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Unrelated Donor Reduced-Intensity Allogeneic Hematopoietic Stem Cell Transplantation for Relapsed and Refractory Hodgkin Lymphoma

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Myeloablative allogeneic hematopoietic cell transplantation (HCT) may cure patients with relapsed or refractory Hodgkin lymphoma (HL), but is associated with a high treatment-related mortality (TRM). Reduced-intensity and nonmyeloablative (RIC/NST) conditioning regimens aim to lower TRM. We analyzed the outcomes of 143 patients undergoing unrelated donor RIC/NST HCT for relapsed and refractory HL between 1999 and 2004 reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). Patients were heavily pretreated, including autologous HCT in 89%. With a median follow-up of 25 months, the probability of TRM at day 100 and 2 years was 15% (95% confidence interval [CI] 10%-21%) and 33% (95% CI 25%-41%), respectively. The probabilities of progression free survival (PFS) and overall survival (OS) were 30% and 56% at 1 year and 20% and 37% at 2 years. The presence of extranodal disease and the Karnofsky Performance Scale (KPS) <90 were significant risk factors for TRM, PFS, and OS, whereas chemosensitivity at transplantation was not. Dose intensity of the conditioning regimen (RIC versus NST) did not impact outcomes. Unrelated donor HCT with RIC/NST can salvage some patients with relapsed/refractory HL, but relapse remains a common reason for treatment failure. Clinical studies should be aimed at reducing the incidence of acute graft-versus-host disease (GVHD) and relapse.

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INTRODUCTION

Although most patients with Hodgkin lymphoma (HL) can expect long-term survival with standard chemotherapy and/or radiation therapy, the prognosis is less favorable for patients with relapsed and/or refractory disease [1]. Most patients with relapsed disease are treated with high-dose chemotherapy and autologous stem cell rescue, based on the results of studies showing durable responses in 40% to 50% of patients with relapsed HL and in 25% to 40% of patients with refractory HL [2-5]. Therapeutic options for patients relapsing after high-dose chemotherapy are limited, and generally noncurative.

Myeloablative allogeneic hematopoietic cell transplantation (HCT) derives its benefit from both the pretransplant conditioning regimen and a posttransplant immune-mediated graft-versus-malignancy effect. Although earlier studies suggested the existence of a graft-versus-HL effect, the high transplant-related mortality (TRM) associated with the use of myeloablative conditioning offset any potential benefit on survival [6-9]. Reduced-intensity conditioning (RIC) regimens have been developed in an attempt to decrease the mortality caused by traditional high-dose chemotherapy and radiation conditioning regimens [10]. A variety of conditioning regimens, ranging in intensity from immune suppressive and truly

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nonmyeloablative to reduced intensity have been introduced into practice. Such regimens have allowed allogeneic HCT in persons who are traditionally not considered for myeloablative transplant regimens because of age or comorbidities [11-13]. In addition, reduced-intensity allogeneic HCT is increasingly used as a salvage strategy for patients who relapse after previous high-dose chemotherapy with autologous stem cell rescue [14].

Data on the use of RIC and nonmyeloablative stem cell transplantation (NST) for patients with relapsed and refractory HL are starting to emerge. Several small single-institution retrospective trials have reported low early TRM and encouraging progression-free survival (PFS) data, although with limited follow-up [15,16]. Data from 3 prospective trials have been reported recently [17-19]. All 3 studies reported on the outcomes of patients with relapsed and/or refractory HL (in many cases after previous high-dose chemotherapy) undergoing allogeneic HCT with a conditioning regimen of fludarabine and melphalan. These studies confirmed a low day 100 TRM (ranging from 4% to 12.5%) with a projected PFS of 32% to 39% at 2-4 years. Disease relapse/progression continued to be the major reason for treatment failure in all 3 publications. A retrospective analysis by the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation (EBMT) comparing RIC outcomes with outcomes after standard myeloablative conditioning also showed a reduction in day 100 TRM (15% with RIC versus 28% with myeloablative conditioning, $P = .003$) and a projected 3-year PFS of 19% after RIC HCT [20].

