Allogeneic Hematopoietic Cell Transplantation for Chemotherapy-Unresponsive Mantle Cell Lymphoma: A Cohort Analysis from the Center for International Blood and Marrow Transplant Research

Mehdi Hamadani, *West Virginia University Hospitals*
Wael Saber, *Medical College of Wisconsin*
Kwang Woo Ahn, *Medical College of Wisconsin*
Jeanette Carreras, *Medical College of Wisconsin*
Mitchell S. Cairo, *New York Presbyterian Hospital*
Timothy S. Fenske, *Medical College of Wisconsin*
Robert Peter Gale, *Imperial College*
John Gibson, *Royal Prince Alfred Hospital*
Gregory A. Hale, *University of South Florida*
Parameswaran N. Hari, *Medical College of Wisconsin*

Only first 10 authors above; see publication for full author list.

Journal Title: Biology of Blood and Marrow Transplantation
Volume: Volume 19, Number 4
Publisher: Elsevier: 12 months | 2013-04-01, Pages 625-631
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.bbmt.2013.01.009
Permanent URL: https://pid.emory.edu/ark:/25593/twtvj

Final published version: http://dx.doi.org/10.1016/j.bbmt.2013.01.009

Copyright information:

Published in final edited form as:
Biol Blood Marrow Transplant. 2013 April ; 19(4): 625–631. doi:10.1016/j.bbmt.2013.01.009.

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR CHEMOTHERAPY-UNRESPONSIVE MANTLE CELL LYMPHOMA: A COHORT ANALYSIS FROM THE CIBMTR

Mehdi Hamadani, MD[1], **Wael Saber, MD, MS**[2], **Kwang Woo Ahn, PhD**[2], **Jeanette Carreras, MPH**[2], **Mitchell S. Cairo, MD**[3], **Timothy S. Fenske, MD, MS**[4], **Robert Peter Gale, MD, PhD**[5], **John Gibson, MBBS, PhD**[6], **Gregory A. Hale, MD**[7], **Parameswaran N. Hari, MD, MS**[2], **Jack W. Hsu, MD**[8], **David J. Inwards, MD**[9], **Rammurti T. Kamble, MD**[10], **Anderas Klein, MD**[11], **Dipnarine Maharaj, MD**[12], **David I. Marks, MD, PhD**[13], **David A. Rizzieri, MD**[14], **Bipin N. Savani, MD**[15], **Harry C. Schouten, MD, PhD**[16], **Edmund K. Waller, MD, PhD**[17], **Baldeep Wirk, MD**[8], and **Hillard M. Lazarus, MD**[18]

[1]West Virginia University Hospitals, Morgantown, WV [2]Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI [3]New York Presbyterian Hospital at Cornell, New York, NY [4]Divisionof Hematology and Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI [5]‘Imperial College, Section of Hematology, Division of Experimental Medicine, Department of Medicine, London, United Kingdom [6]Royal Prince Alfred Hospital Institute of Haematology, Camperdown, Australia [7]All Children’s Hospital, St. Petersburg, FL [8]Shands Healthcare and University of Florida, Gainesville, FL [9]Mayo Clinic Rochester, Rochester, MN [10]Baylor College of Medicine Center for Cell and Gene Therapy, Houston, TX [11]Tufts Medical Center, Boston, MA [12]Bethesda Health City, Boynton Beach, FL [13]Bristol Children’s Hospital, Bristol, United Kingdom [14]Duke University Medical Center, Pediatric Blood and Marrow Transplant, Durham, NC [15]Vanderbilt University Medical Center, Brentwood, TN [16]Academische Ziekenhuis Maastricht, Maastricht, Netherlands [17]Emory University Hospital, Atlanta, GA [18]University Hospitals Case Medical Center, Cleveland, OH

Abstract

Patients with chemorefractory mantle cell lymphoma (MCL) have poor prognosis. We used the CIBMTR database to study the outcome of 202 patients with refractory MCL who underwent allogeneic hematopoietic cell transplantation (allo-HCT) using either myeloablative (MA) or reduced intensity/non-myeloablative conditioning (RIC/NST), during 1998–2010. We analyzed non-relapse mortality (NRM), progression/relapse, progression-free survival (PFS), and overall

Corresponding Author: Wael Saber, MD, MS, Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, 9200 W. Wisconsin Avenue, Suite C5500, Milwaukee, WI 53226, USA; Phone: 414-805-0700; Fax: 414-805-0714; wsaber@mcw.edu.

AUTHOR CONTRIBUTION:
M.H., H.M.L, and W.S designed the study and participated in interpretation of data, manuscript preparation and approval of final manuscript. J.C. and K.W.A did the statistical analysis. M.S.C., T.S.F., R.P.G., J.G., G.A.H., P.N.H., J.W.H., D.J.I., R.T.K., A.K., D.M., D.I.M., D.A.R., B.N.S., H.C.S., E.K.W. and B.W. participated in interpretation of data, manuscript preparation and approval of final manuscript. M.H., H.M.L, and W.S had primary responsibility for manuscript preparation.

