Rituximab and ESHAP as Second-line Therapy for Relapsed or Primary Refractory Diffuse Large B Cell Lymphoma: The Experience of a Single Center in Korea

Ock Bae Ko1, Shin Kim1, Dae Ho Lee1, Sang We Kim1, Jooryung Huh2 and Cheolwon Suh1

Departments of 1 Internal Medicine and 2 Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: The remission status prior to autologous stem cell transplantation (ASCT) influences the transplantation outcome in patients with relapsed or primary refractory diffuse large B cell lymphoma (DLBCL), a complete response (CR) generally being more favorable than a partial response (PR). This study investigated whether the addition of rituximab to the ESHAP chemotherapy regimen (R-ESHAP) could improve the CR rate in patients with relapsed or primary refractory DLBCL.

Methods: Retrospective analysis was performed with DLBCL registry data.

Results: Sixteen patients who had previously received one course of chemotherapy were administered R-ESHAP (median 3 cycles; range 1–6). The overall response rate of 75% (CR=50%; PR=25%), was significantly better than that achieved with ESHAP alone in 13 historical controls (31%; P=0.027). The toxicity was tolerable, with two febrile neutropenia episodes in 51 treatment cycles. Seven of the 12 responders to R-ESHAP underwent ASCT with BEAM. After a median follow-up of 17 months, the median survival endpoints have not been reached.

Conclusion: R-ESHAP appears to induce high CR rates in relapsed or refractory DLBCL with acceptable toxicity. (Korean J Hematol 2007;42:309-316.)

Key Words: Rituximab, ESHAP, Salvage chemotherapy, DLBCL

INTRODUCTION

Approximately half of patients with aggressive B cell non-Hodgkin’s lymphoma (NHL) treated with standard anthracycline-based chemotherapy regimens either fail to achieve a complete response (CR) or relapse after attaining CR.1,2 Recent advances in the treatment for diffuse large B-cell lymphoma (DLBCL), particularly the addition of rituximab (MabThera®) – a chimeric anti-CD20 immunoglobulin G1 monoclonal antibody – to CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) have significantly improved outcomes.3 However, a proportion of patients still relapse or are refractory to treatment.

Second-line chemotherapy for patients with aggressive NHL has historically involved platinum-containing regimens such as dexamethasone, cisplatin, and...
cytarabine (DHAP) and etoposide, methylprednisolone, high-dose cytarabine, and cisplatin (ESHAP). These salvage regimens are rarely curative and the prognosis for patients with relapsed aggressive NHL remains poor. Rituximab has been shown to have single-agent activity in patients with relapsed or refractory DLBCL, with an overall response (OR) rate of 31%. Rituximab is also believed to act in synergy with chemotherapy and adding rituximab to the ifosfamide–carboplatin–etoposide (ICE) chemotherapy regimen has been shown to induce very high CR rates (53%) in patients with relapsed or refractory DLBCL.

High-dose chemotherapy with autologous stem cell transplantation (ASCT) is a promising therapeutic option for patients with relapsed or primary refractory NHL providing that CR or partial response (PR) is attained with second-line salvage therapy. The outcome following ASCT appears to be significantly influenced by the remission status of the disease at the time of transplantation. Patients who undergo transplantation while in CR have better long-term progression-free survival (PFS) than patients who undergo transplantation while in PR. This observation may indicate that the response to second-line chemotherapy is a reflection of the chemosensitivity of the lymphoma. Alternatively, in chemosensitive patients, the efficacy of high-dose therapy may be dependent on tumor burden, such that improving the response to existing second-line regimens may improve the outcome of high-dose therapy.

The improved outcomes observed after ASCT in patients with refractory or relapsed DLBCL in CR have made the attainment of a CR the goal of salvage therapy. At present, however, there is no gold standard salvage treatment for patients with refractory or relapsed DLBCL and the question remains as to which is the ideal chemotherapy regimen to use.

ESHAP is an effective and dose-intense regimen capable of mobilizing peripheral blood progenitor cells with minimal toxicity. The OR rate for ESHAP in patients with relapsed or primary refractory DLBCL has been reported to be approximately 60–70%, with a CR rate of 20–40%. Given the improved response rates observed when combining rituximab with CHOP or ICE, the primary end-point of current study was to investigate whether the addition of rituximab to ESHAP (R-ESHAP) would increase the CR rate of transplant-eligible patients with relapsed or primary refractory DLBCL.

