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Original Article

Absolute lymphocyte count predicts response to rituximab-containing salvage treatment for relapsed/refractory B-cell non-Hodgkin's lymphoma with prior rituximab exposure

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Abstract

Background: Rituximab-containing salvage chemotherapy has shown promising efficacy in patients with relapsed/refractory B-cell non-Hodgkin's lymphoma (NHL). The aim of this study was to examine the efficacy of rituximab-containing treatment in patients with B-cell NHL who developed relapsed or refractory disease after prior rituximab use and to explore the predictive factors of response using this approach.
Methods: Patients with relapsed/refractory B-cell NHL who received rituximab-containing salvage treatment after failing first-line rituximab-combining chemotherapy were enrolled in this retrospective study. The characteristics of the patients were collected and analyzed. Logistic regression analysis was used for determining predictive factors of response to rituximab-containing salvage treatment.
Results: A total of 68 patients were enrolled in this study and the overall response rate to rituximab-containing salvage treatment was 61.7%. The median event-free survival and overall survival with rituximab-containing salvage treatment was 11.3 and 21.73 months, respectively. Results of a multivariate analysis showed high absolute lymphocyte count at the time of rituximab-containing salvage treatment [(ALC-R), ALC-R $\geq$ 1000/UL, $p = 0.003$)], which was the only independent factor predicting response to rituximab-containing salvage treatment.
Conclusion: Our study results show that for patients with relapsed/refractory B-cell NHL, rituximab-containing salvage treatment is feasible and generally tolerable. A high ALC-R value was significantly associated with a better response to this treatment.
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Keywords: absolute lymphocyte count; non-Hodgkin's lymphoma; response; rituximab; salvage treatment

1. Introduction

The combination of rituximab, a chimeric monoclonal anti-CD 20 antibody, with chemotherapeutics has significantly improved therapy for B-cell non-Hodgkin's lymphoma (NHL).[1] The addition of rituximab improves the overall response rate (ORR) and survival of patients with B-cell NHL.[2–5] Frontline rituximab combined with cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone (R-CHOP) or other rituximab-combination regimens have become the standard therapy for most patients with B-cell NHL.[6]

Despite this significant progress, more than half of the patients with B-cell NHL still develop relapse or progressive disease (PD).[7] Salvage therapy for these patients with prior rituximab exposure can be challenging, particularly for those with aggressive B-cell NHL.[8,9] One promising approach to

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improve the outcome of salvage therapy despite not yet being well established involves the re-introduction of rituximab to dose-intensive salvage regimens.[8,10–14] However, only limited data are available in published prospective trials, which address rituximab-containing salvage treatment in patients with relapsed/refractory B-cell NHL.[10,14] Davis et al demonstrated an ORR of 40% to rituximab monotherapy in patients with relapsed low-grade B-cell NHL.[10] In the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study, Gisselbrecht et al compared the efficacy of rituximab, ifosfamide, etoposide, and carboplatin (R-ICE) with rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) before autologous stem cell transplantation in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), and demonstrated an ORR of 51% to rituximab-containing salvage treatment in patients with prior rituximab exposure.[14] Previous retrospective trials have suggested that intensive chemotherapy combined with rituximab, as second-line treatment for relapsed/refractory DLBCL, was an effective method with a reported ORR of approximately 66%.[8,12]

However, the varied patient response to rituximab-containing salvage treatment reported in previously published data and the factors associated with patient response remain to be elucidated. To date, only the Grupo Español de Linfomas/Trasplante de Médula Osea (GEL/TAMO) study[8] and the CORAL study[14] have suggested several factors including a high age-adjusted International Prognostic Index (IPI) score, primary refractory disease, and short relapse-free duration, which may influence the response to rituximab-containing salvage treatment. However, the conclusions they reached are limited in their application to patients with DLBCL receiving certain rituximab-containing regimens (R-ICE, R-DHAP, and rituximab, etoposide, methylprednisolone, cytarabine and cisplatin (R-ESHAP)). For patients with relapsed/refractory B-cell NHL, other than DLBCL, only limited are data available on the significant factors that predict response to rituximab-containing salvage treatment. Therefore, the aim of this study was to re-examine its efficacy and to explore the predictive factors of response to rituximab-containing salvage treatment in patients who previously received rituximab.

