

**REGIONAL DRUG AND THERAPEUTICS CENTRE
(NEWCASTLE)**

**THE USE OF RITUXIMAB IN COMBINATION
WITH CVP CHEMOTHERAPY FOR THE
MANAGEMENT OF FOLLICULAR
NON-HODGKIN'S LYMPHOMA**

**Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH**

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ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre. The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rests solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

Subject	Date issued
Taxanes in breast cancer	July 1997
Somatropin for GHD in adults	January 1998
New drugs for Alzheimer's disease	February 1998
Atypical antipsychotics	February 1998
Dornase alfa for cystic fibrosis	July 1998
Topotecan for ovarian cancer	July 1998
Irinotecan for colorectal cancer	July 1998
Interferon alfa for haematological malignancy	July 1998
Antiretroviral therapy	July 1998
Paclitaxel in ovarian cancer	December 1998 (update)
Interferon in MS	May 1999 (update)
Octreotide	July 1999
Drug treatment of obesity	July 1999
Low molecular weight heparins in venous thrombo-embolic disease	November 1999
Low molecular weight heparins in unstable coronary artery disease	November 1999
Ribavirin and interferon alfa for chronic hepatitis C	March 2000
Temozolomide for high grade gliomas	May 2000
New drugs for rheumatoid arthritis	May 2000
Verteporfin for age related macular degeneration	November 2000
Iloprost and epoprostenol in the management of pulmonary hypertension	February 2001
Atypical antipsychotics in the management of dementia	June 2001
Interferon alfa in the management of malignant melanoma	November 2001
Imatinib (Glivec [®] , STI-571), in the management of chronic myeloid leukaemia	November 2001
Agalsidase alfa and beta in the management of Fabry disease	July 2002
Carbamyl glutamate in the management of N-acetylglutamate synthetase deficiency	July 2002
Erythropoietin in the management of cancer related anaemia	July 2002
Drotrecogin alfa (activated) in the management of severe sepsis	December 2002
An update on newer agents for the treatment of pulmonary hypertension	February 2004
The use of adefovir dipivoxil for the treatment of chronic hepatitis B infection	May 2004
The use of teriparatide in the management of osteoporosis	July 2004
The use of ibandronic acid in the management of hypercalcaemia of malignancy, bone pain and the prevention of skeletal events associated with skeletal metastases	August 2005
The use of pegvisomant in the management of acromegaly	January 2006
The use of pemetrexed in the management of malignant pleural mesothelioma	February 2006
The use of bortezomib second-line in the management of multiple myeloma	March 2006
The adjuvant use of docetaxel or paclitaxel in the management of early stage breast cancer	March 2006
The use of erlotinib in the management of non-small cell lung cancer	March 2006
The use of ibritumomab in the management of B-cell follicular non-Hodgkin's lymphoma	March 2006

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SUMMARY

- The annual incidence in the UK of follicular lymphomas is between 3 – 5 per 100,000 and prevalence is about 40 per 100,000. Most follicular lymphomas present at stages III or IV.
- Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody and is licensed to treat stage III-IV follicular lymphoma;
 - As monotherapy in patients who are chemoresistant or are in 2nd/subsequent relapse after chemotherapy or
 - In combination with CVP chemotherapy in patients who are previously untreated.
- A Single Technology Appraisal is planned by NICE on rituximab assessing first line treatment for low grade non-Hodgkin's lymphoma. This is expected to be published in August 2006.
- One published trial evaluated rituximab + CVP compared to CVP alone in previously untreated patients with stage III/IV follicular lymphoma. The rituximab + CVP regimen significantly lengthened time to treatment failure (27 vs 7 months) and more than doubled time to progression (34 vs 15 months), with significantly improved complete response rates (30% vs 8%), duration of response (38 vs 14 months), disease free survival (45 vs 21 months) and median time to next antilymphoma treatment (not reached vs 12 months). All the primary endpoints of the study were significantly improved except overall survival (89% vs 81%). Other published trials, evaluating rituximab and CHOP chemotherapy regimens, demonstrated similar benefits.
- Therapy with rituximab + CVP was well tolerated and produced a pattern of adverse events broadly similar to CVP alone, with the exception of some mild to moderate infusion related reactions following rituximab administration and a higher incidence of grade 3 or 4 neutropenia, without an increased risk of infection.
- Rituximab is beneficial in terms of efficacy and safety in the treatment of patients with stage III-IV follicular lymphoma and normally considered to be almost unresponsive to conventional chemotherapy.
- Total cost of rituximab per patient for the full eight cycles is £9,779 (exclusive of CVP costs and VAT). Based on an annual incidence of follicular lymphoma of 3 – 5 / 100,000, costs per 100,000 patients could range from £29,337 - £48,895. Using overall survival in the Marcus et al trial^{9, 10} of 81% and 89% in CVP and rituximab-CVP respectively; 13 patients would need to be treated with the rituximab-CVP combination to prevent one death.