### MATERIALS AND METHODS

1. **Patients**

Patients aged ≥15 years who attended the Asan Medical Center between June 2002 and July 2005 and who had DLBCL according to the World Health Organization classification that had relapsed or was refractory to a single induction regimen were eligible for inclusion. Patients were required to have confirmation of CD20-positive DLBCL. All biopsy specimens were reviewed by the same pathologist (JH). All patients underwent pretreatment staging studies that included computed tomography (CT) of the chest, abdomen, and pelvis; [18F]-fluorodeoxyglucose positron emission tomography (PET); and a bilateral bone marrow aspiration smear and biopsies. Patients were required to have normal cardiac, renal, and hepatic functions. Patients were ineligible if they had central nervous system involvement; positive serologic test findings for HIV; active hepatitis B or C; previous cancer for which the disease-free duration was less than 5 years, excluding basal cell carcinoma, cutaneous squamous cell carcinoma, or carcinoma in situ of the cervix, for which they received curative treatment; or any other illness that would preclude the safe administration of R-ESHAP. The second-line age-adjusted International Prognostic Index (sAAIPI) score was determined for each patient prior to initiation of second-line therapy. The Institutional Review Board of Asan Medical Center approved this study and all patients gave written informed consent before enrollment.

2. **R-ESHAP treatment**

Rituximab (375mg/m²) was administered on Day 1 of each cycle according to standard prescribing guidelines following the administration of oral acetaminophen (650mg) and intravenous pheniramine...
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(45.5mg). The ESHAP regimen comprised etoposide (40mg/m², Days 1∼4), methylprednisolone (500mg, Days 1∼5), cytarabine (2g/m², Day 5), and cisplatin (25mg/m², Days 1∼4), using the original dosing schedule with modifications.5,11) Cycles were repeated every 4 weeks, provided that the absolute neutrophil count (ANC) was at least 1.5×10⁹/L and the platelet count was 75×10⁹/L. A maximum of 6 cycles of RESHAP was planned for patients unless a CR or PR was achieved after 2 cycles, in which case ASCT was offered in conjunction with a third cycle (see below).

3. Assessment of response and toxicity

Response was assessed 1 week before the third cycle of R-ESHAP by CT of the chest, abdomen, and pelvis and by PET. Bone marrow biopsies were repeated only if the results were abnormal before treatment. Response to R-ESHAP was assessed using the International Working Group criteria,14) taking into consideration the results of nuclear imaging studies: a CR was defined if nuclear imaging revealed no evidence of disease. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0).

4. Autologous stem cell transplantation

ASCT was offered to patients who achieved a CR or PR after 2 cycles of R-ESHAP. ASCT procedures were performed as previously described.15) Briefly, peripheral blood progenitor cells (PBPCs) were mobilized with the third cycle of R-ESHAP chemotherapy. All patients received daily subcutaneous lenograstim 10μg/kg starting on the day after completion of R-ESHAP chemotherapy and continuing until the last leukapheresis. Numbers of circulating hematopoietic progenitor cells (HPCs) were monitored daily using a Sysmex SE9000 hematology analyzer, and the results were used to determine the initiation date for PBPC collection.16) PBPC harvest was started on the day HPC levels reached ≥5/mm³, following the nadir. The target for PBPC collection was 5×10⁶ CD34-positive cells/kg.

The combination carmustine, etoposide, cytarabine, and melphalan (BEAM) regimen was used for high-dose chemotherapy,17) during which patients were cared for in a single room, with reverse isolation strictly maintained to prevent infectious complications. All patients received lenograstim (5μg/kg subcutaneously) once daily, beginning the day after stem cell infusion and continuing until the ANC exceeded 1.0×10⁹/L for 2 consecutive days.

5. Historical control group

The control group comprised patients with relapsed/primary refractory DLBCL who underwent standard salvage ESHAP chemotherapy at the Asan Medical Center between May 2001 and August 2005.

6. Follow up

Evaluation of lymphoma status was performed every 3 months for 2 years following completion of R-ESAHP or ESHAP treatment and then every 6 months for at least a further 3 years. Overall survival (OS) and PFS were measured from the initiation of R-ESHAP or ESHAP chemotherapy until last follow-up or death, and until the time of disease progression, respectively.

