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Long-Term Sustained Disease Control in Patients with Mantle Cell Lymphoma With or Without Active Disease after Treatment with Allogeneic Hematopoietic Cell Transplantation after Nonmyeloablative Conditioning

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AUTHORSHIP CONTRIBUTIONS

MLS and DGM designed the study; MLS and JV collected data for the study; TTC, RTM, MAP, PH, GGL, MM, GNF, EA, AL, AR, RS, BMS and DGM coordinated the study at their respective centers; BS contributed to study design and performed statistical analyses; JV, MLS, TTC, PH, GGL, MM, GNF, EA, AL, AR, RS, BMS and DGM contributed to interpretation of results; JV and MLS drafted the manuscript; and TTC, PH, GGL, MM, GNF, EA, AL, AR, RS, BMS, and DGM edited the manuscript.

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Abstract

Background—Previously, we reported early results of allogeneic hematopoietic cell transplantation (HCT) after nonmyeloablative conditioning using 2 Gy total body irradiation (TBI) +/− fludarabine and/or rituximab in 33 patients with mantle cell lymphoma (MCL).

Methods—we are reporting on outcomes of total of 70 patients with MCL with an extended follow-up to a median of 10 years for the initial 33 patients. Grafts were from HLA-matched related (47%), unrelated (41%), and HLA antigen mismatch donor (11%).

Results—The 5-year incidence of non-relapse mortality (NRM) was 28%. Relapse rate was 26%. The 5-year rates of overall (OS) and progression-free survival (PFS) were 55% and 46%, respectively. The 10-year rates of OS and PFS were 44% and 41%, respectively. Eighty percent of surviving patients were off of immunosuppression at last follow-up. The presence of relapsed or refractory disease at time of HCT predicted a higher rate of relapse (HR 2.94, p=0.05). Despite this, rates of OS at 5 (51% versus 58%, respectively) and 10 years (43% versus 45%, respectively) were comparable between those with relapsed/refractory disease and those entering transplant with a partial or complete remission. High-risk cytomegalovirus (CMV) status was the only independent predictor of worse OS (HR 2.32 p=0.02). High-risk CMV status and low CD3 dose predicted PFS (HR 2.22 p=0.03).

Conclusions—Nonmyeloablative allogeneic HCT provides long-term survival benefit in patients with relapsed MCL, including those with refractory disease or multiple relapses.

INTRODUCTION

Despite recent progress in conventional treatment,(1;2) allogeneic hematopoietic cell transplantation (HCT) remains the only potentially curative treatment option in patients with mantle cell lymphoma (MCL). Initially, allogeneic HCT was attempted in these patients using high-dose myeloablative regimens,(3–6) but concerns about relatively high risks for treatment related mortality (TRM) have limited its use to younger, medically fit patients. Given that the median age of diagnosis with MCL is beyond the 6th decade,(7) various groups have examined the feasibility of using reduced intensity or nonmyeloablative conditioning regimens among patients with MCL with encouraging results.(8–17) We have used a TBI-based nonmyeloablative regimen comprising 3 doses of fludarabine, 30 mg/m^2, and low dose (2 Gy) of total body irradiation (TBI) to condition patients prior to allogeneic HCT. This regimen relies on graft-versus-lymphoma (GVL) effect for disease control.(18) In 2004, we reported the outcomes of the first 33 MCL patients who were treated with this nonmyeloablative conditioning regimen followed by allogeneic HCT.(8) Rates of relapse

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and non-relapse mortality (NRM) at 2 years were 9% and 24%, while those of overall (OS) and progression-free survival (PFS) were 65% and 60%, respectively. Rate of chronic graft-versus-host disease (GVHD) at 2 years was 64%.

Some critical questions remain. The most important is whether this presumably less-toxic transplant approach provides long-term disease control in patients with and without active disease at the time of HCT. Additional issues to be addressed are the likelihood that surviving patients will experience resolution of chronic GVHD and the identification of predictive factors for long-term outcomes that will help map future improvements. To this end, we present the long-term follow-up of the initially reported 33 patients, as well as interim follow-up of an additional 37 patients who were treated using this nonmyeloablative regimen and allogeneic HCT at 9 participating centers.

