VOLUME 31 · NUMBER 25 · SEPTEMBER 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Hematopoietic Cell Transplantation for Systemic Mature T-Cell Non-Hodgkin Lymphoma

Sonali M. Smith, Linda J. Burns, Koen van Besien, Jennifer LeRademacher, Wensheng He, Timothy S. Fenske, Ritsuro Suzuki, Jack W. Hsu, Harry C. Schouten, Gregory A. Hale, Leona A. Holmberg, Anna Sureda, Cesar O. Freytes, Richard Thomas Maziarz, David J. Inwards, Robert Peter Gale, Thomas G. Gross, Mitchell S. Cairo, Luciano J. Costa, Hillard M. Lazarus, Peter H. Wiernik, Dipnarine Maharaj, Ginna G. Laport, Silvia Montoto, and Parameswaran N. Hari

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on July 29, 2013.

Support information appears at the end of this article.

The views expressed in this article do not reflect the official policy or position of the National Institutes of Health, the Department of the Navy, the Department of Defense, or any other agency of the US Government.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Parameswaran Hari, MD, MS, Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, 9200 W. Wisconsin Ave, Suite C5500, Milwaukee, WI 53226; e-mail: phari@mcw.edu.

0732-183X/13/3125w-3100w/$20.00

DOI: 10.1200/JCO.2012.46.0188

ABSTRACT

Purpose
To analyze outcomes of hematopoietic cell transplantation (HCT) in T-cell non-Hodgkin lymphoma.

Patients and Methods
Outcomes of 241 patients (112 anaplastic large-cell lymphoma, 102 peripheral T-cell lymphoma not otherwise specified, 27 angioimmunoblastic T-cell lymphoma) undergoing autologous HCT (autoHCT; n = 115; median age, 43 years) or allogeneic HCT (alloHCT; n = 126; median age, 38 years) were analyzed. Primary outcomes were nonrelapse mortality (NRM), relapse/progression, progression-free survival (PFS), and overall survival (OS). Patient, disease, and HCT-related variables were analyzed in multivariate Cox proportional hazard models to determine association with outcomes.

Results
AutoHCT recipients were more likely in first complete remission (CR1; 35% *v* 14%; $P = .001$) and with chemotherapy-sensitive disease (86% *v* 60%; $P < .001$), anaplastic large-cell histology (53% *v* 40%; $P = .04$), and two or fewer lines of prior therapy (65% *v* 44%; $P < .001$) compared with alloHCT recipients. Three-year PFS and OS of autoHCT recipients beyond CR1 were 42% and 53%, respectively. Among alloHCT recipients who received transplantations beyond CR1, 31% remained progression-free at 3 years, despite being more heavily pretreated and with more refractory disease. NRM was 3.5-fold higher (95% CI, 1.80 to 6.99; $P < .001$) for alloHCT. In multivariate analysis, chemotherapy sensitivity (hazard ratio [HR], 1.8; 95% CI, 1.16 to 2.87) and two or fewer lines of pretransplantation therapy (HR, 5.02; 95% CI, 2.15 to 11.72) were prognostic of survival.

Conclusion
These data describe the roles of autoHCT and alloHCT in T-cell non-Hodgkin lymphoma and suggest greater effectiveness earlier in the disease course, and limited utility in multiply relapsed disease. Notably, autoHCT at relapse may be a potential option for select patients, particularly those with anaplastic large-cell lymphoma histology.

J Clin Oncol 31:3100-3109. © 2013 by American Society of Clinical Oncology

INTRODUCTION

Peripheral T-cell lymphomas such as T-cell non-Hodgkin lymphoma (T-NHL) are heterogeneous malignancies sharing common elements of chemotherapy resistance and poor outcome with standard treatments. The International T-Cell Lymphoma Project highlights that fewer than one third of patients with T-cell lymphomas survive 5 years, although histology strongly influences survival.[1] Patients with anaplastic lymphoma kinase (ALK) –positive variants of anaplastic large-cell lymphoma (ALCL) have better outcomes, with 5-year survival rates of 70%. In contrast, survival sequentially declines for ALK-negative ALCL (49%), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS; 32%), and angioimmunoblastic T-cell lymphoma (AITL; 14%). The German High Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) similarly reported on more than 200 patients with T-NHL enrolled onto prospective trials; 3-year event-free survival was best for ALK-positive ALCL (75%) and suboptimal for all other histologies.[2]

Attempts to improve outcomes have included autologous or allogeneic hematopoietic

Table 1. Patient Characteristics

Characteristic	Autologous HCT No.	%	Allogeneic HCT No.	%	P
No. of patients*	115		126		
No. of centers	67		72		
Age at transplantation, years					.10
Median	43		38		
Range	4-60		5-60		
≤ 20	11	9	22	17	
21-30	18	16	20	16	
31-40	24	21	27	21	
41-50	21	18	30	24	
51-60	41	36	27	21	
Male	70	61	91	72	.06
Karnofsky score pretransplantation					.62
< 90	31	27	41	33	
Histology†					.04
Anaplastic large-cell lymphoma‡	61	53	51	40	
Peripheral T-cell lymphoma, unspecified	39	34	63	50	
Angioimmunoblastic T-cell lymphoma	15	13	12	10	
B symptoms at diagnosis	67	58	69	55	.13
LDH at diagnosis					.15
Normal	19	17	12	10	
Increased	26	23	39	31	
Unknown	70	61	75	60	
No. of lines of therapy prior to transplantation					
Median	2		3		.002
1	19	17	18	14	< .001
2	55	48	38	30	
≥ 3	39	34	55	43	
Unknown	2	2	7	6	
CNS involvement§	2	2	6	5	.28
BM involvement at diagnosis	21	18	44	35	.0142
BM involvement at time of transplantation	1	1	19	15	< .001
Extranodal involvement at diagnosis	64	56	86	68	.05
PIT at transplantation					.02
0	49	43	42	33	
1	41	36	42	33	
2	3	2	16	13	
Unknown	22	19	26	21	
Disease stage at diagnosis					.28
I	10	9	5	4	
II	21	18	15	12	
III	32	28	36	28	
IV	47	41	64	51	
Unknown	5	4	6	5	
Time from diagnosis to transplantation, months					
Median	10		11		
Range	2-229		3-69		
≤ 6	14	12	22	17	.32
6-12	57	50	53	42	
12-18	15	13	26	21	
18-24	11	10	9	7	
> 24	18	16	16	13	
Follow-up of survivors, months					
Median	71		49		
Range	3-167		3-157		

NOTE. Completeness index follow-up: 96% at 1 year; 88% at 3 years.

Abbreviations: BM, bone marrow; HCT, hematopoietic cell transplantation; LDH, lactate dehydrogenase; PIT, prognostic index of T-cell non-Hodgkin lymphoma.

*Patients who had autologous transplantation followed by allogeneic transplantation (four twins, eight cord blood, 13 other-related) were not included in allogeneic population.

†Pathology reports were reviewed for 143 patients.

‡Anaplastic lymphoma kinase status: positive, n = 14; negative, n = 8; unknown, n = 90.

