RCHOP-14 therapy versus RCHOP-21 therapy for people with aggressive or advanced-stage indolent B-cell non-Hodgkins lymphoma: a systematic review and meta-analysis

Yue He[1], Wenqiang Tao[2], Dexiang Ji[1], Wei Lu[1], Yu Xiong[3], Guoan Chen[1]

[1]Department of Hematology, the 1st Affiliated Hospital of Nanchang University, Nanchang, China; [2]Department of ICU, the 1st Affiliated Hospital of Nanchang University, Nanchang, China; [3]Department of Emergency, the 1st Hospital of Nanchang City, Nanchang, China

Contributions: (I) Conception and design: Y He, W Tao; (II) Administrative support: Y He; (III) Provision of study materials or patients: D Ji, W Lu; (IV) Collection and assembly of data: Y Xiong, G Chen; (V) Data analysis and interpretation: D Ji, W Lu, Y Xiong, G Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Guoan Chen. Department of Hematology, the 1st Affiliated Hospital of Nanchang University, No. 17 Yongwaizheng Street, Donghu District, Nanchang 33000, China. Email: chenguoan2020@yeah.net.

Background: With the advent of rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone (RCHOP) treatment has become considered the appropriate chemotherapy treatment for aggressive or advanced-stage indolent B-cell non-Hodgkins lymphoma (NHL). In recent years, RCHOP-14 seems to have achieved better outcomes in patients with aggressive or advanced-stage indolent B-cell NHL than RCHOP-21.

Methods: To verify the befitting chemotherapy regimens for patients with B-cell NHL, we searched the electronic databases for relevant English-language literature published in January 2020. The primary outcomes were complete response (CR), progression-free survival (PFS), overall survival (OS), and adverse events (AEs). Six eligible Phase II and III randomized controlled clinical trials (RCTs) and two high-quality observational comparative studies (OCSs) were extracted, with 5,565 patients with B-cell NHL involved in the evaluation.

Results: The analysis demonstrated no significant difference in RCHOP-14 and RCHOP-21 CR rates [odds ratio (OR) =0.98, 95% CI: 0.77–1.24, P=0.85]. Compared with RCHOP-21, the merged hazard ratio (HR) after treatment with RCHOP-14 for PFS and OS was 0.94 (95% CI: 0.84–1.06, P=0.32) and 0.91 (95% CI: 0.83–1.01, P=0.08), respectively. A subgroup analysis based on the international prognostic index (IPI) score showed that both chemotherapy regimens were applicable in B-cell NHL patients with different prognoses. The frequency of toxic side-effects was similar between schemes.

Conclusions: The data presented suggest that the efficacy and safety of both regimens are comparable and that RCHOP-14 remains a viable plan in patients with B-cell NHL who prefer a shorter therapy course.

Keywords: Aggressive; indolent; B-cell lymphoma; rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone (RCHOP); a systematic review

Introduction

Aggressive and indolent lymphomas are two subtypes of B-cell-derived non-Hodgkins lymphoma (NHL) and are treated with different chemotherapy regimens depending on the prognosis. Aggressive NHL is a highly aggressive malignancy with a poor outcome. It is a greatly chemo-sensitive tumor and is highly curable (1). An advanced-stage indolent NHL is often incurable and can easily

transform into an aggressive lymphoma. However, it can be alleviated with a regimen of rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone (RCHOP) (2,3). Diffuse large B-cell lymphoma (DLBCL), a disease of biologically, histopathologically, and clinically heterogeneous entities (4), is the most common subtype of aggressive lymphoma. The median survival time of patients with DLBCL who did not undergo prompt treatment is less than 1 year on account of the DLBCL's aggressive nature (5,6). For a long time, the first-line chemotherapy treatment for DLBCL was cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) treatment. It is more reasonable to choose to combine this treatment with CHOP-21 every 3 weeks. Several randomized controlled clinical trials (RCTs) regarding the survival analysis of dose-intensified regimens were conducted, which showed that the CHOP-14 2-week cycle of chemotherapy is superior to the CHOP-21 treatment (7,8).

The human/murine chimeric anti-CD20 monoclonal antibody called rituximab has a credible efficacy. It is well-defined and adequately safe for patients with various CD20-expressing lymphoid malignancies, such as aggressive and indolent forms of B-cell NHL (9). Follicular lymphoma (FL) is a neoplasm comprising germinal center B cells and is a subgroup of indolent lymphomas. The standard option for patients with advanced-stage FL is rituximab-CHOP (10). NHL (PMBL) is a unique subtype of DLBCL originating from thymic B-cells in the mediastinum. The RCHOP regimen, with or without consolidative radiotherapy, is first-line PMBL management (11). It can be observed in all of these diseases, which include DLBL, FL, mantle cell lymphoma, and chronic lymphocytic leukemia, that rituximab-based treatment not only extends the time of the patient's progression-free survival (PFS) but also prolongs his/her overall survival (OS) time (12). Therefore, it is meaningful to discuss the choice between rituximab-based RCHOP-14 and 21 chemotherapy regimens for aggressive or advanced-stage indolent B-cell NHL.

We implement trails from RCTs and observational comparative studies (OCSs) to estimate the efficacy and toxicity of a chemotherapy regimen, comparing RCHOP-14 to RCHOP-21 in patients with B-cell NHL. The results include complete response (CR), PFS, OS, and toxicity levels. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-3123).

Methods

Search strategy

First, we conducted a systematic and comprehensive search from original to January 2020 throughout databases, including PubMed, Web of Science, Embase, Cochrane Library, and ClinicalTrials.gov. The predefined keywords were used with Boolean operators for the search: "RCHOP-14 AND RCHOP-21" OR "dose-dense" AND "lymphoma". The electronic search was complemented by a manual search for additional articles in reference lists and previous reviews, rendering a full-scale investigation.

