Int J Clin Exp Med 2019;12(9):11059-11067
www.ijcem.com /ISSN:1940-5901/IJCEM0094894

Review Article

High efficacy of rituximab plus chemotherapy in treating human immunodeficiency virus-negative adults with Burkitt's lymphoma: a meta-analysis

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Received April 4, 2019; Accepted August 5, 2019; Epub September 15, 2019; Published September 30, 2019

Abstract: Burkitt's lymphoma (BL) is a rare and aggressive type of B-cell lymphoma that constitutes only 1% to 2% of all adult lymphoma cases worldwide. BL is treated with short, intensive combination chemotherapy regimens. The aim of the present study was to analyse the effects and benefits of rituximab in adult BL patients without human immunodeficiency virus. Meta-analysis demonstrated that the addition of rituximab with the hyper-CVAD (composed of hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate, and cytarabine) and CODOX-M-IVAC (composed of cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate alternating with ifosfamide, etoposide, and high-dose cytarabine, along with intrathecal methotrexate and cytarabine) regimens have better outcomes. This pooled study of 455 patients showed a complete response (83.9% vs. 71.8%), while 807 patients demonstrated a higher survival rate (76.1% vs. 54.7%). In comparison with previous studies, our data revealed a complete response range of 66.6% to 94.4%, with an overall survival rate of 70% to 89%. However, some patients developed infection and neutropenia, which was believed to be associated with chemotherapy.

Keywords: Burkitt's lymphoma, rituximab, meta-analysis

Introduction

Burkitt's lymphoma (BL) is a highly aggressive B-cell non-Hodgkin's lymphoma (NHL) accounting for approximately 1% to 2% of all NHL cases in adults; an estimated more than 1,480 new cases of BL were diagnosed in the United States in 2016 [1]. Denis Burkitt, a missionary doctor in east Africa, first described BL in 1958 [2]. BL is associated with the Epstein-Barr virus (EBV), which uniformly involves translocation of the MYC gene. Three subtypes of BL exist: endemic, sporadic, and immunodeficiency-associated [3]. BL is treated with high-dose chemotherapy regimens that have been shown to be more effective in younger patients versus elderly ones [4]. In the past few years, researchers have discovered that B-cell lymphoid malignancy treatments targeting specific B-lineage markers including cluster of differentiation (CD)19, CD20, CD22, and CD52 has shown promising efficacies, despite the observation of some relapsed/refractory cases [5, 6]. Adult patients unafflicted by the human immuno-deficiency virus (HIV) have better outcomes versus BL patients with HIV. Especially, BL patients with HIV with lower CD4 counts have a greater chance of developing infection and major cause of death as compared with those with higher CD4 counts. Recent cancer studies have demonstrated the use of the newer anti-CD20 monoclonal antibody rituximab in combination with chemotherapy in BL yields encouraging results [3]. However, other investigations have suggested there is no benefit of adding rituximab to chemotherapy [7-9].

Considering that rituximab previously showed efficacy, safety, and tolerance in many B-cell-associated malignancies, some research-

ers believe that it could also be introduced into adult BL patients. Rituximab was combined safely in a series of 31 adult BL patients treated with a hyper-CVAD (composed of hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate, and cytarabine) regimen, with results including an excellent overall survival (OS) rate of 89% and no related deaths [4, 10]. Another notable highly effective regimen protocol called CODOX-M-IVAC (composed of cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate alternating with ifosfamide, etoposide, and high-dose cytarabine, along with intrathecal methotrexate and cytarabine) has been developed by Magrath and colleagues at the National Cancer Institute [11]. In one study [12, 13], this regimen was used to treat 72 patients with BL, including 39 adults and 33 children who were stratified into low- and high-risk groups. Low-risk patients with normal Lactate dehydrogenase (LDH) levels and no mass being larger than 10 cm received three consecutive cycles of treatment. The other (high-risk) patients received two alternating cycles of the CODOX-M and IVAC regimens. The two-year progression-free survival and OS rates were 80% and 84%, respectively, for all patients.

