

Rituximab in Combination with CHOP, an Effective and Well-tolerated Salvage Regimen for Diffuse Large B-Cell Lymphoma

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OBJECTIVE To evaluate the clinical effect of the R-CHOP regimen (rituximab in combination with cyclophosphamide, epirubicin, vincristine and prednisone) in treating refractory or relapsed diffuse large B-cell lymphoma (DLBCL), as a salvage therapy for DLBCL.

METHODS Eighteen patients with refractory or relapsed DLBCL who were treated with the R-CHOP regimen from 2001 to 2006 in hospitals in Jilin Province were analyzed retrospectively. The response rate, change of serum lactate dehydrogenase (LDH), time to progression (TTP) and toxicity were observed.

RESULTS The R-CHOP regimen can achieve a higher response rate, decrease serum LDH to a larger extent and obtain longer TTP than a conventional secondary regimen. The main adverse effects were similar to conventional chemotherapy.

CONCLUSION The R-CHOP regimen is one of the most effective secondary therapies for DLBCL.

KEYWORDS: large cell lymphoma, diffuse, rituximab, CHOP regimen.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL), one of the most commonly observed adult lymphatic malignancies, manifesting as a rapidly progressive, strongly aggressive and easily spread disease. A majority of the patients suffering from this disorder are in an advanced stage at diagnosis. As high as 60%~65% of the patients can not achieve complete remission (CR) or will relapse following remission induced by conventional first-line chemotherapy containing anthracycline. Furthermore, the total response rate of conventional second-line regimens, such as EPOCH and ICE, can reach only 25%~30%^[1]. Kewalramani et al.^[2] found that rituximab in combination with the ICE regimen could achieve a higher response rate compared to the common salvage therapies, with only slight adverse effects, thus providing a possible therapy for patients with refractory or relapsed DLBCL. The CHOP regimen, containing cyclophosphamide, doxorubicin or epirubicin, vincristine and prednisone, is a traditional first-line treatment for DLBCL, proven to be most effective and accompanied with less toxicity. It is unknown as to whether rituximab in association with the CHOP (R-CHOP regimen) can provide patients with refractory or relapsed DLBCL more benefit than the common salvage therapy.

MATERIALS AND METHODS

Patients

This study retrospectively analyzed 18 cases with refractory or relapsed DLBCL treated with the R-CHOP regimen from 2001 to 2006 in hospitals in Jilin Province. All the patients were histologically confirmed DLBCL, with positive CD20 immunohistochemistry. The Eastern Cooperative Oncology Group (ECOG) criteria were used to define the performance status. Each patient's International Prognostic Index (IPI) score was evaluated according to the corresponding standard (Table 1).

Table 1. General status of all the patients.

	Number	Percentage
Gender		
Male	12	66.7%
Female	6	33.3%
Age		
>60 years	8	44.4%
≤60 years	10	55.6%
Status		
Relapsed	10	55.6%
Refractory	8	44.4%
Stage		
Stage II	5	27.8%
Stage III	4	22.2%
Stage IV	9	50.0%
B symptoms		
Yes	7	38.9%
No	11	61.1%
LDH		
LDH>normal	10	55.6%
LDH≤normal	8	44.4%
IPI score		
0~2	11	61.1%
3~5	7	38.9%
Diameter of solitary lesion		
>5.0cm	4	22.2%
≤5.0cm	14	77.8%

Treatment

Patients received rituximab 375 mg/m², intravenously (i.v.) on day 1, epirubicin 50 mg/m² i.v. on day 2, cyclophosphamide 600 mg/m² i.v. on day 2, vincristine 1.4 mg/m² i.v. on day 2, and prednisone 1.0 mg/m²-kg orally on days 2~6. The R-CHOP regimen was given for two to eight cycles every 21 days.

Criteria for response and toxicity evaluation

Computer tomography scans were performed after two cycles and repeated subsequently. The response was evaluated by measurements of lesions according to WHO criteria. Serum lactate dehydrogenase (LDH) was measured prior to and after each cycle. We followed the patients to determine the 1-year survival rate and time to progression (TTP). Toxicity was evaluated according to the WHO criteria.

Statistical analysis

LDH changes after utilization of R-CHOP and conventional regimen were compared with the paired *t* test. The survival data and TTP were analyzed by the Kaplan-Meier method. The therapeutic effect was correlated with the IPI score, diameter of solitary lesions and B symptoms, using the Fisher exact possibility test.