Selection criteria

We enrolled trials meeting the below inclusion criteria: (I) high-quality OCS and studies based on RCTs; (II) participants newly diagnosed with aggressive lymphoma at clinical stages I–IV or untreated advanced-stage indolent B-cell NHL; (III) comparative analysis of RCHOP-14 and RCHOP-21 for treating B-cell NHL; (IV) follow-up duration longer than 36 months (V) an existence outcome of CR, PFS or OS in the articles. Duplicated data that might lead to an overestimation of intervention effects was contained cautiously. Review articles, conference abstracts, nonhuman studies, case reports, abstracts, and unpublished data were excluded from consideration. Moreover, studies that did not exclude data were not included. If there were differences regarding which studies should be included, experts decided whether to include them or not.

Data extraction and quality assessment

Relevant Data were independently extracted from included articles by two authors. The following data were extracted: the first author, published year, location, disease, stage, median age, median follow-up, number of patients with international prognostic index (IPI) at different levels, sample size, number of cycles, and clinical outcomes (including CR, PFS, OS and toxicity). We assessed the quality of RCTs using the Cochrane Collaboration's risk of bias tool, Rev Man 5.3. The quality of selected studies was appraised with methodological domains as follows: risks of selection, performance, detection, attrition, and reporting biases. For the included study, types of bias are divided into three levels: low, unclear, high. The Newcastle-Ottawa scale (NOS) uses three categories, the selection of study groups,

2046

He et al. B-cell lymphoma treatment with RCHOP

comparability, and outcome assessment, respectively, to evaluate the risk of OCS biases.

Statistical analysis

A meta-analysis of variables with three or more studies was performed when the outcome was reported. Statistical heterogeneity among individual studies was calculated by the P and I^2 test, where heterogeneity will be considered substantive if $I^2>50\%$ (13). The fixed-effect model and the random-effects models were utilized for both consistent and heterogeneous studies in accordance with the previously published guidelines for statistical reporting and a systematic review manual on Cochrane interventions. PFS and OS, as the dichotomous data, were reported with hazard ratios (HRs) and 95% CIs. HR is calculated by the inverse of variance. It is used to weigh the size of the individual effect. The CR rate was calculated through the odds ratio (OR) with the random-effects model (M-H methods) and adverse events (AEs), used to analyze the risk ratio (RR), were calculated with the same model. Next, the forest map for meta-analysis was drawn. When possible, sensibility analysis was conducted to investigate the origins of heterogeneity. Funnel plots were performed to attest the presence of publication bias. All statistical analyses were conducted in Review Manager 5.3.

Results

Description of studies

A total of 403 potentially relevant studies were ascertained after the initial search (*Figure 1*). Of these, 31 articles were from PubMed, 59 from Embase, 173 from Web of Science, 134 from Cochrane Library and 6 from clinicaltrials. gov. One hundred eighty-one irrelevant articles and 142 duplicated articles were expurgated by carefully reviewing the titles and abstracts. Sixty-six pieces of literature were deleted for the reason that these trials were conference reports, non-original or scarce data, review or meta-analysis, or weren't RCHOP-14 *vs.* RCHOP-21 and related results. Finally, six RCTs—Cunningham *et al.* (2013), Delarue *et al.* (2013), Payandeh *et al.* (2016), Watanabe *et al.* (2018), Li *et al.*, (2019), and Gleeson *et al.* (2016)—and two OCSs—Wästerlid *et al.* (2017) and Knauf *et al.* (2019)—met all inclusion criteria entered in this meta-analysis (14-21).

Patients types

In total, the five studies included 5,565 patients with B-cell NHL, of whom 2,892 underwent RCHOP-14 and 2,673 only underwent RCHOP-21. The experimental characteristics of each RCT are summarized in *Table 1*. Most of the enrolled trials were from different countries, four of which are in Europe. Four trails accounting for studies were from Asia. We collected patients above the age of 18 with clinical stage I–IV aggressive lymphoma and untreated stage III–IVV indolent B-cell NHL. The granulocyte colony-stimulating factor (G-CSF) was applied to both the RCHOP-14 group and the RCHOP-21 group to shorten the CHOP treatment. Stimulating Moreover, the sample sizes for individual studies varied widely from 50 to 2,106 despite being multi-center clinical trials.

Quality assessment

Six RCTs were assessed as low risk in the light of a suitable option (*Figure 2A,B*). However, four RCTs had a high risk of selection bias as allocation concealment (14,16,18,21). All funnel plots of PFS and OS were symmetrical, indicating no publication bias (*Figure 2C,D*). The selection of high-quality OCSs was based on a validated tool. Two OCSs were evaluated by NOS (*Table 2*), and the results suggested that both of them were high-quality literature.

Efficacy

CR rate data were available from eight studies (14-21), incorporating 2,657 patients from the RCHOP-14 therapeutic regimen and 2,415 patients from the RCHOP-21 regimen. A significant heterogeneity was found within these two regimes (χ^2=17.69, P=0.007, I^2=66%) (*Figure 3*). The random-effects model was subsequently used. The CR rate did not meliorate with RCHOP-14 regimens in patients (OR =0.96, 95% CI: 0.76–1.23, P=0.76). The results of the RCTs and OCSs were consistent, so we calculated the data together and displayed it on a graph.

