

# **Rituximab for aggressive non-Hodgkin's lymphoma**

## Technology Appraisal 65

### Rituximab for aggressive non-Hodgkin's lymphoma

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This document has been circulated to the following:

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- Community health councils in England and Wales
- NHS Clinical Governance Support Team
- Patient advocacy groups
- Representative bodies for health services, professional organisations and statutory bodies, and the Royal Colleges

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#### This guidance is written in the following context:

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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## 1 Guidance

- 1.1 Rituximab is recommended for use in combination with a regimen of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) for the first-line treatment of people with CD20-positive diffuse large-B-cell lymphoma at clinical stage II, III or IV (see Section 2.3). Rituximab is not recommended for use when CHOP is contraindicated.
- 1.2 The clinical and cost effectiveness of rituximab in patients with localised disease (Stage I, see Section 2.3) has not been established. It is recommended that rituximab be used in these circumstances only as part of ongoing or new clinical studies.
- 1.3 A specialist in the treatment of lymphomas should supervise the use of rituximab in combination with CHOP for the treatment of diffuse large-B-cell lymphoma.

## 2 Clinical need and practice

- 2.1 Lymphomas are neoplastic diseases of the lymphoreticular cells. They are divided into two broad subgroups: Hodgkin's disease and non-Hodgkin's lymphomas. The non-Hodgkin's lymphomas are a heterogeneous group, which vary considerably in their prognosis and management. They are categorised according to the cell type from which they derive, as well as the clinical features and rate of progression of the disease. Most non-Hodgkin's lymphomas (80–85%) derive from the B lymphocytes, while the remainder derive from T or undifferentiated cells. Rituximab is licensed for the treatment of diffuse large-B-cell lymphoma (DLBCL), a term that is used for a group of intermediate- to high-grade lymphomas that have an aggressive course, but which often respond well to combination chemotherapy. DLBCL is usually fatal within months if left untreated. However, aggressive lymphomas such as DLBCL are potentially curable with intensive therapy.
- 2.2 The incidence of non-Hodgkin's lymphoma in England and Wales in 1997 was approximately 15 cases per 100,000 population. This is consistent with estimates ranging from 6 to 16 per 100,000 population for Western European countries. Non-Hodgkin's lymphoma is thought to be the seventh most common type of cancer in the UK. DLBCL accounts for 30–40% of new cases of non-Hodgkin's lymphoma. Between 3 and 10% of people with AIDS develop aggressive non-Hodgkin's lymphoma, usually large-cell lymphoma.

2.3 DLBCL typically presents as a nodal or extranodal mass, sometimes with systemic symptoms, such as sweats, fatigue and fever. In about 40% of people these lymphomas appear in areas outside lymph nodes, including the digestive tract, skin, bone, thyroid and testes. Surgery is typically carried out for diagnostic purposes; once DLBCL is identified, it is staged to find out how far the disease has spread:

Stage I Involvement of a single lymph-node region [I] or localised involvement of a single extralymphatic organ or site (IE)

Stage II Involvement of two or more lymph-node regions on the same side of the diaphragm [II] or localised involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm (IIE)

Stage III Involvement of lymph-node regions on both sides of the diaphragm [III] that may also be accompanied by localised involvement of an extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIS+E)

Stage IV 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.

2.4 For many years, the standard treatment for DLBCL has been a regimen of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP). Other regimens have been studied, but these have failed to show advantage over CHOP in randomised trials. Treatment with eight cycles of CHOP results in 40–50% of people achieving complete remission and a 3-year survival rate of around 30%.

2.5 Up to 20% of people have localised (stage I) disease at presentation. An abbreviated course of CHOP (three cycles) followed by involved-field irradiation has been reported to achieve complete response in more than 90% of people with localised disease at presentation, and a 5-year disease-free survival rate of 80–85%.

- 2.6 People who relapse after initially successful chemotherapy may be eligible for high-dose chemotherapy in combination with autologous bone marrow transplantation or peripheral blood stem cell transplantation. However, such aggressive treatment is normally considered only for people below the age of 60 years.

