Favorable event free-survival of high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation for higher risk diffuse large B-cell lymphoma in first complete remission

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Abstract

High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) has been applied to patients with diffuse large B-cell lymphoma (DLBCL); it is well established that ASCT shows significant survival benefits for chemosensitive relapse. However, half of relapsed patients are resistant to salvage chemotherapy, indicating that they are not suitable for ASCT. We retrospectively analyzed the clinical records of 47 patients with DLBCL classified as high or high-intermediate (higher) risk, according to the International Prognostic Index, who underwent upfront ASCT in first complete remission (CR1). Compared with 10 patients with similar characteristics who did not receive ASCT, event free survival at 5-year was significantly superior in ASCT group. Toxicity of ASCT was acceptable and therapy-related death was not observed. We therefore propose that upfront ASCT for higher risk DLBCL in CR1 might provide survival benefit, probably because the high-dose therapy removes minimally resided tumor.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent aggressive lymphoma in Japan. Although the majority of patients with DLBCL achieve complete remission (CR), about 40% of them die of the disease.[1] This suggests that minimal residual tumor, that is not detected in clinical CR state, induces relapse. International Prognostic Index (IPI or age-adjusted IPI) is considered the most valuable prognostic indicator of aggressive lymphoma.[2,3] Prognosis of patients classified as high or high-intermediate (higher) risk by IPI is extremely poor, mainly because of the high relapse rate. In order to improve the prognosis of higher risk patients, undetectable residual tumor in first CR (CR1) state should be removed to prohibit relapse.

High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) has been applied to patients with DLBCL in a number of cases.[4-14] Although it is well established that ASCT shows significant survival benefit for chemosensitive relapse of aggressive lymphoma,[15] half of relapsed patients are actually resistant to salvage chemotherapy, resulting in dropout from ASCT.[16] Haioun *et al.* reported that only 21 out of 59 patients who relapsed could receive salvage ASCT because of refractoriness to chemotherapy.[8] Other studies also showed extremely poor prognosis of relapsed aggressive lymphoma despite various salvage therapy,[17,18] indicating that most of relapsed patients are not suitable for ASCT.

We therefore conclude that the reduction of relapse rate of higher risk DLBCL in CR1 might lead to a better prognosis and we retrospectively analyze clinical outcome of upfront ASCT for those patients.

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Materials and Methods

Between April 1997 and March 2014, we treated 224 patients with DLBCL (age <70); among them, 102 were classified as high or high-intermediate risk by IPI (or age-adjusted IPI).[2,3] They were considered as candidates for upfront ASCT when CR, as per International Workshop Criteria,[19] or in combination with fluorine-18-fluorodeoxyglucose positron emission tomography,[20] was achieved within six courses of CHOP or rituximab-combined (R-)CHOP regimen.[21,22] Eligibility criteria were: ejection fraction of 50% (or more) on ultrasound cardiographs, serum creatinine less than 2 mg/dL, total bilirubin less than 3 mg/dL, absence of infections as human immunodeficiency virus or hepatitis B virus, and performance status by Eastern Cooperative Oncology Group 2 or less. Stem cells were harvested with mobilization therapy of high-dose etoposide (500 mg per square on days 1 to 3). After acquiring written informed consent, high-dose chemotherapy of MCVC regimen was administered. The regimen consisted of ranimustine 200 mg per square on day -8 and -3, carboplatine 300 mg per square on days -7 through -4, VP16 500 mg per square on days -6 to -4, and cyclophosphamide 50 mg per kg on days -3 and -2. On day 0, ASCT was carried out.

Regimen related toxicity (RRT) was recorded according to Common Terminology Criteria for Adverse Events v4.0. Re-growth of remitted lesion or appearance of new lesion was defined as relapse. Survival time was calculated from ASCT to death; any cause or relapse was regarded as event. Using SPSS version 19.0, survival rates were estimated by Kaplan-Meier method and compared by log-rank test.

Results

Seventy-five patients (73.5%) achieved CR1. Among these, relapse before ASCT occurred in 14 patients, severe icterus due to liver invasion was observed in one patient, performance status progressed into 3-4 in 3 patients, and 10 patients rejected ASCT. Consequently, only 47 patients in CR1 underwent ASCT. Their characteristics are summarized in Table 1. Histological subtypes were CD5-positive for DLBCL in 7 patients, germinal center B-cell (GCB) type in 7, and non-GCB type in 16. Unfortunately, the subtype of the remaining 17 patients was not determined. R was used in combination with induction, mobilization, and high-dose therapy in 19 patients; 0.7-27.6×10^6/kg of CD34-positive cells were infused (median 6.9). No graft failure was observed. The day of neutrophil recovery over 500/mm^3 ranged from 7 to 14 (median 9) and platelet over 2×10^4/mm^3 from 7 to 26 (median

11.5). Median units of transfusion of red blood cells and platelet were 0 (range 0-8) and 20 (0-60), respectively. Life-threatening RRT was sepsis of methicillin-resistant *Staphylococcus aureus* complicated in a patient (2.1%) (Table 2), while the most common one was febrile neutropenia that occurred in 35 patients (74.5%). Non-hematological RRT was generally acceptable (Table 2). There was no therapy-related death.