Survival

The PFS and OS of RCHOP-14 *vs.* RCHOP-21 was the main long-term clinical outcome evaluation with B-cell

```
┌─────────────────────┐       ┌─────────────────────┐
│  403 of records     │       │ 0 of additional     │
│  identified through │       │ records identified  │
│  database searching │       │ through other       │
│                     │       │ sources             │
└─────────────────────┘       └─────────────────────┘

        ┌───────────────────────────────────────┐
        │  148 of records after duplicates      │
        │  removed                              │
        └───────────────────────────────────────┘

        ┌─────────────────────┐       ┌─────────────────────┐
        │  255 of records     │──────▶│ 181 of records      │
        │  screened           │       │ excluded with       │
        │                     │       │ irrelevant          │
        └─────────────────────┘       └─────────────────────┘

        ┌─────────────────────┐       ┌──────────────────────────────┐
        │  74 of full-text    │──────▶│ 66 of full-text articles     │
        │  articles assessed  │       │ excluded,                    │
        │  for eligibility    │       │                              │
        │                     │       │ -28 not RCHOP-14 vs.         │
        └─────────────────────┘       │  RCHOP-21                    │
                                      │                              │
                                      │ -11 not original data or     │
                                      │  data scarcity               │
        ┌─────────────────────┐       │                              │
        │ Reports included    │       │ -8 meetings or posters       │
        │ in meta-analysis    │       │                              │
        │                     │       │ -12 review or meta-analysis  │
        │ • 6 RCTs            │       │                              │
        │ • 2 OCSs            │       │ -7 not relative results      │
        └─────────────────────┘       └──────────────────────────────┘
```

Figure 1 Flow diagram of the study selection process. RCHOP, rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone; RCTs, randomized controlled clinical trials; OCSs, observational comparative studies.

lymphoma. *Figures 4,5* suggest that no significant between-trial heterogeneity was observed between PFS and OS. Hence, we chose the fixed-effect model. The results of the OCSs were consistent with the RCTs, so we presented these data in a single graph and stratified the clinical outcomes of patients with different prognoses based on the IPI scores. For the comparison, PFS was curtailed in RCHOP-14, but it showed no significant difference (HR =0.94, 95% CI: 0.84–1.06, P=0.32). Results were not altered after differentiating patients with different IPI scores (*Figure 4*). Regarding OS, RCHOP-14 was superior to RCHOP-21 (HR =0.91, 95% CI: 0.83–1.01, P=0.08) (*Figure 5*). However, there was still no statistical difference among the trials. After stratification according to the IPI score, the OS of patients with different prognoses was in agreement with

the outcome indicators of all patients.

Treatment-related toxicity

AEs, including both hematological and non-hematological toxicities, with both RCHOP-14 and RCHOP-21 treatment protocols were reviewed in all RCTs. *Table 3* summarizes the grade ≥3 AEs. We have used RR values to compare the AEs of the five studies in the supplementary picture, and the toxicity of the RCHOP-14 regimen and RCHOP-21 regimen does not have a significantly high risk (RR =0.98, 95% CI: 0.83–1.15, P=0.73). I^2=85% suggested greater heterogeneity among the trials, which was statistically significant. The subgroup analysis results on hematological AEs show that the incidences of thrombocytopenia (RR

Table 1 Description of include studies

Study	Location	Disease	Stage	Median follow-up (months)	Sample size RCHOP-14/RCHOP-21	Number of cycles RCHOP-14/RCHOP-21	Use of G-CSF RCHOP-14	RCHOP-21
Cunningham 2013 (14)	UK	DLBCL	I–IV	46	540/540	6 plus 2 R/8	Given to all patients	54% of patients
Delarue 2013 (15)	France, Belgium, Switzer, Portugal	DLBCL	I–IV	56	304/298	8/8	90% of patients, decision of the treating physician	74% of patients, decision of the treating physician
Gleeson 2016 (21)	UK	DLBCL	I–II	86.4	22/28	6 plus 2 R/8	Given to all patients	54% of patients
Payandeh 2016 (17)	Iran	B-cell NHL	III–IV	45	66/77	6–8/6–8	Given to all patients	At the desertion of the treating physician
Watanabe 2018 (16)	Japan	Untreated advanced-stage FL	III–IV	134.4	151/149	6/6	Given to all patients	At the desertion of the treating physician
Li 2019 (18)	China	DLBCL	I–IV	45.6	349/353	6–8/6–8	Given to all patients	The investigator's discretion
Wästerlid 2017 (20)*	Swedish	PMBL	I–IV	47.4	1196/910	6/6	Not report	Not report
Knauf 2019 (19)*	German	DLBCL	I–IV	60	264/318	6/6	73% of patients use it at least once	48.7% of patients use it at least once