The authors have no relevant conflicts of interest.

survival (OS). Seventy-four patients received MA, and 128 underwent RIC/NST. Median ages are 54 and 59 years for MA and RIC/NST allo-HCT recipients, respectively. Median follow-up after MA and RIC/NST allo-HCT is 35 months and 43 months, respectively. At 3 years, comparing MA with RIC/NST allo-HCT, no significant differences were found in terms of NRM (47% vs. 43%; p-value=0.68), relapse/progression (33% vs. 32%; p-value=0.89), PFS (20% vs. 25%; p=0.53), and OS (25% vs. 30%; p-value=0.45). On multivariate analysis no significant differences were observed in NRM, relapse, PFS and OS between MA and RIC/NST allo-HCT; however, receiving a bone marrow or T-cell depleted allograft was associated with an increased risk of NRM and inferior PFS and OS. Despite a refractory disease state, approximately a fourth of MCL patients can attain durable remissions after allo-HCT. Conditioning regimen intensity did not influence the outcomes of patients after allo HCT.

Keywords

Mantle cell lymphoma; allogeneic transplantation; chemotherapy unresponsive; graft-versus-host disease

INTRODUCTION

Mantle cell lymphoma (MCL) accounts for approximately 6% of non-Hodgkin lymphomas (NHL), and typically presents as advanced stage disease that frequently involves bone marrow, peripheral blood and extra nodal sites(1). MCL generally follows an aggressive clinical course, with frequent relapses after conventional chemotherapy regimens. Over the last decade; strategies including multi-agent immunochemotherapy either alone(2), or as induction followed by consolidation with high dose therapy and autologous hematopoietic cell transplantation (auto-HCT) (3–5)or rituximab maintenance(6, 7), have produced higher response rates and improved disease-free survival. While these modalities have undoubtedly improved the prognosis of patients with MCL(8), the disease course is characterized by frequent relapses. After first relapse, the prognosis of MCL is poor with a median survival of approximately 1 to 2 years(9). This is especially true for relapsed MCL patients with chemotherapy refractory disease. The results of auto-HCT patients with chemorefractory MCL have been uniformly disappointing(10–12). Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative modality for a variety of hematologic malignancies including indolent and aggressive lymphomas(13–17). The advantages of an allo-HCT include a tumor-free graft, as well as a potential allogeneic effect exerted by donor T-cells often referred to as graft-versus-lymphoma (GVL) effect.

Despite the higher risk of transplant-related morbidity and mortality with allo-HCT, select patients with relapsed MCL, especially the subgroup with chemosensitive disease, can achieve long-term remissions after allo-HCT(18–20). MCL patients who are refractory to salvage chemotherapy, however, have a very poor prognosis and there are only limited data available regarding the outcomes after allo-HCT for this extremely high-risk group. However, because the GVL effect can occur even in the absence of chemosensitivity, allo-HCT may still in theory offer benefit even in chemoresistant patients. Moreover, the influence of conditioning regimen intensity, e.g. myeloablative (MA) conditioning versus reduced-intensity conditioning (RIC) or non-myeloablative conditioning (NST) regimens, in this uniquely chemorefractory cohort of patients is not known. We report herein the outcomes of allo-HCT in patients with refractory MCL, relative to the intensity of the transplant conditioning regimens using the observational database of the Center for International Blood and Marrow Transplant Research (CIBMTR. To date, this report represents the largest study of chemotherapy-unresponsive MCL patients undergoing allo-HCT.

MATERIALS AND METHODS

Data sources

The CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR) and the National Marrow Donor Program (NMDP) established in 2004; both entities had been collecting data for more than one decade prior to the merger. This organization comprises a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive auto- and allo-HCTs to a Statistical Center at the Medical College of Wisconsin in Milwaukee, WI and the NMDP Coordinating Center in Minneapolis, MN. Participating centers are required to report all HCTs consecutively, with compliance monitored by on-site audits. Patients are followed longitudinally, with yearly follow-up. Computerized checks for discrepancies, physicians' reviews of submitted data, and onsite 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 NMDP 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.

Patients

The study population included all patients with chemotherapy unresponsive MCL receiving an allo-HCT reported to the CIBMTR between 1998 and 2010. Patients with evidence of chemosensitive disease (i.e. patients in complete remission [CR] or partial remission [PR]) at the time of allo-HCT were excluded. Pediatric patients (n=5), and recipients of planned tandem auto-/allo-HCT (n=50), syngeneic-HCT (n=7) and umbilical cord blood transplantation (n=29) were not included in the analysis. The patient- and disease-related variables that are not reported for registration-only patients are indicated at appropriate places in Table 1.

