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Prognostic Factors and Clinical Outcomes of High-Dose Chemotherapy followed by Autologous Stem Cell Transplantation in Patients with Peripheral T Cell Lymphoma, Unspecified: Complete Remission at Transplantation and the Prognostic Index of Peripheral T Cell Lymphoma Are the Major Factors Predictive of Outcome

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High-dose chemotherapy followed by autologous stem cell transplantation (HDT/ASCT) offers a rescue option for T cell lymphoma patients with poor prognosis. However, the effectiveness of HDT/ASCT in patients with various peripheral T cell subtypes, optimal transplant timing, and the prognostic factors that predict better outcomes, have not been identified. We retrospectively investigated the clinical outcomes and prognostic factors for HDT/ASCT in 64 Korean patients with peripheral T cell lymphoma, unspecified (PTCL-U) between March 1995 and February 2007. The median age at transplantation was 44 years (range: 15-63 years). According to the age-adjusted International Prognostic Index (a-IPI) and the prognostic index of PTCL (PIT), 8 patients (12.5%) were in the high-risk group and 16 (26.6%) had the 2-3 PIT factors, respectively. After a median follow-up of 29.7 months, the 3-year overall survival (OS) and progression-free survival (PFS) rates were 53.0% ± 7.5% and 44.3% ± 7.0%, respectively. Univariate analysis showed that poor performance status, high lactate dehydrogenase (LDH) levels, high a-IPI score, high PIT classes, failure to achieve complete response (CR) at transplantation, and nonfrontline transplantation were associated with poor OS. Multivariate analysis showed that failure to achieve CR at transplantation (hazard ratio [HR] 2.23; 95% confidence interval [CI] 1.78-7.93) and 2-3 PIT factors (HR 3.76; 95% CI 1.02-5.42) were independent prognostic factors for OS. Failure to achieve CR at transplantation and high PIT are negative predictable factors for survival following HDT/ASCT in patients with PTCL-U.

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INTRODUCTION

Peripheral T cell lymphomas (PTCL) are a heterogeneous group of aggressive non-Hodgkin's lymphomas (NHLs). Whereas the effect of the immunophenotype on the outcome of aggressive NHLs is unclear, the T cell phenotype per se is associated with unfavorable

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prognosis, compared with B-cell lymphomas [1-4]. Understanding of the pathophysiology and optimal treatment of T cell lymphomas has been limited by the relative rarity of the condition and histologic subtype heterogeneity, making the determination of the natural course and the prognostic factors relative to each T cell lymphoma subtype difficult. The International Peripheral T Cell Lymphoma Project has recently reported that patients with anaplastic large cell lymphoma (ALCL), whether positive or negative for anaplastic lymphoma kinase (ALK), have superior survival outcomes compared with patients with peripheral T cell lymphomas, unspecified (PTCL-U) [5]. To better define the clinical outcome of PTCL, evaluation of the prognostic markers and treatment strategies for each PTCL subtype should be evaluated.

PTCL-U is the most common subtype of PTCL, and often presents in an advanced stage at the time of diagnosis, and with an aggressive clinical course despite treatment [6,7]. The 5-year survival rate of patients with PTCL-U ranges between 25% and 45% [8-10], which make this T cell lymphoma subtype a risk factor per se, independent of other risk factors such as those shown by the International Prognostic Index (IPI) [6,11]. Although IPI has been reported to be useful in predicting the clinical outcome of PTCL, the impact of IPI on specific PTCL subtypes has not been determined [12,13]. In addition, a new prognostic model for PTCL has been suggested, composed of four independent variables: age, lactate dehydrogenase (LDH), performance status, and bone marrow involvement [14].

High-dose chemotherapy followed by autologous stem cell transplantation (HDT/ASCT) offers a rescue option for PTCL patients with poor prognosis [10,15,16]. However, the effectiveness of ASCT in patients with various PTCL subtypes, the optimal timing of transplantation, and the prognostic factors predicting better outcome, have not been determined. We therefore retrospectively assessed the clinical outcomes of and determined the prognostic factors for HDT/ASCT in 64 Korean patients with PTCL-U.