§CNS involvement was at any time prior to transplantation.

cell transplantation (autoHCT or alloHCT). Single-institution studies and retrospective analyses suggest that both modalities lead to durable remissions in recurrent disease settings and might be important in consolidating first remission.[3-6] However, key questions remain, including identification of optimal populations, relative efficacy of autologous versus allogeneic approaches, and HCT timing (first-line consolidation *v* relapse). Herein, we analyzed outcomes of a large cohort of autoHCT or alloHCT recipients with the three most common T-NHL histologies reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).

PATIENTS AND METHODS

Data Sources

CIBMTR is a voluntary working group of more than 500 transplantation centers worldwide. Participating centers register basic information on consecutive transplantations to a statistical center at the Medical College of Wisconsin with two levels of data collection. Comprehensive patient- and disease-related data were collected by using a weighted randomization scheme in a subset of patients. A larger registration data set consisted of consecutive data on all transplantations from all centers reporting to the CIBMTR and was used to estimate transplantation activity. This registration showed 946 autologous transplantations and 346 allogeneic transplantations from US centers during the period specified. These numbers represent 55% and 95% of all US auto and allo transplantation activity for T-NHL, corresponding to an estimated 1,048 autoHCTs and 629 alloHCTs performed in the United States. We compared outcome data for our selected representative cohort with higher-level data (Case Report Forms) versus the registration data set that included all patients. Outcomes were similar, confirming that our data set was representative of HCT outcomes for T-NHL.

Patients Were Followed Longitudinally, With Annual Follow-Up

Patients with T-NHL age ≤ 60 years who received first autoHCT or alloHCT between 1996 and 2006 were included. Two hundred forty-one patients who underwent autoHCT (n = 115) or alloHCT (n = 126) and restricted to ALCL (n = 112), PTCL-NOS (n = 102), and AITL (n = 27) histologies were identified. Exclusion criteria were precursor T-cell neoplasms, primary cutaneous T-cell lymphomas, or second transplantations as well as identical twin (n = 4), mismatched related donor (n = 13), or cord blood (n = 8) transplantations. When available, primary pathology reports were

reviewed (n = 143). Patients older than age 60 years were excluded because of the small number who underwent alloHCT (n = 6).

Definitions of alloHCT Conditioning Regimens

Lower-intensity conditioning regimens were categorized as nonmyeloablative stem-cell transplantation (NST) or reduced-intensity conditioning (RIC) by using established criteria.[7] Previously validated criteria defined donor-recipient HLA matching quality on the basis of the number of HLA loci examined and resolution of HLA typing at each locus.[8]

End Points

Primary outcomes were nonrelapse mortality (NRM), relapse/progression, progression-free survival (PFS), and overall survival (OS). NRM was defined as death as a result of any cause in the first 28 days or death without evidence of lymphoma relapse/progression; progression, increase of ≥ 25% in lymphoma sites or development of new sites; relapse, recurrence of lymphoma after complete remission (CR); primary induction failure (PIF) sensitive, never in CR but with partial remission to treatment; PIF other, never in CR but with stable or progressive disease on treatment; relapse sensitive, relapsing from prior remission but with a partial remission to treatment for relapse; and relapse other, relapsing from prior remission with stable disease or progression thereafter.

Treatment failure was defined as time of relapse, progression, or death as a result of any cause. Patients alive without evidence of disease relapse/progression were censored at last follow-up, and PFS events were summarized by survival curves. The OS interval variable was time from date of transplantation to date of death or last contact and was summarized by a survival curve. Other outcomes included acute and chronic graft-versus-host disease (AGVHD and CGVHD) and cause of death (COD). AGVHD was defined and graded on the basis of patterns and severity of organ involvement by using established criteria. CGVHD was defined as the development of any chronic GVHD on the basis of clinical criteria. Both events were summarized by corresponding cumulative incidence estimates with death without development of GVHD as the competing risk.

Statistical Analyses

Probabilities of PFS and OS were calculated by using Kaplan-Meier product limit estimates. Probabilities of NRM, lymphoma relapse/progression, and AGVHD and CGVHD were calculated by using cumulative incidence curves to accommodate competing risks. Associations between patient-, disease-, and transplantation-related factors and primary outcomes of interest were assessed by using multivariate Cox proportional hazards regression. Variables in multivariate analyses included the following: (1) main effect was autoHCT versus alloHCT; (2) patient-related variables included age at transplantation (≤ 20 *v* 21 to 40 *v* 41 to 60 years), sex, Karnofsky performance score (≥ 90 *v* ≤ 90); (3) disease-related variables included histology (ALCL *v* PTCL *v* AITL), "B" symptoms, number of lines of therapy before transplantation (1 *v* 2 *v* > 2), disease stage at diagnosis (stage I to II *v* III to IV), extranodal involvement at diagnosis, time from diagnosis to transplantation (≤ 12 *v* > 12 months), disease status before transplantation (CR1 *v* CR2+ *v* primary induction failure *v* relapsed), and chemotherapy sensitivity (sensitive *v* resistant); and (4) treatment-related variables include conditioning regimen (total-body irradiation–containing *v* no total-body irradiation), graft type (bone marrow *v* peripheral blood stem cells, and year of transplantation (1996 to 1998 *v* 1999 to 2001 *v* 2002 to 2004 *v* 2005 to 2006). AlloHCT recipients had additional comparisons: impact of conditioning regimen (myeloablative *v* NST/RIC), donor-recipient sex match, donor-recipient cytomegalovirus status, donor type (HLA-identical sibling *v* matched unrelated *v* mismatched unrelated), and GVHD prophylaxis (T-cell depletion *v* other). A stepwise forward selection multivariate model was built to identify covariates that influenced outcomes. Covariates with a *P* value less than .05 were considered significant. The main effect studied (ie, autoHCT *v* alloHCT) was included in all models. The proportionality assumption for Cox regression was tested by adding time-dependent covariates for each risk factor and each outcome. All variables met the proportional hazards assumption. Results were expressed as relative risks or relative rate of occurrence of the event.