Definitions

The intensity of conditioning regimens was categorized as MA or RIC/NST using established consensus criteria(21). Previously established criteria for categorizing the degree of HLA matching were used (22) for unrelated donor transplants (URD). Well-matched patients had either no identified HLA mismatching and informative data at four loci or allele matching at HLA-A, -B, and -DRB1 (6/6). Partially matched pairs had a defined, single-locus mismatch and/or missing HLA data. Mismatched cases had ≥2 allele or antigen mismatches.

Study Endpoints

Primary outcomes were non-relapse mortality (NRM), progression/relapse, progression-free survival (PFS), and overall survival (OS). NRM was defined as death from any cause during the first 28 days after transplantation or death without evidence of lymphoma progression/

relapse; relapse was considered a competing risk. Progression/relapse was defined as progressive lymphoma after HCT or lymphoma recurrence after a CR; NRM was considered a competing risk. For PFS, a patient was considered a treatment failure at the time of progression/relapse or death from any cause. For relapse, NRM, and PFS patients alive without evidence of disease relapse or progression were censored at last follow-up. The OS was defined as the interval from the date of transplantation to the date of death or last follow-up. Other outcomes analyzed included acute and chronic graft-versus-host disease (GVHD) and cause of death. Acute GVHD was defined and graded based on the pattern and severity of organ involvement using established criteria(23). Chronic GVHD was defined as the development of any evidence of chronic GVHD based on clinical criteria(24). Neutrophil engraftment was defined as the first of 3 successive days with absolute neutrophil count (ANC) $\geq = 0.5 \times 10^9$/L after post-transplantation nadir. Platelet engraftment was considered to have occurred on the first of three consecutive days with platelet count 20×10^9/L or higher, in the absence of platelet transfusion for 7 consecutive days. For engraftment and GVHD, death without the event was considered a competing risk.

Statistical analysis

Probabilities of PFS and OS were calculated using the Kaplan-Meier estimator with variance estimated by the Greenwood formula. Probabilities of NRM, lymphoma progression/relapse, acute and chronic GVHD, and engraftment were calculated using cumulative incidence curves to accommodate for competing risks(25). Patient-, disease- and transplant- related factors were compared between RIC/NST and MA groups using the Chi-square test for categorical variables and the Wilcoxon two sample test for continuous variables. Associations among patient-, disease, and transplantation-related variables and outcomes of interest were evaluated using multivariate Cox proportional hazards regression. A stepwise selection multivariate model was built to identify covariates that influenced outcomes. Covariates with a p-value <0.05 were considered significant. The proportionality assumption for Cox regression was tested by adding a time-dependent covariate for each risk factor and each outcome. Covariates violating the proportional hazards assumption were stratified in the Cox regression model. Results are expressed as relative risk (RR) or the relative rate of occurrence of the event.

The following variables were reported for both registration-level and research-level patients and were considered in multivariate analyses: age at allo-HCT, gender, Karnofsky Performance Score (KPS) at allo-HCT, prior auto-HCT, time interval between diagnosis and allo-HCT, disease status at allo-HCT, conditioning regimen intensity (RIC/NST vs. MA), donor type, donor–recipient gender match, graft source, year of allo-HCT and type of GVHD prophylaxis.

RESULTS

Patient, Disease-, and Transplant-Related Variables

Between 1998 and 2010, 202 patients received allo-HCT for refractory MCL; 74 patients received a MA allo-HCT and 128 received a RIC/NST allo-HCT. Median follow up of survivors for the MA and the RIC/NST groups was 35 months and 43 months, respectively. Completeness of follow up at 3 years was 80% in both groups reflecting good follow up to this time point (26). Table 1 describes patient-, disease- and transplant related characteristics of two cohorts (MA vs. RIC/NST) analyzed. The RIC/NST cohort was older compared with MA cohort (median age 59 years vs. 54 years, p<0.001). Approximately half of the patients had a pre-transplant Karnofsky performance score (KPS) of < 90. Median time from diagnosis to transplant was significantly longer in RIC/NST groups compared to MA cohort (29 months vs. 15 months, p-value<0.001).

No significant difference at baseline was observed between the two groups in terms of disease stage at diagnosis, bone marrow or extranodal involvement, disease bulk, central nervous system involvement, disease status at transplantation (primary refractory disease vs. refractory at relapse) and graft type (bone marrow vs. peripheral blood). Significantly more patients in the RIC/NST group had a prior history of undergoing an auto-HCT (33% vs. 13%; p-value=0.004), received rituximab therapy prior to transplantation (41% vs. 15%; p-value=0.01) and underwent URD allo-HCT (68% vs. 32%; p-value<0.001). Patients in the RIC/NST group were also more heavily pretreated (median lines of prior chemotherapies 4 vs. 3 p=0.02). The conditioning regimens most frequently employed prior to MA allo-HCT were cyclophosphamide/total body irradiation and busulfan/cyclophosphamide, while fludarabine-based conditioning was given more frequently before RIC/NST allografts. The majority of the patients in both cohorts received calcineurin inhibitor-based GVHD prophylaxis.