BACKGROUND

Non-Hodgkin's lymphomas, of which follicular lymphomas are a subgroup, are a heterogeneous group of tumours that affect the lymphatic system. Patients who develop the most common type of follicular lymphoma typically survive for a median of 8 to 10 years. The disease is incurable at advanced stages [stages III or IV, (Appendix 1)], and is curable in only about 5% of patients at earlier stages.¹

The most usual presenting symptom is enlargement of one or more lymph nodes, but the spleen and bone marrow are often also affected. Additionally, generalised symptoms include malaise, weight loss, fevers and night sweats.¹

Non-Hodgkin's lymphomas are traditionally divided into 2 prognostic groups:²

- Indolent or low-grade lymphomas with a long median survival. The majority of lymphomas, including follicular types, fall into this group. They are currently incurable at advanced stages with a median survival of 8 – 10 years.
- Aggressive or high grade lymphomas. These have a short natural history and a 50-60% cure rate.

Lymphomas are graded according to the rate at which the abnormal lymphocyte cells divide. They are termed 'high grade' when they divide quickly and 'low-grade' (or indolent) when they divide slowly. Follicular lymphoma is the most common form of low-grade lymphoma.³

Follicular lymphoma is a chronic disease with a variable course; many patients can be monitored for years without therapy yet others need to be treated aggressively at the onset. The long natural history of the disease obscures the fact that for individual patients, outcomes vary significantly.⁴ Most follicular lymphomas present at stages III or IV.¹

Non-Hodgkin's lymphomas account for about 2% of all malignancies in the UK – there are about 9,000 new cases each year. The annual incidence for men is 15 per 100,000 population and for women it is 10 per 100,000. Between 22% and 40% of non-Hodgkin's lymphomas are follicular, depending on the classification. Annual incidence of follicular lymphomas is between 3 – 5 per 100,000 in the UK and prevalence is about 40 per 100,000.¹

Current NICE guidance states that the main aims of treatment are to achieve remission during relapse and to alleviate symptoms. As the disease progresses, treatment starts with single agents such as an oral alkylating agent such as chlorambucil or combination cyclophosphamide, vincristine and prednisolone (CVP).

When first line treatment fails or relapse occurs, combination chemotherapy is given e.g. cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or CVP.¹

Both combination therapy and radiation therapy (appropriate only in a small proportion of patients) can give prolonged remissions.¹

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences.⁵

Rituximab binds to a target protein – the antigen CD20 located on the surface of specific white blood cells, the B lymphocytes, thereby stopping the pathological growth of these cells.⁷

Rituximab is licensed to treat stage III-IV follicular lymphoma;⁵

- As monotherapy in patients who are chemoresistant or are in 2nd/subsequent relapse after chemotherapy OR
- In combination with CVP chemotherapy in patients who are previously untreated.⁵

Rituximab is also licensed for the treatment of patients with CD20+ diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy.⁵

CURRENT GUIDANCE

NICE guidance evaluated rituximab as treatment for aggressive non-Hodgkin's lymphoma in Sep 2003,⁷ but there is existing guidance on the use of rituximab for recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma, which was published in March 2002¹. This states that;

- 1.1 The use of rituximab for 3rd line or subsequent line, but not 'last-line' treatment of patients with recurrent or refractory stage III or IV follicular lymphoma is not recommended.
- 1.2 For last-line treatment, rituximab is recommended only in the context of a prospective case series. All patients for whom alternative therapies have been exhausted (those that are chemo-resistant or chemo-intolerant) would be appropriate for inclusion in the case series on the basis that data are systematically collected to allow aggregation and analysis at a national level.

