Original Article
Rituximab therapy and increased risk of side effects in patients with relapsed lymphomas: a meta-analysis

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Abstract: Follicular lymphomas (FLs) and diffuse large B-cell lymphomas (DLBCLs) are two frequent types of lymphomas. Controversial results exist about whether rituximab (R) induction therapy or R maintenance therapy is associated with increased risk of side effects. Literature retrieval was performed in three databases up to July, 2015 by two independent investigators basing on predefined strategies. Quality of the included studies was evaluated by the Cochrane bias risk assessment tool. Risk ratio (RR) with corresponding 95% confidence interval (CI) was used as the effect size to evaluate the side effects in a fixed- or randomized-effects model. Ten eligible studies were included in this meta-analysis, and majority of them are high-qualified. As a result, the combination of R with other drugs obviously increased the risk of any grade ≥ 3 adverse event (AE) (R vs. R + drug: RR = 0.52; 95% CI: 0.38, 0.70; \(P < 0.01\)) and any serious AE (R vs. R + drug: RR = 0.65; 95% CI: 0.48, 0.90; \(P = 0.009\)), while the maintenance therapy with R attained a significantly higher risk of Grade III/IV side effects (RR = 1.69; 95% CI: 1.25, 2.30; \(P < 0.01\)) and infections of grade 3/4 (RR = 2.66; 95% CI: 1.20, 5.93; \(P = 0.02\)) than the observation group. R therapy could highly increase the risk of several side effects for the management of relapsed FLs and DLBCLs. It should be cautious when administrate this regimen for the relapsed patients.

Keywords: Follicular lymphomas, diffuse large B-cell lymphomas, relapse, rituximab, infections, meta-analysis

Introduction

Follicular lymphomas (FLs) is one of the most common types of non-Hodgkin lymphomas (NHLs) in adults, characterized by a response to initial treatment, and then relapses [1]. Diffuse large B-cell lymphomas (DLBCLs) is another frequent type of NHL that belongs to the aggressive lymphomas [2]. Reportedly, the 3-year survival rate of DLBCL is about 60% [3]. Additionally, only less than 50% DLBCL patients could be cured by anthracycline-based chemotherapy [4]. The high recurrent rate [5, 6] might be the causative factor.

The application of rituximab (R) into the management of lymphomas of the B-cell lineage has a profound influence on the treatment of these diseases. Combination of R with other chemotherapy is reported to achieve an improved outcome for the treatments of the two most common types of lymphoma, FL and DLBCL [7]. Currently, typical treatment for FL is the chemotherapy combined with the anti-CD20 monoclonal antibody rituximab (RTX) [8]; while the standard treatment for DLBCL is the R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), which contributes much to the improvement of survival rate [9]. Although these combination therapies have achieved several encouraging results, the beneficial value of adding R is not clearly defined in patients with relapsed diseases [10]. Moreover, several side effects after adding R or the maintenance R therapy have been reported [11, 12]. For instance, patients with lymphomas who are treated with R could achieve an increased incidence of infections [13]. However, there is not a consistent conclusion about whether combination therapies of R with other chemotherapy or the maintenance R therapy would increase the risk of hematologic side effects such as hematologic toxicity (Anemia, Neutropenia, and Thrombocytopenia), non-hematologic side effects such as non-hematologic toxicity (infection and pneumonia) and any grade ≥ 3 adverse event (AE) [12, 14].
Therefore, we retrieved the databases basing on predefined searching strategies and conducted this study using meta-analysis, which is statistically powerful for the evaluation of the indicators based on small samples [15], to comprehensively ascertain the adverse effects of adding R therapy on the treatment of relapsed lymphomas such as FLs and DLBCLs.

Materials and methods

Literature retrieval

Literature retrieval was performed in the databases including PubMed, Embase and Cochrane library to search the relevant randomized controlled trials (RCTs), with the key searching terms of “rituximab” AND “lymphoma” AND “relapse” AND “randomized controlled trail”. The searching date was set as before July, 2015.

Study selection

Two investigators independently retrieved the databases basing on the predefined criteria. A discussion with a third investigator was required when disagreements appeared.