*, OCSs. G-CSF, granulocyte colony-stimulating factor; RCHOP, rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone; DLBCL, diffuse large B-cell lymphoma; PMBL, primary mediastinal B-cell lymphoma; R, rituximab; FL, follicular lymphoma; OCSs, observational comparative studies.
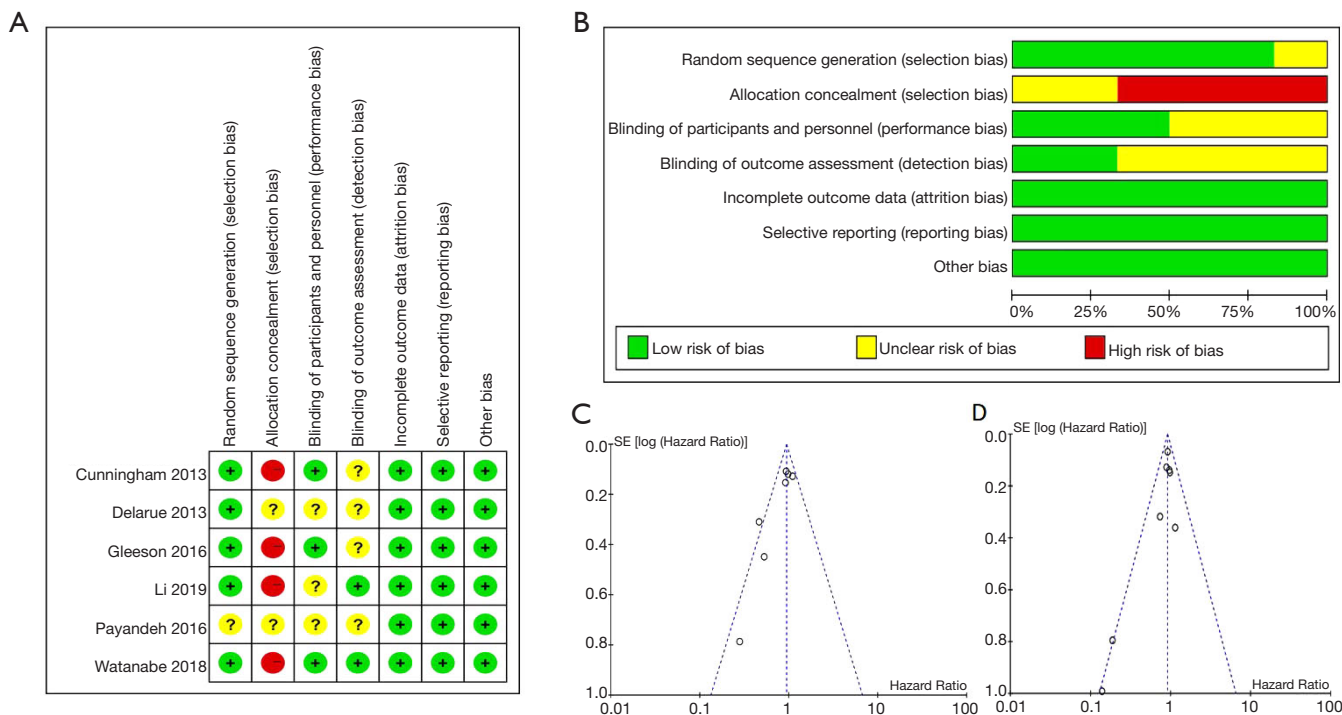
Figure 2 The risk of bias. (A) Risk of bias summary; (B) risk of bias graph; (C) PFS funnel plot; (D) OS funnel plot. PFS, progression-free survival; OS, overall survival.

Table 2 Quality assessment of OCSs by NOS scale

Study	Items	Wästerlid 2017 (20)	Knauf 2019 (19)
Selection	Representativeness of the exposed cohort	*	*
	Selection of the non-exposed cohort	*	*
	Ascertainment of exposure	*	*
	Demonstration that outcome of interest was not present at start of study	*	*
Comparability	Comparability of cohorts on the basis of the design or analysis	**	**
Outcome	Assessment of outcome	*	*
	Was follow-up long enough for outcomes to occur	*	*
	Adequacy of follow up of cohorts	*	*

*, star-rating in NOS, each study can have a maximum of one star per entry in "Selection", "Outcome" and a maximum of two stars per entry in "Comparability". OCSs, observational comparative studies; NOS, Newcastle-Ottawa scale.

=0.87, 95% CI: 0.60–1.25, P=0.44) were higher in the RCHOP-14 arm (9,10,12-14), although this has no statistical significance. One of the subgroup analyses with patients who received RCHOP-21, who have a higher trend of anemia when ceasing treatment Watanabe *et al.* (RR =1.15, 95% CI: 0.88–1.50, P=0.29), was observed (14,17,18). The subgroup analysis on non-hematological AEs indicates that patients treated with RCHOP-21 had a higher risk of neurological-related, which was not statistically significant (RR =1.41, 95% CI: 0.85–2.33, P=0.18).
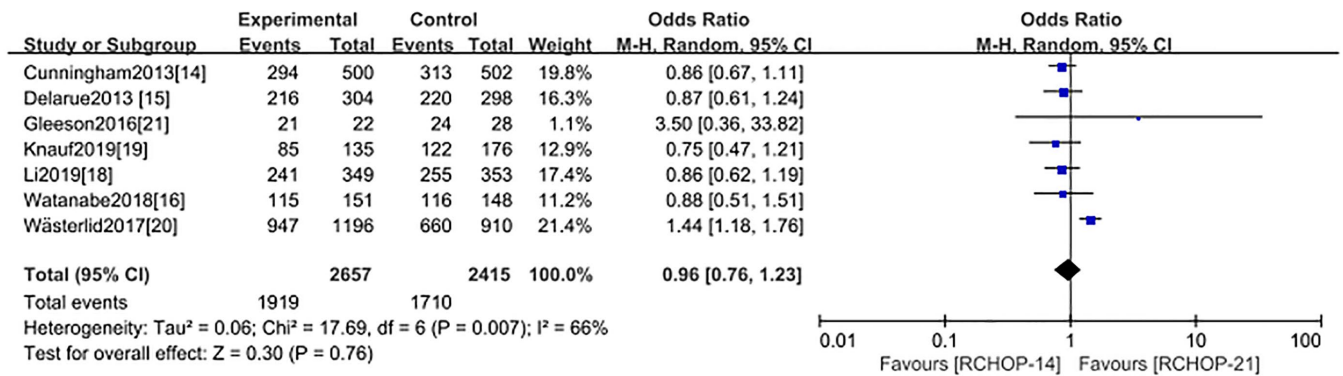
2050

