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Long-Term Outcomes and Safety Trends of Autologous Stem-Cell Transplantation in Non-Hodgkin Lymphoma: A Report From A Tertiary Care Center in India

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PURPOSE Published experience with autologous stem-cell transplantation (ASCT) in non-Hodgkin lymphoma (NHL) from the Indian subcontinent is extremely limited. Here, we describe the activity and outcomes of this treatment modality at a large tertiary care center in India.

PATIENTS AND METHODS We retrospectively analyzed adult patients with NHL who were eligible for ASCT and autografted between January 1, 2002, and December 15, 2020, at our transplant unit. Toxicities, complications, and long-term outcomes were compared between patients who underwent transplant during 2002-2012 (group A) and 2013-2020 (group B).

RESULTS Overall, 80 patients (group A, n = 37; group B, n = 43) underwent ASCT using peripheral blood stem cells. At a median follow-up of 57.6 months, the 5-year event-free survival (EFS) and overall survival (OS) were 43.5% and 47.6%, respectively, for all patients. More recently (group B), patients had reduced 100-day transplant-related mortality (2.3% *v* 21.6%, $P < .01$), improved 3-year EFS (52.9% *v* 37.3%, $P = .04$), and superior OS (at 3-year; 63.4% *v* 43.2%, $P = .02$). Patients in group B also tolerated the procedure better, with improved resource utilization. In multivariate analysis, an International Prognostic Index (IPI) ≥ 3 at diagnosis adversely affected EFS (hazard ratio [HR] = 2.82, $P = .009$) and OS (HR = 2.84, $P = .01$) after ASCT. Low pretransplant serum albumin levels were associated with inferior EFS (HR = 2.68, $P = .02$) and transplant-related mortality (odds ratio = 10.80, $P = .02$) after ASCT.

CONCLUSION It is feasible to achieve comparable short- and long-term outcomes in patients with NHL undergoing ASCT in a resource-poor country with improved supportive care and expertise of the transplant team and center.

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INTRODUCTION

The evolution of contemporary nontransplant strategies has contributed to superior outcomes in the heterogeneous non-Hodgkin lymphoma (NHL) population over the past 2 decades. However, up to 40% of patients with intermediate- or high-grade NHL are either refractory to or relapse after initial treatment.[1,2] High-dose chemotherapy and autologous stem-cell transplantation (ASCT) has been the standard treatment for relapsed/refractory high-grade NHL ever since the classical Parma study demonstrated superior 5-year event-free survival (EFS; 46% *v* 12%, $P = .001$) and overall survival (OS; 53% *v* 32%, $P = .038$) in patients who were chemotherapy sensitive and received consolidation with ASCT compared with those without consolidation.[3] The role of ASCT at stages from diagnosis to first complete remission (CR) is debated because of the lack of sufficiently powered randomized controlled trials. Upfront consolidation with ASCT improves the duration of response in aggressive subtypes such as mantle-cell lymphoma (6-year OS and EFS; 70% and 56%, respectively) or peripheral T-cell lymphomas (5-year OS and PFS; 51% and 44%, respectively), which otherwise have dismal outcomes, thus making ASCT a favored strategy till improved prognostication and innovative therapies are available for these entities.[4,5]

Although lymphomas are among the most common indications of ASCT worldwide, published experience of ASCT in NHL, either in upfront or salvage settings in India, is sparse.[6-8] We retrospectively analyzed the data of patients with NHL who underwent elective

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CONTEXT

Key Objective

We analyzed the trends of safety and outcomes of autologous stem-cell transplantation (ASCT) in non-Hodgkin lymphoma (NHL) at a large tertiary care center in India.

Knowledge Generated

The overall 5-year event-free survival and overall survival are 43.5% and 47.6%, respectively, in patients with NHL undergoing ASCT over the past 2 decades. In recent times, patients have tolerated the procedure better, suffered lower transplant-related mortality at day 100, and demonstrated significantly improved event-free survival and overall survival.

Relevance

In the NHL population undergoing ASCT, given the same level of care, a comparable degree of safety and efficacy are feasible in resource-poor countries such as India.

single ASCT at our institute to determine the tolerability, toxicities, and outcomes associated with this procedure over 2 decades. We also investigated the factors that determined the short- and long-term outcomes of this treatment strategy in our patient population.

PATIENTS AND METHODS

Patient Selection

This study was approved by the Institute Ethics Committee (Ref no: IEC-420/8.5.2020). Inclusion criteria comprised adults (age > 16 years) having histologically confirmed relapsed/refractory intermediate- to high-grade, mature B-/T-cell NHL. We also included patients with peripheral T-cell lymphoma or mantle-cell lymphoma who responded to induction therapy and were consolidated with ASCT. Our center is equipped with an eight-bedded bone marrow transplantation ward that is managed by four teams, including ours. All patients with NHL who underwent ASCT under the care of our team were included in this study.

Patients who did not provide written informed consent for ASCT were excluded. Course of transplant, toxicities, complications, and long-term outcomes were compared between such patients undergoing transplant during 2002-2012 (group A) and 2013-2020 (group B) at Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi.

