Effect of addition of rituximab to salvage chemotherapy on outcome of patients with diffuse large B-cell lymphoma relapsing after an autologous stem-cell transplantation

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Background: We have investigated if rituximab-based salvage regimens improve response rates and survival of patients with diffuse large B-cell lymphoma (DLBCL) relapsing after an autologous stem-cell transplantation (ASCT).

Patients and methods: We have retrospectively analyzed 82 patients with DLBCL who received salvage therapy for relapse or progression after ASCT. Patients were divided into two groups, according to whether rituximab-based salvage regimens were given (n = 42, ’R’ group) or not (n = 40, ’R+’ group) after ASCT.

Results: Patients in the R+ group had better complete remission (CR) (55% versus 21.4%, P = 0.006) and overall response (OR) (75% versus 40.4%, P = 0.001) rates, and better 3-year event-free survival (EFS) (37% versus 9%, P = 0.002) and overall survival (OS) (50% versus 20%, P = 0.005) than patients in the R− group. Patients retreated with rituximab had better CR (42.9% versus 21.4%, P = 0.032) and OR (66.7% versus 40.4%, P = 0.019) rates, and better OS (36.2% versus 20% at 3 years, P = 0.05) and EFS (36.2% versus 9% at 3 years, P = 0.05) than patients who received chemotherapy alone at relapse after ASCT.

Conclusions: The addition of rituximab to salvage chemotherapy improves response rates and EFS in patients with relapsed DLBCL after ASCT. These patients may benefit from rituximab retreatment, although larger prospective studies are needed to confirm these results.

Key words: autologous stem-cell transplantation, diffuse large B-cell lymphoma, rituximab, salvage therapy

introduction

Autologous stem-cell transplantation (ASCT) has become the standard of care for patients with relapsed diffuse large B-cell lymphoma (DLBCL) [1]. Unfortunately, a significant proportion of these patients (35%–55%) still relapse or progress following ASCT [1–3]. Even though it is generally accepted that these patients have very limited therapeutic options [4–10], few studies have analyzed the prognostic factors in this population [6].

Several studies have shown that the rituximab-containing regimens improve response rates and progression-free survival (PFS) in patients with relapsed or refractory DLBCL [11, 12]. In contrast, the role of rituximab in further salvage treatment in CD20+ aggressive lymphomas that relapse after ASCT remains to be determined [5, 13–15]. Another question to be determined is the role of rituximab retreatment in aggressive B-cell lymphomas. In the majority of reports evaluating the efficacy of rituximab-based salvage regimens, patients have not been previously treated with rituximab, while at present, all...
patients with CD20+ DLBCL receive rituximab associated to first-line chemotherapy [16].

In this study, we analyzed data from 82 patients with DLBCL who received salvage treatment for progression or relapse after ASCT, with the following goals: (i) to evaluate the influence of rituximab-based salvage chemotherapy on response rates and survival, (ii) to analyze the effect of retreatment with rituximab-based regimens after ASCT and (iii) to analyze the influence of other prognostic factors on outcomes.

patients and methods

patients and salvage therapy

Twenty-eight Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea (GEL/TAMO) centers participated in this retrospective study. Investigators were required to report all consecutive patients who fulfilled the following inclusion criteria: (i) age between 18 and 70 years, (ii) diagnosis of relapsed or progressive DLBCL following ASCT, (iii) to have achieved at least a partial remission (PR) after ASCT and (iv) exposure to any antitumoral treatment with a curative purpose after post-transplant relapse. The study was approved by the Hospital Universitario Doctor Negrín ethical review board.

Salvage therapy at relapse or progression after ASCT was designed according to the treating physician choice. The patients who were treated with single-agent rituximab were excluded from the study.