### 3 The technology

- 3.1 Rituximab (MabThera) is a monoclonal antibody that targets the CD20 surface marker. This marker is expressed on almost all B-cell lymphomas and testing for its presence is part of the normal diagnostic procedure. CD20 is considered a suitable target for immunotherapy because it does not circulate freely in the plasma, it is not shed from the surface of B cells after binding of anti-CD20 antibodies, and it is not internalised on antibody binding. CD20 occurs on both normal and malignant B cells, but not on precursor B cells. This means that targeting this surface marker should not result in long-term depletion of B cells. Rituximab probably induces the death of CD20-positive cells by a combination of mechanisms including antibody-directed cytotoxicity, complement-dependent cytotoxicity, and the induction of apoptosis. Rituximab also appears to sensitise cells to the action of conventional cytotoxic drugs.
- 3.2 Rituximab is indicated for the treatment of people with CD20-positive diffuse large-B-cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy (see the Summary of Product Characteristics).
- 3.3 The recommended dosage is 375 mg/m<sup>2</sup> body surface area, administered by intravenous infusion on day 1 of each chemotherapy cycle after administration of the corticosteroid component of CHOP.
- 3.4 Adverse events associated with rituximab include infusion-related reactions, which occur in more than 50% of people. These are predominantly seen during the first infusion, usually during the first 1–2 hours, and include fever, chills and rigors. Other adverse events include flushing, angioedema, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, vomiting and tumour pain. In about 10% of people these adverse events are accompanied by hypotension and bronchospasm. There have been

post-marketing reports of more serious infusion-related reactions in a very small proportion of people. Fatal outcomes have been reported for people who developed features of cytokine-release syndrome and/or signs and symptoms of tumour-lysis syndrome. For full details of side effects, precautions and contraindications, see the Summary of Product Characteristics.

- 3.5 The prices to the NHS of 100-mg and 500-mg vials of rituximab are £175 and £873 respectively, excluding VAT (*British National Formulary* 45, March 2003). The cost of a course of rituximab is approximately £9800 (based on eight treatment cycles for a person with a body surface area of 1.7 m<sup>2</sup>). However, costs may vary in different settings because of negotiated procurement discounts.

## 4 Evidence and interpretation

The Appraisal Committee (Appendix A) considered evidence from a number of sources (Appendix B).

### 4.1 Clinical effectiveness

- 4.1.1 The Assessment Group found a single randomised controlled trial comparing the combination of rituximab plus CHOP (R-CHOP) with CHOP alone in people with stage II, III or IV DLBCL. The study involved 399 previously untreated people aged 60–80 years who were judged to have good to fair performance status.
- 4.1.2 Participants were randomly assigned to receive either eight cycles of CHOP every 3 weeks (n = 197) or eight cycles of CHOP plus rituximab at a dosage of 375 mg/m<sup>2</sup> of body surface area on day 1 of each of the eight cycles of CHOP (n = 202). The CHOP regimen was:
- cyclophosphamide, 750 mg/m<sup>2</sup> body surface area on day 1
  - doxorubicin, 50 mg/m<sup>2</sup> body surface area on day 1
  - vincristine, 1.4 mg/m<sup>2</sup> body surface area up to a maximum dose of 2 mg on day 1
  - prednisone, 40 mg/m<sup>2</sup> body surface area per day for 5 days (prednisone is an alternative to prednisolone used in the USA; prednisone is metabolised to prednisolone and the drugs are normally used in equivalent doses).

- 4.1.3 The primary endpoint in the trial was event-free survival, where an event was defined as disease progression, relapse, death or initiation of different treatment. Within the median follow-up period of 24 months, 86 (43%) participants receiving R-CHOP experienced at least one event, as did 120 (61%) of those in the CHOP group. A proportional hazards model showed that the relative risk (RR) of an event with the addition of rituximab to the CHOP regimen was 0.58 (95% confidence interval [CI], 0.44 to 0.77). Adjusting for a number of baseline prognostic factors did little to change this result (RR 0.55; 95% CI, 0.41 to 0.75).
- 4.1.4 Secondary outcomes were overall survival, response rates and adverse events. Health-related quality of life was not measured in the trial.
- 4.1.5 Fifty-nine (29%) of the group receiving R-CHOP died within a median of 2 years' follow-up, compared with 81 (41%) of those receiving CHOP alone. The relative risk of death from any cause with the addition of rituximab was 0.64 (95% CI, 0.45 to 0.89). After adjusting for a number of baseline prognostic factors between the treatment groups, this fell to 0.53 (95% CI, 0.37 to 0.77).
- 4.1.6 Significantly more participants achieved complete response or unconfirmed complete response in the group receiving R-CHOP compared with the group receiving CHOP (76% compared with 63%,  $p = 0.005$ ). The relative increase in the chance of a complete or unconfirmed complete response was 20% (95% CI, 5 to 37). Complete response was defined as the disappearance of all lesions and of radiological or biological abnormalities observed at diagnosis and the absence of new lesions; unconfirmed complete response was defined as a complete response except for the persistence of some radiological abnormalities that had regressed in size by at least 75%.
- 4.1.7 The incidence of severe adverse events (grade 3 or 4 according to the US National Cancer Institute Common Terminology Criteria for Adverse Events, plus grade 2 infections) was 74% in the CHOP arm, compared with 79% in the R-CHOP arm (RR 1.08; 95% CI, 0.96 to 1.20).

