

# Clinical Study of Rituximab Combined With Chemotherapy in the Treatment of Lymphoma with Hypergammaglobulinemia

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## Wu *et al.*: Clinical Efficacy of Rituximab Combined with Chemotherapy in Hypergammaglobulinemia Patients

To further evaluate the clinical influencing factors of rituximab in the treatment of diffuse large B cell lymphoma patients with hypergammaglobulinemia by studying the clinical efficacy of rituximab combined with chemotherapy in patients with hypergammaglobulinemia. 89 patients with diffuse large B cell lymphoma treated in our hospital from January 2011 to December 2020 were selected as subjects. After informed consent, the patients in the control group were divided into two groups: the control group was treated with conventional chemotherapy and the treatment group was treated with rituximab on the basis of conventional chemotherapy. Basic information such as age, sex, past medical history, clinical tumor stage and so on was collected. The venous blood was collected before and after treatment and the levels of hemoglobin, erythrocyte sedimentation rate, albumin, globulin, Lactate dehydrogenase and beta 2-microglobulin were measured by automatic biochemical analyzer and the levels of Immunoglobulin G, Immunoglobulin A and Immunoglobulin M were measured by immunoturbidimetry. Complete remission, partial response, stable disease and disease progression, were recorded and the total effective rate was calculated. There were 27 patients in the control group (14 males and 13 females, 9 patients with hyperimmunoglobulinemia), according to Ann Arbor staging, there were 1 case in stage I, 10 cases in stage II, 7 cases in stage III and 9 cases in stage IV. There were 62 patients in the treatment group, aged  $56.3 \pm 14.2$  y, including 25 males and 37 females, 18 patients with hyperimmunoglobulinemia and according to Ann Arbor staging, there were 7 patients in stage I, 16 patients in stage II, 10 patients in stage III and 29 patients in stage IV. There was no significant difference in age, sex, incidence of hyperimmunoglobulinemia, International prognostic index score, tumor stage and previous history between the two groups. There was no significant difference in the levels of hemoglobin, erythrocyte sedimentation rate, albumin, lactate dehydrogenase and beta 2-microglobulin between the control group and the treatment group before and after treatment. The erythrocyte sedimentation rate after treatment in the treatment group and the control group was lower than that before treatment and the difference was statistically significant ( $p < 0.05$ ). There was no significant difference in the levels of Immunoglobulin G, Immunoglobulin A, Immunoglobulin M and globulin between the control group and the treatment group before treatment, but after treatment, the level of globulin in the treatment group was significantly lower than that in the control group ( $p < 0.05$ ). After treatment with rituximab combined with chemotherapy, the levels of Immunoglobulin G, Immunoglobulin A, Immunoglobulin M and globulin in the treatment group were significantly lower than those before treatment, while the levels of Immunoglobulin G, Immunoglobulin A and globulin in the control group were significantly lower than those before treatment, but there was no significant difference in the level of Immunoglobulin M before and after treatment. After rituximab combined with chemotherapy, the total effective rate of the treatment group was 82.3 %, which was much higher than that of the control group (55.6 %) and the difference was statistically significant ( $p < 0.05$ ). In the treatment group, the total effective rate of patients with hypergammaglobulinemia after rituximab combined chemotherapy was 85.4 %, which was much higher than that in the normal group (26.8 %) and the difference was statistically significant ( $p < 0.05$ ). Rituximab combined with chemotherapy is effective in the treatment of diffuse large B-cell lymphoma with hypergammaglobulinemia. It can effectively reduce the level of immunoglobulin in vivo and provide reference for clinical treatment.