Outcomes

Outcomes after HCT are summarized in Tables 2 and 3.

Engraftment and GVHD

The cumulative incidence of neutrophil engraftment at day +28 was 90% (95% CI 78–95) in the MA cohort and 92% (95% CI 85–96) in the RIC/NST cohort (p-value=0.58) (Table 2). The cumulative incidence of platelet recovery at day +28 was 72% (95% CI 54–84) and 80% (95% CI 70–87) (p-value=0.34) in similar order. Cumulative incidence of grade II-IV acute GVHD at day +100 was 36% (95% CI 23–50) and 37% (95% CI 28–46) in MA and RIC/NST groups (p-value = 0.93), respectively (Table 2). Cumulative incidence of chronic GVHD at 1 year post transplantation in similar order was 35% (95% CI 22–48) and 43% (95% CI 33–52), respectively (p-value = 0.35) (Table 2). The number of patients developing limited and extensive chronic GVHD in MA group was 3 and 13 respectively. The respective numbers for the RIC/NST cohort were 12 and 36. The extent of chronic GVHD (limited vs. extensive) was not known in 3 patients.

Non relapse mortality

Day-100 NRM rates were 33% (95% CI 23–45) for the MA cohort and 26% (95% CI 18–34) for the RIC/NST cohort (p-value=0.28) (Table 2). Cumulative incidence estimate of NRM at 3 years in similar order was 47% (95% CI 35–59) and 43% (95% CI 34–53), respectively (p-value=0.68). On multivariate analysis, receiving a bone marrow allograft (compared to a peripheral blood graft) (RR=1.89, 95% CI 1.10–3.24; p-value=0.02) and GVHD prophylaxis via *ex-vivo* T-cell depletion or CD34+ selection (compared to tacrolimus-based GVHD prophylaxis) (RR=6.11, 95% CI 2.60–14.36; p-value<0.001) were associated with an increased risk of NRM. Conditioning regimen intensity was not associated with NRM (MA vs. RIC/NST, RR 1.04, 95% CI 0.66–1.63; p-value=0.87).

Relapse/Progression

The one- and three- year probability of relapse/progression were similar in both the MA and the RIC/NST groups (Table 2); at three years it was 33% (95% CI 22–45) in the MA cohort and 32% (95% CI 23–41) in the RIC/NST cohort (p-value=0.89). No correlation was observed between the risk of relapse/progression and development of grade II–IV acute GVHD (RR 0.73, 95% CI 0.35–1.51; p-value=0.39), grade III–IV acute GVHD (RR 1.11, 95% CI 0.52–2.36; p-value=0.78), or chronic GVHD (RR 0.77, 95% CI 0.35–1.58; p-value=0.45). None of the variables tested were significantly associated with a risk of relapse/progression on multivariate analysis. Conditioning regimen intensity was not associated with

risk of relapse/progression in multivariate analysis (MA vs. RIC/NST, RR 1.16, 95% CI 0.68–1.99; p-value=0.59).

Progression free survival

PFS estimates were not significantly different between MA and RIC/NST groups, neither at one year (31% [95% CI 20–42] vs. 38% [95% CI 29–48], p=0.32) nor at three years (20% [95% CI 11–32] vs. 25% [95% CI 17–34], p=0.53) (Table 2). On multivariate analysis, receiving a bone marrow allograft (compared to a peripheral blood graft) (RR=1.72, 95% CI 1.11–2.67; p-value=0.02) was associated with inferior PFS. Similarly inferior PFS was associated with *ex-vivo* T-cell depleted or CD34+ selected (RR=4.89, 95% CI 2.36–10.12; p-value<0.001) allo-HCT. Conditioning regimen intensity was not associated with PFS in multivariate analysis (MA vs. RIC/NST, RR 1.09, 95% CI 0.77–1.56; p-value=0.60) (Figure 1).

Overall survival

OS estimates were not significantly different between MA and RIC/NST groups, neither at one year (33% [95% CI 22–44] vs. 46% [95% CI 37–54], p=0.07) nor at three years (25% [95% CI 16–36] vs. 30% [95% CI 22–39], p=0.45) (Table 2). On multivariate analysis, receiving a bone marrow allograft (compared to a peripheral blood graft) (RR=1.84, 95% CI 1.21–2.78; p-value=0.004) was associated with inferior OS. GVHD prophylaxis via *ex-vivo* T-cell depletion/CD34+ selection (RR=3.42, 95% CI 1.64–7.12; p-value=0.001) or with cyclosporine-based regimens (RR=1.42, 95% CI 1.00–2.02; p-value=0.04), were also associated with an inferior OS. Conditioning regimen intensity was not associated with OS (MA vs. RIC/NST, RR 1.22, 95% CI 0.86–1.72; p-value=0.25) (Figure 2).