A Single Technology Appraisal is planned by NICE on rituximab as first line treatment for low grade non-Hodgkin's lymphoma. This is expected to be published in August 2006.³

The Scottish Medicines Consortium published guidance in December 2004, which stated;

'Rituximab is accepted for use within NHS Scotland for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with cyclophosphamide, vincristine and prednisolone (CVP) chemotherapy.

Rituximab is for use only by oncologists or haematologists who have expertise in treating lymphoma. It should be administered in a hospital environment where full resuscitation facilities are available. Limited results show that rituximab plus CVP significantly increased the time to treatment failure compared with CVP alone'.⁸

EFFICACY

Adding rituximab to chemotherapy as first line treatment has been evaluated in four clinical trials, detailed below. One trial combined rituximab with CVP,^{9,10} two combined rituximab with CHOP^{11, 12} and the final trial studied rituximab with either CVP or CHOP,¹³ but with a shorter course of chemotherapy.

RITUXIMAB WITH CVP

This phase III prospective randomised trial (n=321)⁹ evaluated the addition of rituximab to CVP compared to CVP alone, in previously untreated patients with stage III/IV follicular lymphoma.

Patients had untreated CD20+ follicular lymphoma, with stage III or IV disease, an Eastern Clinical Oncology Group performance status of 0 to 2, life expectancy of longer than three months and a need for therapy in the opinion of the participating clinician. Patients treated with CVP (n=159) received a combination of cyclophosphamide and vincristine on day one, and prednisolone on days one to five. Patients with rituximab-CVP (n=162) additionally received 375mg/m² of rituximab intravenously on day one of each therapy cycle. Patients in both groups were treated every 21 days for a maximum of eight cycles.

There were no significant differences between the two groups in terms of baseline characteristics. Median age was 53 and 52 years in the CVP and rituximab-CVP groups respectively.

The eight scheduled cycles of chemotherapy were administered to 68% of CVP patients and 85% of rituximab-CVP patients respectively. The reason for this difference was due to fewer patients in the rituximab-CVP group being withdrawn from treatment because of an insufficient therapeutic response, mainly after cycle four.

The primary endpoint was time to treatment failure. Time to treatment progression was also analysed, although the trial does not clearly state whether this was a primary or secondary endpoint. Secondary endpoints included response rates (complete response, complete response unconfirmed and partial response), duration of response, disease free survival, time to next antilymphoma treatment or death, and overall survival. Results of the intention to treat analysis after 30 months median follow up are summarised in the following table;

30 month data;

End Point	CVP (n=159)	Rituximab-CVP (n=162)	p value
Time to treatment failure	7 months	27 months	p<0.0001
Time to treatment progression	15 months	32 months	p<0.0001
Complete response	n=12 (8%)	n=49 (30%)	p<0.001
Complete response unconfirmed	n=4 (3%)	n=17 (11%)	p<0.001
Partial response	n=74 (47%)	n=65 (40%)	p<0.001
Duration of response	14 months	35 months	p<0.001
Disease free survival	21 months	not reached	p=0.0009
Time to next antilymphoma treatment or death	12 months	not reached	p<0.0001
Overall survival	85%	89%	not significant

Updated data has recently been published showing 42 months median follow up¹⁰, however this is still only in abstract form. These updated figures are shown in the following table;

Updated 42 month data;

End Point	CVP (n=159)	Rituximab-CVP (n=162)	p value
Time to treatment progression	15 months	34 months	p<0.0001
Duration of response	14 months	38 months	p<0.001
Disease free survival	21 months	45 months	p=0.0005
Overall survival	81%	89%	P=0.07

The addition of rituximab to a standard CVP regimen significantly lengthened time to treatment failure and more than doubled time to progression, with significantly improved response rates, duration of response, disease free survival and time to next antilymphoma treatment. This study shows that adding rituximab to CVP significantly improved all the clinical endpoints of the study except overall survival, but the study was inadequately powered to examine this endpoint.