**Key words:** Rituximab, hypergammaglobulinemia, lymphoma

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There are two types of hyperimmune globulinemia (HGG), namely Polyclonal hypergammaglobulinemia (PHG) and monoclonal. The increase in monoclonal antibodies is usually due to tumor transformation of a single clone of plasma cells. During infection and inflammation, elevated serum immunoglobulin levels and obvious antibody responses can be seen. It is generally believed that this is the effect of producing antibodies from active B cells, which have nothing to do with accompanying infections or diseases. Infections commonly associated with hyperimmunoglobulinemia include acquired immunodeficiency syndrome, endocarditis, syphilis, and parasitic infections. Chronic diseases associated with hyperimmunoglobulinemia include systemic lupus erythematosus, cystic fibrosis and rheumatoid arthritis. Infection related polyclonal HGG is usually not involved in the disease process itself, nor is it pathological. Polyclonal HGG is most commonly associated with liver disease, malignancy, autoimmune disease or infection<sup>[1]</sup>. There are only a few studies on hypoimmunoglobulinemia in lymphoproliferative diseases. In the study of lymphoproliferative diseases with hypergammaglobulinemia, most of them are reported as individual case<sup>[2-4]</sup> and the number of cases is limited, mainly including hemangioblastic lymphoma and chronic lymphocytic leukemia<sup>[5]</sup>. There is no related study on lymphoma complicated with hypergamma globulinemia. Diffuse large B cell lymphoma (DLBCL) is the most common subtype of lymphoma in adults worldwide, accounting for about 1/3<sup>rd</sup> of the non-Hodgkin lymphomas (NHL) diagnosed each year. In clinical practice, ABVD regimen (doxorubicin+bleomycin+vincristine+dacarbazine), CHOP regimen (cyclophosphamide + doxorubicin+vincristine+prednisone) and CVP regimen (cyclophosphamide+vincristine+prednisone) were used as the traditional first-line chemotherapy regimen<sup>[6]</sup>. In 2006, the US Food and Drug Administration (FDA) approved rituximab (Rituximab) in combination with conventional chemotherapy regimens for first-line treatment in patients with DLBCL, such as R-CHOP (Rituximab, Cyclophosphamide, doxorubicin, Vincristine, and Prednisone) regimens. Since then, R-CHOP has been included in the standard treatment regimen of DLBCL patients by The National Comprehensive Cancer Network® (NCCN®). However, it was clinically found that the efficacy of rituximab combined with traditional chemotherapy in DLBCL patients varied greatly, with the overall effective rate ranging from 72.0 % to

90.38 %<sup>[7,8]</sup>. In this paper, the clinical efficacy of rituximab combined with chemotherapy on DLBCL patients with hypergamma globulinemia will be studied to further evaluate the clinical influencing factors of rituximab in the treatment of DLBCL patients. A total of 89 patients with DLBCL admitted to our hospital from January 2011 to December 2020, with an age of  $57.0 \pm 13.6$  y, were selected as the research subjects, including 39 males and 50 females. Retrospective collection of patient information was made after approval by the medical ethics committee. All enrolled patients were required to sign informed consent before receiving treatment. Inclusion criteria-It met the diagnostic criteria of the Chinese Guidelines for Diagnosis and Treatment of DLBCL (2013)<sup>[9]</sup> and was diagnosed as DLBCL by immunohistochemistry and pathological tissue diagnosis. In clinical treatment, anthracycline chemotherapy drugs were used as the basis for treatment, without the use of unknown active ingredients such as traditional Chinese medicine or Chinese patent medicine. The normal values of Immunoglobulin G (IgG) *in vivo* ranged from 7.51 to 15.6g/L. IgG<7.51g/L was considered as hypogamma globulinemia and IgG>15.6 g/L was considered as hypergamma globulinemia. The clinical data are complete, with complete information such as medication, diagnosis, incidence and test results during treatment. Exclusion criteria-Have an acquired immune system disease or inherited immune deficiency disease, such as lupus erythematosus, Acquired immune deficiency syndrome (AIDS) or rheumatoid arthritis. Complicated with severe organ function injury, disorder or organic lesions. Patients with mental diseases and unable to cooperate with clinical treatment. Control group-Conventional chemotherapy regimen was used and anthracycline chemotherapy drugs were used. Adjust medication appropriately according to the actual situation of patients. Treatment group-Rituximab (Shanghai Roche Pharmaceuticals Co., Ltd., National Drug Approval J20170034, 100 mg/10 mL) was added on the basis of conventional chemotherapy regimen, and medication was appropriately adjusted according to the actual situation of patients. General information collection-Basic information such as age, gender, past medical history and clinical tumor stage were collected; Biochemical indicators-Venous blood was collected before and after treatment, and the levels of hemoglobin, erythrocyte sedimentation rate, albumin, globulin, LDH and  $\beta_2$  microglobulin were determined by automatic biochemical analyzer; Determination of immunoglobulin levels-Venous blood was collected