PATIENTS AND METHODS

Patient Eligibility

Clinical outcomes following HDT/ASCT were assessed in patients with PTCL-U who were treated at 14 Korean institutions between March 1995 and February 2007. PTCL-U was histologically diagnosed according to the REAL classification [17], which was later modified to conform with the WHO classification. All biopsy specimens with unconfirmed histopathologic features were referred to experienced hematopathologists, and the immunohistochemical and molecular characteristics were assessed during central review committee. The study enrolled 64 patients aged ≤65 years with adequate cardiac, pulmonary, hepatic, and renal function before transplantation. The patients were staged according to the Ann Arbor staging system and evaluated using standard procedures, including physical, laboratory, radiologic, and bone marrow examinations. The same methods were used to evaluate therapeutic responses to primary or salvage chemotherapy, and to HDT/ASCT. Patient prognosis was determined according to the age-adjusted International Prognostic Index (a-IPI) and the Prognostic Index for PTCL (PIT) (Table 1). Frontline HDT/ASCT was permitted in patients with bulky (≥10 cm) or advanced (stage III or IV) disease, or those who had high-risk a-IPI (≥2) or 3-4 PIT factors at diagnosis.

Response Criteria

Responses to primary chemotherapy, salvage chemotherapy, and HDT/ASCT were assessed according to the International Workshop Criteria (IWC) [18]. First complete response (CR1) and first partial response (PR1) were defined as having achieved a CR and PR after primary chemotherapy. Chemosensitive relapsed or refractory CR (CR2) and PR (PR2) were defined as CR and PR after salvage chemotherapy.

Table 1. Patient Pretransplant Characteristics

	N	%
Gender (male/female)	45/19	70.3/29.7
Age, median (years)	44 (15-63)	
Performance status		
0-1	52	81.3
2-3	12	18.8
Stage at diagnosis		
Stage I/II	3/16	4.7/25.0
Stage III/IV	19/26	29.7/40.6
B symptoms	22	34.4
LDH Normal	39	60.9
High	25	39.1
Age-adjusted IPI at diagnosis		
Low	15	23.4
Low-intermediate	21	32.8
High-intermediate	20	31.3
High	8	12.5
PIT at diagnosis		
0 factor	30	46.9
1 factor	18	26.6
2-3 factors	16	26.6
Primary chemotherapy		
CHOP	43	67.2
CHOP and etoposide± gemcitabine	14	21.9
CHOP and alemtuzumab	1	1.6
IMVP-16 or promace cytabom	6	9.5
Response after primary chemotherapy		
CR/PR	33/18	51.6/28.1
SD/PD	4/9	6.3/14.1
Radiation therapy	12	18.8

IPI indicates International Prognostic Index; PIT, prognostic index of PTCL; LDH, lactate dehydrogenase; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease;

Progressive or refractory disease was defined as no response to treatment or progression during or within 1 month after completing treatment. Response to HDT/ASCT was assessed 2 or 3 months after transplantation. Imaging modalities were used to restage tumors every 3 months for the first 2 years after ASCT, every 6 months for the next 2 years, and then yearly or whenever clinically indicated.

Pretransplantation and Transplantation Protocols

Most patients received an anthracycline-based chemotherapy regimen as first-line treatment, except for 6 patients who received IMEP (ifosfamide, methotrexate, etoposide, and prednisolone) or promace cytabom chemotherapy. Patients with relapsed or refractory disease were treated with a salvage chemotherapy regimen, including DHAP (dexamethasone, ara-C, cisplatin), ICE (ifosfamide, carboplatin, etoposide), ESHAP (etoposide, ara-C, cisplatin, methylprednisolone), or dose-adjusted EPOCH (cyclophosphamide, etoposide, vincristine, doxorubicin, and methylprednisolone). Thirty-one patients (48.4%) were mobilized with cyclophosphamide (4 g/m^2) plus granulocyte colony-stimulating factor (G-CSF) (10 μg/kg/day), 9 patients were mobilized with salvage chemotherapy plus G-CSF, and 19 patients (29.7%) were mobilized with G-CSF alone. The median number of stem cell collections was 2 (range: 1-11). The stem cell source in all cases was the peripheral blood.

Statistical Analysis

Descriptive statistics are summarized as frequency counts and percentages for categoric variables and as medians and range for continuous variables. Progression-free survival (PFS) was calculated from the date of ASCT to the first recording of disease relapse, progression, or death from any cause. Patients whose disease did not progress were censored using the date when they were last known to show no progression. Overall survival (OS) was defined as the time from transplantation to the date of last follow-up or death from any cause. The distribution of patients in OS and PFS was estimated using the Kaplan-Meier product-limit method and compared by the log-rank test for the association between clinical prognostic factors and the probability of treatment failure. Multivariate Cox's proportional-hazards models were used to analyze all factors found to be significant during the univariate analysis. Transplant-related mortality included all deaths within 60 days of transplantation without disease progression. Two-tailed P-values $<.05$ were considered statistically significant. All statistical analyses were performed using SPSS statistical software, version 13.0 (SPSS, Inc., Chicago, IL).