The inclusions were: (1) the study was a RCT treating with R in patients with relapsed lymphoma; (2) the induction therapy or the maintenance therapy was concerned in the study; (3) the side effects on the patient after R treatment was considered as the outcomes in the study; (4) for the duplicate publications basing on one data set, we only included the one with the most complete information and high quality; (5) the study should be an English publication.

The exclusion criteria were: (1) the study was a letter, conference abstract or reviewer; (2) the study was with low-quality that did not elaborate the surgical procedure.

Quality assessment and data extraction

The quality assessment and the data extraction were also conducted by two independent investigators. Likewise, the disagreement was resolved through discussion. The required information was abstracted, including the authors’ information, publication time, country, the case inclusion time, follow-up time, lymphoma types, drug administration, case number, mean age of all the cases and the side effects with the treatment. The Cochrane bias risk assessment tool was used to evaluate the qualities of the included studies [16].

Statistical analysis

As the side effects were all dichotomous variables, risk ratio (RR) with the corresponding 95% confidence interval (CI) was used as the effect size to evaluate the side effects. Cochran-based Q statistical and I² test were applied to determine the heterogeneity across studies by Stata 12.0 (STATA, College Station, TX, USA). Significant heterogeneity was indicated when \( P < 0.05 \) or \( I^2 > 50\% \) [17], and anarandomized-effects model was selected to calculate the pooled results; while, a fixed-effects model was used if there lacked significant heterogeneity (\( P > 0.05 \) or \( I^2 < 50\% \)). RevMan 5.3 (Cochrane Collaboration, http://ims.cochrane.org/revman) was utilized to calculate the pooled results. Publication bias was evaluated by Egger’s test, and a \( P < 0.05 \) indicates significant publication bias [18].

Sensitive analysis

To investigate whether the combined result would be affected by a specific study, we conducted the sensitive analysis by comparing the pooled results before and after removing a single study at one time using Stata 12.0 (STATA, College Station, TX, USA). A reverse result indicated an instable result of the meta-analysis.

Results

Eligible studies in the meta-analysis

As a result, a set of 729 studies (165 in PubMed; 429 in Embase and 135 in Cochrane library) were selected with the preliminary retrieval. Then after abstract reading, 37 studies were remained and subjected to the full text reading, by which a total of 27 studies were excluded (18 were non-relapsed lymphoma, 5 were irrelevant with R, 2 were duplicate publications, 1 did not contain the side effects of the outcomes and 1 was non-RCT). Finally, 10 [7, 12, 14, 19-25] eligible studies were included in our meta-analysis. The detailed selection procedures are shown in Figure 1.

Characteristics of the included studies

As presented in Table 1, all the 10 studies in the meta-analysis were RCTs, and 7 [12, 14, 19, 22-25] of them reported the side effects of
Side effects of rituximab on relapsed lymphomas

induction therapy, consisting of 2128 cases (R group: 1058, R + drug group: 1070); while 4 studies [7, 20, 21, 23] examined the side effects of the maintenance therapy involving 889 cases (R group: 442, observation group: 447). Lymphoma type in three studies [19, 21, 23] was DLBCL, while in the remaining ones was FL. Based on the Cochrane evaluation system, all the indicators presented a low bias risk, except “blinding of participants and personnel”, which showed a relative higher bias risk, (Figure 2), and the result suggested a relatively high quality of the included studies.

Outcomes

Comparison of side effects of the induction therapy in R and R + drug groups: For the induction therapy, side effect indicators included the hematologic side effects (hematologic toxicity: anemia, neutropenia and thrombocytopenia); the non-hematologic side effects (non-hematologic toxicity: infection and pneumonia); the overall side effects indexes (any grade ≥ 3 AE, any serious AE and any AE leading to treatment withdrawal) and the deaths within 30 days of last dose of the prescribed drug.

Significant heterogeneity was observed for the evaluation of three indicators (any AE leading to treatment withdrawal, neutropenia and infection) (P < 0.05 or I² > 50%, Figure 3A) and consequently a randomized-effects model was used, whereas all the remaining indicators applied the fixed-effects model due to the lack of obvious heterogeneity. The pooled results indicated that the combination of R with other drugs obviously increased the risk of any grade ≥ 3 AE (R vs. R + drug: RR = 0.52; 95% CI: 0.38, 0.70; P < 0.01) and any serious AE (R vs. R + drug: RR = 0.65; 95% CI: 0.48, 0.90; P = 0.009), compared with the R treatment (Figure 3B). There were no pronounced differences between R and the combination therapy in other indicators (P > 0.05, Figure 3C-I).

