

# **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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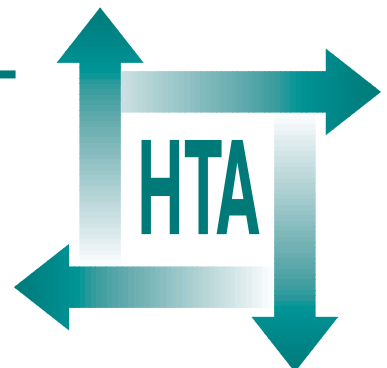
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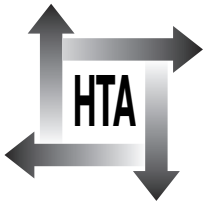
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**Health Technology Assessment  
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# Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation

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## List of abbreviations and glossary

### Abbreviations

AML	acute myeloblastic leukaemia	MRI	magnetic resonance imaging
<i>BNF</i>	<i>British National Formulary</i>	NCI	[US] National Cancer Institute
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisolone	NHL	non-Hodgkin's lymphoma
CI	confidence interval	NICE	National Institute for Clinical Excellence
CLL	chronic lymphocytic leukaemia*	RCT	randomised controlled trial
CT	computed tomography	REAL	Revised European–American Classification of Lymphoid Neoplasms
CVP	cyclophosphamide, vincristine, prednisolone	SCT	stem-cell transplant
ECOG	Eastern Co-operative Oncology Group	TLS	tumour lysis syndrome*
ESR	erythrocyte sedimentation rate		
ILSG	International Lymphoma Study Group		
i.v.	intravenous/intravenously		
IWF	International Working Formulation		
LDH	lactate dehydrogenase		

\* Used only in tables

## Glossary<sup>†</sup>

**Advanced** Synonymous with Ann Arbor Stage III/IV – see Stage below

**Aggressive** Types of NHL in which the cancer cells divide quickly

**Chemoresistant** Generally synonymous with refractory – see below. In the context of the UK licence for rituximab, chemoresistant has been taken to mean that the follicular NHL is refractory to both first- and second-line treatment options

**Complete response** For definition, see *Table 6* (page 22)

**First-line** Treatment options applied when patients with follicular NHL first become symptomatic, that is, after any period of ‘watchful waiting’

**High-grade** Synonymous with aggressive

**Indolent** Types of NHL in which cancer cells divide slowly

**Low-grade** Synonymous with indolent

**Partial response** For definition, see *Table 6* (page 22)

**Recurrence** Resurgence of follicular NHL following a response to treatment, usually marked by onset of new symptoms or return of previously experienced symptoms; the first appearance of symptoms following a period during which the follicular NHL is asymptomatic is **not** a recurrence or relapse

**Refractory** When treatment fails to bring about any response

**Relapse** Synonymous with recurrence

**Remission** Improvement in disease: however, as spontaneous remission is very rare, remission is generally synonymous with response (to treatment); periods in which follicular NHL does not progress are common but these are not remissions as defined

**Response** Improvement brought about by treatment following a recurrence: in research, remission is usually defined on the basis of serial CT or MRI scans; degrees of response are recognised, particularly complete and partial response, but their definitions vary slightly. NB: complete response is **not** synonymous with cure

**Second-line** Treatment options applied when patients have relapsed or disease has recurred following first-line treatment options, or disease has proved refractory/chemoresistant to them

**Stage** In NHL, the degree of dispersion of affected lymph nodes and lymphoid tissue around the body; in the Ann Arbor system, Stage III/IV indicates that affected tissues are widely dispersed around the body

**Third-line** Treatment options applied when patients have relapsed or disease has recurred following both first- and second-line treatment options, or disease has proved refractory/chemoresistant to them

<sup>†</sup> Definitions of terms as used by the authors in the specific context of this report





## Executive summary

### Background

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.

# Chapter I

## Aim of the review

Despite undoubted improvements in the treatment of haematological malignancies, a number of conditions remain difficult to treat. Non-Hodgkin's lymphoma (NHL) is such a condition and consequently the search continues for therapeutic agents that might improve its management. Rituximab is a novel immunotherapeutic agent that has been licensed in recent years.

The research question addressed by this report is:

'What is the clinical effectiveness and cost-effectiveness of rituximab in Stage III or IV follicular NHL that is chemoresistant or in its second or subsequent relapse after chemotherapy?'

Rituximab is currently licensed for use in these circumstances.



# Chapter 2

## Background

### The underlying health problem

#### Nature of the condition

NHLs are a heterogeneous group of cancers affecting the lymphatic system and are usually manifest by enlargement of the lymph nodes, which occur throughout the body. The enlarged lymph nodes may give rise to cosmetic disfigurement, pain and restricted movement. The disease also gives rise to generalised symptoms, such as malaise, weight loss, fevers and night sweats, and, in 15–20% of patients, occurs in other lymphoid tissue, including the spleen.<sup>1</sup> Traditionally, NHLs have been divided into two prognostic groups.

- Indolent or low-grade lymphomas to which the follicular types generally belong. These have a long median survival but are currently incurable at advanced stages. Most patients present with these types.
- Aggressive or high-grade lymphomas. These have a shorter natural history but 30–60% of patients may be cured.<sup>2</sup>

The lymphatic system has a number of different components and the cancer process may affect any of these. This, in turn, gives rise to different specific types of cancer within the broad category of NHL. Classification systems have evolved to capture these different specific types. However, greater understanding about the diversity of cells making up the human immune system and how they are affected by disease had led to the classification system being updated.

One of the main classification systems is the International Working Formulation (IWF) shown in *Table 1*.<sup>3</sup> The main distinction made in this classification is between how quickly the cancer cells divide. In low-grade (indolent) NHL the cells divide relatively slowly; in high-grade (aggressive) NHL they divide quickly.

The IWF classification further distinguishes between specific types of cancer on the basis of the cell types that can be identified when an affected lymph node taken from a patient with NHL is examined microscopically. In the IWF classification, the types of NHL constituting ‘follicular lymphoma’ are B, C and D. Although it is not stated in the

**TABLE 1** IWF classification of NHL<sup>3</sup>

<b>Low-grade NHL</b>	
A	Small lymphocytic, consistent with CLL (SL)
B	Follicular, predominantly small cleaved cell (FSC)
C	Follicular, mixed small cleaved and large cell (FM)
<b>Intermediate-grade NHL</b>	
D	Follicular, predominantly large cell (FL)
E	Diffuse, small cleaved cell (DSC)
F	Diffuse, mixed small and large cell (DM)
G	Diffuse, large cleaved or noncleaved cell (DL)
<b>High-grade NHL</b>	
H	Immunoblastic, large cell (IBL)
I	Lymphoblastic, convoluted or nonconvoluted cell (LL)
J	Small noncleaved cell, Burkitt’s or non-Burkitt’s (SNC)

classification, all these types are derived from B cells (as opposed to T cells, the other main type of cell making up the lymphatic system). Thus, IWF B–D are B cell NHL. It should be noted, however, that there are other types of NHL derived from B cells such as, for example, type J, Burkitt’s lymphoma. In contrast to IWF B–D, which are indolent, this latter type of B cell NHL is aggressive.

As yet, unfortunately, there is not complete agreement on the ideal classification system for NHL and lymphomas/leukaemias in general. Consequently, it is necessary to understand other commonly used classification systems. The Revised European–American Classification of Lymphoid Neoplasms (REAL) system<sup>4</sup> and the US National Cancer Institute (NCI) modification of the REAL system<sup>2</sup> are presented in appendices 1 and 2. The key points to note are that:

- using the REAL system, ‘follicular lymphoma’ corresponds to ‘II. Peripheral B cell neoplasms D. Follicle centre lymphoma, follicular’
- using the NCI modification, ‘follicular lymphoma’ corresponds to ‘III. Indolent lymphoma/leukaemia A. Follicular centre cell lymphoma, follicular. Grades I, II and III’.

The most up-to-date classification is the WHO–REAL system. This was not used in any of the studies considered in this technology appraisal and, hence, is not described further. It is, however, similar to the REAL classification system.

In addition to classifying NHL by the type of cell involved, it is also common to describe its stage. This gives an indication of how widely dispersed the affected lymph nodes are around the body. The intention is similar to staging in other cancers, in that it provides an indication of the prognosis of the particular type of NHL. The Ann Arbor Staging System<sup>5</sup> is still the most commonly used (see *Table 2*). In this report, Stage III/IV follicular lymphoma is the severity level of particular interest.

**TABLE 2** Ann Arbor staging system for NHL<sup>5</sup>

<b>Stage I</b>	Involvement of single lymph node region (I) or localised involvement of single extralymphatic organ or site (IE)
<b>Stage II</b>	Involvement of two or more lymph node regions (II) or localised involvement of a single associated extralymphatic organ or site at its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm (IIE)
<b>Stage III</b>	Involvement of lymph node regions on both sides of the diaphragm (III) that may be accompanied by localised involvement of an extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIS + E)
<b>Stage IV</b>	Disseminated (multifocal) involvement of one or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement
B is added to a stage if there is:	
<ul style="list-style-type: none"> <li>• unexplained loss of more than 10% of bodyweight in the 6 months before diagnosis</li> <li>• unexplained fever with temperatures above 38°C</li> <li>• drenching night sweats</li> </ul>	
These are often referred to as 'B symptoms'	

## Epidemiology

NHL accounts for about 2% of all cancers in the UK, making it about the tenth most common malignancy, with some 2500 new cases reported each year.<sup>1</sup> NHL is an important cause of mortality. In 1998, in England and Wales, there were 3966 deaths from NHL; this accounted for 0.7% of all deaths and 2.9% of all cancer deaths, thus making it the eleventh most common cause of cancer mortality.<sup>6</sup>

The overall incidence rates in England and Wales were estimated by applying averaged age-

specific incidence data from 1991<sup>1</sup> to the 1991 Census population data in 5-year age bands.<sup>6</sup> The overall incidences were estimated as 14.6 and 12.1 per 100,000 population in males and females, respectively. If it is assumed, from a study by the International Lymphoma Study Group (ILSG),<sup>7</sup> that the average overall survival time for NHL patients is 5 years, then the prevalence rates in England and Wales would be approximately 73 and 61 per 100,000 population for males and females, respectively.

NHL is rare in those under 50 years of age. In 1991, the incidence rates at 40 years of age were approximately 7 and 3 per 100,000 population in men and women, respectively. This rises to approximately 47 and 75 per 100,000, respectively, at 75 years of age and above. The increasing longevity of the population alone suggests that the number of cases of NHL will grow. Independently of this, there is some evidence that the incidence of NHL is increasing<sup>8,9</sup> at a rate too great to be accounted for by improved diagnostic techniques alone.<sup>1</sup> In Yorkshire, between 1978 and 1991, there was an upward trend of 5–6% per annum.<sup>10</sup>

Changing classification systems have meant there is uncertainty over the proportion of NHLs that is follicular in origin. The Working Classification Project classified 40% of NHLs as follicular,<sup>3</sup> whereas the ILSG, using the REAL system, classified 22% as follicular lymphoma.<sup>7</sup> Up to 90% of follicular lymphomas present as Stage III or IV disease.<sup>1</sup>

These epidemiological data suggest that the approximate number of new cases per year of Stage III or IV follicular NHL in an average health authority of 500,000 persons would be 13, if 22% of NHL is follicular in origin. If 40% of NHL is follicular in origin, this figure rises to approximately 24 individuals. Assuming a median survival time of 10 years (see below for justification), this suggests that, in the average health authority, the number of prevalent cases will be between 130 and 240, again depending on whether the proportion of NHL that is follicular is 22% or 40%.

## Aetiology and prognosis

The causes of NHL in general, and follicular lymphoma specifically, are unclear. There are a number of well-established risk factors such as, infectious agents (e.g. HIV<sup>11</sup>), immunosuppression (e.g. post organ transplantation<sup>12</sup>), genetic susceptibility (e.g. ataxia telangiectasia<sup>13</sup>), and environmental factors (e.g. exposure to agrochemicals<sup>8</sup>).

There is some debate over the median survival time of low-grade or indolent NHL, including follicular lymphomas, due to its heterogeneous nature. However, typical values are 8–12 years.<sup>14,15</sup> Current treatments appear to make little difference to overall survival and virtually never bring about a permanent cure.<sup>2</sup> The diseases comprise sequential episodes of relapse and remission. Relapse generally results from periods of more rapid growth of the cancerous cells, leading in turn to resurgence of lymph node enlargement and generalised symptoms. Consequently, the aim of treatment during relapse is to achieve remission, abolish the generalised symptoms and restore quality of life. If achieved, periods of remission may last several years. However, with each relapse, remission as a result of treatment becomes harder to achieve (that is, the disease is more likely to become refractory to treatment) and the period of remission becomes shorter. Indolent lymphoma may also convert to an aggressive form that may sustain a complete remission with intensive chemotherapy.<sup>2</sup> The majority of patients will eventually die as a direct result of their lymphoma. However, since they are generally elderly and the disease duration is long, these patients may die of unrelated illnesses also.

High-grade or aggressive types of NHL require immediate therapy, often combination

chemotherapy, in keeping with their rapidly progressive nature. However, paradoxically, the outlook may be better for those responding to currently available treatments, since long-term disease-free survival is achieved in approximately 50% of patients.<sup>1</sup>

### Prognostic factors

A systematic search was undertaken of cohort studies that might provide accurate information on the natural history of NHL, particularly follicular lymphoma. The search strategy used is presented in appendix 3.

The factors that may be associated with length of survival of patients with NHL in four of the studies identified<sup>16–19</sup> are outlined in *Table 3*. The median follow-up time ranged from 51 months to 9 years. The numbers of patients included ranged from 157<sup>18</sup> to 987.<sup>17</sup>

Using univariate analysis, a number of factors associated with the survival of NHL patients were found to be statistically significant. Multivariate analysis identified fewer significant factors, and the important prognostic factors identified differed across different studies. From the multivariate analysis results, the following prognostic factors may be important: age > 60 years, B symptoms, extranodal sites, large tumour size, elevated serum lactate dehydrogenase (LDH),

**TABLE 3** Factors associated with length of survival in NHL

Factor	Univariate analysis	Multivariate analysis
Age	*	*
Gender	*	*
Stage	*	*
B symptoms	*	*
ECOG performance status	*	*
Extranodal sites	*	*
Serum LDH level	*	*
Bone marrow involvement	*	—
Serum albumin level	*	—
Tumour bulk	*	*
Liver involvement	*	—
ESR	*	*
Substantial splenomegaly	*	—
Serous effusion	*	—
Orbital/epidural involvement	*	—
International Prognostic Indicator score	*	—
Cell type	—	—
Haemoglobin level	*	*

poor Eastern Cooperative Oncology Group (ECOG) performance status, erythrocyte sedimentation rate (ESR), haemoglobin levels.

In the one study of direct relevance,<sup>16</sup> 484 patients with low-grade Stage III or IV follicular lymphoma were included and three prognostic factors were identified: B symptoms, at least three nodal sites > 3 cm, age > 60 years. For patients with zero, one, and two/three factors, overall survival rates at 5 years were 74%, 66%, and 45%, respectively.

The results of these recent studies are generally consistent with previous studies. For example, the International Non-Hodgkin's Lymphoma Prognostic Factors Project<sup>20</sup> identified five pre-treatment features that were independently associated with 5-year survival in patients with aggressive NHL: age ( $\leq 60$  versus  $> 60$  years), tumour stage (Stages I or II versus III or IV), number of extranodal sites ( $\leq 1$  versus  $> 1$ ), performance status (0/1 versus  $> 1$ ), serum LDH levels ( $\leq 1$  versus  $> 1$ ). These five patient characteristics were used to develop a model for predicting outcome in patients with aggressive NHL and, although initially constructed for this group of patients, the model has now been applied to other subtypes of NHL, for which it has similar predictive value.<sup>1</sup>

The key point that arises from investigations of prognostic factors in NHL is that they are numerous and that they interact. The corollary of this is that when uncontrolled case series are used to assess effectiveness, minor differences in the prognostic factors of those entering the case series may themselves cause major differences in patient outcome. Thus, without detailed information on prognostic factors, comparing case series treated with one agent with those treated with another, and attempting to impute differences in outcomes to the different treatments, is highly dubious. Even if the prognostic factors are defined in detail, our ability to accurately adjust the outcomes for imbalances in prognostic factors has been questioned. This uncertainty must be even greater when the number of potentially important prognostic factors is large and the nature of the interaction between them uncertain, as is clearly the case for NHL.

### Significance in terms of ill-health (burden of disease)

The nature of NHL in general, and follicular lymphoma in particular, and the duration of the disease suggest that both individually and at a population level it is responsible for a considerable

amount of morbidity and mortality. In 1998, NHL accounted for 0.7% of all deaths and 2.9% of all cancer deaths in England and Wales, making it the eleventh most common cause of cancer mortality,<sup>6</sup> and there is evidence to suggest that its incidence is increasing.<sup>10</sup>

## Current service provision

### Objectives of treatment and important health outcomes

There are at least five potential objectives in treating NHL, or indeed any other cancer:

- to eradicate the cancer, and so effect a long-term cure
- to achieve long-term cancer stasis or regression, with the aim of prolonging life
- to treat symptoms, particularly those arising from relapse or recurrence or disease progression, and so improve quality of life
- to help patients come to terms with their condition, again improving quality of life
- to manage the terminal stages of the disease, so allowing dignified death, free of discomfort and distress.

These objectives predict that the following health outcomes are likely to be of potential importance:

- absence of cancer at given points in time following diagnosis
- mortality, particularly cancer-specific mortality
- duration of survival
- quality of life
- patient and carer satisfaction.

However, in NHL, because the prospect of cure with current treatments is acknowledged to be rare (and there has been no claim that rituximab substantially alters this), the main focus of specific cancer therapy is on treating the symptoms arising from relapse and recurrence, so maximising quality of life during the period of survival.

Specific events that contribute to this, and so might act as proxies for the main objective, can thus be identified as:

- number of relapses/recurrences
- duration of relapses/recurrences
- severity of symptoms associated with the relapses/recurrences
- ability to bring about a remission
- speed of induction of remission



- reduction of symptoms associated with the remission
- adverse events associated with induction of the remission
- duration of remission.

### Current treatment options

For patients presenting with Stage III or IV follicular NHL, several treatment options are available.<sup>2</sup> However, the patients will probably receive all the treatments in the course of their disease. The order in which treatments are offered will be based on the degree to which the chances of achieving a remission are offset by the number and severity of adverse events suffered to achieve remission. A further consideration, particularly in younger patients, is the need to use the available treatment options in an order that does not compromise treatment options at later relapse points.

