A meta-analysis on Rituximab combined CHOP chemotherapy for non-Hodgkin lymphoma in China

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ABSTRACT

الأهداف: تقييم تأثير العلاج الكيميائي الجامع ما بين عقار ريتوكسيماب وبروتوكول شوب والذي يستهدف علاج مرضى الأورام الليمفاوية الاهودجكن في الصين.

الطريقة: أُجريت دراسة التحليل الجمعي هذه في مستشفى شينغ جينغ التابع لجامعة الصين الطبية، شينغ جينغ، الصين وذلك خلال الفترة من يونيو إلى ديسمبر 2010م. لقد لجئنا إلى طريقة مكتبة كوكرين في المراجعة المنهجية للتجارب العشوائية المُقارنة التي سلطت الضوء على فعالية الجمع بين عقار ريتوكسيماب وبروتوكول شوب في علاج مرضى الأورام الليمفاوية الاهودجكن، والتي خُزنت في قواعد البيانات خلال الفترة من 2004م إلى 2009م.

النتائج: لقد قمنا باسترجاع المعطيات من 7 تجارب والتي وصل فيها عدد المرضى إلى 357 مريضاً. أشارت نتائج الدراسة إلى أن معدل الاختفاء الكامل للمرض بعد العلاج بعقار ريتوكسيماب وبروتوكول شوب معاً قد كان أعلى من العلاج الكيميائي باستخدام برتوكول شوب لوحده (odds ratio=3.02, 95% confidence interval: 1.94-4.72, p<0.00001).

خاتمة: أثبتت الدراسة فعالية الجمع بين عقار ريتوكسيماب وبروتوكول شوب في علاج المرضى المصابين بالأورام الليمفاوية الاهودجكن في الصين.

Objectives: To evaluate the curative effect of Rituximab combined CHOP chemotherapy in patients with non-Hodgkin lymphoma in China.

Methods: We conducted this study in the Affiliated Shengjing Hospital of China Medical University, Shenyang, China between June and December 2010. We used the systematic review method of The Cochrane Collaboration to collect randomized controlled trials (RCTs) of Rituximab combined CHOP chemotherapy for non-Hodgkin lymphoma by computer databases during the period 2004-2009.

Results: Seven trials involving 357 patients were retrieved. The complete remission rate of Rituximab combined CHOP chemotherapy was higher than that of CHOP chemotherapy alone (odds ratio=3.02, 95% confidence interval: 1.94-4.72, p<0.00001).

Conclusion: Non-Hodgkin lymphoma treated by Rituximab combined CHOP chemotherapy can produce a positive therapeutic effect in China.

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Non-Hodgkin's lymphoma (NHL) is a group of malignant tumors originating in the lymph nodes or other lymphoid tissues, most of which come from B lymphocytes, 90% of B-cell NHL cells are CD20 expression. Currently, standard treatment for aggressive NHL is CHOP (cyclophosphamide, vincristine, daunorubicin, prednisone), and the long-term remission rate is 40%.[1] Rituximab is a human-mouse chimeric monoclonal antibody that is specific for the CD20 antigen and kills tumor cells. In 1997, the U.S. Food and Drug Administration (FDA) approved the use of Rituximab as an anti-CD20 monoclonal antibody in the treatment of B-cell NHL.[2] In 2002, Coiffier et al[3] of Groupe d'Etude des Lymphomes de I'Adulte, (GELA), a famous adult Lymphoma Study Group of the European), reported a study on the treatment of elderly patients who had diffuse large B lymphoma with complete remission rate of 76%. On the 24th month, results showed an event-free survival (EFS) rate of 57% and overall survival of 70%. Reverse reactions had no significant increased. In this paper, we evaluate the treatment efficacy of B cell NHL with Rituximab

combined CHOP chemotherapy in China from 7 identified randomized controlled trials (RCTs).

Methods. We searched the China National Knowledge Infrastructure (1979-2010), the Chinese Biomedical Database (1979-2010), the Chinese Science and Technology Journal Full-text Database (1989-2010) using Rituximab, and non-Hodgkin's lymphoma as the key words. We conducted this study in the Affiliated Shengjing Hospital of China Medical University, Shenyang, China between June 2010 and December 2010. In this study, we only included the random or quasi-randomized controlled trials comparing Rituximab combined CHOP chemotherapy to CHOP chemotherapy alone in patients with B-cell non-Hodgkin's lymphoma in China during the period 2004-2009; patients had not received any radiation, immunotherapy, and biological therapy during that time. The control group were treated with CHOP chemotherapy alone, while the treatment group were interfered with Rituximab combined CHOP chemotherapy. The efficacy according to WHO standards are divided into complete remission (CR), partial remission (PR), stable disease (SD), and progress disease (PD). We selected the literature meeting standards according to randomized controlled trial quality evaluation criteria in Cochrane Handbook[4] for Systematic Reviews: (1) Which random allocation method was adopted, is this the correct; (2) Was the allocation adequately concealed? (3) In the blind method, who were carried; (4) Lost or Exit? (5) Was adopted the intent-to-treat (ITT) analysis.

