

Role of frontline autologous stem cell transplantation in young, high-risk diffuse large B-cell lymphoma patients

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Background/Aims: Several studies have demonstrated the effect of autologous hematopoietic stem cell transplantation (auto-HSCT) as a salvage treatment for patients with relapsed diffuse large B-cell lymphoma (DLBCL). However, the role of auto-HSCT as a frontline treatment has not been fully investigated in the rituximab era. We validated the age-adjusted International Prognostic Index (aaIPI) score for high-risk DLBCL patients and identified a possible role for frontline auto-HSCT.

Methods: We recommended frontline auto-HSCT for high-risk DLBCL patients who satisfied the criteria of both a higher Ann-Arbor stage (III to IV) and an elevated lactate dehydrogenase (LDH) level at diagnosis with an aaIPI score ≥ 2 . From 2006 to 2011, among the 150 DLBCL patients aged ≤ 60 years who were treated with six cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), 23 high-risk patients with a complete response (CR) were treated with auto-HSCT. For comparison, we selected 35 well-matched high-risk patients with CR who completed R-CHOP treatment alone. In addition, there were 81 low-risk patients and 11 refractory patients.

Results: DLBCL patients with an aaIPI score ≥ 2 showed inferior overall survival (OS; $p = 0.040$) and progression-free survival (PFS; $p = 0.007$) compared to the aaIPI score 0 to 1. Between the two treatment arms among the high-risk DLBCL patients, the clinical parameters were not different. The high-risk group treated with frontline auto-HSCT showed similar OS ($p = 0.392$) and PFS ($p = 0.670$) to those in the low-risk group. Thus, frontline auto-HSCT showed superior PFS ($p = 0.004$), but only a trend towards favorable OS ($p = 0.091$) compared to R-CHOP alone.

Conclusions: We identified the possible role of frontline auto-HSCT for high-risk DLBCL with a higher stage (III to IV) and elevated LDH level.

Keywords: Lymphoma; Lymphoma, large B-cell, diffuse; Autologous hematopoietic cell transplantation

INTRODUCTION

Despite recent advances in the treatment of non-Hod-

gkin's lymphoma (NHL), some patients with advanced stage diffuse large B-cell lymphoma (DLBCL) are not cured by conventional chemotherapy alone, resulting in

poor survival outcomes. The role of high-dose chemotherapy with autologous hematopoietic stem cell transplantation (auto-HSCT) has been proven in chemo-sensitive-relapsed DLBCL [1,2]. However, as a frontline treatment, the role of auto-HSCT is not well recognized, although several randomized studies have evaluated its efficacy during the first remission in high-risk aggressive NHL, including DLBCL.

Several studies addressed the issue before the rituximab era. The French Groupe d'Étude des Lymphomes de l'Adulte (GELA) study [3] and an Italian study [4] showed the benefit of auto-HSCT during the first remission in a subset of patients with a high-intermediate or high risk according to the age-adjusted International Prognostic Index (aaIPI) score. Milpied et al. [5] showed a favorable outcome of auto-HSCT compared to chemotherapy alone in the high-intermediate risk group according to aaIPI, but there were no differences in the event-free survival (EFS) and overall survival (OS) for patients with low or low-intermediate risk. These studies support the role of frontline auto-HSCT in patients with high-risk aggressive DLBCL; however, the benefit was mostly shown in good responders to induction chemotherapy [6]. Conversely, the outcomes of frontline auto-HSCT were similar or inferior to conventional chemotherapy in other reports [7,8]. While none of these trials included rituximab, several randomized phase III trials recently evaluated the role of auto-HSCT after the advent of rituximab-containing immunochemotherapy [9-12].

Given the improved outcome with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) in both younger [13] and older patients with DLBCL [14], it is possible that the benefit of auto-HSCT during the first complete remission may be abrogated by the addition of rituximab, as observed when rituximab was added to dose-intensified chemotherapy (CHOP-14 or CHOEP-14) [15]. Here, we validated the aaIPI score for high-risk DLBCL patients who might be expected to achieve favorable survival outcomes when treated with frontline auto-HSCT. In addition, we compared the clinical outcomes of auto-HSCT and R-CHOP alone among the high-risk DLBCL patients who achieved complete response (CR) after six cycles of R-CHOP.

