NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Rituximab for the first line maintenance treatment of follicular non-Hodgkin's lymphoma

Final scope

Appraisal objective

To appraise the clinical and cost effectiveness of rituximab within its licensed indication, for maintenance treatment following response to first-line chemotherapy for follicular non-Hodgkin's lymphoma.

Background

Lymphomas are cancers of the lymphatic system. They are broadly divided into Hodgkin's lymphoma and non-Hodgkin's lymphomas (NHL). NHL can be divided into low grade and aggressive lymphomas. Low-grade (also called 'indolent') lymphomas are slow growing, with long median survival times but are less likely to be cured by treatment. Follicular lymphoma is a low-grade lymphoma of B-lymphocytes and accounts for approximately 30% of all low-grade lymphomas.

Precise identification of the type of lymphoma and accurate staging of the disease is crucial both for choosing the optimum treatment and for monitoring disease progression. The stage of NHL reflects how many groups of lymph nodes are affected, where they are in the body, and whether other organs such as the bone marrow or liver are affected. One of the most common systems for classifying NHL identifies four stages. Early follicular lymphoma includes stages I and II, and advanced disease includes stages III and IV. In stage I, only one group of lymph nodes in one organ of the body is affected. In stage II, the disease has spread to two lymph groups on the same side of the diaphragm. Stage III disease includes lymph nodes affected on both sides of the diaphragm, and stage IV of the disease usually involves multiple internal organs, for example, the liver, bone marrow, or blood.

NHL accounts for approximately 4% of all cancers diagnosed in the UK, with 9431 new cases registered in England and Wales in 2006, and 3929 registered deaths. Depending on the classification system used, between 22% and 40% of NHLs are follicular. The incidence of follicular lymphoma increases with age, with the median age at diagnosis between 60 and 65 years. Over 70% of people with follicular lymphoma are still alive 5 years after the diagnosis, with median survival over 10 years. Most people will have disease at stage III or IV at the time of diagnosis.

For many people, regular check-ups are the most appropriate clinical management (known as active surveillance or watchful waiting), until active

treatment is needed when symptoms develop. There may be many episodes of remission and relapse, and the nature of the disease can change at relapse, sometimes transforming to a more aggressive type. Treatment for low-grade NHL can lead to partial remission (decrease the size of the lymphoma, or reduce the extent of lymphoma in the body) or to complete remission (when the disease is not detectable anymore).

The aim of current management is to prolong survival, achieve the longest possible remission and improve quality of life. First-line treatment options for stage III or IV follicular lymphoma include single-agent or combination chemotherapy regimens based on alkylating agents, without or with steroids (chemo-immunotherapy). Cyclophosphamide, vincristine and prednisolone (CVP regimen), in combination with rituximab is recommended in NICE guidance (TA110) as a first-line treatment option for symptomatic stage III or IV follicular lymphoma. For people with advanced follicular NHL who have responded to first line induction therapy, observation or 'watchful waiting' is currently the standard treatment option. NICE guidance (TA137) recommends rituximab in people with relapsed stage III or IV follicular NHL for the induction of remission in combination with chemotherapy or as a monotherapy for maintenance treatment. Rituximab is also recommended for the treatment of people in relapsed or refractory stage III or IV follicular NHL, when all alternative treatment options have been exhausted.

The technology

Rituximab (Mabthera, Roche Products) is a genetically engineered monoclonal chimeric (mouse/human) antibody that targets the CD-20 surface marker of mature B-cell lymphocytes. This marker is expressed on almost all B-cell lymphomas and testing for its presence is part of the normal diagnostic procedure.

Rituximab does not have a UK marketing authorisation for maintenance treatment following first line chemotherapy for follicular lymphoma. It is currently being studied as maintenance therapy following response to first line chemotherapy, compared with no maintenance therapy (observation) in people with advanced follicular lymphoma.

Rituximab has a UK marketing authorisation for maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction chemotherapy with or without rituximab, and for the first line treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

Rituximab also has a UK marketing authorisation for the treatment of patients with CD20-positive diffuse large B-cell NHL in combination with CHOP chemotherapy, and as monotherapy for patients with stage III-IV follicular lymphoma who are resistant to chemotherapy or are in their second or subsequent relapse after chemotherapy.

Intervention(s)	Rituximab maintenance therapy
Population(s)	Adults with advanced follicular lymphoma that has responded to first line chemotherapy
Comparators	• Standard management without rituximab maintenance therapy • Ibritumomab tiuxetan
Outcomes	The outcome measures to be considered include: • progression free survival • overall survival • response rates • 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. If evidence allows, the following subgroups will be considered: • whether rituximab was received in combination with first-line chemotherapy • type of first-line chemo-immunotherapy regimen received • type of response (that is, complete versus partial response) achieved after first-line treatment

Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No.137, February 2008 (review of technology appraisal No. 37), "Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma". Review date December 2010. Technology Appraisal No. 110, September 2006; "Rituximab for the treatment of follicular lymphoma". Review date June 2009. Related Guidelines: Clinical Guideline No. CSGHO, October 2003, "Improving outcomes in haemato-oncology cancer" (expected review date TBC).