Table 2. Treatment- and Transplantation-Related Characteristics

Characteristic	Autologous HCT No.	Autologous HCT %	Allogeneic HCT No.	Allogeneic HCT %	*P*
Chemotherapy sensitivity					< .001
Sensitive	99	86	75	60	
Resistant	9	8	37	29	
Untreated	0		2	2	
Unknown	7	6	12	10	
Disease status at transplantation					.001
CR1	40	35	18	14	
CR2+	24	21	20	16	
PIF, sensitive	16	14	23	18	
PIF, other	6	5	23	18	
Relapse, sensitive	17	15	21	17	
Relapse, other	10	9	18	14	
Missing	2	2	3	3	
Conditioning regimen (allogeneic)	N/A				
Myeloablative			74	59	
NST/RIC			45	36	
Unknown			7	5	
Conditioning regimen (autologous)			N/A		
TBI containing	26	23			
BEAM and similar	65	57			
Cyclophosphamide or similar	14	12			
Busulfan + melphalan/busulfan + cyclophosphamide	4	3			
Other	6	5			
Conditioning regimen (allogeneic)	N/A				
TBI containing			60	48	
Donor HLA match	N/A				
HLA-identical sibling			76	60	
Matched unrelated			30	24	
Mismatched unrelated			20	16	
Donor/recipient cytomegalovirus status	N/A				
−/−			39	31	
+/−			23	18	
−/+			21	17	
+/+			38	30	
Unknown			5	4	
Donor-recipient sex match					
Male-male	N/A		52	41	
Male-female			20	16	
Female-male			39	31	
Female-female			15	12	
Graft type					< .001
Bone marrow	10	9	36	29	
Peripheral blood	105	91	90	71	
Year of transplantation					< .001
1996-1998	43	37	16	13	
1999-2001	39	34	23	18	
2002-2004	22	19	39	31	
2005-2006	11	10	48	38	
GVHD prophylaxis	N/A				
T-cell depletion ± other			14	11	
Methotrexate + cyclosporine ± other			46	37	
Cyclosporine ± other			28	22	
Methotrexate + tacrolimus ± other			23	18	
Tacrolimus ± other			12	10	
Other			3	2	

Abbreviations: BEAM, carmustine, etoposide, cytarabine, melphalan; CR1, first complete remission; CR2, second complete remission; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; PIF, primary induction failure; N/A, not applicable; NST, nonmyeloablative stem-cell transplantation; RIC, reduced-intensity conditioning; TBI, total-body irradiation.

RESULTS

Patient-, Disease-, and Treatment-Related Characteristics

Table 1 lists patient characteristics, and Table 2 lists treatment- or transplantation-related features. Most patients in both groups had B symptoms at diagnosis, had more than one line of therapy before transplantation, lacked bone marrow involvement at transplantation, and had advanced disease or extranodal disease at time of diagnosis. There were no differences in median age, age distribution, sex distribution, disease stage, or median time from diagnosis to transplantation by HCT type. AutoHCT patients had more ALCL histology. AlloHCT recipients had more bone marrow involvement, more lines of chemotherapy pretransplantation, extranodal disease at diagnosis, and higher second-line prognostic index of PTCLs[9] at transplantation ($P = .02$).

AutoHCT recipients were more likely in first complete remission (CR1; 35% *v* 14%; $P = .001$) and with chemotherapy-sensitive disease (86% *v* 60%; $P < .001$). Myeloablative (MA) conditioning was more common than NST/RIC for alloHCT, although increased use of alloHCT was seen in later years (69% of alloHCTs were performed after 2002). Forty percent of alloHCT recipients had unrelated donors. Peripheral blood was the most common graft source in both groups.

Univariate Analysis of Outcomes

There were no outcome differences between MA and NST/RIC conditioning (Table 3; Figs 1B and 1C). Both NRM and overall mortality were higher in alloHCT patients (Fig 1). There was no difference in relapse/progression between autoHCT and alloHCT patients. For autoHCT patients, the 1- and 3-year PFS rates were 58% and 47%, and the 1- and 3-year OS rates were 68% and 59%, respectively. For alloHCT, the 1- and 3-year PFS rates were 42% and 37%, and the 1- and 3-year OS rates were 55% and 46%, respectively (Fig 1B; Table 3). Patients in CR1 undergoing autoHCT (n = 40) had 1- and 3-year PFS rates of 75% and 58%, respectively, whereas OS at 1 year and 3 years was 80% and 70%, respectively (data not shown). Few patients (n = 18) underwent alloHCT in CR1.

Univariate outcomes after excluding CR1 patients are listed in Table 3. NRM at all time points was higher for alloHCT recipients. Overall NRM for autoHCT recipients was 6% at 3 years compared with 34% for alloHCT recipients. Unadjusted OS and PFS were similar for both cohorts. When excluding CR1 patients, relapse was lower for the alloHCT cohort (53% *v* 38%; $P = .0437$), but PFS and OS were similar (Fig 1D).

Among 241 patients, 33 were younger than 21 years of age, including 11 patients (eight ALCL, three PTCL-NOS) undergoing autoHCT and 22 (20 ALCL, two PTCL-NOS) undergoing alloHCT. When excluding pediatric patients from the overall NRM, PFS and OS at 1 year and 3 years were similar to those for the entire group (data not shown).

Outcomes by Histology

Subanalyses by histology (ALCL, PTCL-NOS, AITL) were performed (Appendix Table A1, online only). Patients with ALCL undergoing autoHCT (n = 61) had superior PFS (55% *v* 35%; $P = .0319$) and OS (68% *v* 41%; $P = .0034$), with significantly reduced NRM and overall mortality compared with alloHCT recipients (n = 51). Even when excluding CR1 patients, autoHCT recipients had higher 3-year OS (62% *v* 33%; $P = .0088$) and lower transplantation-related mortality (5% *v* 32%; $P < .001$), with no difference in PFS or relapse/progression.

When specifically examining autoHCT recipients beyond CR1 by histology, patients with ALCL (n = 39) had 1-year and 3-year PFS rates of 53% (95% CI, 37% to 69%) and 50% (95% CI, 34% to 66%) and 1-year and 3-year OS rates of 74% (95% CI, 59% to 86%) and 65% (95% CI, 49% to 80%), respectively. Patients with PTCL-NOS (n = 28) had 1-year and 3-year PFS rates of 52% (95% CI, 33% to 71%) and 29% (95% CI, 12% to 50%) and 1-year and 3-year OS rates of 57% (95% CI, 38% to 75%) and 42% (95% CI, 22% to 62%), respectively. Only six patients with AITL underwent autoSCT beyond CR1; they had 1-year PFS and OS rates of 33% (95% CI, 5% to 72%). Histology was included in multivariate analyses but did not have an impact on relapse/progression for patients beyond CR1 (Table 4).

Table 3. Univariate Outcomes of Patients With HCT

	All Patients							Patients Beyond CR1						
	AutoHCT		Myeloablative		NST/RIC			AutoHCT		Myeloablative		NST/RIC		
Variable	%	95% CI (%)	%	95% CI (%)	%	95% CI (%)	*P*	%	95% CI (%)	%	95% CI (%)	%	95% CI (%)	*P*
Nonrelapse mortality														
At 100 days	2	0 to 6	19	11 to 29	18	8 to 30	< .001	3	1 to 8	21	12 to 32	20	9 to 33	< .001
At 1 year	7	3 to 13	29	19 to 40	27	15 to 40	< .001	4	1 to 10	30	19 to 42	27	14 to 41	< .001
At 3 years	11	6 to 17	32	22 to 43	27	15 to 40	< .001	6	2 to 13	34	22 to 46	27	14 to 41	< .001
Relapse/progression														
At 1 year	34	26 to 43	29	19 to 40	38	24 to 52	.5694	46	35 to 57	33	22 to 45	39	24 to 53	.2978
At 3 years	43	33 to 52	32	21 to 43	40	26 to 54	.3282	53	41 to 64	37	25 to 49	42	27 to 56	.1627
Progression-free survival														
At 1 year	58	49 to 67	42	31 to 53	36	22 to 49	.0113	50	38 to 60	37	25 to 49	34	20 to 49	.1813
At 3 years	47	37 to 56	36	25 to 47	33	20 to 47	.1834	41	29 to 52	29	18 to 41	32	18 to 46	.3449
Overall survival														
At 1 year	68	59 to 76	49	37 to 60	59	44 to 72	.0266	62	50 to 72	43	30 to 55	58	41 to 71	.0701
At 3 years	59	49 to 68	39	28 to 51	52	36 to 66	.0356	53	40 to 64	31	20 to 44	50	33 to 64	.0349

Abbreviations: autoHCT, autologous hematopoietic cell transplantation; CR1, first complete remission; NST, nonmyeloablative stem-cell transplantation; RIC, reduced-intensity conditioning.