Overall, data of 82 autografted DLBCL patients from July 1993 to July 2007 who experienced disease progression or relapse after ASCT were analyzed in this study. Patients were divided into two groups, according to whether rituximab-based salvage regimens were given (n = 42, ‘R+’ group) or not (n = 40, ‘R−’ group) after ASCT.

definitions and response criteria

Disease status at salvage therapy after ASCT was defined as ‘progressive disease’ if patients had not achieved complete remission (CR) after ASCT, ‘early relapse’ if CR duration after transplantation was <6 months and ‘late relapse’ if longer. Response to salvage therapy was assessed by conventional diagnostic methods, including computed tomography scanning ~28 days after the last cycle. Responses were classified according to the International Working Group criteria [17].

end point definitions and statistical analysis

End points were assessed on the date of the last patient contact. Analyses focused on response rates to salvage therapy, event-free survival (EFS) and overall survival (OS). EFS was calculated from the date of salvage treatment to the time of failure or death from any cause. OS was defined as the time from lymphoma relapse until last follow-up or death. Follow-up data were obtained up to July 2008.

Chi-square test statistics and nonparametric Mann–Whitney tests were used to compare qualitative and quantitative parameters, respectively, between the R+ and R− groups. For binary outcomes such as response rates, the differences between the two groups were estimated by using the chi-square test. Logistic regression analysis was used to adjust the potential effects of other prognostic factors. Survival times were estimated by the Kaplan–Meier method [18]. Differences in survival between the R+ and R− groups were analyzed by log-rank test. A multivariate Cox model was also used to adjust the potential effects of other prognostic factors with a possible impact upon these outcomes. At present, all patients with DLBCL receive rituximab combined with first-line chemotherapy; for this reason, analysis restricted to patients previously exposed to rituximab were also carried out, focusing in evaluating the efficacy of rituximab retreatment. All P values reported are two-sided and statistical significance is defined as P <0.05. The statistical analyses were computed with SPSS statistical software (SPSS, Inc., Chicago, IL).

results

patient characteristics

Patient characteristics at salvage therapy after ASCT are outlined in Table 1. Patient characteristics were quite well distributed between the R+ and R− groups with regard to the main prognostic factors. Regarding treatment received before the salvage therapy, no significant differences were observed between both groups in the number of treatment lines before ASCT, the conditioning regimens or the response rates to first ASCT (Table 1). Patients in the R− group were transplanted in an earlier period that those in the R+ group. More patients in the R+ group received peripheral blood as source of stem cells (100% versus 85.7%; P = 0.013), as compared with patients in the R− group (Table 1).

response to salvage therapy

Overall, 47 of 82 patients (57.3%) responded to rescue therapy, including 31 patients reaching CR (37.8%) and 14 (17%) PR, and 15 patients had stable disease (18.2%) and 20 (24.3%) progressed after the salvage therapy.

As shown in Table 2, rituximab-based salvage regimens resulted in a significantly higher CR (55% versus 21.4%, P = 0.006) and overall response (OR) (75% versus 40.4%, P = 0.001) rates than chemotherapy alone. Consequently, more patients in the R+ group underwent a second transplant after the salvage therapy (35% versus 14.2%, P = 0.013) (Table 2). As shown in Table 3, these differences in response rates were also significant after adjusting for all covariates which had an impact upon these outcomes.

survival analysis

Overall, the actuarial 3-year EFS and OS were 27% [95% confidence interval (CI) 19% to 35%] and 39% (95% CI 34% to 44%), respectively. Treatment with rituximab-based salvage regimens led to a significantly better EFS (37% versus 9% at 3 years, P = 0.002) and OS (50% versus 20% at 3 years, P = 0.005) than treatment with chemotherapy alone (Table 2; Figure 1A and B). The use of chemotherapy regimens without rituximab was an independent adverse prognostic factor for EFS (relative risk 1.9, 95% CI 1–4, P = 0.026) but not for OS (Table 4). Patients who underwent a second transplantation had a significantly better EFS (55.7% versus 21.8% at 3 years, P = 0.002) and OS (47.7% versus 31.1% at 3 years, P = 0.01) than those that received only salvage therapy. Eight of 11 (72.7%) patients who underwent an allogeneic transplant and 5 of 9 (55.6%) patients who received a second ASCT remain alive and disease free at a median follow-up of 14.2 months (range 5–52) and 49.2 months (range 4.7–121.8), respectively.

