RESEARCH ARTICLE

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

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Abstract

Background: A combination of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is one of the most effective front-line therapies to treat B-cell non-Hodgkin's lymphoma (NHL). The aim of this trial was to evaluate overall survival (OS), progression free survival (PFS) and toxicity of R-CHOP-14 compared to R-CHOP-21 in untreated stage III and IV B-cell NHL patients with Iranian ethnicity. Materials and Methods: In phase III trial, patients with previously untreated stage III and IV indolent and aggressive B-cell NHL were randomly assigned by using a minimization method to receive six to eight cycles of either R-CHOP-21 (administered every 21 days) or R-CHOP-14 (administered every 14 days with granulocyte colony-stimulating factor). Results: A total of 143 patients were randomly enrolled in our study (66 patients in R-CHOP-14 group and 77 patients in R-CHOP-21), between 2011 and 2014. The mean follow-up was 45 months at the time of treatment analysis. The 2-year and 5-year PFS rates for the R-CHOP-14 group were 83.6% vs 73.6% and for R-CHOP-21 group were 75% vs 54%. The 2-year and 5-year OS rates for R-CHOP-14 group were 98% vs 89% and for R-CHOP-21 group were 84.4% vs 67.5%. There was a significant correlation for PFS and OS in the two arms. There was no significant difference between adverse events with the two regimens. Conclusions: In our research improved survival was found with CHOP-14 as compared to CHOP-21. It is possible that drug metabolism in different races/ethnicities may be one important factor.

Keywords: Non-hodgkin's lymphoma - phase III trial - R-CHOP - overall survival - progression-free survival

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Introduction

Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen is a standard treatment for patients with diffuse large B-cell (DLBCL) non-Hodgkin's lymphoma (NHL), and its 5-year overall survival (OS) rate is 30%-40%. Rituximab is a chimeric monoclonal antibody directly against CD20-positive B cells, and has good effect on DLBCL-NHL (Lin et al., 2015). Combination of rituximab to CHOP (R-CHOP) is one of the most effective front-line therapies to treat B-cell NHL (Watanabe et al., 2011). The WHO classification of NHL included DLBCL, mantle cell lymphoma, follicular lymphoma, extranodal marginal zone lymphoma, Burkitt lymphoma, and B-cell lymphoma whose further types were unclassified (Kikuchi et al., 2015).

It was suggested that decreasing the treatment interval from three weeks (CHOP-21) to two weeks (CHOP-14) may improve survival and disease control of patients with aggressive lymphoma. R-CHOP-21 has remained the standard chemotherapy for aggressive non-Hodgkin's lymphoma (Vidal et al., 2015).

Granulocyte colony-stimulating factor (G-CSF) prevents myelotoxicity. Full dose CHOP with G-CSF, based on the leukocyte count oriented schedule, can be achieved with shortened intervals (Sawada et al., 1995; Itoh et al., 2002), an approach which will increase the quality of life for the patients by reducing the days of treatment as well as the cost of G-CSF (Sawada et al., 1995). Most patients with localized high-grade non-Hodgkin's lymphoma (NHL) can be cured with or without adjuvant radiotherapy. High-dose CHOP followed by locoregional radiotherapy is a feasible treatment for localized high-grade NHL (Bernard et al., 2005).

The aim of this trial is to evaluate OS, PFS and toxicity of R-CHOP-14 compared to R-CHOP-21 in untreated stage III and IV B-cell NHL patients with Iranian ethnicity.