METHODS

Patients

This retrospective study was approved by the institutional review boards at each institution. All patients provided consent for their clinical information to be used in research.

Between February of 2000 and August of 2012, 70 patients with biopsy-proven MCL were enrolled on 13 FHCRC protocols for nonmyeloablative HCT. Differences between protocols included the use of HLA-matched related or unrelated grafts, duration and intensity of immunosuppressive medications, the addition of fludarabine and/or rituximab to 2 Gy TBI, and tandem autologous/allogeneic HCT.

MCL patients were eligible if they were < 75 years of age and had either progressed after autologous transplant or were not eligible for autologous transplant due to age, comorbidities, or chemotherapy-refractory disease. Patients were enrolled at 9 participating institutions. The institutional review boards at all sites approved the protocols and consents.

Donor Matching, Immunosuppression, and Graft-Versus-Host Disease

Patients and their donors were evaluated for matches at the HLA-A, -B, and -C antigens by intermediate-resolution DNA typing, and -DRB1 and -DQB1 by high-resolution techniques.(19)

Post-HCT immunosuppression consisted of combinations of a calcineurin inhibitor (cyclosporine or tacrolimus) and mycophenolate mofetil (MMF) with or without rapamycin (Table 1). Types and grades of acute and chronic GVHD were determined using previously described methods.(20;21)

Definitions

Bulky lymphadenopathy was defined as having at least 1 lymph node ≥ 5 cm at the time of pretransplant evaluation. Comorbidities were evaluated per the HCT-Comorbidity Index (CI).(22) CMV serology status was classified as high-risk (all patients who had positive status), intermediate-risk (patients who had negative status but their donors had positive status), or low-risk (both patients and donors had negative status). A partial response (PR)

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was defined by a ≥50% reduction in measurable disease (nodal masses or sum of the product of the diameters of any nodules in spleen or liver) by CT imaging.(23) Complete response (CR) was defined as no measurable disease by CT imaging,(23) bone marrow morphology and/or endoscopy. Refractory disease included responses less than PR following the most recent attempt at cyto-reduction. Untreated-relapse included disease recurring after achieving at least a PR after the most recent therapy.

Statistical Methods

Overall survival (OS) and progression- free survival (PFS) were estimated by the Kaplan-Meier method. Progression-free survival was defined as time free of progression, relapse, or death due to any cause.(24) Cumulative incidence estimates were calculated for acute and chronic GVHD, relapse, and NRM. Primary endpoints were compared using the log rank test. Hazard ratios were estimated from Cox regression models. Deaths were treated as competing events in analyses of the development of GVHD and relapse. NRM and progression were the components of PFS and were treated as competing events.

Proportional hazard models were created to test associations between risk factors and outcomes. Variables tested for an association with OS, PFS, relapse and NRM included disease status at time of transplant, bulky lymph nodes at time of transplant, number of treatment regimens prior to HCT, donor type (related vs. unrelated), receiving a 1 antigen mismatched graft, CMV risk status, age ≥ 55, HCT-CI score, CD34 cell dose, CD3 cell dose and time from diagnosis to HCT (>3 years versus ≤ 3 years). All variables achieving an effect with a p-value of <0.1 were included in multivariate models. Multivariate p-values were based on adjustment for all other variables in the model. P-values were derived from likelihood ratio statistics and were two sided.

RESULTS

Patient Characteristics

Table 1 demonstrates the characteristics of the patient population. Median age was 57 (range of 35 to 75) years. The majority of patients were males (76%). Patients received a conditioning regimen of 2 Gy TBI alone (14%) or combined with fludarabine 30 mg/m^2 for three doses (86%). Ten percent of patients also received rituximab. Five patients (7%) with bulky, rapidly-progressive, refractory disease before HCT received a tandem autologous followed by allogeneic HCT. Patients received a median of 4 (range 1–10) prior chemo-immuno-therapy regimens. Bulky lymphadenopathy at the time of HCT was identified in 12% of patients. Twenty-eight (40%) patients were enrolled after failing autologous HCT. Unresponsive (n=18) or untreated (n=7) relapse prior to HCT was encountered in 36% of patients.