Only a minority of patients in the previously cited studies underwent transplantation with an unrelated donor graft. Recent studies support the notion that the results of unrelated donor HCT are comparable to sibling grafts, if HLA matching at the allele level is employed for unrelated donor selection [21,22]. We therefore analyzed the clinical outcomes of 143 patients undergoing unrelated donor HCT with a RIC/NST conditioning regimen for relapsed and refractory HL.

PATIENTS AND METHODS

Data Sources

The CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR), Autologous Blood and Marrow Transplant Registry (ABMTR), and the National Marrow Donor Program (NMDP), that comprises a voluntary working group of more than 450 transplant centers worldwide that contribute detailed data on consecutive allogeneic and autologous transplants to a Statistical Center at the Health Policy Institute of the Medical College of Wisconsin in Milwaukee or the NMDP Coordinating Center in Minneapolis. Participating centers are required to report all consecutive transplants; compliance is monitored by on-site audits. Subjects are followed longitudinally, with yearly follow-up. Computerized checks for errors, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are done with a waiver of informed consent and in compliance with HIPAA regulations as determined by the institutional review board and the Privacy Officer of the Medical College of Wisconsin.

The CIBMTR collects data at 2 levels: registration and research. Registration data include disease type, age, sex, pretransplant disease stage, and chemotherapy responsiveness, date of diagnosis, graft type (bone marrow- and/or blood-derived stem cells), high-dose conditioning regimen, posttransplant disease progression and survival, development of a new malignancy, and cause of death. Requests for data on progression or death for registered patients are at 6-month intervals. All CIBMTR teams contribute registration data. Research data are collected on a subset of registered patients selected using a weighted randomization scheme and include detailed disease, and pre- and posttransplant clinical information.

Definitions of RIC and Nonmyeloablative Conditioning Regimens

Conditioning regimens were categorized as reduced intensity or nonmyeloablative using consensus criteria proposed by the Regimen-Related Toxicity Working Committee of the CIBMTR. Regimens employing total-body irradiation (TBI) <500 cGy, busulfan doses ≤9 mg/kg, or melphalan doses ≤150 mg/m^2 were categorized as reduced intensity. Regimens using fludarabine without busulfan and/or melphalan and regimens using TBI doses of 200 cGy (with or without fludarabine) were categorized as nonmyeloablative. Regimens that did not fit these criteria were assigned by the authors based on recommendations of the Regimen-Related Toxicity Working Committee. This consensus definition reflects the practice of a large segment of the transplant community and has also been proposed and used by others [23,24].

Patients

There were 143 patients undergoing an unrelated donor HCT between 1999 and 2004 with RIC/NST conditioning for relapsed or refractory HL identified from the CIBMTR database. Patients undergoing a cord blood transplant (n = 4), those undergoing planned tandem (autologous followed by RIC/NST allogeneic) HCT (n = 3), and those who received

a RIC/NST allogeneic HCT for a different second malignancy were excluded from analysis. HLA compatibility of donors and recipients was documented at low resolution (antigen level) for HLA A and B antigens and at high resolution (allele level) for the HLA-DRB1 allele. Chemosensitive disease was defined as a 50% reduction in the sum of the bidimensional diameter of all disease sites with no new sites of disease.

Study Endpoints

Outcomes analyzed included TRM, progression, PFS, and overall survival (OS). TRM was defined as death within 28 days posttransplant or death without lymphoma progression. Subjects with lymphoma progression were censored at the time of progression and a cumulative incidence estimate was derived with progression or relapse as the competing risk. Progression was defined as progressive lymphoma posttransplant (≥28 days) or lymphoma recurrence. It could follow a period of "stable" disease posttransplant, or a partial (PR) or complete remission (CR). Progression represents new or larger areas of lymphoma (≥25% increase in largest diameter) compared to the best posttransplant lymphoma state. Progression was summarized by the cumulative incidence estimate with TRM as the competing risk. For PFS, subjects were considered treatment failures at the time of lymphoma progression or death from any cause. Subjects alive without evidence of lymphoma progression were censored at last follow-up and the PFS event was summarized by a survival curve. The OS interval variable was defined as time from the date of transplant to the date of death or last contact and summarized by a survival curve.