Ten patients in CR1, who did not undergo ASCT, were also analyzed as control group (Table 1). Their survival time was calculated starting from the completion of the 8 cycles of (R-)CHOP instead of ASCT. When we compared both groups (with and without ASCT) using U-test for distribution of age, serum LDH, interleukin-2 receptor (IL-2R) at presentation and chi-square test for proportion of the presence of B-symptom, extranodal lesion, risk classification by IPI, and administration of R, no difference was showed. However, a significantly larger proportion of patients with stage IV was revealed in ASCT group compared with non-ASCT group (P<0.05 by chi-square test). Therefore, we considered that inadequate bias between the 2 groups was minimized. With a median observation period of 61 months (ranging from 11 to 264), 14 patients of ASCT group relapsed. Their relapse sites was brain in 3 patients, bone marrow in 2, testis and liver in 1, respectively. Nodal relapse was seen in the remaining 7. Event-free survival (EFS) of patients who underwent ASCT was 75.8% after 5 years. This was significantly superior to that of those who did not (45%, P=0.03) (Figure 1). Although overall survival (OS) at 5 years tended to be better in ASCT group (79% *vs* 52.5%), no statistical significance was seen (P=0.18). Among ASCT group, age difference, normal or elevated LDH value, localized or advanced stage, presence or absence of extranodal lesion, high or high-intermediate risk by IPI, or normal or elevated serum IL-2R did not affect EFS (Table 3). Unexpectedly, use of R was associated with a tendency of shorter sur-

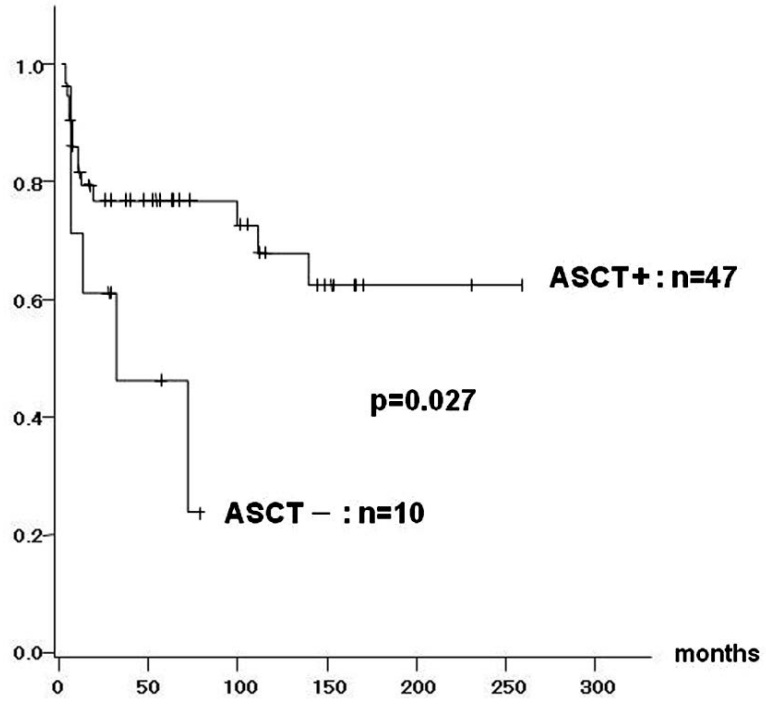

Figure 1. Event free survival of patients with autologous stem cell transplantation (ASCT) compared to those without ASCT. Significant superiority by log-rank test in patients with ASCT is observed (75.8% *vs* 45%).

Table 1. Patients' characteristics.

	ASCT +	ASCT –
Male/Female	29/18	5/5
Age (mean)	23-69 (66.5)	47-68 (60.5)
B symptom	16 (34%)	2 (20%)
Stage III/IV	13/34	7/3
LDH (mean)	140-3405 (509)	138-874 (342)
Extranodal lesion	37 (78.7%)	7 (70%)
H-I/H	29/18	7/3
GCB/non-GCB/CD5+/unknown	7/16/7/17	2/6/2/-
Use of R	18 (38.3%)	5 (50%)
IL-2R (mean)	221-29,000 (2050)	759-15,000 (2050)

ASCT, autologous stem cell transplantation; H-I/H, high-intermediate/high risk according to International Prognostic Index; R, rituximab; GCB, germinal center B-cell type.