- 4.1.8 No comparative data in younger people were identified, but in a small uncontrolled phase II study designed to establish the safety and efficacy of R-CHOP in people with newly diagnosed aggressive lymphoma (n = 33), the response rate to R-CHOP was at least as good in people younger than 60 years of age as in those older than 60 years of age.
- 4.1.9 Data are lacking on the usefulness of rituximab in people with localised disease.

## 4.2 *Cost effectiveness*

- 4.2.1 One economic evaluation of R-CHOP versus CHOP was supplied by the manufacturer. However, the Assessment Group incorporated a number of different assumptions into the framework of the manufacturer's model as part of the review process.
- 4.2.2 Both versions of the model included only the costs to the NHS, expressed health benefits in terms of quality-adjusted life-years (QALYs), and used a 15-year time horizon. Both versions of the model also estimated utilities from the same unpublished study. The estimates of the proportion of people achieving complete response and the overall duration of survival in people receiving the CHOP regimen were based on observational data. The estimate of the relative treatment effect for R-CHOP was based on the single randomised controlled trial. Both versions of the model also used these data to estimate cost effectiveness separately for people younger than 60 years of age.
- 4.2.3 The manufacturer's version of the model produced a cost per life-year gained of approximately £4500 and a cost per quality-adjusted life-year gained (QALY) of £6100 for people aged 60 years and older. For people younger than 60 years, these figures were approximately £4700 and £6800 respectively. Sensitivity analysis showed that these incremental cost-effectiveness ratios (ICERs) were relatively robust to changes in the input assumptions. However, the ICERs approximately doubled when the time horizon was reduced to 5 years.

- 4.2.4 The Assessment Group's version of the model differed from the manufacturer's mainly in the interpretation of the survival curves for people receiving CHOP or R-CHOP and the inclusion of other costs associated with treatment failure (second-line therapies and palliative care costs). The results for people younger than 60 years were slightly less favourable than those from the manufacturer: approximately £8500 per life-year gained and £7500 per QALY gained. In people aged 60 years and older, the ICERs were less favourable: about £9700 per life-year gained and £10,500 per QALY gained. Extensive sensitivity analyses found these results to be robust to changes in the input assumptions. Probabilistic sensitivity analysis estimated that there was only a 5% chance that the cost per additional QALY would exceed £23,400 in people aged 60 years and older, or £19,000 in people younger than 60 years.
- 4.2.5 Both versions of the model suggest that rituximab in combination with each of eight cycles of CHOP is cost effective relative to CHOP used alone.

### **4.3 Consideration of the evidence**

- 4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of rituximab, having considered evidence on the nature of the condition and the value placed on the benefits of rituximab from people with DLBCL, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.3.2 The Committee considered that the evidence reviewed in the Assessment Report – primarily the results of a single randomised trial in people between the ages of 60 and 80 years – supported the case that rituximab in combination with CHOP is clinically and cost effective in people with stage II, III or IV DLBCL.
- 4.3.3 The Committee considered the use of rituximab in people with stage II, III or IV DLBCL who were younger than 60 years. In the absence of a randomised study in this group, the Committee was persuaded by the evidence from experts that it was biologically plausible that rituximab was likely to have the same effect on the disease process in people younger than 60 years as for those aged 60 years and older. In addition, the Committee was aware that the baseline cost-effectiveness estimates from the Assessment Group's version of the model had assumed the same relative risk of disease

progression (0.6) in both age groups but the sensitivity analysis explored a reduced effect (0.8) in the under-60 years age group, thus taking account of possible lesser effectiveness. In considering the clinical effectiveness in this younger age group, the Committee also took into account the evidence from a small phase II study, which supported this view. The Committee members considered that it was appropriate to use the results of the randomised trial in the 60–80 years age group to estimate the clinical and cost effectiveness in people younger than 60 years. The results of the economic evaluations suggest that R-CHOP is likely to be cost effective in both age groups compared with CHOP alone.

