NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Bendamustine in combination with rituximab for the first-line treatment of low-grade non-Hodgkin's lymphoma

Draft scope (Pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indication for the first-line treatment of people with advanced low-grade non-Hodgkin's lymphoma.

Background

Lymphomas are cancers of the lymphatic system, which is a part of the body's immune system. Traditionally, lymphomas are divided into Hodgkin's disease (now known as Hodgkin's lymphoma) and non-Hodgkin's lymphoma (NHL). Non-Hodgkin's lymphomas are a diverse group of conditions which are categorised according to the cell type affected (B-cell or T-cell), as well as the clinical features and rate of progression of the disease. Follicular lymphoma is a common type of non Hodgkin's lymphoma accounting for approximately 30% of non Hodgkin's lymphomas.

Lymphomas are graded according to the rate at which the abnormal lymphocyte cells divide. They are termed 'high-grade' (or aggressive) when they divide quickly and 'low-grade' (or indolent) when they divide slowly. Low-grade lymphomas tend to affect older people. Precise identification of the form of lymphoma and accurate staging is crucial both for choosing the optimum form of treatment and for monitoring disease progression. The Ann Arbor staging system is the most common system for classifying NHL, with four groups ranging from stage I (better prognosis) to stage IV (worse prognosis).

Approximately 9703 people were diagnosed with NHL in England and Wales in 2007 and 3978 people died of NHL in 2008. Survival rates for NHL decrease significantly with age with rates decreasing sharply in people over 50 years, and more than 70% of NHLs are diagnosed in people over 60 years. The median survival for people with follicular lymphoma is in excess of 10 years.

The clinical presentation, rate of disease progression and patterns of treatment vary widely. Localised disease is relatively rare. Most people will have stage III or IV disease at the time of diagnosis. Low-grade lymphomas often grow very slowly and there may be long periods where there is very little, or no, change in the disease. For many people, regular check-ups are often the most appropriate option (known as active surveillance or watchful waiting), with appropriate interventions when symptoms develop. There may

be multiple episodes of remission and relapse, and the nature of the disease can change at relapse, sometimes transforming to a more aggressive type.

The aim of current management for people with NHL is to prolong survival, achieve the longest possible remission and improve quality of life. Treatment for localised low-grade NHL usually consists of radiotherapy to the affected lymph nodes. First line treatment for symptomatic, advanced low-grade NHL is commonly a combination chemotherapy regimen of cyclophosphamide, vincristine and prednisolone (CVP) given with a monoclonal antibody (rituximab). Subsequent treatments include combination chemotherapy (with or without steroids and/or rituximab) single-agent chemotherapy and rituximab monotherapy.

The technology

Bendamustine (Levact, Napp Pharmaceuticals) is an alkylating antitumour agent. The antineoplastic and cytocidal effect of bendamustine hydrochloride is based on a cross-linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired. It is administered by intravenous infusion.

Bendamustine does not currently have a UK marketing authorisation for the treatment of people with previously untreated advanced low-grade NHL. Bendamustine in combination with rituximab has been studied in clinical trials in comparison with rituximab plus cyclophosphamide, vincristine and prednisolone (R-CVP) and rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). The trial populations included people with previously untreated follicular lymphoma, lymphocytic lymphoma, marginal zone lymphomas, mantle cell lymphoma, and immunocytomas. Bendamustine has a CHMP positive opinion as a monotherapy for the treatment of non-Hodgkin's lymphoma in people who have had a relapse following treatment containing rituximab.

Intervention	Bendamustine in combination with rituximab
Population	People with previously untreated advanced low-grade non-Hodgkin's lymphoma
Comparators	• Cyclophosphamide, vincristine and prednisolone plus a monoclonal antibody (rituximab) (R-CVP)

Outcomes	The outcome measures to be considered include: • response rates • duration of response/remission • time to new anti-lymphoma treatment/ time to progression • overall survival • adverse effects of treatment • health related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 110, September 2006, 'Rituximab for the treatment of follicular lymphoma'. Currently being reviewed. Technology Appraisal in Preparation, 'Rituximab within its licensed indication for the maintenance treatment of follicular non-Hodgkin's lymphoma following response to first-line chemotherapy'. Earliest anticipated date of publication TBC. Technology Appraisal in Preparation, 'Bendamustine for the treatment of people with indolent (low-grade) non-Hodgkin's lymphoma (NHL) who are refractory to rituximab or a rituximab-containing regimen'. Currently suspended. Related Guidelines: Clinical Guideline No. CSGHO, October 2003, 'Improving outcomes in haemato-oncology cancer (expected review date TBC).

Questions for consultation

Has the most appropriate comparator for previously untreated advanced low-grade NHL been included in the scope?

- Should cyclophosphamide, doxorubicin, vincristine and prednisolone plus a monoclonal antibody (rituximab) (R-CHOP) be included as a comparator in the scope?

- Should fludarabine containing regimens be included as comparators in the scope? If so, which regimens should be specified?

- Do the comparators for bendamustine in combination with rituximab differ depending on the type of low-grade NHL? If so, which comparators should be included in the scope?

Are there any subgroups of patients in whom bendamustine is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality?

Do you consider bendamustine to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of bendamustine can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)

NICE is currently appraising rituximab in combination with chemotherapy for the first-line treatment of follicular lymphoma (review of technology appraisal guidance TA110). We welcome comments about the appropriateness of separately appraising bendamustine in combination with rituximab for the first-line treatment of non-Hodgkin's lymphoma.