Statistical Analysis

Univariate probabilities of developing TRM and lymphoma relapse/progression were calculated using cumulative incidence curves to accommodate corresponding competing risks [25]. Probabilities of 100-day OS and PFS were calculated using a Kaplan-Meier estimator [26]. Confidence intervals (CIs) were calculated with a log-transformation.

Cox proportional hazards model was used to identify risk factors associated with outcomes. A stepwise forward selection multivariate model was built to identify covariates that influenced outcomes. Any covariate with a P-value $\leq .05$ was considered significant. The proportionality assumption for Cox regression was tested by adding a time-dependent covariate for each risk factor and each outcome. Tests indicated that all variables met the proportional hazards assumption. Results were expressed as relative risks (RR) or the relative rate of occurrence of the event. The following variables were considered in multivariate analyses: age at transplant, Karnofsky Performance Status (KPS) at transplant, disease status, and chemosensitivity at transplant, extranodal involvement prior to transplant, serum lactate dehydrogenase (LDH) concentration at transplant, time from autologous HCT to allogeneic HCT, donor type (HLA matched versus HLA mismatched), donor-recipient gender match (female donor into male recipient versus all other combinations) and donor-recipient cytomegalovirus (CMV) status (both donor and recipient CMV seronegative versus all other combinations) (Table 1). Analyses were performed using SAS software, version 8.2 (SAS Institute, Cary, NC).

RESULTS

Patient, Disease-, and Transplant-Related Variables

Patient, disease, and transplant characteristics are described in Table 2. Ninety-four patients (66%) received RIC regimens, whereas 49 (34%) patients received nonmyeloablative conditioning regimen (Table 3). As expected, this was a group of heavily pretreated patients. Ninety-six percent of patients had been treated with at least 3 previous chemotherapy regimens, and the majority of patients (89%) had received a prior autologous HCT. In addition, 47% had disease characterized as chemoresistant at the time of allogeneic HCT, 50% had extranodal involvement prior to transplant, and 32% had a Karnofsky performance status <90 preallogeneic transplant. Twenty-three percent received a graft from an HLA mismatched unrelated donor; however, we do not have the results of high-resolution HLA typing for class I HLA antigens, and thus the number of patients receiving an allele mismatched product might be substantially higher. Most patients (73%) received a peripheral blood stem cell graft and were transplanted after

Table 1. Variables Tested in Cox Proportional Hazards Regression Models

Patient-related variables:
Age at transplant: 13-20 versus 21-30 versus 31-40 versus 41-50 versus 51-60 years
Karnofsky performance status at transplant: ≥90% versus <90%
Disease related:
Disease status and chemosensitivity at transplant: PIF-sensitive versus PIF resistant versus REL sensistive versus REL resistant versus REL untreated/unknown
Extranodal involvement prior to transplant: yes vs no
LDH concentration at transplant: normal versus abnormal versus unknown
Treatment related:
Time from autologous to allogeneic transplant: <12 versus 12-24 versus ≥24 months
Donor type: HLA-matched unrelated versus HLA-mismatched unrelated
Donor-recipient gender match: F-M versus others
Donor/recipient CMV status: −/− versus others