He et al. B-cell lymphoma treatment with RCHOP

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Cunningham2013[14]	294	500	313	502	19.8%	0.86 [0.67, 1.11]
Delarue2013 [15]	216	304	220	298	16.3%	0.87 [0.61, 1.24]
Gleeson2016[21]	21	22	24	28	1.1%	3.50 [0.36, 33.82]
Knauf2019[19]	85	135	122	176	12.9%	0.75 [0.47, 1.21]
Li2019[18]	241	349	255	353	17.4%	0.86 [0.62, 1.19]
Watanabe2018[16]	115	151	116	148	11.2%	0.88 [0.51, 1.51]
Wästerlid2017[20]	947	1196	660	910	21.4%	1.44 [1.18, 1.76]
Total (95% CI)		**2657**		**2415**	**100.0%**	**0.96 [0.76, 1.23]**
Total events	1919		1710			

Heterogeneity: Tau² = 0.06; Chi² = 17.69, df = 6 (P = 0.007); I² = 66%
Test for overall effect: Z = 0.30 (P = 0.76)

Figure 3 CR rate for RCHOP-14 *vs.* RCHOP-21. CR, complete response; RCHOP, rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone.
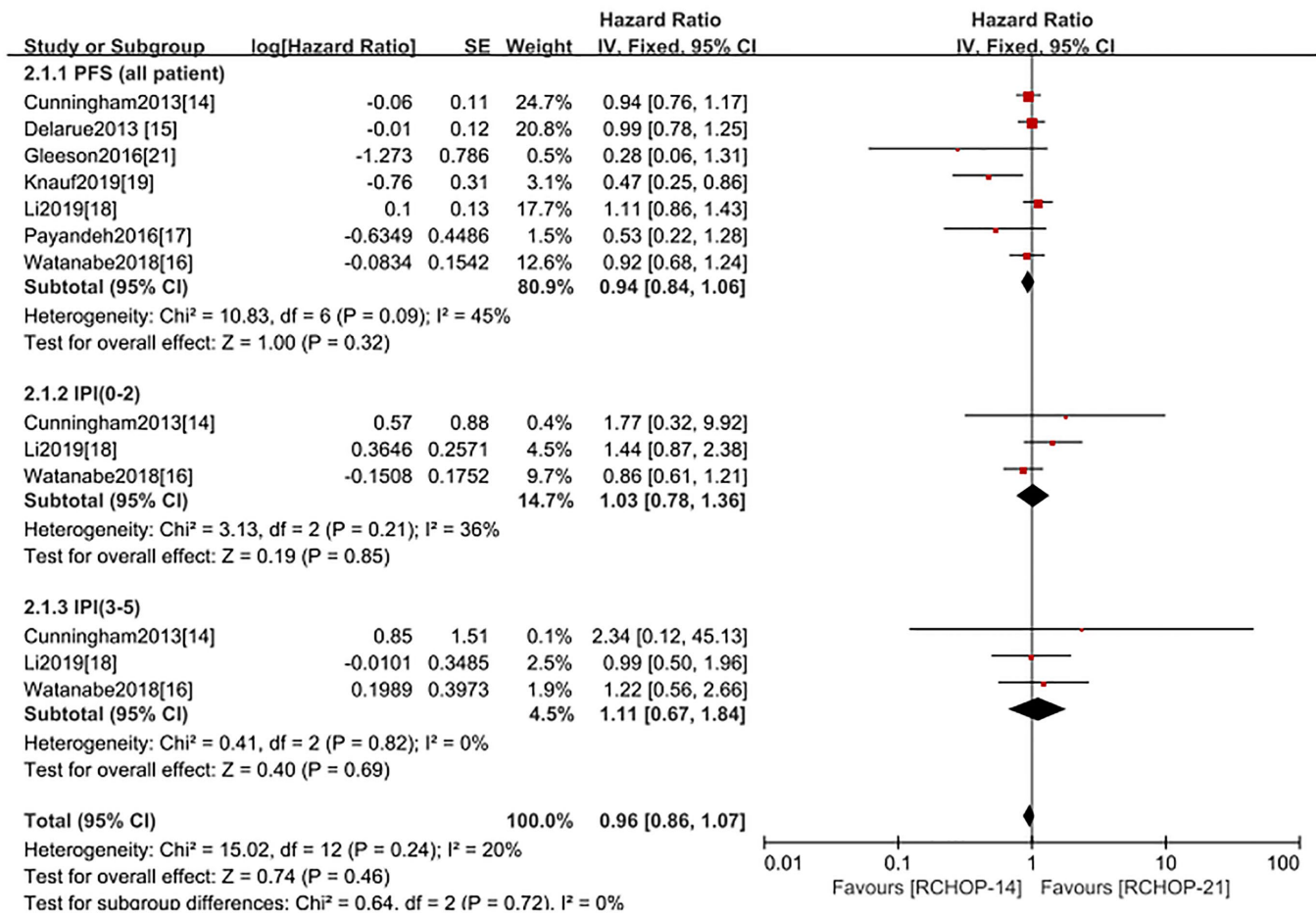
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
2.1.1 PFS (all patient)				
Cunningham2013[14]	-0.06	0.11	24.7%	0.94 [0.76, 1.17]
Delarue2013 [15]	-0.01	0.12	20.8%	0.99 [0.78, 1.25]
Gleeson2016[21]	-1.273	0.786	0.5%	0.28 [0.06, 1.31]
Knauf2019[19]	-0.76	0.31	3.1%	0.47 [0.25, 0.86]
Li2019[18]	0.1	0.13	17.7%	1.11 [0.86, 1.43]
Payandeh2016[17]	-0.6349	0.4486	1.5%	0.53 [0.22, 1.28]
Watanabe2018[16]	-0.0834	0.1542	12.6%	0.92 [0.68, 1.24]
Subtotal (95% CI)			**80.9%**	**0.94 [0.84, 1.06]**