Causes of death

Disease relapse and/or progression accounted for 39% (n=22) morality in the MA cohort and 42% (n=39) in the RIC/NST cohort. Causes of death are summarized in Table 3.

DISCUSSION

The aims of the present study were to define outcomes of chemotherapy unresponsive MCL patients after allo-HCT, relative to the intensity of the conditioning regimens and other variables including graft source and prior use of auto-HCT. This large cohort of refractory MCL patients transplanted across multiple centers provides several important observations. First, despite refractory disease at baseline, approximately a quarter of MCL patients are alive and in remission three years post allo-HCT. Second, intensity of transplant conditioning regimen employed, in this uniquely chemotherapy refractory group, does not appear to significantly affect rates of NRM, relapse/progression, PFS and OS. Third, bone marrow as graft source and *ex-vivo* T-cell depletion seem to be associated with inferior survival outcomes, likely due to associated significantly higher rates of NRM. Fourth, high NRM and relapse rates after allo-HCT in this high-risk group will continue to be the main barrier towards wider application of this modality.

There are limited data published on the role of allo-HCT in patients with chemotherapy refractory MCL (Table 4). The Fred Hutchinson Cancer Center reported 2 year OS and PFS rates of 65% and 60%, respectively, in a cohort of 33 MCL patients undergoing NST allo-HCT with fludarabine and low-dose TBI(19). While this report included 13 patients with refractory disease, their outcomes were not described separately. The M. D. Anderson Cancer Center also described encouraging outcomes (6 year PFS and OS of 46% and 53%, respectively) of relapsed MCL patients (n=35) following NST allo-HCT(27). In this report disease remission at allo-HCT was not significantly associated with survival outcomes, but

only included 6 refractory patients. British Society for Bone Marrow Transplantation registry reported outcomes of MCL following RIC allo-HCT(28), and included 12 refractory patients. The 3 year OS and PFS rates for this very small subgroup of refractory patients were only 38% and 0%, respectively. Along similar lines, the 2 year OS and PFS rates, of 15 refractory patients included in the recently published French experience(29), were 31% and 11% respectively. Our study, the largest report to date, indicates that approximately a fourth of patients with chemotherapy unresponsive MCL can attain a prolonged remission after allo-HCT. It is important to interpret these results in the context of the dismal long-term prognosis of patients with refractory MCL treated with conventional chemotherapies, and the fact, that only 30–40% of patients in our study had a KPS of ≥ 90 before allo-HCT.

In patients with refractory lymphoid malignancies at the time of allo-HCT, the relative importance of conditioning regimen intensity is not known. It is probable that due to their inherent chemoresistance, patients with refractory NHL may derive no net benefit from higher intensity conditioning regimens. In our study the more intense MA conditioning regimens were not associated with reduced risk of relapse/progression or improved OS and PFS. It is, however, important to highlight that our report describes two different populations of patients with significant differences before undergoing allo-HCT. Our study is not a substitute for a randomized comparison of high versus low intensity conditioning regimens. We cannot discount inherent selection bias, i.e. a tendency of transplant physicians to preferentially offer MA allo-HCT to patients with '*higher-risk*', primary-refractory, or blastoid MCL. Whether the MA group were enriched with patients with progressive disease at the time of transplant is unknown since this information is not collected by the registry. Time interval between diagnosis and allo-HCT was shorter in the MA cohort, compared to RIC/NST cohort, which might be an indicator of more aggressive disease biology of patients included in the former group. It is however; worth noting that a significantly higher proportion of patients in RIC/NST cohort were more heavily pretreated, older, had prior rituximab exposure, underwent auto-HCT previously, or received URD allografts. The latter two factors likely contributed to the longer time interval between diagnosis and eventual allo-HCT in the RIC/NST group. With these limitations in mind, our data suggest that in patients with MCL who are refractory to conventional therapies, escalating the intensity of conditioning regimens is unlikely to improve patient outcomes.

It is important to point out that our report included both registration- and research-level patients reported to CIBMTR. The primary objective of this study was to describe transplantation outcomes of chemorefractory MCL patients relative to the intensity of conditioning regimens. Noteworthy variables missing in registration-level patients include disease stage at diagnosis, prior history of radiation, bulky disease status, B-symptoms, serum LDH level, bone marrow involvement, and extranodal involvement at *any* time point before allo-HCT. While some of these variables carry prognostic value for MCL, the significance of their presence at any time point before transplantation (as opposed to their presence at the time of transplantation), in a cohort of exclusively chemotherapy refractory MCL, is not known. Since key data regarding remission status at transplantation, type of conditioning regimens, donor/graft source, patient age, KPS, history of prior auto-HCT and all post-transplantation outcomes of interest (engraftment, GVHD, NRM, OS, PFS, etc.) were available on both registration- and research-level patients, we decided to include both patient populations.