Table 2. Patient-, Disease-, and Transplant Characteristics

Variable	N Eval	N (%)
Number of patients		143
Age, median (range), years	143	30 (13-53)
Male sex	143	82 (57)
Karnofsky score pretransplant	119	
<90		38 (32)
≥90		81 (68)
Histology	143	
Nodular sclerosis		126 (88)
Mixed cellularity		8 (6)
Other[b]		9 (6)
Prior radiation therapy	143	
Yes		38 (27)
No		105 (73)
Number of prior chemotherapy regimens	143	
<3		5 (3)
≥3		137 (96)
Unknown		1 (1)
Chemosensitivity of disease at transplant	141	
Sensitive		62 (44)
Resistant		67 (47)
Untreated		8 (6)
Not evaluable /Unknown		4 (3)
Extranodal involvement prior to transplant	141	
Yes		70 (50)
No		71 (50)
LDH concentration at transplant	143	
Normal		97 (68)
Abnormal		39 (27)
Unknown		7 (5)
Prior autologous HCT	143	
Yes		127 (89)
No		16 (11)
Time from autologous to allogeneic transplant, median (range), months	127	19 (2-156)
Donor/recipient CMV status	142	
−/−		54 (38)
Others		88 (62)
Donor leukocyte infusion	143	
Yes		21 (15)
No		122 (85)
Bone marrow involvement at diagnosis	143	
Yes		9 (6)
No		134 (94)
Donor type	143	
HLA-matched unrelated		110 (77)
HLA-mismatched unrelated		33 (23)
Donor-recipient gender match	143	
F-M		30 (21)
Others		113 (79)
Source of stem cells	143	
Bone marrow		39 (27)
Peripheral blood		104 (73)
Year of transplant	143	
1999-2000		17 (12)
2001-2002		42 (29)
2003-2004	143	84 (59)
GVHD prophylaxis	143	
CsA + MTX ± other		23 (16)
CsA ± other		48 (34)
FK506 ± other		26 (18)
FK506 + MTX ± other		43 (30)
T cell depletion ± other		2 (1)
Given, not specified		1 (1)
Mycophenolate mofetil as GVHD prophylaxis	143	
Yes		55 (38)
No		88 (62)

CsA, cyclosporine; MTX, methotexate; GVHD, graft-versus-host disease; LDH, lactate dehydrogenase; HCT, hematopoietic cell transplantation; CMV, cytomegalovirus.

2000. The median follow-up for survivors was 25 months.

TRM, Progression/Relapse, and Survival

Cumulative incidences for TRM, progression/relapse, acute and chronic graft-versus-host disease (aGVHD, cGVHD) and Kaplan Meier curves for PFS and OS are shown in Figure 1. Cumulative incidence of TRM following unrelated donor RIC/NST for relapsed or refractory HD was 15% at 100 days (95% CI 10%-21%), 30% (95% CI 22%-37%) at 1 year and 33% (95% CI 25%-41%) at 2 years (Figure 1a). In multivariate analysis lower KPS at transplantation (relative risk [RR] 3.05 for KPS <90, $P < .001$) and the presence of extranodal disease at transplantation (RR 2.36, $P = .007$) were associated with an increased risk of TRM (Table 4).

The cumulative incidence of progression/relapse in the RIC/NST group was 40% at 1 year (95% CI 32%-49%) and 47% at 2 years (95% CI 39%-56%) (Figure 1a). No variables were associated with a higher risk of relapse/progression (Table 4). The probability of PFS at 1 year was 30% (95% CI 23%-38%) and at 2 years 20% (95% CI 13%-27%). In multivariate analysis factors with a significant effect on PFS were a lower KPS (RR 2.19 for KPS <90, $P < .001$) and extranodal involvement at transplantation (RR 1.73, $P = .006$) (Table 4).

The probability of survival after RIC/NST was 56% (95% CI 48%-64%) at 1 year and 37% (95% CI 29%-46%) at 2 years (Figure 1b). In multivariate analysis factors significantly affecting survival were a lower KPS (RR 2.33 for KPS <90, $P< .001$), presence of extranodal disease at diagnosis (RR 2.11, $P = .001$), and abnormal serum LDH concentration (RR 1.86, $P = .008$) (Table 4).

RIC versus NST

To separate the effects of differing intensity of conditioning regimens, we analyzed the effects of RIC and nonmyeloablative conditioning separately in a multivariate analysis. There were no significant differences between RIC and NST on the primary outcomes for TRM, progression/relapse, PFS, and OS. The 2 groups were combined for the final analysis to increase the overall power of the study.

Acute GVHD and cGVHD and Effect of Chemosensitivity

RIC/NST conditioning regimens were associated with a high incidence of aGVHD and cGVHD. The probability of grade 2-4 aGVHD by day 100 was 60% (95% CI 51%-69%) (Figure 1c), and the probability of cGVHD was 66% at 1 year (95% CI 58%-74%) and 68% at 2 years (95% CI 60%-76%) (Figure 1d).