2. Methods

2.1. Patients

We first identified patients with pathologically confirmed B-cell NHL that received first-line rituximab-combination regimens, during the period from January 2003 to January 2010. Among these patients, those who received rituximab-containing salvage treatment for relapsed/refractory disease were enrolled for the analysis. The demographic data and clinical characteristics of the study population were obtained from clinical chart review, lymphoma registry information, and physician records, as previously described.[15] The Institutional Review Board of Taipei Veterans General Hospital approved this retrospective study.

2.2. Rituximab for first-line treatment and salvage treatment and response criteria

The dose of rituximab, either for frontline combination treatment or in the salvage setting, was 375 mg/m^2 on day 1 of each treatment cycle. The choice of salvage regimens, with rituximab, was on an individualized basis at the discretion of the attending physicians. The response criteria used for a complete response (CR), partial response (PR), and PD were according to the International Workshop Criteria[16] and were prospectively determined during the course of treatment and retrospectively reviewed for this study. Patients who achieved a CR or PR to rituximab-containing chemotherapy were defined as responders.

2.3. Statistical methods

Event-free survival, with rituximab-containing salvage treatment (EFS-r), was calculated from the date of starting rituximab-containing salvage treatment to the date of disease progression, date of the next treatment, death, or the date of the last consultation. The overall survival after rituximab-containing salvage treatment (OS-r) was calculated from the date of starting rituximab-containing salvage treatment to the date of death or the date of the last consultation. EFS-r and OS-r were estimated using the Kaplan–Meier method and were compared by the logrank test. Categorical variables were compared by the Chi-square or Fisher exact tests as appropriate. The absolute lymphocyte count (ALC) was calculated as the total while cell counts multiplied by the percent lymphocyte, and lymphopenia was defined as an ALC $< 1000/\mu L$. The paired t test was used for comparing the ALC at the time of the diagnosis of lymphoma with the ALC at the time of rituximab-containing salvage treatment (ALC-R). The possible factors associated with response to rituximab-containing salvage treatment were evaluated using univariate and multivariate logistic regression models. Variables with $p < 0.10$ on the univariate analyses were used for the multivariate analyses. A p value < 0.05 was regarded as statistically significant on the two-tailed tests. All statistical analysis was computed using SPSS software (version 17.0; SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Patients' characteristics

From January 2003 to September 2010, a total of 315 patients with B-cell NHL were treated with first-line rituximab-containing treatments at the Taipei Veterans General Hospital. Among these patients, 68 (21.6%) received rituximab-containing salvage treatment for relapsed/refractory disease and were enrolled in this retrospective study. Table 1 lists the characteristics of these 68 patients at the time of rituximab-containing salvage treatment. Male gender, old age (>60 years of age), advanced stage disease (Ann Arbor stages III and IV), aggressive histological subtypes (DLBCL plus mantle

Table 1
Characteristics of patients at the time of rituximab-containing salvage treatment.

Characteristics	Number ($n = 68$)	%
Histology subtype		
Diffuse large B-cell lymphoma	52	76.5
Mantle cell lymphoma	4	5.9
Follicular lymphoma	12	17.6
Gender		
Male	48	70.6
Female	20	29.4
Age (y)		
Median (range)	63 (18–85)	—
Older than 60	37	54.4
Ann Arbor stage		
I–II	26	38.2
III–IV	42	61.8
Bone marrow involvement	4	5.9
No. of prior treatment lines		
1	62	91.2
>2	6[a]	8.8
Prior rituximab exposure, cycles		
Median (range)	5.5 (1–11)	—
Time between first-line treatment and rituximab retreatment (mo)		
Median (range)	6.1 (1–54)	—
Retreatment < 1 y	45	66.2
IPI-R[b]		
0–2	30	44.1
3–5	38	55.9
ALC-R[c]/μL		
Median (range)	959.5 (180–2982)	—
<1000	36	51.9%