before and after treatment and IgG, IgA and IgM levels were measured by immunoturbidimetry; Clinical efficacy indicators-The criteria for judging clinical efficacy are based on the 2007 NHL International Working Group standard<sup>[10]</sup>. Complete remission (CR)-clinical symptoms were eliminated or basically eliminated, abnormal signs and laboratory examination index returned to normal; Partial response (PR)-most of clinical symptoms, more than two kinds of abnormal laboratory indexes improve; Stable disease (Stable disease)-clinical symptoms and abnormal signs and laboratory examination index does not increase, and the improvement is not obvious; Disease progression (PD)-clinical symptoms and abnormal signs and laboratory examination indexes increase gradually. The calculation formula of total efficiency is: total efficiency=(CR+PR)/total number of people×100 %. Before statistical analysis of quantitative data, Kolmogorov-Smirnov was used for normality test. Sig. >0.05 followed normal distribution, otherwise it was non-normal distribution. Quantitative data conforming to normal distribution were expressed as mean±standard deviation ( $\bar{x}\pm s$ ) and differences were analyzed by t test. The non-normal distribution quantitative data were represented by the median ( $P_{25}$ ,  $P_{75}$ ) and the difference was analyzed by rank sum test. Qualitative data was expressed as percentage (%) and difference analysis was conducted by chi-square test.  $p<0.05$  was considered statistically significant. All the above data were analyzed by Statistical package for the social sciences (SPSS) 22 software. The general clinical data are shown in the table below: in the control group, there were 27 patients (age  $58.4\pm 12.2$  y old), including 14 males and 13 females, and 9 patients with hyperc immunoglobulinemia. According to Ann Arbor staging, there were 1 patient with stage I, 10 patients with stage II, 7 patients with stage III, and 9 patients with stage IV. In the treatment group, there were 62 patients (age  $56.3\pm 14.2$  y old), including 25 males and 37 females, and 18 patients with hypergamma immunoglobulinemia. According to the Ann Arbor staging, 7 cases were stage I, 16 cases were stage II, 10 cases were stage III and 29 cases were stage IV. There were no significant differences in age, gender, incidence of hypergamma C immunoglobulinemia, International Prognostic Index (IPI) score, tumor stage and previous medical history between these two groups, as shown in Table 1. The changes of biochemical indexes before and after treatment were analyzed based on Mann-Whitney U test, there was no statistical difference in the levels of hemoglobin, erythrocytic sedimentation rate, albumin,

LDH and  $\beta 2$  microglobulin between the control group and the treatment group before and after treatment ( $p>0.05$ ). The rate of erythrocyte sedimentation rate in the treatment group and the control group after treatment with rituximab combined with chemotherapy was lower than that before treatment, with statistical difference ( $p<0.05$ ), as shown in Table 2. The changes of immunoglobulin levels before and after treatment were analyzed, there was no statistical difference in IgG, IgA, IgM and globulin levels between the control group and the treatment group before treatment ( $p>0.05$ ). After treatment, the level of globulin in the treatment group was significantly lower than that in the control group, with statistical difference ( $p<0.05$ ). Within groups, the levels of IgG, IgA, IgM and globulin in the treatment group after treatment with rituximab combined with chemotherapy were lower than before treatment, with statistical differences ( $p<0.05$ ). The levels of IgG, IgA and globulin in the control group were significantly lower after treatment than before ( $p<0.05$ ) and there was no significant difference in IgM levels before and after treatment ( $p>0.05$ ); Table 3. After traditional chemotherapy plus rituximab, the total effective rate of the treatment group was 82.3 %, which was much higher than that of the control group using traditional chemotherapy (55.6 %) and the difference was statistically significant ( $p<0.05$ ), as shown in Table 4. In the treatment group, the total effective rate of patients with hypergamma globulinemia after rituximab combining with chemotherapy was 85.4 %, which was much higher than the normal group with normal gamma globulin level (26.8 %) and the difference was statistically significant ( $p<0.05$ ), as shown in Table 5. DLBCL is a common malignant lymphoma. Its etiology is closely related to viral infection, bacterial infection, immune system deficiency, bad living habit and its pathological mechanism is complex. Traditional chemotherapy has not a satisfying therapeutic effect on most patients. A large number of domestic and foreign studies have reported that clonal antibody (rituximab) combined with anthracycline chemotherapy has achieved a good therapeutic effect with low adverse reactions, greatly improving the prognosis of patients<sup>[11-13]</sup>. DLBCL expressed a variety of B cell antigens, such as cases positive (CD) CD19, CD22, CD45, CD20, etc., and CD20 was expressed in more than 90 % of them. Rituximab could specifically bind to CD20 to reduce cancer cell proliferation and accelerate apoptosis. Compared with conventional chemotherapy, this study found that the total effective rate was 74.2 % and the complete remission rate was 58.1 % in patients