Transplant Protocol

Details of the procedure, its expected benefits, and complications were shared with the patients and their families. All patients underwent protocol-defined pretransplant evaluation to determine their fitness for ASCT and disease remission status. The hematopoietic cell transplant comorbidity index was calculated retrospectively using the medical history from the case record files in cases where it was not available in the charts. All our patients used peripheral blood stem cells, harvested via peripheral or central vein. The majority (85%) of patients were mobilized using granulocyte colony-stimulating factor (G-CSF) only, 10 μg/kg in two divided doses subcutaneously for 5 days. From day 5 onward, stem-cell harvesting was performed using one of the three apheresis platforms available at our center: Haemonetics cell separator-MCS 3p (Haemonetics, Braintree, MA), Spectra Optia apheresis system (Terumo BCT Inc, Lakewood, CO), and COM.TEC therapeutic apheresis and cell collection (Fresenius Kabi, Bad Homburg, Germany). In patients from cohort B, plerixafor (240 μg/kg subcutaneous, 12 hours before day 5 scheduled apheresis) was also used if the day 4 peripheral blood cell CD34+ cell count was < 20 cells/μL. Stem cells were cryopreserved at –80°C by using a cryoprotectant mixture of 7.5% dimethyl sulfoxide, saline, and albumin. The most common conditioning regimen used was carmustine, etoposide, ara c, and melphalan (BEAM), which consisted of carmustine (BCNU) 300 mg/m^2 intravenous (IV) on day –6, etoposide 800 mg/m^2 IV divided over 4 days from day –5 to day –2, ara c (cytarabine) 1,600 mg/m^2 IV divided into two daily doses from day –5 to day –2, and melphalan 140 mg/m^2 IV on day –1. During the universal scarcity of BCNU in 2000s, it was replaced with lomustine (200 mg/m^2 orally on day –6), and the resultant LEAM (lomustine, etoposide, ara C, and melphalan) regimen was used in nine patients. Six patients received other types of conditioning, most commonly CBV (cyclophosphamide, BCNU, and etoposide) regimen. Patients received prophylaxis against bacterial, fungal, and viral infections with ciprofloxacin, itraconazole, fluconazole, and acyclovir, respectively. Stem cells were transfused as per standard guidelines on day 0, and G-CSF was started at 5 mg/kg subcutaneously once daily doses from day +1 till engraftment of neutrophils. The first of 3 consecutive days with an absolute neutrophil count ≥ 500/mm^3 was considered the day of neutrophil engraftment. Platelet engraftment was defined as the first of seven consecutive days with a platelet count ≥ 20,000/mm^3 (transfusion independence for the last 5 days). Regimen-related toxicities were graded retrospectively using the National Cancer Institute common terminology criteria version 5.0 on the basis of the clinical observations and laboratory/radiologic investigations entered in daily clinical notes by the attending physician during the course of transplant, and managed as per standard institutional practices.[9] WHO criteria were used for grading mucositis, and

Seattle criteria were used for grading veno-occlusive disease.[10,11] Febrile episodes were graded into clinically detected infection, microbiologically detected infections, or fever of unknown origin, and managed as per standard guidelines.[12] Initial workup for neutropenic fever included detailed history, clinical examination (especially previous antibiogram), paired blood cultures before starting antibiotics followed by every alternate day, baseline chest x-ray, and coagulation screening. It is our institutional policy to start with dual antibiotics (cefoperazone-sulbactam or imipenem plus amikacin) once febrile neutropenia is confirmed, often with the addition of gram-positive coverage upfront if any of hemodynamic instability, pneumonia, severe mucositis, skin/soft tissue infections, and clinically evident catheter-related infection are present. If the patient does not respond clinically within 48 hours, antibiotics are changed on the basis of the prevailing clinicoradiological or microbiological evidence of the source of infection. Patients were evaluated at day +100 for post-transplant disease responses. Cheson's criteria were used to define tumor response in this study.[13,14] Follow-up data were obtained via outpatient records or telephone communication.

Statistical Analysis

The cutoff date for statistical analysis of baseline demographic data and clinical outcomes was December 15, 2020. Descriptive statistics were used to show the distribution of variables among the patients. OS was defined as the duration from transplant until death due to any cause or date of the censor. EFS was defined as the interval from the date of transplant to the progression/relapse of disease or death due to any cause. Death within 100 days after transplantation due to causes other than lymphoma is termed transplant-related mortality (TRM). Survival rates were calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. Differences between groups were calculated using the chi-square test or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. Prognostic factors were identified by univariate and multivariate analyses using the Cox regression model. Variables with a value < 0.20 in univariate analysis were included in the multivariate analysis. All statistical tests were two-sided, and $P < .05$ indicated statistical significance. The analysis was carried out using STATA v16.0 software (StataCorp, College Station, TX).

RESULTS

In total, 80 adult patients with NHL were autografted between 2002 and 2020 at our institute: 37 received ASCT between 2002 and 2012 (group A), and 43 patients were transplanted between 2013 and 2020 (group B). Patient's flow through the treatment is summarized in Figure 1.

