

Autologous stem cell transplantation for diffuse large B-cell lymphoma with residual extranodal involvement

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Background/Aims: Diffuse large B-cell lymphoma (DLBCL) in Koreans is frequently accompanied by extranodal (EN) disease at the time of autologous stem cell transplantation (ASCT). We sought to determine whether high EN involvement affected survival following ASCT in Koreans.

Methods: We reviewed 27 patients who had DLBCL with residual disease at ASCT: 13 with residual disease at nodal site(s) only and 14 with nodal and EN disease.

Results: Univariate analysis showed that disease status, lactate dehydrogenase (LDH), and performance status at ASCT were predictors of survival following ASCT. The number of EN sites, as categorized by the International Prognostic Index system, had no prognostic significance. When EN involvement at ASCT was classified as negative or positive, the 2-year overall survival for the negative group was 64%, significantly better than the 14% for the positive group ($p=0.021$), and the event-free survival for the negative group was 62%, significantly better than the 14% for the positive group ($p=0.02$).

Conclusions: Patients who had DLBCL with residual EN involvement at ASCT showed worse outcomes following ASCT compared to those without EN disease.

Key Words: Diffuse large B-cell lymphoma; Autologous stem cell transplantation; Extranodal involvement; Residual disease

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) was the first tumor type to which high-dose therapy, supported by the reinfusion of autologous stem cells, was applied¹, and dose intensification was shown to be able to cure some patients with relapsing or refractory disease^{2,3}. At present, NHL is the second most frequent indication for autologous stem cell transplantation (ASCT) because ASCT has been found to provide an increasing number of patients having the disease with the best opportunity for cure under certain circumstances. Despite recent therapeutic advances, however, many patients with NHL relapse after ASCT. Among the factors having significance in predicting how well

patients will do after ASCT, the most predictive is the sensitivity of the lymphoma to chemotherapy⁴⁻⁸. Factors associated with a poor outcome include elevated lactate dehydrogenase (LDH)⁶, extensive previous treatment⁹, bulky disease¹⁰, poor performance status¹¹, and high-grade histology^{9,12}.

The International Prognostic Index (IPI) is a well established scoring system that predicts the survival of patients with aggressive NHL¹³. IPI has also been evaluated in patients with NHL treated with high-dose therapy and ASCT¹⁴⁻¹⁹. Studies that have assessed the value of IPI for the result of ASCT in patients with selected pathologic subtypes typically use the age-adjusted IPI (AAIPI), rather than the IPI. The AAIPI lacks factors for extranodal (EN) involvement, as well as for age. In Korea, around

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two-thirds of patients who have NHL also have EN involvement at initial presentation²⁰ and over 50% of patients have residual EN disease at ASCT²¹. We therefore hypothesized that EN involvement in NHL may affect survival after ASCT in Korean patients. We now report a Korean single institution study of 27 patients with diffuse large B-cell lymphoma (DLBCL) who had radiologically documented residual lymphoma at the time of high-dose therapy with ASCT.

MATERIALS AND METHODS

Patients

A registry showed that 27 patients with DLBCL and residual disease had been treated with ASCT at the Asan Medical Center between March 1996 and May 2005. Residual disease of at least 1x1 cm was documented by CT scan, performed just prior to high-dose therapy. Each residual EN involvement was documented by pathologic examination. Disease status was assessed by CT of the neck, chest, abdomen, and pelvis, performed just prior to high-dose therapy. Bone marrow biopsies were repeated to evaluate the lymphoma status. All patients were staged, according to the Ann Arbor system. Response was assessed using the International Working Group criteria²². Disease status of eligible patients was classified as initial partial response, chemotherapy-sensitive relapse, and primary refractory disease. Primary refractory disease was defined as stable or progressive disease documented at restaging, immediately after the completion of induction therapy²³. To be eligible for ASCT, patients had to be 15-65 years old and have biopsy-proven DLBCL; adequate hepatic, renal, pulmonary, and cardiac function; negative serology for human immunodeficiency virus; and no history of other malignancies or central nervous system involvement.

All histological specimens were reviewed by one pathologist (JH). Before 1998, histopathological results had been classified according to the International Working Formulation²⁴, but we retrospectively reclassified such specimens according to the World Health Organization/Revised European-American Lymphoma (WHO/REAL) system²⁵. Since 1998, all histologic diagnoses have been performed using the WHO/REAL classification.

The ASCT protocol was approved by the institutional review board of Asan Medical Center. Written informed consent was obtained from each patient.