- 4.3.4 Evidence from the experts suggested that CHOP is an intensive course of chemotherapy that is associated with significant toxicity. There was no evidence showing that rituximab is effective in people for whom CHOP is contraindicated. Therefore it was concluded that rituximab should be used in these circumstances only as part of ongoing or new clinical studies.
- 4.3.5 For people with localised (stage I) disease, the standard treatment is three cycles of CHOP followed by involved-field radiotherapy. The Committee heard from experts that this regimen has been shown to be better than CHOP alone in this patient group, and that it is associated with a 5-year survival of more than 80%. Additionally, there is currently no evidence to support the use of rituximab in people with stage I disease. The Committee concluded that the use of rituximab in this group of patients should therefore be restricted to ongoing or new clinical studies.
- 4.3.6 There is little directly comparative evidence on the effectiveness of R-CHOP in people with AIDS-related lymphoma. After discussion with experts, the Committee concluded that this group should not be treated differently from other people with stage II, III or IV DLBCL.

## 5 Recommendations for further research

- 5.1 There are numerous ongoing studies of rituximab in combination with chemotherapy regimens in different lymphomas including DLBCL. One study, which is currently recruiting participants, is investigating the addition of rituximab to CHOP or similar regimens in people younger than 60 years. In addition, there is an ongoing study investigating the role of extended rituximab treatment in people responding to initial treatment with either R-CHOP or CHOP alone.
- 5.2 Research into the effectiveness of rituximab as an adjunct to an abbreviated course of CHOP followed by involved-field radiotherapy in people with localised disease is needed.

## 6 Implications for the NHS

- 6.1 The annual incidence of DLBCL in England and Wales is approximately 3000. In the absence of R-CHOP, it is estimated that 50% of these people receive treatment with CHOP (n = 1500). If it is assumed that 50–95% of these 1500 people will receive R-CHOP (costing approximately £14,300 per person, excluding VAT, as estimated by the Assessment Group) instead of CHOP (costing approximately £5700 per person, excluding VAT, as estimated by the Assessment Group), and that there will also be a 20% rise in the number of people receiving treatment because of the availability of a more effective therapy (n = 600), the annual treatment costs will increase by £9.1–17.2 million. However, because the annual incidence of DLBCL in England and Wales is increasing by approximately 4% per annum, this annual cost increase could rise to an upper estimate of £27.3 million (excluding VAT) by 2007.
- 6.2 These figures do not include any extra cost of monitoring the first infusion of rituximab but do include some of the extra costs of pharmacy preparation time and cost offsets from the potential avoidance of high-dose chemotherapies and bone marrow transplantations as a result of improved effectiveness.

## 7 Implementation and audit

- 7.1 Clinicians with responsibility for treating people with CD20-positive DLBCL should review their current practice and policies to take account of the guidance set out in Section 1.
- 7.2 Local guidelines, protocols or care pathways that refer to the care of people with CD20-positive DLBCL should incorporate the guidance.
- 7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.
- 7.3.1 An individual with CD20-positive DLBCL at clinical stage II, III or IV is provided with rituximab in combination with a regimen of CHOP for first-line treatment, unless this treatment is contraindicated.
- 7.3.2 An individual with DLBCL that is localised (stage I or IE) is provided with rituximab only as part of ongoing or new clinical studies.
- 7.3.3 A specialist in the treatment of lymphomas supervises the use of rituximab in combination with CHOP to treat DLBCL.

## 8 Related guidance

- 8.1 The Institute issued guidance on the use of rituximab in follicular non-Hodgkin's lymphoma in March 2002.
- National Institute for Clinical Excellence (2002) Guidance on the use of rituximab for recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma. *NICE Technology Appraisal Guidance* No. 37. London: National Institute for Clinical Excellence. Available from: [www.nice.org.uk](http://www.nice.org.uk)

## 9 Review of guidance

- 9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.
- 9.2 The guidance on this technology will be reviewed in August 2006.

Andrew Dillon  
Chief Executive  
September 2003

A version of this guidance for people with non-Hodgkin's lymphoma, and the public is available from the NICE website ([www.nice.org.uk](http://www.nice.org.uk)) or from NHS Response Line (telephone 0870 1555 455 and quote reference number N0286 for an English version and N0287 for a version in English and Welsh).

## Appendix A

### Appraisal Committee members

**NOTE** The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

**Professor Ron Akehurst**  
Dean, School of Health Related  
Research, University of Sheffield

**Dr Tom Aslan**  
General Practitioner, Stockwell,  
London

**Professor David Barnett**  
(Chair)  
Professor of Clinical  
Pharmacology, University of  
Leicester

**Dr Sheila Bird**  
MRC Biostatistics Unit,  
Cambridge

**Dr Richard Cookson**  
Senior Lecturer, Health  
Economics, School of Health  
Policy and Practice, University of  
East Anglia, Norwich

**Professor Gary A Ford**  
Professor of Pharmacology of  
Old Age/Consultant Physician,  
Newcastle upon Tyne Hospitals  
NHS Trust