RESULTS

Pretransplantation Characteristics, Stem Cell Collection, and Conditioning Regimens

The pretransplantation characteristics of the 64 included patients are summarized in Table 1. Their median age was 44 years (range: 15-63 years) and the median time from diagnosis to transplantation was 10.5 months (range: 3.7-74.6 months). Forty-five patients (70.3%) presented in advanced stages (III/IV) and 22 (34.4%) had B symptoms. At diagnosis, 28 patients (43.8%) were classified as high risk according to the a-IPI scoring system and 16 (26.6%) were classified as high risk by the PIT. The overall response rate to primary chemotherapy was 79.7%. There was no significant difference in response rates between patients treated with CHOP alone or CHOP-like chemotherapy and those treated with another nonanthracycline-based chemotherapeutic regimen. Twelve patients (18.7%) received a short course of chemotherapy followed by involved field radiation therapy (IFRT). Twenty-eight patients (43.8%) received HDT/ASCT after primary chemotherapy, whereas 36 patients (56.2%) received 2 or more chemotherapy regimens before transplantation. Sixteen patients (25.0%) underwent HDT/ASCT while in CR1 and 12 (18.8%) while in PR1 after primary chemotherapy. However, 5 patients (7.9%) were transplanted in CR2 and 25 (39.0%) in PR2 after salvage chemotherapy. Overall, 21 patients (32.9%) achieved CR at transplantation and 6 (9.4%) underwent HDT/ASCT when their status was progressive or chemorefractory.

With a median number of 2 stem cell collections (range: 1-11), an average of 6.0×10^6/kg CD34$^+$ cells was infused. The hematologic recovery of granulocytes (absolute neutrophil count [ANC] >500/μL) and platelets (>20,000/μL) occurred at a median time of 12 and 14 days, respectively. Conditioning regimens varied between participating centers. Twenty-five patients (39.1%) were conditioned with BCNU, etoposide, cytarabine, and melphalan (BEAM), and 20 patients (31.3%) with busulfan, cyclophosphamide, and etoposide (BuCyE). Only 3 patients (4.7%) received total-body irradiation (TBI)-based conditioning (Table 2).

The transplant-related mortality (TRM) rate was 6.2%. Two patients died from veno-occlusive disease and 2 from severe neutropenic infections.

Posttransplantation Outcomes and Prognostic Factors

After a median follow-up time of 29.7 months (range: 6.5-155.7 months), 36 patients (56.2%) were alive, whereas 25 (39.1%) had relapsed or progressed. The 3-year OS and PFS rates were 53.0 ± 7.5 % and 44.3 ± 7.0 %, respectively (Figure 1). The similarity

Table 2. Clinical Parameters Associated with HDT/ASCT

Parameters	N	%
Disease status at ASCT		
CR1/PR1	16/12	25.0/18.8
Chemosensitive relapsed/ refractory CR/PR	5/25	7.9/39.0
Progressive or refractory	6	9.4
Mobilization		
G-CSF alone	19	29.7
Salvage chemotherapy and G-CSF	9	14.1
Cyclophosphamide and G-CSF	31	48.4
Other chemotherapy and G-CSF	5	7.8
Number of PBSCC, median	2 (1-11)	
Infused $CD34^+$ cell dose, median	6.0 (1.5-29.1)	
$\geq 6.0 \times 10^6$/kg	37	57.8
$<6.0 \times 10^6$/kg	27	42.2
Conditioning regimen		
BEAM	25	39.1
BuCyE	20	31.3
BEAC	7	10.9
CyTBI	3	4.7
Others (BuCyMel or salvage regimens)	9	14.1
Hematologic recovery after ASCT		
Median days of ANC >500	D+12 (8-52)	
Median days of PLT >20,000	D+14 (6-158)	
Transplant-related mortality	4	6.2
Relapse after ASCT	25	39.1
Median time from diagnosis to ASCT	10.5 (3.7-74.6 months)	

