Biol Blood Marrow Transplant 21 (2015) 1597–1604

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Clinical Outcomes and Prognostic Factors of Up-Front Autologous Stem Cell Transplantation in Patients with Extranodal Natural Killer/T Cell Lymphoma

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Article history:
Received 21 March 2015
Accepted 2 May 2015

Key Words:
Autologous
Stem cell transplantation
Extranodal natural killer/T cell lymphoma
Ann Arbor stage
Prognosis

A B S T R A C T

Limited data exist on up-front autologous stem cell transplantation (ASCT) in extranodal natural killer/T cell lymphoma (ENKTL). Sixty-two patients (43 men and 19 women) with newly diagnosed ENKTL who underwent up-front ASCT after primary therapy were identified. Poor-risk characteristics included advanced stage (50%), high-intermediate to high-risk International Prognostic Index (25.8%), and group 3 to 4 of NK/T Cell Lymphoma Prognostic Index (NKPI, 67.7%). Pretransplant responses included complete remission in 61.3% and partial remission in 38.7% of patients, and final post-transplantation response included complete remission in 78.3%. Early progression occurred in 12.9%. At a median follow-up of 43.3 months (range, 3.7 to 114.6), 3-year progression-free survival (PFS) was 52.4% and 3-year overall survival (OS) was 60.0%. Patients with limited disease had significantly better 3-year PFS (64.5% versus 40.1%, $P = .017$) and OS (67.6% versus 52.3%, $P = .048$) than those with advanced disease. Multivariate analysis showed NKPI and pretransplant response were independent prognostic factors influencing survival, particularly NKPI in limited disease and pretransplant response in advanced disease. Radiotherapy was an independent factor for reduced progression and survival in patients with limited disease, but anthracycline-based chemotherapy was a poor prognostic factor for progression in patients with advanced disease. Up-front ASCT is an active treatment in ENKTL patients responding to primary therapy.

INTRODUCTION

Extranodal natural killer/T cell lymphoma (ENKTL) is a distinct subtype of non-Hodgkin lymphoma that mainly involves nasal, paranasal, and oropharyngeal areas and is closely associated with Epstein-Barr virus (EBV) infection [1,2]. ENKTL is aggressive in nature and is frequently resistant to anthracycline-based chemotherapy [3]. Although ENKTL is more prevalent in East Asia than in Western countries, this disease is generally rare worldwide [4]. Because of the rarity of the disease and the consequent lack of prospective randomized trials, evidence-based standard therapy for ENKTL has not been established. Given the fact that ENKTL is radiosensitive disease [5,6], treatment strategies are mainly affected

Financial disclosure: See Acknowledgments on page 1604.
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http://dx.doi.org/10.1016/j.bbmt.2015.05.003
1083-8791/

by the Ann Arbor stage at initial diagnosis (either limited [stage I or II] or advanced [stage III or IV] disease). Several more recent phase II studies in patients with limited disease suggested that combined chemotherapy–radiotherapy was associated with improvement of clinical outcomes [7-11]. In addition, a small phase II study in patients with advanced disease showed that a regimen of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) had a promising response rate and improved survival [12]. However, a substantial number of patients with ENKTL, especially those with advanced disease, eventually experience relapse after treatments. Moreover, once ENKTL recurs, prognosis is extremely dismal [13]. This suggests that further treatment strategies are needed to prevent relapse and improve the survival.

High-dose therapy with autologous stem cell transplantation (ASCT) can be an attractive option for the treatment of ENKTL as an up-front consolidation strategy [1]. However, the effectiveness of ASCT on patients with distinct risk factors, optimal transplant timing, and available prognostic parameters to predict better outcomes has not yet been determined in ENKTL. Most data regarding ASCT in ENKTL were derived from small case series, and interpretation was complicated by heterogeneous populations [14-19]. In fact, these studies included fewer than 20 cases with up-front ASCT, and results from these studies are therefore not readily applicable in up-front ASCT in ENKTL. It is likely that prospective trials are finally needed to examine the role of ASCT in the treatment of ENKTL. However, before treatment strategies for up-front ASCT in ENKTL can be evaluated prospectively, comprehensive analyses from retrospective data may provide valuable insight into feasibility, response and survival rates, clinical prognostic factors, and treatment failure patterns for up-front ASCT strategies. Therefore, the purpose of this study was to investigate clinical outcomes and available prognostic factors in patients with ENKTL treated by up-front ASCT after primary therapy. These analyses may provide basic data for designing future prospective trials.