**Ms Bethan George**  
Interface Liaison Pharmacist,  
Tower Hamlets PCT and Royal  
London Hospital, Whitechapel

**Dr Trevor Gibbs**  
Head, Global Clinical Safety &  
Pharmacovigilance,  
GlaxoSmithKline, Greenford

**Mr John Goulston**  
Director of Finance, St  
Bartholomew's Hospital and the  
London NHS Trust

**Mr Muntzer Mughal**  
Consultant Surgeon, Lancashire  
Teaching Hospitals NHS Trust,  
Chorley

**Ms Judith Paget**

Chief Executive, Caerphilly Local Health Board, Torfaen

**Mrs Kathryn Roberts**

Nurse Practitioner, Hyde, Cheshire

**Professor Philip Routledge**

Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff

**Ms Anne Smith**

Lay Representative; Trustee, Long-Term Medical Conditions Alliance

**Professor Andrew Stevens**

(Vice-Chair)  
Professor of Public Health, University of Birmingham

**Dr Cathryn Thomas**

General Practitioner/Senior Lecturer, Department of Primary Care and General Practice, University of Birmingham

**Dr Norman Vetter**

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

**Dr David Winfield**

Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

## Appendix B

### Sources of evidence considered by the Committee

- A** The Assessment Report for this appraisal was prepared by the School for Health and Related Research (SchARR), University of Sheffield:

*Rituximab (MabThera) for aggressive non Hodgkin's lymphoma: systematic review, March 2003*

- B** The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I. Manufacturer/sponsors:

- Roche

II. Professional/specialist and patient/carer groups:

- British Oncology Pharmacy Association
- British Society for Haematology
- Cancer Research UK
- CancerBACUP
- Department of Health
- Leukaemia Care Society
- Leukaemia Research Fund
- Lymphoma Association
- Macmillan Cancer Relief
- National Cancer Alliance
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Royal Pharmaceutical Society of Great Britain
- Wales Cancer Network
- Welsh Assembly Government
- British National Formulary
- British National Lymphoma Association
- National Cancer Research Institute
- NHS Quality Improvement Scotland

- C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on the use of rituximab for aggressive non-Hodgkin's lymphoma by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.
- Dr D Milligan, Consultant Haematologist, British Committee for Standards in Haematology
  - Dr Ruth Pettengell, Senior Lecturer in Haemato-Oncology, Department of Haematology, St George's Hospital Medical School
  - Joanne Rule, Chief Executive, CancerBACUP
  - Tracy Williams, Senior Nurse, CancerBACUP

## Appendix C

### Detail on criteria for audit of the use of rituximab for aggressive non-Hodgkin's lymphoma

#### *Possible objectives for an audit*

An audit on the treatment of people with CD20-positive DLBCL could be carried out to ensure that rituximab is being used appropriately.

#### *Possible patients to be included in the audit*

An audit could be carried out on people with DLBCL who are referred over a suitable period, for example, 6 or 12 months.

## Measures that could be used as a basis for an audit

The measures that could be used in an audit of rituximab are as follows.

Criterion	Standard	Exception	Definition of terms
1. An individual with DLBCL at clinical stage II, III or IV is provided with rituximab in combination with a regimen of CHOP for first-line treatment	100% of the individuals with DLBCL at clinical stage II, III or IV	A. CHOP is contraindicated	<p>'CHOP' means a regimen of cyclophosphamide, doxorubicin, vincristine and prednisolone (or prednisone).</p> <p>'Stage II' refers to involvement of two or more lymph-node regions on the same side of the diaphragm (II) or localised involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm (IIE).</p> <p>'Stage III' refers to involvement of lymph-node regions on both sides of the diaphragm (III) that may also be accompanied by localised involvement of an extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIS+E)</p> <p>'Stage IV' refers to 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.</p> <p>Clinicians will need to agree locally on how contraindications will be documented for audit purposes.</p>

Criterion	Standard	Exception	Definition of terms
2. An individual with DLBCL at clinical stage I is provided with rituximab	0% of the people with DLBCL at clinical stage I	A. The individual is participating in a clinical trial	'Stage I' refers to involvement of a single lymph-node region (I) or a single organ outside of the lymphatic system site (IE).
3. A specialist in the treatment of lymphomas supervises the use of rituximab in combination with CHOP to treat DLBCL	100% of the individuals receiving rituximab in combination with CHOP for DLBCL	None	Clinicians will need to agree locally on how supervision of the use of rituximab in combination with CHOP is defined and documented for audit purposes.

## Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the criterion *plus* number of patients who meet any exception}}{\text{Number of patients to whom the measure applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.





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