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ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR MYCOSIS FUNGOIDES AND SEZARY SYNDROME

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Abstract

We describe outcomes after allogeneic hematopoietic cell transplantation (HCT) for mycosis fungoides and sezary syndrome (MF/SS). Outcomes of 129 subjects with MF/SS reported to the Center for the International Blood and Marrow Transplant (CIBMTR) from 2000–2009. Median time from diagnosis to transplant was 30 (4–206) months and most subjects were with multiply relapsed/refractory disease. Majority (64%) received non-myeloablative conditioning (NST) or reduced intensity conditioning (RIC). NST/RIC recipients were older in age compared to myeloablative recipients (median age 51 vs. 44 y $p=0.005$) and transplanted in recent years. Non-relapse mortality (NRM) at 1 and 5 years was 19% (95% CI 12–27%) and 22% (95% CI 15–31%) respectively. Risk of disease progression was 50% (95% CI 41–60%) at 1 year and 61% (95% CI 50–71%) at 5 years. Progression free survival (PFS) at 1 and 5 years was 31% (95% CI 22–40%) and 17% (95% CI 9–26%) respectively. Overall survival at 1 and 5 years was 54% (95% CI 45–63%) and 32% (95% CI 22–44%) respectively. Allogeneic HCT in MF/SS results in 5 year survival in approximately one-third of patients and of those, half of them remain disease-free.

Keywords

Cutaneous T cell lymphoma; Allogeneic hematopoietic cell transplant; Bone marrow transplant; Mycosis fungoides; sezary syndrome

INTRODUCTION

Cutaneous T cell lymphoma (CTCL) constitutes approximately 2% of all lymphomas. Mycosis fungoides (MF) represents the most common subtype. Many patients with MF experience a prolonged clinical course. Patients with stage IVA and IVB disease have a median overall survival (OS) between 1.4 to 3.8 years from the time of diagnosis.^{1,2} Newer treatment modalities have arisen over the last decade, with relapse still being common.

Historically, hematopoietic cell transplantation (HCT) was rarely used to treat MF/SS because of concern regarding the lack of skin integrity and possible increased risk of infection. However, there is renewed interest in consideration of HCT because MF/SS is incurable with conventional therapy. Autologous HCT has not resulted in long-term remissions in CTCL patients^{3–5} and is rarely used now. Relatively small retrospective studies of allogeneic HCT with both myeloablative (MAC) and non-myeloablative conditioning (NST)/reduced intensity conditioning (RIC) regimens have been described.^{5–7} Definitive conclusions are lacking because of small sample size and considerable heterogeneity in subject, disease, and transplant variables. We analyzed outcomes of allogeneic HCT for MF/SS in 129 subjects reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).⁸

PATIENTS AND METHODS

The CIBMTR is a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous hematopoietic cell transplants to a Statistical Center at the Medical College of Wisconsin in

Milwaukee and the NMDP Coordinating Center in Minneapolis. Participating centers are required to report all transplants consecutively; compliance is monitored by on-site audits. Patients are followed longitudinally, with yearly follow-up. Computerized checks for discrepancies, physicians' review of submitted data and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with the Privacy Rule (HIPAA) as a Public Health Authority, and in compliance with all applicable federal regulations pertaining to the protection of human research participants as determined by continuous review of the Institutional Review Boards of the National Marrow Donor Program and the Medical College of Wisconsin since 1985.

The CIBMTR collects data at two levels: Transplant Essential Data (TED) and Comprehensive Report Form (CRF) data. TED data include disease type, age, gender, pre-transplant disease stage and chemotherapy-responsiveness, date of diagnosis, graft type (bone marrow- and/or blood- derived progenitor cells), conditioning regimen, post-transplant disease progression and survival, development of a new malignancy, and cause of death. All CIBMTR teams contribute TED data. More detailed disease and pre- and post-transplant clinical information are collected on a subset of registered patients selected for CRF data by a weighted randomization scheme. TED and CRF level data are collected pre-transplant, 100 days, and six months post transplant and annually thereafter or until death.

Subject selection

We analyzed the outcomes 129 adult (> 18 years) recipients of an allogeneic HLA matched related or unrelated HCT for MF/SS reported to the CIBMTR between 2000 and 2009. A subset of these patients (N=52) were reported at a higher level with comprehensive disease data and complete case report forms (CRF). Median follow up for these 52 patients was 40 months with a range of 3–91 months. The overall cohort of 129 subjects and the comprehensive subset had similar OS outcomes.