Materials and methods

Identification and selection of studies

The PubMed and Web of Science (WOS) electronic databases were reviewed for relevant articles published from January 1997 to October 2018. The following searching syntax "(rituximab[Title/Abstract]) AND (Burkitt[Title/Abstract]) AND (lymphoma[Title/Abstract])" was used for PubMed, while the syntax "TI = (rituximab AND Burkitt AND lymphoma)" was used for WOS. The inclusion criteria were: (1) the study was a prospective or retrospective clinic trial for BL patients; (2) patients in the study were diagnosed with untreated BL; (3) there was a comparison of with rituximab and without rituximab; (4) the study was published in English language; (5) there was an evaluation of efficacy and disease recurrence according to the international curative effect evaluation standard; and (6) the results were expressed in terms of complete response (CR) and OS. Conversely, the following were excluded: (1) nonrandomized studies; (2) studies without clinical outcomes data; (3) studies with data of BL patients with HIV infections but without subgroup analysis; (4) studies of children and adolescents (age younger than 16 years old); and (5) studies about maintenance purging and sequential treatment.

Data extraction

Two investigators conducted this research independently. The quality of the selected studies was carefully assessed. The supervisor subsequently resolved any disagreement after discussion with all authors as soon as possible. The following information was extracted from each included article: first author, year of publication, country, sample size, study type (retro-/pros-), clinical outcome(s), and duration of follow-up.

Statistical analysis

The overall result was measured by odds ratios (ORs) and 95% confidence intervals (CIs). The significance of the pooled ORs was determined by the Z test with a *P* value of less than 0.05. The Q-statistic test and the I^2 test were used to assess the heterogeneity among selected studies [14, 15]. A fixed-effects model was employed when the *P*-value was more than 0.10 for the Q-test and the I^2 statistic was less than 50% (Mantel-Haenszel method); otherwise, a random-effects model was used (DerSimonian and Laird method). Evidence of publication bias was assessed by visual funnel plot inspection and Egger's test for small-study effects ($P > 0.05$). Statistical analyses were conducted using the Stata software (version 14.0; StataCorp LLC, College Station, TX, USA). All tests were two-sided.

Results

Characteristic of the selected studies

The electronic database search identified 118 potentially relevant studies (**Figure 1**). After applying the inclusion criteria, nine articles including a total of 875 patients were ultimately included in the systematic review and meta-analysis. The study selection process is shown in **Figure 1**. The quality of selected studies was accessed by Newcastle-Ottawa Scale (**Table 2**). The country breakdown of the included studies was: three from the United States, one from

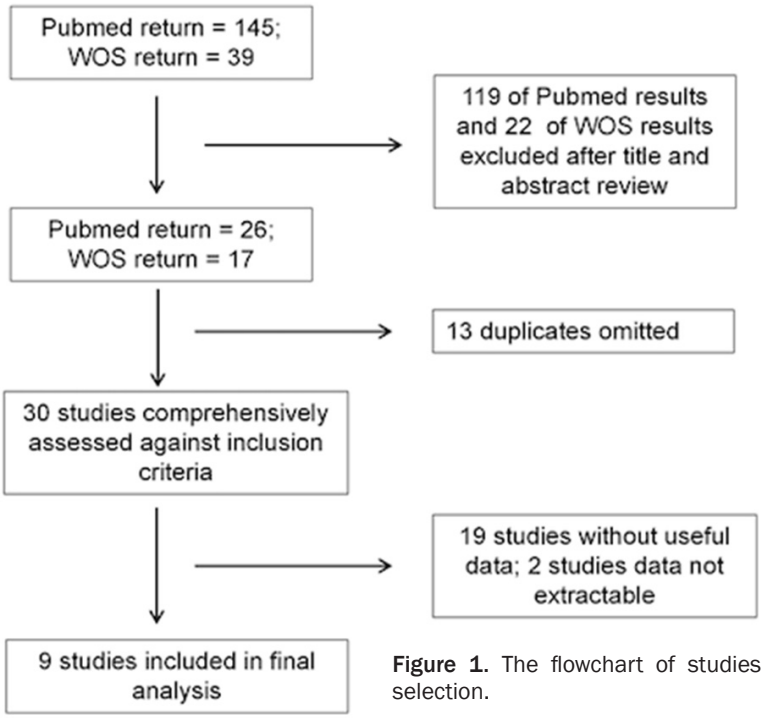

Figure 1. The flowchart of studies selection.