No obvious publication bias was detected across studies that evaluated outcomes such as anemia (P = 0.604), neutropenia (P = 0.186), thrombocytopenia (P = 0.221), infection (P = 0.638), pneumonia (P = 0.520) and any AE leading to treatment withdrawal (P = 0.861).

Comparison of side effects of the maintenance therapy in R and observation groups: For the maintenance therapy, the outcomes were Grade III/IV side effects, neutropenia, infections of grade 3/4 and non-hematologic toxicity of all types.

Due to the absence of significant heterogeneity (P > 0.05 and I² < 50%, Figure 4), the fixed-
### Table 1. Characteristics of the included studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study period</th>
<th>Country</th>
<th>Follow-up</th>
<th>Disease</th>
<th>Study period</th>
<th>Group</th>
<th>Dosing strategy</th>
<th>No. (M/F)</th>
<th>Age, year</th>
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<tbody>
<tr>
<td>Aviles, 2010</td>
<td>NA</td>
<td>Mexico</td>
<td>64.5 months</td>
<td>Relapsed or refractory DLBCL</td>
<td>Induction</td>
<td>R-ESHAP</td>
<td>375 mg/m² day 1 I.V., every cycle 6 cycles of reinduction chemotherapy ESHAP at conventional doses.</td>
<td>47 (20/17)</td>
<td>48.3 (48-61)</td>
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<td>53 (28/25)</td>
<td>51.8 (32-63)</td>
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<tr>
<td>Coiffier, 2011</td>
<td>2006.04-2008.08</td>
<td>29 countries</td>
<td>33.9 months</td>
<td>Relapsed grade 1 or 2 FL</td>
<td>Induction</td>
<td>R</td>
<td>5 cycles (35-day/cycle): R-375 mg/m² on days 1, 6, 15, and 22 of cycle 1, and on day 1 of cycles 2-5, I.V.</td>
<td>340 (137/203)</td>
<td>57 (21-84)</td>
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<td>336 (172/164)</td>
<td>57 (24-83)</td>
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<tr>
<td>Forstpointner, 2006</td>
<td>1998.11-2005.04</td>
<td>Germany</td>
<td>NA</td>
<td>Recurring or refractory FL</td>
<td>Maintenance</td>
<td>R</td>
<td>2 courses of R to be given 3 and 9 months</td>
<td>52 (22/30)</td>
<td>59 (41-78)</td>
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<td>53 (27/26)</td>
<td>61 (35-80)</td>
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<tr>
<td>Ghielmini, 2004</td>
<td>1998.01-2001.02</td>
<td>Switzerland</td>
<td>35 months</td>
<td>Refractory/re-lapsed FL</td>
<td>Maintenance</td>
<td>R</td>
<td>375 mg/m² every 2 months for 4 times</td>
<td>73 (33/40)</td>
<td>56 (31-79)</td>
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<td>78 (29/49)</td>
<td>57 (28-81)</td>
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<td>Gisselbrecht, 2012</td>
<td>NA</td>
<td>USA</td>
<td>44 months</td>
<td>Relapsed CD20+ DLBCL</td>
<td>Maintenance</td>
<td>R</td>
<td>375 mg/m²/8 weekly/12 months</td>
<td>122 (76/46)</td>