Overall Outcomes

At the end of a median follow-up period of 7.1 (0.2– 12.8) years, a total of 34 patients were alive, 30 in continuous remission and 4 alive after salvage therapies given for progression (n=1) or relapse (n=3) following HCT. These 4 patients were alive at a median of 68 (range 50–86) months from the date of transplant. They were salvaged by four weekly doses of

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rituximab in three patients followed by donor lymphocyte infusion (DLI) in one, chemotherapy and local radiation therapy in a second and bortezomib in a third. Salvage treatment is unknown for the fourth patient. Three patients required a second HCT for 1) graft rejection, 2) secondary MDS, and 3) secondary graft failure.

Overall, cumulative incidence of NRM at 5 years was 28%. Causes of NRM included infection (n=9), GVHD (n=7), secondary malignancy (n=2), organizing/idiopathic pneumonia (n=2), pancreatitis (n=1), heart failure (n=1) and an accident (n=1). The cumulative incidence of relapse was 26% at 5 years (Figure 1A). Patients with progression or relapse post-allogeneic HCT (n=17) had a median survival of 9.4 months after documented recurrence. Overall, after 4 years, there were 28 patients at risk of relapse. One last patient relapsed at day 1482 (4.06 years); beyond that date 27 patients remained at risk for relapse. The 5-year rates of OS and PFS were 55% and 46%, respectively (Figure 1B). Cumulative incidences of grades II and III–IV acute GVHD were 33% and 20%, respectively.

Outcomes among patients who failed prior autologous HCT were comparable to those experienced by the entire group. Five-year rates of OS were 53% versus 43% for those failing autologous HCT versus all patients, respectively. The figures for PFS were 30% versus 27%, respectively.

Recipients of HLA-matched related versus unrelated donor grafts experienced 5-year OS of 60% versus 51% (p=0.08) and PFS of 54% versus 40% (p=0.07), respectively. The figures for relapse and NRM were 22% versus 28% (p=0.40) and 24% versus 32% (p=0.10), respectively. The cumulative incidences of grades II–IV acute GVHD at day 100 were 45% and 64%, while those for chronic GVHD at 2 years were 58% and 57%, respectively.

The prevalence of patients who were alive and were tapered off all immunosuppressive medications was 30% at 5 years (Figure 1C). The median time to cessation of immunosuppressive medications was 35 (range 1–95) months. Among the 34 surviving patients, the median Karnofsky performance status (KPS) at last contact was 90% (range, 60–100%).

Comparison of Outcomes between Patients with Chemo-sensitive Versus Unresponsive/ Untreated Relapse Prior to Allogeneic HCT

Overall, 25 patients (36%) were transplanted while in unresponsive/untreated relapse, while 20 (29%) were in partial remission (PR) and 25 (35%) were in complete remission (CR). Patients with unresponsive/untreated relapse were given a greater number of prior regimens (median of 5 versus 3) compared to those who were in CR/PR.

Rates of achieving CR following HCT were 68% and 75%, respectively, at a median duration of 93 days for both groups. Patients with unresponsive/untreated relapse experienced statistically significantly higher rate of relapse at 5 years (45% versus 14%, p=0.007) compared to those who were in CR/PR. NRM at 5 years was less frequently encountered among patients who were in unresponsive/untreated relapse (20% versus 33%), but this difference did not reach statistical significance (p=0.95). No statistical significance

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differences were observed in rates of OS (51% versus 58%, p=0.29) or PFS (35% versus 54%, p=0.08), respectively. Of note, survival rates were overall similar for those who were given transplants while in untreated relapse (n=7) or refractory disease [(n=18), data are not shown].

Long-term Outcomes of the Initially Reported 33 Patients

Among the 33 initially reported patients, 14 survived with a median follow-up of 10.3 (range, 8.6–12.8) years. Rate of relapse at 10-years was 18%, while the cumulative incidence of NRM was 41% (Figure 2). The 10-year rate of OS was 44%, while PFS was 41%.