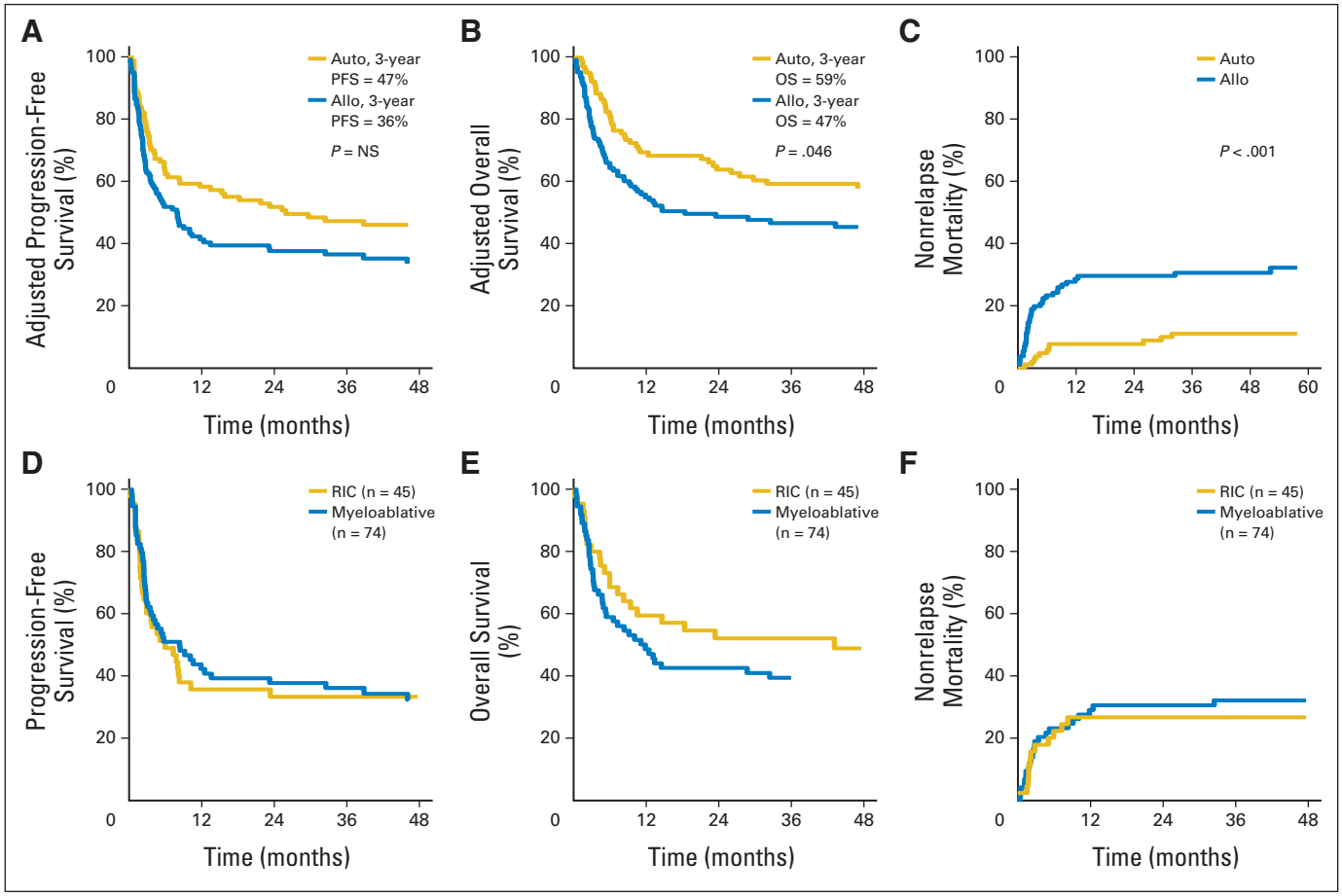

Fig 1. (A) Adjusted progression-free survival (PFS), (B) adjusted overall survival (OS), and (C) nonrelapse mortality (NRM) for all patients (n = 241). (D) PFS, (E) OS, and (F) NRM for patients who underwent nonmyeloablative stem-cell transplantation/reduced-intensity conditioning (RIC) versus myeloablative allogeneic hematopoietic cell transplantation (allo). NS, not significant. (Continued on next page).

Allogeneic Transplantation

Among alloHCT recipients, there was no difference in AGVHD or CGVHD relapse/progression, PFS, OS, or overall mortality when comparing HLA-identical sibling donors (n = 76) and unrelated donors (n = 50; data not shown). Regimen intensity did not have an impact on PFS, OS, or NRM between MA and NST/RIC HCT recipients. Neither AGVHD nor CGVHD affected relapse or survival. Only 14 patients had T-cell depletion as part of their transplantation, and impact on relapse and survival could not be determined.

COD

The most common COD was lymphoma (Appendix Table A2, online only). Progressive lymphoma leading to death in the three groups (auto *v* myeloablative *v* NST/RIC) was significantly higher in the autologous cohort ($P = .0036$).

Multivariate Analysis

In multivariate models (Table 5), alloHCT (hazard ratio [HR], 3.543) or two or more pretransplantation chemotherapy regimens (HR, 4.059 and HR, 7.035, respectively) were strongly predictive of worse NRM, with no improvement in relapse/progression. Chemotherapy-resistant disease doubled the risk of relapse/progression. Among alloHCT recipients, risk of overall mortality and treatment failure was higher in those not in CR or after more than two lines of chemotherapy (Table 4).

When excluding CR1 patients (Table 4), NRM risk was higher in alloHCT recipients, in those who experienced PIF, and in those receiving HCT more than 12 months from diagnosis. Relapse risk was higher for chemotherapy-resistant disease or relapsed disease at time of transplantation. Higher number of chemotherapy lines before HCT correlated with higher risk of mortality and treatment failure.

In multivariate analysis restricted to patients with PTCL-NOS, receipt of alloHCT remained a significant risk factor for NRM (HR, 3.031; 95% CI, 1.025 to 8.961). Similar to the overall group, chemotherapy resistance predicted for increased relapse, increased treatment failure, and worse overall mortality. However, the relative risk of relapse/progression was halved by use of alloHCT (HR, 0.504; $P = .04$). Transplantation type (autoHCT *v* alloHCT) did not have an impact on OS.