#### First-line therapy

Management may initially include 'watch and wait' (i.e. no specific anti-cancer therapy). During this time the disease may remain stable, and the period of watchful waiting may be as long as 72 months. Single agent therapy with an oral alkylating agent such as chlorambucil (with or without oral steroids) is usually the first specific chemotherapy used.

#### Second-line therapy

Following first relapse/recurrence or failure to respond to first-line therapy, combination intravenous chemotherapy containing alkylating agents (e.g. cyclophosphamide) in combination with anthracyclines (e.g. doxorubicin) and other cytotoxic drugs, such as cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) and cyclophosphamide, vincristine and prednisolone (CVP), is usually given until a 'best response' is obtained. After further relapse the patient may be retreated using the same therapy. Fludarabine, although unlicensed for this indication, may be given as an alternative and, indeed, is now being increasingly used as a first-line therapy. This agent may also be used before or after combination chemotherapy, alone or in combination.

#### Third-line therapy

At a point when the cancer has relapsed following all usually applied first- and second-line therapies, or when it has proved chemoresistant/refractory to these therapies, newer therapies may then be used, including rituximab, cladribine (2-chloro-deoxyadenosine), interferon- $\alpha$  or high-dose therapy with stem cell support.

### Evidence on the effectiveness of existing treatments for follicular NHL

A search was carried out for systematic reviews of randomised controlled trials (RCTs) and other rigorous research on the effectiveness of existing treatments for NHL, using the strategy outlined in appendix 4. Unfortunately, there appeared to have been few systematic reviews of the effectiveness of existing agents, particularly as applied to Stage III or IV follicular lymphoma. The two most rigorous and relevant reviews identified are discussed below.

#### Gustafsson, 1996<sup>21</sup>

The conclusions of this review for advanced disease (Stage III or IV low-grade NHL) were as follows.

1. In two studies of limited tumours at Stage III, greatly prolonged remission after extensive radiotherapy or combination therapy was reported. However, extensive irradiation was only appropriate for a small number of patients.
2. In two RCTs, in which chemotherapy and combination therapy at Stage III or IV were compared, different results were obtained: one showed no differences between chemotherapy alone or in combination with total body irradiation, while in the other combination therapy was found to yield significantly longer relapse-free and overall survival. Clinical observation was that total body irradiation is little used in the UK.
3. The value of adjuvant radiotherapy in advanced disease has not been confirmed.

#### Cheson, 1998<sup>22</sup>

This review presented some quantitative results about several 'new' treatment approaches.

1. **Fludarabine** According to the results of several case series, responses to fludarabine occurred in about 50% of patients with indolent NHL who had relapsed following an initial response or who were refractory to prior therapies, including 10–15% complete remissions. Complete remissions were more common in patients who received fludarabine as initial treatment for an indolent NHL, with a frequency of almost 40%, and an overall response rate of about 70%. Major side-effects of fludarabine included moderate myelosuppression, profound immunosuppression and neurotoxicity.
2. **Cladribine** Response rates to cladribine in several case series ranged from 43% to 77% in patients with indolent NHL who had received prior therapy, and from 71% to 100% among

patients with no prior therapy. Side-effects were similar to those for fludarabine.

3. **Interferon- $\alpha$**  There were more than ten RCTs in which interferon- $\alpha$  had been used either during induction or as maintenance therapy, or as both. When incorporated into induction programmes, the effect on response rates was inconsistent. In studies in which interferon- $\alpha$  was combined with chemotherapy agents, there was a longer time-to-treatment failure with interferon in most patients but with an inconsistent effect on survival.
4. **Stem-cell transplantation (SCT)** There were few data available on the use of allogeneic bone marrow transplant in indolent NHL. The experience with autologous SCT for low-grade NHL was greater than bone marrow transplantation. Short-term and long-range complications of autologous SCT included treatment-related mortality, prolonged anaemia or thrombocytopenia, and a markedly increased rate of secondary myelodysplasia and acute myeloblastic leukaemia (AML) (6.8–19%).

### Conclusions

Overall, the identified reviews were predominantly narrative, with little information about quantitative results of primary studies. Some reviews focused on intermediate/high-grade NHL. In one review,<sup>22</sup> some quantitative data on fludarabine for indolent NHL was presented; in the other,<sup>21</sup> CHOP was suggested as a treatment option, with a reference<sup>23</sup> in which long-term follow-up of patients with low-grade malignant lymphomas treated with doxorubicin-based chemotherapy or chem-immunotherapy was described.

An obvious issue that arises is that gauging the relative effectiveness of a new treatment is problematic, because the effectiveness of existing treatments has not been clearly quantified in RCTs.

### Current service cost

Because treatment of follicular lymphoma is part of general haematological or oncology services, the cost of caring for this group of patients is very difficult to derive from routine financial information available in the NHS. However, consideration of the long duration of disease and the variety of treatments to which an individual might be exposed over the course of their illness suggests that the costs of caring for follicular lymphoma are likely to be considerable. In this, the support required from both primary and palliative care services in the terminal stages of the disease should not be underestimated.

### Variation in services

There appears to be some debate about the order in which the available current treatment options described above are delivered. This suggests that there will be variation in the treatments offered by different clinicians. However, guidelines are being developed by the clinical group of the British Committee for Standards in Haematology.

### Description of a new intervention

Rituximab (MabThera<sup>®</sup>) is manufactured by Roche Products Limited. A genetically engineered chimeric mouse/human monoclonal antibody against the CD20 antigen found on the surface of most mature and malignant B lymphocytes,<sup>24</sup> it binds to the CD20 antigen, inducing lysis probably by antibody-dependent toxicity and complement-dependent cytotoxicity.<sup>25</sup>

Rituximab was licensed for the use in the UK and Europe in June 1998 for the “treatment of patients with Stage III–IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy”,<sup>26</sup> that is, as a third-line therapy. It had been previously licensed in the USA by the Food and Drug Administration in November 1997 from Genentech Incorporated and IDEC Pharmaceutical Corporation under the trade name Rituxan (IDEC-C2B8) for patients with relapsed or refractory, low-grade or follicular CD20-positive, B cell NHL.<sup>27</sup>

In the *British National Formulary (BNF)*, the following statement regarding rituximab appears:<sup>27</sup>

“Rituximab ... has recently been introduced for the treatment of chemotherapy-resistant advanced follicular lymphoma... Full resuscitation facilities should be on hand ... treatment should be undertaken under the close supervision of a specialist since fatalities following severe cytokine release syndrome (Tumour Lysis Syndrome – TLS) have occurred 1–2 hours following rituximab.”

Patients with a high tumour burden are at most risk. Also, rituximab should be used with caution in patients with cardiovascular disease. Infusion-related side-effects are said to be common, particularly during the first infusion, and prophylaxis with an analgesic and an antihistamine should be administered. Rituximab is contraindicated during pregnancy and in nursing mothers.<sup>24</sup>

The recommended dosage is 375 mg/m<sup>2</sup> given as an intravenous infusion once weekly for 4 weeks (on days 1, 8, 15 and 22). The average net drug

cost of the four-dose treatment for an average adult (surface area 1.7 m<sup>2</sup>) is approximately £4900. This is based on the cost of one 500 mg vial (£873.15) and two 100 mg vials (£174.63 each) for each of four cycles.<sup>27</sup>

Currently, many clinicians appear to use rituximab as a treatment of last resort. That is, they use rituximab only when other non-contraindicated, currently available treatments have failed, particularly when the disease does not respond to other treatment options, that is, is chemoresistant/refractory. This generally involves prescribing rituximab as the fourth or fifth treatment option, as opposed to the third. This implies that, in the new model of treatment, rituximab is added to the existing range of available treatments, and that it is envisaged that it would be prescribed at some stage of the disease provided that it was not contraindicated. What does not seem to be under consideration is the wholesale replacement of any of the currently used treatment options by rituximab.

## Summary of key points

### Disease

- NHL is a cancer of the lymphatic tissues that causes enlargement of lymph nodes and generalised symptoms.
  - Indolent NHL is widely acknowledged to be incurable and most patients with the disease will die as a direct consequence of their condition.
  - NHL is a heterogeneous condition; the types behave differently.
  - Follicular lymphomas make up 22–40% of NHL and generally behave in an indolent fashion.
  - Up to 90% of follicular lymphomas present with Stage III or IV disease.
  - The average health authority may have between 13 and 24 Stage III or IV follicular NHL patients presenting each year.
  - Most patients will be over 50 years old.
  - The median survival time for indolent NHL is 8–12 years
- Several prognostic factors have been identified and they probably interact in a complex manner.

### Existing treatments

- Management consists of intermittent treatment when the disease relapses and causes symptoms.
- The aim of treatment is thus 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 a patient is asymptomatic (watchful waiting).
- First-line therapy is usually oral chlorambucil (or an equivalent alkylating agent), with or without steroids.
- Second-line treatment is usually an anthracycline-containing chemotherapy regime, such as CHOP or fludarabine.
- The effectiveness of most existing treatments has been poorly quantified using RCTs.

### New treatment

- Rituximab is a novel type of treatment, termed immunotherapy – the drug is directed against a marker found on B cells.
- Rituximab is currently licensed for “treatment of patients with Stage III–IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy”, that is, as third-line therapy.
- Rituximab is administered as a course of four injections over 1 month.
- Care must be taken on first infusion, as severe reactions have been identified.
- The cost of rituximab is approximately £5000 per course of four injections.
- Many clinicians in the UK currently use rituximab as a treatment of last resort.
- In this model of use, rituximab is an additional treatment option to currently established treatments.
- Used in this way, rituximab is unlikely to wholly replace any of the existing treatment options.



# Chapter 3

## Effectiveness

### Objective

To review systematically the evidence of the effectiveness of rituximab for Stage III or IV follicular lymphoma that is chemoresistant or is in its second or subsequent relapse after chemotherapy.

### Methods for reviewing effectiveness

#### Protocol

The review was undertaken in accordance with a pre-defined protocol (see appendix 5).

#### Search strategy

A broad comprehensive search for studies assessing the effectiveness of rituximab was undertaken, as follows.

- Electronic bibliographic database searches: MEDLINE (Ovid), 1966–September 2000; EMBASE (Ovid), 1980–September 2000; Science Citation Index (Web of Science), 1981–October 2000; Cochrane Library 2000, Issue 3 (see appendix 6 for details of search terms used).
- Citation checking of studies and reviews obtained.
- Citation checking of the reference list of the single submission from industry.
- Contacts with experts in the field (see appendix 7 for list).
- Internet search engines.

This search strategy was amplified by identification of potentially relevant citations in the systematic searches conducted for:

- evidence on the effectiveness of treatments other than rituximab for NHL (see appendix 4 for further details)
- identification of ongoing and unpublished trials of rituximab (see appendices 8 and 9 for further details); this included further extensive interrogation of relevant Internet websites, as listed in appendix 8, and a search of the National Research Register 2000 (Issue 4).

It was indicated in the initial protocol that an attempt would be made to search conference abstracts. However, this was not feasible in the time available.

### Inclusion and exclusion criteria

#### Intervention

Rituximab at the dose given in the product information sheet; that is, 375 mg/m<sup>2</sup> given as an intravenous infusion once weekly for four doses.

#### Population

Patients with Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy, as indicated in the UK licensing information.

#### Comparator

Any – this also included no treatment and any of the currently recommended treatments.

#### Outcomes

No restriction was made according to the outcomes measured. However, survival, quality of life and adverse events were the outcomes designated *a priori* as those of greatest interest.

#### Design

The initial inclusion criteria specified RCTs. As stated in the protocol, in the absence of RCTs the inclusion criteria were extended to include controlled trials that were not randomised and studies with no parallel control arm, that is, case series. For the latter, by definition, the inclusion criterion relating to presence of a comparator was dropped. For case series, studies containing fewer than ten patients were excluded.

Two reviewers (BW and CD) undertook the application of inclusion/exclusion criteria. Decisions were made independently of the data extraction and prior to the scrutiny of results.

### Data extraction strategy

Data on study characteristics, study quality and results were extracted independently by two reviewers (BW and CD) using a series of proforma. Any differences were resolved by consensus.

### Quality assessment strategy

A generic framework, as suggested by the Cochrane Collaboration and assessing selection, performance, detection and attrition biases, was employed to describe the strengths and weaknesses of the included studies.<sup>28</sup>

The Jadad checklist<sup>29</sup> that has been used by many reviewers to determine study quality was not relevant here as no RCTs were identified; therefore another checklist for determining quality of case series was used. The strengths and weaknesses of the included studies were assessed using a pre-specified framework incorporating the following:

- an indication that they were conducted prospectively
- (ideally) the results of a consecutive series
- clear indications of patient characteristics, particularly with regard to stage of disease and previous treatments
- losses to follow-up with respect to particular outcomes of interest that were < 10%.

This framework was developed by two of the authors in a previous systematic review on a different topic.<sup>30</sup> The quality assessment was performed independently by two reviewers (BW and CD) with any differences resolved by consensus.

### Analysis

As stated previously, the main method of analysis was qualitative. Meta-analysis was not employed and no subgroup analysis was performed.

## Results

### Quantity and quality of research available

#### Number of studies identified

In all, 269 studies were identified. By applying the inclusion criteria documented above, 13 studies were selected as potentially relevant on the strength of their abstracts. These studies were considered in detail on the basis of the full text of the report, when this was available.

### Number and type of studies included

No RCTs or comparative studies of any description were identified and included.\* Four (5/13 papers as one provided more information on the same study) studies were finally included in the review.<sup>31–35</sup> These were all prospective case series.

### Number and type of studies excluded, with reasons for specific exclusions

Eight of the 13 identified studies were excluded. The main reasons for exclusion were suspicions of duplication, and papers that were reviews only or that did not meet our inclusion criteria. Full details of the excluded studies and the reasons for their exclusion are given in appendix 10.

### Included study characteristics

Population characteristics of the complete cohorts from the included studies are recorded in *Table 4*.

The four included case series were small to moderate in size, ranging from 31<sup>31</sup> to 166<sup>35</sup> included patients. In some respects, the patients in each of these case series were similar, particularly with respect to age and gender. However, given the importance of age as a prognostic factor, it may be that even the small differences in median age observed (55 years; 50 years and 58 years – median age was not given by Ghielmini and colleagues<sup>33</sup>) are important. With respect to stage of disease, all studies were inclusive, not prescribing stage, with the result that as well as including Stages III and IV, Stages I and II were also present. However, again considering the importance of stage as a prognostic factor, variation in the proportions of Stage III or IV disease that might inevitably arise from failure to restrict by stage may present problems in comparing the results. All studies excluded patients with lymphoma who were not positive for the CD20 marker.

There were further important differences. In particular, with respect to condition, Foran and colleagues<sup>32</sup> included follicular lymphoma, Davis and colleagues<sup>31</sup> and McLaughlin and colleagues<sup>35</sup> included IWF type A in addition, and Ghielmini and colleagues<sup>33</sup> included mantle cell lymphoma in addition. There were also variations in the

\* Late in the review, as part of the search for ongoing studies, one RCT was identified in which rituximab was compared directly with rituximab + IDEC-Y2B8 in approximately 150 patients with relapsed or refractory low-grade NHL. Recruitment appears to have finished but the study has not yet been reported in full. An interim analysis, reported in abstract form only, appears to indicate greatly improved response in the rituximab + IDEC-Y2B8 arm. The study is of great interest because information was collected on impact on quality of life. However, the limited reporting of the final results led, for practical purposes, to the exclusion of this study from the systematic review but, clearly, the statement about absence of comparative research needs to be qualified by acknowledgement that this study has been conducted.

inclusion/exclusion criteria relating to prior treatment. Ghielmini and colleagues<sup>33</sup> made no stipulation about prior treatment whereas the other three included studies did. In Foran and colleagues' study<sup>32</sup> the number of prior treatments was not specified; in the study by Davis and colleagues,<sup>31</sup> it was at least one, and in McLaughlin and colleagues' study<sup>35</sup> it was 1–3 prior treatments. This and other variations between inclusion/exclusion criteria in the four included studies strongly predicts that the case-mix varied between the studies, particularly in respect of factors which have a strong influence on prognosis, especially diagnosis and amount of prior treatment. This would not be a problem if homogeneous subsets of included patients could be identified that corresponded as closely as possible to the current licensed indications for use of rituximab.

Our attempts to identify patient subsets directly relevant to assessing the effectiveness of rituximab in its licensed indications within the total cohorts of the included case series are recorded in *Table 5*. In all of these it was clear that substantial numbers of patients were included with the condition/stage/prior treatment characteristics of interest. However, it was impossible, despite further enquiry of lead authors and/or the company sponsoring the studies, to quantify the exact proportion of the total cohort who had Stage III or IV follicular lymphoma that was chemoresistant or in its second or subsequent relapse after chemotherapy.<sup>†</sup> In *Table 5*, the nature of the uncertainty for each of the included case series is expanded. The subsets of most relevance for which results were reported were, with the exception of the study by McLaughlin and colleagues,<sup>35</sup> follicular lymphoma. For the latter study, results were only available for the whole cohort of 166 patients, of whom 130 (78%) had follicular B cell NHL. In all four included case series, although the numbers of patients with follicular lymphoma were clear, the numbers of those with Stage III or IV disease and who were chemoresistant, or in second or subsequent relapse after chemotherapy, were not. Other demographic details of the most relevant subsets were also generally absent.

Details of the interventions and outcomes for the total cohort in the included studies are given in

*Table 6*. The interventions used in all the case series were consistent. By definition, all case series were subjected to rituximab, 375 mg/m<sup>2</sup> weekly, for 4 weeks. There was some variation in the pre-treatment tests employed. All included physical examination and some means of assessing severity of disease, particularly computed tomography (CT), magnetic resonance imaging (MRI) or X-rays. With respect to target outcomes, all included studies measured clinical response and adverse events. There were important differences in the assessment methods used and in the definitions of response. Only McLaughlin and colleagues<sup>35</sup> appeared to have made any attempt to improve the objectivity of the response outcome measure through use of an independent assessment panel. This is an issue of particular concern, given the inevitable openness to detection bias resulting from not having a comparator arm. Time to progression and duration of response were measured in most studies. Although numbers of deaths were recorded in most studies, formal survival analysis was undertaken in none. In none of the included studies was impact on quality of life measured directly.