We evaluated the complete remission rate at the end of treatment by meta-analysis methods using a statistical software package (RevMan, 4.2) (The Cochrane Collaboration; Oxford, UK). First, the test for heterogeneity with x^2 test, $p \geq 0.1$ as a homogeneous between studies, using fixed effect model to describe. Second, $p<0.1$ as a heterogeneity between studies, using random effect model to describe. A p-value less than <0.05 was considered statistically significant. The count data was measured by odds ratio and 95% confidence interval and if the odds ratio was >1 the effect of the rituximab combined CHOP chemotherapy on the B cell non-Hodgkin's lymphoma was better.

Results. During the search, we found 155 relevant documents by reading the title and summary, eliminating duplicates, non-clinical research and non-therapeutic literature, initial screening, and further reading. Out of 155, seven were identified randomized controlled trials.[5-11] On this 7 RCT, there were 357 cases of B-cell non-Hodgkin's lymphoma (178 were treated as treatment group and 179 as control group).

The characteristics of the 7 RCTs, including gender, age, intervention of the study, and therapeutic effect are shown in **Table 1**. Efficacy evaluation of Rituximab combined CHOP chemotherapy in the treatment group and CHOP chemotherapy alone in the control group with B-cell non-Hodgkin's lymphoma showed complete response rates (statistically significant). Heterogeneity test was $p=0.54$, odds ratio=3.02, 95% confidence interval: 1.94-4.72.

The complete response rate between the treatment group and the control group was statistically significant, $p<0.00001$ (**Figure 1**). Side effects were observed in all studies such as: infusion related reactions, neutropenia, thrombocytopenia, anemia, gastrointestinal reactions, liver damage, and so forth. Those associated with rituximab, infusion-related reaction was noted during the first intravenous infusion, such as fever, chills, rash, facial flushing, and others, and were mostly mild to moderate, and patient's tolerability. The administration of oxygen before the rituximab injection pulse, oral paracetamol, intravenous injection of hormones, and slowing down the speed of infusion, can greatly reduce the rituximab infusion-related adverse reactions. There were no treatment-related deaths. In addition to infusion-related reactions that mainly occurred in the rituximab group, the differences between the side effects in the 2 groups were not statistically significant.

Discussion. Because of the distant spread and extranodal infiltrative tendency of NHL, the treatment strategy should be based chemotherapy. The CHOP chemotherapy regimen has high efficacy, and low toxicity compared with others. This program is the standard treatment for aggressive NHL, but its long-term remission rate is not high. Rituximab is produced by recombinant DNA technology as a human-mouse chimeric anti-CD20 monoclonal antibody. Its high purity-variable region part (V area) is derived from mouses and the stable part (C area) is derived from human. In the human body, rituximab can specifically combine with CD20 of B lymphocytes, and kill B-cells by complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, inducing tumor cell apoptosis, chemosensitivity and other anti-tumor effects.[12] Rituximab combined CHOP chemotherapy (R-CHOP program), as first-line treatment of NHL, has been reported in the National Comprehensive Cancer Network guidelines for non-Hodgkin lymphoma's treatment.[13]

In this study, we summarized the research, and evaluated the efficacy of rituximab combined CHOP chemotherapy and CHOP chemotherapy alone. The meta-analysis concludes that the combination of rituximab and CHOP chemotherapy is superior to CHOP chemotherapy alone. There was no significant

Table 1 - The characteristics of 7 randomized controlled trials.