Japan, one from Italy, one from Croatia, one from Denmark, one from India, and one from France. Four studies were prospective and five studies were retrospective. The shortest follow-up duration was 15.6 months, while the longest was more than 10 years. The regimens used were Hyper-CVAD plus-/minus- (one study), CODOX-M/IVAC plus-/minus- (two studies), Lymphome malin B (LMB) (one study), and more than one regimen plus-/minus- (five studies). Characteristics of the studies included in this meta-analysis are presented in **Table 1A**, **1B**.

Clinical outcomes

Two studies (Wasterlid and Ribrag) without CR data were ruled out, while seven articles with 455 patients total reported on CR outcomes. The rate of CR was higher with patients in the R-plus group than that in R-free group (83.9% vs. 71.8%). As shown in **Figure 2**, the pooled OR for CR presented a significant difference between these two groups (OR: 2.061, 95% CI: 1.300-3.268; P = 0.002), suggesting that patients receiving R-plus treatment had a better end-of-treatment outcome than did patients with R-free regimens. No significantly heterogeneity was found between studies (I^2 = 35.8%; P = 0.155). Meanwhile, seven studies (excluding Patekar and Corazzelli) with 807 patients reported mortality during the follow-up period. The OS rate was much higher in the R-plus group than in the R-free group (76.1% vs. 54.7%). As shown in **Figure 3**, the pooled OR for OS was significantly different between the two groups (OR: 2.766, 95% CI: 2.023-3.781; P < 0.001). No significant heterogeneity was found between studies (I^2 = 16.7%; P = 0.302). The pooled survival rate was also calculated in this study. Three studies reported OS results and their 95% CIs were used to calculate the pooled survival rate of R-plus treatment. As presented in **Figure 4**, the estimate survival rate of patients with R-plus treatment was 81% (76.1%-85.8%). Separately, three studies reported on hazard ratio (HR) by comparing the R-plus and R-free groups to calculate the pooled HR. For these studies, the pooled HR was 0.457 (0.305-0.686) which means that patients receiving R-plus treatment may have a better prognosis.

Publication bias

Begger's funnel plots were conducted to assess the publication bias of the studies in each pooled analysis. The shape of the funnel plots did not reveal any evidence of funnel plot asymmetry, and the Begger's test for small-study effects showed *P* value of more than 0.05. Thus, as presented in **Figure 4**, there was not any significant publication bias found in this meta-analysis.

Discussion

BL is a rare and aggressive type of B-cell lymphoma found in only 1% to 2% of adult lymphoma cases around the world. BL can be divided into three variants: endemic, sporadic, and immunodeficiency-associated. Unlike the other two, sporadic BL is rarely associated with the Epstein-Barr virus and accounts for 30% to 50% of childhood lymphoma cases [16]. Of note, the outcome of paediatric BL has im-

Table 1A. The characteristic of the selected studies

First Author	Years	Country	Age (median, IQR)	Study Type	Regimen	Follow-up Duration	Patients Number		
							Total	with R	without R
Thomas	2006	USA	R (46, 17-77); without R (48, 16-79)	Pros	Hyper-CVAD	22 (9-65) mos/74 (11-154) mos	79	31	48
Maruyama	2010	JP	39 (19-59)	Retro	Multi-	74 (16-126) mos	15	9	6
Corazzelli	2011	Italy	52	Pros	CODOX-M/IVAC	4 yrs	50	30	20
Dujmovic	2011	Croatia	35 (16-63)	Retro	Multi-	43 mos	20	12	8
Wasterlid	2013	Denmark	56 (15-93)	Retro	Multi-	2 yrs	163	111	52
Rizzieri	2010	USA	R (52, 25-77); without R (50, 20-83)	Retro	Lymphome malin B (LMB)	6.4 (2.4-10.3) yrs	238	105	133
Wildes	2014	USA	44 (20-74)	Retro	Multi-	1.7 (0-12) yrs	35	18	17
Ribrag	2016	France	NA	Pros	Multi-	38 (24-59) mos	257	128	129
Patekar	2018	India	38 (19.0-64.0)	Pros	CODOX-M/IVAC	15.6 (2.5-49.2) mos	18	12	6

Multi-represents more than one regimen in the study. R, rituximab; Pros, represents prospective study; Retro, retrospective study; CR, complete remission; OS, overall survival; NA, not available.