The cumulative incidence of chronic GVHD was 65%. The prevalence of patients who were alive and were tapered off all immunosuppressive medications was 35% at 10 years, which constituted 80% of all surviving patients.

There were 14 patients transplanted with unresponsive or untreated relapse versus 19 who were in CR/PR. Similar to the overall population, patients with unresponsive/untreated relapse had statistically significantly higher rates of relapse at 10 years (36% versus 5%, p=0.03) compared to those who were in CR/PR. No statistical significant differences could be observed between the two groups for NRM (29% versus 50%, p=0.43), OS (43% versus 45%, p=0.89), or PFS (36% versus 45%, p=0.62).

Assessment of Prognostic Variables on Outcome

High-risk CMV status was the only statistically significantly independent predictor of worse OS (HR 2.32 p=0.02) and PFS (HR 2.22 p=0.03, Table 2), respectively, but not relapse (2.59, p=0.11 in multivariate analysis) or NRM (association did not qualify to enter multivariate model). Low CD3 cell dose ($<3 \times 10^8$/kg) was associated with 2-fold increase in the risks for worse OS and PFS, but these associations had only borderline statistical significance (p = 0.07 and 0.05, respectively).

The presence of unresponsive or untreated relapse at the time of HCT had borderline statistical significance for association with higher risk of relapse (HRs 2.94, p=0.05) and it had no statistically significant association with worse OS (association did not qualify to enter multivariate model) or PFS (HRs 1.64, p=0.13).

Receiving HLA-antigen mismatched graft was also associated with an increased risk of post-HCT relapse/progression (HR 5.97, p=0.0041). When examined as a time-dependent covariate, the development of cGVHD was not statistically significantly associated with risk of relapse (HR=0.28, p=0.17).

No factors met statistical significance for associations with higher risks of NRM even though low CD3 cell dose (HR 2.54 p= 0.08) and HCT-CI score of ≥3 (HR 1.71 p=0.22) showed higher HR for that outcome.

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DISCUSSION

In this study, we show that patients with previously treated and advanced MCL achieve prolonged and sustained PFS when treated with nonmyeloablative conditioning and allogeneic HCT. This is a particularly important finding in our field, as it showcases the ability of the graft-versus-lymphoma (GVL) effect to sustain long-term disease control in MCL. This fact is particularly highlighted in Figure 1a, which shows that relapses among our 70 patients plateaued after about 4 years. Indeed, of the 28 patients who were at risk of relapse at 4 years post-HCT, only 1 experienced relapse (at 4.06 years). The remaining patients were alive and free of disease at the time of last follow-up. Moreover, while chronic GVHD developed in 65% of patients, the majority of survivors (80%) came off all immunosuppressive medications with a median KPS of 90% at last contact. Therefore, we believe that prolonged responses are plausible without the expense of significant long-term toxicity.

The 5-year OS among our patients was 55%. Previously reported survival rates after allogeneic HCT utilizing high-dose regimens were in the range of 25–49%(4;6), while those after reduced intensity conditioning (RIC) regimen were 21%–53%, respectively.(16;17) The 5-year NRM experienced by our patients was 28%. Previous results on NRM rates following high-dose or RIC regimens ranged between 38-58% and 17–28%, respectively.(25–28) Comparing results across sites and datasets is not possible due to variability in patient characteristics and regimens. Nevertheless, a subset of MCL patients seems to benefit from allogeneic HCT. While our study provides promising results, future prospective studies are needed to explore which regimen is more suitable to which group of MCL patients with a given set of characteristics.

A significant proportion of patients (37%) who had active disease at the time of transplant were able to achieve a sustained long-term survival (5-year OS 55%, 10-year OS 43%). This finding is encouraging, as it suggests that some chemo-refractory disease may still respond to the graft-versus-lymphoma effect. Outcomes after allogeneic HCT in patients with relapsed/refractory MCL were recently examined using registry data.(25) Similar to our findings, their results found that a subset of patients with refractory disease experienced sustained 3-year OS (30%) and PFS (25%) after being treated with of RIC/nonmyeloablative conditioning. Historically, patients with refractory MCL have had dismal outcomes using traditional treatment methods.(29–31) Our results, in addition to the registry study, support the use of allogeneic HCT as an important salvage option for those with relapsed/refractory disease.