METHODS

Patient Population and Diagnostic Evaluation

Patients were recruited from 9 institutions belonging to the Consortium for Improving Survival of Lymphoma of the Korean Society of Hematology Lymphoma Working Party. Patients were eligible for inclusion in the study if they had received a diagnosis of ENKTL and underwent up-front ASCT after primary therapy between January 2004 and December 2013. Diagnoses of all patients included in this analysis were pathologically confirmed by tumor tissues obtained from the site of the disease, which were based on typical histologic features: positive immunohistochemical expression of cytoplasmic CD3, CD56, and cytotoxic molecules and positive EBV in situ hybridization results [20]. Patients were excluded if they had been diagnosed with aggressive NK cell leukemia. Patients who underwent salvage ASCT after disease progression were also excluded.

In all patients complete staging procedures, including medical history, physical examination, complete blood count, serum biochemistry with lactate dehydrogenase, computed tomography (CT) scan or magnetic resonance imaging scan of the involved region, CT scan of chest and abdomen, and bilateral bone marrow trephination biopsies, were performed. Baseline positron emission tomography (PET)-CT scan was performed at the discretion of the physicians based on their institution's policy. Using the results of these staging procedures, patients were classified into 2 groups: limited disease and advanced disease groups. The limited disease group included patients with stage I or II disease and the advanced disease group included patients with stage III or IV disease. Prognosis was determined according to the International Prognostic Index and the NK/T Cell Lymphoma Prognostic Index (NKPI) [21].

Based on the site of primary tumor, ENKTL cases were divided into 2 groups: the upper aerodigestive tract NK/T cell lymphoma (UNKTL) and extra-upper aerodigestive tract NK/T cell lymphoma (EUNKTL) groups [22]. In brief, UNKTL was defined as that involving the nasal cavity, nasopharynx, and upper aerodigestive tract, whereas EUNKTL was defined as the presence of primary tumors at other regions in the absence of nasal disease. All patients provided written informed consent in accordance with institutional guidelines, and the study protocol was reviewed and approved by the institutional review board at each participating institution.

Initial Treatment and Response Evaluation

Initial primary therapy consisted of the following treatment modalities: anthracycline-based primary chemotherapy with or without involved-field radiotherapy (IFRT), non–anthracycline-based chemotherapy with or without IFRT, and concurrent chemoradiotherapy with cisplatin followed by non–anthracycline-based chemotherapy. The anthracycline-based chemotherapeutic regimens used were cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone. Non–anthracycline-based chemotherapeutic regimens included SMILE; etoposide, ifosfamide, dexamethasone, and L-asparaginase (VIDL); ifosfamide, methotrexate, etoposide, prednisone plus L-asparaginase (IMEP plus L-asp); and etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD). In patients with limited disease, IFRT was administered after the completion of chemotherapy at the discretion of the treating physician. Concurrent chemoradiotherapy consisted of radiation therapy with a total dose of 36 to 44 Gy in 18 to 22 fractions and weekly administration of 30 mg/m^2 cisplatin for 4 weeks.

According to primary chemotherapy, patients were categorized into 2 groups: anthracycline-based chemotherapy and non–anthracycline-based chemotherapy groups (regardless of the sequence of chemotherapy and [chemo]radiotherapy). Patients generally proceeded to ASCT when they completed preplanned cycles of chemotherapy and achieved objective response. However, patients could proceed to ASCT if they had significant regimen-related toxicities or reasons other than disease progression to discontinue chemotherapy, which was at the discretion of the physician.

Tumor responses were assessed using the revised International Working Group criteria [23]. If PET-CT was performed, the response of PET-CT was assessed according to rules proposed by the International Harmonization Project in lymphoma [24]. Pretransplant response was assessed within 4 weeks before conditioning chemotherapy was administered, and response to ASCT was assessed 2 to 3 months after transplantation.

Stem Cell Mobilization and High-Dose Therapy with ASCT Procedure

Stem cell mobilization for ASCT was performed according to published recommendations [25]. Conditioning chemotherapy consisted of total body irradiation (TBI)–based and non–TBI-based regimens. The TBI-based regimen was etoposide, cyclophosphamide, and fractionated TBI [19], whereas non–TBI-based regimens included busulfan, cyclophosphamide, and etoposide; busulfan, melphalan, and etoposide; busulfan, etoposide, cytarabine, and melphalan; carmustine, etoposide, cytarabine, and melphalan; and busulfan and thiotepa.

Statistical Analysis

The primary endpoints were progression-free survival (PFS) and overall survival (OS) after ASCT. Survival endpoints were calculated from the date of ASCT until progression, death, or last follow-up, as appropriate. PFS and OS were estimated using the Kaplan-Meier method. Clinical variables were compared using Pearson's chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney test for continuous variables. Differences in PFS and OS among comparison groups were tested using a log-rank test in univariate analyses. Multivariate analysis was carried out using Cox proportional hazards models. Variables with $P < .10$ in univariate analyses were included in the multivariate model. The results were reported with a hazard ratio (HR) and 95% confidence interval (CI). $P < .05$ was considered to reflect statistical significance. All statistical analyses were performed using SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient Cohort

From 2004 to 2013, 66 patients with ENKTL who underwent up-front ASCT were recruited. Of these 66 patients, 4 did not meet the entry criteria: 2 patients were initially diagnosed with aggressive NK cell leukemia and 2 patients underwent ASCT after salvage chemotherapy. In total, 62 patients were registered for this analysis.