METHODS

Patients and definitions for response evaluation

Between June 2006 and December 2011, 186 patients with newly diagnosed DLBCL at the Catholic Blood and Marrow Transplantation Center in South Korea were included in the study. All of the analyses were performed according to the Institutional Review Board guidelines of the Catholic Medical Center with respect to the Declaration of Helsinki. The diagnosis of DLBCL was based on morphological studies with immunohistochemical analysis. Among the 186 DLBCL patients, we first selected 150 patients aged ≤ 60 years, because all of the patients who underwent frontline auto-HSCT were aged ≤ 60 years. We identified 23 patients who underwent planned frontline auto-HSCT after six cycles of R-CHOP due to a high-risk status at initial presentation (high-risk, auto-HSCT group). The remaining patients were treated with six cycles of R-CHOP and completed treatment with chemotherapy alone or underwent salvage chemotherapy. After three cycles of R-CHOP, the response was evaluated by both computed tomography (CT) and fluorine 18-fluorodeoxyglucose positron emission tomography (FDG-PET). If the patients achieved a CR or a partial response (PR), we applied an additional three cycles of R-CHOP (for a total of six cycles) and completed treatment if the patients achieved CR. When the disease progressed during treatment, or if the patients failed to achieve at least PR (chemorefractory status), we changed the regimen to salvage chemotherapy. To determine the treatment outcome of frontline auto-HSCT compared to R-CHOP alone in high-risk DLBCL patients with CR, we selected 35 well-matched patients with a similar risk status and performance status (PS), and all of the patients were without significant comorbidities. All of the 35 patients were in CR after six cycles of R-CHOP and completed treatment (high-risk, R-CHOP alone group) (Fig. 1).

The definition of CR required regression of the entire palpable mass and regression to a normal size on CT with negative FDG-PET. FDG-PET was evaluated according to the criteria of the standardized uptake value [16]. CT and FDG-PET were performed after every three cycles of R-CHOP and 1 month before HSCT. If bone marrow (BM) was initially involved, a BM biopsy was performed after six cycles of R-CHOP. PR required

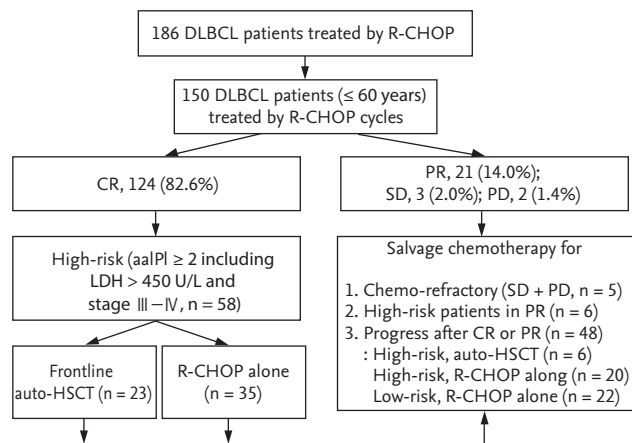


Figure 1. Consort diagram of the treatment course and high-risk diffuse large B-cell lymphoma (DLBCL) patients selected according to the higher age-adjusted International Prognostic Index (aaIPI) score, which included an elevated lactate dehydrogenase (LDH) level and higher stage (III to IV). R-CHOP, rituximab plus cyclophosphamide, hydroxydaunorubicin, oncovin (vincristine), prednisolone; CR complete response; PR, partial response; SD, stable disease; PD, progressive disease; HSCT, hematopoietic stem cell transplantation.

a reduction of at least 50% in the sum of the products of the dimensions on CT with positive FDG-PET without a newly developed lesion. Disease progression was defined as an increase in the lesion size of more than 25% compared to the sum of the sizes of the pretreatment lesions, or the appearance of new lesions. Relapse was defined as new disease in CR patients or progressive disease in PR patients.

