

## Original Article

# Efficacy and safety of rituximab combined with chemotherapy in the treatment of diffuse large B-cell lymphoma: a meta-analysis

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Received August 8, 2015; Accepted October 5, 2015; Epub October 15, 2015; Published October 30, 2015

**Abstract:** The aim of this study is to systematically evaluate the safety and efficacy of rituximab plus CHOP (R-CHOP combined regimen) in patients with previously untreated diffuse large B cell lymphoma (DLBCL). Electronic database were searched for randomized-controlled studies only comparing R-CHOP to CHOP standard alone in patients with untreated DLBCL were included. The risk ratios (RRs) with their 95% corresponding intervals (95% CI) were employed to estimate the efficacy of overall response (OR), complete response (CR), risk of dying and relapse rate in followed-up period. Total ten case-control studies containing 2941 patients met the inclusion criteria. The addition of R to standard CHOP were showed to increase the proportion of CR (RR=1.23, 95% CI=1.13-1.35,  $P<0.00001$ ) and OR (RR=1.39, 95% CI=1.24-1.55,  $P<0.00001$ ) in a fixed-effect model, indicating that rituximab combined with CHOP regimen is efficacy than CHOP alone. It did not increase the overall risk of dying as a consequence of infection (RR=0.79, 95% CI=0.55-1.13,  $P=0.20$ ). Furthermore, the relapse rates is significantly lower in R-CHOP (RR=0.52, 95% CI=0.38-0.71,  $P<0.0001$ ). The adverse effects were also not significant ( $P>0.05$ ). In summary, R-CHOP regimen is superior to standard CHOP in terms of overall response and complete response. It does not increase the incidence of adverse effects. However, more studies concerning different age groups and special patients are needed to discuss the potential role of R in DLBCL.

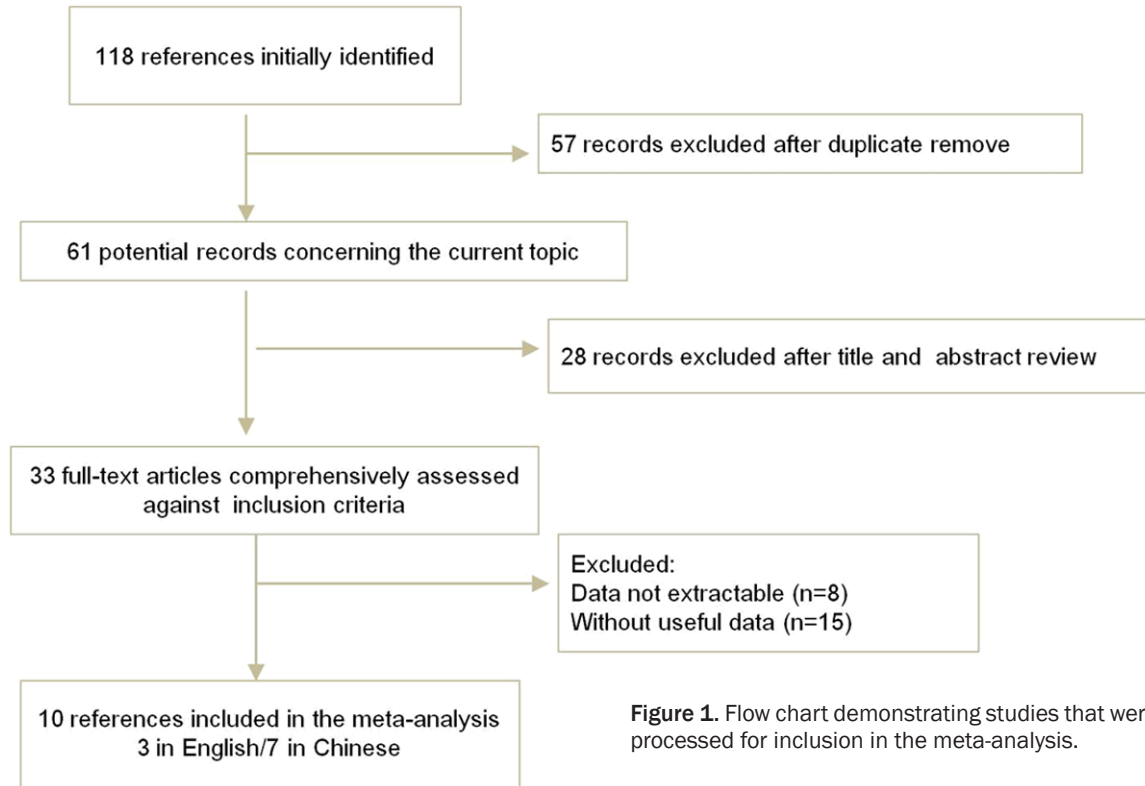
**Keywords:** Diffuse large B-cell lymphoma, rituximab, CHOP, meta-analysis

## Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent lymphoid malignancy, comprising 30%-40% of all new diagnoses of non-Hodgkin lymphoma (NHL) [1]. It is characterized by heterogeneity involving clinical presentation, morphology, and molecular pathogenesis [2]. DLBCL is consisted of molecularly distinct subtypes that differ in gene expression, oncogenic aberrations and clinical outcome [3]. The 4th edition of the WHO Classification of Tumors of Haematopoietic and lymphoid tissues creates that DLBCL includes the categories of "diffuse large cell" and "immunoblastic" lymphoma from the Working Formulation and "centroblastic" and "immunoblastic" lymphoma in the Kiel classification [4]. DLBCLs are aggressive but potentially curable malignancies. Management of elderly patients is challenging as critical comorbidities often account for increased number of treatment-related complications.

The combination of cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) has been the standard therapy for DLBCL since 1970s with the 5-year survival of 30-35% [5]. However, CHOP is associated with a high risk of developing febrile neutropenia, which is an important cause of treatment failure in DLBCL patients for the occurrence of treatment-related morbidities. Rituximab is a chimeric monoclonal antibody that targets the CD20 molecule on the surfaces of normal and malignant pre-B and mature B lymphocytes [6]. It depletes B lymphocytes through a variety of mechanisms. Rituximab alone has a reaction rate of 30-40% in relapsed DLBCL [7]. In 2002, the addition of the chimeric anti-CD20 monoclonal antibody rituximab to CHOP (R-CHOP) was shown to significantly improve the prognosis of patients with DLBCL. In patients with relapsed/resistant DLBCL, R-CHOP increased the 5-year overall survival of 58% compared with 45% for CHOP alone [8]. R-CHOP has modified the prognostic

## R-CHOP regimen versus CHOP alone in treatment of DLBCL



**Figure 1.** Flow chart demonstrating studies that were processed for inclusion in the meta-analysis.

factors and biological prognostic factors must be re-evaluated in the era of rituximab especially with young patients with poor prognosis.

The combination of rituximab and CHOP chemotherapy (every 14 or 21 days) has since become the standard treatment for DLBCL patients. However, over 30% of patients will not respond to currently available regimens or will relapse with resistant disease. The aim of this study is to systematic assess the efficacy and safety of rituximab combined with chemotherapy in the treatment of DLBCL.

### Materials and methods

#### *Identification and selection of relevant studies*

The electronic database of PubMed, Medline, Embase and CNKI (China National Knowledge Infrastructure) were employed for searching relevant articles published between January 2002 and March 2014 (Any new reports need to be updated?). The following terms: “diffuse large B-cell lymphoma or DLBCL”, “rituximab”, “combined”, “CHOP”, and “versus or compare” as well as their combinations were used. References of retrieved articles were searched with no language restrictions. Only full-text arti-

cles and the most recent studies were included in this meta-analysis.

#### *Criteria for inclusion*

The inclusion criteria were as follows: 1) the paper should be randomized-controlled studies; 2) all patients were diagnosed with untreated DLBCL; 3) the R-CHOP group and CHOP group were matched in age, sex, ECOG scores and serum LDH level; 4) evaluation of efficacy and disease recurrence according to the international curative effect evaluation standard [9]; and 5) the results were expressed in complete response (CR), overall response (OR), overall survival (OS) and adverse effect.