Patient Characteristics

For the entire cohort, the median age at transplant was 38 (interquartile range [IQR], 22-60) years; the male to female ratio was 4:1, and the median time from diagnosis to transplant was 15.1 (IQR, 8.8-22.8) months. The most common histology was diffuse large B-cell lymphoma (62.5%), followed by peripheral T-cell lymphoma (21.3%). The median time from primary diagnosis of NHL

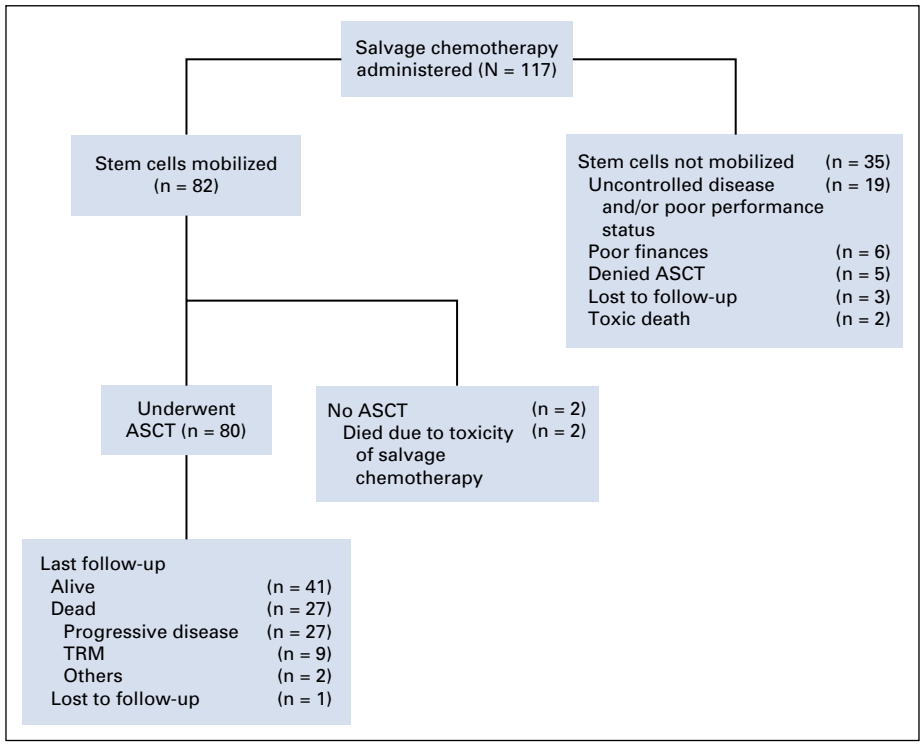

FIG 1. Patient flow through the treatment in overall cohort. ASCT, autologous stem-cell transplantation; TRM, transplant-related mortality.

TABLE 1. Patient Characteristics

Variable	Group A (n = 37)	Group B (n = 43)	Overall (N = 80)	*P*
Age, median (IQR), years	36 (22-56)	40 (25-60)	38 (22-60)	.75
Sex, No. (%)				.73
Female	8 (21.6)	8 (18.6)	16 (20.0)	
Male	29 (78.3)	35 (81.4)	64 (80.0)	
Diagnosis, No. (%)				.07
DLBCL	22 (59.4)	28 (65.1)	50 (62.5)	
PTCL	7 (18.9)	10 (23.3)	17 (21.3)	
MCL	1 (2.7)	4 (9.3)	5 (6.3)	
T-LBL	5 (13.5)	0	5 (6.2)	
Other	2 (5.4)	1 (2.3)	3 (3.7)	
Stage, No. (%)				.74
Early (I/II)	11 (31.5)	15 (34.9)	26 (33.3)	
Advanced (III/IV)	24 (68.5)	28 (65.1)	52 (66.7)	
IPI at diagnosis, No. (%)				.51
0-2	19 (76.0)	26 (64.8)	45 (71.4)	
> 2	6 (24.0)	12 (31.6)	18 (28.6)	
First-line regimen, No. (%)				.20
RCHOP	15 (40.6)	20 (46.5)	35 (43.7)	
CHOP	16 (43.2)	11 (25.6)	27 (33.8)	
E-CHOP	0	6 (13.9)	6 (7.6)	
NHL 98-01	5 (13.5)	0	5 (6.2)	
RCHOP/RDHAP	0	2 (4.6)	2 (2.5)	
Other	1 (2.7)	4 (9.4)	5 (6.2)	
Response to initial treatment, No. (%)				.14
CR	17 (45.9)	22 (51.2)	39 (48.7)	
PR	7 (18.9)	14 (32.6)	21 (26.3)	
Not evaluated	2 (5.4)		2 (2.5)	
First salvage regimen, No. (%)				.16
ICE ± R	19 (65.5)	21 (65.6)	39 (48.7)	
DHAP ± R	7 (24.2)	1 (3.1)	8 (13.1)	
MINE ± R	2 (6.2)	6 (18.8)	8 (13.1)	
Other	1 (3.1)	4 (12.5)	5 (8.2)	
Lines of therapy, No. (%)				.39
1	11 (29.7)	8 (18.6)	19 (23.8)	
2	14 (37.9)	22 (51.2)	36 (45.0)	
3 or more	12 (32.4)	13 (30.2)	25 (31.2)	
Pretransplant disease status, No. (%)				.05
CR	27 (73)	26 (60.5)	53 (66.2)	
PR	5 (13.5)	15 (34.9)	20 (25)	
PD	5 (13.5)	2 (4.6)	7 (8.8)	
Pretransplant chemosensitivity, No. (%)				.43
Chemosensitive	32 (86.5)	41 (94.5)	73 (90.5)	
Chemoresistant	5 (13.5)	2 (5.5)	7 (9.5)	