Table 3. Conditioning Regimens Used for RIC/NST

Regimen	N (%)
TBI dose <500 cGy single dose or <800 cCy fractionated	8 (6)
Melphalan dose ≤150 mg/m^2	50 (34)
Busulfan dose ≤9 mg/kg	36 (25)
TBI dose = 200 cGy	25 (17)
Fludarabine + cyclophosphamide	23 (16)
Fludarabine + Thiotepa + ATG	1 (1)

ATG indicates antithymocyte globulin; RIC, reduced-intensity conditioning; NST, nonmyeloablative.

In our multivariate analysis sensitivity to chemotherapy immediately prior to transplant was not identified as a characteristic with a significant effect on PFS or OS. Because prior studies have identified chemosensitivity as an important predictor for survival we performed an additional analysis for the effect of chemosensitivity on PFS and OS. The Kaplan-Meier curves for PFS and OS for chemosensitive and chemoresistant patients are shown in Figure 2.

Causes of Death

Causes of death are listed in Table 5. Relapse/progression was the main cause of death after RIC/NST transplantation. Infection was the second most common cause of death, whereas organ failure and interstitial pneumonitis were rare after RIC/NST.

DISCUSSION

Treatment options for patients with relapsed or refractory HL, in particular, patients who relapse after previous high-dose chemotherapy treatment, remain limited. The use of allogeneic HCT with a RIC/NST conditioning regimen has theoretic appeal for those patients, but reported outcome data are sparse and mostly limited to patients receiving matched sibling grafts. Our study represents the largest group of unrelated donor HCT recipients with RIC/NST for relapsed/refractory HL analyzed to date, and almost all patients in our analysis underwent RIC/NST HCT as a salvage strategy after previously failed high-dose chemotherapy with autologous stem cell rescue. This study confirms the feasibility of RIC/NST unrelated donor allogeneic HCT and shows that approximately 20% of patients with multiply relapsed or refractory HL may experience prolonged PFS with a projected 2-year OS of 37%. Not unexpectedly, relapse/progression remains a significant problem in this group of heavily pretreated patients.

Our survival results are comparable with previously published data. The recently published EBMT experience reports a 3-year PFS of 19% (95% CI 11%-28%), with a 3-year OS of 35% (95% CI 24%-45%) [20]. Slightly better survival results have been reported in the 3 prospective studies. Peggs et al. [17] reported a 4-year actuarial PFS of 22.6% and