Exclusion criteria: 1) non-randomized studies; 2) without data about clinical outcome; 3) including non-lymphoma patients; 4) without identical CHOP in both arms or an R-free arm; and 5) studies about maintenance purging and sequential treatment.

#### *Data extraction*

Two investigators (only one author?!) independently assessed the quality of the included studies. Any disagreement was subsequently

## R-CHOP regimen versus CHOP alone in treatment of DLBCL

**Table 1.** Main characteristic of the included studies

First author	Year	Country	Age	Patients			Clinical stage	Duration of follow-up
				Total	Cases	Controls		
Feugier	2005	Belgium	60-75	399	202	197	I-IV	60
Wang YH	2006	China	24-78	48	26	22	I-IV	24
Aviles-a	2007	Mexico	65-85	204	101	103	IV	60
Aviles-b	2007	Mexico	25-65	196	98	98	III-IV	53.4
Jia XL	2011	China	23-76	36	18	18	II-IV	26 (12-48)
Yang SL	2011	China	18-78	49	23	26	I-IV	35 (4-66)
Jin H	2012	China	19-78	43	25	18	I-IV	12-36
Liu J	2012	China	19-82	116	52	64	I-IV	12-36
Xu SF	2013	China	14-74	73	39	34	I-IV	28 (6-59)
Zeng AP	2013	China	29-69	48	24	24	I-IV	36

**Table 2.** Outcomes of the retrieved articles during follow-up period

	R-CHOP				CHOP group			
	CR	OR	Death	Relapse	CR	OR	Death	Relapse
Feugier	106	121	17	40	72	83	5	67
Wang YH	20	22	3	8	13	14	5	13
Aviles-a	75		33	20	73		30	20
Aviles-b	79		20		77		19	
Jia XL	10	16	5		7	11	11	
Yang SL	19		7	3	17		14	6
Jin H	21	22	6	1	12	14	10	6
Liu J	18	39	28		10	34	30	
Xu SF	16	38	3	10	12	23	5	12
Zeng AP	20	22	4	9	13	16	12	15

CR, complete response; OR, overall response.

resolved by discussion with a third author. The following information was extracted from each article: first author, year of publication, country, ethnicity, sample size, clinical stage and duration of follow-up.

### Statistical analyses

The overall result was measured by risk ratios (RRs) and 95% confidence interval (CI) [10]. The significance of the pooled ORs was determined by the Z test with a *P* value less than 0.05. The Q-statistic test and the *I*<sup>2</sup> test were used to assess the heterogeneity among included studies. The fixed-effect model was employed when the *P*-value more than 0.10 for the Q-test and *I*<sup>2</sup> less than 50%, assuming homogenous among studies; Otherwise, the random-effect model was used. The evidence of publication bias was assessed by visual funnel plot inspect-

ion. Statistical analyses were conducted in Review Manager (version 5.2, The Cochrane Collaboration). All the tests were two-sided.

### Results

#### Characteristics of studies included

The electronic database search identified 118 references. After applying the inclusion criteria, 10 articles (3 in English and

7 in Chinese) including 2941 patients were ultimately included in the systematic review and meta-analysis. The study selection process is shown in **Figure 1**.

Of them, seven was from China, one from Belgium [8], and two from Mexico [11, 12]. The number of patients range from 36 to 399. The median age was more than 50 year old. The clinical stage is from I to IV, and the follow-up period is from 1 to 66 months. Characteristics of the studies included in this analysis were presented in **Table 1**. **Table 2** summarized the main outcomes of included articles.

#### Clinical outcomes

All the ten articles reported the outcome of CR. The rate of CR was higher with patients in R-CHOP group than that in CHOP group (63.2% versus 50.7%). As shown in **Figure 2**, the pooled RRs of risk for CR has a significantly difference between these two groups (RR=1.23, 95% CI=1.13-1.35, *P*<0.00001), which suggested that patients receiving R-CHOP had a better end of treatment outcome, than patients in CHOP arm.