Table 2. Adverse events related to autologous stem cell transplantation.

Event	N. (%)
Therapy-related death	0
Febrile neutropenia	35 (74.5)
MRSA sepsis	1 (2.1)
Fungemia	1 (2.1)
CMV antigenemia	1 (2.1)
Duodenal ulcer	1 (2.1)

MRSA, methicillin resistant Staphylococcus aureus; CMV, cytomegalovirus.

Table 3. Univariate analysis for 5-year event free survival in patients with autologous stem cell transplantation.

	Number	EFS, %	P-value
Age			0.82
<60	18	77.4	
≥60	29	74.8	
Stage			0.16
I/II	3	66.7	
III/IV	44	76.4	
LDH			0.88
N	11	78.8	
E	36	73.4	
Extranodal lesion			0.23
Yes	37	70	
None	10	77.6	
IPI		0.99	
H	18	79	
H-I	29	70.1	
Serum IL-2R			0.24
N	13	100	
E	34	58.2	
Use of Rituximab			0.05
Yes	18	58.2	
No	29	85.7	

N, normal range; E, elevated; H-I/H, high-intermediate/high risk according to International Prognostic Index.

vival (5-year OS 80.5% *vs* 67.6%; P=0.25, EFS 80.5% *vs* 58.4%, P=0.08).

Discussion

Progression free survival rate of patients with higher risk group DLBCL is unsatisfactory even in the R-era.[16] The majority of them experience relapse and the cure is hardly acquired. Although definite usefulness of high-dose therapy followed by ASCT is limited to cases with chemosensitive relapse,[15] Caballero *et al.* demonstrated significantly superior OS and EFS of ASCT for DLBCL in CR1 to those in second CR or refractory diseases.[10] It is suggested that high-dose therapy eliminates minimally resided lesion in clinical CR state. Controversial results are also found in randomized trials.[4,5,9,11] However, the latter studies include some concerns. Application of various chemotherapy regimens or dose intensity introduced in those studies disturbs to evaluate therapeutic outcomes. Moreover, uneven risk assessment of patients among each study is not capable of precise indication of ASCT. It is particularly unfavorable that the number of induction chemotherapy cycles before ASCT in those studies is too small.[9,11] On the contrary, studies showing encouraging data contain full course induction,[7,8] or additional consolidation therapy following induction.[12] Since the dose intensity of preceding chemotherapy to ASCT might lead to deeper remission, benefit of upfront ASCT as post-remission consolidation might be enhanced.

We therefore analyzed outcome of upfront ASCT employing six courses of (R-)CHOP followed by high-dose chemotherapy to examine whether it prolongs survival in patients with DLBCL classified as higher risk. Consequently, significant superiority in EFS of patients of ASCT group to those without ASCT was observed, although the former included significantly larger number of patients with stage IV than the latter. Despite variant histological subtypes included in our study, influence on their prognosis was unclear because of too small numbers of patients with respective subtypes. We consider that any bias is not contained in our study. It is notable that a considerable number of patients with ASCT (13 of 47, 27.7%) have uneventfully survived more than 10 years.

In the last decade, introduction of R has apparently improved prognosis of DLBCL.[22,23] R also appears to purge contaminated lymphoma cells in harvested stem cells to prevent dissemination when transplanted. Feasibility, safety, or survival benefit of the addition of R to ASCT was actually demonstrated,[24-28] although our present study failed to prove it. That is probably because relatively frequent brain relapse was occurred in patients who received R (3 of 19, 15.8% *vs* 0 of 28, 0%). Poor delivery of R to central nervous system should be overcome.

Controversy about indication of ASCT partly depends on enhanced toxicity. Increase of adverse event by high-dose therapy is an important matter of concern. Kameoka *et al.* observed sinusoidal obstructive syndrome (SOS) in 16 patients out of 30 who received ASCT with identical conditioning regimen as ours.[28] However, there was no SOS in our study. Accurate frequency of such severe complication of ASCT should be clarified. Hematological or non-hematological adverse events were generally acceptable.

Conclusions

We thus conclude that upfront ASCT is well tolerable and safe and contributes to survival benefit of higher risk DLBCL, supporting previously described positive data.[4,12,25,27] Prospective study including a larger number of patients is required to establish appropriate candidates for upfront ASCT among patients with higher risk DLBCL.

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