**TABLE 1: COMPARISON OF GENERAL CLINICAL DATA (n=89)**

Index	Control group	Treatment group	t/ $\chi^2$	P
Case (n, %)	27 (30.3 %)	62 (69.7 %)	-	-
Age ( $\bar{x} \pm s$ )	58.4 $\pm$ 12.2	56.3 $\pm$ 14.2	0.646	0.520
Gender (n, %)				
Male	14 (51.9 %)	25 (40.3 %)	1.016	0.314
Female	13 (48.1 %)	37 (59.7 %)		
Gamma immunoglobulinemia (n, %)				
High	13 (14.6 %)	41 (46.1 %)	8.138	0.017
Normal	11 (12.4 %)	21 (23.6 %)		
Low	3 (3.4 %)	0 (0.0 %)		
IPI score				
low risk 0-1	6 (22.2 %)	15 (24.2 %)	3.755	0.440
middle risk 2-3	17 (63.0 %)	36 (58.1 %)		
high risk 4-5	4 (14.8 %)	11 (17.7 %)		
Tumor stage (n, %)				
I a	(0.0 %)	7 (11.3 %)	17.438	0.258
I b	1 (3.7 %)	(0.0 %)		
II a	7 (25.9 %)	13 (21.0%)		
II b	3 (11.1 %)	3 (4.8 %)		
III a	1 (3.7 %)	8 (12.9 %)		
III b	5 (18.5 %)	2 (3.2 %)		
III c	1 (3.7 %)	(0.0 %)		
IV a	6 (22.2 %)	15 (24.2 %)		
IV b	3 (11.1 %)	14 (22.6 %)		
Previous medical history (n, %)				
Hepatitis C	(0.0 %)	3 (4.8 %)	31.140	0.119
Hypertension	4 (14.8 %)	8 (12.9 %)		
Diabetes	2 (7.4 %)	3 (4.8 %)		
Coronary heart disease (CHD)	2 (7.4 %)	2 (3.2 %)		
Thyroid neoplasm	1 (3.7 %)	1 (1.6 %)		
Cerebral infarction	(0.0 %)	1 (1.6 %)		
Myocardial infarction (ami)	1 (3.7 %)	1 (1.6 %)		
Hepatitis B	2 (7.4 %)	4 (6.5 %)		
Sjogren's syndrome	(0.0 %)	1 (1.6 %)		
Chronic kidney disease	(0.0 %)	1 (1.6 %)		
Epilepsy	1 (3.7 %)	(0.0 %)		
Tuberculosis (TB)	1 (3.7 %)	(0.0 %)		
Crohn's disease	1 (3.7 %)	(0.0 %)		
Rheumatoid	1 (3.7 %)	(0.0 %)		
Evans syndrome	1 (3.7 %)	(0.0 %)		
Pneumonia	1 (3.7 %)	1 (1.6 %)		