HDT/ASCT indicates high-dose chemotherapy followed by autologous stem cell transplantation; ANC, absolute neutrophil count; G-CSF, granulocyte-colony stimulating factor; PBSCC, peripheral blood stem cell count; CR, complete remission; PR, partial remission.

between OS and PFS arose because of the small effect of retreatment in patients who were not cured with HDT/ASCT. Univariate analysis of factors influencing OS and PFS was presented in Table 3. We found that poor OS was associated with high PS score, high LDH, high a-IPI, and high PIT. Both a-IPI and PIT showed good ability to predict OS and PFS. That is, the 3-year OS rates were 64% and 64.8% in the low-risk a-IPI and PIT 0 group, respectively; 48.1% and 49.0% in the low- to intermediate-risk a-IPI and PIT 1 group, respectively; and 43.9% and 7.5% in the high- to intermediate-risk a-IPI and PIT 2-3 groups, respectively (Figure 2). We also found that disease status at transplantation, achievement of CR at transplantation, and frontline transplantation during CR1 or PR1, all showed prognostic significance on OS. However, disease status at transplantation and transplant timing did not have prognostic significance on PFS (Figure 2). Other clinical factors, such as the dose of infused $CD34^+$ cells, the conditioning regimen, and the number of courses of salvage chemotherapy, had no prognostic significance on either OS or PFS.

Multivariate analysis showed that failure to achieve CR at transplantation (hazard ratio [HR] 2.23; 95% confidence interval [CI] 1.78–7.93) and high PIT scores of 2-3 (HR 3.76; 95% CI 1.02-5.43) were independent prognostic factors for OS, and that high PIT was an independent prognostic factor for PFS (HR 3.76; 95% CI 1.023-5.428).

DISCUSSION

HDT/ASCT is widely accepted as the treatment of choice for patients with chemosensitive relapsed or refractory aggressive B cell lymphoma with long-term PFS of 40% to 50% [19,20]. However, the role of this procedure in PTCL is still unclear. Most retrospective studies have shown comparable outcomes of HDT/ASCT in cases of relapsed or refractory PTCL [21-25]. However, these studies included heterogeneous populations with varying IPI or PIT scores, various subtypes of PTCL, and different disease status at transplantation, making determination of clinical application and role of HDT/ASCT somewhat ambiguous.

In this study, we retrospectively evaluated the clinical outcome of transplantation in patients with PTCL-U. The 3-year OS and PFS rates were 53%

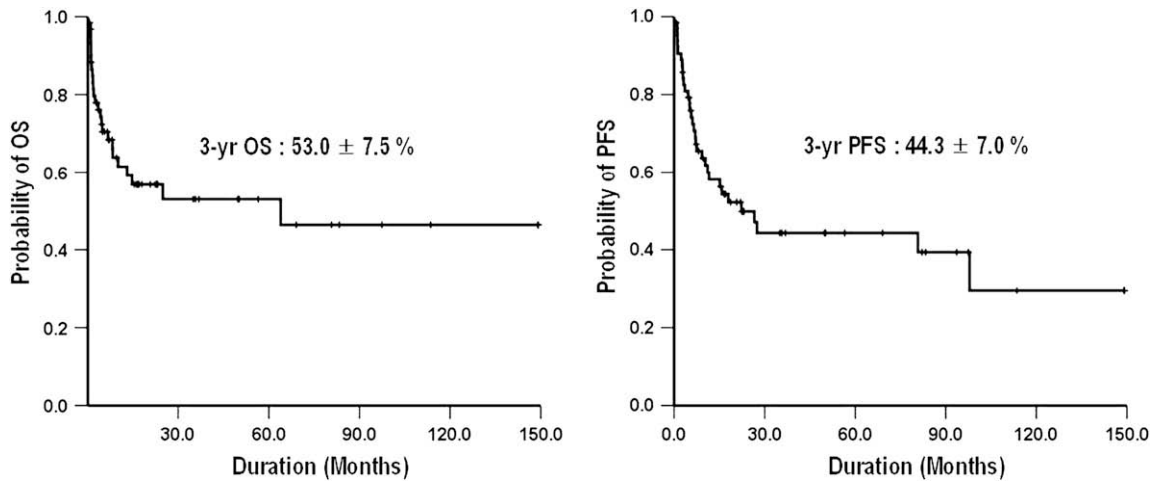

Figure 1. Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) in 64 patients with PTCL-U who received HDT/ASCT.