Patients treated with frontline auto-HSCT

We calculated the IPI [17] and aaIPI [18] scores in all patients at diagnosis, and started R-CHOP chemotherapy. In calculating the IPI score, we found that an initial poor PS might improve during chemotherapy, and the extranodal status was highly correlated with Ann Arbor stage. For auto-HSCT candidates, we selected high-risk DLBCL patients aged 60 years or younger who satisfied the criteria of both an elevated lactate dehydrogenase (LDH) level (> 450 U/L) and a higher Ann Arbor stage (III to IV) at initial presentation that conclusively resulted in aaIPI ≥ 2 (high-intermediate to high risk). PS and extranodal status were not used to select high-risk patients. After three cycles of R-CHOP, all of the high-risk patients (aged ≤ 60 years) in CR or PR were recom-

mended for auto-HSCT after explaining the relapse risk and necessity for high-dose chemotherapy. Conclusively, frontline auto-HSCT was performed strictly according to the patient’s final decision, and the comparative R-CHOP alone group consisted of patients who satisfied the criteria of the same high-risk DLBCL category with similar PS and comorbidities.

Treatment protocols

To initiate R-CHOP chemotherapy, rituximab was infused at 375 mg/m² on day 1, and then every 3 weeks. Chemotherapies included cyclophosphamide (750 mg/m², administered intravenously on day 1), doxorubicin (50 mg/m², administered intravenously on day 1), vincristine (1.4 mg/m², but not more than 2.0 mg in total, administered intravenously on day 1), and prednisolone (100 mg/m², orally administered on days 1 to 5) every 3 weeks [19]. Autologous stem cell mobilization was performed after three cycles of R-CHOP as well as response evaluation of patients in whom auto-HSCT was planned. We started with granulocyte-colony stimulating factor (filgrastim, 10 µg/kg) at 48 hours after the sixth cycle of R-CHOP, and when the leukocyte count and peripheral CD34 count were elevated, we performed apheresis. For auto-HSCT, we used a BuMelTT protocol that consisted of intravenous busulfan, melphalan, and thiotepa with a 20% dose reduction compared to that in previous reports [20-22]. Our dose-reduction was based on our own experiences and previous reports (including one Korean report) that addressed the excessive toxicity of the BuMelTT protocol [23,24]. Busulfan was administered at a dose of 2.4 mg/kg/day for three consecutive days (D-8, D-7, and D-6; total 7.2 mg/kg); melphalan was administered at a dose of 40 mg/m² per day for 2 days (D-5 and D-4; total, 80 mg/m²); and thiotepa was administered at a dose of 200 mg/m² per day for 2 consecutive days (D-3 and D-2; total, 400 mg/m²). Stem cells were infused 48 hours after the final dose of thiotepa.

Statistical analysis

The purpose of this study was to assess the clinical outcomes in high-risk DLBCL patients according to the treatment strategy: frontline auto-HSCT versus R-CHOP alone. All of the categorical variables were compared by chi-square analysis and Fisher exact test, and continuous variables were assessed by Student *t* test

and Wilcoxon rank-sum test. OS measured the proportion of people who were alive at a specified time from diagnosis, and progression-free survival (PFS) measured the proportion of progression or death from any cause from the first day of R-CHOP. EFS was measured from diagnosis to any treatment failure, including disease progression, death, discontinuation of treatment for any reason, or initiation of new treatment without documented progression. Survival outcomes were estimated using the Kaplan-Meier survival method, and log-rank analysis was used to evaluate differences between survival distributions under various clinical conditions. A Cox proportional regression model was used to calculate the survival hazard ratio (HR). All of the statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and R software version 2.15.1 (The R Foundation for Statistical Computing, 2012; <http://www.r-project.org/>). Statistical significance was set at a *p* value less than 0.05.

RESULTS

Patient baseline characteristics

Fig. 1 shows the Consolidated Standards of Reporting Trials (CONSORT) diagram for DLBCL patients treated at the Catholic BMT Center. Among the 150 DLBCL patients aged ≤ 60 years who were treated with six cycles of R-CHOP, 124 (82.6%) achieved CR and 21 (14.0%) achieved PR. Five patients (3.4%) were refractory to R-CHOP chemotherapy. Among the 21 patients with PR, 15 low-risk patients completed therapy with R-CHOP alone. The remaining six high-risk patients with PR and five refractory patients were treated with immediate salvage chemotherapy. Among the 124 patients with CR after R-CHOP, 66 were low-risk patients (53.3%) who completed therapy with R-CHOP alone, and the remaining 58 were high-risk patients (46.7%) with aaIPI ≥ 2 satisfying the criteria of both an elevated LDH level and a higher Ann Arbor stage (III to IV). Fifty-eight high-risk patients were divided into two groups according to the treatment: a frontline auto-HSCT group ($n = 23$) and an R-CHOP alone group ($n = 35$). Between the two groups, the distributions of age, gender, IPI score, aaIPI score, and Ann Arbor stage at initial presentation were not significantly different. In addition, the diagnostic