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TABLE 1. Patient Characteristics (Continued)

Variable	Group A (n = 37)	Group B (n = 43)	Overall (N = 80)	*P*
HCT-CI, No. (%)				.65
0-1	29 (78.4)	30 (69.8)	59 (73.7)	
2	7 (18.9)	10 (23.3)	17 (21.3)	
3 or more	1 (2.7)	3 (6.9)	4 (5.0)	
Pretransplant albumin, No. (%)				.82
Normal (3.5 g/dL or more)	30 (81.1)	34 (79.1)	64 (80.0)	
Low (< 3.5 g/dL)	7 (18.9)	9 (20.9)	16 (20.0)	
Mobilization regimen, No. (%)				< .01
G-CSF only	35 (97.3)	13 (30.2)	49 (61.2)	
G-CSF plus plerixafor	0	19 (44.2)	19 (23.8)	
Chemomobilization	1 (2.7)	11 (25.6)	12 (15.0)	
Stem-cell dose, median (IQR), million cells/kg	2.1 (0.9-5.2)	2.6 (1.8-8.3)	2.3 (0.9-8.3)	.01
Conditioning regimen, No. (%)				< .01
BEAM	26 (70.3)	39 (90.7)	65 (81.2)	
LEAM	9 (24.3)	0	9 (11.2)	
Other	2 (5.4)	4 (9.3)	6 (7.5)	
Day of engraftment, median (IQR)				
Neutrophils	15 (11-25)	11 (9-15)	12 (9-25)	< .01
Platelets	19 (15-37)	14 (10-18)	16 (10-37)	< .01
Duration of G-CSF, median (IQR)	17.5 (12-25)	12 (10-15)	13 (9-25)	< .01
Grade 3 or 4 regimen-related toxicities, No. (%)				
Mucositis	28 (80)	20 (46.5)	48 (61.5)	< .01
Vomiting	3 (8.5)	7 (16.2)	10 (12.8)	.25
Diarrhea	13 (37.1)	13 (30.2)	26 (33.3)	.52
Hepatic dysfunction	3 (8.1)	1 (2.3)	4 (5.0)	.06
Pulmonary dysfunction	2 (5.4)	1 (2.3)	3 (3.7)	.42
Renal dysfunction	1 (2.7)	0	1 (1.2)	.46
Cardiac dysfunction	2 (5.4)	1 (2.3)	3 (3.7)	.25
Length of stay, median (IQR)	25 (10-41)	18 (13-37)	21 (10-43)	.01
TRM, No. (%)	8 (21.62)	1 (2.3)	9 (11.2)	< .01

Abbreviations: BEAM, carmustine, etoposide, ara c, melphalan; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete remission; DHAP, dexamethasone, high-dose cytarabine, cisplatin; DLBCL, diffuse large B-cell lymphoma; E-CHOP, etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, granulocyte colony-stimulating factor; HCT-CI, hematopoietic cell transplant comorbidity index; ICE, ifosfamide, carboplatin, etoposide; IPI, International Prognostic Index; IQR, interquartile range; LEAM, lomustine, etoposide, ara C, melphalan; MCL, mantle-cell lymphoma; MINE, mesna, ifosfamide, mitoxantrone, etoposide; NHL, non-Hodgkin lymphoma; PD, progressive disease; PR, partial remission; PTCL, peripheral T-cell lymphoma; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RDHAP, rituximab, dexamethasone, high-dose cytarabine, cisplatin; T-LBL, T-lymphoblastic lymphoma; TRM, transplant-related mortality.

to transplant in our series was 15.1 (IQR, 8.8-22.8) months, and the median time from the last cycle of salvage chemotherapy to transplant was 67 (IQR, 45.5-96.5) days. Patient-, disease-, and treatment-related characteristics before transplantation were not significantly different between the study groups (Table 1).

Transplant-Related Characteristics

Stem-cell dose. To collect at least 2 million CD34+ stem cells per kilogram of body weight, patients received a median of two harvest sessions. Overall, the median stem-cell dose transfused was 2.3 (IQR, 0.9-8.3); patients in group B received significantly higher doses than those in group A (2.6 million/kg *v* 2.1 million/kg, $P = .01$), likely because of increased use of plerixafor (44.4% *v* 0, $P < .001$) and chemotherapy-based mobilization (25.6% *v* 2.7%, $P < .001$) after 2013 (Table 1). Overall, 21 patients (15 in group A, six in group B) received inadequate stem-cell doses (defined as < 2 million CD34+ cells/kg). Group A had a significantly higher