<td>54 (19-65)</td>
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<td>120 (83/37)</td>
<td>54 (19-65)</td>
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<tr>
<td>Glass, 2014</td>
<td>2004.06-2009.03</td>
<td>Germany</td>
<td>4.5 years</td>
<td>Aggressive B-cell or T-cell lymphoma</td>
<td>Induction</td>
<td>R-drug</td>
<td>fludarabine (125 mg/m²), busulfan (12 mg/kg oral or 9.6 mg/kg I.V.), and cyclophosphamide (120 mg/kg)</td>
<td>42 (33/9)</td>
<td>47 (38-54)</td>
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<td>42 (25/17)</td>
<td>49.5 (43-57)</td>
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<tr>
<td>Habermann, 2006</td>
<td>1998.02-2001.07</td>
<td>USA</td>
<td>3.5 years</td>
<td>Relapsed DLBCL</td>
<td>Induction</td>
<td>R-CHOP</td>
<td>375 mg/m² and 3 days before cycle 1 and 2 days before cycles 3, 5 CHOP Administered in the standard dosage</td>
<td>267 (52/215)</td>
<td>69 (60-92)</td>
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<td>279 (48/231)</td>
<td>70 (60-90)</td>
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<td>174</td>
<td>NA</td>
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<tr>
<td>Hainsworth, 2014</td>
<td>2005.08-2012.03</td>
<td>USA</td>
<td>34 months</td>
<td>Relapsed FL</td>
<td>Induction</td>
<td>R</td>
<td>375 mg/m² I.V. weekly for 4 weeks</td>
<td>31 (18/13)</td>
<td>65 (47-80)</td>
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<td>29 (13/16)</td>
<td>68 (45-91)</td>
</tr>
<tr>
<td>van Oers MH, 2006</td>
<td>1998.11-2004.04</td>
<td>Canada, Australia/New Zealand, Europe, and South Africa</td>
<td>7 years</td>
<td>Relapsed/resistant FL (CD20+ grade 1 to 3)</td>
<td>Induction</td>
<td>R-B</td>
<td>375 mg/m² I.V., day 1</td>
<td>234 (108/126)</td>
<td>54 (26-80)</td>
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<td>231 (118/113)</td>
<td>55 (27-78)</td>
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<tr>
<td>Zinzani, 2012</td>
<td>2006.04-2008.08</td>
<td>29 countries</td>
<td>35.2 months</td>
<td>High-risk, relapsed, rituximab-naïve or rituximab-sensitive FL</td>
<td>Induction</td>
<td>R</td>
<td>R: 375 mg/m², days 1, 8, 15, and 22, cycle 1, and day 1, cycles 2-5 R-B: B: 1.6 mg/m², days 1, 8, 15, and 22, all cycles</td>
<td>98 (42/56)</td>
<td>60 (21-84)</td>
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<td>103 (53/50)</td>
<td>61 (38-83)</td>
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Abbreviations: R: rituximab; ESHAP: etoposide, methylprednisolone, cytosine arabinoside, and platinum; B: bortezomib; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; DHAP: cisplatin/cytarabine-dexamethasone; O: observation; FL: follicular lymphoma; DLBCL: diffuse large B-cell lymphoma; I.V. intravenous; NA: not available.
Side effects of rituximab on relapsed lymphomas