Study endpoints and definitions

Outcomes analyzed included treatment related mortality (NRM), relapse/progression, progression-free (PFS), and overall survival (OS). Patient staging was done by Ann Arbor staging criteria at the time of treatment. Data for ISCL/EORTC for MF/SS was not captured in this data set. The intensity of conditioning was categorized based on consensus criteria.⁹ Neutrophil recovery was defined as the first of three subsequent days with absolute neutrophil counts $\geq 0.5 \times 10^9/L$ without growth factor support. Platelet recovery was defined as the first of seven subsequent days with platelet counts $\geq 20 \times 10^9/L$ without platelet transfusions. NRM was defined as death from any cause in the first 28 days after HCT or death without evidence of MF/SS progression/relapse. Progression was defined as an increase of $\geq 25\%$ in the sites of lymphoma or development of new sites. Relapse was defined as recurrence of lymphoma after a complete remission (CR). For PFS, patients were considered treatment failures at the time of relapse/progression or death from any cause. Patients alive without evidence of disease relapse or progression were censored at last follow up and the PFS event was summarized by a survival curve. The OS interval variable was defined as the time from date of transplant to date of death or last contact and summarized by a survival curve.

Other outcomes analyzed included the incidence of acute (aGVHD) and chronic graft versus host disease (cGVHD) graded by established criteria and cause of death.

Statistical analysis

Subject-, disease-, and transplant-related variables are described for the entire cohort along with an additional subset with higher level CRF data. Univariate probabilities of NRM, relapse/progression, aGVHD, cGVHD, PFS and survival were described and compared. Causes of death are described.

RESULTS

Patients and Transplant Characteristics

129 MF/SS patients received an allogeneic transplant with characteristics described in Table 1. The majority received NST/RIC (n=83), 64% vs. 36% receiving MAC. The NST/RIC cohort was older with a median age at transplant of 51 (27–72) years vs. 44 (22–63) years in the MAC cohort (P=0.005). Eighty nine percent (n=74) of patients were transplanted 12 months or longer from diagnosis, with 49% (n=41) transplanted more than 36 months after diagnosis. Only one patient received allogeneic HCT in first CR while 37% never achieved CR prior to transplant. No patient had a prior autologous HCT.

The majority of patients (64%) were transplanted after 2006. A greater utilization of NST/RIC regimens was noted for this patient population. Bone marrow grafts were used in 13%, peripheral blood grafts in 86% and cord blood in one (1%) patient. Fludarabine based combination conditioning regimens were used in 66 of the 83 (80%) patients receiving NST/RIC. Specific NST/RIC regimens are detailed in Table 1. Cyclophosphamide with total body irradiation (TBI) was the most common MAC regimen used 16 of 45 or (35%) of patients.

A subset of 52 patients had higher level reporting with more disease-related information available for analysis (CRF cohort, Table 2). In this subset, 25 of 52 patients or 48% had 4 or more lines of chemotherapy prior to transplant. The use of alemtuzumab prior to transplant was limited to (13% of patients) and total skin electron beam (TSEB) radiation was used in only one patient recorded. Radiation therapy was used before transplant in 19% of 52 patients.

Engraftment

Neutrophil engraftment was achieved in 95% (95% CI 88–98) of patients at day 28. Platelet engraftment was achieved in 89% (95% CI 76–95%) of patients at day 100 (Table 3).

GVHD

The incidence of grade II–IV aGVHD was 41% (95%CI 32–51%). The incidence of cGVHD was 33% (95% CI 23–43%), 42% (95%CI 31–52%), and 43% (95%CI 33–54%) at 180 days, 1 and 2 years respectively (Table 3).

Treatment and Disease Outcomes (Table 3 and 4)

Irrespective of conditioning regimen intensity OS was similar at 56% (95% CI 45–67%) and 41% (95% CI 29–53%) at 1 and 3 years respectively for NST/RIC and 51% (95% CI 35–66%) and 31% (95% CI 16–49%) respectively for MAC (log Rank P-Value=0.277) shown in Figure 1A. NRM for registered patients at 1 y and 5y was 19% (95% CI 12–27%) and 22% (95% CI 15–31%). NRM did not differ significantly between the NST/RIC and MAC cohorts (Table 4). Progression/relapse was 50% (95% CI 41–60%) at 1 year and 61% (95% CI 50–71%) at 5 years. PFS at 1 year was 31% (95% CI 22–40%) and at 5 years 17% (95% CI 9–26%). There was no significant difference in PFS between the NST/RIC and MAC cohorts (P value=0.149; Figure 1B). There was no significant difference in the incidence of NRM with MAC vs. NST/RIC (Figure 1C). There was no significant difference in PFS based on interval of diagnosis to transplant (Figure 1D). Progressive disease was the primary cause of death and treatment failure in this cohort of patients with advanced disease. Other causes of death are summarized in Table 5.