Significant advances have been made in treating persistent MCL after allogeneic HCT with interventions like donor lymphocyte infusions (DLI),(17;32) maintenance immunotherapy,(33;34) novel biologic agents such as BTK inhibitors and immunomodulatory agents,(35;36) and the genetically modified donor chimeric antigen receptor (CAR) T cells.(37;38) We compared the 5 and 10-year OS between those who received allogeneic HCT in CR/PR versus those with refractory/untreated relapse. The OS was not different between these two groups, although the latter group did experience a higher rate of relapse. Results remained valid when we analyzed patient with refractory disease separately from those with untreated

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relapse at time of HCT, suggesting equal GVL benefit for both groups. It is conceivable that by lowering the toxicity profiles of conditioning regimen, we may be leaving room for treatment with effective salvage therapies after HCT, thereby extending survival. Using some of the novel approaches (BTK inhibitor or CAR T cells) mentioned above may further improve survival of those who progress or relapse after HCT.

We did attempt to identify factors that might predict which patients derive the best outcomes from nonmyeloablative allogeneic HCT. Having a high-risk CMV status was the only statistically significant negative predictor of PFS and OS in our study. The relatively small sample size was probably responsible for not demonstrating strong association between CMV status and either risk of relapse or NRM. The receipt of a lower CD3 cell dose showed an association with poorer PFS. While again the small sample size limits our conclusion about this association, one explanation could be related to the importance of immune reconstitution in these patients, both as a protector against subsequent infection and NRM, as well as being the underlying mediator of the GVL effect. Of note, receiving related vs. unrelated grafts did not influence outcomes in our study. This supports the idea that unrelated donors are suitable option for patients with MCL lacking identical sibling grafts. Only 7 patients received HLA-antigen mis-matched grafts, but this was strongly associated with an increased risk of relapse (HR 5.97, p=0.004). Prolonged durations of GVHD-prophylaxis immunosuppressive therapy as well as use of systemic steroids to treat acute and/or chronic GVHD that developed in 4 of these patients might be, in part, responsible for increasing risks of relapse. However, these results must be interpreted with caution given the small number of recipients of HLA-antigen mismatch grafts.

Study limitations include the retrospective nature of the study and the relatively small number of patients. Nevertheless, this study had complete follow-up data with almost no missing information, despite patients being treated at multiple academic centers. The use of a uniform nonmyeloablative conditioning regimen in this group of MCL patients allowed us to better reveal the real effect of GVL effect in disease control.

Our results confirm the ability of minimally toxic nonmyeloablative conditioning followed by allogeneic stem cell transplant to secure limited treatment-related mortality that optimizes the benefit from the strong GVL effect. At our collaborating sites, it is becoming a standard practice to offer nonmyeloablative conditioning to all patients older than 50 years or those with multiple comorbidities presenting for allogeneic HCT. In the current era, only a rare group of young and healthy patients are offered high-dose regimens given the high possibility of NRM. However, as there are the multiple treatment options now available for relapsed MCL, exactly who will derive the most benefit from this form of therapy warrants further investigation, which may be best accomplished with multi-institutional randomized clinical trials.