LDH level, distribution of Eastern Cooperative Oncology Group status, and extranodal involvement status (including BM) were not different. Overall, the entire cohort was divided into four groups according to the risk stratification and treatment strategies: a low-risk group that completed treatment with R-CHOP alone ($n = 81$), a high-risk group treated with frontline auto-HSCT ($n = 23$), a high-risk group treated with R-CHOP alone ($n = 35$), and a non-CR group treated with immediate salvage chemotherapy ($n = 11$). The baseline characteristics are displayed in Table 1.

Survival outcomes according to risk stratification and treatments

DLBCL patients with an aaIPI score ≥ 2 showed significantly inferior OS (HR, 2.191; 95% confidence interval [CI], 1.119 to 4.291; $p = 0.040$) and PFS (HR, 2.192; 95% CI, 1.249 to 3.848; $p = 0.007$) compared to an aaIPI score 0 to 1 (Fig. 2). Next, we compared the clinical outcomes of the four patient groups divided according to risk and treatment strategies. The high-risk group treated with auto-HSCT showed similar OS (HR, 1.602; 95% CI, 0.544 to 4.715; $p = 0.392$), PFS (HR, 1.234; 95% CI, 0.469 to 3.248; $p = 0.670$), and EFS (HR, 1.030; 95% CI, 0.389 to 2.725; $p = 0.952$) to that of the low-risk group. In addition, both the high-risk group treated with auto-HSCT and the low-risk group showed superior PFS (HR, 0.338; $p = 0.022$) and HR 0.274 ($p < 0.001$), respectively, and EFS (HR, 0.297; $p = 0.013$) and HR 0.288 ($p < 0.001$), respectively, compared to the high-risk group treated with R-CHOP alone. However, only the low-risk group showed superior OS (HR, 0.338; 95% CI, 0.148 to 0.772; $p = 0.110$), whereas the high-risk group treated with auto-HSCT did not show significantly superior OS (HR, 0.542; 95% CI, 0.192 to 1.528; $p = 0.102$) compared to the high-risk group treated with R-CHOP alone (Fig. 3). There was no therapy-related mortality after auto-HSCT.

Frontline auto-HSCT versus R-CHOP alone for high-risk DLBCL

Conclusively, among the high-risk DLBCL patients, Kaplan-Meier analysis estimated that frontline auto-HSCT showed significantly superior PFS ($p = 0.004$), but showed only a trend towards favorable OS ($p = 0.091$) compared to R-CHOP alone (Fig. 4). With a median follow-up duration of 30.5 months (range, 10.1 to 77.1),

Table 1. Characteristics of diffuse large B-cell lymphoma patients stratified according to aaIPI score (elevated LDH level and stage III to IV) and final treatment strategy