#### **Included study quality**

Quality assessment details are presented in *Table 7*, including summaries of threats to validity and threats to relevance of included studies. These were assessed in relation to information available for the whole cohort in the case series, not the subset of greatest relevance. Although obvious, the absence of comparison groups deserves emphasising as a threat to validity. This not only causes difficulties when comparing the outcomes observed with those that would have occurred if no treatment or other commonly used treatments had been applied to similar patients at the same stage of disease, but also makes the possibility of detection bias much more likely. Detailed information on all the important prognostic factors was sometimes lacking.<sup>32,33</sup> In none of the case series was it specified how the patients actually included related to the total population at the institutions undertaking the study who might have been eligible for inclusion. This leaves open the possibility of selection bias. The simplest way of conveying that this was unlikely would have been to state that consecutive patients presenting with the inclusion criteria were included, unless they

<sup>†</sup> During peer review, there were several comments that, of the current licensed applications, it was the effectiveness of rituximab in chemoresistance (as opposed to relapse) that was of the greatest interest. As stated in the protocol, it was not intended to attempt any subgroup analysis according to either of the two main groups of indications. However, the difficulties we encountered in identifying subgroups from the included case series that were wholly relevant to the licensed indications as a whole meant, inevitably, that examining the effectiveness of rituximab for the indication of chemoresistance, as opposed to relapse, would have been impossible.

refused to give informed consent, but in none of the included studies was this stated. Attrition bias or loss to follow-up did not appear to be a problem since, for most reported outcomes, a majority of the patients entering the case series appeared to have been accounted for in the results.

With regard to threats to relevance to the stated object of the review, it should be reiterated that the reported results, even when for the most relevant subset, referred to patient groups who did not completely correspond to the current licensed indications for the use of rituximab.

### Results

These are presented in *Tables 8–10*.

**Clinical response – overall response rates** Results for the total cohorts were available for three of the included studies,<sup>31,32,35</sup> and were 39%, 46% and 48%, respectively. For the most relevant subsets, the results for the three studies<sup>31–33</sup> for which overall response rates were available were 55%, 36% and 52%, respectively.

**Clinical response – complete responses** Rates of complete response contributing to overall response were very low. For the total cohorts,<sup>31,32,35</sup> they were 3%, 3% and 6%, respectively. The pattern was repeated in the two studies providing complete response data for the most relevant subsets<sup>31,33</sup> – 5% and 3%, respectively.

### Clinical response – partial responses (PR)

As a corollary of the low complete response rates, partial responses constituted most of the overall response rate. For the total cohorts, the partial response rates for the three studies for which this information was available<sup>31,32,35</sup> were 35%, 43% and 42%, respectively.

**Duration of response (in those with partial or complete responses)** For the three studies in which data on this outcome were reported,<sup>31,32,34</sup> the median durations were 5.9 months (range, 2.8 to > 12.1), 11 months and 11.2 months (approximate 95% confidence interval (CI) read from graph:<sup>34</sup> 9–16.5), respectively. It should be noted that these figures are not mean or median durations of response for the cohort as a whole but refer to responders alone. No data on duration of response were available for the most relevant subsets in the included case series.

**Time to progression (in those with partial or complete responses)** This was generally slightly longer than duration of response. In two of the

included studies,<sup>31,35</sup> median times to progression were reported as 8.1 months (range, 4.5 to > 18.6) and 13 months, respectively. In a third included study,<sup>32</sup> time to progression was reported to be 15/32 having progressed at median follow-up of 1.5 years. In approximate terms this equates to a median time to progression of at least 18 months. Again, it should be clearly noted that these results do not refer to the whole cohort, just to those who responded. McLaughlin and colleagues<sup>35</sup> gave an indication of the true median time to progression of all patients (as opposed to responders only). In this study the median time to progression for 151 assessable patients out of 166 in total was given as 9.0 months (95% CI, 6.7 to 11.4).

No data on time to progression were available for the most relevant subsets in the included case series.

**Overall survival** No data on overall survival were provided by the authors of any of the included studies.

**Quality of life** No direct measure of impact on quality of life was provided in any of the included studies. A little information was available on impact on symptoms. In the study by McLaughlin and colleagues,<sup>34</sup> 26% of patients had constitutional or disease-related symptoms at baseline. The nature of the symptoms and the degree to which they resolved are tabulated in *Table 9*. The results confirm that the symptoms did resolve – not only in responders but, to a large degree, in non-responders also. A notable feature, however, is the low proportion of patients apparently suffering symptoms.

These findings were confirmed by Davis and colleagues<sup>31</sup> who reported that:

“Of 10 [ $n = 31$ ] patients with ‘B’ symptoms or other disease-related signs and symptoms at baseline, eight experienced complete resolution or transient relief. Two patients with continuing symptoms did not respond to rituximab therapy”.

**Adverse events and toxicity** Adverse events as reported were frequent. In the study by Davis and colleagues,<sup>31</sup> 93% of patients experienced adverse events; 199 events were reported in 70 patients by Foran and colleagues,<sup>32</sup> and 733 events and 68 infections in 165 patients were reported by McLaughlin and colleagues.<sup>34</sup> Ghielmini and colleagues<sup>33</sup> did not report overall adverse event rates. The majority of adverse events were categorised as mild-to-moderate in severity. When different types of adverse event were enumerated,



fever and rigors/chills were the most common. Ghielmini and colleagues<sup>33</sup> gave a breakdown of whether these events occurred in relation to first or subsequent infusions. For fever, 36% of patients suffered this adverse event during the first infusion and 9–11% in subsequent infusions. For rigors, the corresponding figures were 18% and 3–6%. Other specified mild-to-moderate adverse events included infections, leucopenia, asthenia, nausea, dizziness and hypotension.

Severe adverse events were not infrequent. In the study by McLaughlin and colleagues,<sup>34</sup> 38 of 166 patients (23%) experienced 44 serious adverse events. The numbers of serious adverse events in the other three included studies,<sup>31–33</sup> were 4, 12 and 10, respectively. Four fatal events (possibly related to rituximab) were reported over all four of the included studies, giving an approximate fatal adverse event rate of 10 per 1000 patients treated (95% CI, 3 to 26 – assuming a Poisson distribution). However, three of these deaths occurred in mantle cell NHL, which is not a currently licensed indication for rituximab.

Further details on the nature of adverse events are provided in *Table 10*. Importantly, it includes additional data on adverse events supplied by the manufacturer. There was considerable inconsistency between the numbers presented in the published reports and those presented in the full trial reports provided by Roche. However, critically, there was consistency about the pattern of adverse events – most patients experienced some adverse events; the majority of these were mild to moderate; the number of patients affected by severe adverse events was not insubstantial. These statements remained true even if the adverse events considered were restricted to those considered as possibly, probably or of unknown relationship to the study treatment in two studies,<sup>31,35</sup> or as probably related in another study.<sup>32</sup>

### Discussion

The key issue highlighted by this systematic review of the evidence on the effectiveness of treatment with rituximab in Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy, is the frailty of the evidence base. Major concerns include the following.

- There were no comparative trial data.
- There were no data wholly relating to the target population with the condition/severity/and prior treatment record of interest.

- There were no data on key outcomes such as overall survival and impact on quality of life.
- The numbers of patients examined were limited, particularly for the purposes of establishing relatively rare but influential fatal adverse events.
- Allowing for the fact that the study design considered most acceptable to demonstrate effectiveness was non-comparative, the case series as executed do not minimise bias to the greatest extent possible. Reporting of how the cases in the series were drawn from the total populations who might have been eligible was universally absent, and the definition and measurement of clinical response was such as to make detection bias, the likelihood of which is raised by not having a control arm, even higher.
- Data on key prognostic variables in the included case series were frequently absent, reducing the likelihood of valid indirect comparison with case series conducted on the effects of alternative treatments.

With respect to openness to bias, consistency, which undeniably existed for the response rates, should not be confused with accuracy. Unfortunately, all the included case series suffered from the same problems in relation to openness to bias, and the possibility that they all gave inaccurate estimates of the effects and effectiveness of rituximab must be seriously considered.

Given all these concerns, the degree of caution needed to be exercised in interpreting the results of the included studies is at a level at which very little can be categorically stated on the basis of the reported results from the four included effectiveness studies.

### Assessment of effectiveness

Overall effectiveness can only be assessed if accurate information on all the main areas of expected impact have been assessed. In the introduction, the importance of impact on quality of life was highlighted. That quality of life has not been measured directly must therefore be considered a major handicap when assessing the effectiveness of rituximab. Absence of information on overall survival is also problematic, although the difficulty of obtaining such information in NHL needs to be acknowledged.

In lieu of this, information is available that purports to accurately indicate resolution of baseline symptoms, clinical response rates, duration of

response and time to progression. However, to reiterate, all of these are proxies for the main objective of treatment, that is maximising quality of life for the remaining period of life of patients with follicular NHL.

Baseline symptoms were present but, in the reported research, in only approximately one-quarter to one-third of patients. They appeared to resolve in all patients making complete and partial responses to rituximab and, to some extent, in 'non-responders' too. This observation needs, however, to be tempered by the fact that assessment of this outcome, like all others reported below, was open to bias.

For response rates, the best estimate that can be made for overall response rates, taken from the most relevant subsets in the included total cohorts, is a range, from 36%<sup>32</sup> to 55%.<sup>31</sup> However, great caution needs to be exercised in relying on these numerical values, principally because of the likelihood of detection bias in uncontrolled studies. Further, it must also be noted that these overall response rates did not relate directly to the population of particular interest. As to how good an indication of impact on quality of life the response achieved might be, consideration needs to be given to the observation that most of the responses fall into the partial response category, generally defined as  $\geq 50\%$  decrease in size of lesions and no new lesions. Conversely, it should also be recognised that failure to achieve a partial response does not exclude the possibility that some benefit to the patient had occurred. Indeed, the fact that symptoms resolved in some 'non-responders' supports this.

For duration of response, figures were only available for the total cohorts of the included studies. Thus, the proportion of directly relevant patients is likely to be even smaller than for response rates. With this proviso, the range of duration of response ranged from medians of 5.9 months (range, 2.8 to  $> 12.1$ )<sup>31</sup> to 11.2 months (approximate 95% CI, 9 to 16.5).<sup>34</sup> However, again great caution is required in taking these values literally. First, they are likely to be open to levels of detection bias similar to those discussed for response rates and, second, careful consideration needs to be given to the fact that these are median durations of response for responders. As non-response rates were generally over 50% for the total cohorts, and it can reasonably be assumed that the response durations in these were zero, it can be firmly predicted that, although not stated in the reports, the median response duration for the total

cohort, the measure by which effectiveness results would be judged for most cancer therapies, will be 0 months.

For time to progression, again figures were only available for the total cohorts and not for the most relevant subsets of the included studies, with similar implications concerning relevance as for duration of remission. The range of times to progression was 8.1 months (range, 4.5 to  $> 18.6$ )<sup>31</sup> to approximately 18 months (no range given).<sup>32</sup> However, once again all the reasons for caution in interpreting these figures mentioned for duration of response apply. As the only time to progression figure available for both responders and 'non-responders' in the study by McLaughlin and colleagues,<sup>35</sup> 9.0 months (95% CI, 6.7 to 11.4), was not dramatically different from time to progression in responders alone, this could lend further support to the likelihood that some 'non-responders' do get benefit.

The only other outcome on which information was provided in the included studies was adverse events. As for beneficial effects, care needs to be taken in interpreting the numerical values. Experience from placebo-controlled trials clearly indicates that patients may misattribute symptoms stemming from the disease itself to the new treatment to which they are self-evidently being exposed. Even with this in mind, it seems clear that the vast majority of patients experienced adverse events of mild–moderate severity. More significantly, in terms of impact on overall effectiveness, severe adverse events were not infrequent. The most easily comprehensible figure was provided in the study by McLaughlin and colleagues,<sup>34</sup> in which 38/166 (23%) patients were reported to have suffered severe adverse events. However, this rate appears high when compared with other included studies, in which the maximum percentages of patients affected (assuming only one severe event was experienced by any one patient) were 13%, 17% and 8%. Consideration of data supplied by the manufacturer, however, suggested that the figure reported by McLaughlin and colleagues<sup>34</sup> actually appears to be more typical for the proportion of patients affected by a severe adverse event.

Finally, from the total series of 387 patients, four fatal adverse events were recorded. The fact that deaths were noted draws attention to the possibility that rituximab-related deaths can occur, and that great care is required in administering the drug and in avoiding patients in whom TLS is most likely to occur.

For adverse events in general, aside from the problems of the numerical accuracy of the reported figures, some account needs to be taken of the likelihood that the adverse events reported in trials undertaken when experience with rituximab was less advanced may to some extent be avoidable. Careful attention to methods of administration, optimal use of prophylactic agents to counteract known side-effects and restricting administration to personnel/units with greatest experience in the use of rituximab could mean that the adverse events reported in trials overstate the best adverse event rates that could be achieved in current practice. Unfortunately, the degree to which this might be true is unquantifiable and so, for the purposes of this technology appraisal, only the reported rates, acknowledging their imperfections, can be relied on.

In summary, the main likely benefits and disbenefits of rituximab are as follows.

- (a) Rituximab does achieve clinical responses in some patients with Stage III or IV follicular lymphoma that is chemoresistant or is in its second or subsequent relapse after chemotherapy.
- (b) Most of these clinical responses are partial (generally defined as  $\geq 50\%$  decrease in size of lesions and no new lesions).
- (c) The duration of such responses in responders appears to be of a length that would be clinically useful.
- (d) This assumes that partial response brings about abolition of symptoms associated with relapse/recurrence and that the increase in quality of life is sufficient to offset the impairment of quality of life associated with the treatment.
- (e) Prior to treatment, symptoms appear to be present in a minority of patients but these symptoms are abolished completely in responders and, to some extent, in 'non-responders' too.
- (f) Mild-to-moderate adverse events occur in most patients, severe adverse events occur in a minority of patients, and fatal adverse events are very rare, but do occur.
- (g) Some non-responders will experience the adverse effects of rituximab without great benefit.

In the view of the authors, none of these outcomes has been quantified with sufficient accuracy to allow a reliable judgement to be made on whether the overall benefits outweigh the disbenefits, with

particular relevance to the absence of any direct measures of impact on quality of life.

A further major problem in interpreting the available research stems again from an absence of any comparative trials. Without these there is no direct information on how the balance of benefits and disbenefits compares with alternative treatments that might be considered in Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy. This is important in a disease in which it is widely acknowledged that other treatment options, such as CHOP, and newer (although unlicensed) agents, such as fludarabine, suffer similarly from incomplete response rates and significant rates of adverse events, which are often as severe if not more severe in nature. Thus, viewed in isolation, the results for rituximab may appear unpromising but, in relation to alternatives that are currently used, rituximab may represent an improvement. A more unequivocal answer would arise if direct comparisons were made, particularly if they included measurement of impact on quality of life. However, at present there seems to be little impetus for any such RCT to be undertaken.

In such a situation, it is tempting to attempt an indirect comparison of the results of case series on rituximab with results of research on the effectiveness of alternatives. Many researchers consider that such an approach is intrinsically unsound. However, accepting that such an approach might be considered expedient, the following specific reasons are offered as to why, in this review, indirect comparison of the results of separately conducted research is highly likely to yield erroneous results.

- Information on all potentially important outcomes is not available for rituximab studies.
- For rituximab, the information on response rate, duration of response, time to progression and adverse events are likely to be subject to bias and, hence, inaccuracy.
- The information on the effects and effectiveness of the alternative regimes are either absent or open to as much bias as those for rituximab.
- Given the large number of potentially important prognostic factors in NHL and Stage III or IV follicular lymphoma, it appears highly unlikely that sufficient data on these factors have been collected to even begin to attempt to correct the estimates of effects and effectiveness for small but potentially extremely influential differences in prognostic factors, which alone might account for or obscure differences in the outcomes observed.

Finally, with respect to comparators, it should be noted that in the situation where rituximab is being used as a treatment of last resort, that is, as fourth- or fifth-line therapy, the comparator of interest is likely to be supportive treatment only. This appears to be particularly true when the disease is chemoresistant or refractory to earlier treatment options. In this circumstance, although the absence of any direct comparisons of effectiveness still presents problems, these are possibly fewer because the natural history at this stage of the disease is clearer; that is, it is safer to assume that **any** clinical response observed is likely to be associated with useful improvements in quality of life. Controlled trials would still be the ideal evidence base for assessing effectiveness in this situation but uncontrolled trials may provide an acceptable alternative.

One included study<sup>34</sup> did provide brief information on response rate in ‘highly chemoresistant disease’, defined as never having achieved any response to previously attempted treatment. In this very small subgroup, for which the authors gave no definite information about stage, type of prior treatment or diagnosis, 6/21 (29%; 95% CI, 9 to 48) achieved a response with rituximab in a situation where no clinical response might have been expected. However, there is no further information on what the impact on the patients of such responses might have been. The Roche submission to the National Institute for Clinical Excellence (NICE)<sup>36</sup> does provide further unpublished information on subgroup analyses from the study by McLaughlin and colleagues<sup>34,35</sup> by other categories of ‘patients without satisfactory treatment options’, representing 118 patients out of the whole cohort of 166. This figure included the following categories: at least three prior chemotherapy treatments (74 patients); resistant to last chemotherapy treatment (44); resistant to all chemotherapy treatments (16); failing prior autologous bone marrow transplantation (23); relapsed and  $\geq 70$  years of age (25);  $> 60$  years of age with concomitant disease (22). The response rates and median times to progression are reported as being similar to those achieved overall. Again, this provides some support for the likelihood that, at points in disease process at which other currently available treatment options would be rejected, use of rituximab does bring about clinical responses in sufficient numbers of patients and of durations that are likely to be clinically useful. However, the provisos concerning the accuracy of the numerical data provided through openness to bias, the degree to which the subgroups map on to the licensed indications, and whether the

clinical responses observed are translated into useful improvement in quality of life that outweighs the adverse events associated with treatment, must be vigorously reiterated.

As to the degree to which our conclusions confirm or differ from those of other systematic reviews of effectiveness, no other systematic reviews were found of the effectiveness of rituximab in Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy, other than that conducted in this report. Good summaries of the existing evidence were encountered in two reports in particular: the Roche submission to NICE<sup>36</sup> and the Cancer Care Ontario Practice Guideline Initiative Evidence Summary on Rituximab in Lymphoma.<sup>37</sup> Although the search strategies employed in each of these reports were rigorous, both lacked detailed critical assessment of the quality of included studies and formal consideration of the potential impact of bias on how the results should be interpreted. Comparing the review of effectiveness in this technology appraisal with the other summaries identified revealed little disagreement about the studies that should be included or in the main details of the results that these studies contained. In comparison with the Roche submission, there were differences concerning abstracted data on adverse events and the interpretation of the research results generally (it should also be noted that Roche were no better able than ourselves to isolate the results of those patients in the included case series that were directly relevant to the current licensed indications for rituximab). The implications of these differences are considered in more detail in the next chapter (economic analysis). However, in essence, the main difference related to the certainty with which the observed results of research were translated into firm conclusions. Taking the nature of the available research evidence fully into account (that is, the lack of any RCTs or any trials with comparators), it is considered that caution should be used when drawing any solid conclusions, when considering not only clinical effectiveness but also quality of life evidence, although there is some evidence that rituximab produces a ‘useful’ clinical response. Such caution is not evident in the Roche submission to NICE.<sup>36</sup> In contrast, in the Cancer Care Ontario Practice Guideline Initiative Evidence Summary on Rituximab in Lymphoma,<sup>37</sup> it is clear that, although not formally assessed, the authors did recognise the bias to which the available evidence on effectiveness was open. Consequently, they felt unable to issue a formal

practice guideline without high quality effectiveness data provided by RCTs.