Pretransplant Characteristics and ASCT Procedures

The pretransplant clinical characteristics of the 62 patients are summarized in Table 1. The median age was 45.5 years (range, 18 to 64), and the male-to-female ratio was 2.26:1. Most patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (n = 55, 88.7%) and mainly presented as UNKTL (n = 50, 80.6%). Primary lesion locations of EUNKTL (n = 12, 19.4%) included the gastrointestinal tract (n = 4), soft tissue (n = 3), liver (n = 2), skin (n = 2), and testis (n = 1). More than 80% of patients (n = 51, 82.3%) were initially treated with non–anthracycline-based chemotherapy, including SMILE, VIDL, IMEP plus L-asp, and VIPD. Based on the Ann Arbor stage, 31 patients (50%) were categorized as belonging to the limited disease group and 31 patients (50%) as belonging to the advanced disease group. The number of extranodal organs involved was significantly greater in the advanced disease group ($P < .001$), and the number of patients with EUNKTL was greater in the advanced disease group, although this was of marginal significance ($P = .054$). Thus, the advanced disease group had more patients with higher risk International Prognostic Index and NKPI scores than did the limited disease group. In terms of treatment, more patients in the advanced disease were initially treated with non–anthracycline-based chemotherapy, although this difference was marginally significant ($P = .096$, Table 1). Twenty-three of 31 patients (74.2%) in the limited disease group had received radiotherapy before they were offered ASCT. Other characteristics did not differ significantly between the 2 groups.

Clinical parameters associated with transplantation procedures are listed in Table 2. Although most patients (n = 54, 87.1%) received non–TBI-based conditioning regimens, the number of patients who received TBI-based conditioning therapy was significantly higher in the advanced disease group (8 of 31, 25.8%; $P = .005$). The median time from diagnosis to transplant was significantly shorter in the advanced disease group ($P < .001$), which was associated with both higher median cycles of systemic chemotherapy and integration of radiotherapy in patients with limited disease. Only 1 patient (1.6%) experienced transplant-related mortality due to severe sepsis.

Treatment Outcomes and Therapy after Relapse

For the whole cohort, pretransplant responses consisted of a complete remission (CR) in 38 patients (61.3%) and a partial remission (PR) in 24 patients (38.7%). Final post-transplant responses were evaluated in 60 of 62 patients (96.7%). Of these patients, 47 (78.3%) achieved CR and 5

Table 1
Pretransplant Clinical Characteristics of Patients with ENKTL

	Total (n = 62)	Limited Disease (n = 31)	Advanced Disease (n = 31)	*P*
Age, yr				.587
Median	45.5	46.0	45.0	
Range	18-64	34-64	18-63	
Sex				.409
Male	43 (69.4%)	20 (64.5%)	23 (74.2%)	
Female	19 (30.6%)	11 (35.5%)	8 (25.8%)	
ECOG performance status				.104
0-1	55 (88.7%)	30 (96.8%)	25 (80.6%)	
2-4	7 (11.3%)	1 (3.2%)	6 (19.4%)	
B symptoms				.288
Absent	40 (64.5%)	22 (71.0%)	18 (58.1%)	
Present	22 (35.5%)	9 (29.0%)	13 (41.9%)	
LDH				.307
Normal	34 (54.8%)	19 (61.3%)	15 (48.4%)	
Elevated	28 (45.2%)	12 (38.7%)	16 (51.6%)	
Anatomic subtypes				.054
UNKTL	50 (80.6%)	28 (90.3%)	22 (71.0%)	
EUNKTL	12 (19.4%)	3 (9.7%)	9 (29.0%)	
Extranodal organ involved				<.001
Median	1	1	2	
Range	1-5	1	1-5	
IPI				<.001
Low to LI	46 (74.2%)	31 (100.0%)	15 (48.4%)	
HI to high	16 (25.8%)	0 (0%)	16 (51.6%)	
NKPI				<.001
Low (groups 1-2)	20 (32.3%)	20 (64.5%)	0 (0%)	
High (groups 3-4)	42 (67.7%)	11 (35.5%)	31 (100.0%)	
Primary chemotherapy				.096
Anthracycline-based	11 (17.7%)	8 (25.8%)	3 (9.7%)	
CHOEP	9	6	3	
CHOP	2	2	0	
Non–anthracycline-based	51 (82.3%)	23 (74.2%)	28 (90.3%)	
SMILE	23	1	22	
VIDL	14	11	3	
IMEP plus L-asp	10	8	2	
VIPD	4	3	1	
IFRT ± chemotherapy				<.001
No	35 (56.5%)	7 (22.6%)	28 (90.3%)	
Yes	27 (43.5%)	24 (77.4%)	3 (9.7%)	
Pretransplant response				.118
CR	38 (61.3%)	22 (71.0%)	16 (51.6%)	
PR	24 (38.7%)	9 (29.0%)	15 (48.4%)	

LDH indicates lactate dehydrogenase; IPI, International Prognostic Index; LI, low-intermediate; HI, high-intermediate; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone.