DISCUSSION

To the best of our knowledge, this analysis represents the largest reported descriptive cohort of patients receiving allogeneic HCT for MF/SS. While we reviewed the data from 2000 until 2009 the majority of patients were transplanted in the latter five years. This may be due to increased availability of NST/RIC regimens, recognition of the safety of HCT in this population, and the more integrated multidisciplinary care these patients are receiving. Also surprisingly, our cohort demonstrated only 39% of the patients having stage IV MF/SS. Presumably this cohort represents a minority of the patients with MF/SS, who may have had very aggressive disease.

Molina et al. in an early report described eight patients undergoing HCT with both MAC and NST/RIC. All patients achieved complete clinical remission and resolution of molecular and cytogenetic markers of disease within 30 to 60 days after HCT. Two patients died from transplantation-related complications. A comparison of NST/RIC vs. MAC was not done due to small patient numbers.⁶ The European Group for Blood and Marrow Transplantation (EBMT) reviewed 60 recipients of HCT for MF and SS.⁷ This study confirmed the feasibility of HCT with NST/RIC or T cell depletion in MF/SS with a 10% NRM at 2 years. Our data demonstrates a NRM of 22% at 3 years which was previously thought. Duarte et al also reported the adverse impact of patient outcomes based on advanced disease phase at transplant. Although follow up is longer in our series, we did not have enough patients with limited disease to compare with late stage disease patients for survival differences. We did not find statistically significant differences in survival based on duration from diagnosis to transplant (Figure 1D). Our data also found that conditioning intensity did not have an impact on NRM, or OS. However, a prior EBMT study did show survival advantage for NST/RIC.⁷

In addition, our data did not find any difference in PFS with conditioning regimens. In our study the relapse was noted in 50% of patients at 1 year and 61% at 5 years. This may indicate relapses are most common in the first year post transplant and much less of a chance of progression after 1 year. Others have described evidence for a graft-versus-

lymphoma (GVL) effect in CTCL patients.¹⁰ Paralkar et al. reported evidence of GVL in two CTCL patients after complete remission was achieved after post allogeneic HCT relapse with either withdrawal of immunosuppression or donor lymphocyte infusion (DLI).^{11,12} In our series, 4 of 55 patients received DLI, however no additional data on GVL effect was available. Further prospective study will be needed to address treatment of post transplant relapse.

One of the limitations to this analysis is the capturing of staging in this population. In 2007, the International Society for Cutaneous Lymphomas (ISCL)¹³ published their consensus recommendations for the staging of MF and SS and later validated independently.² Our data did not capture all of the components of the ISCL/EORTC staging for each patient in order to be able to assign this staging approach to our patient population. Our data set relies on the diagnosis and staging at individual sites. Their data was not captured for the updated staging criteria and therefore is not consistent with this manuscript.

Duvic et al. described a prospective series of 19 patients with advanced CTCL (median age, 50 years; four prior therapies) who underwent total skin electron beam (TSEB) radiation followed by HCT with fludarabine and melphalan based conditioning. Of these patients 18 engrafted with fifteen achieving full donor chimerism. At a medium follow-up of 1.7 years, 13 of the 19 patients were still alive. Causes of death included bacterial sepsis, chronic GVHD, fungal infection and secondary malignancy. While 8 patients had relapse in their skin alone, two patients died of progressive disease. Two-year OS and PFS were 79% and 53% respectively¹⁴. Progressive disease was the primary cause of treatment failure in this cohort of patients with advanced phase disease. In the recent retrospective French cohort of 37 cases of advanced and transformed MF treated with allogeneic transplantation¹⁵, six of the 19 patients with post-transplant relapse achieved a CR with salvage therapy. While our data has a median follow up for NST/RIC patients of 39 months (3–122) and PFS at 3 years of 24%, we do not have sufficient data to be able to confirm this observation.

Duvic et al. postulate the use of TSEB may have improved allogeneic HCT outcomes by reducing antigen presenting cells in the skin. Only one of our patients, by report, had TSEB therapy prior to transplant. It is of interest whether TSEB conditioning is superior in inducing a remission prior to HCT or if there will be a prolongation of the disease-free interval with longer follow-up from Duvic's study. Newer approaches to MF/SS such as TSEB, new anti-neoplastic and immunosuppressive agents may improve these patients' outcomes.