Materials and Methods

Patients

This trial was approved by Kermanshah University

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Ethics Committee, Kermanshah, Iran. In phase III study, patients with previously untreated stage III and IV indolent and aggressive B-cell NHL according to the WHO classification (Jaffe et al., 2001) were randomly assigned by using a minimization method to receive six to eight cycles of either R-CHOP-21 (arm A) or R-CHOP-14 (arm B). A requirement for therapeutic intervention was not well defined and, consequently, some of the patients enrolled were treated immediately after diagnosis without watchful waiting. All patients gave written, informed consent before enrollment. R-CHOP-21 was intravenous cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m2, vincristine 1.4 mg/m^2 (maximum dose 2 mg), and rituximab (MabThera®) 375 mg/m^2 on day 1, and oral prednisolone 100 mg/m^2 on days 1-5, administered every 21 days. R-CHOP-14 was intravenous cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 2 mg, rituximab(MabThera®) 375 mg/m^2 on day 1, and oral prednisolone 100 mg on days 1-5, administered every 14 days. G-CSF has been used in a few patients as secondary prophylaxis (based on the patient's need) in R-CHOP-21 group and has been used in all patients for prevention in R-CHOP-14 group. 92.4% patients received adjuvant radiotherapy in R-CHOP-14 group and 93.5% patients in R-CHOP-21 group. Age, sex, type of NHL, subtype, Ki-67 index, organomegaly, lymphadenopathy and radiotherapy, anatomic sites of NHL and recurrence were checked in all patients. Patients with cardiovascular, renal, hepatic disease (hepatitis B or hepatitis C) and T-cell lymphoma and also patients with initial neutrophil count <1.5×10^9 per L and initial platelet count <100×10^9 per L were excluded. 61 patients (92.4%) were treated with radiotherapy after chemotherapy in R-CHOP-14 group and 72 patients (93.5%) were treated with radiotherapy after chemotherapy in R-CHOP-21 group.

Patients were assessed before treatment; at each attendance for treatment; and then after treatment every 3 months until 1 year, then every 6 months until 2 years, and thereafter every year. Details of treatment and adverse effects, performance status, and results of blood counts and other reports were checked by clinicians. An immunohistochemical panel was done for all available

Table 1. The baseline characteristics for the patients with Non-Hodgkin's Lymphoma based on R-CHOP regimens (n=143)

Variables	R-CHOP-14	R-CHOP-21	P-value
	N=66	N=77	
Age, year			
Mean	46.3	46	0.871**
Range	20-82	16-78	
≤60	17(25.7%)	16(20.7%)	0.306#
>60	49(74.3%)	61(79.3%)	
Sex			0.421#
Male	40(60.6%)	49(63.6%)	
Female	26(39.4%)	28(36.4%)0	
Type of NHL			0.139#
Nodal	42(63.6%)	41(53.2%)	
Extra nodal	24(36.4%)	36(46.8%)	
Subtype			0.158#
Aggressive	61(92.4%)	68(88.3%)	
Indolent	5(7.6%)	11(14.3%)	
Ki-67 expression*			
Mean	59	55	0.112**
<65%	28(42.4%)	23(29.9%)	0.269#
≥65%	38(57.6%)	54(70.1%)	
Organomegaly			0.267#
Yes	4(6.1%)	8(10.4%)	
No	62(93.9%)	69(89.6%)	
Lymphadenopathy			0.557#
Yes	37(56.1%)	43(55.8%)	
No	29(43.9%)	34(44.2%)	
Adjuvant radiotherapy			0.527#
Yes	61(92.4%)	72(93.5%)	
No	5(7.6%)	5(6.5%)	

* Ki67 index was tested for 51 patients in R-CHOP-14 group and 36 patients in R-CHOP-21 group, **T-test, #Chi-square test. R-CHOP-21=cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone every 21 days. R-CHOP-14=cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone every 14 days with granulocyte colony-stimulating factor

Table 2. Anatomic Sites for NHL and Recurrence Based Treatment Regimens

Variables	R-CHOP-14	R-CHOP-21
Anatomic site of NHL, n		
GIT	8	11
Bone	4	11
Axillary LN	4	9
Cervical LN	14	11
Inguinal LN	3	5
Mediastenal LN	11	5
Abdominal LN	2	4
Muscle	3	3
Others	17	18
Total	66	77
Anatomic site of recurrence, n		
GIT	0	2
Bone	1	4
Abdominal LN	2	3
Axillary LN	1	2
Inguinal LN	3	5
Cervical LN	3	2
Mediastenal LN	1	1
Supraclavicular LN	0	2
Gland	2	2
Brain	5	1
Lung	1	2
Total	19	25

NHL, non-Hodgkin's lymphoma; GIT, gastrointestinal stromal tumors; LN, lymph node. R-CHOP-21=cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone every 21 days. R-CHOP-14=cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone every 14 days with granulocyte colony-stimulating factor

specimens and included CD20, CD99, CD15, CD3, CD2, Ki-67 expression.