Table 1B. The characteristic of the selected studies

With R				Without R				HR	*P* value
CR	Total Alive	Total Death	OS	CR	Total Alive	Total Death	OS		
24	26	5	0.89	41	25	23	0.53	NA	NA
8	8	1	0.89	5	5	1	0.83	NA	NA
28	25	5	0.82 (0.65-0.99)	14	NA	NA	NA	NA	NA
10	10	2	0.83	3	3	5	0.38	NA	NA
NA	75	36	0.73	NA	29	23	0.558	0.4 (0.2-1.1)	0.07
87	77	28	0.78 (0.69-0.85)	92	58	75	0.52 (0.42-0.6)	NA	NA
17	13	5	0.72	12	5	12	0.294	0.38 (0.15-0.99)	0.048
NA	106	22	0.83 (0.75-0.88)	NA	90	39	0.70 (0.62-0.78)	0.51 (0.30-0.86)	0.012
8	NA	NA	NA	4	NA	NA	NA	NA	NA

CR, complete remission; OS, overall survival; HR, Hazard Ratio; NA, not available.

proved substantially over the past decades, with survival rates now exceeding 90% [17, 18], and the similar treatment protocol of short and intensive regimens introduced to adult patients produced similar OS rates. However, a substantial number of patients are intolerant to this protocol setting, especially those who are elderly. Rituximab is a chimeric monoclonal antibody against CD20 that is regularly used in low-grade or follicular B-cell NHL, such as the classic R-CHOP regimen for diffuse large B lymphoma [19, 20]. Considering that the typical immune-phenotype of BL also presents as CD20-positive, the addition of rituximab to a BL treatment regimen might improve both patients' outcomes and their treatment tolerance. Previous studies largely have not reached a consensus, however [7, 21]. In the combination antiretrovial therapy era, the outcomes of HIV patients have been further improved [22, 23]. Considering the complexity of HIV patients in terms of their genetic, biologic, and medical conditions, the role of rituximab in the treatment of immunodeficiency-associated lymphoproliferative disorders still remains controversial. Although prior studies suggested that a rituximab-plus regimen achieved a better clinical outcome in NHL regardless of HIV infection status, patients with a very low level of CD4 count (< 50/uL) were more likely to develop a late fatal infection, and a lack of further observation data persisted [24, 25]. Elsewhere, a previous meta-analysis has indicated that rituximab addition therapy could be appropriate and safe in adult BL patients, but the selected studies did not exclude HIV-positive patients [26]. In order to clarify the benefits of rituximab in BL patients, we designed the present meta-analysis to focus on sporadic BL patients without HIV infections and we believe that it is the first and largest meta-analysis for rituximab-plus treatment in adult BL patients performed to date.

The pooled 455 patients in our study showed that the rituximab-plus treatment might yield a

Table 2. Newcastle-Ottawa scale for included studies

Study	Selection				Compa-rability	Outcome			Quality
	Representative R-plus group	Representative R-minus cohort	Ascertainment of treatment	Demonstration for the interested outcome at start		Assessment of outcome	Long enough follow-up for occurrence of outcome	Adequate follow-up	
Thomas (2006)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Maruyama (2010)	No	No	Yes	No	No	Yes	Yes	Yes	Poor
Corazzelli (2011)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Dujmovic (2011)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Wasterlid (2013)	No	No	Yes	No	Yes	Yes	Yes	Yes	Fair
Rizzieri (2010)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Wildes (2014)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Ribrag (2016)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Petekar (2018)	No	No	Yes	No	No	Yes	Yes	Yes	Poor