The 3 year relapse/progression and NRM rates of approximately 30% and 45%, respectively, observed in our study are high. In prior reports of (predominantly chemosensitive) MCL patients undergoing RIC/NST allo-HCT, the rates of disease relapse at 5 years have ranged from 30–65%(27, 28), while reported rates NRM at 2 years have been approximately 20–35% (19, 29). One-third of the RIC/NST patients in our study

previously received an auto-HCT, a potential reason for high NRM. The multivariate analysis, however, did not identify this factor as associated with a higher NRM and other investigators also have not consistently found a prior auto-HCT to significantly influence NRM after the allogeneic procedure(16, 17). Nonetheless, it is clear that mitigating NRM and relapse rates by developing novel conditioning regimens designed to provide improved disease control while maintaining acceptable NRM rates, are urgently needed. Along these lines Gopal et al. (30)have reported a 30 month 54% survival with a NRM rate of 16% with radioimmunotherapy-based NST in a cohort of mostly refractory B-cell NHL patients, findings similar to those of Bethge and co-workers (31).

On multivariate analysis bone marrow as graft source and *ex-vivo* T-cell depletion/CD34+ cell selection in our study were consistently associated with higher NRM and inferior PFS and OS. Since these two variables were not associated with higher risk of disease relapse/progression, we speculate that inferior OS and PFS in these patients are likely due to higher rates of NRM. A possible explanation of higher NRM with bone marrow allografts and with *ex-vivo* T-cell depletion is delayed immune-reconstitution and resultant higher infectious complications in these patients. However, caution must be exercised in interpreting these results due to the small number of patients in subgroup undergoing *ex-vivo* T-cell depletion/CD34+ cell selection. Use of peripheral blood as a graft source has previously been reported to improve PFS in patients with MCL undergoing allo-HCT(27).

In conclusion, our analysis of this large set of registry data demonstrate that approximately a fourth of patients with refractory MCL can attain durable remissions after allo-HCT and that the intensity of the conditioning regimens did not influence their outcomes. In the absence of a clinical trial, consideration of a T-cell replete, allogeneic peripheral blood transplant is a viable option for otherwise healthy patients with refractory MCL.

Acknowledgments

We thank Ulrike Bacher, César O Freytes, Miguel-Angel Perales and Sonali Smith for their helpful comments and insights as members of the study committee. The CIBMTR is supported by Public Health Service Grant/Cooperative Agreement U24-CA76518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); a Grant/Cooperative Agreement 5U01HL069294 from NHLBI and NCI; a contract HHSH234200637015C with Health Resources and Services Administration (HRSA/DHHS); two Grants N00014-06-1-0704 and N00014-08-1-0058 from the Office of Naval Research; and grants from Allos, Inc.; Amgen, Inc.; Angioblast; Anonymous donation to the Medical College of Wisconsin; Ariad; Be the Match Foundation; Blue Cross and Blue Shield Association; Buchanan Family Foundation; CaridianBCT; Celgene Corporation; CellGenix, GmbH; Children's Leukemia Research Association; Fresenius-Biotech North America, Inc.; Gamida Cell Teva Joint Venture Ltd.; Genentech, Inc.; Genzyme Corporation; GlaxoSmithKline; HistoGenetics, Inc.; Kiadis Pharma; The Leukemia & Lymphoma Society; The Medical College of Wisconsin; Merck & Co, Inc.; Millennium: The Takeda Oncology Co.; Milliman USA, Inc.; Miltenyi Biotec, Inc.; National Marrow Donor Program; Optum Healthcare Solutions, Inc.; Osiris Therapeutics, Inc.; Otsuka America Pharmaceutical, Inc.; RemedyMD; Sanofi; Seattle Genetics; Sigma-Tau Pharmaceuticals; Soligenix, Inc.; StemCyte, A Global Cord Blood Therapeutics Co.; Stemsoft Software, Inc.; Swedish Orphan Biovitrum; Tarix Pharmaceuticals; Teva Neuroscience, Inc.; THERAKOS, Inc.; and Wellpoint, Inc. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, or any other agency of the U.S. Government.