Table 2
Clinical Parameters Associated with ASCT Procedures

	Total (n = 62)	Limited Disease (n = 31)	Advanced Disease (n = 31)	*P*
Mobilization				.307
G-CSF alone	28 (45.2%)	16 (51.6%)	12 (38.7%)	
Chemotherapy plus G-CSF	34 (54.8%)	15 (48.4%)	19 (61.3%)	
Cyclophosphamide	15	1	15	
SMILE	16	11	4	
DHAP	2	2	0	
VIPD	1	1	0	
Infused $CD34^+$ cells ($\times 10^6$/kg)				.221
Median	7.02	6.78	7.80	
Range	1.69-36.19	1.69-22.10	2.01-36.19	
Conditioning therapy				.005
TBI-based	8 (12.9%)	0 (0%)	8 (25.8%)	
VCT	8	0	8	
Non–TBI-based	54 (87.1%)	31 (100%)	23 (74.2%)	
BuCyE or BuMelE	39	22	17	
BuEAM	10	4	6	
BEAM	3	3	0	
BuT	2	2	0	
Transplant-related mortality	1 (1.6%)	0 (0%)	1 (3.2%)	
No. of chemotherapy received				.064
Median	4	4	3	
Range	3-8	3-8	3-8	
Time from diagnosis to ASCT, mo				<.001
Median	6.6	7.2	4.7	
Range	3.0-10.3	4.1-10.3	3.0-10.0	

G-CSF indicates granulocyte colony-stimulating factor; DHAP, dexamethasone, cytarabine, cisplatin; VCT, etoposide, cyclophosphamide, TBI; BuCyE, busulfan, cyclophosphamide, etoposide; BuMelE, busulfan, melphalan, etoposide; BuEAM, busulfan, etoposide, cytarabine, melphalan; BEAM, camustine, etoposide, cytarabine, melphalan; BuT, busulfan, thiotepa.

(8.3%) achieved PR. Another 8 patients (12.9%) progressed within 3 months after transplantation (Table 3). Seven of 9 patients with pretransplant PR in the limited disease group upgraded to CR after transplantation, but only 6 of 13 patients with pretransplant PR in the advanced disease group achieved post-transplant CR. Thus, the number of patients achieving post-transplant CR was significantly higher in the limited disease group (28 of 31, 90.3%) than the advanced disease group (19 of 29, 65.5%; $P = .020$; Table 3). With a median follow-up of 43.3 months (range, 3.7 to 114.6), 30 patients (48.4%) had progressed, whereas 35 patients (56.5%) were alive. The 3-year PFS rate was 52.4% (95% CI, 39.9% to 64.9%), and the 3-year OS rate was 60.0% (95% CI, 47.5% to 72.5%). In the limited disease group, the 3-year PFS and OS rates were 64.5% (95% CI, 47.6% to 81.4%) and 67.6% (95% CI, 51.1% to 84.1%), respectively, and in the advanced disease group the 3-year PFS and OS rates were 40.1% (95% CI, 22.3% to 57.9%) and 52.3% (95% CI, 34.1% to 70.5%), respectively. Both PFS and OS rates of the limited disease group were significantly better than those in the advanced disease group (PFS, $P = .017$; OS, $P = .048$; Figure 1A, B).

Among the 30 patients who progressed after ASCT, 18 patients (60%) received salvage chemotherapies, which consisted of L-asparaginase–containing regimens (n = 11), including SMILE (n = 8); platinum-containing regimens (n = 6), including dexamethasone, cytarabine, cisplatin (n = 3) and ifosfamide, carboplatin, and etoposide (n = 3); and alemtuzumab with CHOP (n = 1). Of those who had undergone salvage chemotherapy, only 5 patients (16.7%) achieved objective responses (3 CR, 2 PR), and 2 patients (6.7%) underwent allogeneic SCT while on remission.