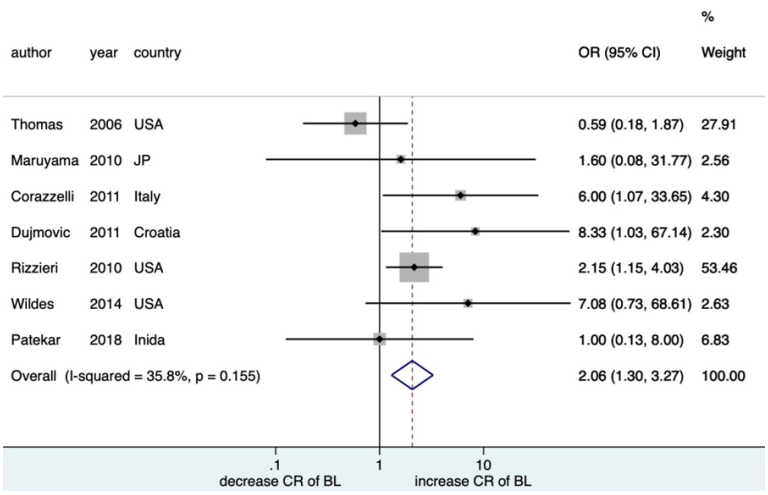

Figure 2. The forest plot of pooled CR. The CR rates (95% CI) of selected studies are show in the diagram. The shape of square represents the Weight of the studies. The pooled CR for rituximab plus regimen is 2.061 (95% CI: 1.30-3.27).

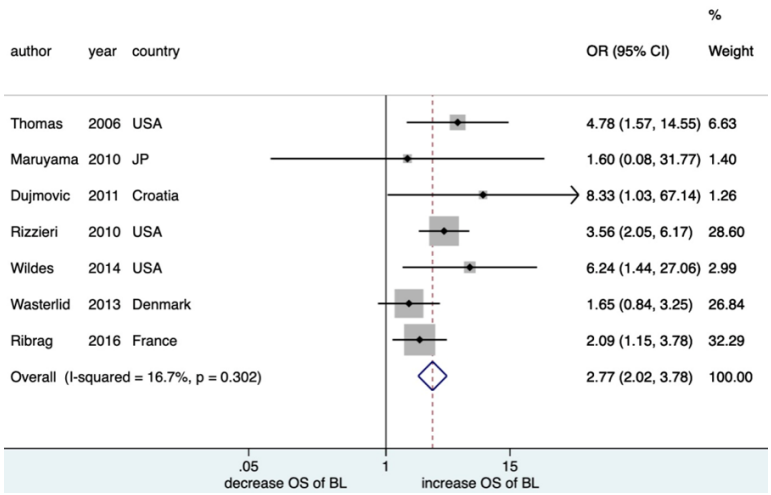

Figure 3. The forest plot of pooled OS. The OS rates (95% CI) of selected studies are show in the diagram. The shape of square represents the weight of the studies. The pooled OS for rituximab plus regimen is 2.77 (95% CI: 2.02-3.78).

better CR result (83.9% vs. 71.8%). Meanwhile, the pooled 807 patients showed a higher survival rate (76.1% vs. 54.7%). Our data are consistent with those of the other published studies, where the range of CR was 66.6% to 94.4% and the OS was 70% to 89% [4, 6, 7, 10, 16, 22-25]. Nonunique regimen selection could have led to the variation in patients' outcomes among these studies. All chemotherapy regimens currently used in BL are based on the same following characteristics: short-term, dose-intensive, and multiagent. However, this strategy could increase the risk of the morbidity and mortality of patients. In our study, the hyper-CVAD and CODOX-M/IVAC protocols were the commonly used regimens. The common rituximab-associated adverse events were infection and neutropenia. No significant differences were found between the chemotherapy-alone and rituximab-plus groups. More importantly, long-term efficacy and safety were also demonstrated, since the longest follow-up duration was more than 10 years [6, 16]. The largest prospective trial (with 257 patients) included in this meta-analysis used the LMB protocol as a therapy method, showing that the rituximab group achieved a better event-free survival and did not differ with regard to adverse events seen in the with and without rituximab groups. However, clinical use of the LMB protocol may be handicapped by its complexity [27-31]. The regimens supplemented with rituximab, which is nontoxic and highly targeted to CD20+ lymphoma, suggesting that it could be an attractive therapy for BL patients. Further well-designed randomized controlled trials (RCTs) of hyper-CVAD plus rituximab as well as CODOX-M/IVAC plus rituximab should be conducted in multiple centres.