Peripheral blood progenitor cell mobilization

In patients assessed as candidates for ASCT, peripheral blood progenitor cell (PBPC) mobilization and collection were performed as described previously²⁶. PBPCs were mobilized with chemotherapy, followed by lenograstim (Neutrogin, Choongwae

Ltd., Seoul, Korea), both to reduce the tumor burden and to facilitate PBPC harvesting. The chemotherapy regimens for mobilization were 4 g/m² cyclophosphamide or ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), with or without rituximab. All patients received 10 μg/kg/day lenograstim subcutaneously, starting on the day after the completion of mobilization chemotherapy and continuing until the last leukapheresis procedure. PBPCs were collected with a continuous-flow blood cell separator (Fenwal CS3000 plus, Baxter Healthcare, Deerfield, IL, USA). The total CD34⁺ cell count was monitored daily following each collection, with the target amount being 5×10⁶ CD34⁺ cells per kilogram patient weight.

IPI and age-adjusted IPI at ASCT

The IPI consists of five risk factors: age older than 60 years, LDH greater than the upper limit of normal, ECOG performance status greater than 1, stage III or IV disease, and more than one EN site. The age-adjusted IPI (AAIPI) consists of three of the IPI risk factors: LDH, stage, and ECOG performance status¹³.

ASCT procedure

The BEAM¹⁵ or BEAC³ regimen was used as a high-dose conditioning regimen, and lenograstim was used to facilitate engraftment. Patients were cared for in a single room, with reverse isolation strictly maintained to prevent infectious complications. All patients were administered prophylactic antimicrobials, consisting of ciprofloxacin, fluconazole, and acyclovir. Patients received transfusions of red blood cells and platelets as clinically indicated. Generally, platelets were single donor transfusions, administered to keep the platelet count above 20,000/mm³ or to relieve clinical bleeding.

Statistical analysis

All continuous variables were analyzed using the Mann-Whitney test. Proportions were compared using the χ^2 test or Fisher's exact test, as appropriate. Overall survival (OS) was defined as the time from the date of transplantation until death or the last follow-up. Event-free survival (EFS) was measured from the date of ASCT until the time of a relapse, evidence of disease progression, or death, regardless of cause. The date of the first event was used in calculating EFS. Survival curves were plotted using the product-limit method, according to Kaplan and Meier, and were compared using the log-rank test. The Cox proportional hazards regression model was used for multivariate analysis. Statistical analysis was performed with SPSS (version 12.0 for Windows, SPSS Inc., Chicago, IL, USA) and the significance level was set at 0.05.

Table 1. Patient characteristics at autologous stem cell transplantation

Characteristic	No residual EN involvement (n=13)	1 or more residual EN involvement (n=14)	<i>p</i>
Age, year			NS
Median (range)	37 (15-65)	51 (18-64)	
Sex			NS
Male	10	7	
Female	3	7	
First line chemotherapy			NS
CHOP	10	9	
R-CHOP	2	1	
Others	1	4	
Second line chemotherapy			NS
ESHAP/DHAP	3	3	
R-ESHAP/R-DHAP	5	2	
Others	3	5	
Radiotherapy prior to mobilization			NS
Not performed	3	4	
Performed	10	10	
Disease status			NS
Initial partial response	3	3	
Sensitive relapse	9	4	
Refractory	1	7	
Age categorized			NS
60 years or younger	11	11	
Over 60 years	2	3	
LDH categorized			0,018
Normal	8	2	
Above normal	5	12	
Performance categorized			NS
0-1	13	11	
2-4	0	3	
Stage categorized			<0,001
I, II	11	1	
III, IV	2	13	
EN categorized			0,007
0-1	13	8	
>1	0	6	
IPI			0,033
Low/ Low-intermediate	12	7	
High-intermediate/ High	1	7	
AAIPI			0,001
Low/ Low-intermediate	12	4	
High-intermediate/High	1	10	

EN, extranodal; NS, not significant; R, Rituximab; LDH, Lactate dehydrogenase; IPI, International Prognostic Index; AAIPI, Age-adjusted International Prognostic Index

RESULTS

Patient characteristics

Twenty-seven patients with DLBCL were eligible for this analysis. Of them, 13 (48%) had no residual EN involvement and 14 (52%) had one or more residual EN disease at ASCT. Characteristics of the groups of patients at ASCT are listed in Table 1. Age and gender were not different between the groups. The most frequent first-line chemotherapy regimens were CHOP and rituximab plus CHOP. Dose-intense regimens, such as

