 21-year-old male with stage IIB supradiaphragmatic Hodgkins lymphoma (HL) who was treated with six cycles of adriamycin (doxorubicin), bleomycin, vinblastine and dacarbazine (ABVD) followed by autologous stem cell transplantation (ASCT) due to primary refractory disease and local mediastinal radiotherapy, obtaining a partial response (PR). After 32 months, the patient was then treated with bleomycin and vinblastine (BV), obtaining a complete response (CR) after the first three cycles. BV was discontinued after 10 cycles due to neurological toxicity. After 4 months from the last BV course, the patient presented with a mediastinal relapse and was treated with bendamustine. Four cycles were completed obtaining a PR. Three months after the last course of bendamustine, the patient underwent an allogeneic transplantation (matched unrelated donor) in PR status. The patient was in continuous CR 6 months after transplantation.

The second case was a 32-year-old male with stage IIB HL who was treated with six cycles of ABVD. The patient then underwent ASCT for primary refractory disease, obtaining a CR. After 9 months the patient presented with a mediastinal relapse and was treated with BV for a total of 12 cycles: the patient achieved a PR after three courses. Evaluation after 12 BV courses showed a clear lymphoma recurrence and the patient received 6 cycles of bendamustine. Evaluation after four and six cycles showed a markedly progressive lymphoma reduction consistent with a PR if compared with the basal evaluation before bendamustine. There was no available donor for allogeneic transplantation and the patient suffered disease progression after 6 months.

Howell et al (2016) reported in a letter on the treatment of 10 consecutive patients with relapsed and/or refractory HL over 3 years. The average age was 26 years (range 19–40). All were heavily pre-treated (median 4 prior lines). First-line therapy was ABVD (n = 8), ChlVPP (chlorambucil, vinblastine, procarbazine prednisone; n = 1) or ChlVPP/EVA (chlorambucil, vinblastine, procarbazine prednisone/ etoposide, vincristine doxorubicin; n = 1). All but one patient received platinum-based salvage treatment at first relapse and BV in lines 3–6. One patient failed both BV and nivolumab.

All 10 patients responded to a median of three cycles (range 2–6), including eight complete and two partial metabolic remissions. Five patients proceeded to high dose therapy consolidation (four alloSCT, one ASCT) immediately after bendamustine salvage and one remained waiting. Two did not proceed because of donor unavailability or early disease progression. A further two responding patients did not initially undergo HDT by patient choice or inadequate lung function due to transient drug-related pneumonitis; both subsequently underwent alloSCT at a later date after successful re-induction with further treatment. At the time of writing, median progression free survival for all patients was 7 months (2–35.8 months). Six patients were alive including five without lymphoma; four died (three of lymphoma, one due to complications of alloSCT). There were no treatment-related deaths. All grade 3/4 toxicities were haematological, including grade 3/4 neutropenia in 50% of cases and grade 3/4 thrombocytopenia in 40% of cases. There were no neutropenic sepsis or significant bleeding events.

There is very limited evidence about the effects of using bendamustine for relapsed/refractory classical Hodgkin lymphoma. It is not possible to have any level of confidence about either the effectiveness or the toxicity of bendamustine in this group of patients.

Adverse events

There are no overriding patient safety or other clinical issues that require an immediate clinical commissioning position to be implemented. The use of bendamustine for the treatment of relapsed/refractory classical Hodgkin lymphoma is outside the terms of its licence.

Implementation

Criteria

Not applicable.

Effective from

July 2020.

Recommendations for data collection

Not applicable.

Mechanism for funding

Not applicable.

Policy review date

This is a policy statement, which means that the full process of policy production has been abridged: a full independent evidence review has not been conducted; and public consultation has not been undertaken. If a review is needed due to a new evidence base then a new Provisional Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Links to other policies

Not applicable.

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.

References

Cancer Research UK. 2018. *Hodgkin lymphoma incidence statistics*, CRUK London. Available at:- https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma/incidence [Accessed 23rd August 2018].

Howell M, Gibb A, Radford J, Linton K. 2016. Bendamustine can be a bridge to allogenic transplantation in relapsed Hodgkin Lymphoma refractory to brentuximab vedotin. *British Journal of Haematology* 179: 838-857

Zinzani P, Derenzini E, Pellegrini C, Celli M, Brocolli A, Argnani L. 2013. Bendamustine efficacy in Hodgkin lymphoma patients relapsed / refractory to brentuximab vedotin. *British Journal of Haematology* 163: 674-687