There are several limitations in this study. First, most of the included studies were retrospective in nature, which may have reduced the quality of our pooled data. Therefore, well-designed, multicentre, head-to-head RCTs with large populations are required to confirm the efficacy and safety of rituximab-plus Regimens. Second, there has not been an overly common regimen with rituximab administered by researchers to date. We believe that hyper-CVAD and CODOX-M/IVAC should be focused on as reliable options for future studies. Third, there was not a standard dosage or course of rituxi-

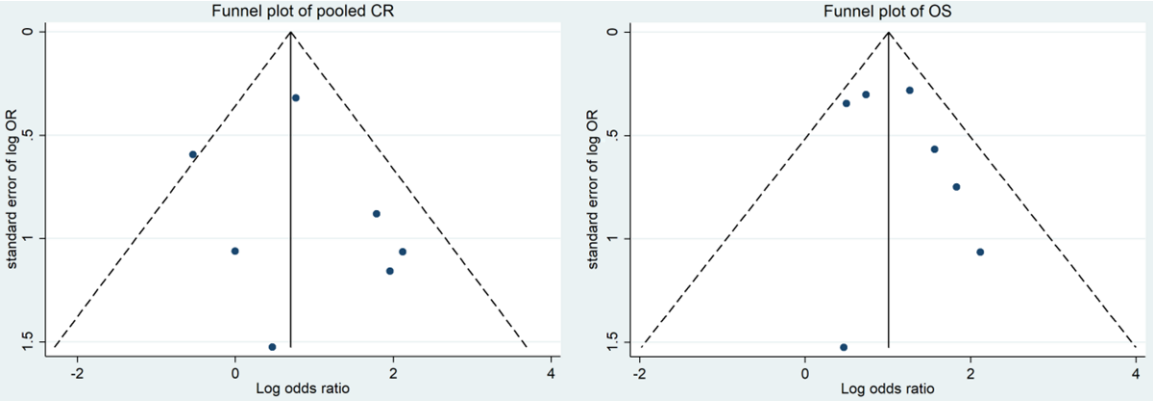

Figure 4. The funnel plots of publication bias. Each point represents a separate study and horizontal line represents the mean effect size.

mab recommended across the studies in this meta-analysis, which could decrease the clinical practicability. Fourth, as presented in this paper, elderly patients are more likely to experience adverse outcomes. However, the age stratification of patients was not analysed in this study due to the limited information provided. Thus, the conclusions of this study should be interpreted with caution and an eye on further research.

Conclusions

Combination rituximab and chemotherapy regimens could be effective, safe, and tolerable for HIV-free adult BL patients. The results of this meta-analysis support the clinical applicability of rituximab in BL patients, providing a relatively high level amount of evidence and up-to-date data. However, further well-designed, large-scale RCT studies are needed to better elucidate the value of rituximab-plus therapy.

Acknowledgements

This work was supported by the Construction Project of Fujian Medical Center of Hematology (Min201704); the Special Fund from Fujian Provincial Department of Finance (2016B041); the Cooperation Project of University and Industry in Fujian Province (2017Y4005); the Joint Research Project of Health and Education (WKJ2016-2-06); the Joint Funds for the Innovation of Science and Technology, Fujian province (2016Y9029, 2016Y9032); the National Natural Science Foundation of China (81570-162); the Natural Science Foundation of Fujian Province (2013Y0044); and the Backbone Talents Training Project of the Fujian Bureau of Public Health, P.R.C. (2014-ZQN-ZD-8). We acknowledge all the patients and their families.

Disclosure of conflict of interest

None.

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