Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin’s lymphoma: a systematic review and economic evaluation

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Executive summary

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Non-Hodgkin’s lymphoma (NHL) is a cancer of the lymphatic tissue causing enlargement of lymph nodes and generalised symptoms. It is a heterogeneous condition. Follicular lymphoma behaves in an indolent fashion, with a median survival of 8–12 years. However, it is incurable and most patients with the disease will die from it. In an average health authority covering 500,000 individuals, between 13 and 24 patients will present each year with Stage III or IV follicular NHL. Most will be over 50 years of age.

Management consists of intermittent treatment when the disease relapses and causes symptoms. The aim is to maximise quality of life by inducing remission, abolishing the symptoms associated with relapse, with minimal treatment side-effects. Cancer-specific treatment is not usually instituted while the patient is asymptomatic (‘watchful waiting’). First-line therapy is usually oral chlorambucil (or an equivalent alkylating agent). Second-line treatment is usually an anthracycline-containing chemotherapy regime.

Objective

To determine whether rituximab, a novel immunotherapeutic agent, should be more widely used in its currently licensed indication for Stage III or IV follicular NHL that is chemoresistant or in its second or subsequent relapse after chemotherapy, that is, as a third line of treatment.

Methods

In accordance with a pre-defined protocol, systematic reviews were undertaken of (a) the effectiveness of rituximab and (b) the evidence relating to costs and health economic impact. Electronic bibliographic databases, bibliographies and the Internet were searched for information on relevant studies. Experts in the field and the pharmaceutical company manufacturing rituximab were contacted for further information. Inclusion and quality criteria were assessed and data were extracted by two reviewers independently, with any discrepancies being resolved through consensus.

Results

Number and quality of studies, and direction of evidence

In the systematic review of effectiveness, no randomised controlled trials (RCTs) or comparative studies were identified. Four prospective case series were included, incorporating information on 387 patients. All were open to substantial bias and considerable caution was applied in interpreting the results.

No information was available on overall survival, nor was there any direct measurement of impact on quality of life. Rituximab did achieve clinical responses in some patients but most of these were partial (generally defined as at least a 50% decrease in size of lesions and no new lesions). The duration of responses appeared to be sufficiently long to be clinically useful. Symptoms at baseline were abolished completely in responders and, to some extent, in ‘non-responders’ also. However, before treatment, symptoms only appeared to be present in a minority of patients. Mild-to-moderate adverse events occurred in most patients and severe adverse events occurred in a minority; fatal adverse events were very rare but did occur. Some non-responders experienced the adverse effects of rituximab without great benefit.

Costs

The drug cost of rituximab is high – approximately £4900 per treatment cycle. However, the cost of administration is, at worst, similar to other commonly used treatments, because there are fewer adverse events. Arguably, therefore, the cost per course of treatment for rituximab is actually less but depends on the degree to which the incidence of adverse events is lower. Even if a lower cost per treatment course for rituximab is accepted, however, this will not convert into cost savings for the NHS unless rituximab replaces existing treatments. This seems unlikely; rituximab is more likely to be regarded as an additional treatment option rather than as an alternative.
A crude upper estimate of the budget impact on the NHS in England and Wales is £17.4 million per year.

**Acceptability to patients**

This is likely to be high because of the fewer number of times that rituximab needs to be administered and the shorter period over which treatment is completed.

**Conclusions**

The extent to which beneficial effects are outweighed by adverse events is impossible to quantify. Qualitatively, rituximab is probably effective. Any impression of a poor ratio of benefit to disbenefit should be tempered by the observation that incomplete response rates and severe adverse events are common to all currently used third-line treatments for follicular NHL. The absence of direct comparative data makes it very difficult to assess whether the ratio of benefits to disbenefits with rituximab is better, worse or the same as currently used alternatives.

Reliable estimates of the relative cost-effectiveness and cost-utility of rituximab cannot currently be provided, given the uncertainties surrounding the level of net benefits.

**Recommendations for research**

1. Further research on the effectiveness of rituximab and, indeed, all currently used therapies for NHL is of great importance.
2. A trial of alternative treatment strategies over the whole course of disease, though difficult to design, could be a powerful way of taking this issue forward.
3. Direct measurement of impact on quality of life is essential in future RCTs.

**Publication**

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The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Rapid reviews are completed in a limited time to inform the appraisal and guideline development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidelines produced by NICE are informed by a wide range of sources.

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