Heterogeneity: Chi² = 10.83, df = 6 (P = 0.09); I² = 45%
Test for overall effect: Z = 1.00 (P = 0.32)

2.1.2 IPI(0-2)				
Cunningham2013[14]	0.57	0.88	0.4%	1.77 [0.32, 9.92]
Li2019[18]	0.3646	0.2571	4.5%	1.44 [0.87, 2.38]
Watanabe2018[16]	-0.1508	0.1752	9.7%	0.86 [0.61, 1.21]
Subtotal (95% CI)			**14.7%**	**1.03 [0.78, 1.36]**

Heterogeneity: Chi² = 3.13, df = 2 (P = 0.21); I² = 36%
Test for overall effect: Z = 0.19 (P = 0.85)

2.1.3 IPI(3-5)				
Cunningham2013[14]	0.85	1.51	0.1%	2.34 [0.12, 45.13]
Li2019[18]	-0.0101	0.3485	2.5%	0.99 [0.50, 1.96]
Watanabe2018[16]	0.1989	0.3973	1.9%	1.22 [0.56, 2.66]
Subtotal (95% CI)			**4.5%**	**1.11 [0.67, 1.84]**

Heterogeneity: Chi² = 0.41, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)

Total (95% CI)			**100.0%**	**0.96 [0.86, 1.07]**

Heterogeneity: Chi² = 15.02, df = 12 (P = 0.24); I² = 20%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Chi² = 0.64. df = 2 (P = 0.72). I² = 0%

Figure 4 PFS for RCHOP-14 *vs.* RCHOP-21 of all patients and different IPI scores patient. PFS, progression-free survival; RCHOP, rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone; IPI, international prognostic index.
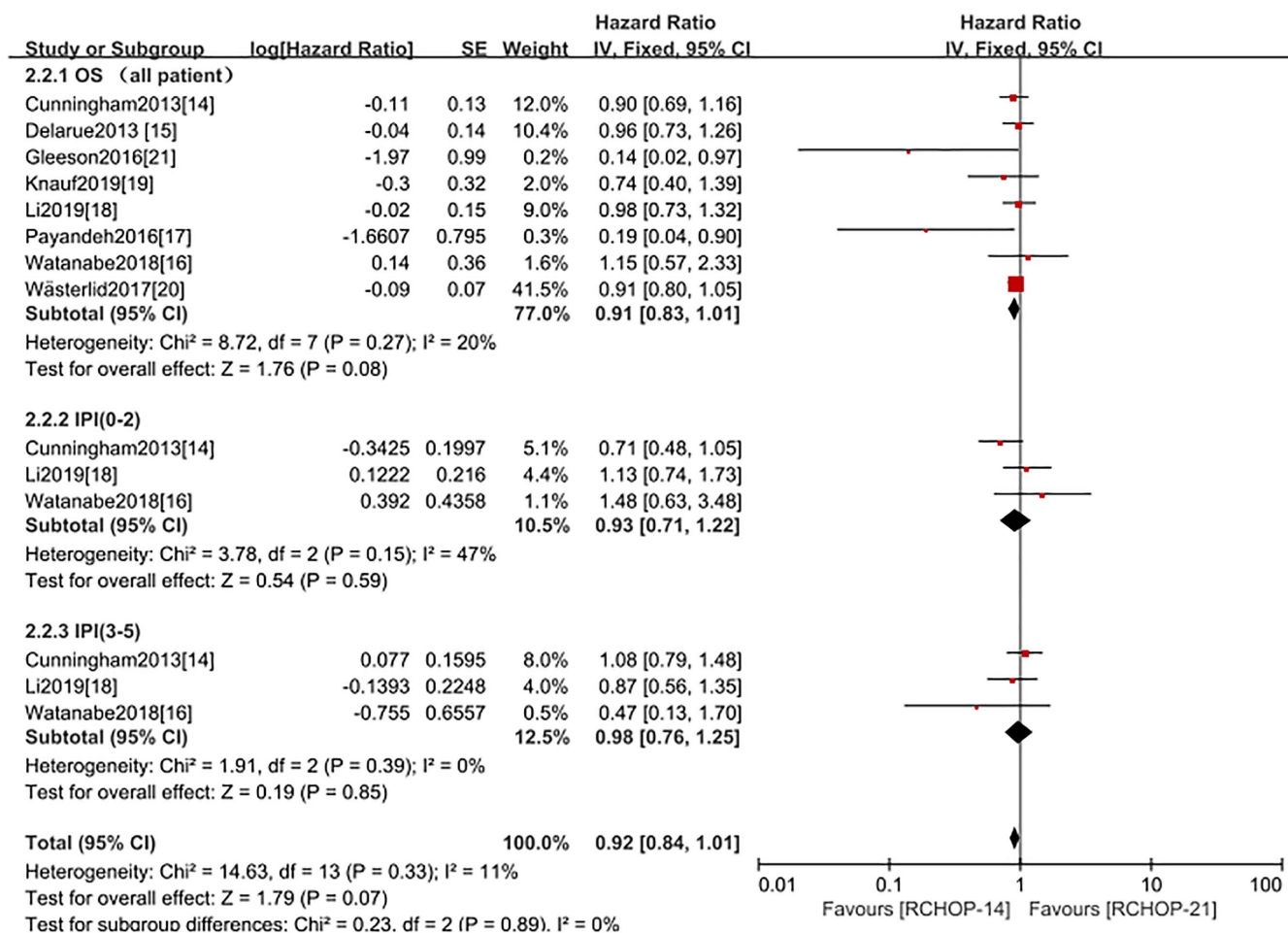
Figure 5 OS for RCHOP-14 *vs.* RCHOP-21 of all patients and different IPI scores patient. OS, overall survival; RCHOP, rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone; IPI, international prognostic index.