Table 3. Univariate analysis of prognostic factors associated with overall survival (OS) and progression-free survival (PFS)

	N	3-yr OS (95% CI)	*P*	N	3-yr PFS (95% CI)	*P*
PS						
0 - 1	52	52.9 ± 7.9	0.002	52	56.7 ± 8.1	0.124
2 – 4	12	9.0 ± 8.9		12	40.9 ± 16.3	
LDH						
Normal	39	57.5 ± 9.1	0.016	39	67.0 ± 8.8	0.012
High	25	24.2 ± 9.6		25	34.3 ± 11.3	
Stage						
I – II	19	54.7 ± 12.0	0.235	19	62.1 ± 12.6	0.602
III – IV	45	39.4 ± 8.5		45	49.1 ± 9.2	
BM						
Involved	14	11.5 ± 10.5	0.023	14	35.0 ± 15.4	0.156
Not involved	50	52.1 ± 8.0		50	57.7 ± 8.3	
B symptom						
Yes	22	29.2 ± 10.2	0.237	22	39.0 ± 11.8	0.245
No	42	56.6 ± 8.6		42	63.2 ± 8.7	
Age-adjusted IPI						
Low	15	66.5 ± 14.0%	0.039	15	64.0 ± 13.1	0.014
Low-intermediate	21	60.3 ± 12.0%		21	48.1 ± 14.6	
High-intermediate	20	53.3 ± 13.6%		20	43.9 ± 12.3	
High	8	Not reached		8	Not reached	
PIT						
0	30	71.7 ± 9.2	0.004	30	64.8 ± 9.9	0.001
1	18	57.3 ± 14.2		18	49.0 ± 13.3	
2 - 3	16	20.8 ± 12.4		16	7.5 ± 6.7	
Disease status at transplant						
CR	21	71.8 ± 11.0	0.001	21	53.1 ± 12.5	0.263
PR	37	42.6 ± 8.6		37	55.1 ± 9.5	
Progressive/refractory	6	Not reached		6	Not reached	
Transplant timing						
Frontline	28	60.0 ± 9.9	0.047	28	61.7 ± 10.3	0.188
Non-frontline	36	32.6 ± 9.4		36	46.3 ± 10.4	

IPI indicates International Prognostic Index; CR, complete remission; PR, partial remission; PIT, prognostic index of PTCL; BM, bone marrow; LDH, lactate dehydrogenase; PS, performance status.

and 44.3%, respectively. These results were similar or superior to those of previous studies [23,26-28]. At a median follow-up time of 29.7 months, 39.1% of the patients had relapsed and 56.2% were alive without disease. When we compared the survival outcome of our patients with outcomes seen in previous studies, which included conventional chemotherapy treatment or stem cell transplantation for PTCL-U, we found that patients with low a-IPI or PIT scores had more favorable prognoses after HDT/ASCT. However, HDT/ASCT showed no benefit in patients with high a-IPI or PIT (Table 4).

Although both a-IPI and PIT were good prognostic indices in patients with PTCL-U who underwent transplantation, PIT had better discriminatory power for predicting OS and PFS in subgroup analysis. After excluding the age factor of PIT (because 93.7% of transplanted patients were <60 years old), 2 of the remaining 3 factors were shared with a-IPI. Thus, BM involvement could play an important role in creating a prognostic difference between a-IPI and PIT. Patients with BM involvement consisted mainly of those in the PIT 2-3 group (71.4%), whereas only 14.3% were classified into the high-risk group of a-IPI.

In a recent study of the long-term clinical outcomes of HDT/ASCT in patients with heterogeneous subtypes of PTCL, disease status at transplantation was the major factor predicting clinical outcome [29]. The 5-year PFS and OS rates for patients in CR1/PR1 groups were 51% and 76%, respectively, decreasing to 12% and 40%, respectively, for patients in CR2/PR2. We observed similar results for HDT/ASCT in patients with PTCL-U. The 3-year OS rate for patients who achieved CR (n = 21), regardless of transplant timing, was 71.8%. We found, however, that 3-year OS rates differed significantly in patients undergoing transplantation in CR1/PR1 (60%) and those undergoing transplantation in a salvage setting (37.7%). However, the 3-year OS rate for patients in CR2 was 70.9%, compared with 50% for those in PR1. Consequently, the achievement of CR at the time of transplantation was a more significant factor for predicting survival than was transplant timing.