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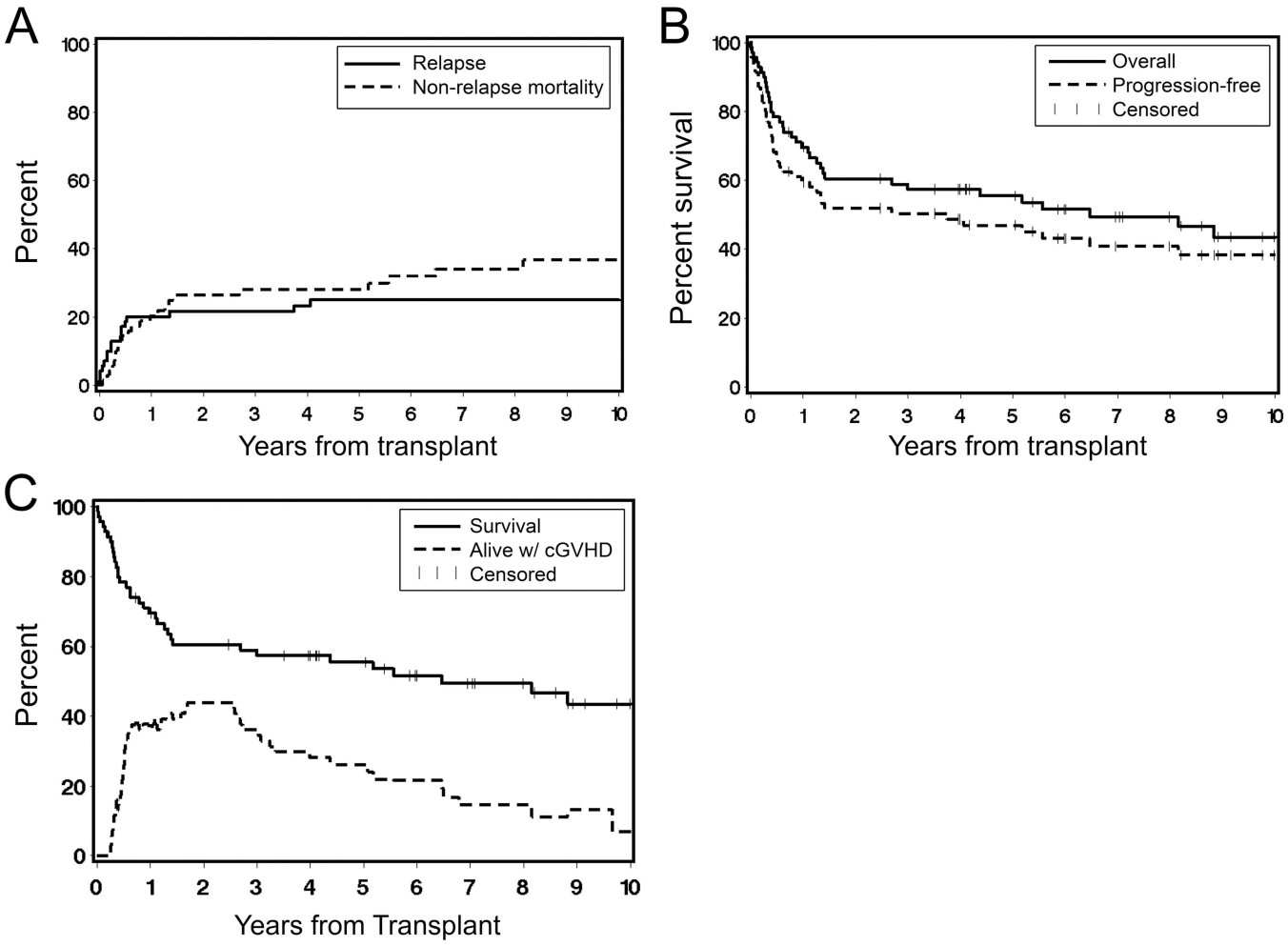

Figure 1.

(A) Cumulative incidences of non-relapse mortality and progression/relapse, (B) Kaplan-Meier estimates of overall and progression-free survival, (C) Kaplan-Meier estimate of overall survival with prevalence of chronic graft-versus-host disease requiring immunosuppressive therapy among patients with mantle cell lymphoma, who were given non-myeloablative conditioning and allogeneic HCT.

