Original Article

Outcome of Autologous Transplantation for Relapsed/Refractory Diffuse Large B-cell Lymphoma in Rituximab Era

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Background: *Autologous stem cell transplantation (ASCT) has been a standard treatment for chemo-sensitive relapsed/refractory diffuse large B-cell lymphoma (DLBCL) since pre-rituximab era. Many studies showed prior Rituximab (R) as frontline treatment was an adverse prognostic factor of post ASCT outcome. We studied survival outcome according to the R exposure in relapsed/refractory DLBCL patients who underwent ASCT.* ***Materials and Methods:*** *This is a single-center retrospective study. Thirty-nine relapsed/refractory DLBCL patients who underwent ASCT were analyzed. All patients received cyclophosphamide, BCNU and etoposide (CBV) as conditioning regimen followed by peripheral blood stem cells infusion.* ***Results:*** *The median age was 41 years (range, 17-56). Male: female ratio was 1.3:1. Thirty-nine patients were categorized into 3 groups; 15 patients in R-naïve group (R-/R-), 12 patients in R-salvage with no prior R group (R-/R+) and 12 patients in prior R as first-line treatment group (R+/R±). The 3-year progression free survival (PFS) of R-/R- vs R-/R+ vs R+/R± group was 33.3% vs 50% vs 51.9%. The 3-year overall survival (OS) was 46.7% vs 55.6% vs 51.4%, respectively. The complete remission (CR) before ASCT was the only significant positive factor for PFS. (HR = 0.373, 95%CI: 0.142-0.979, p = 0.045).* ***Conclusions:*** *Our study showed prior R before ASCT did not yield poorer outcome, and showed trend towards improved PFS, compared with R-naïve group. Patients who achieved CR before ASCT were significantly associated with better outcome post ASCT. Our results need to be confirmed in a large prospective study.*

Keywords : ● *Autologous stem cell transplantation* ● *Rituximab* ● *Diffuse large B-cell lymphoma*

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Introduction

The high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT) is a standard treatment for patients with relapsed chemo-sensitive diffuse large B cell lymphoma (DLBCL). These data came from Parma trial in the pre-rituximab era.[1] In rituximab era, a combination of rituximab with CHOP-like chemotherapy regimen is the first line treatment in newly diagnosed DLBCL patients. For relapsed DLBCL patients, rituximab combined with salvage chemotherapy shows benefits compared with the chemotherapy alone. The benefits of ASCT following rituximab retreatment may associate with the period of rituximab-exposed pre-transplantation. In addition, prospective and retrospective studies showed the significant difference of progression free survival (PFS) after ASCT in favor of rituximab

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combination with salvage chemotherapy.[2-4]

Although the highly effectiveness of R-CHOP in newly diagnose DLBCL patients, the question arises regarding the outcome of ASCT for patients who relapse after R-CHOP induction compared with those of patients who were rituximab naïve.[5-8] The patients who relapse after a R-containing regimen may have very aggressive diseases with poor survival after ASCT.

Furthermore, some key factors such as the ethnicity and the treatment protocol could influence the treatment outcome. Particularly, the effect of prior exposure to rituximab on the outcome of ASCT has never been reported in our group of patients. As a result, we designed this retrospective study to evaluate whether prior exposure to rituximab of the patients with relapsed or refractory DLBCL could affect the outcome of ASCT in our center.

Materials and Methods

The retrospective analytical study recruited relapsed/refractory DLBCL patients who underwent ASCT at King Chulalongkorn Memorial Hospital (KCMH) from 1997 to Dec 2012. The patients with no record of identifying CD20 positive large cell in tissue pathology and no survival outcome record or evidence of relapsed disease were not excluded from the study. The protocol was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

The total of 125 Non-Hodgkin's lymphoma (NHL) patients underwent hematopoietic stem cell transplantation (HSCT) at KCMH. Fifty three patients with T/NK cell NHL, small-cell indolent NHL, mantle cell lymphoma, Burkitt lymphoma and primary CNS lymphoma were excluded. The other 23 patients with diagnosis of NHL, diffuse large cell type for which the tissues were not available for review and further immunohistochemistry staining were also excluded.

