

# Use of Rituximab in Combination with Conventional Chemotherapy for the Treatment of Non-Hodgkin's Lymphoma of the Head and Neck

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**Abstract.** *Background:* Rituximab, an anti-CD20 chimeric monoclonal antibody that specifically depletes mature B cells, is an effective single agent in the treatment of relapsed or refractory indolent lymphomas, and has been shown to improve the survival rate of elderly patients with diffuse large-B-cell lymphoma when used in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). *Patients and Methods:* The combined effect of rituximab and CHOP has been comparatively studied against CHOP alone in 18 elderly patients with non-Hodgkin's lymphoma of the head or neck treated in the 1st Department of Otolaryngology at Hippokration Hospital between January 1998 and January 2004. *Results:* Response rates were 91% and 100% in patients treated with rituximab plus CHOP and with CHOP alone, respectively. Overall survival and disease-free survival rates were 91% in the rituximab plus CHOP group, compared with 83% and 60%, respectively, in the CHOP alone group ( $p=0.75$  and  $p=0.24$  for the differences between the groups, respectively). The rituximab plus CHOP therapy was generally well tolerated, with few adverse events reported. *Conclusion:* The results of this small case series, although not statistically significant, suggest that rituximab in combination with CHOP may represent an effective treatment option for elderly patients with non-Hodgkin's lymphoma of the head and neck.

Diffuse large B-cell lymphoma is the most common type of non-Hodgkin's lymphoma (NHL), representing approximately 40% of new cases of lymphoma (1). Of the 34,000 diagnosed

cases of NHL in the USA each year, approximately 15% affect the head and neck (2-4). For more than 25 years, cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) have comprised the standard treatment for diffuse large B-cell lymphoma, curing approximately 30-40% of patients (5). In an attempt to improve its efficacy other cytotoxic agents have been added to the CHOP regimen (6, 7); however, the majority of these supplemental agents have not further improved clinical outcomes (6). Subsequently, there has been a shift towards the use of standard chemotherapy in combination with targeted monoclonal antibodies.

Rituximab is a genetically engineered chimeric monoclonal antibody that selectively depletes CD20+ B cells, but does not deplete CD20- cells, such as stem cells, dendritic cells or plasma cells. Rituximab exerts its effect by initiating complement-mediated B-cell lysis, subsequently stimulating cell-mediated cytotoxicity via macrophages and natural killer cells, and inducing apoptosis (8-10). Rituximab is effective as a single agent in the treatment of relapsed or refractory indolent lymphoma and has activity in relapsed or refractory diffuse large-B-cell lymphoma (11-14). In combination with CHOP chemotherapy, rituximab has a good safety profile and induces responses in over 90% of patients with indolent or aggressive lymphoma (15, 16). In elderly patients with diffuse large-B-cell lymphoma, addition of rituximab to the CHOP regimen increases the complete-response rate and prolongs event-free and overall survival, without a clinically significant increase in toxicity (17). In this article, we present a prospective single-centre study of 18 patients with head and neck NHL who were treated either with CHOP alone or a combination of CHOP plus rituximab is presented.

## Patients and Methods

A prospective study was conducted of 18 adult patients with localised NHL of the head and neck who were treated between January 1998 and January 2004. The study was approved by the appropriate institutional review board and written consent was

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Table I. Baseline characteristics of patients in the two treatment arms.

Characteristic	CHOP group (n=6)	CHOP + rituximab group (n=12)
Gender (M:F)	(2:4)	(8:4)
Age (years, mean±SD)	64.5±8.6	62.8±12.4
Tumour stage		
I	2 (33.3%)	2 (16.7%)
II	2 (33.3%)	5 (41.7%)
III	2 (33.3%)	4 (33.3%)
IV	0	1 (8.3%)
Surgical excision of 1° tumour	3 (50%)	5 (41.7%)
Radiotherapy	2 (33.3%)	3 (25%)
Follow-up time (months, median; range)	20.5; 12-75	15; 6-34

obtained from all human subjects. Twelve male (66%) and six female (33%) patients were included in the study with a mean age of  $63.3 \pm 10.9$  years. All patients were diagnosed with B-cell lymphoma and had an ECOG performance status of 1 and a tumour stage ranging from I to IV according to the Ann Arbor Classification (Table I). The locations of the tumour were as follows: lateral cervix (n=6), tonsils (n=3), rhinopharynx (n=3), base of tongue (n=2), mandible (n=2), submandible (n=1), parotid gland (n=1).