RITUXIMAB IN COMBINATION WITH CHOP – UNLICENSED USE

Rituximab has also been evaluated, in two further clinical trials, in combination with an alternative chemotherapy regimen – CHOP.^{11,12}

A small phase II, open label, single arm, multicentre study in 40 patients¹¹ compared rituximab and CHOP in combination. Patients were newly diagnosed or relapsed/refractory with histologically documented low grade or follicular B-cell non Hodgkin's lymphoma and measurable progressive disease.

The primary endpoint was disease progression, partial response and complete response. Secondary efficacy endpoints were time to treatment progression and disease progression free interval.

35 out of 40 patients received all six infusions of rituximab and six cycles of CHOP. All 40 patients were included in the intent to treat analysis. Median time to response was 47 days. Overall response rate was 95% in the intention to treat population. 55% (22/40 patients) experienced a complete response, 40% (16/40 patients) had a partial response.

There were 24 assessable newly diagnosed patients with a follicular histology and they all responded to therapy (16 complete response and 8 partial response). Median duration of response and time to treatment progression had not yet been reached after a median observation time of 29+ months.

Another more recently conducted trial (n=630), evaluated CHOP combined with rituximab vs CHOP alone.¹² This was a randomised, prospective, open label multicentre phase III trial that investigated patients with previously untreated advanced stage III or IV follicular lymphomas (grades I and II according to World Health Organisation classification).

Primary and secondary endpoints were not clearly stated, but parameters that were tested included overall response rate (equal to complete plus partial responses), time to treatment failure, complete and partial remission, response duration and overall survival.

In the R-CHOP arm a significantly higher overall response rate of 96% vs 90% for CHOP alone was observed (p=0.011). The complete remission rates were not statistically different (20% vs 17% respectively). Partial remission rates were 77% vs 73% for rituximab-CHOP and CHOP respectively. In the rituximab-CHOP arm, 28/223 patients (13%) had experienced a treatment failure by 3 years and in CHOP 61/205 patients had experienced a treatment failure by 3 years (30%) (p<0.0001). Median overall survival had not been reached. After 3 years, 3% (6/223 patients) in the rituximab-CHOP arm had died, and 8% (17/205) in the CHOP arm had died (p=0.016).

Rituximab could therefore also be prescribed in combination with CHOP instead of CVP, although this would currently be an unlicensed use. The trial data above shows that rituximab-CHOP is better than CHOP alone, but does not address whether it is better than rituximab-CVP or CVP alone.

RITUXIMAB WITH SHORT COURSE CVP AND CHOP

This non-randomised, multicentre, phase II trial (n=86) evaluated the feasibility and efficacy of rituximab with short duration chemotherapy in the first-line treatment of patients with follicular non-Hodgkin's lymphoma.¹³

Delivery of a full six to eight courses of chemotherapy can be difficult for patients who are elderly, due to treatment related toxicity, hence the need to assess short duration chemotherapy. Patients thought to be poor candidates for CHOP (because of either cardiac problems or general debility) were allowed to receive rituximab plus CVP instead.

Patients had previously untreated stage II-IV follicular non-Hodgkin's lymphoma, grade 1 or 2 (as defined by the revised European-American Lymphoma Classification).

All patients received four weekly doses of rituximab 375mg/m² by intravenous infusion, followed by three courses of combination chemotherapy (either CHOP or CVP) plus rituximab, administered at 21 day intervals. After completing the chemotherapy, patients received two additional doses of rituximab (375mg/m²) during weeks 14 and 15. Patients had a median age of 57 years.

Primary efficacy endpoint was rate of clinical complete response. Progression free survival and overall survival were also measured. 82/86 (95%) patients completed the entire course of treatment and were assessable for response. 60/86 (70%) patients received CHOP and 25/86 (29%) received CVP.

After a median follow up of 42 months, 58 patients (67%) remained progression free. Average progression free survival at 3 years was 71%. 55% (47) patients had complete response or unconfirmed complete response at the time of restaging. Results for complete response or unconfirmed complete response are similar to that seen in other phase II and III studies of chemotherapy/rituximab regimens, using full courses of chemotherapy.

CHOP and CVP were not separated in terms of how patients responded to each regimen respectively, and all results were combined.