[a] Four patients received two lines and two patients received three lines of treatment before starting rituximab-containing salvage treatment.
[b] International Prognostic Index score at the time of rituximab-containing salvage treatment.
[c] Absolute lymphocyte count at the time of rituximab-containing salvage treatment.

cell lymphoma), and high IPI scores at the time of rituximab-containing salvage treatment (IPI-R $\geq$ 2) were the predominant characteristics of the study group. There were only four (5.9%) patients received this salvage strategy at the third-line setting, and two (2.9%) as a fourth-line treatment. Most patients (91.2%) received rituximab-containing salvage treatment as a second-line treatment, whereas four (5.9%) patients received rituximab as a third-line, and two (2.9%) as a fourth-line treatment. Notably, the ALC-R was lower than at the time of lymphoma diagnosis (median 959.5/μL vs. 1323/μL, $p = 0.045$). In addition, the proportion of patients with lymphopenia was higher at the time of rituximab-containing treatment (51.1% vs. 33.8%, $p = 0.011$).

3.2. Rituximab-containing salvage treatment regimen

All study patients received rituximab in combination with chemotherapy in the salvage setting. The regimens used were the following: ESHAP ($n = 36$, 52.9%), ICE ($n = 12$, 17.6%), CHOP ($n = 11$, 16.2%), fludarabine ($n = 3$, 4.4%), and others ($n = 6$, 8.8%). The median cycles of rituximab used in the salvage setting was three (range: 1–16).

3.3. Peripheral blood stem cell transplantation

Fifteen patients (22.1%) received peripheral blood stem cell transplants (PBSCT) during the study period. Of the 15 patients, 12 received autologous PBSCT following rituximab-containing salvage treatment; eight (66.7%) achieved a CR and were considered to have a long-term disease-free status at the last follow-up, whereas the remaining four (33.3%) patients had either progression of the disease or severe sepsis after PBSCT. The other three patients who received rituximab-containing salvage treatment ultimately failed salvage PBSCT for relapsed disease (one relapsed after autologous PBSCT and two after allogeneic PBSCT). One of these three patients survived after rituximab-containing salvage treatment.

3.4. Rituximab-containing salvage treatment response and safety

The ORR to rituximab-containing salvage treatment was 61.7%, which included 19 patients (27.9%) who achieved a CR, and 23 patients (33.8%) who achieved a PR.

Compared with patients with follicular lymphoma, patients with aggressive disease, including DLBCL and mantle cell lymphoma, had a slightly lower ORR to rituximab-containing salvage treatment (60.7% vs. 66.7%, $p = 0.24$). However, the difference observed in the ORR did not reach statistical significance. Furthermore the duration between the first and the second rituximab exposure (longer and shorter than 1 year) did not have a significant impact on ORR to the rituximab-containing salvage treatment (65.2% vs. 60.0%, $p = 0.32$).

The most commonly observed adverse event was febrile neutropenia, which occurred in 31 patients (45.6%) during the salvage treatment period, followed by re-activation of herpes zoster (14.7%).

3.5. Factors associated with response to rituximab-containing treatment

As shown in Table 2, a higher ALC-R (ALC $\geq$ 1000/μL), lower IPI (IPI-R $\leq$ 2), and less-intensive disease involvement (re-stage 1–2) at the time of rituximab-containing salvage treatment were univariate factors associated with a better response to re-treatment. The multivariate analysis showed that a higher ALC-R was the only independent predictive factor for response to rituximab-containing salvage treatment.