ESHAP, DHAP, and ICE, were administered to one patient in the no-EN group and four patients in the residual-EN group, who were found to have a significant tumor burden and poor prognostic features by their treating physicians. First-line chemotherapy regimens showed no statistically significant difference between the groups. For salvage regimens, ESHAP, DHAP, rituximab plus ESHAP, or rituximab plus DHAP were administered to the majority of patients. Three patients from the no-EN group and five patients from the residual-EN group were given aggressive regimens, such as CODOX-M/IVAC and

Table 2. Distribution of extranodal involvement sites

No. of involved extranodal sites per case	1	2	3	Total
Lung & pleura	3	2	1	6
Stomach	2		1	3
Head & neck	1	2		3
Intestine*	1	1		2
Liver	1	1		2
Bone marrow		1		1
Skin		1		1
Breast		1		1
Bone		1		1
Abdominal organ other than GIT or liver**			1	1
Sites/Cases	8/8	10/5	3/1	21/14

GIT, Gastrointestinal tract

*EN sites of Intestine were duodenum and ileum. They were diagnosed by endoscopic biopsies.

**EN site of other abdominal organ was adrenal gland. Without pathologic confirm, it was possible to diagnose according to the radiologic finding.

Table 3. Prognostic factors at autologous stem cell transplantation in univariate analysis

Prognostic factors	% survival at 2 years (95% CI)	<i>p</i> value
Overall survival		
Disease status (sensitive vs refractory)	38 (16-60) vs 13 (0-36)	0,039
LDH (normal vs above normal)	83 (60-100) vs 12 (0-27)	<0,001
Performance (0-1 vs >1)	35 (16-54) vs 0	<0,001
Extranodal involvement (0 vs 1 or more)	64 (38-90) vs 14 (0-32)	0,021
Event-free survival		
Disease status (sensitive vs refractory)	45 (23-67) vs 13 (0-36)	0,019
LDH (normal vs above normal)	90 (71-100) vs 6 (0-17)	<0,001
Performance (0-1 vs >1)	40 (20-60) vs 0	<0,001
Extranodal involvement (0 vs 1 or more)	62 (37-87) vs 14 (0-32)	0,020

LDH, Lactate dehydrogenase

GMALL, chosen by the treating physician. Two patients from the no-EN group and four patients from the residual-EN group were not administered second-line salvage chemotherapy because of their initial partial response (PR) status, and their PBPCs were mobilized by high-dose cyclophosphamide. Salvage chemotherapy regimens showed no difference between the groups. Radiotherapy history and disease status at ASCT were not different between the groups. Among the IPI factors, age and performance status were not significantly different between the groups. Patients showing LDH above the normal range were more frequent in the residual-EN group (86%) than in the no-EN group (39%; $p=0.018$). Advanced stage III/IV disease was observed in 13 patients (93%) in the residual-EN group (93%) and in one patient (15%) in the no-EN group ($p < 0.001$). EN involvement score, categorized by the IPI system, was significantly worse in the residual-EN group than in the no-EN group ($p=0.007$). The IPI score was high-intermediate or high in seven patients (50%) in the residual-EN group and in one patient (8%) in the no-EN group ($p=0.033$). Ten patients (71%) in the residual-EN group had high-intermediate or high AAPI scores

and 12 patients (92%) in the no EN group showed low or low-intermediate risk ($p=0.001$).

Details of the distribution of EN involvement sites at ASCT are presented in Table 2. Eight patients had involvement of one EN site, five had involvement of two EN sites, and one had involvement of three EN sites. Of the 21 total EN sites in these 14 patients with residual EN disease at ASCT, the most frequently observed were the lung and pleura (6 sites), followed by the stomach (3 sites), head and neck (3 sites), intestine (2 sites), and liver (2 sites).

Response to ASCT

Because no ASCT-related mortality occurred in the 27 patients, all were evaluable for response. Twelve patients (44%) achieved a complete response (CR) post-ASCT, seven patients (26%) a PR, and eight patients (30%) failed. Of 19 patients transplanted in chemosensitive status, 11 (58%) achieved CR with the ASCT. However, only one patient (13%) of the eight transplanted in chemoresistant status achieved a CR ($p=0.03$)