References

1. Zhou Y, Wang H, Fang W, et al. Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004. Cancer. 2008; 113:791–798. [PubMed: 18615506]
2. Romaguera JE, Fayad LE, Feng L, et al. Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol. 2010; 150:200–208. [PubMed: 20528872]

3. Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood. 2005; 105:2677–2684. [PubMed: 15591112]
4. Damon LE, Johnson JL, Niedzwiecki D, et al. Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. J Clin Oncol. 2009; 27:6101–6108. [PubMed: 19917845]
5. Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood. 2008; 112:2687–2693. [PubMed: 18625886]
6. Kenkre VP, Long WL, Eickhoff JC, et al. Maintenance rituximab following induction chemo-immunotherapy for mantle cell lymphoma: long-term follow-up of a pilot study from the Wisconsin Oncology Network. Leuk Lymphoma. 2011; 52:1675–1680. [PubMed: 21864042]
7. Kluin-Nelemans JC, Hoster E, Walewski J, et al. R-CHOP Versus R-FC Followed by Maintenance with Rituximab Versus Interferon-Alfa: Outcome of the First Randomized Trial for Elderly Patients with Mantle Cell Lymphoma. Blood. 2011; 118:439.
8. Herrmann A, Hoster E, Zwingers T, et al. Improvement of overall survival in advanced stage mantle cell lymphoma. J Clin Oncol. 2009; 27:511–518. [PubMed: 19075279]
9. Zucca E, Roggero E, Pinotti G, et al. Patterns of survival in mantle cell lymphoma. Ann Oncol. 1995; 6:257–262. [PubMed: 7612491]
10. Till BG, Gooley TA, Crawford N, et al. Effect of remission status and induction chemotherapy regimen on outcome of autologous stem cell transplantation for mantle cell lymphoma. Leuk Lymphoma. 2008; 49:1062–1073. [PubMed: 18452065]
11. Vandenberghe E, Ruiz de Elvira C, Loberiza FR, et al. Outcome of autologous transplantation for mantle cell lymphoma: a study by the European Blood and Bone Marrow Transplant and Autologous Blood and Marrow Transplant Registries. Br J Haematol. 2003; 120:793–800. [PubMed: 12614212]
12. Vose JM, Bierman PJ, Weisenburger DD, et al. Autologous hematopoietic stem cell transplantation for mantle cell lymphoma. Biol Blood Marrow Transplant. 2000; 6:640–645. [PubMed: 11128815]
13. Khouri IF, McLaughlin P, Saliba RM, et al. Eight-year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after nonmyeloablative conditioning with fludarabine, cyclophosphamide, and rituximab. Blood. 2008; 111:5530–5536. [PubMed: 18411419]
14. Corradini P, Dodero A, Zallio F, Caracciolo D, et al. Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. J Clin Oncol. 2004; 22:2172–2176. [PubMed: 15169805]
15. Le Gouill S, Milpied N, Buzyn A, et al. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. J Clin Oncol. 2008; 26:2264–2271. [PubMed: 18390969]
16. Thomson KJ, Morris EC, Bloor A, et al. Favorable long-term survival after reduced-intensity allogeneic transplantation for multiple-relapse aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2009; 27:426–432. [PubMed: 19064981]
17. van Kampen RJ, Canals C, Schouten HC, Nagler A, Thomson KJ, Vernant JP, et al. Allogeneic stem-cell transplantation as salvage therapy for patients with diffuse large B-cell non-Hodgkin's lymphoma relapsing after an autologous stem-cell transplantation: an analysis of the European Group for Blood and Marrow Transplantation Registry. J Clin Oncol. 2011; 29:1342–1348. [PubMed: 21321299]
18. Robinson SP, Goldstone AH, Mackinnon S, et al. Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. Blood. 2002; 100:4310–4316. [PubMed: 12393626]

19. Maris MB, Sandmaier BM, Storer BE, et al. Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. Blood. 2004; 104:3535–3542. [PubMed: 15304387]
20. Corradini P, Dodero A, Farina L, et al. Allogeneic stem cell transplantation following reduced-intensity conditioning can induce durable clinical and molecular remissions in relapsed lymphomas: pre-transplant disease status and histotype heavily influence outcome. Leukemia. 2007; 21:2316–2323. [PubMed: 17597807]
21. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant. 2009; 15:1628–1633. [PubMed: 19896087]
22. Weisdorf D, Spellman S, Haagenson M, et al. Classification of HLA-matching for retrospective analysis of unrelated donor transplantation: revised definitions to predict survival. Biol Blood Marrow Transplant. 2008; 14:748–758. [PubMed: 18541193]
23. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995; 15:825–828. [PubMed: 7581076]
24. Shulman HM, Sullivan KM, Weiden PL, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med. 1980; 69:204–217. [PubMed: 6996481]
25. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999; 18:695–706. [PubMed: 10204198]
26. Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. Lancet. 2002; 359:1309–1310. [PubMed: 11965278]
27. Tam CS, Bassett R, Ledesma C, et al. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood. 2009; 113:4144–4152. [PubMed: 19168784]
28. Cook G, Smith GM, Kirkland K, et al. Outcome following Reduced-Intensity Allogeneic Stem Cell Transplantation (RIC AlloSCT) for relapsed and refractory mantle cell lymphoma (MCL): a study of the British Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2010; 16:1419–1427. [PubMed: 20399879]
29. Le Gouill S, Kroger N, Dhedin N, et al. Reduced-intensity conditioning allogeneic stem cell transplantation for relapsed/refractory mantle cell lymphoma: a multicenter experience. Ann Oncol. 2012; 10:2695–2703. [PubMed: 22440229]
30. Gopal AK, Guthrie KA, Rajendran J, et al. (9)(0)Y-Ibritumomab tiuxetan, fludarabine, and TBI-based nonmyeloablative allogeneic transplantation conditioning for patients with persistent high-risk B-cell lymphoma. Blood. 2011; 118:1132–1139. [PubMed: 21508413]
31. Bethge WA, Lange T, Meisner C, et al. Radioimmunotherapy with yttrium-90-ibritumomab tiuxetan as part of a reduced- intensity conditioning regimen for allogeneic hematopoietic cell transplantation in patients with advanced non-Hodgkin lymphoma: results of a phase 2 study. Blood. 201; 116:1795–1802. [PubMed: 20530284]