7. Statistical methods

All continuous variables were analyzed using the Mann–Whitney test. Proportions were compared using the Chi-squared test or Fisher’s exact test, as appropriate. Survival was estimated using the product–limit method according to Kaplan and Meier and were compared using the log-rank test. Statistical analysis was performed with SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL, USA) and significance levels were two-sided at the 5% level.

RESULTS

1. Patient characteristics

Sixteen patients were treated with R-ESHAP as second-line salvage chemotherapy and were available for analysis. Patient characteristics are shown in Table 1. All patients had been exposed to only one chemotherapy regimen prior to R-ESHAP. The patients who had received ESHAP and ICE were assessed by the
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>R-ESHAP (n=16)</th>
<th>ESHAP historical controls (n=13)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>47 (15~70)</td>
<td>57 (18~73)</td>
<td>NS</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (69)</td>
<td>7 (54)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>5 (31)</td>
<td>6 (46)</td>
<td></td>
</tr>
<tr>
<td>Previous chemotherapy, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP</td>
<td>8 (50)</td>
<td>12 (92)</td>
<td>NS</td>
</tr>
<tr>
<td>ESHAP</td>
<td>2 (13)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ICE</td>
<td>2 (13)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>R-CHOP</td>
<td>4 (25)</td>
<td>1 (8)</td>
<td></td>
</tr>
<tr>
<td>Disease status, n (%)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Relapsed</td>
<td>4 (25)</td>
<td>7 (54)</td>
<td></td>
</tr>
<tr>
<td>Primary refractory</td>
<td>12 (75)</td>
<td>6 (46)</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted IPI, n (%)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Low/low-intermediate</td>
<td>4 (25)</td>
<td>2 (15)</td>
<td></td>
</tr>
<tr>
<td>High-intermediate/high</td>
<td>12 (75)</td>
<td>11 (85)</td>
<td></td>
</tr>
<tr>
<td>Median chemotherapy cycles (range)</td>
<td>3 (1~6)</td>
<td>3 (1~6)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: NS, not significant; IPI, International Prognostic Index.

treating physician as having a significant tumor burden and a poor prognosis. Four patients had relapsed after an initial CR with previous chemotherapy and twelve patients were classified as being primary refractory after failing to respond to first-line chemotherapy.

There were no significant differences in patient characteristics between the R-ESHAP group and a historical control group of 13 patients with DLBCL who had been treated with ESHAP while in relapsed or primary refractory status (Table 1). The distribution of patients in the sAAIPI categories was similar in the two groups. There was no statistically significant difference in the median time between first- and second-line treatment for the RESHAP group (153.5 days; range, 21~2, 853 days) and the historical ESHAP group (197 days; range, 23~1, 180 days).

In total, 51 cycles of R-ESHAP were delivered and were included in the assessment of toxicity. The median number of cycles per patient was 3 (range, 1~6). Five patients declined ASCT and were administered ≥4 cycles of R-ESHAP.

2. Response to therapy

Eight of the 16 R-ESHAP-treated patients (50%) achieved a CR, with no evidence of disease detectable on the CT and PET-CT scans. Four patients (25%) attained a PR. The OR rate was 75% (Table 2). In contrast, only 4 of 13 historical control patients responded to ESHAP, resulting in an OR rate of 30.8% (CR 15.4%; PR 15.4%). Patients treated with R-ESHAP showed a marginally better response than those treated with ESHAP, when the response categories (CR, PR, stable disease and progressive disease) were analyzed together (P=0.077) or when CR rates alone were compared (P=0.051). However, the OR rate of R-ESHAP was statistically significantly better than that of ESHAP (75% [95% confidence interval (CI), 54~96%] vs 30.8% [95% CI, 6~56%]; P= 0.027).

Seven (5 CR and 2 PR) of the 12 responding patients underwent mobilization and collection of PBPCs with the third cycle of R-ESHAP. A median of 10.8×10^6 (range, 4.9~52.6×10^6) CD34-positive cells/kg was collected in a median of 3 leukapheresis sessions (range, 2~5 sessions). No patient failed to attain adequate collection of PBPCs with R-ESHAP. After high-dose chemotherapy with BEAM followed by ASCT, the median time to neutrophil engraftment
Fig. 1. Overall survival of patients treated with R-ESHAP or ESHAP.

Fig. 2. Progression-free survival of patients treated with R-ESHAP or ESHAP.

Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. (%) of cycles R-ESHAP (51 cycles)</th>
<th>ESHAP historical controls (36 cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>2 (4)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2 (4)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (6)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Documented infection</td>
<td>1 (2)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Azotemia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Toxicity was graded according to the National Cancer Institute common toxicity criteria, version 3.0.

DISCUSSION

The goal of second-line salvage chemotherapy for relapsed or primary refractory DLBCL is the induction of response, preferably CR. Achieving a response is clinically significant because, although

blood cell nadirs. Neutropenia (grade 3/4) occurred in 2 cycles and thrombocytopenia (grade 3–4) occurred in 3 cycles. Febrile neutropenia developed in 2 cycles and *Escherichia coli* bacteremia occurred in 1 cycle; these conditions resolved with appropriate antibiotic treatment, guided by sensitivity testing. There was no delay of planned chemotherapy schedules due to cytopenia or infection episodes. No other serious adverse events were reported. The toxicity of ESHAP in the historical control population was also minimal (Table 3).
ASCT is the most curative treatment modality for relapsed and primary refractory DLBCL, its benefits are generally restricted to patients with chemosensitive disease. It has been reported that transplantation is associated with better outcomes in patients with CR than in patients with PR. The CR rates of the commonly used second-line regimens ESHAP, DHAP, and ICE are approximately 20–40%, and no single regimen appears superior, although studies directly comparing these regimens have not been performed.

Rituximab, when used as a single-agent, has been shown to induce response in 31% of patients with relapsed or primary refractory DLBCL. However, it is believed to sensitize tumor cells to the effects of chemotherapy and when added to CHOP regimens, rituximab significantly increases the CR rate, compared with CHOP alone, in elderly patients with previously untreated DLBCL. In the present study, the addition of rituximab to ESHAP was associated with a significant increase in the CR rate compared with ESHAP alone (50% vs. 15%) in patients with relapsed or primary refractory DLBCL. As the R-ESHAP- and ESHAP-treated patients were similar with respect to disease status and sAAIPI, it is likely that despite the small sample size, the difference in outcome can be attributed to the treatment modality. We believe that the results reflect an effect of rituximab in potentiating chemotherapy sensitivity, thereby improving the quality of response. To our knowledge, only one other study has compared R-ESHAP with ESHAP as a salvage therapy for relapsed aggressive NHL. In that study patients (predominantly with DLBCL) treated with a median of 3 cycles of R-ESHAP achieved CR and OR rates of 28% and 56%, respectively, compared with 11% and 45%, respectively, for patients treated with ESHAP alone, although the differences in response between treatment regimens did not reach statistical significance. In addition, an early analysis of another small study has shown R-ESHAP to be well tolerated as a salvage therapy for patients with relapsed/refractory aggressive NHL. Recently, Kewalramani and colleagues reported that rituximab in combination with ICE (RICE) was particularly beneficial in patients with relapsed disease: the CR rate in patients treated with RICE was 65% compared with 34% in patients treated with ICE. In addition, the CR rate (53%) in patients with high-intermediate- or high-risk disease was the same as in patients with low-or low–intermediate-risk disease, suggesting that adding rituximab to ICE might overcome the unfavorable sAAIPI risk factors. The authors commented that the basis for this observation was unclear, and that these results should be confirmed in a larger cohort of patients. We were unable to evaluate these factors in detail in the current study due to the limitation of small sample size.

An important consideration with regard to improving the CR rate in patients with primary refractory or relapsed DLBCL is whether this leads to improved outcomes following ASCT. Although both OS and PFS were better with R-ESHAP than with ESHAP, the differences were not statistically significantly different, possibly due to the small sample size. Furthermore, the fact that only 1 patient in the ESHAP group underwent ASCT precluded analysis of the survival data.

R-ESHAP was well tolerated in this study, with negligible serious toxicity. Febrile neutropenia occurred in only 2 of 51 cycles administered and resolved with appropriate treatment. There were no episodes of azotemia in the current study. Our data also suggest that RESHAP is appropriate for the mobilization and collection of autologous PBPCs.

The current study was based on a retrospective comparative analysis of two relatively small samples; however, all diagnostic and therapeutic procedures were performed in a strictly controlled manner at a single institution, which allowed for a meaningful comparison. The results suggest that the addition of rituximab to ESHAP improves both response rates and response quality, especially CR rates. R-ESHAP is well tolerated and provides the basis for optimal mobilization and collection of autologous PBPCs in patients with relapsed or refractory DLBCL.
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REFERENCES