TABLE 2. Univariate and Multivariate Models of Factors for Day 100 Mortality

			Univariate Analysis		Multivariate Analysis	
Variable	**Category**	**No. (%)**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age, years	< 50	62 (77.5)	1.5 (0.35 to 6.70)	.56		
	≥ 50	18 (22.5)				
Sex	Female	16 (20.0)	1.01 (0.19 to 5.33)	.98		
	Male	64 (80.0)				
IPI	0-2	45 (71.4)	0.58 (0.06 to 5.65)	.64		
	> 2	18 (28.6)				
Lines of therapy	≤ 2	55 (68.7)	0.50 (0.09 to 2.54)	.40		
	> 2	25 (31.3)				
HCT-CI	0-1	59 (73.7)	0.27 (0.03 to 2.29)	.23	0.18 (0.01 to 1.83)	.14
	> 1	21 (26.3)				
Pretransplant albumin, g/dL	< 3.5	16 (20.0)	3.1 (0.77 to 12.97)	.10	10.80 (1.32 to 88.2)	.02
	≥ 3.5	64 (80.0)				
Conditioning regimen	BEAM	74 (92.5)	1.07 (0.20 to 5.67)	.93		
	Other	6 (7.5)				
Mobilization regimen	G-CSF alone	49 (61.2)	0.15 (0.01 to 1.27)	.08	0.09 (0.006 to 1.26)	.07
	G-CSF plus plerixafor/ chemomobilization	31 (38.8)				
Use of antifungal	Therapeutic	44 (55.0)	3.66 (0.72 to 18.52)	.11	8.38 (0.98 to 71.73)	.05
	Prophylactic	36 (45.0)				
Stem-cell dose, million/kg	≤ 2	26 (32.5)	0.70 (0.17 to 2.74)	.61		
	> 2	54 (67.5)				
Type of FN	MDI	26 (32.5)	3.94 (1.00 to 15.54)	.05	3.81 (0.78 to 18.60)	.09
	Non-MDI	54 (67.5)				

Abbreviations: BEAM, carmustine, etoposide, ara c, melphalan; FN, Febrile Neutropenia; G-CSF, granulocyte colony-stimulating factor; HCT-CI, hematopoietic cell transplant comorbidity index; IPI, International Prognostic Index; MDI, microbiologically detected infection; OR, odds ratio.

number of patients with inadequate stem-cell doses than group B (40.5% *v* 13.9%, $P < .01$).

Engraftment. The median times taken for neutrophil and platelet engraftment were 12 (IQR, 9-25) days and 16 (IQR, 10-37) days, respectively, for the overall cohort. All patients who underwent ASCT were analyzed, including those who did not undergo engraftment (n = 10). Patients in group B had a lower median time to platelet (14 *v* 19 days, $P < .001$) or neutrophil (11 *v* 15 days, $P < .001$) count. Patients in group B also required less supportive care in terms of the number of PRBC units (3 *v* 2, $P = .02$), single-donor platelet units (5 *v* 3, $P < .001$), and days of G-CSF injections (12 *v* 17.5, $P < .001$).

Infections. All patients developed febrile neutropenia at a median of 4 (IQR, 0-8) days after transplant. The focus of infection was clinically detected infection in 24 patients (30.0%), and no focus was found in 30 (37.5%) patients. Microbiological evidence of infection was available in 26 (32.5%) patients overall: gram-negative bacteria in 17 (21.2%), gram-positive isolates in six (7.5%), and mixed organism growth in three (3.7%) patients. A median of 5 (IQR, 2-8) antibiotics were used for a duration of 13 days (median, 7-37) days. Forty-four (55.0%) patients required therapeutic antifungals beginning on day 8 (median, IQR 5-13) and amphotericin B was most commonly used (54.5%). Patients in group B used fewer numbers (4 *v* 5, $P = .004$) and durations (11 *v* 16 days, $P = .01$) of antibiotics, but therapeutic antifungal use was not different among the study groups.

Regimen-related toxicities. The most common grade 3 or 4 regimen-related toxicities were mucositis (61.5%), diarrhea (33.3%), and vomiting (12.8%). The incidence of grade 3/4 mucositis decreased (46.5% *v* 80%, $P = .002$) after 2012, whereas other organ-related toxicities were similar (Table 1). On long-term follow-up, two patients developed head and neck squamous cell cancers: one was cured with surgery and the second succumbed to disease.

Treatment-related mortality. Overall, nine (11.2%) patients died within 100 days after transplantation; sepsis was the cause in seven (8.7%) patients, followed by pulmonary alveolar hemorrhage in two (2.5%). The TRM was significantly reduced in group B (2.3% *v* 21.6%). In the multivariate

TABLE 3. Univariate and Multivariate Models of Factors for Post-Transplant Remission

			Univariate analysis		Multivariate analysis	
Variable	**Category**	**No. (%)**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age, years	< 50	62 (77.5)	0.78 (0.24 to 2.51)	.680		
	≥ 50	18 (22.5)				
Sex	Female	16 (20.0)	0.71 (0.22 to 2.26)	.570		
	Male	64 (80.0)				
Initial treatment	Rituximab	38 (47.5)	1.50 (0.57 to 3.92)	.400		
	No rituximab	42 (52.5)				
IPI	0-2	45 (71.4)	2.16 (0.66 to 7.04)	.200	2.48 (0.58 to 10.44)	.21
	> 2	18 (28.6)				
Bulky disease	Yes	17 (21.3)	2.63 (0.88 to 8.12)	.090	3.0 (0.8 to 11.2)	.10
	No	63 (78.7)				
Diagnosis	B-cell	58 (72.5)	1.01 (0.35 to 2.90)	.980		
	T-cell	22 (27.7)				
Response to first-line therapy	CR	39 (48.7)	4.97 (1.70 to 14.48)	.003	10.52 (1.60 to 68.90)	.01
	No CR	41 (51.3)				
Lines of therapy	≤ 2	55 (68.7)	1.33 (0.48 to 3.64)	.570		
	> 2	25 (31.3)				
HCT-CI	0-1	59 (73.7)	0.82 (0.27 to 2.45)	.720		
	> 1	21 (26.3)				
Pretransplant albumin, g/dL	< 3.5	16 (20.0)	5.33 (1.66 to 17.12)	.005	4.14 (0.93 to 18.44)	.06
	≥ 3.5	64 (80.0)				
Conditioning regimen	BEAM	74 (92.5)	2.23 (0.70 to 7.07)	.170	4.82 (0.71 to 32.50)	.10
	Other	6 (7.5)				
Pretransplant disease status	Chemosensitive	73 (90.5)	3.23 (0.66 to 15.73)	.140	1.94 (0.15 to 24.3)	.60
	Chemoresistant	7 (9.5)				