Prognostic Factors for PFS and OS

Univariate and multivariate analyses to identify the prognostic factors for PFS and OS were performed separately in 2 steps. In the first step, the analysis included all patients (n = 62). Age, sex, ECOG performance status, serum lactate dehydrogenase level, Ann Arbor stage, B symptoms, pretransplant response, International Prognostic Index, NKPI, anatomic subtypes, and primary chemotherapy were included as independent variables for the analyses. In the univariate analysis for PFS and OS, advanced stage was associated with earlier progression ($P = .017$) and death ($P = .048$, Table 4). However, in the multivariate analysis, advanced stage was not predictive of increased risk of progression and death. On the other hand, pretransplant PR

Table 3
Post-Transplant Responses According to Pretransplant Responses

	Post-Transplant Response								*P*
	Limited Disease (n = 31)				Advanced Disease (n = 29*)				
	CR	PR	PD	Sum	CR	PR	PD	Sum	
Pretransplant response									
CR	21 (95.5%)	—	1 (4.5%)	22	13 (81.3%)	—	3 (18.8%)	16	
PR	7 (77.8%)	1 (11.1%)	1 (11.1%)	9	6 (46.2%)	4 (30.8%)	3 (23.1%)	13	
Total	28 (90.3%)	1 (3.2%)	2 (6.5%)	31	19 (65.5%)	4 (13.8%)	6 (20.7%)	29	.020

PD indicates progressive disease.

* Post-transplant response status was not available in 2 patients with pretransplant PR in the advanced disease group, because of early death without the evidence of disease progression at 1.4 and 2.0 months after transplantation, respectively.

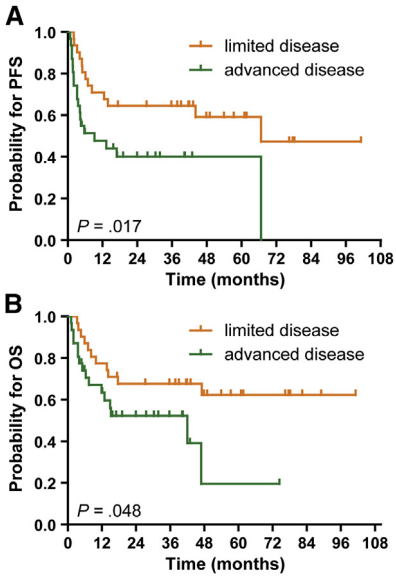

Figure 1. Survival outcomes according to Ann Arbor stage. The limited disease group had significantly longer (A) PFS and (B) OS rates than the advanced disease group.

(PFS: HR, 4.12 [95% CI, 1.90 to 8.91]; OS: HR, 3.22 [95% CI, 1.15 to 8.98]) and high-risk NKPI (PFS: HR, 2.85 [95% CI, 1.09 to 7.49]; OS: HR, 2.60 [95% CI, 1.19 to 5.66]) were independent prognostic factors for shorter PFS and OS (Table 5, All patients). Poor ECOG performance status was also associated with lower PFS (HR, 4.31 [95% CI, 1.48 to 12.60]) but was not predictive of reduced OS (Table 5, All patients).

In the second step, statistical analyses were performed separately based on Ann Arbor stages. In the limited disease group (n = 31), IFRT to the primary lesion was additionally included as an independent variable for this analysis. In the limited disease group, NKPI ($P = .025$) and IFRT to the primary lesion ($P = .009$) were significantly associated with PFS in the univariate analysis (Figure 2A,B). Moreover, anatomic subtypes ($P = .014$) were also significantly related to progression. Based on the multivariate model, high-risk NKPI (HR, 3.92 [95% CI, 1.05 to 14.67]) and EUNKTL (HR, 11.60 [95% CI, 2.29 to 58.83]) were independent prognostic factors for increased risk of progression, whereas IFRT to the primary lesion (HR, .24 [95% CI, .06 to .92]) was independently associated with a lower risk of progression (Table 5, Limited disease patients). With other variables, such as serum lactate dehydrogenase level and pretransplant response, the statistical significance in the univariate analysis disappeared after the multivariate analysis. In the multivariate analysis for OS, only IFRT to the primary lesion was associated with a reduced risk of death (Table 5, Limited disease patients).

In the advanced disease group (n = 31), conditioning regimen was included as a variable for the analysis. In the advanced disease group, pretransplant response ($P = .009$) and primary chemotherapy ($P < .001$) were significantly associated with PFS in the univariate analysis (Figure 2C, D). In the multivariate analysis for PFS, pretransplant PR (HR, 3.09 [95% CI, 1.06 to 9.05]) and anthracycline-based primary chemotherapy (HR, 10.44 [95% CI, 2.02 to 53.96]) were independent prognostic factors for reduced PFS (Table 5,

