

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Rituximab for the treatment of recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma (Review of TA 37)

Final scope

Remit / appraisal objective:

To appraise the clinical and cost effectiveness of rituximab for recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma.

Background

Lymphomas are cancers of the lymphatic system. They are broadly divided into Hodgkin's lymphoma and the non-Hodgkin's lymphomas (NHL). Follicular lymphoma is a common histological type of NHL. It is derived from B-lymphocytes.

Non-Hodgkin's lymphomas can be divided into the indolent lymphomas and the aggressive lymphomas. The indolent (low-grade) lymphomas are slow growing, with long median survival times but are less likely to be cured by treatment. Most follicular lymphomas are low-grade, and most (70% of) low-grade lymphomas are follicular.

Staging is important in selecting a treatment and also for prognosis. The most widely used staging for lymphomas is the Ann Arbor system. Stage III implies involvement of lymph nodes on both sides of the diaphragm Stage IV is disseminated (multifocal) involvement of one or more organs.

NHL accounts for about 2% of all malignancies diagnosed in the UK. In 2002, the number of new cases of non-Hodgkin's lymphoma diagnosed was 9,423. Between 22% and 40% of NHLs are follicular, depending on the system used, to classify them (22% using the REAL classification). The annual incidence of follicular lymphomas is approximately 3 to 5 per 100,000 and increases with age. Median age at diagnosis is 60-65 years. Most (90%) follicular lymphomas present at Stage III or IV. In 2004 there were 4,418 deaths in the UK from non-Hodgkin's lymphoma. It is the 9th most common cause of death from cancer in the UK.

The overall survival rate at 5 years for follicular lymphomas is 72-77% and median survival is approximately 8-10 years. This disease is characterised by periods of remission and progression. Disease progression is unpredictable, and only patients with symptoms or with actively progressing disease will usually be treated. After successive episodes of chemotherapy, the

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frequency of relapse generally increases and the periods of progression-free survival shorten. The majority of patients die from the disease.

The aim of current management is to achieve the best possible remission for the longest period, and to prolong survival. First-line treatment options for stage III or IV follicular lymphoma include single-agent or combination chemotherapy regimens based on alkylating agents, with or without steroids. Rituximab in combination with cyclophosphamide, vincristine and prednisolone is also a first-line treatment option. Current management of recurrent or refractory disease consists of combination chemotherapy, which often contains anthracyclines. Fludarabine has been used to treat patients with relapsed or refractory disease.

The technology

Rituximab is a chimeric (mouse/human) genetically engineered monoclonal antibody. It 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 holds a marketing authorisation for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. It also holds a marketing authorisation for maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab.

Intervention(s)	Rituximab as induction and as maintenance therapy.
Population(s)	<p><u>For induction of remission</u></p> <p>Adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.</p> <p><u>For maintenance therapy</u></p> <p>Adults with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab.</p>

<p>Current standard comparators</p>	<p>Comparison will be made with:</p> <ul style="list-style-type: none"> • Cyclophosphamide, hydroxydaunomycin, Oncovin (vincristine), and prednisone (CHOP) • Fludarabine, as a single agent, or in combination with mitoxantrone and dexamethasone (FMD). • Cyclophosphamide, vincristine, and prednisone (CVP) • Chlorambucil • Best supportive care.
<p>Outcomes</p>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • Partial/complete response rates • Duration of response/remission • Health related quality of life • Event free survival • Time to new anti-lymphoma treatment/ time to progression • Overall survival • Adverse effects of treatment, including serious infection/ immunologic competence

<p>Economic analysis</p>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>The time horizon for the economic evaluation should be based on life expectancy.</p> <p>Costs should be considered from a NHS and Personal Social Services perspective.</p>
<p>Other considerations</p>	<p>Guidance will only be issued in accordance with marketing authorisation.</p> <p>Where the evidence allows, subgroups of patients with stage 3 and 4 follicular lymphoma who are more likely to benefit from these drugs should be identified. Such subgroups may be on the basis of, though not limited to, prior treatments, duration of previous remissions, histological subtypes, sites of involvement, stage at initial diagnosis, prognostic risk factors, and ability to tolerate further chemotherapy.</p>
<p>Related technology appraisals:</p>	<p>Rituximab for the treatment of follicular lymphoma No.110. Published September 2006.</p> <p>Rituximab for aggressive non-Hodgkin's lymphoma No 65. Published September 2003</p> <p>Guidance on the use of rituximab for recurrent or refractory stage 3 or 4 follicular non-Hodgkin's lymphoma No. 37. Published March 2002.</p>