DISCUSSION

To the best of our knowledge, this is the largest report on the outcomes and analyses of patient-, disease-, and treatment-related factors for patients with systemic T-NHL undergoing HCT. HCT, whether

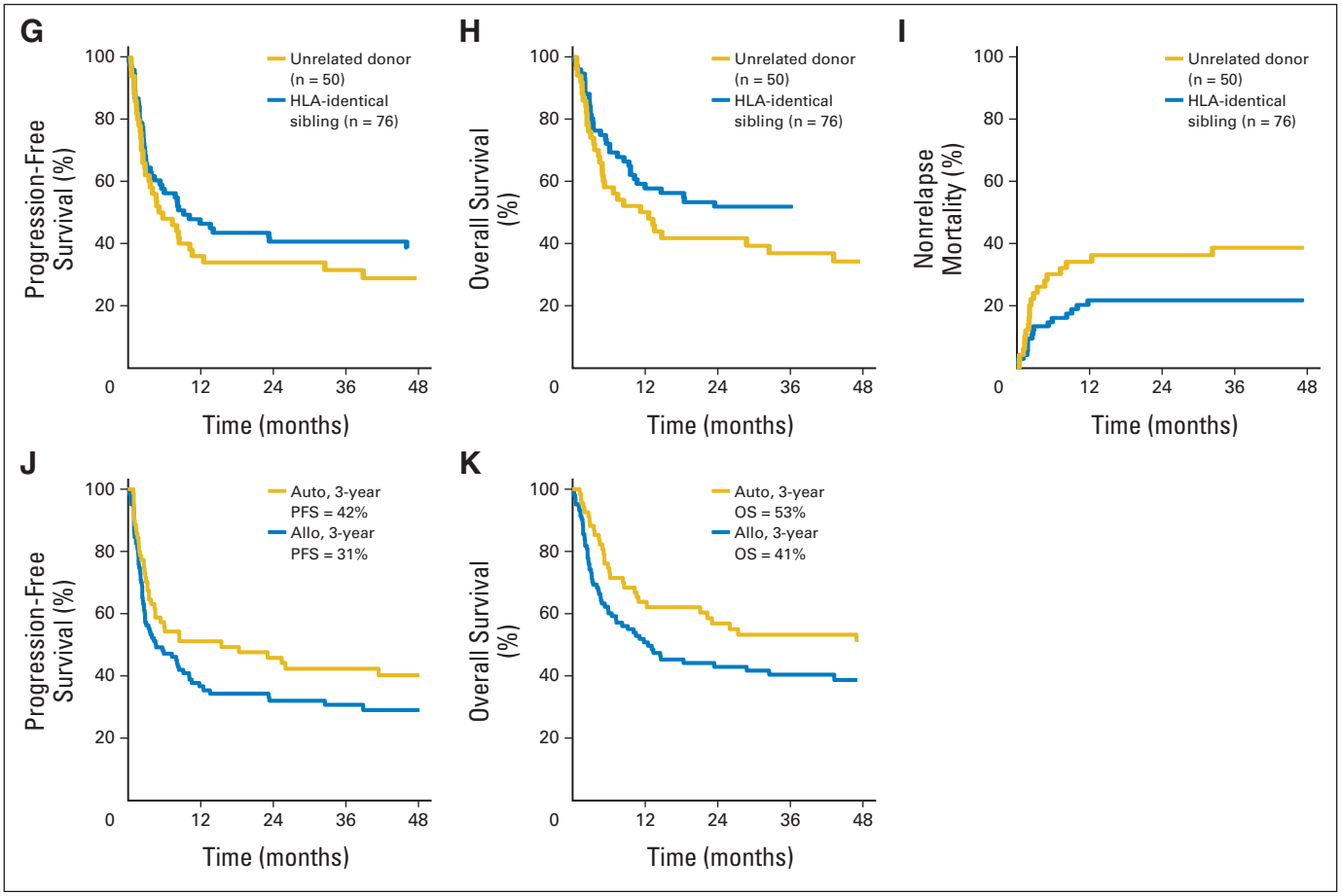

Fig 1. (Continued). (G) PFS, (H) OS, and (I) NRM for patients who underwent HLA-identical sibling versus unrelated donor allo. (J) PFS and (K) OS for patients who underwent autologous HCT (auto) and allo when excluding patients in first complete remission.

autologous or allogeneic, can benefit a considerable subset of patients with T-NHL, with few patients relapsing beyond 3 years. Despite baseline differences in autoHCT and alloHCT recipients, a unifying finding was that transplantation was often offered late in the disease course, with 50% of alloHCT and 30% of autoHCT patients receiving more than two prior treatment regimens. Such late referral was detrimental; the use of either modality for patients receiving more than two lines of therapy was associated with a three-fold increased risk of relapse, five-fold increased risk of overall mortality, and a seven-fold increased risk of NRM. A corollary of the number of regimens is chemotherapy sensitivity; patients with chemotherapy-resistant disease had essentially a two-fold increased risk of relapse, treatment failure, and overall mortality. Considering that chemotherapy-resistant patients more often receive more than two lines of pretransplantation therapy, these findings are likely related. The main implication is that if transplantation is to be applied, both toxicity and efficacy are optimized by fewer prior chemotherapy regimens, and transplantation is most beneficial when offered as part of first- or second-line therapy.

The initial intent was to compare autoHCT *v* alloHCT outcomes, but there were substantially differing baseline characteristics by treatment modality. Patients undergoing autoHCT were more likely to be in CR1, have chemotherapy-sensitive disease, have ALCL subtype, and have two or fewer lines of prior therapy. To account for these differences, an adjusted model was used in multivariate analysis to assess the relative risk of autoHCT *v* alloHCT and evaluate prognostic factors. This model did not find a difference in relapse/progression between autoHCT and alloHCT, although the latter significantly increased NRM (HR, 3.543).

An intriguing finding is that high-dose chemotherapy as part of autoHCT can be beneficial at relapse, which conflicts with several prior reports.[10-13] When excluding patients in first remission, the aggregate group of autoHCT recipients had 3-year PFS and OS rates of 41% and 53%, respectively, with a robust median follow-up time of 73 months. In particular, patients with ALCL undergoing autoHCT at relapse had superior overall survival compared with alloHCT recipients; similar conclusions for other histologies is precluded by small numbers. NRM, although higher than that reported in many B-cell lymphoma series, was 4% at 1 year and 6% at 3 years. These findings along with the results of the multivariate analysis (Table 4) suggest that, despite discouraging retrospective reports previously discussed, a subset of relapsed patients with T-NHL can benefit from effective salvage treatment with autoHCT, particularly if performed as part of second-line therapy and if chemotherapy sensitivity is demonstrated. Given that half the pool of patients undergoing autoSCT beyond CR1 had ALCL histology, this likely influences the results of the multivariate analysis; however, histology did not specifically emerge as a significant factor.