analysis of rituximab cohorts

Three cohorts of patients were identified according to the exposure or not to rituximab before the salvage therapy, as shown in Table 5. The best results in terms of CR and OR rates...
and 3-year EFS and OS were observed in the group of patients who were rituximab-naive and received rituximab-based salvage therapy (61.1%, 83.3%, 44.2% and 61.5%, respectively), followed by the group of patients retreated with rituximab-based salvage therapy (42.9%, 66.7%, 36.2% and 36.2%, respectively) (Table 5; Figure 1C and D).
Patients with DLBCL relapsing after ASCT have a poor outcome, with <20% of them surviving in the long term [4–10]. The addition of rituximab to chemotherapy regimens has been shown to significantly improve the CR rate and survival in patients with relapsed or refractory DLBCL [11, 12, 19, 20]. However, the role of rituximab-based salvage regimens after ASCT has been less analyzed. Some retrospective studies have shown that rituximab as single-agent [13, 14, 16, 21–24] or associated to chemotherapy [15] leads to acceptable results in term of response and survival in rituximab-naive patients with relapsed DLBCL following autologous transplantation. In a study of 14 patients with DLBCL treated with R-CHOP (rituximab plus a combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone) plus granulocyte colony-stimulating factor, the OR rate was 71%, resulting in 4-year PFS and OS rates of 43% and 58%, respectively [15]. No randomized studies have been reported comparing the efficacy of salvage chemotherapy alone or associated with rituximab for relapsed aggressive lymphomas after ASCT.

We have analyzed 82 DLBCL patients who received salvage therapy for relapse or progressive disease after ASCT to evaluate the efficacy of adding rituximab to salvage chemotherapy, as well as the influence of prior exposure to rituximab. In our analysis, patients receiving rituximab-based salvage regimens had significantly better response rates, which translate into better EFS and OS, as compared with patients treated with chemotherapy alone. These data are consistent with previously reported by Kewalramani et al. [5] in a series of 47 patients with chemosensitive relapsed or refractory lymphoma following ASCT and also with the results of a nationwide retrospective survey [6] that included 52 relapsed lymphoma patients after ASCT. However, both studies analyzed a heterogeneous series of patients with different lymphoma subtypes and rituximab was only used in a minority of patients (42% and 5.7%, respectively) [5, 6].

The response rates to salvage therapy in our study were superior to previously reported [4, 6]. Nevertheless, median survival in patients treated with salvage chemotherapy without rituximab was 4.7 months, consistent with previous reports [4, 6, 10]. Consequently, our better results are probably explained by the addition of rituximab to salvage chemotherapy.

In the rituximab era, an important question is the role of rituximab-based salvage therapy in patients previously treated with rituximab. In a previous study, our group reported that prior exposure to rituximab was an independent adverse prognostic factor for EFS and OS in patients with relapsed or progressive DLBCL treated with R-ESHAP (rituximab plus etoposide, cytarabine, cisplatinum and methylprednisolone)
Figure 1. Kaplan–Meier estimation of survival according to the type of salvage therapy after the transplant, (A) event-free survival and (B) overall survival, and according to prior exposure to rituximab, (C) event-free survival and (D) overall survival. R+ group, patients treated with rituximab-based salvage therapy; R− group, patients treated with salvage chemotherapy without rituximab; R-naive, rituximab-naive patients at the time of salvage therapy and R-exposed, patients previously exposed to rituximab.