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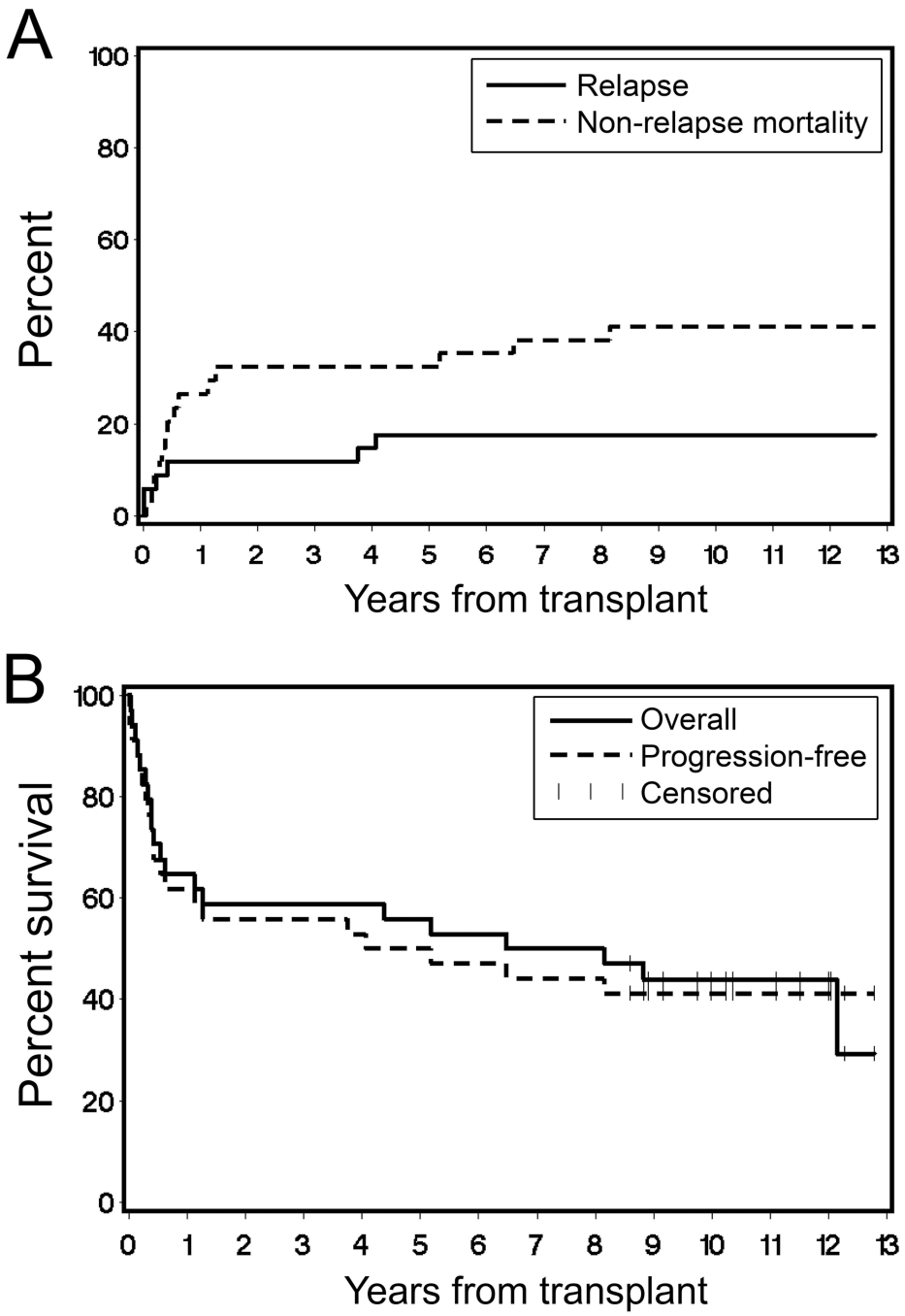

Figure 2.

Cumulative incidences and rates of (A) non-relapse mortality and progression/relapse and (B) overall and progression-free survival among the 33 initially reported patients with mantle cell lymphoma, who were given non-myeloablative conditioning.