Table 4. Multivariate Analysis of Prognostic Factors for AutoHCT and AlloHCT Recipients, Excluding CR1 Patients (significant covariates are shown)

Variables	No. of Patients	Nonrelapse Mortality*			Relapse/Progression†			Treatment Failure‡			Overall Mortality§		
		RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Main effect													
AutoHCT	72	1.00 (ref)			1.00 (ref)			1.00 (ref)			1.00 (ref)		
AlloHCT	99	6.836	2.399 to 19.483	< .001	0.696	0.428 to 1.133	.1451	1.24	0.818 to 1.880	.3108	1.515	1.001 to 2.294	.0494
Time from diagnosis to HCT, months													
≤ 12	87	1.00 (ref)											
> 12	84	2.394	1.164 to 4.922	.0176									
No. of chemotherapy lines prior to transplantation										.0308‖			.0022‖
1	17							1.00 (ref)			1.00 (ref)		
2	68							2.312	0.978 to 5.468	.0563	3.31	1.176 to 9.316	.0234
> 2	86							3.012	1.286 to 7.058	.0111	5.139	1.858 to 14.210	.0016
Chemotherapy-sensitive disease													
Sensitive	110				1.00 (ref)			1.00 (ref)					
Resistant	44				1.97	1.114 to 3.487	.0198	1.744	1.116 to 2.725	.0146			
Disease status prior to transplantation				.0221‖			.0226‖						
CR2+	42	1.00 (ref)			1.00 (ref)								
PIF	67	2.447	1.004 to 5.965	.0489	1.377	0.690 to 2.749	.3648						
Relapse	62	0.815	0.304 to 2.189	.6853	2.259	1.180 to 4.324	.0139						

Abbreviations: alloHCT, allogeneic hematopoietic cell transplantation; autoHCT, autologous HCT; CR1, first complete remission; CR2, second complete remission; PIF, primary induction failure; ref, reference group; RR, relative risk.

*PIF *v* relapse, $P = .0119$.

†Chemotherapy-sensitive disease: resistant *v* unknown, $P = .6435$; disease status prior to transplantation: CR2+ *v* PIF, $P = .3799$; disease status prior to transplantation: PIF *v* relapse, $P = .0544$.

‡No. of chemotherapy treatments prior to transplantation: 2 *v* > 2, $P = .2086$; chemotherapy-sensitive disease: resistant *v* unknown, $P = .1808$.

§No. of chemotherapy treatments prior to transplantation: 2 *v* > 2, $P = .0429$.

‖Overall *P* value.

Table 5. Multivariate Analysis of Prognostic Factors for AutoHCT and AlloHCT Recipients (significant covariates are shown)

Variable	Nonrelapse Mortality*			Relapse/Progression			Treatment Failure†			Overall Mortality‡		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Main effect												
AutoHCT	1.00 (ref)			1.00 (ref)			1.00 (ref)			1.00 (ref)		
AlloHCT	3.543	1.795 to 6.993	< .001	0.728	0.460 to 1.150	.1738	1.274	0.876 to 1.852	.2047	1.425	0.948 to 2.141	.0883
No. of chemotherapy lines prior to transplantation			.0118§						.0024§			< .001§
1	1.00 (ref)						1.00 (ref)			1.00 (ref)		
2	4.059	0.932 to 17.665	.0619				2.069	1.072 to 3.990	.0301	3.385	1.432 to 7.997	.0054
> 2	7.035	1.671 to 29.612	.0078				2.988	1.564 to 5.708	< .001	5.016	2.147 to 11.720	< .001
Chemotherapy-sensitive disease						.0323§			.0076§			.0332§
Sensitive				1.00 (ref)			1.00 (ref)			1.00 (ref)		
Resistant				2.006	1.137 to 3.539	.0163	1.981	1.285 to 3.052	.0019	1.821	1.155 to 2.872	.0099
Disease status prior to transplantation						.0012§						
CR1				1.00 (ref)								
CR2+				1.626	0.736 to 3.591	.2293						
PIF				2.215	1.066 to 4.606	.0331						
Relapse				3.661	1.834 to 7.309	< .001						

Abbreviations: alloHCT, allogeneic hematopoietic cell transplantation; autoHCT, autologous HCT; CR1, first complete remission; CR2, second complete remission; PIF, primary induction failure; ref, reference group; RR, relative risk.

*No. of chemotherapy treatments prior to transplantation: 2 *v* > 2, *P* = .0802 (nonrelapse mortality).

†No. of chemotherapy treatments prior to transplantation: 2 *v* > 2, *P* = .0569; chemotherapy-sensitive disease: resistant *v* unknown, *P* = .3014.

‡No. of chemotherapy treatments prior to transplantation: 2 *v* > 2, *P* = .0583; chemotherapy-sensitive disease: resistant *v* unknown, *P* = .1430.

§Overall *P* value.

AlloHCT has been proposed as an alternative to autoHCT, given the potential for graft-versus-leukemia effects and reports of durable remissions and few late relapses.[14-17] Among 126 patients undergoing alloHCT in our series, we did not find differences in outcome on the basis of either donor type (related *v* unrelated) or regimen intensity (myeloablative *v* NST/RIC). When considering regimen intensity, there are few comparative reports, but La Société Française de Greffe de Moëlle et de Thérapie Cellulaire (SFGM-TC) found no difference in either toxicity or survival between MA and NST regimens; the impact of regimen intensity on relapse was not reported.[18] Of note, a single-center review of 52 patients found that RIC regimens conferred a seven-fold increased risk of relapse but no difference in either PFS or OS.[19] Our series found no difference in 3-year transplantation-related mortality, PFS, OS, or risk of relapse/progression by alloHCT regimen intensity. In addition, neither AGVHD nor CGVHD correlated with outcome, although patients not in remission at time of transplantation had a four-fold increased risk of CGVHD.

A limitation of this analysis was lack of central pathology review for all patients. For example, the WHO defines two distinct subsets of ALCL on the basis of ALK status that differ by age. ALK-positive ALCL occurs primarily in males younger than age 30 years, and many consider this a pediatric disease. In contrast, ALK-negative ALCL is more common beyond age 40. Despite the impact of ALK on response to initial treatment, we were unable to include ALK status in our analysis because of unavailable data. Several lines of evidence suggest that higher International Prognostic Index and increased age are powerful surrogates for ALK, with high-risk patients faring poorly, independent of ALK status.[20] A subanalysis of the International T-Cell Lymphoma Project observed that patients older than age 40 years had no differential outcome (PFS or OS) on the basis of ALK positivity.[21] In our analysis, the median age of patients was 43 years for autoHCT and 38 years for alloHCT recipients, making a high proportion of ALK-positive patients unlikely. Furthermore, the significance of ALK status at relapse is unknown, suggesting an attenuated impact of ALK status in this setting that hopefully limits the impact of this deficiency.

Another issue inherent to transplantation registries is that only patients undergoing transplantation are included, with no data regarding patients unable to receive HCT because of refractory disease, age, comorbidities, or other factors. In light of the advanced median age of patients with T-NHL, clearly only a portion of them undergo transplantation. Furthermore, there is keen awareness of inadequate first-line regimens, with primary refractory disease often precluding transplantation. A Spanish intent-to-treat analysis found that only 40% of patients undergoing induction underwent autoHCT because of primary treatment failure,[22] although other prospective trials show that higher proportions of patients (66% to 80%) of patients can proceed.