## Summary of effectiveness

- A systematic review of effectiveness was undertaken.
- The review question was, 'What is the effectiveness of rituximab for Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy?'
- The comprehensive search for studies assessing the effectiveness of rituximab was based on interrogation of four large bibliographic databases (MEDLINE, EMBASE, Science Citation Index and the Cochrane Library).
- The initial inclusion criteria on study design and population had to be relaxed in order to include any studies assessing effectiveness at all.
- No comparative studies were identified.
- Four case series were finally included, incorporating information on 387 patients.
- All were open to substantial bias, which suggests a high level of caution is required in interpreting results, particularly their numerical values.
- No information was available on overall survival or direct measurement of impact on quality of life.
- Rituximab does achieve clinical responses in some patients with Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy.
- Most of these clinical responses are partial (generally defined as  $\geq 50\%$  decrease in size of lesions and no new lesions).
- Duration of responses in responders appear to be of a length that would be clinically useful.
- This assumes that partial response brings about abolition of symptoms associated with relapse/ recurrence and that the increase in quality of life is sufficient to offset the impairment of quality of life associated with the treatment.
- Prior to treatment, symptoms appear to be present in a minority of patients. These symptoms are abolished completely in responders and, to some extent, in 'non-responders' also.
- Mild-to-moderate adverse events occur in most patients; severe adverse events occur in a minority of patients; fatal adverse events are very rare but do occur.
- Some non-responders will experience the adverse effects of rituximab, without great benefit.
- The extent to which beneficial effects are outweighed by adverse events is impossible to quantify.
- Any impression of a poor ratio of benefit to disbenefit needs to be tempered by the observation that incomplete response rates and severe adverse events are common to all currently used treatments for this condition.
- 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 for currently used alternatives.
- There are strong arguments that indirect comparison, which might be considered expedient in the absence of direct comparisons, would yield highly erroneous estimates of relative effectiveness.
- The need for direct comparisons may be least when rituximab is being used as a treatment of last resort, that is, as fourth- or fifth-line treatment, especially when the lymphoma is chemoresistant or refractory.
- The need for circumspection about concluding that the rituximab is definitely effective was shared by one of two other good recent summaries of research.

**TABLE 4** Population characteristics of total cohorts

Study characteristic	Davis et al., 1999 <sup>31</sup>	Foran et al., 2000 <sup>32</sup>	Ghielmini et al., 2000 <sup>33</sup>	McLaughlin et al., 1998 <sup>34,35</sup>
Type	Case series	Case series	Case series	Case series
Aim	To evaluate the safety and efficacy of rituximab in bulky relapsed or refractory low-grade follicular NHL	To confirm the activity of rituximab follicular lymphoma including monitoring of blood and bone marrow for Bcl-2/JH gene rearrangement	Interim report of efficacy and toxicity of induction treatment of ongoing randomised trial rituximab vs extended rituximab in follicular and mantle cell lymphomas	Pivotal trial on the safety and clinical efficacy of rituximab in relapsed indolent lymphoma
Total number of patients	31	70	120	166
<b>Demographics</b>				
Age, years	Median 55 (range 33–79)	Median 50 (range 35–77)	Not given overall	Median 58
Gender	52% male, 48% female	54% male, 46% female	Not given overall	57% male, 43% female
<b>Inclusion/exclusion criteria given</b>				
Condition	Yes: low grade or follicular B cell NHL, IVF types A–D	Yes: follicular lymphoma	Yes: follicular and mantle cell lymphoma	Yes: low grade or follicular B cell lymphoma (only 130 are follicular NHL)
Stage	No: all stages included	No: stage not given	No: all stages included	No: all stages included
Prior therapy	Yes: primary therapy failure/relapsed	Yes: patients must have been previously treated	No: treated and untreated included	Yes: patients must be relapsed ( $\leq 4$ times)
Age	Yes: $\geq 18$ years	No: but all patients $> 18$ years old	Yes: $> 18$ years	Yes: adult
Gender	No: male and female included	No: male and female included	No: male and female included	No: male and female included
CD20 status	Yes: CD20+ only	Yes: CD20+ only	Yes: CD20+ only	Yes: CD20+ only
Performance status	Yes: WHO status 0–2 only	No: but all patients' performance status 0–2	No: but 94% of follicular patients' performance status $\leq 1$	Yes: Zubrod performance status 0–2
Pregnancy/lactation	Yes: must not be pregnant or lactating and using birth control	No	No	No
Other serious disease/infection	No	No	Yes: excluded	Yes: excluded
HIV/hepatitis	No	Yes: excluded	Yes: excluded	Yes: excluded
CNS involvement	No	Yes: excluded	Yes: excluded	Yes: excluded
Other anti-cancer	No	No	Yes: must be $\geq 30$ days since prior treatment therapy	Yes: must be $\geq 3$ weeks since therapy
Other criteria	Blood counts; must have bidimensionally measurable disease; at least 1 lesion $> 10$ cm; life expectancy $\geq 4$ months	Transformation to diffuse large B cell lymphoma excluded	Must have measurable disease	Must have progressive measurable disease, patients with lesions $\geq 10$ cm, recent major surgery excluded

**TABLE 5** Population characteristics of most directly relevant subsets of patients

<b>Study characteristic</b>	<b>Davis et al., 1999<sup>31</sup></b>	<b>Foran et al., 2000<sup>32</sup></b>	<b>Ghielmini et al., 2000<sup>33</sup></b>	<b>McLaughlin et al., 1998<sup>34,35</sup></b>
Total number in study	31	70	120	166
Percentage of patients relevant to review, i.e. meeting current licensing indications	Not known	Not known	Not known	Not known
Reasons for uncertainty	71% have follicular B cell NHL but only 68% of 31 are Stage III/IV. Patients (%) having two or more relapses unknown	Only 55/70 had two or more previous treatments and stage for all patients is not given	78/120 have follicular lymphoma but only 84% have Stage III/IV disease and only 76% have had two or more relapses	Of 130/166 patients with follicular B cell NHL, percentage with Stage III/IV disease not known (overall 147/166). Patients with ≥ 2 relapses not known (overall 73/166)
Nearest relevant subset of cohort for which results are given	22 patients with follicular B cell NHL	55 follicular lymphoma patients with two or more previous treatments	78 patients with follicular lymphoma	No other cohort available
Information not given about this subset	Percentage who are Stage III/IV with two or more relapses	Percentage who are Stage III/IV	Percentage who are Stage III/IV with two or more relapses	N/A
<b>Demographics of this subset</b>				
Age, years	Not known	Not known	Median 57 (range 31–78)	N/A
Gender	41% male, 59% female	Not known	Not known	

**TABLE 6** Details of interventions and outcomes for total cohorts

	<b>Davis et al., 1999<sup>31</sup></b>	<b>Foran et al., 2000<sup>32</sup></b>	<b>Ghielmini et al., 2000<sup>33</sup></b>	<b>McLaughlin et al., 1998<sup>34,35</sup></b>
<b>Intervention</b>	375 mg/m <sup>2</sup> i.v. infusion once weekly for four doses; initial dose 50 mg/h for first hour then up to maximum of 400 mg/h	375 mg/m <sup>2</sup> once weekly for 4 weeks i.v. in 1 litre normal saline	375 mg/m <sup>2</sup> i.v. over 3–5 hours on weeks 1–4 on same day of week	375 mg/m <sup>2</sup> i.v. once weekly x 4 weeks (days 1, 8, 15, 22)
<b>Concomitant treatment</b>				
Corticosteroids banned	Yes	Yes	Yes	Yes
Other treatment allowed	Prophylactic allopurinol (four patients)	Antipyrexics, antihistamines, allopurinol and hydration for those at risk of TLS	Antihistamines, paracetamol, allopurinol and hydration	Acetaminophen/diphenhydramine
<b>Pre-treatment tests stated</b>				
CT/MRI scans/X-rays	Yes	Yes	No	Yes
Serum chemistries	No	Yes	No	Yes
Blood counts	No	Yes	No	Yes
Physical examination	Yes	Yes	Yes	Yes
Pathology specimen	No	No	Yes	No
Bone marrow tests	Yes	Yes	Yes	Yes
<b>Outcome measures</b>				
Clinical response	Yes	Yes	Yes	Yes
Adverse events	Yes	Yes	Yes	Yes
Survival analysis	No	No	No	No
Quality of life	No	No	No	No
Time to progression	Yes	Yes	No	Yes
Duration of response	Yes	Yes	No	No
Other	Mortality	Mortality, molecular response	Mortality, molecular response	Pharmacokinetic analysis, monitoring B cell parameters
<b>Clinical response assessment methods</b>	Serial physical examination, CT/MRI scans; investigator and sponsor assessments only	Not detailed; no mention assessment by independent assessment panel	Not available	Serial physical examination; CT/MRI scans; all patients > 40% reduction assigned final response status by blinded independent panel of radiologists and oncologists

continued



TABLE 6 contd Details of interventions and outcomes for total cohorts

	Davis et al., 1999 <sup>31</sup>	Foran et al., 2000 <sup>32</sup>	Ghielmini et al., 2000 <sup>33</sup>	McLaughlin et al., 1998 <sup>34,35</sup>
<b>Clinical response definitions</b>				
Complete response*	All visible lymph nodes on CT scans of neck, chest, abdomen, pelvis < 1 cm <sup>2</sup> , any previously palpable node no longer palpable or negative on biopsy/ fine needle aspiration. Bone marrow negative, liver and spleen returned to normal size; confirmed at ≥ 28 days	Disappearance of all clinically detectable disease (including bone marrow), nodes ≤ 1 cm <sup>2</sup> on two occasions ≥ 4 weeks apart	Not stated	Resolution of all symptoms for ≥ 28 days
Partial response*	≥ 50% decrease lesion size/no new lesions; confirmed at ≥ 28 days	≥ 50% decrease lesion size on two occasions 1 month apart or estimated ≥ 50% decrease of unmeasurable disease; no new lesions	Not stated	≥ 50% decrease in size of lesions, no evidence of progressive disease ≥ 28 days
Stable disease	Did not show ≥ 50% increase or decrease in size lesions	< 50% decrease in lesion size or < 25% increase in lesion size and/or unmeasurable disease	Not stated	Non-responder
Progressive disease	≥ 50% increase lesion size/new lesions	≥ 25% increase size one or more lesions or any new lesions	Not stated	No complete or partial response
* Complete and partial response rates often combined into overall response rate				

TABLE 7 Quality assessment, threats to validity and relevance

	Davis et al., 1999 <sup>31</sup>	Foran et al., 2000 <sup>32</sup>	Ghielmini et al., 2000 <sup>33</sup>	McLaughlin et al., 1998 <sup>34,35</sup>
Number in case series	31	70	120	166
Source of case series	No information given	70 eligible patients from eight UK institutions over 12-month period; no other information given	Reports on first 120 patients entered into trial; no other information given	166 eligible patients enrolled at 31 centres in USA and Canada in 12-month period; no other information given
<b>Characteristics well defined?</b>				
Whole cohort	Yes	No; no stage given	No; gender not given	Yes
Parent population	No	No	No	No
<b>Cohort percentage relevant to review?</b>				
	Not known	Not known	Not known	Not known
<b>Follow-up</b>				
Adequate (< 10% unreported)	Not stated	Not stated	Not stated	Not stated
Length	At least 1 year	Median 1.5 years	12-week assessment; no follow-up	Median 36 months
<b>Could analysis be done according to possible prognostic factors?</b>				
Stage	Yes	No	No	No (Yes*)
Performance status	Yes	No	No	No (Yes*)
Age	Yes	No	No	Yes
Gender	Yes	No	No	Yes
Previous treatment/relapses	Yes	Yes	Yes	Yes
Resistance	Yes	No	No	Yes
Blood counts/serum chemistries	Yes	No	Yes	Yes
Presence of B symptoms	Yes	No	Yes	No (Yes*)
Other	Bone marrow infiltration, extranodal disease, splenomegaly	–	–	Positive bone marrow tests
<b>Threats to validity</b>				
Selection bias	Yes	Yes	Yes	Yes
Not enough information on prognostic factors	–	Yes	Yes	–
No comparator	Yes	Yes	Yes	Yes
Non-blinded assessment of outcome	Yes	Yes	Yes	–
Inadequate follow-up time	Yes	Yes	Yes	–
Not enough information on follow-up	Yes	Yes	–	Yes
Threats to relevance	71% had follicular B cell NHL but only 68% of 31 were Stage III/IV. Percentage of patients having two or more relapses unknown	Only 55/70 had two or more previous treatments and the stage for all patients was not given	78/120 had follicular lymphoma but only 84% had Stage III/IV disease and only 76% have had two or more relapses	Of 130/166 patients with follicular B cell NHL, percentage with Stage III/IV disease not known (overall 132/166). Patients with ≥ two relapses not known (overall 73/166)
* Additional information obtained from data submitted by manufacturer				

**TABLE 8** Results of rituximab case series

	Davis et al., 1999 <sup>31</sup>	Foran et al., 2000 <sup>32</sup>	Ghielmini et al., 2000 <sup>33</sup>	McLaughlin et al., 1998 <sup>34,35</sup>
<b>Study characteristics</b>				
Total number in study	31	70	120	166
Follow-up period	At least 1 year	Median 1.5 years	12 weeks assessment, no further follow-up	Median 36 months
Losses to follow-up and reasons	Not stated	Not stated	N/A	None
Drop-outs/exclusions before assessment and reasons	Three excluded (one treated with corticosteroids, two with incomplete response evaluations)	Three patients didn't complete treatment due to adverse events	2/78 excluded as not follicular lymphoma; 1/78 excluded as had previous treatment < 28 days before; others unknown	15 (one did not start treatment; eight took corticosteroids; one had surgery; one lacked measurable lesions; four dropped out due to adverse events)
Deaths	None during treatment; one during follow-up at 10 months	Not stated	5/120 before or during treatment	27 during follow-up: progressive disease
Patients evaluated for response	28	70	74/78 follicular lymphoma patients, of whom five missing; 36/42 mantle cell lymphoma	166
Evaluated as intention-to-treat?	Yes	Yes	No	Yes
<b>Clinical response rates</b>				
Overall response rate	39% (95% CI, 22 to 56)	46% (95% CI, 33 to 59)	Not given overall	48% (95% CI, 41 to 56)
Complete response	3%	3%	–	6%
Partial response	35%	43%	–	42%
<b>Adverse events</b>				
Number of patients evaluated	Not stated	70	Not stated	165
Total events (further details, see Table 9)	93% of patients	189 events	Not stated	733 events + 68 infections in year after treatment
Mild–moderate events	Fever (61%), chills (36%), leucopenia (23%), nausea (19%), dizziness (19%), throat infection (19%), infections (six cases)	177 events, of which 12 were infections; pain/lethargy/fever in 39% patients	Fever (36% patients at first infusion, 9–11% at following infusions); rigors (18% at first infusion, 3–6% at following infusions); 20% asthenia, 17 cases hypotension	94% of events
Severe events	Four events	12 events of which two were infections	Ten events	23% patients
Fatal events including TLS	None	Not stated	Four events	None

continued

**TABLE 8 contd** Results of rituximab case series

	Davis et al., 1999 <sup>31</sup>	Foran et al., 2000 <sup>32</sup>	Ghielmini et al., 2000 <sup>33</sup>	McLaughlin et al., 1998 <sup>34,35</sup>
<b>Other outcomes</b>				
Time to progression (in responders)	Median 8.1 months (range 4.5 to > 18.6)	15/32 progressed at median follow-up 1.5 years	Not given	Median 13 months
Duration of response (in responders)	Median 5.9 months (range 2.8 to > 12.1)	Median 11 months	Not given	Median remission duration 11.2 months
Quality of life	Not given	Not given	Not given	Not given
Survival analysis	Not given	Not given	Not given	Not given
Other	–	–	Values of lymphocyte subsets: B cell counts reduced during treatment	–
<b>Nearest subset of relevant patients, i.e. meeting licensing indications</b>				
	Patients with follicular B cell NHL (n = 22)	Patients with follicular B cell NHL in second or subsequent relapse (n = 55)	Patients with follicular B cell NHL	No other subsets given
<b>Response rates for subset</b>				
Overall response rate	55% 75% responders female	36%	52% (SD 28%; percentage difference 15%; missing 5%)	N/A
Complete response	5%	–	3%	–
Partial response	50%	–	49%	–
Other outcomes for subset	None given	None given	Molecular response: gene rearrangement in 33/37 follicular lymphoma patients	N/A
<i>SD, standard deviation</i>				

**TABLE 9** Resolution of symptoms in study by McLaughlin and colleagues, 1999<sup>34</sup>

Symptom	Responders (n = 80)		Non-responders (n = 86)	
	Number at baseline	Number resolving	Number at baseline	Number resolving
Weight loss	2	2 (100%)	3	3 (100%)
Fever	2	2 (100%)	4	2 (50%)
Night sweats	6	6 (100%)	8	4 (50%)
Pain	13	12 (92%)	7	6 (86%)

**TABLE 10** Detailed table of adverse events (by patients affected (%) where possible)

	Davis et al., 1999 <sup>31</sup>	Foran et al., 2000 <sup>32</sup>	Ghielmini et al., 2000 <sup>33</sup>	McLaughlin et al., 1998 <sup>34,35</sup>
<b>Study characteristics</b>				
Total number in study	31	70	120	166
Evaluated for toxicity	Not stated	70	Not stated	165
Timescale of adverse events	Events observed during treatment period and up to 30 days after. Incidence of events declined after first infusion	All events stated as infusional except for infections	All adverse events are during treatment (14 serious adverse events overall reported in study)	During treatment or up to 30 days after (infections up to 1 year after treatment). Most seen in first infusion; 55% had no toxicity for rest of treatment
Deaths	No deaths during treatment No TLS reported	None stated	Four deaths (one infection, three cardiovascular); three were myeloid cell leukaemia patients	No treatment-related deaths
Number of events (treatment-related in parentheses)				
Mild–moderate	*	*	Not given	*
Severe	*	*	10 events	*
Total	*	*	Not given	*
Any events (treatment-related in parentheses) (bold confirms figure as reported)				
Mild–moderate	†	†	Not given	<b>23%*</b>
Severe	*	*	Not given	*
Total	–	–	Not given	–
<b>Haematological events</b>				
<b>Anaemia</b>				
Mild–moderate	Not given	17%	Not given	1%
Severe	Not given	4%	1%	1%
<b>Leucopenia</b>				
Mild–moderate	23% (all grades)	36%	Not given	7%
Severe		3%	Not given	1%
<b>Neutropenia</b>				
Mild–moderate	Not given	7%	Not given	4%
Severe	Not given	7%	Not given	1%
<b>Thrombocytopenia</b>				
Mild–moderate	Not given	Not given	Not given	1%
Severe	Not given	Not given	Not given	3%
<b>Non-haematological events</b>				
<b>Pain</b>				
Mild–moderate	Not given	37%	Not given	13%
Severe	3%	7%	Not given	0%
<b>Fever</b>				
Mild–moderate	61% (all grades)	26%	36% (first infusion)	51%
Severe		0%	Not given	0%
<b>Nausea/vomiting</b>				
Mild–moderate	19% (all grades)	21%	Not given	28%
Severe		0%	Not given	1%

continued

**TABLE 10 contd** Detailed table of adverse events (by patients affected (%) where possible)

	Davis et al., 1999 <sup>31</sup>	Foran et al., 2000 <sup>32</sup>	Ghielmini et al., 2000 <sup>33</sup>	McLaughlin et al., 1998 <sup>34,35</sup>
<b>Non-haematological events contd</b>				
Rigors				
Mild–moderate	Not given	23%	Not given	Not given
Severe	Not given	0%	Not given	Not given
Chills				
Mild–moderate	36% (all grades)	Not given	Not given	31%
Severe		Not given	Not given	1%
Headache				
Mild–moderate	Not given	7%	Not given	16%
Severe	Not given	0%	Not given	1%
Bronchospasm				
Mild–moderate	Not given	3%	Not given	9%
Severe	6%	1%	Not given	1%
Hypotension				
Mild–moderate	Not given	17%	14% (first infusion)	11%
Severe	3%	1%	Not given	1%
Rash and pruritis				
Mild–moderate	Not given	6%	Not given	22%
Severe	Not given	1%	Not given	1%
Arrhythmia				
Mild–moderate	Not given	Not given	Not given	3%
Severe	Not given	Not given	Not given	2%
Dizziness				
Mild–moderate	19% (all grades)	6%	Not given	7%
Severe		1%	Not given	0%
Asthenia				
Mild–moderate	Not given	Not given	20%	15%
Severe	Not given	Not given	Not given	0%
Infections				
Mild–moderate	16%	17%	Not given	61 events
Severe	0%	3%	1%	7 events
* Additional information obtained from data submitted to NICE by manufacturer				
† Mild–moderate adverse events are taken to be WHO scale grades 1–2; severe events are grades 3–5				

# Chapter 4

## Economic analysis

### Objectives

The original objectives, as defined in the protocol, were amended slightly, and restated as follows.