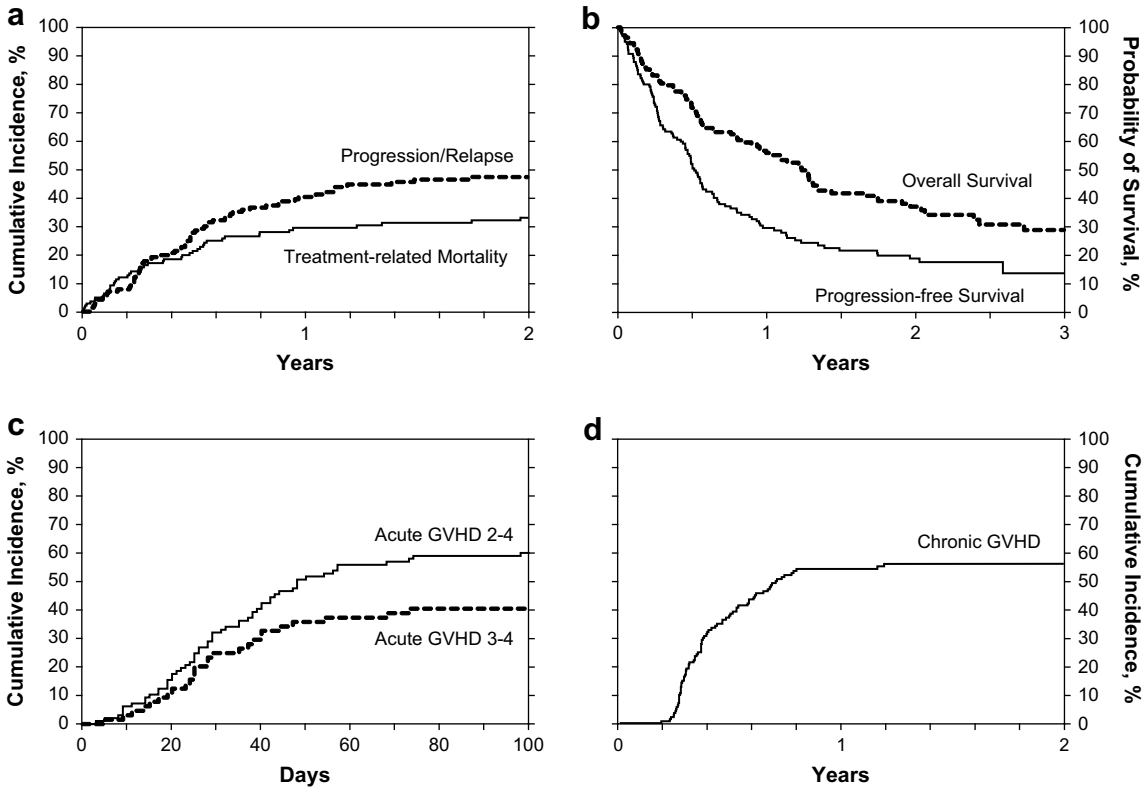

Figure 1. TRM, relapse/progression (a), PFS, and OS (b), aGVHD (c), and cGVHD (d) after unrelated donor RIC/NST HCT for relapsed/refractory HL.

Table 4. Multivariate Analyses Comparing TRM, Progression/Relapse, PFS, and OS for Unrelated Donor NST/RIC HCT for Relapsed/Refractory HD

Variables	N	Relative Risk (95% CI)	*P*-Value
TRM:			
Karnofsky score pretransplant			
≥90%	79	1.00	
<90%	37	3.05 (1.58-5.87)	<.001
Extranodal involvement			
No	71	1.00	
Yes	68	2.36 (1.26-4.41)	.007
Progression/relapse:		N/A	
No significant variables			
PFS:			
Karnofsky score pretransplant			
≥90%	79	1.00	
<90%	37	2.19 (1.42-3.39)	<.001
Extranodal involvement			
No	71	1.00	
Yes	68	1.73 (1.17-2.55)	.006
OS:			
Karnofsky score pretransplant			
≥90%	74	1.00	
<90%	36	2.33 (1.45-3.75)	<.001
Extranodal involvement			
No	65	1.00	
Yes	69	2.11 (1.34-3.31)	.001
LDH concentration			
Normal	96	1.00	
Abnormal	38	1.86 (1.18-2.93)	.008

CI indicates confidence interval; NA, not applicable; LDH, lactate dehydrogenase; PFS, progression-free survival; OS, overall survival; TRM, treatment-related mortality..

OS of 45% for recipients of an unrelated donor graft in their prospective study. PFS at 2 years was 32% ± 10% in the Spanish prospective trial, but only 2 of 40 patients in this study received an unrelated donor graft [18]. In the M.D. Anderson study, 2-year PFS was 32% (95% CI 20%-45%), and no difference was noted between recipients of related (n = 25) and unrelated (n = 33) donor grafts [19]. The apparent survival difference between the prospective trials and the registry data is not unexpected, and probably explained by the carefully controlled eligibility criteria and therapeutic conditions that apply to prospective trials.

RIC regimens are designed to limit TRM, and several studies have reported low TRM after reduced intensity HCT. The day-100 TRM of 15% (95% CI 10%-21%) and TRM of 30% (95% CI 22%-37%) at 1 year and 33% (95% CI 25%-41%) at 2 years therefore seem somewhat disappointing. In the EBMT study cumulative TRM was 15% at 3 months (95% CI 9%-24%), 23% at 1 year (95% CI 15%-34%), and 24% at 3 years (95% CI 16%-35%) [20]. This study, however, included predominantly matched sibling donors (86.5%), and fewer patients had failed a previous autologous HCT (61.8%). Much lower cumulative incidences of TRM were reported in the UK study (4.1% at 100 days and 16.3% at 2 years) and the Spanish study (12.5% at 100 days and 25% at 3 years) [17,18]. However, in the UK study TRM at 2 years was significantly higher with an unrelated donor HCT than when a matched sibling donor was used (34.1% [16.5-70.3] versus 7.2% [1.9-27.5], $P = .02$). The most favorable TRM data come from the M.D. Anderson patient cohort, where day 100 TRM was 7% (95% CI 2%-12%) and 2-year TRM was 15% (95% CI 8%-28%), with no significant difference noted between related and unrelated graft recipients [19]. A comparison of TRM between studies is difficult without adjustment for some of the known risk factors for TRM after allogeneic HCT; of note is that the patients in our study represented a poor-risk group, including KPS <90 for one-third of all RIC/NST recipients.