Abbreviations: BEAM, carmustine, etoposide, ara c, melphalan; CR, complete remission; HCT-CI, hematopoietic cell transplant comorbidity index; IPI, International Prognostic Index; OR, odds ratio.

analysis, pretransplant hypoalbuminemia (< 3.5 mg/dL) was associated with higher TRM (odds ratio = 10.80; 95% CI, 1.32 to 88.2; *P* = .02; Table 2).

Post-transplant Outcomes

Response to transplant. Among 51 (63.7%) patients who were found to have CR of their disease at day 100 using standard response criteria, 39 (48.7% of total patients) were already in CR at the time of transplant and 12 (15% of total patients) had active disease before transplantation. Sixteen (20.2%) patients had persistent disease even after ASCT, and the response status was unknown in four patients. Although response to first-line therapy and pretransplant albumin level were predictive of post-transplant response in univariate analysis, only response to first-line therapy remained significant (odds ratio = 10.52; 95% CI, 1.60 to 68.90; *P* = .01) in multivariate analysis (Table 3).

Survival. The median follow-up of full cohort was 57.6 (95% CI, 37.2 to 97.0) months: 149.2 months (95% CI, 127.0 to 170.4) for group A and 26.2 months (95% CI, 14.0 to 42.1) for group B. The median EFS and OS for the whole cohort were 30.1 months and 45.6 months, respectively. Similarly, for the total population (n = 80), the 5-year EFS and OS rates were 43.5% and 47.6%, respectively. Both EFS (*P* = .04; hazard ratio = 0.51; 95% CI, 0.27 to 0.97) and OS (*P* = .02; hazard ratio = 0.44; 95% CI, 0.22 to 0.87) improved significantly in group B, with 3-year EFS of 52.9% versus 37.3% and 3-year OS of 63.4% versus 43.2%, respectively (Fig 2).

In multivariate analysis, a higher International Prognostic Index (IPI) at diagnosis (3-year EFS: 56.7% in the low/low intermediate-risk group *v* 23.4% in the high intermediate- and high-risk groups) and pretransplant hypoalbuminemia (3-year EFS: 45.6% in those with normal albumin *v* 14% in patients with low albumin levels) predicted worse EFS.

Likewise, higher IPI alone was associated with poor OS (3-year OS: 71.3% in low/low intermediate-risk group*v* 24.0% in high intermediate/high-risk group; Table 4).

Current status. At the last follow-up, 39 (48.7%) patients were disease-free, 27 (33.7%) died due to disease progression, and two (2.5%) were alive with persistent disease.