Statistical analysis

Outcomes for this study were OS, PFS and toxicity. Comparison between OS and PFS for two arms was checked by GraphPad Prism 5 software that the log-rank test was used to compare the Kaplan-Meier curves for OS and PFS. Chi-square test and T-test in SPSS software were used for to compare the differences in the benefits of R-CHOP-14 in different patients sub-grouped according to baseline variables. Also, Cox proportional hazard regression analysis was used to check the effects of various parameters on the primary analysis. P-value<0.05 was considered as statistically significant.

Results

Between 2011 and 2014 from two centers, 143 patients were randomly enrolled (66 patients in R-CHOP-14 group and 77 patients in R-CHOP-21). The baseline variables were balanced in the patients for two groups (Table 1). The mean dose received for each drug by treatment group was similar in the R-CHOP-21 and R-CHOP-14 groups. Table 2 shows sites of NHL and recurrence for the patients in two arms.

The mean follow-up was 45 months at the time of treatment analysis. The 2-year PFS rate for R-CHOP-14 group was 83.6% *vs*. 75% for R-CHOP-21 group and also the mean PFS was 24 months for R-CHOP-14 group *vs*. 19 months for R-CHOP-21 group that different was no significant(hazard ratio [HR] 0.53, 95% CI 0.22-1.30; p<0.1710) (Figure 1).

The 2-year OS rate (the mean OS) for R-CHOP-14 group and R-CHOP-21 was 98% (24 months) and 84.4% (19.5 months), respectively that different was significant (HR 0.19, 95% CI 0.04-0.60; p<0.0062). The 5-year PFS rate for R-CHOP-14 group was 73.8% *vs*. 54% for R-CHOP-21 group and also the mean PFS was 24 months for R-CHOP-14 group *vs*. 19 months for R-CHOP-21 group that there was a significant difference between arms (HR 0.51, 95% CI 0.29-0.89; p=0.0188). The 5-year OS rate (the mean OS) for R-CHOP-14 group and R-CHOP-21 was 98% (24 months) and 84.4% (19.5 months), respectively that there was no significant difference between arms (HR 0.33, 95% CI 0.16-0.68; p<0.0027).

A Cox proportional hazard regression analysis was used to assess the effects of various parameters on the primary analysis. These factors did not affect the point estimate of the treatment arms. (Table 3) There were no unfavorable predictors for PFS or OS (Table 4).

Table 5 shows comparison of adverse events for two arms. Although neutropenia and fever were higher in R-CHOP-14 group, but there was no significant different between adverse events in two regimens (P>0.05).

Table 3. Multivariate Survival Analysis Using Cox's Regression Model for Affecting of Variables on Progression Free Survival

Variables	P-value	HR*	95% CI
Treatment arm, R-CHOP-14 v R-CHOP-21	0.061	1.73	0.975-3.069
Age (years), > 60 v ≤60	0.873	1.05	0.576-1.916
Sex, male v female	0.692	0.908	0.562-1.466
Type, nodal v extra nodal	0.172	1.553	0.826-2.920
Subtype, aggressive v indolent	0.736	0.87	0.385-1.962
Ki-67 expression, <65% v ≥65%	0.657	1.127	0.665-1.907
Organomegaly, yes v no	0.383	1.561	0.574-4.248
Lymphadenopathy, yes v no	0.985	0.995	0.544-1.819
Adjuvant radiotherapy, yes v no	0.508	0.806	0.426-1.526

*HRs are presented as the risk of the right-side category (ie, right side of v in Parameter column) to the left-side category (ie, left side of v). Abbreviations: MFS, metastasis-free survival; HR, hazard ratio; NHL, non-Hodgkin's lymphoma. R-CHOP-21=cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone every 21 days. R-CHOP-14=cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone every 14 days with granulocyte colony-stimulating factor.