Seven studies involved the OR (complete response and partial response). As shown in **Figure 3**, we found a significantly difference between these two groups (RR=1.39, 95% CI=1.24-1.55, *P*<0.00001), indicating that rituximab combined with CHOP regimen is efficacy than CHOP alone. No significantly hetero-

## R-CHOP regimen versus CHOP alone in treatment of DLBCL

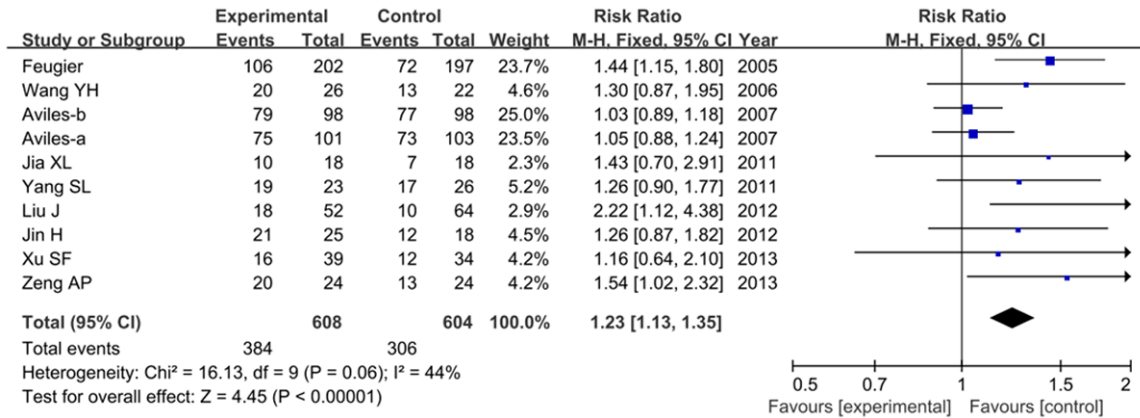


Figure 2. Clinical outcome of complete response with R-CHOP compared with CHOP alone.

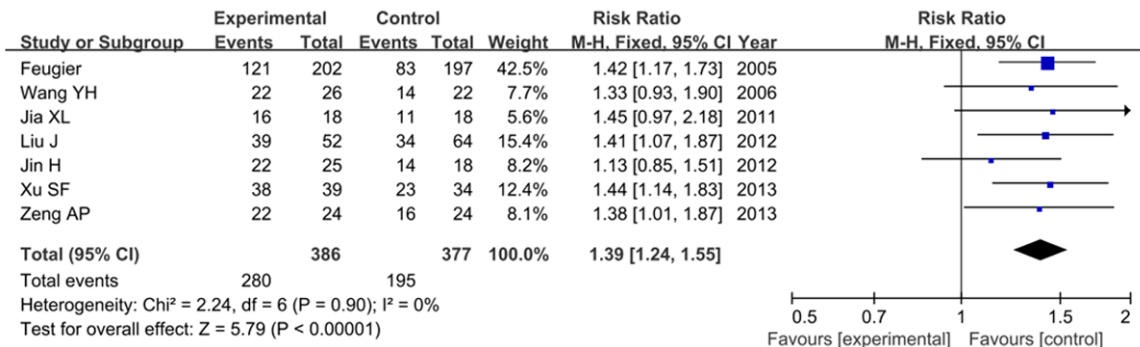


Figure 3. Forest plot for risk ratios of overall response with R-CHOP compared with CHOP alone.