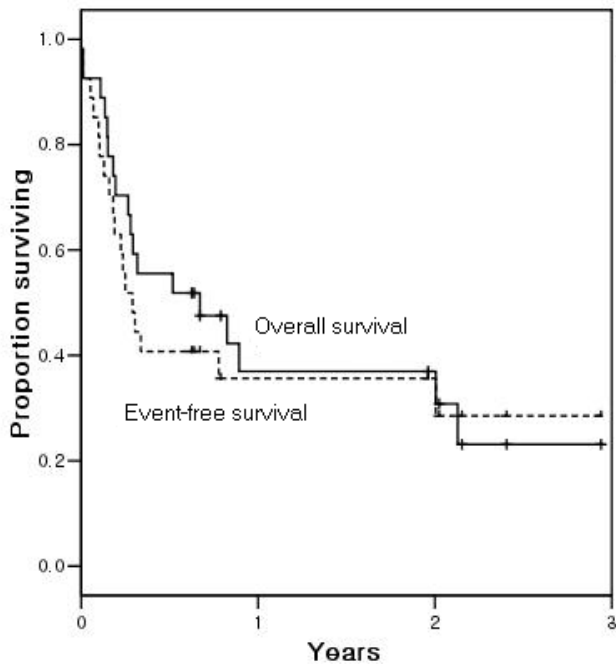


Figure 1. Overall survival and event-free survival for all 27 patients. The Kaplan-Meier curves show that the overall survival 2 years after autologous stem cell transplantation was 37% and the proportion of patients remaining event-free at 2 years was 36%.

Survival

The median follow-up duration for survivors was 24 months (range, 7-36). Eighteen patients (67%) have died and nine patients are alive. Twelve patients died of disease progression and six patients died of other illnesses. No occurrence of secondary neoplasm was observed. The Kaplan-Meier estimate of the proportion of patients remaining alive at 2 years following ASCT was 37%, with an estimated EFS at 2 years of 36% (Figure 1).

Predictors of outcome following ASCT

The univariate analysis for OS and EFS is shown in Table 3. A better outcome was associated with chemosensitive disease status at ASCT, normal LDH level, good performance, and no EN involvement at ASCT. However, based on a multivariate analysis, only normal LDH level [hazard ratio (HR) 0.05; 95% confidence interval (CI) 0.01-0.39; $p=0.004$ for OS; and HR 0.04; 95% CI 0.01-0.35; $p=0.003$ for EFS] was associated with superior survival.

EN involvement as a predictor of outcome following ASCT

Note that when categorized according to the original IPI, the 2-year OS was 37% for patients with 0-1 EN sites and 33% for those with more than 1 EN involvement at ASCT ($p=0.874$;

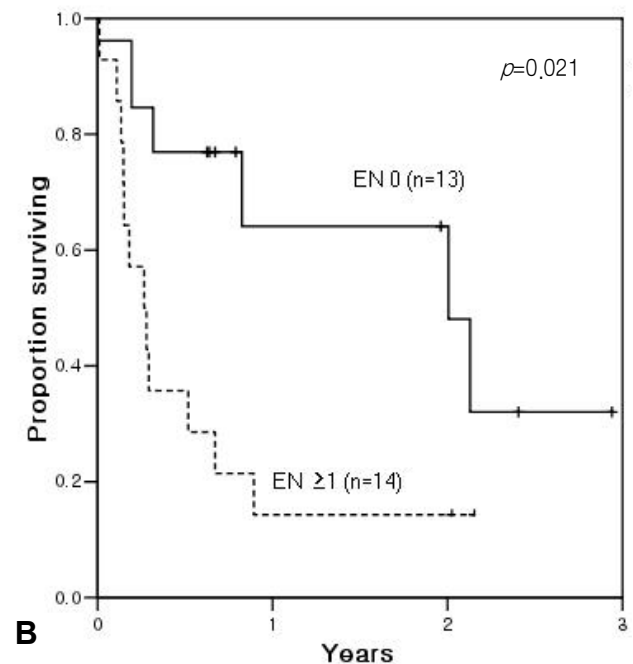
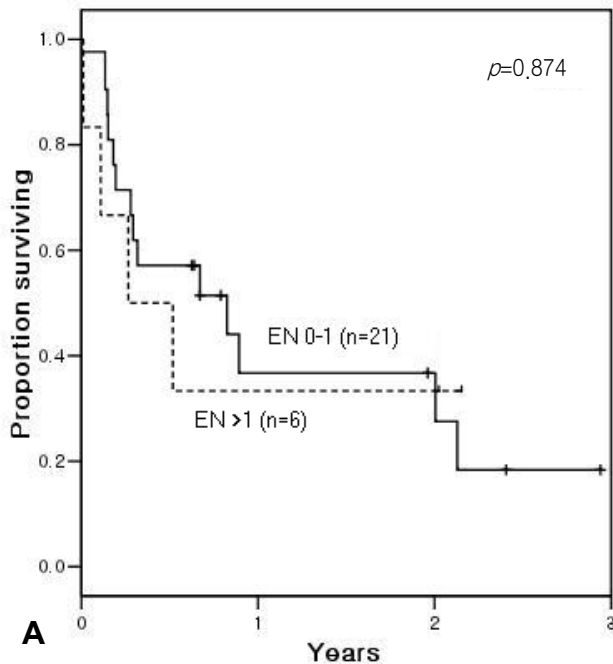


