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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.

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