In conclusion, this large series of allogeneic HCT in MF/SS confirms feasibility, acceptable NRM (19–28%) and evidence of benefit in an advanced cohort of MF/SS patients. Allogeneic HCT in MF/SS appears to be superior to autologous transplantation based on previous reports but relapse remains the major cause of mortality^{3–5}. Prospective studies will be necessary to determine the role of new modalities of therapy as well as the optimal timing of allogeneic HCT.

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Figure 1A: Probability of Overall Survival

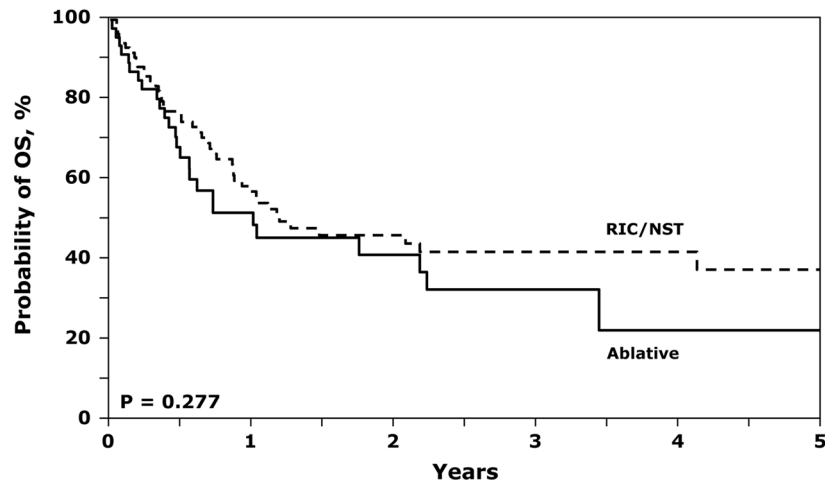


Figure 1B: Probability of Progression-free Survival

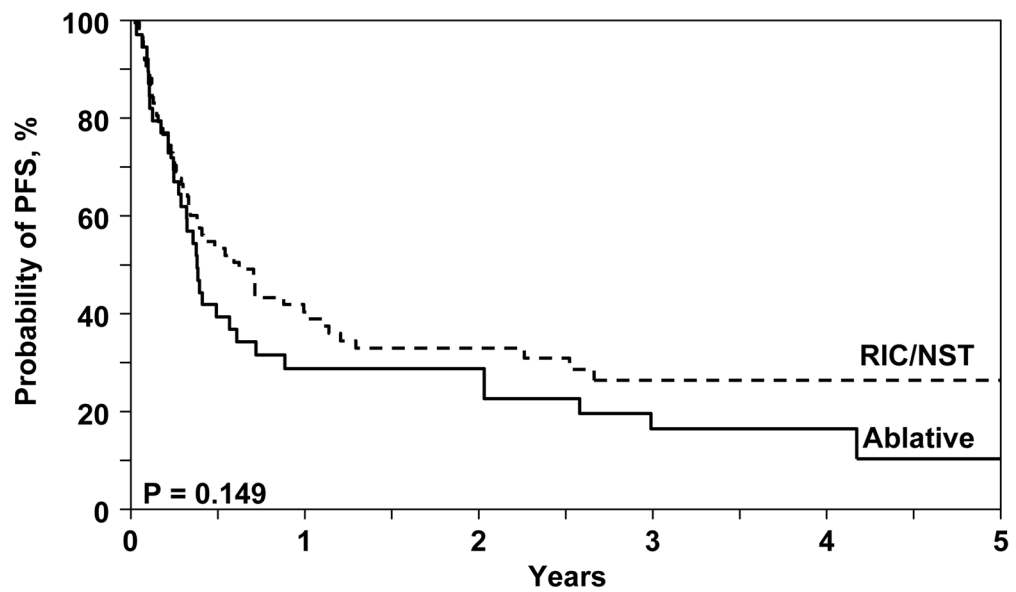


Figure 1C: Cumulative Incidence of Non-Relapse Mortality

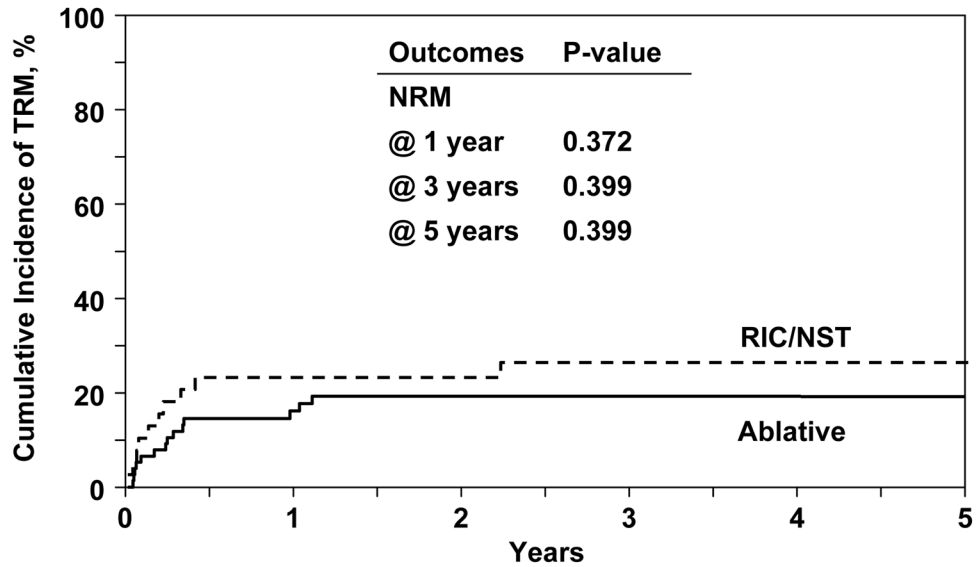


Figure 1D: Probability of Progression-free Survival

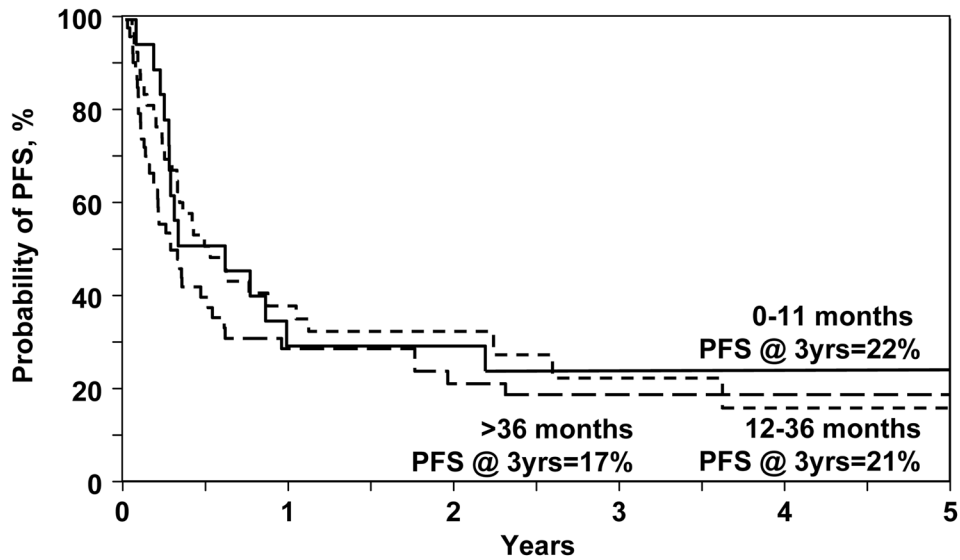


Figure 1E: Probability of Overall Survival

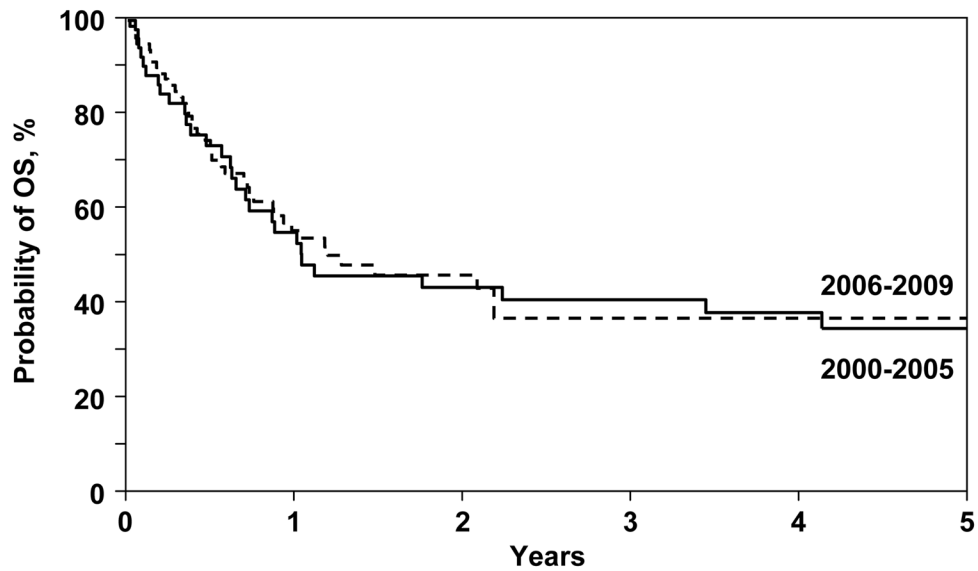


Figure 1.

- (A) Probability of OS difference between NST/RIC and MAC patients in the registered patients.
- (B) Probability of PFS difference between the NST/RIC and MAC in the registered patients
- (C) Cumulative incidence of NRM between NST/RIC and MAC in the registered patients.