A high incidence of aGVHD was noted in our study, with a 60% probability of grade 2-4 aGVHD at 100 days (95% CI 51%-69%). For comparison, the incidence of grade 2-4 aGVHD in the M.D. Anderson unrelated donor cohort was 39% (95% CI 26%-60%) [19]. The UK study does not allow for a meaningful comparison of aGVHD incidence, as in vivo T cell depletion with alemtuzumab was an integral part of the conditioning regimen on that protocol. Any discussion of the differences in TRM and aGVHD incidence between our study and some of the referenced trials remains necessarily speculative. The extent of HLA matching at the allele level was not available for most of the patients in our database, precluding an analysis of the effect of allele matching on outcomes, in particular, incidence of GVHD. The presence of a significant number of HLA mismatched donor-recipient pairs (23%), even at this low level of HLA matching, could explain the relatively high incidence of aGVHD in this study.

The primary causes of death of nonrelapse mortality (NRM) in our study were infectious in 22% and GVHD in 9% of all deaths. One could hypothesize that the high incidence of aGVHD in this study can at least partially explain the significant TRM, as infectious complications and occurrence of GVHD are often related. This would suggest that attempts to reduce the incidence of aGVHD could result in more favorable TRM. In support of this hypothesis are the findings by Peggs et al. [27] that the use of alemtuzumab in the conditioning regimen resulted in lower incidences of NRM and aGVHD and cGVHD without affecting the incidence of relapse/progression after matched sibling RIC HCT.

We were not able to show a significant effect of the intensity of the conditioning regimen (nonmyeloablative versus reduced intensity) on TRM or survival. Our study had only very limited power to detect differences between these 2 transplant approaches, and great care should therefore be used in interpreting these results. Anderlini et al. [16] have suggested a benefit of RIC with fludarabine and melphalan over nonmyeloablative conditioning with fludarabine and cyclophosphamide. Because the current study included a wide