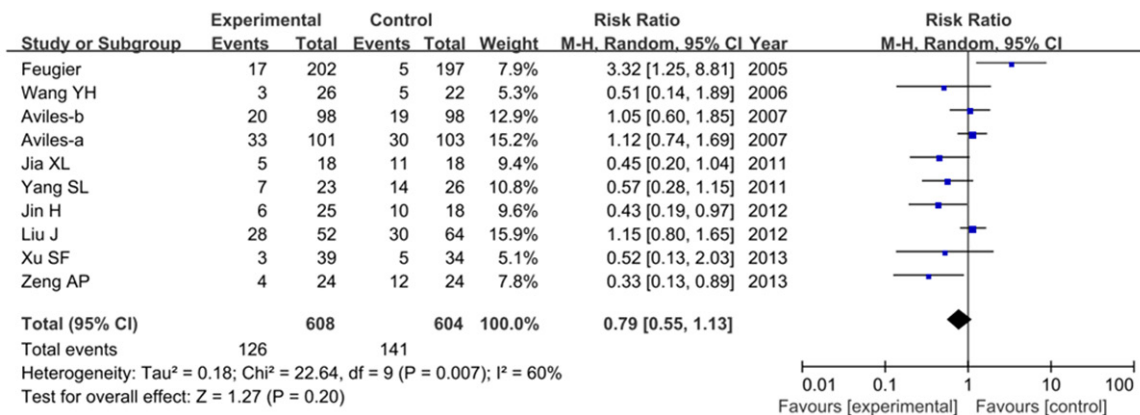


Figure 4. Risk ratios of mortality with R-CHOP compared with CHOP alone.

ogeneity was found between studies (I<sup>2</sup>=0, P=0.90).

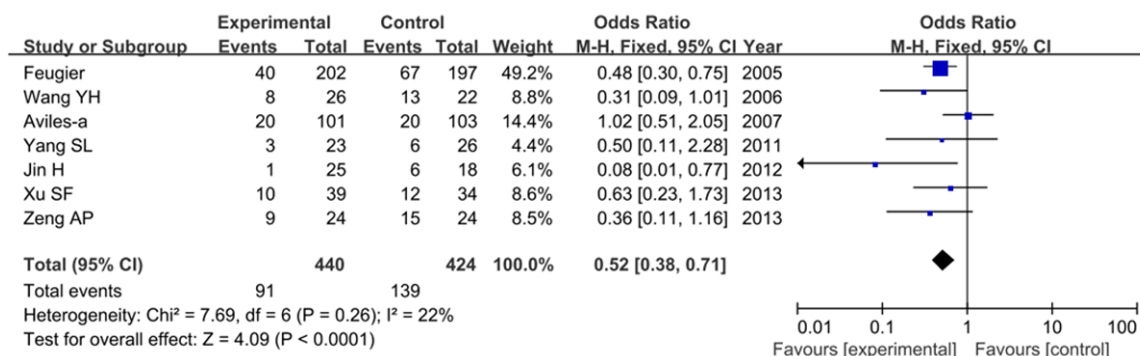
### Overall survival and relapse during follow-up period

All ten studies reported mortality during follow-up period. The mortality rate was lower in R-

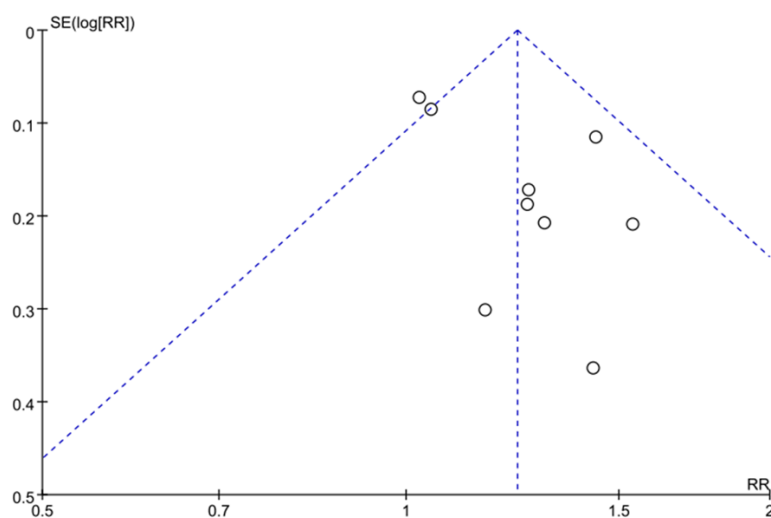
CHOP group. As shown in **Figure 4**, no significant difference was noted between these two groups (RR=0.79, 95% CI=0.55-1.13, P=0.20) in a random-effect model.

Seven articles considered the relapse cases. The frequency of relapse rate is lower with patients in R-CHOP group than that in CHOP

## R-CHOP regimen versus CHOP alone in treatment of DLBCL



**Figure 5.** Risk of relapse rate when comparing R-CHOP with CHOP alone.



**Figure 6.** Funnel plot analysis on the detection of publication bias in the meta-analysis.

group (20.7 vs. 32.8). **Figure 5** showed the forest plots with results of relapse rates ( $\text{RR} = 0.52$ ,  $95\% \text{ CI} = 0.38-0.71$ ,  $P < 0.0001$ ), indicating that patients with R-CHOP has a good prognosis than that with CHOP alone.