- (D) Probability of PFS divided by time between diagnosis and transplant.
- (E) Probability of OS difference between year of transplant in the registered patients.

Table 1

Characteristics of patients who underwent allogeneic transplantation for mycosis fungoides and Sezary syndrome, *registered* to the CIBMTR, between 2000 and 2009.

Patient characteristics^a	<u>NST/RIC</u> N%	<u>Myeloablative</u> N%
<u>Patient-related</u>		
Number of patients	83	46
Number of centers	37	31
Age at transplant, median (range) years	51 (27–72)	44 (22–63)
21–30	1 (1)	3 (7)
31–40	12 (14)	11 (24)
41–50	24 (29)	21 (46)
51–60	35 (42)	8 (17)
> 60	11 (13)	3 (7)
Male sex	52 (63)	18 (39)
Karnofsky score		
< 90	32 (39)	28 (61)
90	35 (42)	11 (24)
Missing	16 (19)	7 (15)
Self Reported Racial group		
White	73 (88)	30 (65)
Black	7 (8)	15 (33)
Asian	3 (4)	1 (2)
<u>Disease-related</u>		
Disease status at transplant		
Never in CR (PIF)	31 (37)	13 (28)
First complete remission	1 (1)	2 (4)
Second complete remission	2 (2)	3 (7)
First relapse	10 (12)	0
Second relapse	12 (14)	6 (13)
Missing	27 (33)	22 (48)
Interval from diagnosis to transplant, median (range), months	36 (4–206)	20 (4–174)
<12	9 (11)	12 (26)
12–36	33 (40)	17 (37)
> 36	41 (49)	17 (37)
<u>Transplant-related</u>		
Graft type		