ADVERSE EFFECTS

The proportion of patients reporting at least one adverse effect in the Marcus et al trial⁹ was comparable between the CVP (95%) and rituximab-CVP (97%) groups.

More patients in rituximab-CVP group experienced an adverse effect within 24 hours of infusion (71% vs 51% respectively). 9% (14 patients) had a grade 3 or 4 rituximab infusion related reaction. Incidence of grade 3 or 4 neutropenia was higher during treatment with rituximab-CVP (24%) compared to CVP (14%). There was no difference between the groups in the overall infection rate or incidence of neutropenic sepsis.

Therapy with rituximab-CVP was well tolerated and produced a pattern of adverse effects broadly similar to CVP alone, with the exception of some mild to moderate infusion related reactions following rituximab administration and a higher incidence of grade 3 or 4 neutropenia, without an increased risk of infection.⁹

The most frequently experienced adverse effects in the rituximab combination with CHOP¹¹ were neutropenia (77.5%), alopecia (75%), nausea (67.5%) and fever (57.5%). 75% of the adverse effects were attributed to the CHOP regimen specifically by the treating physicians. The most frequent adverse effect attributed to rituximab were infusion related events (19% overall).

In the CHOP vs rituximab-CHOP trial,¹² treatment associated haematological side effects were mainly myelosuppression and granulocytopenia. Granulocytopenia grade 3 and 4 occurred after 63% rituximab-CHOP cycles compared to 53% CHOP courses (p=0.01). Infections were encountered after 5% of rituximab-CHOP and 7% of CHOP courses. Non-haematological side effects consisted mainly of alopecia, nausea and vomiting which occurred at similar frequencies after both regimens, and were mostly mild to moderate.

DOSAGE, ADMINISTRATION AND COST

The recommended dosage for rituximab in follicular non-Hodgkin's lymphoma, in combination with CVP chemotherapy, is 375 mg/m² body surface area for eight cycles (21 days/cycle). This is administered on day one of each chemotherapy cycle after IV administration of the corticosteroid component of CVP. Premedication consisting of an analgesic and antihistamine should always be administered before each infusion of rituximab. Premedication with corticosteroids should also be considered if rituximab is not given in combination with CHOP chemotherapy.⁵

Monitoring requires full blood count including platelet counts, at regular intervals. This is reviewed more frequently in patients who develop cytopenias. Patients who develop clinically significant arrhythmias or with pre-existing cardiac conditions should have cardiac monitoring during and after subsequent infusions.

Patients at high risk of hepatitis B virus infection should be screened prior to initiation of therapy; carriers of hepatitis B virus should be monitored for signs of active hepatitis B virus infection and for signs of hepatitis throughout therapy and for several months after therapy.¹⁴

Current costs of rituximab are, 100mg in 10 mL, £349.25 (2 vials) and 500mg in 50 mL = £873.15 (1 vial) (all costs are exclusive of VAT).¹⁵

Assuming a typical patient has a body surface area of 1.75m², the total cost of rituximab per patient for the full 8 cycles is **£9,779** (ex VAT). Based on an annual incidence of follicular lymphoma of 3 – 5 / 100,000, costs per 100,000 population could range from **£29,337 - £48,895**. These costs are purely the rituximab costs and do not take into account extra costs associated with service provision, e.g. CVP costs. They also assume that patients will complete the full eight cycles, in line with the licensed dose.

Using overall survival in the Marcus et al trial^{9, 10} (the only trial comparing CVP and rituximab-CVP) of 81% and 89% in CVP and rituximab-CVP respectively; 13 patients would need to be treated with the rituximab-CVP combination to prevent one death.

PLACE IN TREATMENT

Rituximab is marketed as an add-on to current chemotherapy options.² For the indication discussed within this document, NICE guidance currently states that rituximab is recommended only as last line treatment in the context of a prospective case series.¹ NICE guidance on rituximab as first line treatment for low grade non Hodgkin's lymphoma is scheduled for publication in August 2006. In the meantime, patients with advanced follicular lymphoma may be considered for treatment with combination rituximab and CVP. Trial evidence has shown that when rituximab + CVP was compared to CVP alone, time to treatment failure was significantly lengthened (27 vs 7 months)⁹ and time to progression was more than doubled (34 vs 15 months).¹⁰

ARRANGEMENTS FOR PRESCRIBING

Treatment should be prescribed and response supervised by an oncologist or haematologist experienced in the use of anti-cancer therapies. Shared care is not an appropriate option at this time.