Figure 2. Overall survival according to extranodal (EN) disease status at autologous stem cell transplantation, (A) Comparison between 0-1 EN site and more than 1 EN site showed no difference in overall survival, (B) Modified categorization: patients with no remaining EN site had a 2-year overall survival rate of 64%, significantly better than the 14% rate observed in patients with remaining EN site(s) at autologous stem cell transplantation.

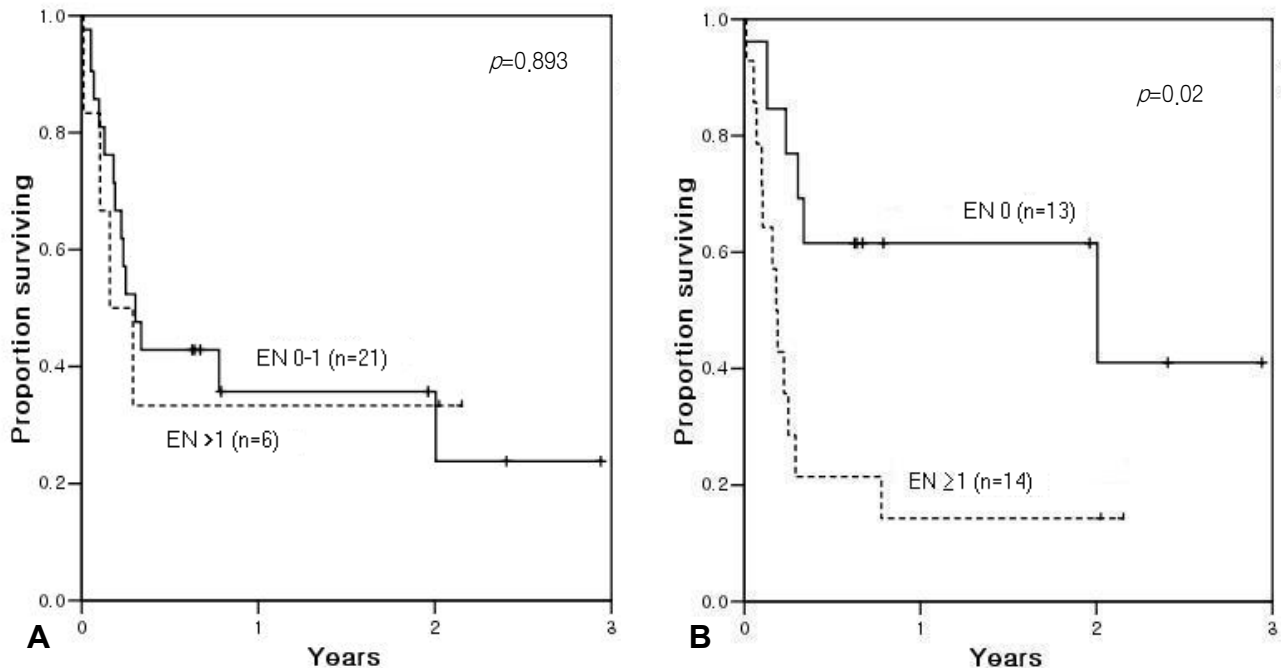


Figure 3. Event-free survival according to extranodal (EN) disease status at autologous stem cell transplantation. (A) Comparison between 0-1 EN site and more than 1 EN site showed no difference in event-free survival. (B) Modified categorization: patients with no remaining EN site had a 2-year event-free survival rate of 62%, significantly better than the 14% rate observed in patients with remaining EN site(s) at autologous stem cell transplantation.

Figure 2A). When we applied a modified categorization of EN involvement, grouped as negative or positive, the 2-year OS was 64% for patients with no EN site at ASCT, significantly better than the 14% 2-year OS in patients with EN involvement at ASCT ($p=0.021$; Figure 2B). The 2-year EFS was 36% for patients with 0-1 EN site and 33% with more than 1 EN involvement at ASCT ($p=0.893$; Figure 3A). With the modified categorization of EN involvement, the 2-year EFS was 62% for patients with no residual EN site at ASCT, significantly better than the 14% 2-year EFS in patients with residual EN involvement at ASCT ($p=0.02$; Figure 3B).