Despite these caveats, this large series shows that HCT can benefit patients with T-NHL in both relapsed and first-line settings, and with both autoHCT and alloHCT approaches. Importantly, approximately 40% of patients undergoing autoHCT at the time of relapse attain long-term benefit and disease control, particularly for ALCL histology. One-third of alloHCT recipients remain progression-free at 3 years, despite being more heavily pretreated and having more refractory disease. Our results suggest that if HCT is considered, outcomes are best in chemotherapy-sensitive patients at the time of first- or second-line therapy, perhaps supporting evolving treatment paradigms in T-NHL in which HCT is considered earlier in overall management.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Koen van Besien, Center for International Blood and Marrow Transplant Research (U); Ritsuro Suzuki, EUSA Pharma (C); Leona A. Holmberg, Seattle Genetics (C), Genzyme (C); Thomas G. Gross, Roche (C), Eli Lilly (C); Peter H. Wiernik, Celgene (C) **Stock Ownership:** None **Honoraria:** Ritsuro Suzuki, Kyowa Hakko Kirin; Jack W. Hsu, MedTrend; Peter H. Wiernik, Novartis; Silvia Montoto, Roche, Celgene **Research Funding:** Leona A. Holmberg, Merck, Millennium Pharmaceuticals, Otsuka Pharmaceutical, Sanofi/Genzyme, Seattle Genetics; Silvia Montoto, Genentech **Expert Testimony:** None **Patents:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Sonali M. Smith, Linda J. Burns, Jennifer LeRademacher, Harry C. Schouten, Robert Peter Gale, Luciano J. Costa, Ginna G. Laport, Silvia Montoto, Parameswaran N. Hari
Collection and assembly of data: Linda J. Burns, Wensheng He, Parameswaran N. Hari
Data analysis and interpretation: Sonali M. Smith, Linda J. Burns, Koen van Besien, Jennifer LeRademacher, Wensheng He, Timothy S. Fenske, Ritsuro Suzuki, Jack W. Hsu, Harry C. Schouten, Gregory A. Hale, Leona A. Holmberg, Anna Sureda, Cesar O. Freytes, Richard Thomas Maziarz, David J. Inwards, Thomas G. Gross, Mitchell S. Cairo, Hillard M. Lazarus, Peter H. Wiernik, Dipnarine Maharaj, Ginna G. Laport, Silvia Montoto, Parameswaran N. Hari
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Vose J, Armitage J, Weisenburger D: International peripheral T-cell and natural killer/T-cell lymphoma study: Pathology findings and clinical outcomes. J Clin Oncol 26:4124-4130, 2008
2. Schmitz N, Trumper L, Ziepert M, et al: Treatment and prognosis of mature T-cell and NK-cell lymphoma: An analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 116: 3418-3425, 2010
3. Kyriakou C, Canals C, Goldstone A, et al: High-dose therapy and autologous stem-cell transplantation in angioimmunoblastic lymphoma: Complete remission at transplantation is the major determinant of Outcome-Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 26:218-224, 2008
4. Nademanee A, Palmer JM, Popplewell L, et al: High-dose therapy and autologous hematopoietic cell transplantation in peripheral T cell lymphoma (PTCL): Analysis of prognostic factors. Biol Blood Marrow Transplant 17:1481-1489, 2011
5. Reimer P, Rüdiger T, Geissinger E, et al: Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: Results of a prospective multicenter study. J Clin Oncol 27:106-113, 2009

6. Rodríguez J, Conde E, Gutiérrez 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 79:32-38, 2007

7. Bacigalupo A, Ballen K, Rizzo D, et al: Defining the intensity of conditioning regimens: Working definitions. Biol Blood Marrow Transplant 15:1628-1633, 2009

8. Weisdorf D, Spellman S, Haagenson M, et al: Classification of HLA-matching for retrospective analysis of unrelated donor transplantation: Revised definitions to predict survival. Biol Blood Marrow Transplant 14:748-758, 2008

9. 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 103:2474-2479, 2004

10. 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 14:741-747, 2008

11. Feyler S, Prince HM, Pearce R, et al: The role of high-dose therapy and stem cell rescue in the management of T-cell malignant lymphomas: A BSBMT and ABMTRR study. Bone Marrow Transplant 40:443-450, 2007

12. Kewalramani T, Zelenetz AD, Teruya-Feldstein J, et al: Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. Br J Haematol 134:202-207, 2006

13. Song KW, Mollee P, Keating A, et al: Autologous stem cell transplant for relapsed and refractory peripheral T-cell lymphoma: Variable outcome according to pathological subtype. Br J Haematol 120:978-985, 2003

14. 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 22:2172-2176, 2004

15. Delioukina M, Zain J, Palmer JM, et al: Reduced-intensity allogeneic hematopoietic cell transplantation using fludarabine-melphalan conditioning for treatment of mature T-cell lymphomas. Bone Marrow Transplant 47:65-72, 2012

16. Dodero A, Spina F, Narni F, et al: Allogeneic transplantation following a reduced-intensity conditioning regimen in relapsed/refractory peripheral T-cell lymphomas: Long-term remissions and response to donor lymphocyte infusions support the role of a graft-versus-lymphoma effect. Leukemia 26:520-526, 2012

17. Zain J, Palmer JM, Delioukina M, et al: Allogeneic hematopoietic cell transplant for peripheral T-cell non-Hodgkin lymphoma results in long-term disease control. Leuk Lymphoma 52:1463-1473, 2011

18. Le Gouill S, Milpied N, Buzyn A, et al: Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: A study by the Société Française de Greffe de Moëlle et de Thérapie Cellulaire. J Clin Oncol 26:2264-2271, 2008

19. Jacobsen ED, Kim HT, Ho VT, et al: A large single-center experience with allogeneic stem-cell transplantation for peripheral T-cell non-Hodgkin lymphoma and advanced mycosis fungoides/Sezary syndrome. Ann Oncol 22:1608-1613, 2011

20. Suzuki R, Kagami Y, Takeuchi K, et al: Prognostic significance of CD56 expression for ALK-positive and ALK-negative anaplastic large-cell lymphoma of T/null cell phenotype. Blood 96:2993-3000, 2000

21. 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 111:5496-5504, 2008

22. Mercadal S, Briones J, Xicoy B, et al: Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation in previously untreated patients with peripheral T-cell lymphoma. Ann Oncol 19:958-963, 2008