Variable	Low-risk R-CHOP alone (n = 81)	High-risk R-CHOP alone (n = 35) ^a	High-risk auto-HSCT (n = 23) ^a	Progression salvage CTx (n = 11) ^b	p value ^a
Age, yr	45.6 (17–59)	46.8 (17–59)	42.1 (21–60)	44.5 (24–59)	0.093
Male sex	43 (53.1)	25 (71.4)	14 (60.9)	8 (72.7)	0.402
IPI					
Low	63 (77.7)	0	0	1 (9.1)	-
Intermediate	18 (22.3)	26 (74.3)	16 (69.6)	9 (81.8)	0.694
High	0	9 (25.7)	7 (30.4)	1 (9.1)	0.694
aaIPI score					
0–1	78 (96.3)	0	0	6 (54.6)	-
2	3 (3.7)	25 (71.4)	18 (78.3)	4 (36.4)	0.561
3	0	10 (28.6)	5 (21.7)	1 (9.1)	0.561
Stage					
I	32 (39.5)	0	0	1 (9.1)	-
II	29 (35.8)	0	0	1 (9.1)	-
III	6 (7.4)	5 (14.3)	5 (21.7)	0	0.462
IV	14 (17.3)	30 (85.7)	18 (78.3)	9 (81.8)	0.462
LDH	378 (220–1,245)	755 (460–2,919)	784 (465–1,862)	590 (430–1,413)	0.796
ECOG ≥ 2	11 (13.6)	10 (28.6)	5 (21.7)	4 (36.4)	0.561
Extranodal ≥ 2	15 (18.5)	24 (68.6)	16 (69.6)	8 (72.7)	0.936
BM involvement	4 (4.9)	6 (17.6)	4 (17.4)	3 (30.0)	0.573

Values are presented as median (range) or number (%).

aaIPI, age-adjusted International Prognostic Index; LDH, lactate dehydrogenase; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone; HSCT, hematopoietic stem cell transplantation; CTx, chemotherapy; ECOG, Eastern Cooperative Oncology Group; BM, bone marrow.

^ap value was calculated between the two high-risk groups: R-CHOP alone vs. frontline auto-HSCT.

^bGroup of patients with disease progression during six cycles of R-CHOP who needed urgent salvage chemotherapy.

frontline auto-HSCT showed 3-year OS and PFS rates of 75% and 66%, respectively, whereas the R-CHOP alone group showed 3-year OS and PFS rates of 49% and 39%, respectively. In addition, treatment of high-risk DLBCL with R-CHOP alone showed a higher incidence of relapse than the auto-HSCT group (20 of 35 patients [57.1%] vs. 6 of 23 patients [26.1%], $p = 0.020$). Among the 20 patients who relapsed after R-CHOP alone, 13 died of disease progression during salvage chemotherapy, and only one patient remains alive with CR after salvage chemotherapy. Among the remaining six patients who were treated with second-line auto-HSCT after salvage chemotherapy, two (33.3%) are alive with CR, but four patients (66.7%) relapsed.

DISCUSSION

Prior to the advent of rituximab, the benefits of frontline auto-HSCT were verified mostly in good responders to induction chemotherapy [6]. Furthermore, several studies reported that the outcome of auto-HSCT was worse than that of chemotherapy alone when an abbreviated course of chemotherapy was performed before auto-HSCT, or when auto-HSCT was applied as an early intensified therapy. Three studies—the French randomized trial LNH93 to 3 [7], an Italian multicenter randomized trial [8], and a phase III study from the German Lymphoma Study Group [25]—that addressed early intensification with auto-HSCT showed no significant difference in OS or PFS compared to conventional che-