Table 4. Prognostic factors for survival: univariate and multivariate analysis

<table>
<thead>
<tr>
<th>Patients</th>
<th>Overall survival</th>
<th>Event-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P*</td>
<td>P*</td>
</tr>
<tr>
<td>Hemoglobin level at relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 g/l</td>
<td>0.004</td>
<td>0.326</td>
</tr>
<tr>
<td>Age-adjusted IPI at relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>&lt;0.0001</td>
<td>0.042</td>
</tr>
<tr>
<td>Rituximab-based regimens at relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.002</td>
<td>0.242</td>
</tr>
<tr>
<td>SCT after salvage therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.002</td>
<td>0.683</td>
</tr>
<tr>
<td>Partial remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonresponse</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

*P value is for univariate analysis.

bP value is for multivariate analysis.

RR, relative risk; CI, confidence interval; IPI, International Prognostic Index; SCT, stem-cell transplantation.
before ASCT [19]. Preliminary results of the CORAL randomized trial comparing R-ICE (rituximab plus ifosfamide, carboplatin and etoposide) with R-DHAP (rituximab plus dexamethasone, cytarabine and cisplatin) in patients with relapsed or refractory DLBCL also indicate that exposure to rituximab before salvage therapy is associated with a worse outcome [20]. No reports have evaluated the role of retreatment with rituximab-based regimens in patients with relapsed or progressive DLBCL after ASCT. In our study, approximately half of the patients (48.7%) have received rituximab-based salvage regimens and 37.8% of these patients had previously been treated with rituximab-containing salvage regimens. The best results in terms of response rates and survival were observed in the group of patients who were rituximab-naive and received rituximab-based salvage therapy but, interestingly, patients retreated with rituximab had significantly better response rates and survival than patients who received salvage chemotherapy without rituximab, as shown in Table 5. The worst results in terms of CR and OR rates and 3-year EFS and OS were observed in the 10 rituximab-exposed patients who received salvage chemotherapy without rituximab (11%, 22%, 0% and 0%, respectively), suggesting that rituximab should not be excluded from the salvage regimen, even in patients previously exposed to this agent.

Regarding other relevant prognostic factors for survival, response to salvage therapy was one of the most powerful predictive factors, with the best results for patients achieving CR. The most significant adverse prognostic factors for response to salvage therapy in addition to the use of chemotherapy regimens without rituximab were the presence of an hemoglobin level <100 g/l or an age-adjusted International Prognostic Index (aaIPI) >1. Regarding the role of a second transplant after the salvage therapy, in our study, almost two-thirds of the patients receiving an allogeneic transplant and >50% of those who underwent a second ASCT are long-term survivors.

As in other multicenter retrospective studies, the results from this study need to be viewed in the outlook of its limitations. First, patients in the R− group were treated in an earlier period. This fact could explain in part why the R+ (later) group had many more allogeneic salvage transplants. But we must also take into account that the response rates were significantly higher in the R+ group as compared with the R− group, allowing more patients in the R+ group to be considered as candidates to a allogeneic transplant. Secondly, salvage therapy at relapse or progression after ASCT was designed according to the treating physician choice, and it is possible that the decision making not to use rituximab were based in the poor prognosis for these patients or in the refractoriness to prior rituximab-based regimens. However, as shown in Table 1, patient characteristics were quite well distributed between the R+ and R− groups with regard to the treatment lines received before the transplant and to the main prognostic factors, such as the aaIPI or the disease status at the time of salvage therapy. Moreover, in our study, all the patients were responders to previous rituximab-based chemotherapy, accordingly the election of type of chemotherapy and the use of rituximab at relapse was independent of the earlier response to immunochemotherapy. Thirdly, although rituximab-based regimens appear to offer a benefit over chemotherapy alone in patients previously exposed to rituximab, the retrospective character of this analysis and the small size of the patient population preclude drawing definitive conclusions regarding the role of rituximab retreatment in patients previously exposed to this mAb.

This is the first study that evaluates the efficacy of rituximab-containing salvage therapy in DLBCL patients relapsing after ASCT. Our results indicate that, until new therapies can be incorporated, rituximab should not be excluded from the salvage regimens in DLBCL patients who have been sensitive to ASCT and subsequently relapse. Although the retrospective multicenter design and the small size of the rituximab cohorts hamper the interpretation of the results, the difficulty of designing a prospective study within this setting, due to the widespread use of rituximab at present, increases the value of our findings.