B symptoms (weight loss, fever, drenching night sweats) were present in three cases and bone marrow involvement was positive in one case. Patients were ineligible for the study if they had a T-cell lymphoma, a history of indolent lymphoma, central nervous system involvement, active cancer or a serious concomitant disease. All tumours were primary, with the exception of one secondary lymphoma that was ascribed to post-operative radiation administered for another primary malignancy.

After extensive preoperative work-up, the possibility of an *in situ* or metastatic residual tumour was ruled out. Eight patients (44%) underwent surgical excision of the primary tumour, including three local excisions, three tonsillectomies, one superficial parotidectomy and one splenectomy to improve staging in a patient with lateral cervical involvement. Radiotherapy was applied in five patients (28%).

Patients were assigned to receive either CHOP chemotherapy alone (n=6), or CHOP chemotherapy plus rituximab (n=12). Patients received 750 mg/m<sup>2</sup> cyclophosphamide, 50 mg/m<sup>2</sup> doxorubicin and 1.4 mg/m<sup>2</sup> vincristine (maximum dose of 2.0 mg) on day 1 of each chemotherapy cycle, and 40 mg/m<sup>2</sup> prednisone for 5 days. Eight chemotherapy cycles were administered at 3-weekly intervals. Patients treated with CHOP plus rituximab additionally received 375 mg/m<sup>2</sup> rituximab on day 1 of each cycle. Chemotherapy was interrupted in case of oedema, chills, fever, hypotension or any other complication. Chemotherapy was applied as adjuvant treatment following surgical excision of the primary tumour or administration of locoregional radiotherapy.

At the end of treatment, tumour response was defined as complete if there was no radiological or biological evidence of the prior lesions or no *de novo* lesions. Partial tumour response was defined as regression of all measurable lesions by more than 50%. The mean follow-up time from the end of chemotherapy ranged from 6 to 75 months (median: 18 months).

Table II. Tumour response rates in the two treatment arms. No significant differences were reported between the groups. (In CHOP + rituximab group, one patient discontinued chemotherapy).

Tumour response	CHOP group (n=6)	CHOP + rituximab group (n=11)
Complete	6	10
Partial	0	0
None	0	1

Table III. Patient survival and disease-free survival in the two treatment arms; at the end of therapy and after two years of follow-up.

Parameter	CHOP group	CHOP + rituximab group	P
At end of treatment			
n	6	11	
Overall survival (%)	83.3	90.9	0.75
n	5	11	
Disease-free survival (%)	60	90.9	0.26
After 24 months of follow-up			
n	4	5	
Overall survival (%)	75	80	0.94
Disease-free survival (%)	50	80	0.47

## Results

There were no significant differences between the two groups of patients with regards to clinical or clinicopathological characteristics at baseline (Table I). All treatment courses were completed, with the exception of one patient in the CHOP plus rituximab group, who presented with cardiac disturbances; this patient was excluded from the analysis.

Adverse events were observed in one patient (17%) in the CHOP alone group (infection) and in four patients (37%) in the CHOP plus rituximab group (two cases of infection and two of anaemia) ( $p=0.62$  for the difference between the groups). The adverse events delayed but did not cancel the scheduled chemotherapy regimens.

Complete tumour responses at the end of treatment were observed in 10 of the 11 patients (91%) treated with CHOP plus rituximab, compared with all the patients who received CHOP alone (Table II). The only patient in the CHOP plus rituximab group who did not show a complete response was classified as non-responsive. Despite showing a partial tumour response (more than 50% of all measurable lesions) during therapy, early relapse was observed in the respective patient before completion of the eighth cycle of chemotherapy.