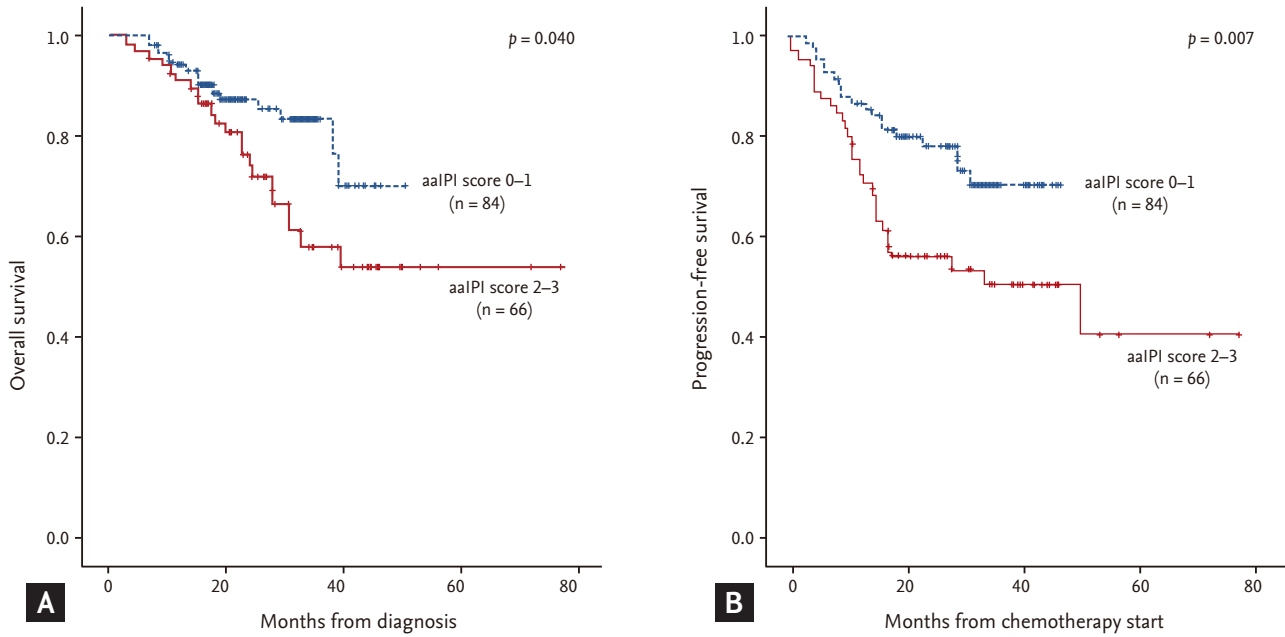


Figure 2. Kaplan-Meier estimated (A) overall survival and (B) progression-free survival in the entire cohort according to age-adjusted International Prognostic Index (aaIPI) score.

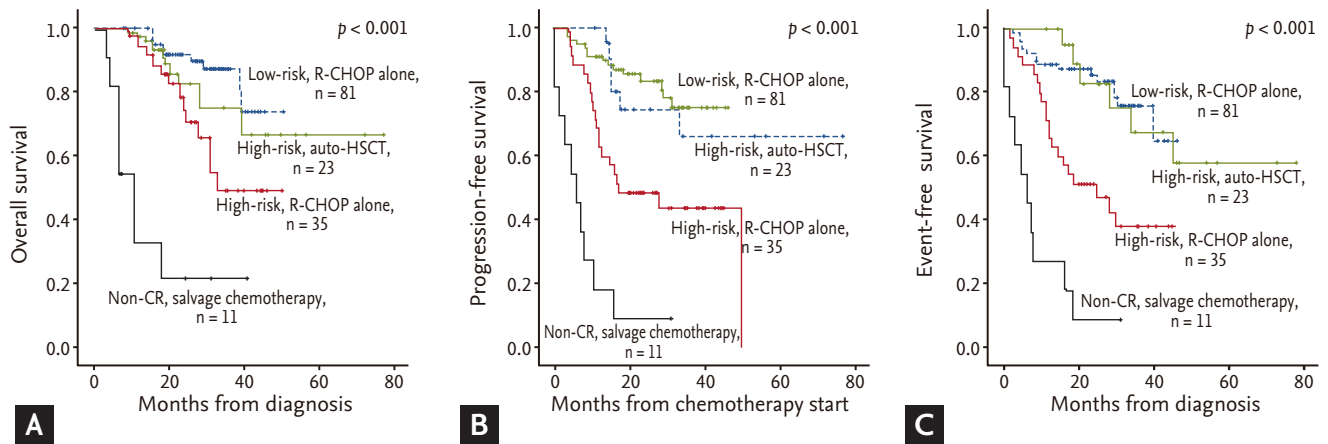


Figure 3. Kaplan-Meier estimated (A) overall survival, (B) progression-free survival, and (C) event-free survival of the entire cohort stratified based on risk and final treatment strategies. R-CHOP, rituximab plus cyclophosphamide, hydroxydaunorubicin, oncovin (vincristine), prednisolone; HSCT, hematopoietic stem cell transplantation; CR complete response.

motherapy. These studies showed that achieving CR with full courses of induction therapy before frontline auto-HSCT is important, and that auto-HSCT should not be performed too early during the course of treatment. Although some of the results showed the possible role of frontline auto-HSCT, the role of auto-HSCT as a first line treatment is still a matter of debate in the present rituximab era.