3.6. OS-r and EFS-r

The median EFS-r and OS-r values were 11.3 and 21.73 months, respectively (Fig. 1). Factors that predicted a better response to rituximab-containing salvage treatment were also found to be associated with better EFS. For patients with a lower ALC-R and high IPI-R, the EFS was significantly poorer ($p = 0.009$ for ALC-R and $p = 0.001$ for IPI-R, respectively).

Table 2
Factors predicting response to rituximab-containing salvage treatment.

Factor	ORR (%)	Univariate		Multivariate	
		Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Gender					
Male	60.4	0.82 (0.41−3.6)	0.72	—	—
Female	65.0	1		—	
Lymphoma subtype					
Indolent	66.7	2.09 (0.51−8.57)	0.30	—	—
Aggressive	60.7	1		—	
IPI-R					
0−2	76.7	3.29 (1.14−9.47)	0.028	1.92 (0.59−6.24)	0.28
3−5	50.0	1		1	
ALC-R, /μL					
≥1000	81.3	5.42 (1.80−16.35)	0.003	4.61 (1.44−14.73)	0.01
<1000	44.4	1		1	
Interval between first-line and salvage setting					
≥12 mo	65.2	1.25 (0.44−3.55)	0.674	—	—
<12 mo	60.0	1		—	
Prior rituximab dose					
≥5 cycles	63.6	1.17 (0.44−3.11)	0.76	—	—
<5 cycles	60.0	1		—	
Prior rituximab response					
CR/PR	62.1	1.09 (0.28−4.30)	0.90	—	—
PD	60.0	1		—	
Bone marrow involvement					
Yes	75.0	1.89 (0.18−19.29)	0.593	—	—
No	61.4	1		—	
Age at salvage treatment					
<60	68.0	1.64 (0.57−4.70)	0.356	—	—
≥60	56.4	1		—	
Stage at salvage treatment					
1−2	76.9	3.03 (1.01−9.06)	0.047	2.52 (0.76−8.43)	0.13
3−4	52.4	1		—	

ALC-R = absolute lymphocyte count at the time of rituximab-containing salvage treatment; CI = confidence interval; CR = complete response; IPI-R = International Prognostic Index score at the time of rituximab-containing salvage treatment; ORR = overall response rate; PR = partial response; PD = progressive disease.

4. Discussion

The goal of this study was to determine the efficacy of rituximab-containing salvage treatment for patients with relapsed/refractory B-cell NHL who received first-line rituximab combination therapy. The efficacy of rituximab-containing salvage treatment was shown by a considerable CR rate and a favorable ORR (61.7%) in the study patients. The response rate reported in this study was consistent with that reported in the literature from Western countries.[8,12,13] Moreover, the ALC-R was found to predict response to rituximab-containing salvage treatment. However, the varied response to rituximab re-treatment is likely multifactorial. A better understanding of the relationship between predictive factors and patient responses may help clinicians to more effectively undertake individualized patient decision-making with regard to rituximab re-treatment in patients with relapsed or refractory B-cell NHL.

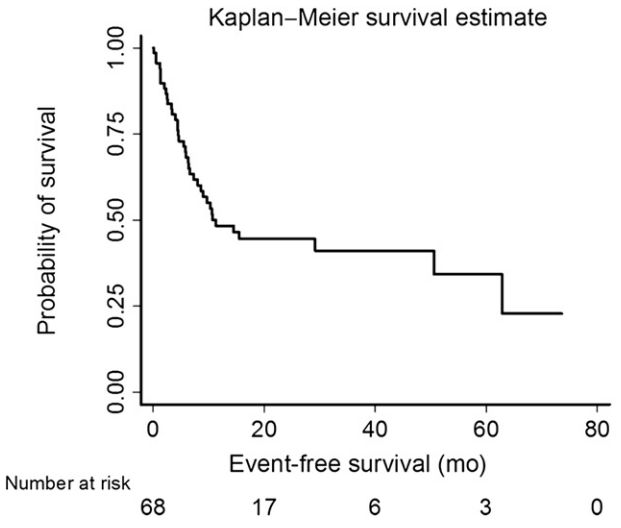

Fig. 1. Kaplan−Meier estimation of event-free survival from rituximab-containing salvage treatment was 11.3 months.