Table 4. Multivariate Survival Analysis Using Cox's Regression Model for Affecting of Variables on Overall Survival

Variables	P-value	HR*	95% CI
Treatment arm, R-CHOP-14 v R-CHOP-21	0.349	1.326	0.735-2.391
Age (years), > 60 v ≤ 60	0.875	0.955	0.537-1.699
Sex, male v female	0.263	0.756	0.463-1.233
Type, nodal v extra nodal	0.342	1.321	0.744-2.347
Subtype, aggressive v indolent	0.285	0.634	0.275-1.462
Ki-67 expression, <65% v ≥65%	0.704	0.907	0.549-1.500
Organomegaly, yes v no	0.321	1.66	0.610-4.516
Lymphadenopathy, yes v no	0.609	1.159	0.658-2.042
Adjuvant radiotherapy, yes v no	0.511	1.24	0.653-2.355

*HRs are presented as the risk of the right-side category (ie, right side of v in Parameter column) to the left-side category (ie, left side of v). Abbreviations: MFS, metastasis-free survival; HR, hazard ratio; NHL, non-Hodgkin's lymphoma. R-CHOP-21=cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone every 21 days. R-CHOP-14=cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone every 14 days with granulocyte colony-stimulating factor.

Table 5. Grade 3 or 4 Adverse Events for Treatment Regimens

Variables	R-CHOP-14	R-CHOP-21	P-value
Neutropenia (% grade 3, 4)	16(25.7%)	12(15.8%)	P>0.05
Anemia (% grade 3)	6(9.1%)	7(9.1%)	P>0.05
AST(% grade 3)	3(4.5%)	3(3.9%)	P>0.05
ALT(% grade 3)	3(4.5%)	4(5.2%)	P>0.05
Infection due to sepsis(% grade 4)	7(10.6%)	7(9.1%)	P>0.05
Fever (% grade 3, 4)	17(25.8%)	12(15.6%)	P>0.05
Thrombocytopenia (% grade 4)	8(12.1%)	9(11.7%)	P>0.05

Data are number (%), R-CHOP-21=cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone every 21 days. R-CHOP-14=cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone every 14 days with granulocyte colony-stimulating factor.

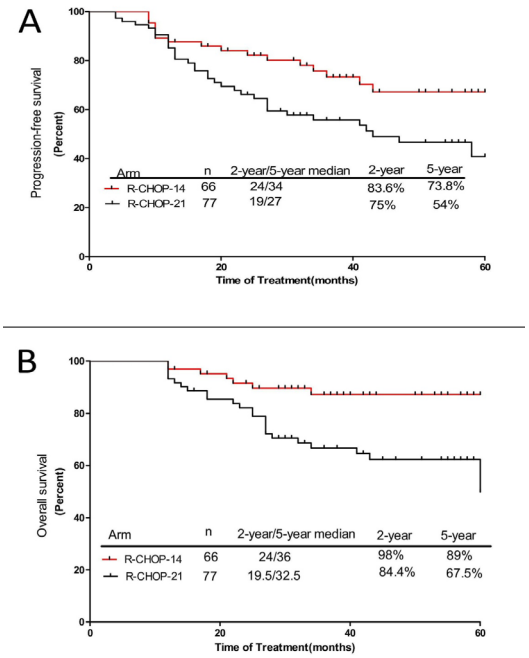

Figure 1. A) Progression-free Survival and (B) Overall Survival for Patients with B-cell non-Hodgkin's lymphoma. R-CHOP-14, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) administered every 2 weeks with granulocyte colony-stimulating factor; R-CHOP-21, R-CHOP administered every 3 weeks