Reasearch	Sex (male/ female)	Median age (max-min)(year)	Intervention study			Therapeutic effect					
			Control group (C)	Treatment group (T)		Total	CR	PR	SD	PD	Exit
Xu Caigang	39/29	53(36-69)	C: 600mg/m^2,d1 H: 30mg/m^2,d1 O: 1.5mg/m^2,d1 P: 1mg/kg/d, d1-5.21d/course, 3-6 course	R: 375mg/m^2, 3 days before administration of CHOP, the rest with the former	T	32	18	10			
					C	36	5	18			
Wu Hongju	35/37	(20-79)	C: 750mg/m^2,d1 H: 50mg/m^2,d1 O: 1.4-2mg/m^2,d1 P: 100mg/d1-5.21d/course, 6 course	R: 375mg/m^2, 2 days before administration of CHOP, the rest with the former	T	34	23	7	0	2	2
					C	38	19	8	2	7	2
Wang Yanhua	29/19	T: 61(24-75) C:63(29-78)	C: 750mg/m^2,d1 H: 30-50mg/m^2,d1 O: 1.4mg/m^2,d1. P: 60mg/d, d1-5.21d/course, 6-8 course	R: 375mg/m^2, 2 days before administration of CHOP, the rest with the former	T	26	20	2	0	1	3
					C	22	13	1	1	2	5
Shuang Yuerong	33/12	45(25-79)	C: 750mg/m^2,d1 H: 60mg/m^2,d1 O: 1.4mg/m^2,d1 P: 100mg,d1-5.21d/course, 4-6 course	R: 375mg/m^2, 2 days before administration of CHOP, the rest with the former	T	22	15	3			
					C	23	8	10			
Xu Zhiqiao	14/8	(28-79)	C: 600mg/m^2,d1 ADM: 60mg/m^2,d1 O: 1.4mg/m^2,d1 P: 100mg/m^2,d1-5.21d/course, 6 course	R: 375mg/m^2, 2 days before administration of CHOP, the rest with the former	T	11	7	3	1		
					C	11	3	3	5		
Dai Zhaoxia	24/16	T: 49 C: 48	C: 750mg/m^2,d1 ADM: 50mg/m^2,d1 O: 1.4mg/m^2,d1 P: 100mg,d1-5.21d/course, 6 course	R: 375mg/m^2, 1 days before administration of CHOP, the rest with the former	T	19	10	7			
					C	21	9	6			
Huang Xiaobing	32/30	49(21-65)	C: 600mg/m^2,d1 ADM: 60mg/m^2,d1 O: 1.4mg/m^2,d1 P: 100mg/m^2,d1-5.21d/course, 6 course	R: 375mg/m^2, 2 days before administration of CHOP, the rest with the former	T	34	27	4	2	1	
					C	28	16	4	4	4	

C - cyclophosphamide, H - Adriamycin, O - vincristine, P - prednisone, R - Rituximab, ADM - doxorubicin.

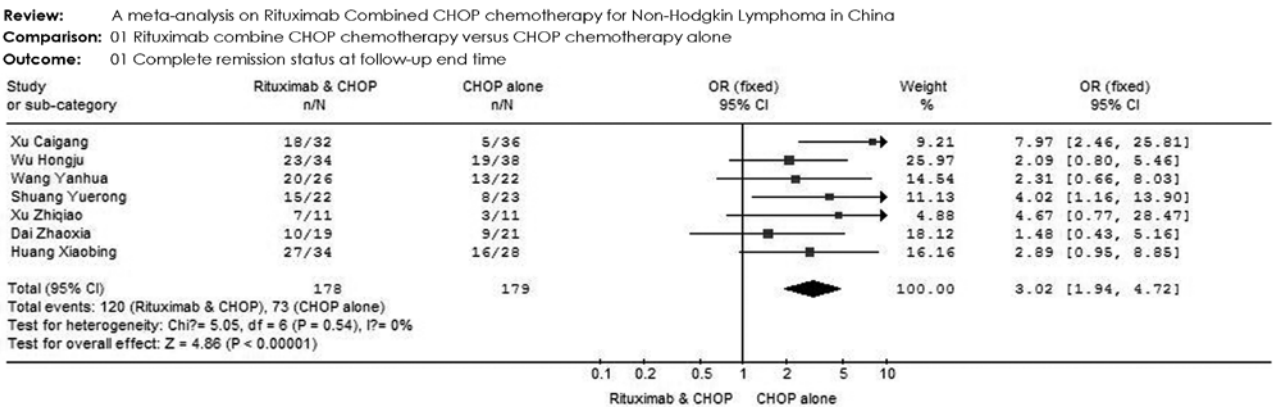

Figure 1 - Meta-analysis of treatment group and control group on the complete remission rate of B-cell non-Hodgkin's lymphoma.

difference in the incidence of adverse reactions. The treatment and control groups were comparable, and had followed up reports to ensure the reliability of this systematic review.

The limitation of this study was: all the literature did not report randomization, there was no blinding, no allocation concealment, and no cost-benefit analysis provided, so the overall quality of research was low. All studies were of C-level (worst). The included 7 RCTs in this study with NHL had no further detailed classification of the specific type, whether diffuse large B-cell or follicular type, thus, we cannot fully explain whether the therapy in a particular type is more effective. These limitations may affect the conclusions of this study, so it is necessary to continue a series of multi-center, prospective, randomized, double-blinded, longer-time follow-up in order to provide high quality evidence for systematic reviews.

In conclusion, rituximab combined with CHOP chemotherapy is more effective than CHOP chemotherapy alone, with no difference in the incidence of adverse reactions.

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Related topics

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