The ALC at the time of the diagnosis of lymphoma has been shown to be an important prognostic factor in patients with NHL. Lymphopenia at diagnosis has been shown to be associated with a poor prognosis in patients with NHL.[17−19] Patients with DLBCL who complete the standard first-line R-CHOP treatment and have lymphopenia have been reported to have a higher risk for relapse as well as a poor prognosis.[20,21] However, the prognostic value of ALC after salvage treatment has not yet been confirmed. The results of this study

support the predictive value of ALC in patients with relapse/refractory B-cell NHL who receive rituximab-containing salvage treatment after the first-line R-CHOP failure. The association between ALC and response to lymphoma therapy, particularly to rituximab treatment, might reflect the importance of an immune system response to lymphoma treatment. The ALC might be a surrogate marker of the host immune status,[17,19] which the presence of lymphopenia suggests could be a pre-existing immunosuppressed condition that facilitates malignant lymphoma cells to escape from immune surveillance.[20] In addition, natural killer cells (NK cells) might play a key role in antibody-dependent cellular cytotoxicity (ADCC), one of the major mechanisms thought to be involved in the efficacy of rituximab against lymphoma cells.[22] The depletion of NK cells, resulting from lymphopenia, may lead to ineffective ADCC, and may be associated with a poor disease outcome.[23,24] Moreover, lymphopenia may also result from lympholytic cytokines produced by lymphoma cells that might be consistent with a more aggressive behavior and thus more resistant to treatment.[18] In this study, the predictive and prognostic values of ALC-R in patients receiving rituximab-containing salvage treatment were demonstrated. Patients with a high ALC-R (ALC $>$ 1000/UL) not only had a better response to rituximab re-treatment (odds ratio $=$ 5.42, $p = 0.003$) but also had a better EFS. The findings suggest a fundamental role of host immunity in NHL and its response to treatment, particularly in the era of rituximab.

Another prognostic factor for patients with NHL was the IPI. IPI at diagnosis[25] and relapse[26,27] is a well-established scoring system used to predict survival in patients with lymphoma. In this study, the IPI-R was significantly associated with EFS after salvage treatment but not with the response to rituximab-containing salvage treatment. IPI scores may reflect tumor aggressiveness, patient response to disease, and tolerability of intensive therapy[25,28]; patients with a lower IPI may have less aggressive lymphoma, which may result in a better outcome.

Interestingly, the prior response to rituximab-containing treatment, which has been shown to influence the response to rituximab-containing salvage therapy in the GEL/TAMO study[8] and the CORAL study,[14] was not a predictive factor of response in this study. Possible explanations may be related to the relatively earlier shift to rituximab in the current study, as reflected by 55% of the patients receiving rituximab within a year, and the higher ORR (88.9%) to first-line rituximab treatment in the patient population enrolled in this study. Consistent with the results of previous reports,[8,12–14] rituximab re-treatment was generally well tolerated, with febrile neutropenia being the most common adverse event. This might have been related to the combined salvage chemotherapy.

This study was limited by its retrospective design, the heterogeneity of the salvage protocols, and a small patient study group. Moreover, the treatment effect might have mainly been due to the combination of rituximab and the salvage chemotherapy. Nevertheless, this study adds useful information to the limited available data on rituximab-containing salvage treatment in patients with relapsed/refractory B-cell NHL after first-line rituximab combination therapy.

In conclusion, rituximab-containing salvage therapy appears to be a reasonable approach in patients with relapsed/refractory B-cell NHL. A higher ALC-R may predict patient response to this treatment approach. These findings warrant further prospective studies on rituximab-containing salvage therapy in patients with relapsed/refractory B-cell NHL.

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