Recently, one phase III randomized study reported high-risk DLBCL with an aaIPI score ≥ 2 with an age range of 18 to 65 years. All of the patients received eight cycles of R-CHOP with two different doses, and one arm underwent auto-HSCT followed by BEAM conditioning. The authors reported that auto-HSCT showed a 70% 3-year PFS compared to 59% in the chemotherapy alone group ($p = 0.010$), but the 3-year OS was 81% in the

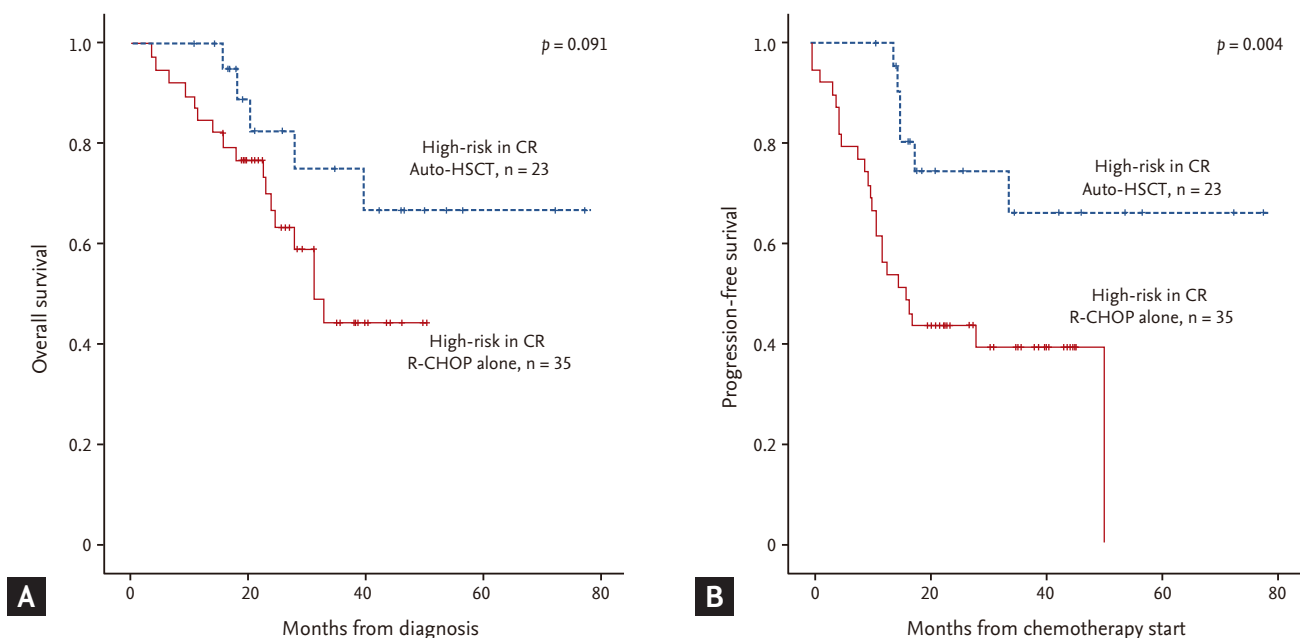


Figure 4. Kaplan-Meier estimated (A) overall survival and (B) progression-free survival according to the treatment strategy in the high-risk diffuse large B-cell lymphoma group. CR complete response; HSCT, hematopoietic stem cell transplantation; R-CHOP, rituximab plus cyclophosphamide, hydroxydaunorubicin, oncovin (vincristine), prednisolone.

auto-HSCT group compared to 78% in the chemotherapy alone group; the difference not statistically significant between the two treatment arms ($p = 0.556$) [9]. The SWOG S9704 study also showed similar results in high-risk DLBCL patients with an IPI score ≥ 3 , and showed a favorable 2-year PFS ($p = 0.005$) in auto-HSCT after six cycles of R \pm CHOP compared to eight cycles of R \pm CHOP alone. However, this study included patients who were not treated with rituximab [11,12]. Another phase III study analyzed the possible role of repetitive dose-escalated sequential chemotherapy followed by repetitive auto-HSCT in high-risk DLBCL patients with aaIPI ≥ 2 . However, this protocol was somewhat different from traditional ones, and the results were confounded by the toxicity of high-dose chemotherapy [26].