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Table 1

Patient Characteristics

	Median	Range
Age (years)	57	32–75
	N	%
Sex		
F	17	24
M	53	76
Conditioning Regimen		
2 Gy TBI	4	6
2 Gy TBI + Auto	4	6
2 Gy TBI + Flu 30 mg/m^2 × 3	55	79
2 Gy TBI + Flu 30 mg/m^2 × 3 + Rituxan	5	7
2 Gy TBI + Rituxan	2	3
Donor type		
HLA Matched Related	33	47
HLA Matched Unrelated	29	41
HLA 1 Antigen mismatched	8	11
GVHD prophylaxis		
Cyclosporine/MMF	49	70
Cyclosporine/MMF/Rapamycin	2	3
Tacrolimus/MMF	15	21
Tacrolimus/MMF/Rapamycin	4	6
HCTCI		
0	12	17
1 or 2	26	37
3 or greater	30	43
Unknown	2	3
Number of prior regimens		
1 to 2	15	21
3 to 4	27	39
5 to 6	16	23
7 or greater	12	17
Previous autologous transplant		
Failed	28	40
Planned as part of tandem auto/allo	7	10
No	35	50
Disease status at time of transplant		
CR	26	37
PR	19	27
Refractory	18	26
Untreated Relapse	7	10

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	Median	Range
Blastic variant		
Y	7	10
N	63	90
Bulky lymphadenopathy (5 cm or >)		
Y	12	17
N	58	83
Disease burden		
Minimal (LN < 1.5 cm)	39	56
Moderate (LN 1.5 to <5)	19	27
Significant (LN 5 cm or greater)	12	17
CMV risk		
High	38	54
Intermediate	8	11
Low	24	34

Abbreviations: TBI = total body irradiation; Flu=fludarabine; HLA=Human Leukocyte Antigen; GVHD=graft-versus-host disease; MMF=mycophenolate mofetil; HCT-CI= Hematopoietic Stem Cell Transplant Comorbidity Index; CMV=Cytomegalovirus.

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Table 2

Risk factors for various outcomes in 70 mantle cell lymphoma patients

	Univariate[1]		Multivariate	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**
Overall Mortality (OS), 36 events				
CD3 dose < 3×10^8/kg (n=37)	2.33 (1.2–4.7)	0.02	2.02 (1.0–4.3)	0.07
Unrelated donor (n=37)	1.83 (0.9–3.6)	0.08	1.66 (0.8–3.5)	0.18
High risk CMV (n=38)	2.01 (1.0–4.0)	0.05	2.32 (1.1–4.8)	0.02
Bulky LN (n=12)	2.05 (1.0–4.4)	0.06	1.57 (0.7–3.4)	0.25
NRM + relapse/progression (PFS), 40 events				
CD3 dose < 3×10^8/kg (n=37)	2.23 (1.2–4.3)	0.02	2.04 (1.0–4.2)	0.05
Unrelated donor (n=37)	1.80 (0.9–3.4)	0.07	1.53 (0.7–3.2)	0.26
Antigen MM (n=8)	2.28 (0.9–5.9)	0.09	1.92 (0.7–5.2)	0.20
Relapse/refractory (n=26)	1.76 (0.9–3.3)	0.08	1.64 (0.9–3.1)	0.13
High risk CMV (n=38)	1.95 (1.0–3.7)	0.05	2.22 (1.1–4.5)	0.03
Relapse/progression, 17 events				
Antigen MM (n=8)	4.31 (1.4–13.4)	0.01	5.97 (1.8–20.2)	0.004
Relapse/refractory (n=26)	3.75 (1.4–10.1)	0.009	2.94 (1.0–8.7)	0.05
High risk CMV (n=38)	3.08 (1.0–9.4)	0.05	2.59 (0.8–8.4)	0.11
Bulky LN (n=12)	3.05 (1.1–8.3)	0.03	1.73 (0.6–5.2)	0.32
Non-relapse mortality, 23 events				
CD3 dose < 3×10^8/kg (n=37)	2.86 (1.2–7.0)	0.02	2.54 (0.9–7.3)	0.08
Unrelated donor (n=37)	2.04 (0.9–4.8)	0.10	1.00 (0.4–2.8)	0.99
HCT-CI ≥ 3 (n=31)	2.15 (0.9–4.9)	0.07	1.71 (0.7–4.1)	0.22

[1] Factors significant at the 0.10 level in univariate analysis, which are then entered together in multivariate model

Other factors considered which did not reach the 0.10 level for any endpoint: age ≥ 55, CD34 dose < 7.8×10^6/kg, number of prior regimens ≥ 4, failed prior auto, ANC < ULN (1.8), time from Dx to HCT > 3 years