RESULTS

Response rate

A total of 82 chemotherapy cycles of R-CHOP were administered to the 18 patients (median four, range two to eight). Nine patients (50.0%) achieved complete remission and six patients partial remission (33.3%), thereby reaching a total response rate of 83.3%. The response rate was more favorable for patients with a low or low-intermediate IPI (IPI≤2) compared to those in the intermediate-high or high IPI group (*P*=0.043). Diameter of solitary lesions and B symptoms did not significantly affect the response rate (*P*=0.108, 0.326, respectively).

Average serum LDH decreased by 76.8 U/L after conventional chemotherapy, while with R-CHOP the average decrease was 106.5 U/L, resulting in a significant difference (*P*<0.01, Table 2).

Table 2. Effect of R-CHOP on patients with different characteristics.

Characteristic	CR rate	PR rate	Response rate
IPI≤2	72.7% (8/11)	27.3% (3/11)	100% (11/11)
IPI>2	14.3% (1/7)	42.8% (3/7)	57.1% (4/7)
Diameter≤5cm	64.3% (9/14)	28.6% (4/14)	92.9% (13/14)
Diameter>5cm	0/4	50.0% (2/4)	50.0% (2/4)
With B symptoms	28.6% (2/7)	42.9% (3/7)	71.4% (5/7)
Without B symptoms	63.6% (7/11)	27.3% (3/11)	90.9% (10/11)

Survival data

The median follow-up time was 22 months, with a follow-up rate of 94.4%. The 1-year survival rate was 72.2% and the median TTP was 16 months. The IPI score, diameter of the solitary lesions and B symptoms did not affect the 1-year survival rate, ($P=0.2812, 0.2875$ and 0.9556 respectively) nor the TTP ($P=0.0658, 0.1617$ and 0.7918 , respectively).

Prior to administration of R-CHOP, the diseases of ten patients underwent a relapse after remission induced by conventional chemotherapy, such as CHOP and CHOP-E. The median TTP achieved by conventional therapy was 6 months, while that by R-CHOP was 18.5 months, resulting in a significant difference ($P=0.04466$, Fig.1.).

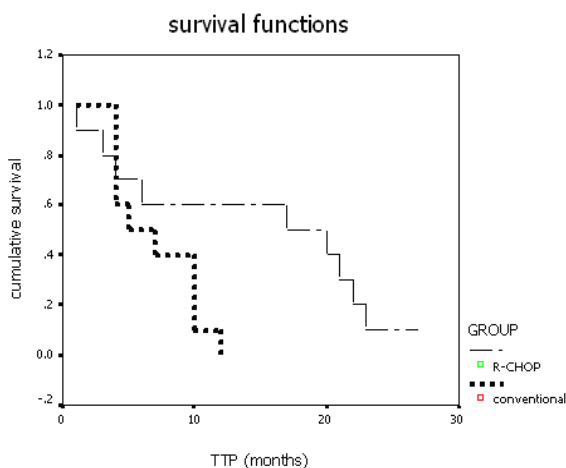


Fig 1. Time to progression of relapsed patients after conventional first-line therapy and the R-CHOP regimen.

Toxicity

Before administering rituximab, glucocorticoid or antihistamine therapy was utilized to prevent fever, palpitation or bronchospasm. Allergic reactions, such as dyspnea, only occurred in one 65-year-old man, who previously had been diagnosed with hypertension and coronary heart disease.

Grade III and IV leucopenia was observed in four patients, and grade III and IV thrombocytopenia in one patient. Bacterial infection developed in two patients. The degree of common toxicities caused by R-CHOP failed to differ from the conventional regimen.

One 56-year-old man with previous viral hepatitis B cirrhosis died of cirrhotic complications due to liver malfunction. But his blood lymphocyte count was not lower than the normal range.

Since every patient had undergone bone marrow aspiration, no evidence of the myelodysplastic syndrome or other secondary malignancy, which have been reported by some other studies, was found (Table 3).

DISCUSSION

DLBCL is the most common adult aggressive lymphoma. The CD20 antigen is expressed on the surface of all the tumor cells and rarely diffuses into the blood circulation. Besides, antigenic modulation does not occur after CD20 binds with its corresponding antibody. The above-mentioned features make CD20 an ideal therapeutic target. Rituximab, the chimeric human-murine monoclonal antibody to CD20, can treat DLBCL through the following mechanisms: 1) complement dependent cytotoxicity (CDC)^[3]; 2) antibody dependent cellular cytotoxicity (ADCC)^[4]; 3) B-cell apoptosis induction^[5]; and 4) drug-resistance inhibition^[6]. Presently, rituximab is mainly utilized as a first-line regimen for aggressive lymphoma, as well as a first-line and salvage treatment for indolent lymphoma^[7].