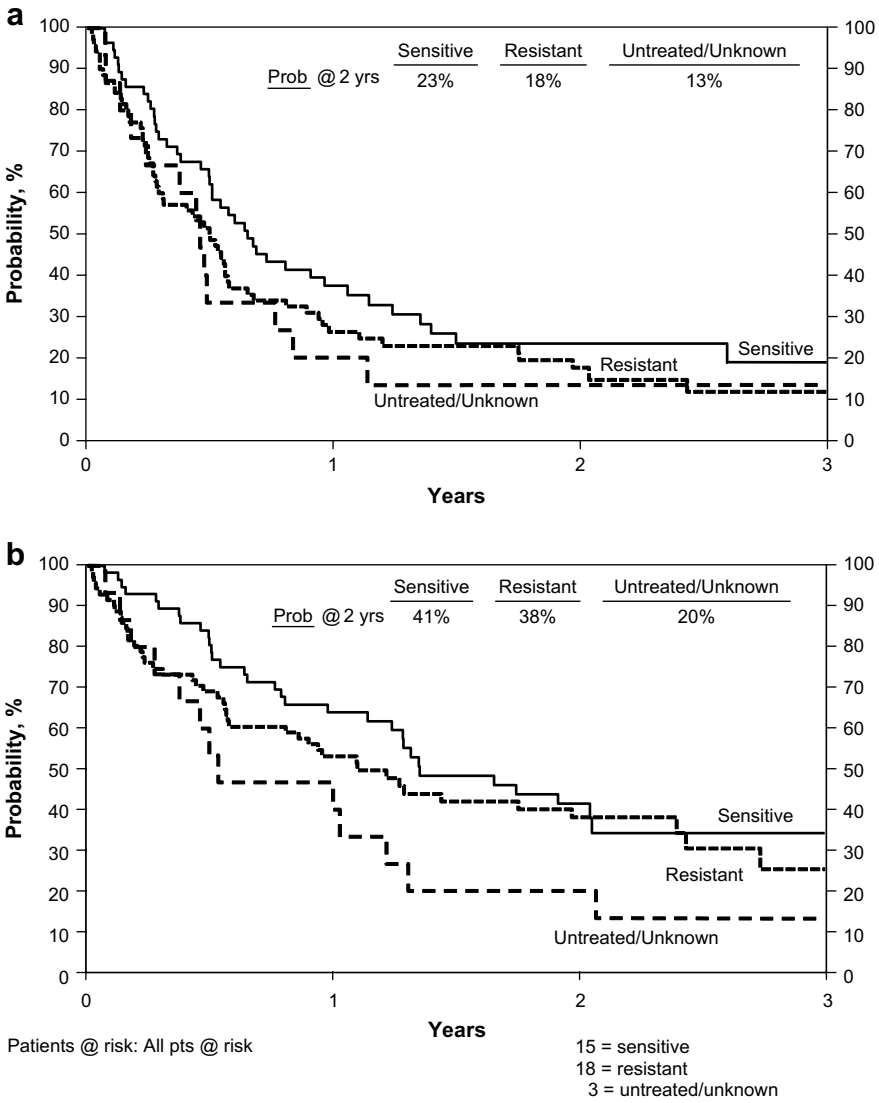

Figure 2. Effect of chemosensitivity at the time of transplantation on PFS (a) and OS (b) after unrelated donor RIC/NST HCT for relapsed/refractory HL.

variety of nonmyeloablative and RIC regimens, it is not very suitable for a direct comparison between the various regimens. In addition, retrospective studies cannot control for potential bias resulting in the selection of 1 conditioning regimen over another for any particular patient.

Our study did not show an effect of pretransplant chemosensitivity on survival in the multivariate analysis. The reasons for this discrepancy between our findings and previously reported effects of chemosensitivity remain speculative. Selection bias might have played a role; the reason for administration of a RIC/NST conditioning is not collected by the CIBMTR, and patients with highly refractory disease might therefore preferentially have been treated with more intense conditioning regimens or might have been denied RIC/NST procedures altogether. The relatively recent introduction of PET scanning might have resulted in more accurate but altered definitions of remission status at the time of transplantation and precludes comparison between studies. Finally, prognostic differences between the patients in our study and in other studies may explain the lack of effect attributable to chemosensitivity.

In summary, our study shows that some patients with highly refractory/relapsed HL can be salvaged with the use of unrelated donor RIC/NST HCT. The results of our and other recently published analyses establish the feasibility of this procedure for patients with relapsed or refractory HL. However, both in our and in other studies relapse/progression continues to be the most common cause of treatment failure, and long-term prognosis continues to be largely determined by patient-related (KPS) and disease-related (extranodal disease) factors rather than by the choice of conditioning approach. These data

Table 5. Causes of Death of Unrelated Donor NST/RIC HCT for Relapsed/Refractory HD

Causes of Death	N Eval	N (%)
Number of patients	88	
Primary disease		39 (44)
GVHD		8 (9)
IpN		5 (6)
Infection		19 (22)
Organ Failure		11 (13)
Other/Unknown*		6 (6)

GVHD indicates graft-versus-host-disease; NST/RIC, nonmyeloablative and reduced-intensity conditioning.
*Other includes: PTLD (n = 1), hemorrhage (n = 1), accidental (n = 1), neuropathy (n = 1), unknown (n = 2).

support the notion that careful patient selection remains the single most important factor to improve outcomes from RIC/NST unrelated donor HCT for this indication. In addition, approaches to further reduce the incidence of GVHD and TRM after RIC/NST HCT should result in more favorable outcomes. This should foremost include HLA matching at the allele level, and could also include the addition of alemtuzumab to the conditioning regimen, the use of umbilical cord blood grafts, or the use of a tandem approach (high-dose chemotherapy with autologous stem cell rescue followed by an allogeneic HCT with nonmyeloablative conditioning) in high-risk patients [27-29]. Development of multi-institutional clinical trials to examine these options is highly desirable.

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