Table 4
Univariate Analysis for PFS and OS

Variables	No. of Patients	3-Year PFS	*P*	3-Year OS	*P*
Age at diagnosis, yr			.513		.473
<60	55	48.5 (35.2-61.8)		57.1 (43.8-70.4)	
≥60	7	85.7 (59.9-10.0)		85.7 (59.8-100.0)	
Sex			.532		.453
Male	43	48.2 (33.1-63.3)		56.9 (41.8-72.0)	
Female	19	62.7 (40.7-84.7)		67.4 (45.8-89.0)	
Ann Arbor stage			.017		.048
Limited	31	64.5 (47.6-81.4)		67.6 (51.1-84.1)	
Advanced	31	40.1 (22.3-57.9)		52.3 (34.1-70.5)	
B symptoms			1.0		.889
Absent	40	53.9 (38.2-69.6)		61.3 (45.8-76.8)	
Present	22	50.0 (29.0-71.0)		58.2 (37.2-79.2)	
ECOG performance status			.006		.117
0-1	55	55.4 (42.1-68.7)		62.1 (49.0-75.2)	
2-4	7	28.6 (0-62.1)		42.9 (6.2-79.6)	
LDH			.221		.413
Normal	34	58.0 (41.1-74.9)		66.2 (49.7-82.7)	
Elevated	28	45.7 (27.1-64.3)		52.6 (33.8-71.4)	
Pretransplant response			<.001		.004
CR	38	73.1 (58.8-87.4)		72.4 (57.7-87.1)	
PR	24	20.8 (4.5-37.1)		40.9 (20.9-60.9)	
IPI			.121		.280
Low to LI	46	55.9 (41.4-70.4)		64.3 (50.2-78.4)	
HI to high	16	42.2 (17.3-67.1)		48.1 (23.0-73.2)	
NKPI			.004		.008
Low risk (groups 1-2)	20	75.0 (56.0-94.0)		80.0 (62.6-97.4)	
High risk (groups 3-4)	42	41.5 (26.2-56.8)		50.5 (35.0-66.0)	
Anatomic subtypes			.282		.377
UNKTL	50	55.5 (41.6-69.4)		63.1 (49.6-76.6)	
EUNKTL	12	38.9 (10.1-67.7)		46.9 (17.5-76.3)	
Primary chemotherapy			.383		.882
Non–anthracycline-based	51	49.8 (35.9-63.7)		59.0 (45.1-72.9)	
Anthracycline-based	11	54.5 (25.1-83.9)		54.5 (25.1-83.9)	

Values are percents, with 95% CIs in parentheses.

Table 5
Multivariate Analyses to Identify Prognostic Factors for PFS and OS

Variables	HR	95% CI	*P*
PFS			
All patients (n = 62)			
NKPI			
Low risk (groups 1-2)	1		
High risk (groups 3-4)	2.85	1.09-7.49	.033
Pretransplant response			
CR	1		
PR	4.12	1.90-8.91	<.001
ECOG performance status			
0-1	1		
2-4	4.31	1.48-12.60	.008
Limited disease patients (n = 31)			
NKPI			
Low risk (groups 1-2)	1		
High risk (groups 3-4)	3.92	1.05-14.67	.043
Anatomic subtypes			
UNKTL	1		
EUNKTL	11.60	2.29-58.83	.003
IFRT to primary lesion			
No	1		
Yes	.24	.06-.92	.038
Advanced disease patients (n = 31)			
Pretransplant response			
CR	1		
PR	3.09	1.06-9.05	.039
Primary chemotherapy			
Non–anthracycline-based	1		
Anthracycline-based	10.44	2.02-53.96	.005
OS			
All patients (n = 62)			
NKPI			
Low risk (groups 1-2)	1		
High risk (groups 3-4)	3.22	1.15-8.98	.026
Pretransplant response			
CR	1		
PR	2.60	1.19-5.66	.016
Limited disease patients (n = 31)			
IFRT to primary lesion			
No	1		
Yes	.24	.07-.80	.021
Advanced disease patients (n = 31)			
Primary chemotherapy			
Non–anthracycline-based	1		
Anthracycline-based	51.58	5.40-493.07	.001

Advanced disease patients). ECOG performance status (P = .004) was significantly associated with progression in the univariate analysis but was not an independent predictive factor for PFS in the multivariate model. In the multivariate analysis for OS, anthracycline-based primary chemotherapy was the only independent factor for increased risk of death (Table 5, Advanced disease patients).

DISCUSSION

This study is the first to investigate clinical outcomes of up-front ASCT with a large patient cohort, considering the rarity of ENKTL. Because the data were collected retrospectively and ASCT itself is influenced by age and/or comorbidity, a degree of patient selection would be present in this study. However, it is noteworthy that up-front ASCT in ENKTL has been generally considered for patients responding to initial therapy, whereas it is rarely offered to patients who are unresponsive to primary therapy. Considering that about 15% to 30% of patients with B or T cell lymphoma initially considered for up-front ASCT could not proceed to transplantation due mainly to disease progression [26,27], our study might represent the group of patients who are transplant-eligible after primary therapy. Additionally, compared with previously published series of ENKTL [21,28,29], the cohort in this study was concordant with typical features and characteristics of ENKTL patients (male dominant by 2.26-fold, median age 45.5 years, and primary lesions predominantly around the nasal cavity [80.4%]). Therefore, these findings suggest that our cohort might be considered as representative of typical ENKTL cases responding to initial primary therapy.