- To review systematically the evidence on costs and health economic impact of rituximab in Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy.
- To identify the strengths and weaknesses of available cost-effectiveness studies and identify those areas that might be revised or extended.
- To undertake some further analysis selectively using published data.

### Methods for economic analysis

It was anticipated *a priori* that the quality of evidence on effectiveness would be the main limiting factor in an accurate assessment of health economic impact, and the pre-specified method was designed on this basis. Following confirmation from the systematic review of effectiveness that this prior assumption was confirmed, no amendments to the protocol relating to economic analysis were made.

### Search strategy

A specific search strategy for information on costs, cost-effectiveness and quality of life involved searches of:

- bibliographic databases – MEDLINE (Ovid) 1966–September 2000, NHS Economic Evaluation Database
- Internet sites of UK health economics units.

Details of the search terms used are given in appendix 11. Searches for economics information on rituximab and fludarabine (see *Health Technology Assessment*, vol 6, no 2) were conducted jointly. The industry submission from Roche Products Ltd to NICE in support of rituximab was treated as one of the included existing economic evaluations considered in the economic analysis.<sup>36</sup> In addition to the specific search strategy for economic evaluations specified above, any study encountered in the searches for

effectiveness that referred in any way to costs was also considered.

### Handling of the information identified

The inclusion criteria allowed all information on costs, quality of life or previous health economics evaluations of rituximab in the treatment of NHL to be included. The quality of all included studies was assessed. In the case of full economic evaluations, the criteria used were based on the *BMJ* guidelines for economic appraisals.<sup>38</sup> All data from the included studies were abstracted into tables for presentation in this report and for consideration of conclusions.

### Results

#### Estimation of net benefits (that is, taking account of disbenefits)

No further information was identified that challenged the assessment of net benefits expressed in chapter 2. It must be emphasised that the nature of the evidence precludes accurate quantitative estimates of net effect, although qualitatively it is acknowledged that net benefit is likely to accrue, despite the considerable uncertainties. The uncertainties are considered to make it impossible to assess reliably whether the net benefit associated with rituximab is the same, less or more than alternatives. The implications of this are greatest in attempting to decide whether rituximab should be used at the earliest stage allowed by the current licence (that is, as a third-line treatment option), and least when it is being used as a treatment of last resort.

#### Estimation of net costs

Availability of information on costs was limited. The best study of costs, particularly the wider costs of rituximab, was conducted by Sweetenham and colleagues,<sup>39</sup> and was updated in the Roche submission to NICE. This study<sup>39</sup> also provided information on the costs of the alternative treatment options, CHOP and fludarabine, which again fed into the economic assessment presented by Roche. These latter components are discussed further in the critique of other authors' attempts to assess cost-effectiveness.

The method of assessing costs employed by Sweetenham and colleagues<sup>39</sup> involved collecting information on adverse events and resource use over a 6-month period, in parallel with one of the effectiveness case series included in the systematic review of effectiveness.<sup>32</sup> Data were obtained for 64 of the 70 patients included. Data on the remaining six patients were unavailable. Unit costs were applied to resource use identified in the following areas: tests; adverse event treatment; drug acquisition; drug administration in inpatient setting; drug administration in outpatient setting. Unit costs in the updated costing in the Roche submission to NICE were derived from a variety of specified sources: for example, Personal Social Services Research Unit; Pharmaceutical Information Costs Assessment System; *BNF*.

On this basis, the costs per patient of a full course of rituximab were as follows.

Cost of administration while an inpatient	£370
Cost of administration while an outpatient	£424
Drug acquisition cost	£4890
Cost of adverse events	£119
Cost of tests	£741
Total costs	£6544

In relation to the cost of other second-line therapies (CHOP £8744; fludarabine £11,808), the high acquisition cost for rituximab was offset by greatly reduced costs of adverse events. Thus, overall, it appeared to be the cheapest option. However, with respect to the costs attributable

to adverse events, a note of concern needs to be raised, as the adverse events profile stated as being derived from 64/70 patients from the study by Foran and colleagues seemed to underestimate the published adverse events rates.<sup>32</sup> The two are compared in *Table 11*.

Even allowing for the fact that all observed adverse events in the case series may not have required treatment, and taking into account the fact that the adverse events reported in the published paper are for patients (many of whom may have suffered more than one adverse event), the disparity between the number of treated adverse events in the costing study by Sweetenham and colleagues<sup>39</sup> and the original study<sup>35</sup> gives a warning that the cost figure of £6544 per patient may be an underestimate. In the comparison of costs of administration of rituximab with those of CHOP and fludarabine, there are further concerns relating to the population and manner used to derive resource use for CHOP and fludarabine. These concerns are discussed further below. Despite this, it seems likely that the costs of administering rituximab are, at worst, similar to those of administering two commonly used alternative treatment regimes for NHL.

### Cost impact of rituximab

NHS savings from the use of rituximab seem unlikely, based on the consideration that rituximab seems to represent an additional treatment option for Stage III or IV relapsed/refractory follicular NHL. This is because it is being used in a condition with a prolonged course, during which as many available treatments as seem to offer some hope of achieving response will be applied, and

**TABLE 11** Comparison of adverse events as reported in original publication and economic analysis derived from the same study

Adverse event	Foran et al., 2000 <sup>32</sup> n = 70		Sweetenham et al., 1999 <sup>39</sup> n = 64
	Number of patients affected		Number of treated adverse events
	Mild-moderate	Severe	All grades
Nausea/vomiting	15	0	8
Neutropenia	5	5	0
Leucopenia	25	2	Not stated
Infection	12	2	16
Fever	18	0	
Thrombocytopenia	Not stated	Not stated	1
Anaemia	12	3	0
Other	Not calculable		43
<b>Total</b>	58 (mild) 37 (moderate)	14	68



it seems highly unlikely that treatment with rituximab will completely displace any existing currently available treatment options. Hence, overall NHS costs can only increase. The size of this increase will depend on the number of patients with Stage III or IV follicular lymphoma who receive rituximab at some stage in their disease. On this basis, a crude worst estimate of the total budget impact can be derived based on annual incidence. This assumes that the annual incidence acts as a rough proxy for the number of patients who, in any year, will be entering a defined period of their disease in which rituximab may be considered the most appropriate treatment option. The calculation is as follows.

Approximate annual overall incidence of NHL	13.4/100,000
Incidence of NHL in England and Wales (population 55 million)	7370
Incidence of Stage III or IV follicular lymphoma (assuming that 40% rather than 22% of NHL is follicular)	2653
Cost of administering one course of rituximab	£6544
Total cost per annum	£17.4 million

This represents a steady-state assessment and, in the short term, the budget impact may be higher as individuals in the prevalent pool receive treatment. However, the fact that a number of patients will already be receiving rituximab argues that the effect will not be overwhelming and, indeed, a proportion of the £17.4 million may already have been accounted for in the NHS budget. Another consideration which suggests that £17.4 million figure is an overestimate is the likelihood that not all patients will receive rituximab at some stage in the management of their condition; considerations which suggest that this figure is an underestimate are that the suggested cost of administration of rituximab is too low at £6544, and that some patients may receive repeated courses of rituximab. Finally, it should be noted that this estimate is unlikely to change greatly whether rituximab is used as early in the course of disease as is currently allowed (second relapse/third-line treatment option) or as a treatment of last resort. Clearly, the estimate will be somewhat less if rituximab is used as a treatment of last resort because, inevitably, some patients will die between the third- and fourth-/fifth-line treatment options being offered. However, the size of the reduction will be small relative to the high proportion of patients who would, the

authors consider, be offered rituximab at some stage of their disease if it were freely available.

Irrespective of the above observations on the potential for inaccuracy, the total budget impact overall would be relatively modest. For an average health authority with a population of 500,000, the worst-case estimate of annual additional cost would be £160,000.

### Other attempts to assess cost-effectiveness

Only one relevant published paper was found, that by Sweetenham and colleagues.<sup>39</sup> This paper formed the basis of the economic analyses reported in the Roche submission to NICE and, hence, the critique below focuses solely on the Roche submission.<sup>36</sup> In *Tables 12–14*, some of the key study characteristics are described and the results reported for the base-case cost-effectiveness analyses.

The economic analysis reported in the Roche submission to NICE<sup>36</sup> considered the use of rituximab in patients with Stage III or IV follicular lymphoma who are chemoresistant or in their second or subsequent relapse after chemotherapy. The comparators used in the incremental analysis were two alternative forms of chemotherapy, fludarabine and CHOP, which represented 'standard clinical practice in the NHS'. The central assumption was that there were equivalent clinical outcomes for the three interventions of interest (rituximab, CHOP and fludarabine). This was held to be the case for both the response rate to therapy and, for those patients who do respond, the duration of the response. On the basis of this assumption, a cost-minimisation analysis was undertaken that focussed solely upon the costs associated with the alternative treatments. This was undertaken from the perspective of the NHS and the main result was that, overall, rituximab was associated with a lower cost, because of its favourable side-effects profile. It was therefore defined as the 'dominant' alternative.

As discussed above, the evidence supporting the assumption of equivalent clinical outcomes is very weak. However, given that the results indicated that rituximab was associated with a lower cost, the strengths and weaknesses of the cost analysis also needed to be explored. Many of the data on resource use associated with the use of rituximab were drawn from the Phase II clinical trial, whereas similar data for CHOP and fludarabine were taken from a separate observational study.

**TABLE 12** Assessment of cost-effectiveness analyses: study characteristics and results

Roche submission to NICE <sup>36</sup>		
Comparators	Two alternative comparators (to rituximab) are used: CHOP and fludarabine	
Perspective	Health sector	
Type of economic evaluation	Main analysis	Cost-minimisation analysis
	Further analysis	Cost-utility analysis (referred to as an 'illustrative analysis')
Base case effectiveness result	Response rates	No difference between treatments
	Response durations	Rituximab assumed to be 'at least as good as the alternatives considered in terms of response duration'
	Adverse events	Rituximab associated with fewer serious adverse events
Base case cost result	CHOP	£8,744
	Fludarabine	£11,808
	Rituximab	£6,544
Base case incremental cost-effectiveness ratio	Not estimated	
	Dominance observed for rituximab (i.e. lower cost, similar clinical effectiveness and fewer adverse events)	

**TABLE 13** Assessment of cost-effectiveness analyses: effectiveness and cost data

Roche submission to NICE <sup>36</sup>	
Source(s) of effectiveness data	Phase II trials for rituximab and observational studies for CHOP and fludarabine (Hochester <i>et al.</i> , 1992; Redman <i>et al.</i> , 1992) <sup>*</sup>
Analysis of effectiveness data	No further analysis reported in cost-effectiveness section of report
Quality-of-life data	Time in treatment and remission states: based on assumptions
	Utility scores associated with treatment and remission states: derived from data relating to women with early stage breast cancer (Jansen <i>et al.</i> , 1998) <sup>*</sup>
Resource use data	For rituximab, most data used in analysis were taken from Phase II trial <sup>32</sup> ( $n = 64$ ), except for data on use of tests/investigations, which were assumed to be mean across CHOP and fludarabine For CHOP ( $n = 48$ ) and fludarabine ( $n = 50$ ), data taken from observational study
Source(s) of cost data	Taken from range of national and local sources, e.g. University of Kent annual survey, BNF, and local hospital trusts
Analysis of cost data	No statistical analysis reported, cost data simply compared
Price year	2000
Discounting	Not relevant: data related to 6-month period only
<sup>*</sup> Citations provided in Roche submission:	
Hochester HS, Kyungmann K, Green M, et al. Activity of fludarabine in previously treated non-Hodgkin's low grade lymphoma: results of an Eastern Cooperative Oncology Group study. <i>J Clin Oncol</i> 1992;10:28–32	
Redman J, Cabanillas F, Velasquez W, et al. Phase II trial of fludarabine phosphate in lymphoma: an effective new agent in low-grade lymphoma. <i>J Clin Oncol</i> 1992;10:790–4	
Jansen S, Stiggelbout A, Wakker P, et al. Patients' utilities for cancer treatments: a study of the chained procedure for the standard gamble and time tradeoff. <i>Med Decis Making</i> 1998;18:391–9	

**TABLE 14** Assessment of cost-effectiveness analyses: sensitivity analyses

Roche submission to NICE <sup>36</sup>	
Approach	One-way sensitivity analysis only
Parameters	Incidence of adverse events (arbitrarily varied by $\pm 25\%$ ) Administration of chemotherapy (arbitrarily varied by $\pm 25\%$ ) Tests (i.e. explored impact of removing variation across treatments in use of tests and investigations) Variation in setting for treatment of adverse events (i.e. oncology and general clinics/wards)
Results	Incremental results not highly sensitive to variation in parameters within the ranges explored

There were similar patient numbers in each group (rituximab,  $n = 64$ ; CHOP,  $n = 48$ ; fludarabine,  $n = 50$ ). These resource use data were then converted into costs through the use of unit costs taken from a variety of appropriate sources.

One of the principal concerns about the cost analysis relates to the lack of comparability of the resource use data from the three patient groups. It is clear that the approaches to data collection were not common across the three groups. For example:

- the source of data (and, hence, the data collection mechanisms) was different for rituximab, since these data were collected within the context of the Phase II trial
- not all the resource use data used in the analysis were observed, for example:
  - for rituximab, no data were collected on the use of tests/investigations and so the analysts used the average for the resource use data seen across both the CHOP and fludarabine groups
  - data collection for the CHOP and fludarabine groups related to a single cycle, which was then extrapolated to give the cost for six cycles
- the sample selection process by which patients were included in the studies was not clear and may have been different across the resource utilisation studies.

This final point is borne out by the data on sample characteristics reported in the Roche submission.<sup>36</sup> These data reveal that the three patient groups were not similar, particularly in terms of their mean age and median number of relapses. Patients in the CHOP study had fewer relapses, on average, compared with the other two groups. As part of the Roche submission, the analysts therefore argued that the data they reported represented a ‘conservative comparison’ with regards to rituximab, since the costs of CHOP were likely to be underestimated and hence the

incremental cost of rituximab would be overstated. While this line of argument is intuitively appealing, further data on the side-effects profile for patients with a greater number of relapses receiving CHOP would have been helpful.

A further point is the comprehensiveness of the resource use data reported in this analysis. The data collection was retrospective for the CHOP and fludarabine groups and thus relied on routine data sources. Neither the Roche submission to NICE<sup>36</sup> nor the paper by Sweetenham and colleagues<sup>39</sup> indicated whether the data collection for rituximab patients was prospective or retrospective.

The results of the cost analysis were reported as point estimates for a course of treatment. There was clearly some level of uncertainty around these point estimates but this information was not provided. Given that the estimates were based on individual patient resource use data, it would have been possible for CIs (either conventional or bootstrap) to have been estimated. A sensitivity analysis was conducted that allowed some of the uncertainty in the point estimates to be explored. However, the analysis was very limited: single parameters were varied independently through one-way sensitivity analyses and the values on selected resource use data were varied by an arbitrary figure of  $\pm 25\%$ . No justification for the range was provided.

In the Roche submission to NICE,<sup>36</sup> an ‘illustrative analysis’ was reported in which quality of life issues were explicitly considered. This represents an attempt to extend the earlier analysis using a cost–utility framework. It was argued that all treatments considered in the analysis were associated with some level of toxicity and so the quality of life experienced during the treatment period was poorer than that experienced during remission. This was clearly an advantage for rituximab since the duration of the treatment period was shorter. While the logic of the argu-

ment is sound, there are some weaknesses in the analysis reported.

- The utility data used in the analysis were taken from patients with early breast cancer. The relevance of such data to a patient group with NHL has to be questioned.
- The estimates of time in treatment and remission health states were given without any indication of the uncertainty in these point estimates. The results of the utility analysis are clearly sensitive to variation in these time intervals and it is known from other sources that not all patients receiving CHOP or fludarabine undergo a full course of six cycles.