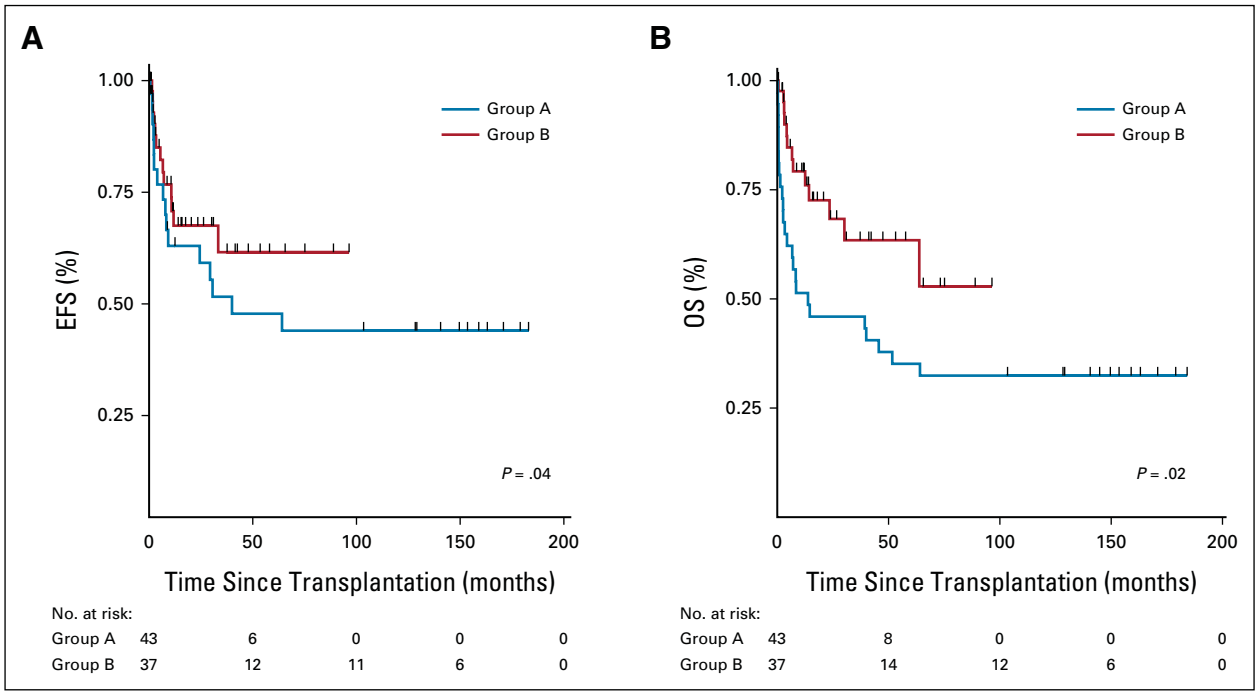

FIG 2. (A) EFS in patients from group A and group B; (B) OS in patients from group A and group B. EFS, event-free survival; OS, overall survival.

Apart from nine toxic deaths, two (2.5%) patients died due to causes other than disease progression: one died due to head and neck squamous cell cancer and one patient who had sudden onset cardiac arrest; the cause of death was not known.

DISCUSSION

ASCT continues to be the curative option for eligible patients with NHL, and sustained efforts to improve patient outcomes with this approach are pertinent. The data on ASCT in NHL from India are limited to a few studies, with NHL constituting only a small subgroup of patients in them.[7,8,15]

ASCT improved survival in our NHL population; the observed 5-year OS and EFS of 47.6% and 43.5%, respectively, were comparable with those reported for ASCT in NHL using peripheral blood stem cells, notwithstanding the higher fraction of T-cell NHL population in our cohort.[3,8,16,17] These outcomes need to be interpreted against the backdrop of a higher proportion of T-cell lymphoma (27.5%) in our series, a trend that has been observed consistently in studies reported from other Asian populations as well.[18] Younger age at transplant, predominance of male sex, or B-cell variety in our study mirrors the general epidemiology of NHL in India.[19,20] Even if the two study groups were similar in terms of their pretransplant disease-related characteristics and were treated in a uniform manner, we were able to achieve a significant reduction in TRM (21.6%-2.3%), and improvement in 3-year EFS (37.3%-52.9%) and OS (43.2%-63.4%) over the past decade, possibly by improving the safety and reducing the toxicity of the approach.

Year 2013 onward, introduction of plerixafor and increased use of chemomobilization for collection of stem cells improved the median stem-cell doses transfused compared with transplants during 2002-2012 (2.6 *v* 2.1 million cells/kg) leading to earlier engraftment of stem cells. Subsequently, the requirement of supportive care in terms of antibiotic use, blood product transfusions, duration of G-CSF, and length of hospital stay were significantly reduced in group B. Overall, patients were discharged at a median of 21 days from the day of stem-cell infusion. These data are in line with the previously reported experience of ASCT in the NHL population.[21,22] Notably, 40% of patients in group A received inadequate stem-cell doses, and in addition to compromised nutritional status, this may also have contributed to a more complicated transplant course and excessive early mortality in this subgroup.

Overall, our study cohort tolerated conditioning regimens well. GI involvement is the most common form of regimen-related toxicity. The overall incidence of severe oral mucositis (grade 3 or 4) was 61.5%; improved supportive care, even without the use of palifermin, led to a significant reduction in its incidence in patients who received transplants after 2012 (46.5%), which matches international data.[23,24] Similarly, the incidence of other major organ toxicities was not in excess of what was previously reported in patients with NHL using mainly BEAM conditioning and did not differ between the two study groups.[7,25,26] All patients developed febrile neutropenia, and bacteremia was detected in nearly one third (30%) of patients with at least one febrile episode. Nearly half (55%) of the