Among the remaining 49 patients who have received HSCT, ten of them were excluded because of undergoing upfront ASCT in one and RIC-allogeneic stem cell transplant in nine. Only 39 relapsed/refractory DLBCL patients who underwent ASCT were eligible for analysis. Our protocols for ASCT included CBV (cyclophosphamide 100 mg/kg, BCNU 450 mg/m^2 and VP-16 60 mg/kg) as the conditioning regimen and peripheral blood stem cells (PBSC) as stem cell source.

The primary endpoint was the analysis of the progression free survival (PFS) advantage of prior rituximab-exposed group after ASCT. The secondary endpoint included the analysis of the overall survival (OS) and relapsed/progressive rate post ASCT, and the associated factors affecting transplant outcomes. The response was evaluated according to international workshop for NHL by Cheson et al.[9] The PFS was defined as the time from day 0 of ASCT to relapse or progression of disease or death in remission. The OS was the time from day 0 of ASCT until death from any cause or censored at last known date of survival. The relapsed disease was any new lesion or increase by equal or greater than 50% of previously involved sites from nadir after complete remission (CR). The refractory disease meant refractory to first-line treatment. The transplant-related mortality (TRM) was death without disease progression within 3 months post-ASCT. We censored patients at death or last follow-up.

The probabilities of PFS and OS were analyzed by Kaplan-Meier analysis. The survival outcome between risk factor was compared by log-rank test. If any factors had $p \leq 0.1$, the multivariate analysis by Cox-regression model would be done. All analysis was performed by using SPSS program.

Results

Thirty-nine relapsed/refractory DLBCL patients were divided into 3 groups; 15 patients in R-naïve group (R-/R-), 12 patients in R-salvage with no prior R group (R-/R+) and 12 patients in prior R as first-line

treatment group (R+/R±). Median age was 41 years old (range 17-56). The male to female ratio was 1.3:1. Most patients (87.2%) have undergone ASCT during 2002-2012 and received less than 3 regimens prior ASCT (74.3%). The baseline characteristics of relapsed/refractory patients, diseases, treatments and outcomes were summarized in Table1. The prior R group (R+/R±) contained more patients who achieved complete remission before ASCT and relapsed equal or greater than 12 months than other groups. The transplant-related mortality (TRM) was found in 3 (7.7%). Four patients (10.2%) were diagnosed with BCNU-induced pneumonitis. Fifteen patients (38.5%) relapsed after ASCT. Median time to relapse post ASCT were 10 months.

The 3-year PFS of R-salvage (R-/R+) and prior R (R+/R±) groups were 50% and 51.9% respectively compared with R-naïve (R-/R-), which was 33.3% (p = 0.182, p = 0.109). (Figure 1) The 3-year OS of R-salvage (R-/R+) and prior R (R+/R±) groups were 55.6 and 51.4% respectively compared with R-naïve (R-/R-) which was 46.7% (p = 0.407, p = 0.397). (Figure 2) There was not statistically significant in survival outcome between cohorts. We also evaluated the association between PFS and other factors such as R-exposure, remission duration, disease status before ASCT, number of prior chemotherapy, secondary age-adjusted international prognostic index at relapse (saaIPI), the years of undergoing ASCT, salvage regimen and BM involvement by univariate analysis. The univariate analysis of disease status (CR) before ASCT and R-exposure (front-line or salvage treatment) tended to impact PFS after ASCT (3-year PFS; CR vs. no CR: 58.8% vs. 32.7%, p = 0.051 and R-exposure vs. no R-exposure: 50.6% vs. 33.3%, p = 0.07). The multivariate analysis showed only CR before ASCT was statistically significant in better PFS. (HR = 0.373, 95%CI: 0.142-0.979, p = 0.045)

