NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

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

Final Scope

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 advanced indolent 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. Most people diagnosed with NHL (around nine out of ten) have a B-cell lymphoma. The most common B-cell lymphomas are diffuse large B-cell lymphoma and follicular lymphoma. Other less common types of B-cell lymphoma include extra-nodal marginal zone lymphoma of mucosa-associated tissue, mantle cell lymphoma, Burkitt lymphoma, mediastinal large B-cell lymphoma, nodal marginal zone lymphoma, small lymphocytic lymphoma and lymphoplasmacytic lymphoma. T-cell lymphomas include peripheral T-cell lymphoma, skin lymphomas and anaplastic large cell lymphoma.

Lymphomas are graded according to the rate at which the abnormal lymphocyte cells divide. They are termed 'aggressive' (or high-grade) when they divide quickly and 'indolent' (or low-grade) when they divide slowly. 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 used for staging the lymphoma with respect to the number and spread of abnormal lymph, with four groups ranging from stage I (better prognosis) to stage IV (worse prognosis).

Approximately 12294 people were diagnosed with NHL in UK in 2009 and 4452 people died of NHL in 2010. 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 for patients with indolent non-Hodgkin's lymphoma vary widely. Localised disease is relatively rare. Most people will have stage III or IV

disease at the time of diagnosis. Indolent 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 indolent NHL usually consists of radiotherapy to the affected lymph nodes. First line treatment for symptomatic, advanced indolent NHL is commonly a combination chemotherapy regimen of cyclophosphamide, vincristine and prednisolone in combination with rituximab (R-CVP) or cyclophosphamide, doxorubicin, vincristine and prednisolone in combination with rituximab (R-CHOP). Rituximab targets the CD-20 surface marker of mature B-cell lymphocytes. Chlorambucil, with or without rituximab, is typically given to people in whom these regimens are not considered appropriate.

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 indolent NHL. Bendamustine in combination with rituximab has been studied in a clinical trial in comparison with R-CHOP. The trial population included people with previously untreated follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphomas, mantle cell lymphoma, and immunocytomas. Bendamustine is also being studied in combination with rituximab in comparison with R-CVP or R-CHOP in the first-line treatment of advanced indolent NHL or mantle cell lymphoma. Bendamustine has a UK marketing authorisation for the treatment of indolent non-Hodgkin's lymphoma as monotherapy in people who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen.

Intervention	Bendamustine in combination with rituximab
Population	People with previously untreated advanced indolent non-Hodgkin's lymphoma that requires therapy

Comparators	• cyclophosphamide, vincristine and prednisolone in combination with rituximab (R-CVP) • cyclophosphamide, doxorubicin, vincristine and prednisolone in combination with rituximab (R-CHOP) • chlorambucil in combination with rituximab (for people in whom R-CVP or R-CHOP are not considered to be appropriate treatments)
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 • progression free 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. 243 (review of Technology Appraisal No. 110), January 2012, 'Rituximab for the first-line treatment of stage III-IV follicular lymphoma'. Technology Appraisal No. 226, June 2011, 'Rituximab for the treatment of follicular non-Hodgkin's lymphoma (maintenance treatment following response to first-line chemotherapy). Technology Appraisal No. 137 (review of Technology Appraisal No. 37), February 2008, 'Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma'. Technology Appraisal No. 206 (terminated) 'Bendamustine for the treatment of indolent (low-grade) non-Hodgkin's lymphoma (NHL) that is refractory to rituximab'. Technology Appraisal in preparation, 'Bendamustine in combination with rituximab for the first-line treatment of mantle cell lymphoma'. Earliest anticipated date of publication: October 2013. Technology Appraisal in preparation, 'Bortezomib for the treatment of relapsed or refractory follicular non-Hodgkin's lymphoma'. Earliest anticipated date of publication: TBC (suspended). Related Guidelines: Clinical Guideline No. CSGHO, October 2003, 'Improving outcomes in haemato-oncology cancer (expected review date TBC).