### Further exploration of assumptions in other attempts to assess cost-effectiveness

Two further sensitivity analyses were undertaken, using the data from the Roche submission to NICE.<sup>36</sup>

1. The incidences of adverse events in the CHOP and rituximab groups were equalised, as far as possible. Two methods were applied. For the first, the two groups were simply combined. For example (from Roche submission<sup>36</sup>), a total of 37 from 112 patients (33%) suffered nausea or vomiting. All the incidences were adjusted to the common value except for neutropenia and anaemia in the rituximab group, as no costs for these were available in the Roche submission. This was a pragmatic decision and it is accepted that there may be some differences in these costs. For the second method, an adjustment was made to allow for the different sample sizes. The incidences used are shown in *Table 15*, and the results are presented in *Table 16* (discrepancies between the base-case values shown and those from the Roche submission result from rounding errors).

**TABLE 15** Incidences of adverse events used in sensitivity analysis

Adverse event	Incidence (%)	
	First method	Second method
Nausea	33	36
Neutropenia	18	21
Fever/infection	26	26
Thrombocytopenia	15	17
Anaemia	19	22
Other	56	54

**TABLE 16** Effect of equal incidence of adverse events

	Total costs per patient per course (£)	
	CHOP	Rituximab
Base case	8743	6545
First method	6909	6596
Second method	7138	6605

2. The costs of adverse events were equalised. Again, simple weighted averages of the costs in the two arms were used and a weighted average adjusted for the sample sizes. Since the incidences were returned to those shown in the Roche submission to NICE, the costs for neutropenia and anaemia applied only to the CHOP group. The costs used are presented in *Table 17*, with the results shown in *Table 18*.

**TABLE 17** Costs of adverse events used in sensitivity analysis

Adverse event	Costs (£)	
	First method	Second method
Nausea	353	373
Neutropenia	3396	3396
Fever/infection	3203	3694
Thrombocytopenia	1456	1471
Anaemia	2844	2844
Other	441	508

**TABLE 18** Effect of equalising costs of adverse events

	Total costs per patient per course (£)	
	CHOP	Rituximab
Base case	8743	6545
First method	7350	7590
Second method	7528	7760

These analyses should be regarded as purely illustrative. There are difficulties, in that neutropenia and anaemia occurred only in the CHOP group, and that costs for adverse events listed as 'Chest', 'Pain-related', and 'Skin' were given only for the rituximab group. Equalising incidence or costs between the two groups may be considered an unrealistic extreme.

Subject to our concerns about the appropriateness of using cost-minimisation analysis, the sensitivity

analysis given here supports the robustness of the claim that rituximab is associated with a lower cost per treatment course. However, this should not be interpreted as meaning that rituximab is cost-saving. That would only be true if rituximab treatment replaced existing treatment options. If it merely displaced them, any cost will be in addition.

## Summary of economic analysis

- The nature of the evidence on effectiveness precludes accurate quantitative estimates of net effect.
- Despite considerable uncertainties, net benefit is likely to accrue with rituximab treatment in Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy.
- The uncertainties, however, make it impossible to assess reliably whether the net benefit associated with rituximab is the same, less or more than alternatives.
- The implications of this are greatest in attempting to decide whether rituximab should be used at the earliest stage allowed by the current licence, that is, second relapse/third-line treatment option, and least when it is used as a treatment of last resort.
- The net costs to the NHS of administering a course of rituximab are estimated to be approximately £6500 per patient, the majority of this cost being drug acquisition (£5000).
- This estimate assumes a very low level of adverse events; the level used is open to challenge.
- The net cost to the NHS of administering a course of rituximab appears to be considerably less than administering CHOP and fludarabine.
- It is claimed that the much higher drug acquisition costs for rituximab, particularly in comparison to CHOP, are completely offset by the lower costs associated with administration and treatment of adverse events.
- The possibility that the costs associated with administering rituximab have been underestimated must be considered in accepting this claim.
- A crude upper estimate of the total annual cost to the NHS in England and Wales of making rituximab available is approximately £17.4 million.
- Only two related assessments of health economic impact were identified.
- Both approaches, which included the Roche submission to NICE, relied on cost-minimisation analysis, comparing rituximab with CHOP and fludarabine; cost-minimisation assumes that effectiveness is equal.
- The invalidity of the main assumption by virtue of absence of accurate relative effectiveness data, together with concerns about the conduct of the cost-minimisation exercises, suggests the need for caution in interpreting the results of these assessments.
- Even if claims that the cost per treatment course for rituximab is lower than for CHOP or fludarabine are accepted, this should not be interpreted as meaning that rituximab treatment is cost-saving. For this to be the case, rituximab would need to replace existing treatment options, and this seems unlikely.
- Little guidance can be provided on whether cost relative to net benefit for investment of NHS resources in rituximab would be the same, better or worse than investment in other areas of health activity, particularly new treatments for other cancers.



## Chapter 5

# Implications for other parties

The findings of this review have wide implications for all parties involved in the healthcare process. However, one aspect was identified which does deserve special emphasis.

This relates to the implications, for patients, their families and their carers, of the simpler administration schedule for rituximab. The two key points are:

- each course of rituximab is delivered over 1 month as opposed to 6 months for CHOP and fludarabine
- the number of administrations is four – again less than for CHOP and fludarabine.

This strongly suggests that rituximab is likely to be less disruptive for patients, their families and their carers, with the attendant impact on quality of life and patient-borne costs.

The only currently used treatment that is probably less disruptive is oral alkylating-agent therapy, such as chlorambucil, which is commonly used as first-line therapy. However, consideration needs to be given to the advent of an oral preparation of fludarabine, which might considerably reduce the inconvenience to patients of this treatment option.





# Chapter 6

## Research in progress

### Method

Early in the course of the appraisal, the severe limitations on the quality of the evidence on effectiveness were identified as likely to be a key issue, suggesting at least the need for further research. Consequently, it was considered essential to provide as rigorous an inventory as possible of ongoing research.

The objective was to identify all randomised trials which included rituximab that were planned, ongoing and completed, and to indicate key information relating to the nature of these trials (intervention, comparison groups, outcomes and size) and when they were likely to complete recruiting or be published. No restriction was placed on the condition of interest, although the main studies focussed on in the results in this section are for NHL. The search strategy used incorporated interrogation of bibliographic databases, particularly MEDLINE, EMBASE and the Cochrane Library, and a wide range of Internet websites of organisations involved in or providing listings of trials in progress. Further details on the search strategy, inclusion criteria and data abstraction process are provided in appendices 8 and 9.

### Results

The ongoing trials, subdivided by the condition of interest, and whether patients are treated or untreated, are listed in *Table 19*.<sup>40-52</sup>

#### Current licensed indications for rituximab – previously treated low-grade NHL

There are no directly relevant randomised trials in progress. In particular, there are no trials directly comparing rituximab to the most commonly considered alternatives, such as CHOP or fludarabine.

There is a randomised comparison of rituximab and a novel radioimmunotherapy agent in relapsed/refractory low-grade NHL. This appears to have been completed but has not been fully published. It is of particular interest because it appears to have measured directly the impact on quality of life. If the results of this trial had been

available, they could have been of value in this report, enhancing the estimates of the impact of rituximab; hence, it should be considered in any further reviews in this area.

Other randomised trials in progress in previously treated NHL make the following comparisons:

- CHOP + rituximab versus CHOP alone
- high-dose therapy + autologous bone marrow transplantation + rituximab versus high dose therapy + bone marrow transplantation alone
- rituximab maintenance versus no rituximab maintenance, both arms having received rituximab for induction of response.

It is possible that the results of these trials might provide further important insights into the value of rituximab in its currently licensed indications, and it would be worth revisiting the role of rituximab in relapsed/refractory Stage III or IV follicular lymphoma when the results are available.

#### Ongoing randomised trials of rituximab in previously untreated low-grade NHL

There appears to be considerable interest in exploring the value of rituximab as a first-line therapy in low-grade NHL, including follicular lymphoma. Three identified ongoing randomised trials made the following comparisons:

- rituximab maintenance versus no rituximab maintenance, in patients who have already received induction therapy with either cyclophosphamide and fludarabine or CVP
- CHOP + rituximab versus CHOP alone
- rituximab maintenance versus no rituximab maintenance, both arms having received rituximab for induction of response

Although these comparisons will undoubtedly provide valuable information in assessing the value of rituximab in first-line therapy for low-grade NHL, the startling omission is a randomised trial making the obvious comparison of the current well-established first-line treatment for low-grade NHL, oral chlorambucil, with rituximab. Again, the absence of direct measurement of impact on quality of life as an outcome in any of the trials is a major cause for concern.

### **Ongoing randomised trials of rituximab in other types of NHL – intermediate and high grade**

As in the use of rituximab in low-grade NHL, this is clearly an area of major interest. Without listing the trials in detail, it is clear that two of the major concerns raised above apply to this body of ongoing work also; viz:

- simple direct comparisons between rituximab and the obvious currently employed alternatives do not seem to be made
- there is no intention in any ongoing trial to make a direct measurement of impact on quality of life.

### **Summary of key points**

- There appears to be information on the impact on quality of life, collected in the course of a recently completed randomised trial which might amplify the assessment of impact of rituximab on quality of life in this technology appraisal.

- There are no other ongoing randomised trials that will provide rigorous assessments of effectiveness for the indication of rituximab considered in this report.
- There is clear interest in use of rituximab as a first-line treatment for low-grade NHL and for intermediate- and high-grade NHL. NICE needs to expect decisions to be required on use of rituximab in these circumstances over the next few years.
- In this respect, it is of considerable concern that direct measurement of impact on quality of life does not feature in the outcomes of ongoing trials in these areas and that trials making simple direct comparisons of rituximab, alone or in combinations, with the main current standard treatments do not seem to have been instituted.
- There is no evidence of intent to embark on large-scale trials that address the key but extremely difficult question of which treatment strategy employing all the currently recognised standard treatments for follicular lymphoma, in particular, is optimal in terms of overall survival and impact on quality of life during the course of the disease.

TABLE 19 Ongoing and completed but unpublished trials of rituximab

Study	Intervention	Comparator	Condition	Population	Outcomes	Design and size	End
<b>Haematological malignancies: low-grade NHL (prior treatment)</b> IDEC-106-04 <sup>40,41</sup>	Rituximab	Rituximab + IDEC-Y2B8 (radio-immunotherapy)	Low-grade NHL (IVF types A-D)	Recurrent or refractory	Unclear, but probably: • disease response • toxicity • quality of life	RCT; target total 150	Completed; no publication
EORTC 20981 <sup>42</sup>	CHOP + rituximab (a) induction (x 6) and/or (b) maintenance (maximum 2 years)	CHOP (induction can be stopped in both arms after three doses if no response)	Low-grade NHL (REAL follicle centre lymphoma, follicular, grades I-III) Stage III/IV	Relapse following chemotherapy with ≤ 2 non-anthracycline containing regimens	• Disease response • Progression-free survival • Overall survival • Toxicity	RCT; target total 600	Recruiting ends 2003
EBMT-LYM1 <sup>43</sup>	High-dose therapy + autologous bone marrow transplantation + rituximab (a) purging and/or (b) maintenance	High-dose therapy + autologous bone marrow transplantation	Low-grade NHL (IVF types B-D or REAL follicle centre lymphoma, follicular) Stage not stated	Second or third remission – must have complete response or very good partial response	• Disease response • Progression-free survival (10) • Overall survival • Toxicity and safety	RCT; target total 460	Recruiting ends 2003
Swiss IACR <sup>44</sup>	Rituximab consolidation Both arms receive rituximab induction	No consolidation	Mixed low- and intermediate-grade NHL (follicular and mantle cell)	Mixed relapsed/refractory and untreated	• Disease response • Progression-free survival • Toxicity	RCT; target total 240	Recruiting ends 2001 or 2002
<b>Haematological malignancies: low-grade NHL (no prior treatment)</b> E-1496 <sup>45</sup>	Rituximab maintenance Following induction with either: fludarabine + cyclophosphamide or CVP	No maintenance	Low-grade NHL (small lymphocytic, follicular small cleaved cell, follicular mixed cleaved cell, follicular large cell) Stage III/IV	Untreated	• Progression-free survival • Overall survival	RCT; target total 400	Temporarily closed
Swiss IACR <sup>44</sup>	Rituximab consolidation Both arms receive rituximab induction	No consolidation	Mixed low- and intermediate grade NHL (follicular and mantle cell)	Mixed untreated and relapsed/refractory	• Disease response • Progression-free survival • Toxicity	RCT; target total 240	Recruiting ends 2001 or 2002

continued

TABLE 19 contd Ongoing and completed but unpublished trials of rituximab

Study	Intervention	Comparator	Condition	Population	Outcomes	Design and size	End
<b>Haematological malignancies: low-grade NHL (no prior treatment) contd</b>							
SWOG-0016 <sup>46</sup>	Rituximab + CHOP	CHOP or CHOP + I <sup>31</sup>	Low-grade NHL (follicular)	Untreated	<ul style="list-style-type: none"> <li>• Disease response</li> <li>• Progression-free survival</li> <li>• Overall survival</li> <li>• Toxicity</li> </ul>	RCT; target total 775	Recruiting not yet commenced
		Tositumomab	Bulky Stage II, Stage III/IV				
<b>Haematological malignancies: intermediate- or high-grade NHL</b>							
Swiss IACR <sup>44</sup>	Rituximab consolidation	No consolidation	Mixed intermediate- and low-grade NHL (follicular and mantle cell)	Mixed untreated and relapsed/refractory	<ul style="list-style-type: none"> <li>• Disease response</li> <li>• Progression-free survival</li> <li>• Toxicity</li> </ul>	RCT; target total 240	Recruiting ends 2001 or 2002
Coiffier et al., 1998 <sup>47</sup>	Rituximab (higher dose: one infusion of 375 mg/m <sup>2</sup> followed by seven weekly infusions of 500 mg/m <sup>2</sup> )	Rituximab (lower dose: eight weekly infusions of 375 mg/m <sup>2</sup> )	Intermediate- or high-grade NHL (especially diffuse large B cell lymphoma and mantle cell lymphoma)	In relapse 1 or 2 if refractory to initial therapy, if progressed after partial response to initial therapy, or if elderly (age > 60 years) and not previously treated	<ul style="list-style-type: none"> <li>• Disease response</li> <li>• Progression free survival</li> </ul>	RCT; 28 + 26	Completed and published
E-4494 (Phase I) <sup>48</sup>	Rituximab + CHOP	CHOP	Intermediate- or high-grade NHL (diffuse mixed, diffuse large, immunoblastic large B cell NHL, mantle cell lymphoma excluded)	Untreated; aged over 60 years	<ul style="list-style-type: none"> <li>• Disease response</li> <li>• Progression-free survival</li> <li>• Overall survival</li> <li>• Toxicity</li> </ul>	RCT; target total 630	Recruiting ends 2002
E-4494 (Phase II) <sup>48</sup>	Rituximab maintenance	No maintenance	Intermediate- or high-grade NHL (details as above)	Complete or partial response to CHOP ± rituximab in Phase I of E-4494; aged over 60 years	<ul style="list-style-type: none"> <li>• Disease response</li> <li>• Progression-free survival</li> <li>• Overall survival</li> <li>• Toxicity</li> </ul>	RCT; target total 630	Recruiting ends 2002

continued

TABLE 19 contd Ongoing and completed but unpublished trials of rituximab

Study	Intervention	Comparator	Condition	Population	Outcomes	Design and size	End
<b>Haematological malignancies: intermediate- or high-grade NHL</b>							
NCI-G99-1601 <sup>49</sup>	Rituximab + CHOP	CHOP	Aggressive B cell NHL (especially mantle cell, diffuse large/mixed/small cleaved cell, anaplastic large cell [B cell type], marginal zone lymphoma) Stage II-IV	Untreated	<ul style="list-style-type: none"> <li>• Disease response</li> <li>• Progression-free survival</li> <li>• Toxicity</li> </ul>	RCT; target total 270	Recruiting ends 2002
SWOG-0019 <sup>50</sup>	Rituximab + ifosfamide + carboplatin + etoposide	Ifosfamide + carboplatin + etoposide	Aggressive B cell NHL (diffuse large-cell, small non-cleaved cell/Burkitt's lymphoma) containing regime	Relapsed/refractory to combination chemotherapy with anthracycline-containing regime	<ul style="list-style-type: none"> <li>• Disease response</li> <li>• Progression-free survival</li> <li>• Overall survival</li> <li>• Toxicity</li> </ul>	RCT; target total 376	Recruiting not yet commenced
<b>Haematological malignancies: HIV-associated NHL</b>							
AMC 010 <sup>51</sup>	Rituximab (induction and maintenance) + CHOP + fligrastrim	CHOP + fligrastrim	HIV-associated NHL Stages I-IV	Untreated	Unclear, probably disease response	RCT; target total 120	Recruiting ends 2001
<b>Haematological malignancies: CLL</b>							
CLB-9712 <sup>52</sup>	Rituximab + fludarabine Both arms also receive consolidation with rituximab	Fludarabine	B cell CLL	Untreated; all stages Stratification by I/II and III/IV * Toxicity	<ul style="list-style-type: none"> <li>• Disease response</li> <li>• Progression-free survival</li> <li>• Overall survival</li> </ul>	RCT; target total 100	Completed; no publication



# Chapter 7

## Discussion

### Main results of report informing conclusions

This rapid technology appraisal has generated many important findings, which are highlighted at the end of each chapter. In this chapter, the results that have been most influential in informing our conclusions are discussed.

The dominant observation is the poor quality and openness to bias of the evidence on effectiveness. This applies not just to that on rituximab but to all other standard current therapies applied in the treatment of NHL, particularly Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy. There are no published RCTs and few comparative studies of any kind. Research in progress will not substantially alter this situation.

The invidious consequence of this is that the only evidence available on effectiveness is from uncontrolled prospective case series. Critical appraisal of these studies confirms them as being highly susceptible to bias; consequently, the authors have been extremely circumspect about taking the numerical values of clinical response rates, duration of response and time to progression at face value. Data on adverse events show important discrepancies, depending on where the results are reported. No directly measured evidence at all was available on the key outcomes of impact on quality of life and overall survival. There was no directly measured comparison of the impact of rituximab with other currently used standard treatments for relapsed/refractory Stage III or IV follicular lymphoma.

Despite these considerable uncertainties, qualitatively there is evidence that rituximab produces clinical responses of a duration that are likely to be useful clinically. Arguably, the situation in which this observation appears least susceptible to the uncertainties identified is when rituximab is used as a treatment of last resort, that is, fourth- or fifth-line treatment, especially when the disease is chemoresistant or refractory. This should not be taken as a definite indication that rituximab should not be applied at the earliest stage

allowed by the current licence, that is, following second relapse (as third-line treatment), as there is no rigorous evidence one way or the other.

Other key observations relating to whether rituximab should be made available are that its cost is, at worst, similar to those of other currently used treatments, such as CHOP and fludarabine. Claims that the cost is considerably less need to be subjected to close scrutiny, because of the uncertainties about the true incidence and nature of adverse events. It is more certain that, for patients, rituximab treatment is likely to be more acceptable than CHOP because of the shorter duration of treatment (1 month as opposed to 6 months).