In contrast, we believe that our study cohort satisfied the following conditions: first, all of the patients were treated with six full cycles of R-CHOP; second, all of the patients achieved CR by FDG-PET criteria after six cycles of R-CHOP; third, all of the patients who were recommended for frontline auto-HSCT satisfied the high-risk criteria of aaIPI ≥ 2 , which included both an elevated LDH level and Ann Arbor stage III to IV. Several studies have shown that the pre-HSCT disease status evaluated by FDG-PET was the most significant independent fac-

tor for the prediction of relapse after auto-HSCT [27-29]. It is now clearly suggested that patients with persistent FDG-PET positivity do not benefit from auto-HSCT; therefore, we used interim FDG-PET every three cycles of R-CHOP or before auto-HSCT. All of the 58 high-risk patients in this study satisfied the pre-HSCT condition that included the regression of previously enlarged mass lesions clinically and on conventional CT examination with a complete metabolic response by FDG-PET before HSCT.

Several prognostic factors that may predict the outcome of auto-HSCT were identified in relapsed or refractory DLBCL. As described above, the benefit of auto-HSCT has been verified mostly in chemosensitive disease with negative residual disease activity before transplantation [6,28]. In addition, Hamlin et al. [18] evaluated aaIPI at the initiation of second-line chemotherapy in relapsed or refractory DLBCL patients who were treated with salvage chemotherapy followed by auto-HSCT. They compared three aaIPI subgroups and showed significantly different predictable values for OS and PFS, and also presented the possibility as a useful prognostic marker for evaluating new treatment approaches. In addition, some studies evaluated aaIPI and pre-HSCT FDG-PET findings simultaneously. One

study showed that only FDG-PET was significantly predictive of survival outcome, and another showed that both aaIPI and FDG-PET were independent predictors of failure-free survival [30,31]. We tried to use aaIPI to determine the high-risk DLBCL patients who were scheduled to undergo frontline auto-HSCT. Our data finally showed the criteria are useful with statistical significance for the determination of high-risk DLBCL; for high-risk chemosensitive DLBCL, we may also expect better treatment outcomes with frontline auto-HSCT in the rituximab era.

Among the 58 high-risk patients who completed treatment with either auto-HSCT or R-CHOP alone, we identified 26 relapsed patients (six patients after frontline auto-HSCT and 20 patients after R-CHOP alone). Among the 20 relapsed patients after R-CHOP alone, 14 underwent salvage chemotherapy, and six received second-line auto-HSCT. Finally, only three patients (15.0%; two after auto-HSCT and one after salvage chemotherapy) are alive without disease progression at the time of analysis. These data cautiously suggest that the role of auto-HSCT for a long-term survival outcome after relapse is questionable for patients with high-risk DLBCL.

Unfortunately, we did not perform gene expression profiling to analyze the different sub-entities of DLBCL. Although DLBCL is a well-defined entity, it is heterogeneous, and many biomarkers are being investigated to understand its biological basis. Thus, even patients with the same IPI score may exhibit extreme variability in treatment outcomes, suggesting the presence of heterogeneity. Furthermore, in addition to rituximab, several novel agents have been deemed useful based on the genetic subentities in DLBCL; thus, the role of auto-HSCT might be challenged more strongly in the near future.

Although our results did not originate from a prospective clinical trial, the minimal dataset prevents definite conclusions. Furthermore, the treatments between the R-CHOP alone and frontline auto-HSCT groups were performed strictly according to the patient's decision, a finding that could cause a selection bias in the present study. However, two high-risk groups presented well-matched comparative parameters with acceptable results, possibly supporting recent large prospective trials [9-12,26]. In conclusion, our data suggest that auto-HSCT may have a beneficial effect in chemosensitive high-risk DLBCL patients compared to R-CHOP alone.

High-risk DLBCL patients who are fit for frontline auto-HSCT may be identified by aaIPI, which satisfies the criteria of an elevated LDH level and higher Ann Arbor stages at diagnosis.

KEY MESSAGE

1. Frontline autologous hematopoietic stem cell transplantation can be considered for high-risk diffuse large B-cell lymphoma patients with the expectation of favorable survival outcomes.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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