TABLE 4. Univariate and Multivariate Models of Factors for EFS and OS

			EFS				OS			
			Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
Variable	Category	No. (%)	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, years	< 50	62 (77.5)	1.22 (0.59 to 2.49)	.580			1.45 (0.70 to 2.99)	.310		
	≥ 50	18 (22.5)								
Sex	Female	16 (20.0)	0.70 (0.34 to 1.44)	.330			0.78 (0.36 to 1.65)	.520		
	Male	64 (80.0)								
Diagnosis	B-cell	58 (72.5)	0.93 (0.45 to 1.90)	.840			1.06 (0.51 to 2.18)	.870		
	T-cell	22 (27.7)								
Bulky disease	Yes	17 (21.3)	1.15 (0.54 to 2.42)	.700			1.13 (0.53 to 2.40)	.730		
	No	63 (78.7)								
IPI	0-2	45 (71.4)	2.56 (1.26 to 5.20)	.009	2.82 (1.29 to 6.18)	.009	2.76 (1.30 to 5.84)	.008	2.84 (1.23 to 6.52)	.01
	> 2	18 (28.6)								
Extranodal disease	Yes	37 (48.7)	1.66 (0.85 to 3.24)	.130	0.81 (0.35 to 1.89)	.640	1.86 (0.91 to 3.77)	.080	1.05 (0.42 to 2.61)	.91
	No	39 (51.3)								
Initial treatment	Rituximab	38 (47.5)	1.18 (0.63 to 2.19)	.590			1.22 (0.64 to 2.33)	.530		
	No rituximab	42 (52.5)								
Response to first-line chemotherapy	CR	39 (48.7)	2.09 (1.10 to 3.96)	.020	2.02 (0.86 to 4.73)	.100	2.05 (1.06 to 3.99)	.030	2.27 (0.94 to 5.45)	.06
	No CR	41 (51.3)								
Lines of therapy received	≤ 2	55 (68.7)	1.31 (0.69 to 2.49)	.400			1.44 (0.75 to 2.77)	.260		
	> 2	25 (31.3)								
Baseline ECOG PS	0-1	68 (85.0)	1.23 (0.54 to 2.78)	.610			1.26 (0.55 to 2.86)	.570		
	2	12 (15.0)								
HCT-CI	0-1	59 (73.7)	0.80 (0.40 to 1.61)	.540			0.96 (0.48 to 1.95)	.930		
	> 1	21 (26.3)								
Pretransplant disease status	Chemosensitive	73 (90.5)	1.88 (0.73 to 4.82)	.180	2.37 (0.67 to 8.38)	.170	2.05 (0.80 to 5.29)	.130	2.28 (0.64 to 8.10)	.20
	Chemoresistant	7 (9.5)								
Pretransplant albumin, g/dL	< 3.5	16 (20.0)	2.87 (1.50 to 5.51)	.001	2.68 (1.12 to 6.40)	.020	2.25 (1.13 to 4.48)	.020	1.83 (0.72 to 4.65)	.20
	≥ 3.5	64 (80.0)								
Conditioning regimen	BEAM	74 (92.5)	0.96 (0.58 to 1.57)	.870			1.09 (0.50 to 2.41)	.810		
	Other	6 (7.5)								

Abbreviations: BEAM, carmustine, etoposide, ara c, melphalan; CR, complete remission; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EFS, event-free survival; HCT-CI, hematopoietic cell transplant comorbidity index; HR, hazard ratio; IPI, International Prognostic Index; OS, overall survival.

patients, none with proven fungal infections, received therapeutic antifungals. This is consistent with previous Western and Indian studies on ASCT in patients with lymphoma.[7,27] It has been our institutional policy to start empirical antifungal therapy (amphotericin B) in patients with febrile neutropenia that do not respond to antibiotics by 96 hours because of the high reported incidence of invasive fungal infection in our patients.[28] Sepsis with multiorgan dysfunction was the main cause of TRM (seven of nine patients). Likewise, the most common cause of treatment failure or death after ASCT in our study was progression of primary NHL. These findings are comparable with those of previous studies.[29,30] Similarly, we did not find an association between the presence of bacteremia and increased TRM ($P = .09$); however, there was a statistically insignificant trend of increased 100-day mortality in patients who required therapeutic antifungal agents.[27,31]

Previous large studies have shown that second-line IPI or age-adjusted IPI at relapse can help differentiate patients with relapsed refractory NHL, who are less likely to benefit when treated with autotransplantation.[32,33] As a surrogate marker of disease biology, IPI at baseline has been used to predict survival in treatment-naive aggressive NHL; however, its effect on outcomes after ASCT has not been studied thoroughly. We show that compared with a baseline IPI of 0-2, a higher IPI of 3-5 was associated with worse OS (71.3% *v* 24%) and EFS (56.7% *v* 23.4%) after ASCT in our rather small NHL population with predominantly aggressive subtypes. Therefore, the baseline IPI seems to identify patients at a high risk of transplant failure even before second-line treatment is undertaken. Low serum albumin level has been correlated with early mortality after transplantation, but its role in determining long-term outcomes, especially in NHL, remains unexplored. Pretransplant hypoalbuminemia was associated with a higher TRM and inferior EFS in our cohort of patients undergoing ASCT. Although the biological basis of these associations requires further investigation, low serum albumin is often believed to represent poor nutritional status, poor hepatic function, or an inflammatory state secondary to underlying malignancy or infection.[34,35] Nutritional buildup and complete amelioration of salvage regimen-related infectious or hepatic complications before taking the patient for transplant to improve outcomes after ASCT have been suggested previously.[31,36] The sensitivity of tumors to first-line therapy predicted the response after ASCT in our patients. Those who achieved complete response with first-line therapy were more likely to achieve remission with ASCT in the future course of their disease than those with residual or progressive disease after first-line treatment. These findings are similar to those of the previous studies.[37,38] However, we could not demonstrate an association between pretransplant chemosensitive disease and ASCT outcomes, probably because of the lack of statistical power owing to the smaller sample size compared with other studies. However, the multivariate analysis in our study was limited by the small sample size.

Our study has several limitations. As this was a single-center series using a historical cohort, inherent selection bias was expected. Moreover, statistically meaningful subgroup analysis in terms of histology or timing of transplant was not feasible because of the small sample size; therefore, careful interpretation of the results is warranted. In addition, information on the baseline IPI was not available for 17 patients.

In conclusion, given the same level of care and expertise, it is possible to achieve comparable survival in patients with NHL undergoing ASCT in resource-limited countries, such as India. The baseline IPI and pretransplant serum albumin levels predicted survival in our patient cohort.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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