DISCUSSION

Patients with DLBCL can be cured by anthracycline-based chemotherapy. The recent introduction of rituximab and dose-dense chemotherapies has improved survival in these patients^{27, 28}. However, at least 50% of patients with DLBCL fail to achieve a CR, or relapse after CR. Half of the relapsing or refractory patients respond to salvage chemotherapy, but cure is expected in fewer than 10%. Eventually, almost 50% of patients with DLBCL die of their disease²⁹. High-dose therapy followed by ASCT has been widely used to improve the prognosis in these patients and has prolonged survival, especially in those with

chemosensitive disease.

Over the past 10 years, ASCT for DLBCL performed at our institution resulted in poor outcomes for patients who were not in CR at ASCT, with a 37% rate of 2-year OS, and a 36% rate of 2-year EFS. The poor outcomes we observed may have been due to the possibly unique biology of DLBCL in Koreans or other unknown factors. We sought to discover factors predicting prognosis of these patients with residual disease at ASCT, especially focusing on the influence of EN involvement. Thus, all patients had to have had residual disease at the time of ASCT to join this study. When this condition was met, we included any patients with DLBCL for whom ASCT had been performed at our institution.

In the current study, disease status at the time of ASCT was a significant factor predicting OS and EFS. Among the five IPI factors, LDH and performance status had statistical significance as predictors for OS and EFS. Age and stage showed no significance, although that may have been the result of our small sample size. EN involvement categorized by the original IPI system did not show a survival difference.

Our initial expectation with this retrospective analysis was that EN involvement may have a significant prognostic value. While EN lymphomas represent 30 ~ 40% of all lymphoid neoplasms in Western countries, around two-thirds of Korean NHLs are classified as extranodal²⁰. This high frequency of EN involve-

ment may be associated with poorer survival rates in Korean patients. Fourteen of 27 patients (52%) in the current study had residual EN disease, even at ASCT. A univariate analysis, however, showed no significant difference between patients with 0-1 EN site and those with more than 1 EN sites based on the IPI system. When patients were stratified into those with or without residual EN sites at the time of ASCT, a statistically significant difference was observed in the 2-year OS (14% vs. 64%) and 2-year EFS (14% vs. 62%).

Almost all reports dealing with the clinical course and outcome following ASCT in NHL have classified EN involvement as 0-1 versus more than 1 site, as in the original IPI system. In a study categorizing EN disease as 0 versus 1 or more sites, a statistically significant difference in the 5-year OS ($p=0.004$) was detected³⁰. Note that while they used a different categorization from the original IPI system, they did not provide an explanation for this. They analyzed 114 patients with DLBCL who did not achieve CR after induction chemotherapy and were set to be treated with ASCT. Seventy-one patients (62%) had EN involvement at diagnosis and 39 patients (35%) had residual EN disease at ASCT. The 5-year OS was 52% in patients with no residual EN disease, significantly better than the 25% for the 5-year OS in patients with residual EN involvement. Age-adjusted IPI, EN disease (0 versus ≥ 1) and disease status were significant prognostic factors for overall survival in a univariate analysis in that report.

Considering both the report from the GEL/TAMO group³⁰ and the results of the current study, categorization into negative versus positive EN involvement had predictive value. Patients with DLBCL and residual EN disease at ASCT did poorly compared to those with no residual EN involvement. This categorization may be valid especially when the EN involvement is more prevalent. In the current study, EN involvement at ASCT categorized as absent or present showed a strong association with predictors of poor prognosis, such as LDH above a normal range, advanced stage, higher IPI, and higher AAIPI at ASCT. Why patients with residual EN disease at ASCT have poor survival remains to be answered.

Patients with DLBCL and residual EN disease at ASCT may have poor survival with ASCT and should be given other novel therapies. Because this was a retrospective study performed with a limited number of patients, the results should be interpreted cautiously. A small sample size and short follow-up period cause limitations in statistical power.

In conclusion, Korean patients with DLBCL and residual disease at ASCT have frequent EN involvement, and patients with residual EN involvement show poor outcomes following ASCT. A modified categorization of EN involvement into negative versus positive may be more useful in predicting outcome following ASCT, especially when EN disease is prevalent.

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