Affiliations

Sonali M. Smith, University of Chicago Hospitals, Chicago, IL; Linda J. Burns, University of Minnesota Medical Center, Minneapolis; David J. Inwards, Mayo Clinic Rochester, Rochester, MN; Koen van Besien, Weill Cornell Medical College; Peter H. Wiernik, Continuum Cancer Centers of New York at St Luke's-Roosevelt Hospital and Beth Israel Medical Center, New York City; Mitchell S. Cairo, New York Medical College, Valhalla, NY; Jennifer LeRademacher, Wensheng He, and Parameswaran N. Hari, Center for International Blood and Marrow Transplant Research; Timothy S. Fenske, Medical College of Wisconsin, Milwaukee, WI; Ritsuro Suzuki, Nagoya University School of Medicine, Nagoya, Japan; Jack W. Hsu, Shands HealthCare and University of Florida, Gainesville; Gregory A. Hale, All Children's Hospital, St Petersburg; Dipnarine Maharaj, South Florida Bone Marrow Stem Cell Transplant Institute, Boynton Beach, FL; Harry C. Schouten, Academische Ziekenhuis Maastricht, Maastricht, the Netherlands; Leona A. Holmberg, Fred Hutchinson Cancer Research Center, Seattle, WA; Anna Sureda, Addenbrooke's Hospital-Cambridge University, Cambridge; Robert Peter Gale, Imperial College London; Silvia Montoto, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Cesar O. Freytes, South Veterans Health Care System and University of Texas Health Science Center, San Antonio, TX; Richard Thomas Maziarz, Oregon Health & Science University, Portland, OR; Thomas G. Gross, Nationwide Children's Hospital, Columbus; Hillard M. Lazarus, University Hospitals Case Medical Center, Cleveland, OH; Luciano J. Costa, Medical University of South Carolina, Charleston, SC; and Ginna G. Laport, Stanford Hospitals and Clinics, Stanford, CA.

Support

Supported by Public Health Service Grant No. U24-CA76518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases; Grant No. 5U01HL069294 from NHLBI and NCI; Contract No. HHSH234200637015C with Health Resources and Services Administration, Department of Health and Human Services; Grants No. N00014-06-1-0704 and N00014-08-1-0058 from the Office of Naval Research; and grants from Allos Therapeutics; Amgen; Angioblast Systems; anonymous donation to the Medical College of Wisconsin; Ariad Pharmaceuticals; Be the Match Foundation; Blue Cross and Blue Shield Association; Buchanan Family Foundation; CaridianBCT; Celgene; CellGenix; Children's Leukemia Research Association; Fresenius-Biotech North America; Gamida Cell-Teva Joint Venture; Genentech; Genzyme; GlaxoSmithKline; HistoGenetics; Kiadis Pharma; The Leukemia & Lymphoma Society; The Medical College of Wisconsin; Merck; Millennium Pharmaceuticals; The Takeda Oncology Company; Milliman USA; Miltenyi Biotec; National Marrow Donor Program; OptumHealth Care Solutions; Osiris Therapeutics; Otsuka America Pharmaceutical; RemedyMD; Sanofi; Seattle Genetics; Sigma-Tau Pharmaceuticals; Soligenix; StemCyte; STEMSOFT Software; Swedish Orphan Biovitrum; Tarix Pharmaceuticals; Teva Neuroscience; Therakos; and WellPoint.

Acknowledgment

We thank Laren C. Pinter-Brown, Maria L. Delioukina, Christopher Dvorak, Mark B. Juckett, Mary Jo Lechowicz, Miguel A. Pavlovsky, and Julie M. Vose for their helpful comments and insights as members of the study committee.

Appendix

Table A1. Subset Analysis by Histology: Univariate Probabilities of Outcome for ALCL, PTCL, and AITL

	ALCL					PTCL					AITL				
	AutoHCT (n = 61)		AlloHCT (n = 51)			AutoHCT (n = 39)		AlloHCT (n = 63)			AutoHCT (n = 15)		AlloHCT (n = 12)		
Outcome Event	%	95% CI (%)	%	95% CI (%)	*P*	%	95% CI (%)	%	95% CI (%)	*P*	%	95% CI (%)	%	95% CI (%)	*P*
Acute GVHD, grades 2 to 4															
At 100 days			18	9 to 30				10	4 to 19				8	0 to 30	
Chronic GVHD															
At 1 year			20	10 to 32				41	28 to 53				27	6 to 56	
At 3 years			22	12 to 34				43	30 to 55				27	6 to 56	
Nonrelapse mortality															
At 100 days	2	0 to 8	22	12 to 34	< .001	3	0 to 12	16	8 to 26	.0115	0		8	1 to 31	
At 1 year	10	4 to 19	29	18 to 42	.0093	3	0 to 12	28	17 to 39	< .001	7	0 to 26	8	1 to 31	.8709
At 3 years	10	4 to 19	31	19 to 44	.0046	15	5 to 31	29	19 to 41	.1164	7	0 to 26	8	1 to 31	.8709
Relapse/progression															
At 1 year	31	20 to 43	31	19 to 44	.9989	37	22 to 52	32	21 to 44	.6399	40	16 to 63	25	6 to 50	.399
At 3 years	35	23 to 47	33	21 to 46	.8679	56	37 to 71	38	26 to 50	.098	47	21 to 69	25	6 to 50	.2274
Progression-free survival															
At 1 year	59	45 to 70	39	26 to 52	.0376	60	43 to 74	40	28 to 52	.045	53	26 to 74	67	34 to 86	.4767
At 3 years	55	42 to 67	35	22 to 48	.0319	29	14 to 47	33	22 to 45	.7188	47	21 to 69	67	34 to 86	.2858
Overall survival															
At 1 year	73	60 to 83	49	35 to 62	.0072	64	46 to 77	52	38 to 64	.25	60	35 to 82	92	70 to 100	.034
At 3 years	68	54 to 78	41	27 to 54	.0034	45	27 to 62	42	30 to 55	.7979	51	26 to 76	83	56 to 98	.077
Overall mortality															
At 30 days	0		8	3 to 20		0		2	0 to 11		7	1 to 39	8	1 to 46	.87
At 100 days	7	3 to 17	33	22 to 48	< .001	8	3 to 22	22	14 to 35	.0315	13	4 to 44	8	1 to 46	.67

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; alloHCT, allogeneic hematopoietic cell transplantation; autoHCT, autologous HCT; GVHD, graft-versus-host disease; PTCL, peripheral T-cell lymphoma.

Table A2. Cause of Death by Transplantation Modality

	AutoHCT			Myeloablative			NST/RIC		
Cause of Death	No. of Patients	No.	%	No. of Patients	No.	%	No. of Patients	No.	%
No. of patients	115			74			45		
No. of deaths	51			45			24		
Primary disease		37	73		18	40		11	46
Infection		4	8		2	4		3	13
IPn		0			4	9		2	8
ARDS		2	4		2	4		0	
Organ failure		4	8		10	22		3	13
Accidental death		1	2		0			0	
Graft failure		1	2		0			0	
Hemorrhage		0			3	7		1	4
GVHD		0			3	7		2	8
Pulmonary toxicity		0			2	4		0	
Vascular (cardiac or cerebral)		0			1	2		1	4
Other, not specified		2	4		0			1	4

Abbreviations: ARDS, acute respiratory disease syndrome; autoHCT, autologous hematopoietic cell transplantation; GVHD, graft-versus-host disease; IPn, interstitial pneumonitis; NST, nonmyeloablative stem-cell transplantation; RIC, reduced-intensity conditioning.