FUTURE DEVELOPMENTS

It is possible that a license may be requested for the use of rituximab in combination with CHOP chemotherapy in patients who are previously untreated. New therapies in follicular lymphoma include myeloablative therapy followed by peripheral stem cell transplantation in younger patients.¹² Ibritumomab is an additional treatment option in rituximab refractory patients.

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APPENDIX 1: ANN ARBOR STAGING SYSTEM FOR NHL¹

- Stage I** Involvement of single lymph node region or localised involvement of single extralymphatic organ or site
- Stage II** Involvement of 2 or more lymph node regions 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
- Stage III** Involvement of lymph node regions on both sides of the diaphragm that may be accompanied by localised involvement of an extralymphatic organ or site, by involvement of the spleen, or both
- Stage IV** Disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

APPENDIX 2: SUMMARY OF TRIALS

Key: A/E – adverse effect; CHOP - cyclophosphamide, doxorubicin, vincristine and prednisolone ; CR – complete response; Cru – complete response unconfirmed; CVP – cyclophosphamide, vincristine and prednisolone; DFS – disease free survival; DR – duration of response; ECOG - Eastern Cooperative Oncology Group; - NHL – non-Hodgkins lymphoma; ORR: overall response rate; PFS – progression free survival; PR – partial response; R-CVP – rituximab + cyclophosphamide, vincristine and prednisolone; TTF – time to treatment failure; TTP – time to progression; WHO – world health organisation

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Marcus R, Imrie K, Belch A et al. 2005 ⁹	Prospective randomised trial.	CVP arm - cyclophosphamide day 1, vincristine day 1 and prednisolone days 1-5. Patients treated every 21 days for max of 8 cycles.	159	18 years or older with untreated CD20+ follicular lymphoma. Patients had stage III or IV disease, ECOG 0 to 2, life expectancy of > 3 months and a need for therapy in the opinion of the participating clinician.	Evidence of histologic transformation to high grade or diffuse large B-cell lymphoma, central nervous system involvement or history of severe cardiac disease or previous malignancy other than in situ carcinoma of cervix and basal cell carcinoma of the skin.	Primary endpoint was TTF. TTP was also analysed. Additional parameters included response rates, overall survival, duration of response, time to next antilymphoma treatment or death and disease free survival.	At median follow up of 30 months, median TTF was 7 months in the CVP arm, and 27 months in the R-CVP arm (p<0.0001). Median TTP is 15 months in the CVP arm and 32 months in the R-CVP arm with 72% CVP patients experiencing an event compared to 48% in the R-CVP group (p<0.0001). Median DR was 14 months in the CVP group vs 35 months in the R-CVP group (p<0.0001). In patients achieving CR or Cru after initial therapy, median DFS was 21 months in CVP patients and has not yet been reached in R-CVP arm (p=0.0009).	Proportion of patients reporting at least one A/E was comparable between the two groups - 95% for CVP arm and 97% for R-CVP arm. More patients in R-CVP group experienced an A/E within 24 hours of infusion (71% vs 51% respectively). 9% (14 patients) had a grade 3 or 4 rituximab infusion related reaction. Incidence of grade 3 or 4 neutropenia was higher during treatment with R-CVP (24%) compared to CVP (14%). There was no difference between the groups in the overall infection rate or incidence of neutropenic sepsis.
		R-CVP arm - As above plus rituximab 375mg/m ² IV on day 1. Patients treated every 21 days for max of 8 cycles.	162					