Table1. Baseline characteristics of relapsed/refractory DLBCL patients

	R-naïve (R-/R-) (n = 15)	**R-salvage (R-/R+) (n = 12)**	**Prior-R (R+/R) (n = 12)**
Age (years)	37 (26-53)	41.5 (20-56)	46 (17-56)
Male (%)	8 (53.3)	8 (66.7)	6 (50)
Any BM involvement	2 (13.3)	5 (41.7)	2 (16.7)
Year at ASCT			
- 1997-2001	5 (33.3)	0	0
- 2002-2012	10 (66.7)	12 (100)	12 (100)
Disease, n (%)			
- relapsed/refractory < 12 months	12 (80)	10 (83.3)	7 (58.3)
- relapsed ≥ 12 months			
Number of treatment	3 (20)	2 (16.7)	5 (41.7)
- < 3 regimens			
- ≥ 3 regimens	11 (73.3)	7 (58.3)	11 (91.7)
Disease status	4 (26.7)	5 (41.7)	1 (8.3)
- CR			
- PR	5 (33.3)	4 (33.3)	9 (75)
- SD and PD	8 (53.3)	7 (58.3)	3 (25)
saaIPI	2 (13.4)	1 (8.3)	0
- Low risk (0-1)	(n = 10, missing = 5)	(n = 6, missing = 6)	(n = 7, missing = 5)
- High risk (2-3)	8	4	6
	2	2	1

saaIPI = secondary age-adjusted international prognostic index at relapse

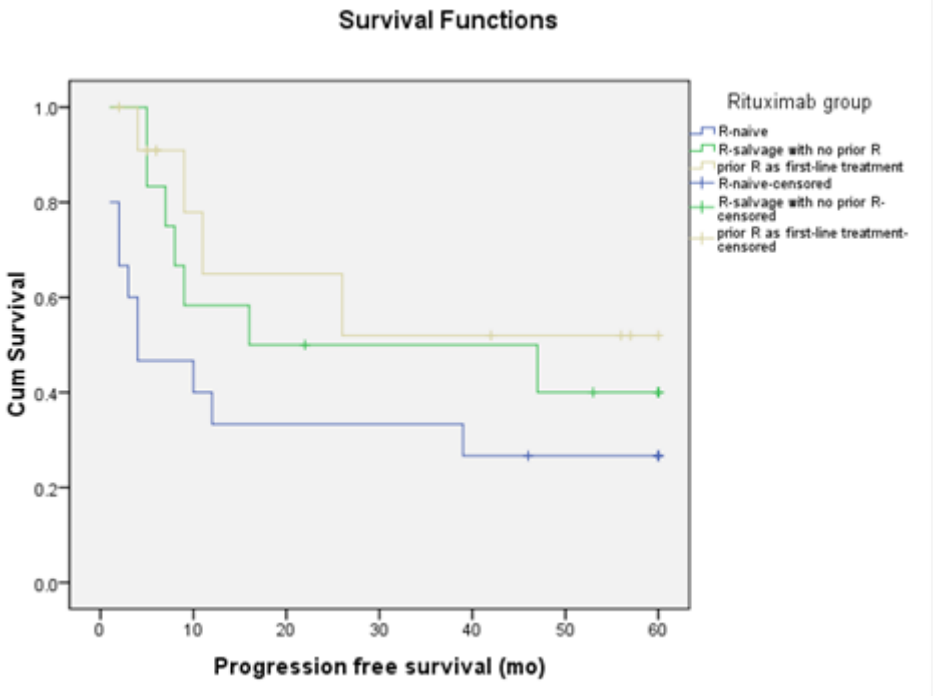

Figure 1. 3-year PFS in relapsed/refractory DLBCL according to period of R-exposed
The 3-year progression free survival (PFS) of R-/R- compared with R-/R+ and R+/R± group was 33.3% vs. 50% vs. 51.9% (p = 0.183, p = 0.109, respectively).