Discussion

At a clinical level, RCHOP-14 and RCHOP-21 are the two different international standards used for the treatment of B-cell lymphoma. This manuscript implies that the CR rate, PFS, and OS were higher in patients who were assigned RCHOP-14 therapy. However, its outcomes did not differ significantly. This indicates that improvement of the CR rate, PFS, and OS in these patients may not be possible through RCHOP-14. More RCTs are required in order to confirm whether the addition of radiotherapy can change this outcome or not. The previous meta-analysis shows that the treatment options of RCHOP were manifested to prolong OS when given every 14 days instead of 21 days in case rituximab was omitted (22). Our analysis showed

that RCHOP-14 and RCHOP-21 have no statistically significant difference in PFS and OS.

Toxicity was an important endpoint of our study. There is a higher risk of infectious complications associated with RCHOP14, particularly febrile neutropenia, due to infections caused by opportunistic pathogens (23-25). However, our study shows that the toxicity of RCHOP-14 regimen is the same as the toxicity of the RCHOP-21 regimen in B-cell patients, rather than higher. One reason why the RCHOP-14 regimen has the same safety-rate as the prophylactic recombinant human G-CSF. G-CSF has often been used to potentiate the antibody-dependent cell-mediated cytotoxicity of rituximab (26,27), after which CHOP intervals can be shortened (7,8,28,29). More patients who were given the prophylactic recombinant

2052

He et al. B-cell lymphoma treatment with RCHOP

Table 3 Incidence and relative risk of specific SAEs in included trials

Specific AEs	Number of studies	RCHOP-14	RCHOP-21			Heterogeneity	
		Pts with SAE/total pts	Pts with SAE/total pts	Relative risk (95% CI)	P value	P value	I² (%)
Neutropenia	5	722/1,340	896/1,408	0.93 (0.64–1.36)	0.71	<0.00001	98
Thrombocytopenia	5	102/1,340	132/1,408	0.87 (0.60–1.25)	0.44	0.15	41
Anemia	4	121/770	97/874	1.15 (0.88–1.50)	0.29	0.48	0
Febrile neutropenia	3	103/989	134/978	0.66 (0.33–1.30)	0.23	0.001	85
Infection	4	209/1,238	225/1,331	1.18 (0.72–1.91)	0.51	0.0003	84
Gastrointestinal toxicity	4	70/1,238	74/1,331	1.00 (0.73–1.38)	0.98	0.52	0
Increase in amount of liver enzymes	3	21/521	21/521	1.04 (0.58–1.86)	0.9	0.99	0
Cardiac-related	3	15/521	14/521	1.04 (0.15–7.34)	0.97	0.02	74
Neurological-related	3	80/989	57/978	1.41 (0.85–2.33)	0.18	0.19	40

SAE, severe adverse event; AE, adverse event; RCHOP, rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone.

human G-CSF every 14 days developed grade 3–4 neutropenia than reported previously (14). One type of toxicity is thrombocytopenia, especially in the RCHOP-14 regimen. It may increase the chance of intravenous platelet. Meanwhile, anemia is more likely to occur for RCHOP-21, which leads frequent transfusions. Another apparent reason is that there is greater heterogeneity between subgroups and the results may be unreliable.

As far as we can see, this study is the first meta-analysis to assess the efficacy and toxicity of the CHOP regimen in patients with aggressive or advanced-stage indolent B-cell NHL based on rituximab. It is also the first to analyze survival outcomes for patients with different prognostic outcomes based on IPI scores. The data suggests that we could face type 2 errors in the RCTs. The main argument for including OCSs is trying to avoid making this mistake. However, the meta-analysis still has some limitations. Firstly, it is possible that two studies caused performance and detection biases because of they were open-label trails. In the second place, the low number of included studies made it difficult for a detailed, in-depth probe and an interpretation of a potential underlying heterogeneity. When ascertaining heterogeneity among individual studies for toxicity, which is still significantly high after removing the relevant study. The reason for the high heterogeneity may be the different B-cell NHL prognoses and the inconsistent chemotherapy cycle. Therefore, we need more RCTs to explore the potential causes of heterogeneity.

In the end, other covariates, such as supportive therapy, preventive measures of toxicity, and the proficiency of a doctor, could not be balanced in the study.

Conclusions

To sum up the study, an analysis of data from clinical trials of RCHOP-14 treatment showed that the therapies are safe and effective compared with the RCHOP-21 treatment. However, there was no significant difference in PFS and OS, and that it produces clinical responses similar to those in CR rate. Additional considerations in regard to choosing the treatment strategy and balancing treatment-related toxicity may help us to decide whether to treat with RCHOP-14 or RCHOP-21.