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Hainsworth J D, Litchy S, Morrissett L H et al. 2005 ¹³	Multicentre, non- randomised phase II trial.	Initial 4 week course of single agent rituximab weekly, followed by 3 courses of chemo with rituximab + CHOP at standard doses, at 21 day intervals. If patients were unsuitable for CHOP, they received CVP instead.	86	Biopsy proven follicular NHL, grade 1 or 2. Patients with stages II, III and IV lymphoma were eligible, as were patients who had previously presented with early stage disease (stages I or II) and relapsed after radiation alone. Performance status of ECOG 0, 1 or 2.	Patients with small lymphocytic lymphoma or other subtypes of indolent NHL. Patients who had central nervous system involvement (parenchymal brain or meningeal) were ineligible	Primary efficacy endpoint was the rate of clinical CR. Achievement of a CR rate more than 50%, with median progression free survival greater than 36 months, was considered indicative of further development. PFS and OS were also measured.	55% (47 patients) had CR or CrU at the time of restaging. After median follow up of 42 months, 58 patients (67%) remained progression free. Actuarial progression free survival at 3 years was 71%.	During the initial 4 weeks of rituximab, only one patient had grade 3 toxicity (dyspnoea) during infusion. 24% (21 patients) had grade 1 or grade 2 infusion related toxicity, usually during the first rituximab infusion.

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Czuczman M, Grillo-Lopez A J, White C A et al 1999 ¹¹	Phase II, open label, single arm, multicentre study.	Patients received a total of six intravenous infusions of 375mg/m ² rituximab and six cycles of CHOP, given every 3 weeks.	40	Newly diagnosed and relapsed/refractory patients at least 18 years old, with histologically documented low grade or follicular B-cell NHL and measurable progressive disease. Tumours were CD20+, and patients had an expected survival of 3 months or more, prestudy performance status of 0, 1 or 2 (WHO scale), recovery from any significant toxicity associated with anticancer therapy, adequate haematologic, renal and hepatic function within 7 days of initial therapy.	Bulky disease (single mass >10cm in diameter), prior therapy with anthracyclines, anthrapyrazoles or drugs that were classified as investigational phase I or II antineoplastic agents, prior radioimmunotherapy, cancer radiotherapy, immunotherapy or chemotherapy within 3 weeks of the scheduled first study treatment; nitrosourea or mitomycin therapy within 6 weeks of the first scheduled study therapy, or presence of central nervous system lymphoma.	Primary endpoint was the response of B-cell lymphoma to treatment (overall response rate). Secondary endpoints were the time to progression and response duration.	Median time to response was 47 days. ORR was 95% in the intent to treat population. 22 patients (55%) experienced a CR and 16 (40%) had a PR. 24 assessable patients had follicular histology and all responded to therapy (16 CR and 8 PR). Median duration of response was yet to be reached at 29+ months.	Most frequent adverse events were neutropenia (31 patients), alopecia (30 patients), nausea (27 patients) and fever (23 patients). 8 patients were hospitalised with febrile neutropenia and 2 with neutropenia and a documented infection. 75% of the adverse events were attributed to CHOP.

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Hidde mann W, Kneba M, Dreyling M et al 2005 ²	Phase III, prospective, randomised, open label, multicentre trial.	Patients were randomised to CHOP alone (n=205) or combined with rituximab (n=223). Treatment cycles were repeated every three weeks for a total of six to eight cycles. Patients randomised into the R-CHOP arm received a dose of 375mg/m ² /d rituximab on the day before the respective R-CHOP course.	428	Patients aged 18 or older with previously untreated advanced stage follicular lymphomas grades I and II (WHO classification). Patients had stage III or IV disease and a requirement for therapeutic intervention defined by presence of B-symptoms and/or bulky disease, and/or an impairment of normal hematopoiesis and/or a rapidly progressive disorder.	Not stated.	Primary endpoint was not clearly stated. Response was measured by complete remission, partial remission, time to treatment failure, response duration and overall survival.	R-CHOP patients experienced a significantly higher ORR of 96% vs 90% for CHOP alone. Other parameters measured included CR (20% vs 17%), PR (77% vs 73%) and progression during therapy (1% vs 3%) for R-CHOP vs CHOP respectively. Median time to treatment failure for both regimens was not reached in the patients under 60 years, and in patients over 60 years, was 29 months for CHOP and was not reached for R-CHOP.	Granulocytopenia of grades 3 and 4 occurred after 63% of R-CHOP as compared to 53% of CHOP. Non-hematologic side effects consisted mainly of alopecia, nausea and vomiting (mostly mild to moderate) and occurred at similar frequencies after both regimens.