A

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias

Figure 2. Quality assessments of the included studies. A: Bias risk of the identified studies; B: Sensitivity and specificity of the 10 studies, where “+” denotes Low risk of bias; “?” represents unclear risk of bias; and “-” denotes high risk of bias.

A

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias

B

van Oers et al. 2006
van Heereweg et al. 2006
Habermann et al. 2006
Gisselbrecht et al. 2012
Ghazinouri 2006
Wong et al. 2011
Ayres 2010

Likewise, there did not observe significant publication bias across studies regarding to outcomes such as Grade III/IV side effects (P = 0.250) and non-hematologic toxicity of all types (P = 0.634).

Sensitive analysis

The results suggested that for the induction therapy, after eliminating the study of Habermann et al. [23] or van Oers et al. [25], a reverse result was discovered for the indicator of neutropenia (data not shown). The same result was detected for the indicator thrombocytopenia after eliminating the study of Habermann et al. [23] (data not shown). These all suggested instable results on the two indicators; hence more RCTs with large scaled samples are needed to provide a more exact evaluation on the indicator of neutropenia and thrombocytopenia. Nevertheless, in other indicators, any reverse result was not observed.

Discussion

Relapsed lymphoma is the major cause for poor survival rate after chemotherapy treat-
Side effects of rituximab on relapsed lymphomas

A

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>R</th>
<th>R+drug</th>
<th>Risk Ratio</th>
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<td>R</td>
<td>50</td>
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<th>Study or Subgroup</th>
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<th>R+drug</th>
<th>Risk Ratio</th>
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<th>Risk Ratio</th>
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<td>R</td>
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<th>Risk Ratio</th>
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<td>R</td>
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Side effects of rituximab on relapsed lymphomas

Rituximab is considered as an active monotherapy in relapsed DLBCL patients [27]. A number of studies have confirmed the beneficial effect of adding R to the chemotherapy (such as R-CHOP) for elder patients with DLBCL, with a tolerable toxicity [28, 29]. However, controversial results are exhibited for the treatment of relapsed DLBCL. A phase 2 trial finds that only one patient (the total sample size is 23) exhibits mild reaction with the combination of R and lenalidomide [30]. Additionally, no pronounced differences are detected between the R + group (R-ESHAP [rituximab plus etoposide, cytarabine, cisplatinum and methylprednisolone], patient: 94) and the R-group (without R patient: 69) with regard to the hematological or infectious toxicity [31]. By contrast, serious AEs such as...
Side effects of rituximab on relapsed lymphomas

as infection, neutropenia and grade 3-4 non-hematologic toxicities are reported in another study with large sample size (396 patients) in the combination of R with other agents, such as R-ICE (rituximab, ifosfamide, etoposide, and carboplatin) and R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin) [32]. For the treatment of FL, most studies also confirm that addition of R in chemotherapies such as cyclophosphamide, CVP (vincristine and prednisone) could not induce any excessive hematological toxicity [33]. However, Coiffier et al. find a higher rate of serious AEs in the combination group (R plus bortezomib) than in R group (18% vs. 11%) for the treatment of FL, with a large sample size of 339 patients [12]. In accordance with this finding, a randomized phase 3 LYM3001 trial involving 201 patients also discovers that R plus bortezomib achieves an increased occurrence of grade ≥ 3 AEs (51% vs. 32%) and serious AEs (22% vs. 16%), compared with the monotherapy of R [14]. These instances collectively suggest that the sample size might be the major factor leading to the inconsistent results.

Maintenance therapy for FLs and DLBCLs are also widely applied. For the management of

Figure 4. Association of maintenance rituximab (R) and the risk of side effects in patients with relapsed lymphomas. A: Comparison of Grade III IV side effects between R plus drugs and R groups; B: Comparison of neutropenia between two groups; C: Comparison of infections of grade 3-4 between two groups; D: Comparison of non-hematologic toxicity between two groups. Squares represent the study-specific outcome estimates, and the size of the square represents the study-specific weight. Horizontal lines and figures in parentheses denote the 95% confidential interval (CI). Diamonds represent the overall outcomes with the corresponding 95% CI.
DLBCL, the R maintenance therapy after autologous stem-cell transplantation (ASCT) shows a slightly higher AE rate than the observation group (9% vs. 2.4%) [25]. The common concept is that R maintenance therapy will not increase the risk for infections [34]. However, several studies point out although no accumulated toxicities are detected in patients receiving R maintenance therapy, compared with observation regimen for low-grade lymphomas, B-cells are depleted during the maintenance period and prone to increase the patients’ risk for infections [35]. A meta-analysis incorporating 5 RCTs concludes that R maintenance therapy is tightly associated with the increased risk of infection and neutropenia in patients with lymphoma [35]. Interestingly, our study also suggested that R maintenance therapy could remarkably increase the risk of side effects such as infections of grade 3/4.

Despite the obvious advantages of this meta-analysis, such as the high quality of majority of the included studies, we should note that there are several limitations. First, as indicated in the sensitive analysis, two indicators attained reverse results after eliminating a certain study, suggesting the instability of several combined results; second, substantial heterogeneity were exhibited among several studies, which might derive from different therapies before the application of R, different degree of the disease severity and different nursing care due to diverse living standard; and this consequently might distort the final determination; third, we did not conduct the subgroup analysis or the meta-regression analysis due to a small bunch of available studies. These collectively suggested that more RCTs with large samples are warranted to support our findings.

In conclusion, adding R to other chemotherapies or the maintenance R therapy could highly increase the risk of several side effects for the management of relapsed FLs and DLBCLs. Therefore it should be cautious when administrate this regimen for patients with relapsed DLBCL or FL.

Disclosure of conflict of interest

None.

References


Side effects of rituximab on relapsed lymphomas


therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005; 106: 3725-3732.