It was demonstrated in this study of refractory and relapsed DLBCL, that rituximab in combination with the CHOP regimen could achieve a higher response rate than with conventional salvage treatment, 83.3% vs. 25%~30%^[1]. In addition, R-CHOP therapy had resulted in a similar CR rate with rituximab combined with an ICE regimen as salvage treatment reported by

Table 3. Toxicity caused by the R-CHOP regimen.

	Grade I	Grade II	Grade III	Grade IV	Total	Conventional total incidence
Leucopenia	38.9%	27.8%	22.2%	0	88.9%	94.4%
Thrombocytopenia	16.7%	0	5.6%	0	22.2%	22.2%
Nausea and vomiting	27.8%	5.6%	5.6%	0	38.9%	33.3%
Increase of ALT or AST	5.6%	5.6%	5.6%	0	16.7%	11.1%
Increase of BUN	5.6%	0	0	0	5.6%	5.6%
Impairment of heart function	0	0	5.6%	0	5.6%	5.6%

ALT indicating alanine aminotransferase AST indicating aspartate aminotransferase BUN indicating blood urea nitrogen

Kewalramani et al.^[2], 50.0% vs. 53%. Consequently, it is confirmed that rituximab in association with either the ICE or CHOP regimen can achieve excellent short-term efficacy.

Stratification analysis showed that patients with lower IPI score responded better than the higher IPI group. Perhaps this is due to the latter's poor general condition and advanced stage. Patients with a larger solitary lesion responded not as well as those with a smaller tumor, but the difference was not significant. Coiffier et al.^[8] found that rituximab alone, as secondary treatment for aggressive non-Hodgkin lymphoma, could achieve a response rate as high as 46% if the solitary lesion was less than 5 cm, but the rate declined to 21% when lesion diameter was between 5 cm and 10 cm. As long as the lesion grew more than 10 cm, no significant response could be observed. Therefore our hypothesis is that under the same circumstances, the monoclonal antibody and cytotoxic drug concentration in the tumor may decrease dramatically as the tumor load increases, leading to a decline in the response rate. Serum LDH is positively related to the tumor load and is also one important prognostic indicator for DLBCL. It was found that R-CHOP could decrease the LDH level to a greater extent than conventional therapy, indicating notable reduction of the tumor load.

R-CHOP can achieve the median TTP of 16 months, significantly better than 7 months, the median overall survival achieved by the common salvage regimen^[1]. Jermann et al.^[1] utilized a combination of rituximab and EPOCH for refractory or relapsed DLBCL, accomplishing a median EFS of 11.8 months, similar to our results. TTP was not influenced by the IPI or the tumor load according to our research. We propose R-CHOP may overcome some negative predictors, resulting in similar long-term effect.

The side effects of rituximab usually noted are fever, chills and bronchospasm in mild or moderate degree. Allergic reactions, such as hypotension, vascular edema and eruption can occur in certain patients, maybe due to release of large amount of cytokines and congregation of tumor cells in the circulation^[9]. Only one patient with previously diagnosed coronary heart disease had dyspnea in the study. We suggest utilization of anti-allergy drugs, like glucocorticoids, should be administered routinely. Besides, previous heart disease must be considered and cautiously evaluated. Following R-CHOP, one patient with viral hepatitis B cirrhosis deteriorated, which may result from transient immunodepression and hepatitis B viral proliferation. Based on similar reports, a warning

has been added on the drug instructions that rituximab may cause fulminant hepatitis, hepatic failure or even death for hepatitis virus B carriers. Among the main adverse effects of rituximab combined with the CHOP regimen which occurred were leucopenia, digestive symptoms and thrombocytopenia, with a percentage similar to conventional chemotherapy.

Our study demonstrated that a combination of rituximab and CHOP chemotherapy was well tolerated and effective for patients with refractory or relapsed DLBCL. To provide more convincing evidence, a randomized controlled trial with a large sample size is required. Furthermore, one recent study proved that R-CHOP in a shorter interval, 14 days, gave more long-term benefits as first-line therapy^[10]. It is predictable that enhancing the dose intensity of R-CHOP will also be a future focus in treatment of refractory or relapsed DLBCL.

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