### Adverse effect

The adverse events were not consistent with the expected toxic effects of CHOP chemotherapy and occurred with similar frequency in both groups. So we can't perform statistical analysis. No differences were observed in relation to toxicity and other adverse effect when comparing these two groups.

### Publication bias

Begger's funnel plot was conducted to assess the publication bias of the literature. The shape

of funnel plots did not reveal any evidence of funnel plot asymmetry. As shown in **Figure 6**.

### Discussion

DLBCL, a heterogeneous group of lymphomas, is considered an aggressive lymphoma [13]. Although new developments in chemotherapy have improved the survival of patients with DLBCL, to date, there is still no absolute consensus of the efficacy and safety of rituximab in DLBCL. Our data demonstrate that R-CHOP is safe and highly effective for the management of DLBCL, with

less relapse rate and morality during follow-up period.

Rituximab is a chimeric monoclonal antibody against CD20 and is the first monoclonal antibody approved for the treatment of low-grade or follicular B-cell non-Hodgkin's lymphoma in relapse or refractory stage [14]. It can induce a high level of complete response when used as a first-line treatment in follicular lymphoma [15]. The addition of rituximab to chemotherapy has improved the overall survival of the patients to 50-80% [16]. Researchers have showed that rituximab can improve the efficacy of chemotherapy after relapse [17]. However, the rationale for including an independently active agent with non-overlapping toxicity is strong.

Rituximab added to six cycles of CHOP-like chemotherapy improved long-term outcomes of



## R-CHOP regimen versus CHOP alone in treatment of DLBCL

young patients with good-prognosis DLBCL [18]. Long-term outcome of patients in the LNH-98.5 trial conducted by Coiffier et al. found that the end points of survival were improved in patients treated with R-CHOP: the 10-year progression-free survival and overall survival was 36.5% and 43.5%, respectively, compared with 20% and 27.6% with CHOP alone [19]. Rituximab is partially antagonistic with inhibitors of the B-cell receptor pathway in DLBCL [20], which regulates signaling pathways and alters gene expression associated with cell death and survival in DLBCL, and may provide new targets in future treatment protocols [21].

Rituximab can also combine with other monoclonal antibodies or chemotherapies to improve the results. Fu et al. proved that bevacizumab combined with R-CHOP regimen is effective for untreated DLBCL [22]. Ruan et al. showed that bortezomib with R-CHOP-21 can be safely administered and may enhance outcomes, particularly in non-germinal center B cell DLBCL, justifying randomized studies [23]. Recher et al. identified that intensified immunochemotherapy with R-ACVBP significantly improves survival of patients aged 18-59 years with DLBCL with low-intermediate risk according to the International Prognostic Index when compared with standard R-CHOP [24]. Katterer et al. found that rituximab combined with three cycles of ACVBP plus consolidation is significantly superior to ACVBP plus consolidation alone in young patients with low-risk localized DLBCL [25]. Phan's study showed significant improvements in OS and PFS among patients who received consolidation RT after R-CHOP chemotherapy for DLBCL [26].

Several limitations are presented in this meta-analysis. First, real associations between R-CHOP and countable outcomes may be misinterpreted. Second, several risk factors such as the age group should be considered [27]. Third, the method of rituximab administration should be considered. Studies have shown that R-CHOP-21 remains the standard first-line treatment in patients with this haematological malignancy [28]; In elderly patients with untreated DLBCL, a 2-week dose-dense R-CHOP regimen did not improve efficacy compared with the 3-week standard schedule [29].

### Conclusions

In conclusion, our results indicate that R-CHOP is an effective regimen for management of

untreated DLBCL. However, the value of adding rituximab to standard CHOP remains to be determined in more well-designed, large-scale randomized trials.

### Disclosure of conflict of interest

None.

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## R-CHOP regimen versus CHOP alone in treatment of DLBCL

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