The difficulty of accurately quantifying the net benefit of rituximab, let alone its alternatives, means that it is impossible to provide valid estimates of cost-effectiveness and cost-utility, even using economic modelling techniques that were actively considered. Great circumspection needs to be applied to those economic evaluations that have been attempted.

Consideration of research in progress suggests that future decisions on the use of rituximab in other circumstances may face exactly the same difficulties as for its use in Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy. Only new, directly relevant RCTs instituted in the near future will change this situation.

### Assumptions, limitations and uncertainties

There can be little disagreement about most of the main findings reported. The systematic review employed an extremely comprehensive search and explicit inclusion/exclusion procedures and defined methods of quality assessment, data abstraction and analysis were used. The absence of RCTs or other comparative studies is undeniable and widely acknowledged. There was no disagreement about the studies that offered the best available evidence on effectiveness of

rituximab – nor was there disagreement about the numerical results of these studies. The only exception was the discrepancy in portrayal of adverse event profiles between published reports and the data used to make assessments of the implications of adverse events on the costs of administration. It was assumed that, in general, the data available in the published reports gave the most accurate portrayal of adverse events, as it was these that were most consistent with the full study data that were supplied by the manufacturer.

The issue that, it is expected, will cause most debate is the handling of the uncertainties identified in the effectiveness data, particularly the biases to which uncontrolled studies are open. Many researchers working on assessment of effectiveness and reviewing it would undoubtedly reject the evidence identified, as being so biased that the only available option would be to insist that further primary research on effectiveness, particularly RCTs, was undertaken before a decision on the use of rituximab could be made. At the other extreme, many would play down the uncertainties identified and proceed with a decision, taking the numerical values of the effectiveness research at face value. The authors have tried to take a middle course between these, recognising that the evidence is highly subject to bias but accepting that there is evidence concerning direction of effect. In such circumstances, it may sometimes be possible to incorporate uncertainty concerning key parameters into models.

This was not open to us in this technology appraisal, as it was not considered possible, given the very high degree of uncertainty, to hazard plausible ranges for estimates of, say, clinical response. In the case of this outcome, the uncertainty was emphasised still further by the degree that clinical response, generally measured by serial CT or MRI scans, was acting

as an accurate proxy of improved or maintained quality of life, the outcome of greatest interest.

## Need for further research

Specific areas in which further research is required have already been indicated. It is debatable whether it is reasonable or practically feasible to reduce the uncertainties concerning the effectiveness of use of rituximab in the circumstances considered in this technology appraisal. However, what is certain is that the decision on rituximab in Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy should be reconsidered in the light of further evidence on the general use of rituximab, as it becomes available.

It is likely that similar reviews may be necessary for other uses of rituximab; the RCTs currently planned will not completely answer the obvious effectiveness and cost-effectiveness questions that will be posed. RCTs comparing rituximab with current standard treatments for NHL are urgently required. As well as clinical response and survival outcomes, these trials must address the impact on patient quality of life, as the prospects for improving longevity remain distant.

Finally, the general need for research on effectiveness and cost-effectiveness in the treatment of NHL is highlighted. The difficulties of assessing the effectiveness of rituximab lie as much in the generally poor evidence base underpinning the use of all treatments for NHL as in the lack of rigorous comparative research on rituximab itself. Although ambitious and long-term, the key research question that remains unaddressed relates to the effectiveness of treatment strategies – comparing different ways of deploying all the currently available standard treatments for NHL – on overall survival and quality of life.



# Chapter 8

## Conclusions

### Clinical effectiveness

Rituximab is probably effective but there is limited knowledge relating to the extent of its effectiveness in the treatment of NHL.

There is no evidence that rituximab improves survival in patients with Stage III or IV follicular NHL. Rituximab does achieve clinical responses in some patients with Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy. However, most of these clinical responses are partial (generally defined as  $\geq 50\%$  decrease in size of lesions and no new lesions).

The duration of responses in responders appear to be of a length that would be clinically useful. However, this assumes that partial response brings about abolition of symptoms associated with relapse/recurrence and that the improvement in quality of life is sufficient to offset the impairment of quality of life associated with the treatment.

According to the available research, symptoms were only present in a minority of patients prior to treatment. These symptoms were completely alleviated in responders and, to some extent, in 'non-responders' also. Mild-to-moderate adverse events occurred in most patients and severe adverse events occurred in a minority of patients; fatal adverse events were very rare but did occur. Some non-responders experienced the adverse effects of rituximab without great benefit.

Whether rituximab is more, less or equally effective as other commonly used treatments in relapsed/refractory Stage III or IV follicular lymphoma is unknown.

### Cost-effectiveness

The drug cost of rituximab is high at approximately £4900 per treatment cycle. However, the cost of administering rituximab is, at worst, similar to other commonly used treatments, because the number of adverse events is less. It can be argued that the cost per course of treatment for rituximab is actually less but this depends on the degree to which the incidence of adverse events is lower. However, even if the lower cost per treatment course for rituximab is accepted, this will not convert into cost-savings for the NHS unless rituximab replaces an existing treatment.

In England and Wales, a crude upper estimate of the impact on the NHS budget of using rituximab in relapsed/refractory Stage III or IV follicular lymphoma is £17.4 million per annum. However, reliable estimates of the relative cost-effectiveness and cost-utility of rituximab cannot be provided, because of the uncertainties surrounding the level of net benefit.

The acceptability of rituximab to patients is likely to be high because of the reduced number of times it needs to be administered and the shorter period over which the treatment is completed.

### Further research

- Further research on the effectiveness of rituximab and, indeed, of all currently used therapies for NHL is of great importance.
- 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.
- Direct measurement of impact on quality of life is essential in any future RCTs.





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Beverley Wake: main project worker; development of protocol; systematic review of effectiveness

Stirling Bryan: systematic review of cost-effectiveness

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Anne Fry-Smith: searches; proof-reading

Claire Davenport: data extraction; quality assessment; proof-reading

Fujian Song: general support; assessment of evidence on natural history

Chris Hyde: development of protocol; advice on conduct of systematic reviews of effectiveness; searches for ongoing trials; initial drafting of final report.

All the named authors commented on and agreed the final version of this report. The views expressed are those of the authors, who are also responsible for any errors.

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Neither the members of the review team nor the units to which they belong at the University of Birmingham have any pecuniary relationship with sponsors, specific and non-specific.





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## Appendix I

# The Revised European–American Classification of Lymphoid Neoplasms (REAL) system<sup>4</sup>

### B cell neoplasms

- I. Precursor B cell neoplasm: B lymphoblastic leukaemia/lymphoma
- II. Peripheral B cell neoplasms
  - A. B cell chronic lymphocytic leukaemia (CLL)/prolymphocytic leukaemia/small lymphocytic lymphoma
  - B. Lymphoplasmacytoid lymphoma/immunocytoma
  - C. Mantle cell lymphoma
  - D. Follicle centre lymphoma, follicular
    - 1. Provisional cytological grades
      - (i) small cell
      - (ii) mixed small and large cell
      - (iii) large cell
    - 2. Provisional subtype: diffuse, predominantly small cell type
  - E. Marginal zone B cell lymphoma
    - 1. Extranodal (MALT type  $\pm$  monocytoid B cells)
    - 2. Provisional subtype: nodal ( $\pm$  monocytoid B cells)
  - F. Provisional entity: splenic marginal zone lymphoma ( $\pm$  villous lymphocytes)
  - G. Hairy cell leukaemia
  - H. Plasmacytoma/plasma cell myeloma
  - I. Diffuse large cell B cell lymphoma
    - 1. Subtype: primary mediastinal (thymic) B cell lymphoma
  - J. Burkitt's lymphoma
  - K. Provisional entity: high-grade B cell lymphoma, Burkitt's-like

### T cell and putative natural killer (NK) cell neoplasms

- I. Precursor T cell neoplasm
  - 1. T precursor lymphoblastic lymphoma/leukaemia
- II. Peripheral T cell and NK cell neoplasms

- A. T cell CLL/prolymphocytic leukaemia
- B. Large granular lymphoproliferative (LGL) disorder
  - 1. T cell type
  - 2. NK cell type
- C. Mycosis fungoides/Sezary's syndrome
- D. Peripheral T cell lymphoma, unspecified
  - 1. Provisional cytologic categories: medium-sized cell, mixed medium and large cell, large cell, lymphoepithelioid cell
  - 2. Provisional subtype: hepatosplenic gamma/delta T cell lymphoma
  - 3. Provisional subtype: subcutaneous panniculitic T cell lymphoma
- E. Angioimmunoblastic T cell lymphoma (AILD)
- F. Angiocentric lymphoma
- G. Intestinal T cell lymphoma (enteropathy associated)
- H. Adult T cell lymphoma/leukaemia (ATL/L)
- I. Anaplastic large cell lymphoma (ALCL), CD30+, T and null-cell types
  - 1. CD30+ cell type
  - 2. T cell type
  - 3. Null-cell types
- J. Provisional entity: anaplastic large cell lymphoma, Hodgkin's-like

### Hodgkin's disease

- I. Lymphocyte predominance
- II. Nodular sclerosis
- III. Mixed cellularity
- IV. Lymphocyte depletion
- V. Provisional category: lymphocyte-rich classic Hodgkin's disease
- VI. Provisional category: anaplastic large cell lymphoma, Hodgkin's-like

### Unclassifiable

- 1. B cell lymphoma, unclassifiable (low grade/high grade)
- 2. T cell lymphoma, unclassifiable (low grade/high grade)
- 3. Malignant lymphoma, unclassifiable



## Appendix 2

### US NCI modification of REAL classification system<sup>2</sup>

#### I Plasma cell disorders

#### II Hodgkin's disease

#### III Indolent lymphoma/leukaemia

- A. Follicular centre cell lymphoma, follicular
  1. Grade I follicular small cleaved cell
  2. Grade II follicular mixed
  3. Grade III follicular large cell (some controversy, therefore may be aggressive)
- B. Diffuse small lymphocytic lymphoma/CLL  
Distinguish: Prolymphocytic leukaemia (aggressive)  
Large granular lymphocytic leukaemia
- C. Lymphoplasmacytoid/Waldenstrom's
- D. Marginal zone lymphoma
  1. MALT (extranodal)
  2. Monocytoid B cell lymphoma (nodal)
  3. Splenic lymphoma with villous lymphocytes
- E. Hairy cell leukaemia
- F. Mycosis fungoides/Sezary syndrome

#### IV Aggressive lymphoma/leukaemia

- A. Diffuse large cell lymphoma includes diffuse mixed cell, diffuse large cell, immunoblastic  
Distinguish: primary mediastinal B cell lymphoma, anaplastic large cell lymphoma, angiocentric lymphoma (includes nasal T cell and pulmonary B cell), angioimmunoblastic T cell lymphoma, peripheral T cell lymphoma, intestinal T cell lymphoma, intravascular lymphomatosis
- B. Burkitt's lymphoma/diffuse small non-cleaved cell lymphoma
- C. Lymphoblastic lymphoma/leukaemia
- D. CNS lymphoma
- E. Adult T cell leukaemia/lymphoma
- F. Mantle cell lymphoma (controversial therefore may be low grade)
- G. Post-transplantation lymphoproliferative disorder
- H. AIDS-related lymphoma
- I. True histiocytic lymphoma
- J. Primary effusion lymphoma



## Appendix 3

### Search strategies to identify prospective cohort studies on the natural history of NHL

#### **MEDLINE (Ovid), 1997–August 2000**

- |    |                              |    |                    |
|----|------------------------------|----|--------------------|
| 01 | lymphoma non hodgkin/        | 08 | lymphoma b cell/   |
| 02 | lymphoma follicular/         | 09 | or/1–8             |
| 03 | lymphoma intermediate grade/ | 10 | prognosis/         |
| 04 | lymphoma large cell/         | 11 | survival rate/     |
| 05 | lymphoma low grade/          | 12 | survival analysis/ |
| 06 | lymphoma mixed cell/         | 13 | or/10–12           |
| 07 | lymphoma small cell/         | 14 | 9 and 13           |



## Appendix 4

### Search strategy to identify effectiveness of any treatments for NHL

This strategy was designed specifically to target published systematic reviews and was based on the ARIF (Aggressive Research Intelligence Facility) search protocol. The following strategies were executed in the electronic databases.

#### MEDLINE (Ovid), 1990–September 2000

- 01 Exp lymphoma non hodgkin/dt,th,rt
- 02 (meta-analysis or review literature).sh.
- 03 meta-analy\$.tw.
- 04 metaanal\$.tw.
- 05 meta-analysis.pt.
- 06 (systematic\$ adj4 (review\$ or overview\$)).tw.
- 07 review,academic.pt.

- 08 case report.sh.
- 09 letter.pt.
- 10 historical article.pt.
- 11 review of reported cases.pt.
- 12 review,multicase.pt.
- 13 review literature.pt.
- 14 1 or 2 or 3 or 4 or 5 or 6 or 12
- 15 7 or 8 or 9 or 10 or 11
- 16 not 15
- 17 1 and 16

#### Cochrane Library 2000, Issue 4

- 01 exp lymphoma non hodgkin:ME
- 02 lymphoma\*
- 03 1 or 2





## Appendix 5

# Protocol for the review of rituximab and fludarabine for blood cancers: NHL and CLL

### Full title of research question

Rituximab and fludarabine for blood cancers: NHL and CLL

### Clarification of research question and scope

Rituximab and fludarabine are two relatively new agents for the treatment of blood cancers; consequently, it is necessary to confirm that the benefits of these new drugs are worth the costs.

Haematological malignancies are a particularly heterogeneous group of cancers. This is particularly true in the case of NHL, for which complex classification systems have been developed. Inevitably some types of blood cancer may be more susceptible to rituximab and fludarabine than others, particularly the former, which targets a particular marker found only on B lymphocytes.

Therefore the main focus of this report is on the effectiveness and cost-effectiveness of rituximab for Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy, and fludarabine for patients with B cell CLL with sufficient bone marrow reserve that have not responded to or have progressed during or after treatment with at least one standard alkylating agent-containing regimen. These are the specific conditions for which these drugs have been licensed.

However, we are aware that these drugs are currently being used and investigated in the treatment of other related conditions, as well as earlier in the course of the diseases for which licences have been granted. Therefore we will also provide a formal scoping review to identify research, both complete and ongoing, in conditions outside the licensed implications to indicate where the agents of interest might be applied in the future and whether there will be rigorous research to support the use in these areas.

Thus, the specific objectives of the report will be as follows (in the order in which they will be tackled).

1. To identify trials, published, unpublished and ongoing, examining the use of rituximab and fludarabine in haematological malignancies.
2. To review systematically the evidence of the effectiveness of rituximab for Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy, as indicated in the drug licensing information.
3. To review systematically the evidence of the effectiveness of fludarabine for patients with B cell CLL with sufficient bone marrow reserve that have not responded to or have progressed during or after treatment with at least one standard alkylating agent-containing regimen, as indicated in the drug licensing information.
4. To review systematically the evidence on costs and health economic impact of rituximab and fludarabine in B cell NHL and B cell CLL, as described in (2) and (3).
5. To relate the effects identified in (2) and (3) to costs identified in (4) and, therefore, to consider the validity of any existing estimates of health economic impact, particularly cost-effectiveness.

### Report methods

#### General

There will be no language restrictions and all searches will stop on 1 September 2000.

#### Formal scoping search to indicate developments in the use of rituximab and fludarabine (i.e. RCTs published and ongoing)

##### Searches

Studies will be identified using electronic databases, such as the Cochrane Library, MEDLINE, EMBASE, Science Citation Index and the National Research Register; internet search engines; drug company submissions invited by NICE; citation lists and conference abstracts.

**Inclusion criteria****Intervention**

Rituximab and/or fludarabine.

**Comparator**

Any.

**Population**

Any haematological malignancy.

**Outcomes**

Survival, quality of life and adverse events.

**Design**

RCT.

**Analysis**

As the main purpose will be to indicate the current and future availability of high-quality research evidence on rituximab and fludarabine outside of the licensing implications, no attempt to summarise the data will be made. The characteristics or planned characteristics of the trials identified will be presented and subdivided by the intervention and target condition.

### **Systematic review of the effectiveness of rituximab for NHL and fludarabine for CLL**

**Searches**

Studies will be identified using electronic databases, such as the Cochrane Library, MEDLINE, EMBASE, Science Citation Index and the National Research Register; internet search engines; drug company submissions invited by NICE; citation lists; conference abstracts.

**Inclusion criteria****Intervention**

Rituximab at the dose given on the product information sheet and fludarabine at the dose given on the product information sheet.

**Comparator**

Any, including no treatment.

**Population**

For rituximab, patients with Stage III or IV follicular B cell NHL that is chemoresistant or in its second or subsequent relapse after chemotherapy. For fludarabine, patients with B cell CLL with sufficient bone marrow reserve who have not responded to or have progressed during or after treatment with at least one standard alkylating agent-containing regime.

**Outcomes**

Survival, quality of life and adverse events. The value of tumour response will be explored to indicate impact on quality of life if no other data are available.

**Design**

Ideally RCTs. However, it is anticipated that there will be insufficient numbers to adequately answer the question posed. In this event, the included studies will be extended to non-randomised controlled clinical trials and, if these are not available, before/after studies, that is, with no parallel control arm. In this last instance, quality criteria will be introduced as part of the inclusion/exclusion decisions. These will be designed to protect against the possibility of eligible studies presenting the results of patients unrepresentative of the stated target population.

On this basis, included before/after studies will:

- need to indicate that they were conducted prospectively
- ideally present the results of a consecutive series
- give clear indications of patient characteristics, particularly with regard to stage of disease and previous treatments
- have losses to follow-up, with respect to particular outcomes of interest, of < 10%
- include > 10 patients.

Imputing the effectiveness of rituximab/fludarabine in such studies will inevitably require indirect comparison with information about the natural history of patients in the given condition. A systematic search for prospective cohort studies will be conducted for series giving such information. Information provided within studies, for example, from a case-control methodology, will not be acceptable.

The application of inclusion/exclusion criteria will be undertaken by two reviewers. Decisions will be made independently of the data extraction and prior to the scrutiny of results.

**Quality assessment**

This is partly implicit in the inclusion criteria. If RCTs are present, details of relative strengths and weaknesses will be assessed in relation to selection, performance, detection and attrition biases. If non-randomised controlled clinical trials are identified, established checklists, for example, Jadad,<sup>29</sup> will be employed.

**Data extraction**

This will be carried out by two reviewers independently.

**Analysis**

This will be qualitative and will be amplified by meta-analysis if appropriate. No subgroups have been identified *a priori*.