Bone marrow	11 (13)	7 (15)
Peripheral blood	71 (86)	36 (78)
Cord blood	1 (1)	3 (7)
Year of transplant		
2000–2002	5 (6)	8 (17)
2003–2005	25 (30)	13 (28)

Patient characteristics^a	<u>NST/RIC</u> N%	<u>Myeloablative</u> N%
2006–2008	40 (48)	14 (30)
2009	13 (16)	11 (24)
Donor type		
HLA-matched related	45 (54)	19 (41)
Unrelated donor	34 (41)	22 (48)
HLA-mismatched related	4 (5)	5 (11)
Conditioning regimen at transplant		
Fludarabine + Melphalan	36 (43)	14 (30)
Busulfan + Cyclophosphamide	0	4 (9)
Cyclophosphamide + TBI	3 (4)	16 (35)
Fludarabine + Busulfan ± Other	30 (36)	7 (15)
TBI only	9 (11)	5 (11)
BEAM	2 (2)	0
TLI + ATG	3 (4)	0
GVHD prophylaxis		
In vivo T-cell depletion	1 (1)	0
CSA + Alemtuzumab	0	1 (2)
CSA ±MTX ± Other	21 (25)	8 (17)
FK506/CSA + MMF ± Other	22 (27)	8 (17)
FK506 ± MTX ± Other	35 (42)	25 (55)
Alemtuzumab alone	3 (4)	0
<i>Missing</i>	1 (1)	4 (9)
Median follow-up of survivors, median (range), months	39 (3–91)	32 (3–97)

Abbreviations: EVAL = evaluable; CMV= cytomegalovirus; NST = non-myeloablative; RIC = reduced intensity conditioning; Cy = cyclophosphamide; TBI = total body irradiation; GVHD = graft versus host disease; CSA = cyclosporine; MMF= mycophenolate; MTX = methotrexate; FK506 = tacrolimus; HLA= human leukocyte antigen.