Discussion

Immunochemotherapy with R-CHOP has become the standard of care for elderly patients with DLBCL (Delarue et al., 2013). In a study, 1080 patients were assigned to R-CHOP-21 or R-CHOP-14 with G-CSF that around half of cases received radiotherapy after chemotherapy in every arm, 2-year OS was more in R-CHOP-14 group than R-CHOP-21 group and also 2-year PFS was better in R-CHOP-14 than R-CHOP-21, but there was no significant correlation between OS and PFS in two arms. Grade 3 or 4 neutropenia was higher in the R-CHOP-21 group (60% v 31%), grade 3 or 4 thrombocytopenia was higher with R-CHOP-14 (9% v 5%) and infection (23% v 18%). Frequencies of non-hematological adverse events were similar in the R-CHOP-21 and R-CHOP-14 groups (Cunningham et al., 2013). Three-hundred patients in Watanabe's research (1) with untreated stages III to IV indolent B-cell lymphoma were randomly assigned to six cycles of R-CHOP-21 or R-CHOP-14 with G-CSF. There was no significant difference in PFS between arms (the median was 3.7 (R-CHOP-21) v 4.7 years (R-CHOP-14)). Also, PFS rate was 57% v 58% at 3 years and 41% v 43% at 6 years, respectively. Also, 6-year OS was 87% [R-CHOP-21] v 88% [R-CHOP-14]. There was no significant correlation between two groups for OS or PFS. Although grade 4 neutropenia and grade 3 infections were more frequent in the R-CHOP-21 group, R-CHOP was feasible in both arms (Watanabe et al., 2011). A Japanese research (Ohmachi et al., 2011), reported that eight-year OS and PFS rates were more in R-CHOP-21 compared to R-CHOP-14, but no substantial differences were observed in between two arms. The 3-year PFS was 58% for patients treated with R-CHOP-21 in a study matched that for the control patients in the Primary Rituximab and Maintenance (PRIMA) study (Salles et al., 2011). Hiddemann (2005) reported that grade 4 neutropenia and grade 3 infection occurred more often during R-CHOP-21 than during R-CHOP-14. Although a total 50 patients in R-CHOP-21 group (40%) received G-CSF. In 1829 adults receiving (± R)CHOP-14 or (± R)CHOP-21. Overall, 33% of patients were anemic during chemotherapy (Haioun et al., 2011). In patients aged 60-80 years, R-CHOP given every 14 days did not demonstrate survival advantage over R-CHOP 21 (Armitage,2015; Delarue et al., 2009), that 3-year event-free survival was 56% in the R-CHOP14 group and 60% in the R-CHOP21 group and the frequency of toxic side-effects was similar between regimens(Grade 3-4 neutropenia occurred in 74% patients allocated R-CHOP14 and 64% assigned R-CHOP21) (Delarue et al., 2013). In others hand, a research reported that recent phase III trials have demonstrated improved survival by modifying CHOP either through adding rituximab or shortening the time between cycles to 14 days (Halaas et al., 2005). Therefore, adding the immunotherapeutic agent rituximab to either CHOP has been shown to improve outcomes significantly, such that six cycles of R-CHOP plus two cycles of rituximab are as effective as eight cycles of R-CHOP, and R-CHOP-21 appears to be at least as effective as the more dose-intense R-CHOP-14 (Gisselbrecht, 2011). Six courses of R-CHOP 21 with radiotherapy to the sites of previous bulky disease was shown to be effective in this group of patients (Pfreundschuh et al., 2006). In this trial, OS and PFS were better in R-CHOP-14 group with G-CSF and two cycles rituximab compared to R-CHOP-21 and two cycles rituximab. Almost more patients were treatment with

adjuvant chemotherapy in two arms. There was significant correlation between them and also percentage of adverse events were almost similar in two arms and very lower than other studies that also Cunningham (2013) showed that R-CHOP-14 had efficacy in patients with DLBCL and Halaas (2005) reported that R-CHOP-14 was feasible and early results showed favorable efficacy compared to R-CHOP-21, similar to German group for CHOP regimen (Pfreundschuh et al., 2004). Our study was done in patients with Iranian ethnicity that Wang (2008) documented the impact of racial and ethnic disparities in access to treatment for DLBCL that could increase disparities in outcomes such as survival in the presence of R-CHOP. Also, Levi (2013) reported that affecting of treatment in NHL patients may be different in ethnic groups.

In conclusion, In our research that why the improved survival reported with CHOP-14 like German group is still uncertain, but it is possible that drug metabolism in different races/ethnicities be one important factor. Also, adverse events in two our arms were very lower than other studies.

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