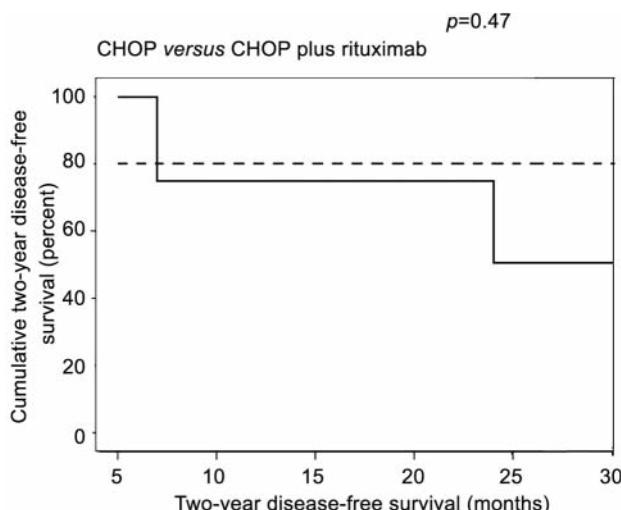


Figure 1. A Kaplan Meier curve demonstrating a decreased two-year disease-free survival rate in the CHOP plus rituximab group (continuous line) compared to the CHOP alone group.

The mean survival time after treatment was 23.5, months (median: 18 months, range: 6-75 months). In the univariate analysis the overall survival rate was 91% in the CHOP plus rituximab group and 83% in the CHOP alone group ( $p=0.75$ ) (Table III). Amongst those patients who were followed up for at least 2 years ( $n=9$ ), the two-year survival rate was 80% in the CHOP plus rituximab group and 75% in the CHOP alone group ( $p=0.94$ ) (Table III).

The mean disease-free survival rate was 20.52 months (median: 17 months, range: 5-54 months). The overall disease-free survival rate was 91% in the CHOP plus rituximab group and 60% in the CHOP alone group ( $p=0.24$ ) (Table III). Amongst those patients who were followed up for at least 24 months, 20% of patients in the CHOP plus rituximab group showed signs of recurrence in the first 2 years of follow-up, compared with 50% of patients in the CHOP alone group ( $p=0.47$ ) (Figure 1) (Table III).

## Discussion

Lymphomas of the head and neck comprise approximately 15% of the 34,000 diagnosed cases of NHL in the US (2-4). More than half of all primary extranodal lymphomas of the head and neck occur in the Waldeyer's ring (18,19), with the tonsils being the most frequent site (40-79% of all primary lesions), followed by the nasopharynx, the base of the tongue, the soft palate, and other less frequented sites (20-23). In the study presented here of elderly patients, the majority of the lesions were located in the lateral cervical area, with the rest situated in the oropharynx, nasopharynx, mandible and parotid gland.

In an earlier study of 399 NHL patients over 60 years old who had been previously untreated, Coiffier *et al.* compared the efficacy and safety of rituximab plus CHOP with CHOP alone (17). The combined therapy resulted in a higher rate of complete remission (76% vs. 63%,  $p=0.005$ ), and a statistically significant improvement in survival was observed. The survival rate was 70% in the CHOP plus rituximab group and 57% in the CHOP alone group at a median follow-up of two years (17).

In this study, even higher rates of response to therapy, disease-free survival and overall survival were observed following therapy with rituximab in combination with CHOP. With a median follow-up time of 18 months, the disease-free survival and overall survival rates in the CHOP plus rituximab group were 91% (compared with 60% and 83.3% in the CHOP alone group). Due to the small number of patients, these differences did not reach statistical significance.

Treatment failure was recorded in only one patient in the CHOP plus rituximab arm. In this patient, recurrence occurred very early on, *i.e.* before the end of the chemotherapy cycles, despite having shown a partial response to therapy prior to recurrence. In the CHOP alone group, recurrence occurred in two of the four patients followed for at least two years. Again, due to the small numbers of patients, this trend was not statistically significant.

Adverse events were reported in only four of the eleven patients treated with CHOP plus rituximab, two cases each of anaemia and infection. All adverse events were temporary and resolved spontaneously. These findings are consistent with the findings of Coiffier *et al.*, where the toxicity attributed to rituximab was minimal (17).

## Conclusion

The presented study reports similar disease-free and overall survival rates as those reported by Coiffier *et al.* (17), indicating that CHOP plus rituximab may be an effective and well-tolerated treatment in elderly patients with NHL of the head and neck.

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