Table 2

Characteristics of patients who underwent allogeneic bone marrow or peripheral blood transplantation for mycosis fungoides and Sezary syndrome, *reported* to the CIBMTR, between 2001 and 2009.

Patient characteristics	N eval	N (%)
<u>Patient-related</u>		
Number of patients		52
Number of centers		31
Age at transplant, median (range) years	52	49 (27–72)
21–30		1 (2)
31–40		10 (19)
41–50		21 (40)
51–60		15 (29)
> 60		5 (10)
Male sex	52	30 (58)
Karnofsky score at transplant < 90	45	19 (37)
Race	52	
White		42 (81)
Black		8 (15)
Asian		1 (2)
Missing		1 (2)
<u>Disease-related</u>		
Disease status at transplant	52	
Primary induction failure (Never in CR)		33 (63)
First complete remission		2 (4)
First relapse		7 (13)
Second relapse		10 (19)
Interval from diagnosis to transplant, median (range), months	52	38 (6 – 129)
<12		7 (13)
12–36		18 (35)
> 36		27 (52)
Disease stage at diagnosis	49	
I		10 (20)
II		9 (17)
III		9 (20)
IV		19 (39)
Other ^b		2 (4)
LDH > upper limit at diagnosis ^c	8	5 (71)
Extranodal or splenic involvement at diagnosis?	49	
Yes		36 (74)
No		13 (26)
Extranodal or splenic involvement sites prior to conditioning	52	
Yes		34 (65)

Patient characteristics	N eval	N (%)
No		11 (21)
<i>Missing</i>		7 (13)
Alemtuzumab used	52	7 (13)
<u>Transplant-related</u>		
Year of transplant	52	
2001		3 (6)
2002		3 (6)
2003		7 (13)
2004		3 (6)
2005		7 (13)
2006		11 (21)
2007		6 (12)
2008		6 (12)
2009		6 (12)
Graft type	52	
Bone marrow		8 (15)
Peripheral blood		43 (83)
Cord blood		1 (2)
Prior radiation therapy received?	52	10 (19)
Site for prior radiation received	5	
Local ^d		4 (80)
Total skin		1 (20)
Number of lines of prior chemotherapy	52	
0		3 (5)
1		5 (10)
2		7 (14)
3		12 (23)
4		13 (25)
5		12(23)
Donor type	52	
HLA identical sibling		20 (38)
Well matched unrelated		15 (29)
Partially matched unrelated		10 (19)
Mismatched unrelated		5 (10)
HLA –matched other relative		1 (2)
HLA-mismatched other relative		1 (2)
Subsequent DLI?	52	2 (4)
Conditioning regimen type	52	
Myeloablative		9 (17)
NST/RIC		43 (83)
Conditioning regimen	52	
Fludarabine + Melphalan		19 (36)

Patient characteristics	N eval	N (%)
Bu + Cyclophosphamide		1 (2)
Cyclophosphamide + TBI ± Other		5 (10)
Busulfan + Fludarabine ± Other		18 (35)
TBI ± Other		7 (13)
BEAM		2 (4)
GVHD prophylaxis	52	
In vivo T-cell depletion		1 (2)
CSA ± MTX ± Other		10 (19)
FK506/CSA + MMF ± Other		13 (25)
FK506 ± MTX ± Other		23 (44)
ATG + Sirolimus		1 (2)
Missing		4 (8)
Median follow up of survivors, range, months	22	40 (3–91)

Abbreviations: EVAL = evaluable; CMV= cytomegalovirus; NST = non-myeloablative; RIC = reduced intensity conditioning; Bu = busulfan; LPAM = melphalan; Cy = cyclophosphamide; TBI = total body irradiation; GVHD = graft versus host disease; CSA = cyclosporine; MMF= mycophenolate; MTX = methotrexate; FK506 = tacrolimus; HLA= human leukocyte antigen; NMDP=national marrow donor program; DCI=donor cell infusion (DLI).

^b Other disease stage at diagnosis (n=2) includes: IA: T1 Nomo (n=1); Skin (n=1)

^c 45 patients have missing LDH values

^d Local site for prior radiation received include: Back, pelvis, arms (n=1), right upper ankle (n=1); scalp (n=1), local (n=1)

Table 3

Univariate outcomes of patients who underwent allogeneic bone marrow or peripheral blood transplantation for mycosis fungoides and Sezary syndrome, *registered* with the CIBMTR, between 2000 – 2009^a.