In this present analysis, we demonstrated that ASCT is a feasible and effective therapy in ENKTL patients who respond to initial primary therapy. In the limited disease group, clinical outcomes after transplantation were strongly associated with NKPI at diagnosis and IFRT to the primary lesion. This finding may imply that patients with a low-risk NKPI had excellent outcomes compared with those with a high-risk NKPI. However, given the excellent outcomes in several phase II studies regarding treatment strategies using non–anthracycline-based chemotherapy and (chemo) radiotherapy in patients with limited-stage ENKTL (PFS, 60% to 86% at 2 to 3 years; OS, 73% to 88% at 2 to 3 years), the survival outcomes of our study were similar to those of previous prospective studies [7-11]. Although more patients with limited disease had a high-risk NKPI in this study compared with previous studies (36% versus 20% to 30%) [7-10], these findings suggest that up-front ASCT should not be performed uniformly in all patients with limited disease but may be considered in highly selected cases. In this sense, it is important to consider parameters that may predict which patients would receive the most benefit from up-front ASCT strategies. Using a matched control method, Lee et al. [14] investigated the impact of ASCT on clinical outcomes in 47 ENKTL patients, including 31 cases of stage I/II disease, and demonstrated that survival was not different between the transplant group and matched control group. However, in the subgroup analysis, ASCT conferred a survival benefit in patients who attained CR and had a high-risk NKPI [14]. Furthermore, Kim et al. [30] recently reported that combined analyses of both circulating EBV DNA and PET-CT response could predict recurrence of ENKTL in patients treated with concurrent chemoradiotherapy or non–anthracycline-based chemotherapy. In this report, they showed that approximately 60% of patients with EBV DNA positivity or Deauville score 3 to 4 of PET-CT results after the completion of chemotherapy would have recurrence, which was significantly higher than those with both negative EBV DNA and Deauville score 1 to 2 of PET-CT. Thus, application of ASCT in limited-stage ENKTL should be tailored to patients most likely to benefit from this approach. In future studies, risk-, biomarker-, and response-adapted treatment strategies using NKPI [14], EBV DNA [30-32], and PET-CT findings [30] need to be investigated in this group of patients.

Interestingly, omitting radiotherapy in limited disease was a worse prognostic factor for PFS and OS, which might be related to frequent failure around the primary lesion. This finding was consistent with previous studies regarding the therapeutic role of radiotherapy [6,20,33]. Based on reports, disease progression during chemotherapy occurred in 30% to 40% of patients, requiring salvage radiotherapy [6,20]. These findings may implicate that chemotherapy, even high-dose therapy, does not satisfactorily prevent local failure. Conversely, radiotherapy should be an integral part of treatment, even if followed by ASCT. Therefore, our data highlight the importance of radiotherapy for the treatment of limited-stage ENKTL.