Despite the limitations of retrospective analyses, we found that HDT/ASCT in PTCL-U played a less significant role in determining clinical outcome in patients with adverse prognostic factors. Several small studies have assessed the feasibility and long-term survival of myeloablative or nonmyeloablative SCT as salvage therapy in patients who were not chemosensitive or who displayed both adverse factors [30-33]. Allogeneic SCT in patients with PTCL can give rise to graft-versus-lymphoma (GVL) effects, which may improve the therapeutic outcomes, but may also

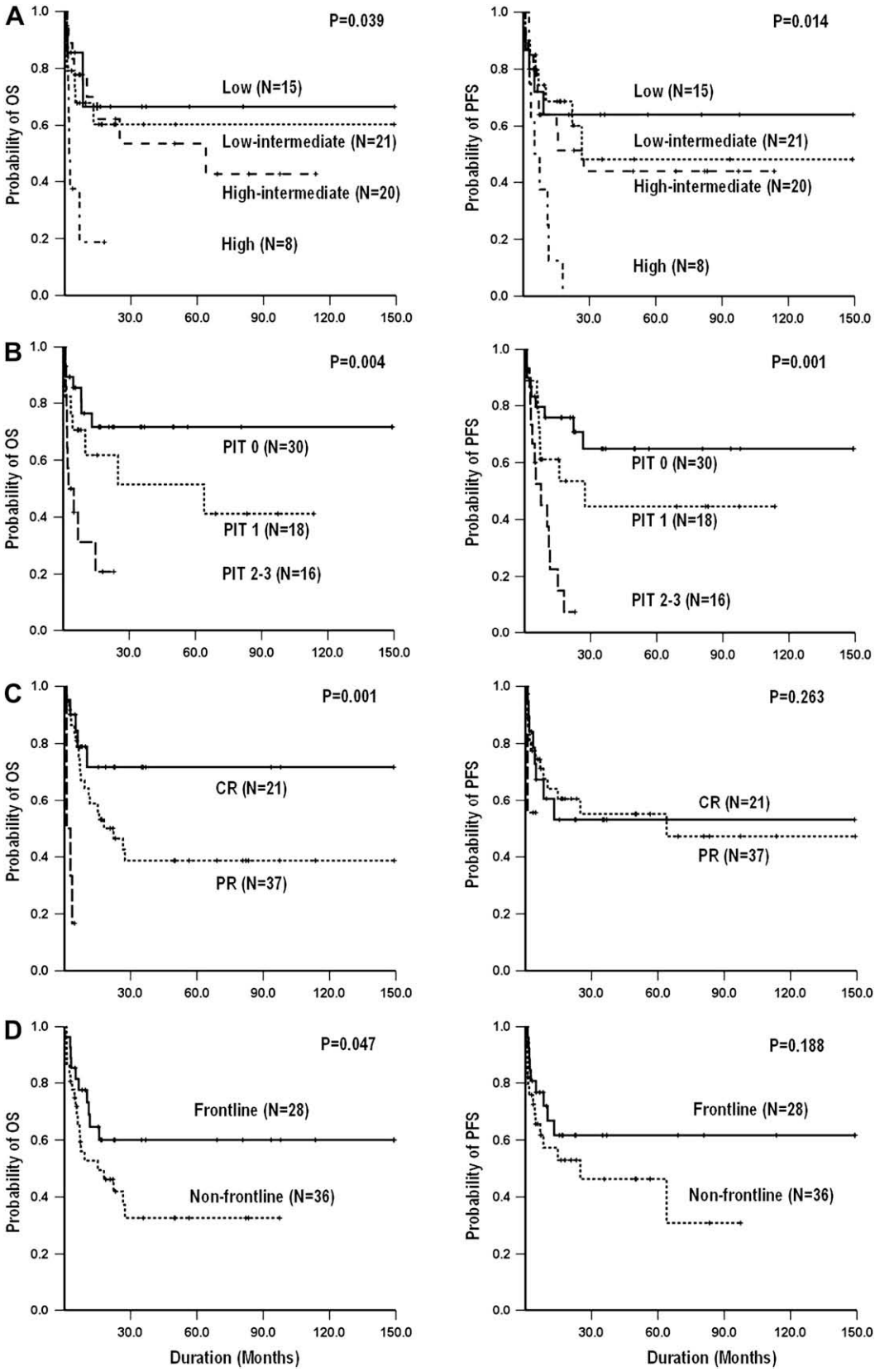

Figure 2. Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) according to prognostic factors. (A) Age-adjusted IPI, (B) prognostic index for PTCL-U, (C) disease status at transplantation, and (D) transplant timing.