Acknowledgments

Footnote

Peer Review File: Available at http://dx.doi.org/10.21037/tcr-20-3123

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-3123). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Mugnaini EN, Ghosh N. Lymphoma. Prim Care 2016;43:661-75.
2. Mondello P, Steiner N, Willenbacher W, et al. Bendamustine plus rituximab versus R-CHOP as first-line treatment for patients with indolent non-Hodgkin's lymphoma: evidence from a multicenter, retrospective study. Ann Hematol 2016;95:1107-14.
3. Igarashi T, Ogura M, Itoh K, et al. Japanese phase II study of rituximab maintenance for untreated indolent B-cell non-Hodgkin lymphoma with high tumor burden. Int J Hematol 2016;104:700-8.
4. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503-11.
5. Flowers CR, Sinha R, Vose JM. Improving outcomes for patients with diffuse large B-cell lymphoma. CA Cancer J Clin 2010;60:393-408.
6. Sinha R, Nastoupil L, Flowers CR. Treatment strategies for patients with diffuse large B-cell lymphoma: past, present, and future. Blood Lymphat Cancer 2012;2012:87-98.
7. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 2004;104:634-41.
8. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood 2004;104:626-33.
9. Salles G, Barrett M, Foa R, et al. Rituximab in B-cell hematologic malignancies: a review of 20 years of clinical experience. Adv Ther 2017;34:2232-73.
10. Ando K. Follicular lymphoma: recent advances. Rinsho Ketsueki 2018;59:2104-8.
11. Soumerai JD, Hellmann MD, Feng Y, et al. Treatment of primary mediastinal B-cell lymphoma with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone is associated with a high rate of primary refractory disease. Leuk Lymphoma 2014;55:538-43.
12. Economopoulos T, Psyrri A, Dimopoulos MA, et al. CEOP-21 versus CEOP-14 chemotherapy with or without rituximab for the first-line treatment of patients with aggressive lymphomas: results of the HE22A99 trial of the Hellenic Cooperative Oncology Group. Cancer J 2007;13:327-34.
13. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
14. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet 2013;381:1817-26.
15. Delarue R, Tilly H, Mounier N, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. Lancet Oncol 2013;14:525-33.
16. Watanabe T, Tobinai K, Wakabayashi M, et al. Outcomes after R-CHOP in patients with newly diagnosed advanced follicular lymphoma: a 10-year follow-up analysis of the JCOG0203 trial. Lancet Haematol 2018;5:e520-31.
17. Payandeh M, Najafi S, Shojaiyan FZ, et al. Phase III of study of R-CHOP-21 vs R-CHOP-14 for untreated stage III and IV B-cell non-Hodgkin's lymphoma: a report from Iran. Asian Pac J Cancer Prev 2016;17:1513-7.
18. Li X, Huang H, Xu B, et al. Dose-dense rituximab-CHOP versus standard rituximab-CHOP in newly diagnosed

Chinese patients with diffuse large B-cell lymphoma: a randomized, multicenter, open-label phase 3 trial. Cancer Res Treat 2019;51:919-32.

19. Knauf W, Abenhardt W, Mohm J, et al. Similar effectiveness of R-CHOP-14 and -21 in diffuse large B-cell lymphoma-data from the prospective German Tumour Registry Lymphatic Neoplasms. Eur J Haematol 2019;103:460-71.

20. Wästerlid T, Hartman L, Székely E, et al. Impact on survival of addition of etoposide to primary chemotherapy in diffuse large B-cell lymphoma: a Swedish Lymphoma Registry study. Hematol Oncol 2017;35:151-7.

21. Gleeson M, Hawkes EA, Cunningham D, et al. Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) in the management of primary mediastinal B-cell lymphoma: a subgroup analysis of the UK NCRI R-CHOP 14 versus 21 trial. Br J Haematol 2016;175:668-72.

22. Vidal L, Shpilberg O, Gurion R, et al. CHOP-like-14 compared to CHOP-like-21 for patients with aggressive lymphoma--a meta-analysis of randomized controlled trials. Acta Oncol 2016;55:77-84.

23. Brusamolino E, Rusconi C, Montalbetti L, et al. Dose-dense R-CHOP-14 supported by pegfilgrastim in patients with diffuse large B-cell lymphoma: a phase II study of feasibility and toxicity. Haematologica 2006;91:496-502.

24. Kamel S, O'Connor S, Lee N, et al. High incidence of Pneumocystis jirovecii pneumonia in patients receiving biweekly rituximab and cyclophosphamide, adriamycin, vincristine, and prednisone. Leuk Lymphoma 2010;51:797-801.

25. Tadmor T, McLaughlin P, Polliack A. A resurgence of Pneumocystis in aggressive lymphoma treated with R-CHOP-14: the price of a dose-dense regimen? Leuk Lymphoma 2010;51:737-8.

26. Hernandez-Ilizaliturri FJ, Jupudy V, Ostberg J, et al. Neutrophils contribute to the biological antitumor activity of rituximab in a non-Hodgkin's lymphoma severe combined immunodeficiency mouse model. Clin Cancer Res 2003;9:5866-73.

27. Cartron G, Zhao-Yang L, Baudard M, et al. Granulocyte-macrophage colony-stimulating factor potentiates rituximab in patients with relapsed follicular lymphoma: results of a phase II study. J Clin Oncol 2008;26:2725-31.

28. Ohmachi K, Tobinai K, Kobayashi Y, et al. Phase III trial of CHOP-21 versus CHOP-14 for aggressive non-Hodgkin's lymphoma: final results of the Japan Clinical Oncology Group Study, JCOG 9809. Ann Oncol 2011;22:1382-91.

29. Itoh K, Ohtsu T, Fukuda H, et al. Randomized phase II study of biweekly CHOP and dose-escalated CHOP with prophylactic use of lenograstim (glycosylated G-CSF) in aggressive non-Hodgkin's lymphoma: Japan Clinical Oncology Group Study 9505. Ann Oncol 2002;13:1347-55.