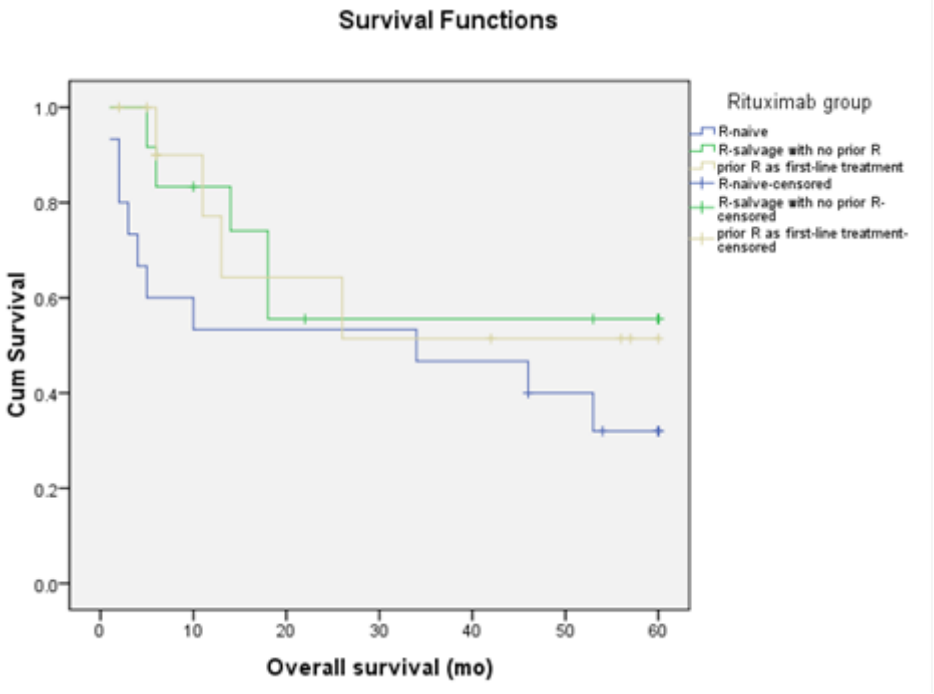

Figure 2. 3-year OS in relapsed/refractory DLBCL according to period of R-exposed
The 3-year overall survival (OS) of R-/R- compared with R-/R+ and R+/R± group was 46.7% vs. 55.6% vs. 51.4% (p = 0.407, p = 0.397, respectively).

Discussion

The present study revealed that prior R plus chemotherapy was not related to adverse outcome after ASCT for relapses. In addition, R-containing induction and/or salvage chemotherapy regimens may be associated with better PFS compared with R-naïve patients. However, the differences were not statistically significant. According to our results, rituximab could be given to all DLBCL as first and second lines therapy without affecting outcomes following high-dose therapy and ASCT. ASCT alone cannot replace the effects of Rituximab in the courses of relapsed/refractory DLBCL.

In relapsed/refractory DLBCL patients, as we know, the R-naïve cohort tended to show worse PFS than other groups. Although in our study, this difference was not statistically significant. This may be from a small number of patients. R-salvage chemotherapy was likely to show benefit to relapsed/refractory R-naïve patients who required ASCT from many previous studies. From our study, the efficacy of ASCT for relapsed/refractory patients with prior R as first-line treatment (R+/R±) had similar survival outcomes compared with R-salvage cohort (R-/R+). Due to a small number of patients, this may be biased by chance that the prior R group (R+/R±) had patients who were in complete remission and late relapsed more than other groups. According to our study, the CR before ASCT was positive predicting factor for post-transplant outcome. But this outcome should not mislead timing to go on transplantation in chemo-sensitive relapsed/refractory patients. The large number of patients and further prospective study are warranted.

Conclusions

Our study showed the outcome of prior R as first-line treatment group (R+/R±) was not inferior to R-naïve group and R-containing group showed a trend toward a better outcome. Patients who achieved CR before ASCT had better survival outcome post ASCT.