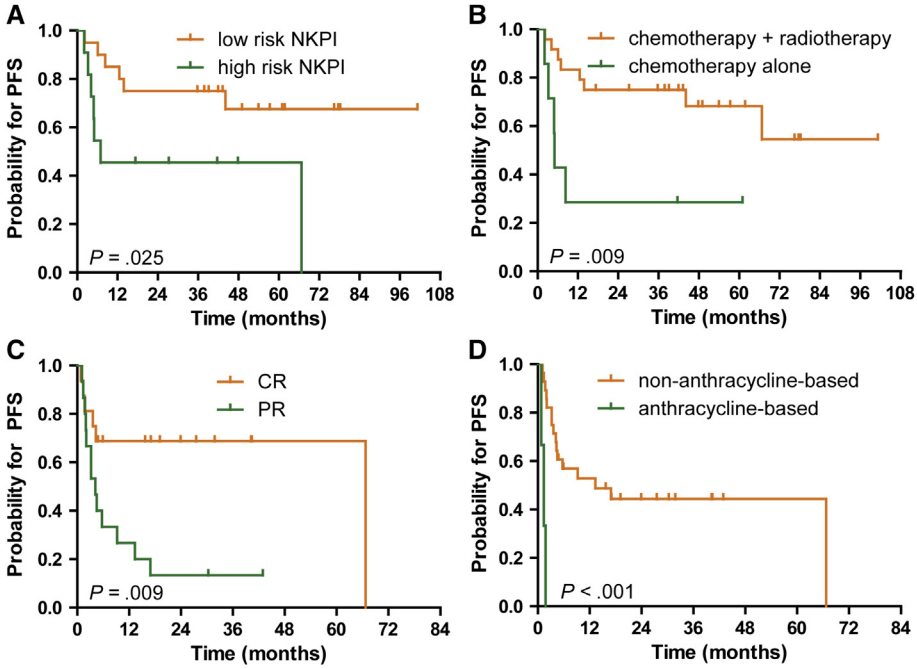

Figure 2. PFS in the (A and B) limited disease group and (C and D) advanced disease group. Comparison according to the (A) NKPI and (B) radiotherapy to the primary lesion in the limited disease group showed that a low-risk NKPI and combined chemotherapy–radiotherapy were associated with significantly longer PFS rates than a high-risk NKPI and chemotherapy alone, respectively. When we compared PFS in patients with advanced disease according to (C) pretransplant response and (D) primary chemotherapy, pretransplant CR achievement and non–anthracycline-based primary chemotherapy were associated with significantly better PFS than pretransplant PR and anthracycline-based chemotherapy, respectively.

In the present analysis, advanced disease was not an independent factor for increased risk of progression or death. This may be associated with better than expected outcomes of patients with advanced disease. Current non–anthracycline-based chemotherapy might induce improved disease control before ASCT, which translated into survival outcomes after transplantation, especially in patients with pretransplant CR. Indeed, the survival outcomes (3-year PFS, 40%; 3-year OS, 52%) of patients with advanced-stage ENKTL were quite beyond expectations. Additionally, multivariate analysis showed that pretransplant PR and anthracycline-based chemotherapy were important predictors for disease progression. The prognostic significance of pretransplant disease status has already been suggested in several retrospective studies investigating ASCT in ENKTL [14,15]. These findings suggest that patients achieving CR with primary therapy might be most likely to benefit from up-front ASCT strategies. Therefore, advanced-stage ENKTL patients achieving CR after non–anthracycline-based chemotherapy need to be considered for up-front ASCT. On the other hand, in the present study, the outcomes of patients in the advanced disease group achieving PR with primary therapy were dismal; a 13.3% 3-year PFS rate was observed. Given the extremely poor outcomes of advanced-stage patients with PR, up-front ASCT might not be a feasible treatment strategy in the PR cohort. Thus, novel treatment approaches are urgently needed to improve outcomes for the PR cohort.

However, even if encouraging survival outcomes were observed after up-front ASCT, approximately 20% of patients with advanced disease progressed within 3 months after transplantation. Current data have suggested that non–anthracycline-based chemotherapy, such as SMILE, may be a mainstay of treatment in advanced-stage ENKTL [12,34]. In our study, 90.3% of the patients with advanced disease received non–anthracycline-based chemotherapy, mostly the SMILE regimen. This finding indicates that further effective treatment modalities are needed for advanced-stage ENKTL. Thus, treatment intensification of primary chemotherapy or other novel treatment strategies needs to be urgently investigated in this group of patients.

There are several limitations of our study. First, the current analysis is based on retrospective data with a relatively short follow-up duration. Additionally, the small number of cases in the subgroup analyses may restrict the generalizability of our findings. This should always be considered when interpreting the results; therefore, the data presented here could be used as a historical reference before generating a hypothesis for designing prospective trials. Second, the results of circulating EBV DNA levels, recently identified as a valuable biomarker of tumor load [30-32,35,36], was not included in the current analysis, because measurement timing, interval, frequency, and assay methods of EBV DNA were different according to each participating institution's policy. Considering the prognostic role of circulating EBV DNA levels in recently published series for ENKTL, it should be measured in future prospective studies regarding ASCT in ENKTL [30-32,35,36].

In conclusion, up-front ASCT may be a feasible and active treatment option in patients with ENKTL who respond to primary therapy. NKPI and pretransplant response are important factors for predicting clinical outcomes, particularly NKPI in limited disease and pretransplant disease status in advanced disease. Additionally, radiotherapy plays an essential role in the treatment of limited-stage disease, even if ASCT is offered. Alternatively, in the management of advanced disease, anthracycline-based chemotherapy should be avoided because it is

associated with inferior outcomes, and patients who achieved CR after non–anthracycline-based chemotherapy should be considered for studies evaluating up-front ASCT strategies. To improve outcome in patients with advanced disease, novel treatment strategies need to be further explored. Finally, the present data provide reference points for future studies regarding up-front ASCT in ENKTL.

ACKNOWLEDGMENTS

This study was presented in part at the 56th American Society of Hematology Annual Meeting in San Francisco, California, December 6-9, 2014.

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: H.Y.Y. designed the research, analyzed data, and wrote the manuscript. J.S.K., Y.C.M., J.H.M., Y.S.C., Y.P., J.C.J., S.J.K., D.H.Y., J.W.C., J.W.K., J.J.L., W.S.K., and C.S. recruited patients and recorded the data. D.H.Y. designed the research, analyzed data, and critically revised the manuscript.

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