**Systematic review of the cost-effectiveness of rituximab for NHL and fludarabine for CLL**

The review question is in relation to the applications of rituximab and fludarabine in objectives (2) and (3) above – to assess the costs and relate these to the identified effects and effectiveness of the two agents.

**Method**

Systematic review of cost assessments and economic evaluations.

**Search**

Information on cost-effectiveness and quality of life will be sought from MEDLINE, HEED (Health Economic Evaluations Database), NHS Economic Evaluation Database (NEED), Database of Abstracts of Reviews of Effectiveness (DARE), EMBASE, Science Citation Index and Internet sites of UK health economics units.

**Quality assessment**

Quality of any identified evaluations will be undertaken using a specifically designed checklist based on the *BMJ* guidelines for economic appraisals.<sup>38</sup>

**Analysis**

As a minimum, a cost–consequence analysis will be conducted. Ideally, if quality-of-life data can be identified, a cost–utility analysis will be undertaken giving cost per quality-adjusted life-year for each intervention. Where cost data are uncertain, a

sensitivity analysis will be carried out. The perspective for the health economic analysis will be that of the NHS. The main focus of the analyses will be on marginal changes.

**Handling the company submissions**

Industry submissions will be used to identify effectiveness information, cost data and assessments of health economic impact that meet the inclusion criteria. Any information indicated as being confidential will be marked as such in the final report.

**Research in progress**

None identified at this stage of the project.

**Project management****Timetable**

Deadline for submission of protocol to HTA programme: 22 September 2000.

Deadline for submission of progress report to HTA programme: 7 December 2000.

Deadline for submission of draft report to HTA programme: 9 January 2001.

[The draft report, without reviewers' comments, to be sent to NICE: 21 December 2000.]

**Competing interests**

Members of the project management group and advisory panel have been asked to declare any interest they may have. (A 'declaration of competing interests' form has already been returned.) None were identified for any of the members of the review team.

**Project management group**

This review will be carried out under the guidance of a project management group, which comprises a lead reviewer (CH), a main author (BW), an information scientist (AFS), a health economist (TR) and an assistant reviewer (CD). A further senior reviewer may be added to this team.



## Appendix 6

### Search strategies to identify studies on effectiveness of rituximab in NHL

#### MEDLINE (Ovid), 1966–September 2000

- 1 randomized controlled trial.pt.
- 2 controlled clinical trial.pt.
- 3 randomized controlled trials/
- 4 random allocation/
- 5 double blind method/
- 6 double blind method/
- 7 single blind method/
- 8 or/1–7
- 9 (animal not human).sh.
- 10 8 not 9
- 11 clinical trial.pt.
- 12 exp clinical trials/
- 13 (clin\$ adj25 trial\$).ti,ab.
- 14 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
- 15 placebos/
- 16 placebo\$.ti,ab.
- 17 random\$.ti,ab.
- 18 research design/
- 19 or/11–18
- 20 19 not 9
- 21 20 not 10
- 22 comparative study/
- 23 exp evaluation studies/
- 24 follow up studies/
- 25 prospective studies/
- 26 (control\$ or prospectiv\$ or volunteer\$).ti,ab.
- 27 or/22–26
- 28 27 not 9
- 29 27 not (10 or 21)
- 30 10 or 21 or 29
- 31 rituximab\$.mp.
- 32 mabthera\$.mp.
- 33 idec-c2b8\$.ti,ab.
- 34 rituxan\$.mp.
- 35 or/31–34
- 36 exp lymphoma non-hodgkin/
- 37 (non adj hodgkin\$ adj lymphoma\$).ti,ab.

- 38 b cell lymphocytic.ti,ab.
- 39 (follicular adj lymphoma\$).ti,ab.
- 40 or/36–39
- 41 40 and 35 and 30

#### EMBASE (Ovid), 1980–September 2000

- 1 exp nonhodgkin lymphoma/
- 2 non hodgkin\$ lymphoma\$.ti,ab.
- 3 b cell lymphocytic.ti,ab.
- 4 follicular lymphoma\$.ti,ab.
- 5 or/1–4
- 6 controlled trial/
- 7 randomized controlled trial/
- 8 clinical trial/
- 9 prospective study/
- 10 double blind procedure/
- 11 randomization/
- 12 major clinical study/
- 13 trial\$.ti,ab.
- 14 or/6–13
- 15 rituxan\$.mp.
- 16 rituximab\$.mp.
- 17 idec-c2b8\$.ti,ab.
- 18 mabthera\$.mp.
- 19 or/15–18
- 20 5 and 14 and 19

#### Science Citation Index (Web of Science), 1981–October 2000

- 01 rituximab\*
- 02 mabthera\*
- 03 rituxan\*
- 04 idecc2b8\*
- 05 1 or 2 or 3 or 4
- 06 lymphoma\*
- 07 5 and 6

#### Cochrane Library 2000 Issue 3

As for search in appendix 9



## Appendix 7

### Experts contacted as part of search

Professor AK Burnett  
Chairman of the Haemato-Oncology Task  
Force of the British Committee for Standards in  
Haematology, on behalf of the British Society of  
Haematology and the University of Wales, Cardiff  
Department of Haematology  
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Department of Haematology  
South Warwickshire General Hospital  
Lakin Road  
Warwick CV34 5BW  
UK





## Appendix 8

### Search strategy and methods to identify ongoing trials of rituximab

The following sources were searched to identify specifically ongoing or completed but currently unpublished RCTs involving rituximab.

- (1) Bibliographic database search (see appendix 9 for further details): four citations scanned.
- (2) Cochrane Library 2000, Issue 4 – Cochrane Controlled Trials Register (CD-ROM): three hits scanned.
- (3) National Research Register 2000, Issue 4 (URL: <http://www.update-software.com>): 51 hits scanned – included ongoing and completed studies.
- (4) British Society for Haematology website (URL: <http://www.blacksci.co.uk/uk/society/bsh>): no trials listing available.
- (5) British National Lymphoma Investigation website (URL: <http://www.bnli.ucl.ac.uk>): 14 listed trials scanned.
- (6) European Organisation for Research and Treatment of Cancer website (URL: <http://www.eortc.be>): 26 ‘immunotherapy’ trial protocols scanned.
- (7) European Group for Blood and Marrow Transplantation website (URL: <http://www.ebmt.org>): ongoing studies for each working party scanned.
- (8) Leukaemia Research Fund (URL: <http://dSPACE.dial.pipex.com/lrf//research/director.pdf>): no hits in research directory.
- (9) Medical Research Council and Current Controlled Trials website (URL: <http://www.controlled-trials.com>): 11 hits scanned.
- (10) National Institutes of Health/CancerNet site (URL: <http://www.cancertrials.nci.nih.gov>): 42 hits scanned – included open and closed studies.
- (11) Roche company website (URL: <http://www.roche.com/>): no trials listing available.
- (12) General search of World Wide Web, using Google search engine: 94 hits scanned.
- (13) Roche submission to NICE: all reference lists scanned; did not include anything marked ‘commercial-in-confidence’ unless already identified by one of other elements of search strategy above.

In general, where search terms could be used, the text words ‘RITUXIMAB’, ‘RITUXAN’, ‘IDEC-C2B8’ or ‘MABTHERA’ were employed. For the general World Wide Web search, the phrase ‘(RANDOMISED OR RANDOMIZED) AND CONTROLLED TRIAL’ was used in addition. Potentially relevant hits were scanned and a judgement made on whether a study was likely to be an RCT and whether it was likely that the effectiveness of fludarabine was being tested. When search terms could not be used, details of all identifiable trial entries were scanned using the same criteria. If an entry appeared to relate to a trial, and information was brief, further details were sought either from the organisation coordinating the trial or the lead investigator. Whenever possible, a full copy of the trial protocol was obtained. All searches were conducted over the period 1 November–15 December 2000.



## Appendix 9

### Bibliographic database search employed to identify ongoing trials involving rituximab

#### MEDLINE (Ovid), 1966–August 2000

- 01 rituximab.mp.
- 02 idec-c2b8\$.ti,ab.
- 03 rituxan.mp.
- 04 mabthera.mp.
- 05 or/1–4
- 06 exp hematologic neoplasms/
- 07 exp leukemia/
- 08 exp lymphoma/
- 09 or/6–8
- 10 5 and 9
- 11 randomized controlled trial.pt.
- 12 controlled clinical trial.pt.
- 13 randomized controlled trials/
- 14 random allocation/
- 15 double blind method/
- 16 single blind method/
- 17 or/11–16
- 18 animal/ not human/
- 19 17 not 18
- 20 clinical trial.pt.
- 21 exp clinical trials/
- 22 (clin\$ adj25 trials\$).ti,ab.
- 23 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
- 24 placebos/
- 25 placebo\$.ti,ab.
- 26 random\$.ti,ab.
- 27 research design/
- 28 or/20–27
- 29 28 not 18
- 30 29 not 19
- 31 19 or 30
- 32 10 and 31

#### EMBASE (Ovid), 1980–May 2000

- 1 rituximab.mp.
- 2 mabthera.mp.
- 3 idec-c2b8\$.ti,ab.
- 4 rituxan.mp.
- 5 or/1–4
- 6 or/1–4

- 7 exp hematologic disease/
- 8 exp leukemia/
- 9 exp lymphoma/
- 10 malignan\$.ti,ab.
- 11 cancer\$.ti,ab.
- 12 leuk?emia.ti,ab.
- 13 lymphoma\$.ti,ab.
- 14 or/7–13
- 15 controlled trial/
- 16 randomized controlled trial/
- 17 clinical trial/
- 18 controlled study/
- 19 clinical study/
- 20 prospective study/
- 21 double blind procedure/
- 22 randomization/
- 23 major clinical study/
- 24 trial\$.ti,ab.
- 25 study.ti,ab.
- 26 studies.ti,ab.
- 27 or/15–26
- 28 5 and 14 and 27
- 29 limit 28 to human

#### Science Citation Index (BIDS), 1981–2000

- 01 rituximab\*
- 02 mabthera\*
- 03 (idec-c2b8\*)
- 04 rituxan\*
- 05 (lymphoma\* or malignan\* or cancer\* or leukaemia\* or leukemia\*)
- 06 1 or 2 or 3 or 4
- 07 5 and 6

#### Cochrane Library 2000 Issue 3

- 01 rituximab\*
- 02 mabthera\*
- 03 (idec-c2b8\*)
- 04 rituxan\*
- 05 1 or 2 or 3 or 4



## Appendix 10

### Excluded studies and reasons for exclusion

Rituximab: encouraging preliminary results.  
*Prescribe Int* 1999;**18**:109–11.

Reason for exclusion: review.

Berinstein NL, Grillo-Lopez AJ, White CA, Bence-Bruckler I, Maloney D, Czuczman M, *et al.* Association of serum Rituximab (IDEC-C2B8) concentration and anti-tumor response in the treatment of recurrent low-grade or follicular non-Hodgkin's lymphoma. *Ann Oncol* 1998;**9**:995–1001.

Reason for exclusion: suspicion of duplication (McLaughlin *et al.*, 1998<sup>35</sup>).

Czuczman MS. CHOP plus rituximab chemo-immunotherapy of indolent B-cell lymphoma. *Semin Oncol* 1999;**126** Suppl 14:88–96.

Reason for exclusion: did not meet inclusion criteria – not rituximab as a single agent.

Maloney DG, Grillo-Lopez AJ, Bodkin DJ, White CA, Liles TM, Royston I, *et al.* IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. *J Clin Oncol* 1997;**15**:3266–74.

Reason for exclusion: suspicion of duplication (McLaughlin *et al.*, 1998<sup>35</sup>).

Maloney DG, Grillo-Lopez AJ, White CA, Bodkin D, Schilder RJ, Neidhart JA, *et al.* IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. *Blood* 1997;**90**:2188–95.

Reason for exclusion: suspicion of duplication (McLaughlin *et al.*, 1998<sup>35</sup>).

Nguyen DT, Amess JA, Doughty H, Hendry L, Diamond LW. IDEC-C2B8 anti-CD20 (rituximab) immunotherapy in patients with low-grade non-Hodgkin's lymphoma and lymphoproliferative disorders: evaluation of response on 48 patients. *Eur J Haematol* 1999;**62**:76–82.

Reason for exclusion: suspicion of duplication (Foran *et al.*, 2000<sup>32</sup>).

Onrust SV, Lamb HM, Barman Balfour JA. Rituximab. *Drugs* 1999;**58**:79–88.

Reason for exclusion: review.

Sweetenham J, Hieke K, Kerrigan M, Howard P, Smartt PFM, McIntyre A-M, *et al.* Cost-minimization analysis of CHOP, fludarabine and rituximab for the treatment of relapsed indolent B-cell non-Hodgkin's lymphoma in the UK. *Br J Haematol* 1999;**106**:47–54.

Reason for exclusion: cost-effectiveness study only.



## Appendix II

### Search strategies to identify cost and quality-of-life studies

The NHS Economic Evaluation Database was searched using the following terms: fludara\$, rituximab, mabthera, idec-c2b8\$, rituxan.

Internet sites of the following health economics units were also searched: University of York Centre for Health Economics; Health Economics Research Unit; Health Economics Research Group.

The following strategy was executed in MEDLINE (Ovid), 1966–September 2000:

01 economics/  
 02 exp “costs and cost analysis”/  
 03 cost of illness/  
 04 exp health care costs/  
 05 economic value of life/  
 06 exp economics medical/  
 07 exp economics hospital/  
 08 economics pharmaceutical/  
 09 exp “fees and charges”/  
 10 (costs or cost or costed or costly or  
 costing).tw.  
 11 (economic\$ or pharmaco-economic\$ or  
 price\$ or pricing).tw.  
 12 or/1–11  
 13 fludara\$.mp.  
 14 12 and 13

15 rituximab\$.mp.  
 16 mabthera\$.mp.  
 17 idec-c2b8\$.ti,ab.  
 18 rituxan\$.mp.  
 19 or/15–18  
 20 12 and 19  
 21 quality of life/  
 22 life style/  
 23 health status/  
 24 health status indicators/  
 25 treatment outcome/  
 26 “outcome assessment (health care)”/  
 27 or/21–26  
 28 exp lymphoma non-hodgkin/  
 29 non hodgkin\$ lymphoma\$.ti,ab.  
 30 b cell lymphocytic.ti,ab.  
 31 follicular lymphoma\$.ti,ab.  
 32 or/28–31  
 33 27 and 32  
 34 exp leukemia b cell chronic/  
 35 cll.ti,ab.  
 36 b-cll.ti,ab.  
 37 chronic lymphocytic leukemia.ti,ab.  
 38 or/34–37  
 39 38 and 27

Set 20 is the output of the search on costs.

Set 39 is the output of the search on quality of life.







# Health Technology Assessment Programme

## Prioritisation Strategy Group

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### Members

<b>Chair</b> <b>Professor Kent Woods</b> Director, NHS HTA Programme, & Professor of Therapeutics University of Leicester	Professor Shah Ebrahim Professor of Epidemiology of Ageing University of Bristol	Dr Ron Zimmern Director, Public Health Genetics Unit Strangeways Research Laboratories, Cambridge
Professor Bruce Campbell Consultant General Surgeon Royal Devon & Exeter Hospital	Dr John Reynolds Clinical Director Acute General Medicine SDU Oxford Radcliffe Hospital	

## HTA Commissioning Board

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### Members

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Professor John Bond Director, Centre for Health Services Research University of Newcastle- upon-Tyne	Dr Alastair Gray Director, Health Economics Research Centre Institute of Health Sciences University of Oxford	Professor Gillian Parker Nuffield Professor of Community Care University of Leicester	Dr Jeremy Wyatt Senior Fellow Health Knowledge Management Centre University College London
	Professor Mark Haggard Director, MRC Institute of Hearing Research University of Nottingham	Dr Tim Peters Reader in Medical Statistics University of Bristol	
		Professor Martin Severs Professor in Elderly Health Care University of Portsmouth	

continued

## Diagnostic Technologies & Screening Panel

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<p>Dr Philip J Ayres Consultant in Epidemiology &amp; Public Health The Leeds Teaching Hospitals NHS Trust</p>	<p>Professor Howard Cuckle Professor of Reproductive Epidemiology University of Leeds</p>	<p>Dr Tom Fahey Senior Lecturer in General Practice University of Bristol</p>	<p>Dr Peter Howlett Executive Director – Development Portsmouth Hospitals NHS Trust</p>
<p>Mrs Stella Burnside Chief Executive, Altnagelvin Hospitals Health &amp; Social Services Trust Londonderry Northern Ireland</p>	<p>Dr Carol Dezateux Senior Lecturer in Paediatric Epidemiology Institute of Child Health London</p>	<p>Dr Andrew Farmer General Practitioner &amp; NHS Clinical Scientist Institute of Health Sciences University of Oxford</p>	<p>Professor Alistair McGuire Professor of Health Economics City University, London</p>
<p>Dr Paul O Collinson Consultant Chemical Pathologist &amp; Senior Lecturer St George's Hospital, London</p>	<p>Professor Adrian K Dixon Professor of Radiology Addenbrooke's Hospital Cambridge</p>	<p>Mrs Gillian Fletcher Antenatal Teacher &amp; Tutor National Childbirth Trust Reigate</p>	<p>Mrs Kathlyn Slack Professional Support Diagnostic Imaging &amp; Radiation Protection Team Department of Health London</p>
		<p>Professor Jane Franklyn Professor of Medicine University of Birmingham</p>	<p>Mr Tony Tester Chief Officer, South Bedfordshire Community Health Council Luton</p>

## Pharmaceuticals Panel

### Members

<p><b>Chair</b> <b>Dr John Reynolds</b> Clinical Director – Acute General Medicine SDU Oxford Radcliffe Hospital</p>	<p>Mrs Jeannette Howe Senior Principal Pharmacist Department of Health, London</p>	<p>Dr Frances Rotblat Manager, Biotechnology Group Medicines Control Agency London</p>	<p>Dr Richard Tiner Medical Director Association of the British Pharmaceutical Industry London</p>
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	<p>Mrs Marianne Rigge Director, College of Health London</p>	<p>Dr Ross Taylor Senior Lecturer Department of General Practice &amp; Primary Care University of Aberdeen</p>	

## Therapeutic Procedures Panel

### Members

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## Expert Advisory Network

### Members

<p>Professor John Brazier Director of Health Economics University of Sheffield</p>	<p>Dr Neville Goodman Consultant Anaesthetist Southmead Hospital, Bristol</p>	<p>Dr Sue Moss Associate Director, Cancer Screening Evaluation Unit Institute of Cancer Research Sutton, Surrey</p>	<p>Dr Sarah Stewart-Brown Director, Health Services Research Unit University of Oxford</p>
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### **Feedback**

The HTA Programme and the authors would like to know your views about this report.

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***We look forward to hearing from you.***

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