**TABLE 2: CHANGES OF IMMUNOGLOBULIN LEVELS BEFORE AND AFTER TREATMENT**

Group		Hemoglobin (g/L)	ESR (mm/h)	Albumin (g/L)	LDH (U/L)	$\beta_2$ microglobulin (mg/L)
Control group	Before treatment	124.5 (104.3, 150)	43 (16, 121)	38 (32.8, 44.1)	207 (132, 461)	2.99 (1.78, 4.18)
	After treatment	121.9 (87.1, 155)	21 (11, 78) <sup>#</sup>	42.3(32.8, 48.2)	208 (128, 562)	2.63 (1.64, 4.46)
Treatment group	Before treatment	121.3 (99, 140)	44.5 (22, 83)	41.25 (36.1, 44.4)	220 (160, 392)	2.51 (1.85, 4.3)
	After treatment	116 (101, 143)	20 (13, 36) <sup>#</sup>	42.9 (35.7, 47.1)	211 (164, 326)	2.435 (1.7, 4.03)

Note: Compared with before treatment, \*p<0.05; compared with control group, <sup>#</sup>p<0.05.

treated with rituximab. Rituximab can bind with immune cells or complement component 1q (C1q), which is conducive to the recognition and killing of cancer cells by immune cells. However, C1q can bind to the CH2 site of IgG molecule to form immune complex, and when C1q binds to IgG or IgM, classical

**TABLE 3: CHANGES OF IMMUNOGLOBULIN LEVELS BEFORE AND AFTER TREATMENT**

Group		Hemoglobin (g/L)	IgA (g/L)	IgM (g/L)	Globulin (g/L)
Control group	Before treatment	15.20 (12.10, 28.70)	3.61 (1.72, 6.36)	1.52 (0.5, 4.38)	32.3 (29.2, 53.3)
	After treatment	12.50 (9.70, 14.80)*	2.78 (1.89, 3.89)*	1.56 (0.76, 5.63)	29.7 (24.3, 37.8)*
Treatment group	Before treatment	18.35 (13.20, 22.40)	4.02 (2.06, 5.75)	1.535 (0.75, 4.87)	33.4 (29.3, 41.7)
	After treatment	11.10 (8.00, 14.30)*	2.41 (1.59, 3.22)*	1.07 (0.55, 2.09)*	26.2 (22.4, 30)*#

Note: Compared with before treatment, \*p<0.05; compared with control group, #p<0.05.

**TABLE 4: CLINICAL EFFICACY ANALYSIS**

Group	Efficacy				Total effective rate
	CR	PR	Stable disease	Disease progression	
Control group	10 (37.0 %)	4 (14.8 %)	3 (11.2 %)	10 (37.0 %)	51.9 %
Treatment group	36 (58.1 %)	10 (16.1 %)	14 (22.6 %)	2 (3.2 %)	74.2 %#
$\chi^2$					4.274
p					0.039

Note: Compared with control group, \*p<0.05.

**TABLE 5: INFLUENCE OF HYPERGAMMA GLOBULINEMIA ON RITUXIMAB**

Group	Efficacy				Total effective rate
	CR	PR	Stable disease	Disease progression	
Hypergamma globulinemia	30 (73.2 %)	5 (12.2 %)	5 (12.2 %)	1 (2.4 %)	85.4 %#
Normal group	6 (14.6 %)	5 (12.2 %)	9 (22.0 %)	1 (2.4 %)	26.8 %
$\chi^2$					7.891
p					0.00497

Note: Compared with normal group, #means p<0.05.

complement activation pathway will be initiated<sup>[14]</sup>. Patients with hypergamma globulinemia have higher IgG levels and complement dependent cytotoxicity (CDC) of rituximab is enhanced by complement activation<sup>[15]</sup>. In this study, patients with hypergamma globulinemia treated with rituximab had a total effective rate of 85.4 %, better than patients with normal gamma globulinemia. Therefore, rituximab combining with chemotherapy has an obvious effect on diffuse large B-cell lymphoma complicated with hypergamma globulinemia, which can effectively reduce the level of immunoglobulin *in vivo*, providing a reference for clinical treatment.

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### Conflicts of interest:

The authors report no conflicts of interest.

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