Acknowledgment: Cancer Run

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ผลการรักษาผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิด Diffuse Large B-cell lymphoma ที่กลับเป็นซ้ำด้วยการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดจากตนเองในยุค Rituximab

จันทิญา จันทร์สว่างภูวนะ ธานินทร์ อินทรกำธรชัย พลภัทร โรจน์นครินทร์ และ อุดมศักดิ์ บุญวรเศรษฐ์

ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย และโรงพยาบาลจุฬาลงกรณ์

บทคัดย่อ *การรักษาด้วยการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดจากตนเองเป็นการรักษามาตรฐานในผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิด diffuse large B-cell lymphoma (DLBCL) ที่กลับเป็นซ้ำและตอบสนองต่อยาเคมีบำบัดตั้งแต่ยุคก่อนมี Rituximab (R) มีหลายการศึกษาแสดงถึงการที่เคยได้รับ R ตั้งแต่เริ่มวินิจฉัยนับเป็นปัจจัยที่ส่งผลไม่ดีต่อผลการรักษาหลังปลูกถ่ายไขกระดูก การศึกษานี้เพื่อศึกษาถึงผลการรักษาหลังการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดจำแนกตามช่วงระยะเวลาของการได้ R ในผู้ป่วย DLBCL ที่กลับเป็นซ้ำ* ***วัสดุและวิธีการ*** *เป็นการศึกษาเชิงวิเคราะห์แบบย้อนหลังในสถาบันเดียว มีผู้ป่วย DLBCL ที่กลับเป็นซ้ำ 39 ราย ผู้ป่วยทุกรายได้รับยา cyclophosphamide, BCNU และ etoposide (CBV) เป็นยาเคมีบำบัดขนาดสูงก่อนการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดและใส่เซลล์ต้นกำเนิดเม็ดเลือดตนเองที่เก็บจากเลือด* ***ผลการศึกษา*** *ผู้ป่วยมีอายุเฉลี่ย 41 ปี (พิสัย 17-56 ปี) เพศชายต่อเพศหญิง 1.3:1 แบ่งผู้ป่วยเป็น 3 กลุ่ม กลุ่มแรกคือผู้ป่วยที่ไม่เคยได้รับ R มี 15 ราย กลุ่มที่ 2 คือผู้ป่วยที่ไม่ได้ R ตอนเริ่มวินิจฉัยแต่ได้รับ R ในการรักษาตอนกลับเป็นซ้ำ 12 ราย และกลุ่มที่ 3 คือผู้ป่วยที่ได้รับ R ในการรักษาตั้งแต่เริ่มวินิจฉัยและมีโรคกลับเป็นซ้ำ 12 ราย อัตราการรอดชีวิตโดยปราศจากโรคที่ 3 ปี คือร้อยละ 33.3 ร้อยละ 50 และร้อยละ 51.9 ตามลำดับ อัตราการรอดชีวิตที่ 3 ปี คือร้อยละ 46.7 ร้อยละ 55.6 และร้อยละ 51.4 ตามลำดับ การที่มีภาวะโรคสงบก่อนการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดเป็นปัจจัยเดียวที่มีผลต่อการเพิ่มอัตราการรอดชีวิตโดยปราศจากโรคอย่างมีนัยสำคัญทางสถิติ (HR = 0.373, 95%CI: 0.142-0.979, p = 0.045)* ***สรุป*** *ผู้ป่วยที่ได้รับ rituximab ในการรักษาตั้งแต่เริ่มวินิจฉัยและ/หรือโรคกลับเป็นซ้ำมีผลการรักษาภายหลังการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดจากตนเองไม่ได้ด้อยไปกว่าและมีแนวโน้มว่าอาจจะดีกว่ากลุ่มที่ไม่ได้รับ rituximab ผู้ป่วยที่มีภาวะโรคสงบก่อนการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดจากตนเองมีผลการรักษาที่ดีกว่ากลุ่มที่ยังมีโรคอยู่อย่างมีนัยสำคัญทางสถิติ ผลการศึกษานี้ยังต้องการการศึกษาขนาดใหญ่ต่อไป*

Keywords : ● *การปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือด* ● *Rituximab* ● *มะเร็งต่อมน้ำเหลือง*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2557;24:31-6.