Acknowledgements

MDC and JMVC conceived, designed and were responsible for analysis and interpretation, drafting the paper and final approval. JMVC wrote the article. EGB and MDC coordinated the study and contributed to writing the paper. AM contributed to analysis and interpretation of data and to write the paper. EC, AP, IH, RV, JR, MJP, MJRS, MJP and EMD were

Table 5. Outcomes of the patients according to rituximab cohorts

<table>
<thead>
<tr>
<th>Patients’ groups</th>
<th>Number of patients</th>
<th>Complete remission %</th>
<th>Overall response %</th>
<th>3-Year event-free survival % (95% CI)</th>
<th>3-Year overall survival % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R−/R+)/R−</td>
<td>42</td>
<td>21.4 0.032&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40.4 0.019&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9 (4–14) 0.05&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20 (14–26) 0.05&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>R−/R+</td>
<td>19</td>
<td>61.1 0.002&lt;sup&gt;b&lt;/sup&gt;</td>
<td>83.3 0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>44.2 (32–56) 0.0005&lt;sup&gt;b&lt;/sup&gt;</td>
<td>61.5 (50–73) 0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>R+/R+</td>
<td>21</td>
<td>42.9 0.375&lt;sup&gt;c&lt;/sup&gt;</td>
<td>66.7 0.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>36.2 (24–48) 0.21&lt;sup&gt;c&lt;/sup&gt;</td>
<td>36.2 (24–48) 0.3&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>P value for comparison between (R−/R+)/R− group and R+/R+ group.
<sup>b</sup>P value for comparison between (R−/R+)/R− group and R−/R+ group.
<sup>c</sup>P value for comparison between R−/R+ group and R+/R+ group.

CI, confidence interval; (R−/R+)/R− (rituximab-naive and rituximab-exposed patients) treated with salvage chemotherapy without rituximab after ASCT; R−/R+, rituximab-naive patients treated with rituximab-based salvage therapy after ASCT; R+/R+, patients previously exposed to rituximab retreated with rituximab-based salvage therapy after ASCT; ASCT, autologous stem-cell transplantation.
responsible for drafting and revising critically the manuscript. The order of the authors reflects their contribution to this study in their own centers. We are grateful to Manuel Ruiz and Tomás Serrano for their collaboration in carrying out this multicenter study and to Marco Gandarillas, data manager of the GEL/TAMO cooperative group, who contributed data for preparing the manuscript.

disclosure
None of the authors declare conflicts of interest. Redundant publications: no substantial overlapping with previous papers.

references

appendix
In addition to the authors, the following investigators (listed in alphabetical order) have participated in this study. Rafael Andreu (Hospital Doctor Peset, Valencia), Reyes Arranz (Hospital Universitario La Princesa, Madrid), Javier Briones (Hospital de la Santa Creu i Sant Pau, Barcelona), Juan N. Rodriguez (Hospital Juan Ramón Jiménez, Huelva), Emilia Pardal (Hospital San Pedro Alcántara, Cáceres), Soledad Durán (Hospital Universitario de Jaén), Francisco J. Peñalver (Hospital de Alcorcón, Madrid), José A. García-Marco (Hospital Universitario Puerta de Hierro, Madrid), Rodolfo Mataix (Hospital Universitario Doctor Negrín, Las Palmas de Gran Canaria), Germán Navarro (Hospital Carlos Haya, Malaga), Sara Nistal (Hospital de Getafe, Madrid), Jose A. Quezán (Hospital General de Segovia, Segovia), Antonio Salar (Hospital del Mar, Barcelona), Juan M. Sancho (Hospital German Trias I Pujol, Barcelona), Josep Sarrá (Institut Catalá d’Oncologia-Hospital Duran i Reynals, L’Hospitalet de Llobregat, Spain).