Table 4. Comparison of survival outcomes of PTCL-U with those of previous studies

	In this study (after HDT/ASCT)	Gallamini *et al.* (14)	The International T-cell lymphoma project. (5)
	Actuarial 5-year OS	5-year OS	5-year OS
International Prognostic index			
Low	66.5%	58.9%	52%
Low-intermediate	60.3%	45.6%	33%
High-intermediate	43.9%	39.7%	16%
High	Not reached	18.3%	13%
Prognostic index of PTCL			
0 factor	71.7%	62.3%	Nearly 50%
1 factor	51.7%	52.9%	Nearly 30%
2 factors	20.8%	38.8%	Nearly 20%
3 or 4 factors	Not reached	18.3%	Nearly 10%

OS indicates overall survival.

be accompanied by high nonrelapse mortality (NRM) after a myeloablative regimen and high relapse rate after nonmyeloablative conditioning. Outcomes in 17 patients with relapsed PTCL who received salvage chemotherapy followed by reduced-intensity allogeneic SCT were improved, with estimated 3-year OS and PFS rates of 81% and 64%, respectively, suggesting that the graft-versus-T lymphoma effect may have been responsible [34].

In conclusion, we have shown here that HDT/ASCT was effective in patients with PTCL-U who achieved CR at transplantation, regardless of transplant timing. PIT reliably predicted the clinical outcome of ASCT. However, HDT/ASCT was less useful for those with high a-IPI or PIT scores. These patients may achieve CR using a new combination therapy regimen, following which intensified consolidation using autologous or allogeneic SCT should be considered.

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REFERENCES

1. Cheng AL, Chen YC, Wang CH, et al. Direct comparisons of peripheral T-cell lymphoma with diffuse B-cell lymphoma of comparable histological grades—should peripheral T-cell lymphoma be considered separately? *J Clin Oncol*. 1989;7:725-731.
2. Coiffier B, Brousse N, Peuchmaur M, et al. Peripheral T-cell lymphomas have a worse prognosis than B-cell lymphomas: a prospective study of 361 immunophenotyped patients treated with the LNH-84 regimen. The GELA (Groupe d'Etude des Lymphomes Agressives). *Ann Oncol*. 1990;1:45-50.
3. Kwak LW, Wilson M, Weiss LM, et al. Similar outcome of treatment of B-cell and T-cell diffuse large-cell lymphomas: the Stanford experience. *J Clin Oncol*. 1991;9:1426-1431.
4. Morabito F, Gallamini A, Stelitano C, et al. Clinical relevance of immunophenotype in a retrospective comparative study of 297 peripheral T-cell lymphomas, unspecified, and 496 diffuse large B-cell lymphomas: experience of the Intergruppo Italiano Linformi. *Cancer*. 2004;101:1601-1608.
5. Savage KJ, Harris NL, Vose JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. *Blood*. 2008;111:5496-5504.
6. Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. *Ann Oncol*. 2004;15:1467-1475.
7. Kojima H, Hasegawa Y, Suzukawa K, et al. Clinicopathological features and prognostic factors of Japanese patients with "peripheral T-cell lymphoma, unspecified" diagnosed according to the WHO classification. *Leuk Res*. 2004;28:1287-1292.
8. Savage KJ. Aggressive peripheral T-cell lymphomas (specified and unspecified types). *Hematology Am Soc Hematol Educ Program*. 2005;267-277.
9. Arrowsmith ER, Macon WR, Kinney MC, et al. Peripheral T-cell lymphomas: clinical features and prognostic factors of 92 cases defined by the revised European American lymphoma classification. *Leuk Lymphoma*. 2003;44:241-249.
10. Zaja F, Russo D, Silvestri F, et al. Retrospective analysis of 23 cases with peripheral T-cell lymphoma, unspecified: clinical characteristics and outcome. *Haematologica*. 1997;82:171-177.
11. Rodriguez-Abreu D, Filho VB, Zucca E. Peripheral T-cell lymphomas, unspecified (or not otherwise specified): a review. *Hematol Oncol*. 2008;26:8-20.
12. Sonnen R, Schmidt WP, Muller-Hermelink HK, Schmitz N. The International Prognostic Index determines the outcome of patients with nodal mature T-cell lymphomas. *Br J Haematol*. 2005;129:366-372.
13. Rodriguez J, Conde E, Gutierrez A, et al. The adjusted International Prognostic Index and beta-2-microglobulin predict the outcome after autologous stem cell transplantation in relapsing/refractory peripheral T-cell lymphoma. *Haematologica*. 2007;92:1067-1074.
14. Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. *Blood*. 2004;103:2474-2479.
15. Haioun C, Lepage E, Gisselbrecht C, et al. Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor-risk aggressive non-Hodgkin's lymphoma: updated results of the prospective study LNH87-2. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 1997;15:1131-1137.
16. Rodriguez J, Munsell M, Yazji S, et al. Impact of high-dose chemotherapy on peripheral T-cell lymphomas. *J Clin Oncol*. 2001;19:3766-3770.
17. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood*. 1994;84:1361-1392.
18. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol*. 1999;17:1244.

19. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med*. 1995;333:1540-1545.
20. Haioun C, Lepage E, Gisselbrecht C, et al. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol—a groupe d'Etude des lymphomes de l'Adulte study. *J Clin Oncol*. 2000;18: 3025-3030.
21. Jantunen E, D'Amore F. Stem cell transplantation for peripheral T-cell lymphomas. *Leuk Lymphoma*. 2004;45:441-446.
22. Kewalramani T, Zelenetz AD, Teruya-Feldstein J, et al. Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. *Br J Haematol*. 2006;134:202-207.
23. Smith SD, Bolwell BJ, Rybicki LA, et al. Autologous hematopoietic stem cell transplantation in peripheral T-cell lymphoma using a uniform high-dose regimen. *Bone Marrow Transplant*. 2007;40:239-243.
24. Rodriguez J, Caballero MD, Gutierrez A, et al. High-dose chemotherapy and autologous stem cell transplantation in peripheral T-cell lymphoma: the GEL-TAMO experience. *Ann Oncol*. 2003;14:1768-1775.
25. Rodriguez J, Caballero MD, Gutierrez A, et al. High dose chemotherapy and autologous stem cell transplantation in patients with peripheral T-cell lymphoma not achieving complete response after induction chemotherapy.The GEL-TAMO experience. *Haematologica*. 2003;88:1372-1377.
26. Kim MK, Kim S, Lee SS, et al. High-dose chemotherapy and autologous stem cell transplantation for peripheral T-cell lymphoma: complete response at transplant predicts survival. *Ann Hematol*. 2007;86:435-442.
27. Rodriguez J, Conde E, Gutierrez A, et al. The results of consolidation with autologous stem-cell transplantation in patients with peripheral T-cell lymphoma (PTCL) in first complete remission: the Spanish Lymphoma and Autologous Transplantation Group experience. *Ann Oncol*. 2007;18:652-657.
28. Rodriguez J, Conde E, Gutierrez A, et al. Frontline autologous stem cell transplantation in high-risk peripheral T-cell lymphoma: a prospective study from The Gel-Tamo Study Group. *Eur J Haematol*. 2007;79:32-38.
29. Chen AI, McMillan A, Negrin RS, et al. Long-term results of autologous hematopoietic cell transplantation for peripheral T cell lymphoma: the Stanford experience. *Biol Blood Marrow Transplant*. 2008;14:741-747.
30. Hamadani M, Awan FT, Elder P, et al. Allogeneic hematopoietic stem cell transplantation for peripheral T cell lymphomas; evidence of graft-versus-T cell lymphoma effect. *Biol Blood Marrow Transplant*. 2008;14:480-483.
31. Doocey RT, Toze CL, Connors JM, et al. Allogeneic haematopoietic stem-cell transplantation for relapsed and refractory aggressive histology non-Hodgkin lymphoma. *Br J Haematol*. 2005;131:223-230.
32. Le Gouill S, Milpied N, Buzyn A, et al. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. *J Clin Oncol*. 2008;26:2264-2271.
33. Corradini P, Dodero A, Farina L, et al. Allogeneic stem cell transplantation following reduced-intensity conditioning can induce durable clinical and molecular remissions in relapsed lymphomas: pre-transplant disease status and histotype heavily influence outcome. *Leukemia*. 2007;21:2316-2323.
34. Corradini P, Dodero A, Zallio F, et al. Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. *J Clin Oncol*. 2004;22: 2172-2176.