Outcome of interest	N(eval)	Probability (95 % CI)
Total number of patients	129	
Mortality		
@ 30 days	129	6 (3–11)
@ 100 days		16 (10–23)
Neutrophil engraftment	110	
@ 28 days		95 (88–98)
@ 100 days		95 (89–98)
Platelet engraftment (20,000 × 10 ⁹ /L)	53	
@ 28 days		70 (55–81)
@ 100 days		89 (76–95)
Acute GVHD	95	
Grade II–IV @ 100 days		41 (32–51)
Chronic GVHD	87	
@ 180 days		33 (23–43)
@ 1 year		42 (31–52)
@ 2 years		43 (33–54)
Non relapsed mortality	119	
@ 1 year		19 (12–27)
@ 3 year		22 (15–31)
@ 5 year		22 (15–31)
Progression relapse	119	
@ 1 year		50 (41–60)
@ 3 year		58 (48–68)
@ 5 year		61 (50–71)
Progression free survival	119	
@ 1 year		31 (22–40)
@ 3 year		19 (12–28)
@ 5 year		17 (9–26)
Overall survival	129	
@ 1 year		54 (45–63)
@ 3 year		38 (28–48)
@ 5 year		32 (22–44)

Abbreviations: GVHD= graft vs. host disease

Probabilities of overall survival, mortality and progression free survival were calculated using the Kaplan-Meier product limit estimate.

Probability of neutrophil & platelet engraftment, treatment related mortality, progression relapse, AGVHD and CGVHD were calculated using the cumulative incidence function.

Table 4

Comparison of univariate outcomes between ablative and NST/RIC conditioning among patients who underwent allogeneic bone marrow or peripheral blood transplantation for mycosis fungoides and Sezary syndrome, reported to the CIBMTR, between 2000–2009^a.

Outcomes	N	RIC/NST	N	Myeloablative	P-value ^b
Mortality	82		45		0.271
@ 30 days		5 (1–11)		9 (2–19)	0.394
@ 100 days		15 (8–23)		18 (8–31)	0.612
Neutrophil engraftment	68		42		
@ 28 days		96 (86–99)		93 (79–98)	0.567
@ 100 days		97 (89–99)		93 (79–98)	0.353
Platelet engraftment	32		21		
@ 28 days		75 (54–87)		62 (38–79)	0.335
@ 100 days		88 (69–95)		90 (66–98)	0.739
Acute GVHD (II–IV)	63		32		
Grade II–IV @ 100 days		46 (34–58)		32 (17–49)	0.163
Chronic GVHD	56		31		
@ 180 days		31 (20–44)		37 (21–55)	0.576
@ 1 year		39 (26–52)		48 (30–66)	0.416
@ 2 years		39 (26–52)		52 (34–69)	0.254
NRM	77		42		
@ 1 year		16 (9–26)		24 (12–38)	0.372
@ 3 years		20 (11–30)		27 (14–42)	0.399
@ 5 years		20 (11–30)		27 (14–42)	0.399
Progression relapse	77		42		
@ 1 year		50 (39–62)		50 (35–66)	0.982
@ 3 years		57 (45–69)		60 (44–75)	0.764
@ 5 years		57 (45–69)		67 (49–82)	0.367
Progression free survival	77		42		
@ 1 year		33 (23–45)		26 (13–41)	0.412
@ 3 years		23 (13–35)		13 (4–26)	0.194
@ 5 years		23 (13–35)		6 (0–21)	0.029

Outcomes	N	RIC/NST	N	Myeloablative	P-value ^a
Overall survival	83		46		
@ 1 year		56 (45–67)		51 (35–66)	0.587
@ 3 years		41 (29–53)		31 (16–49)	0.358
@ 5 years		36 (23–50)		21 (5–43)	0.208

^aProbability of treatment related mortality, progression relapse, were calculated using the cumulative incidence function.

^bPointwise p-value

Table 5

Reported primary causes of death.

Causes of Death	NST/RIC N (%)	Myeloablative N (%)
Number of deaths	32	37
Primary disease	14 (44)	21 (57)
New malignancy	0	1 (3)
GVHD	3 (9)	3 (8)
Interstitial Pneumonitis	2 (6)	0
Hemorrhage	0	1 (3)
Infection	4 (13)	4 (11)
Organ failure	1 (3)	2 (4)
Other cause-not specified	8 (25)	5 (14)

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