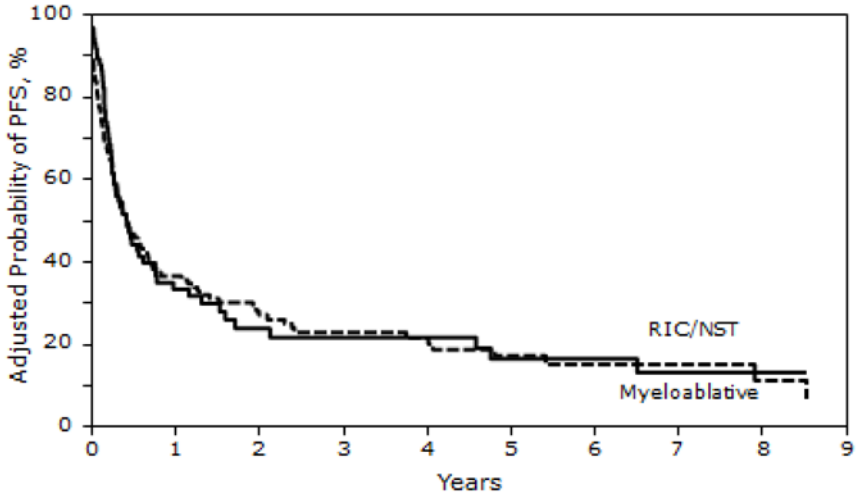

Figure 1.
Kaplan-Meier estimates of adjusted progression free survival following allogeneic transplantation for mantle cell lymphoma

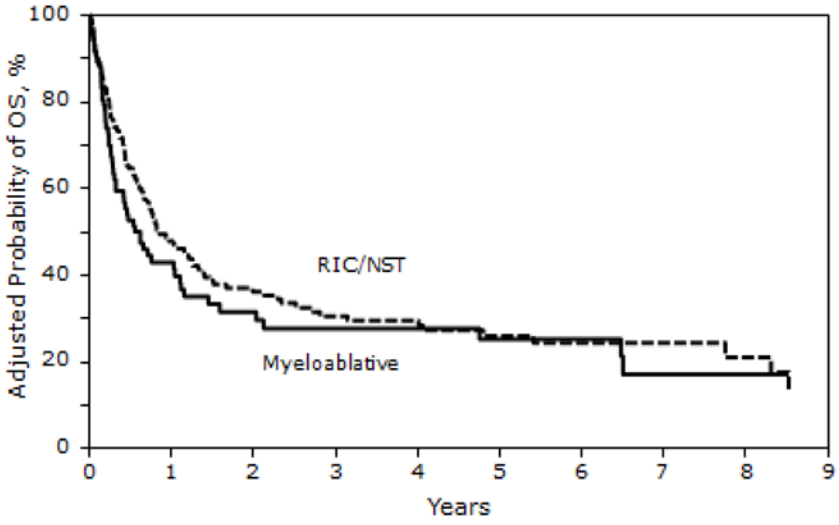

Figure 2.
Kaplan-Meier estimates of adjusted overall survival following allogeneic transplantation for mantle cell lymphoma

Table 1

Characteristics of refractory mantle cell lymphoma patients that underwent an allogeneic transplant reported to the CIBMTR between 1998 and 2010

Variable	Myeloablative	RIC/NST	P-value
Patient related:			
Number of patients	74	128	
Number of centers	28	63	
Age, median (range), years	54 (27–69)	59 (42–75)	<0.001
Male Sex	63 (85)	99 (77)	0.181
Karnofsky score, <90%	36 (49)	61 (48)	0.264
Disease related:			
Disease stage at diagnosis *			0.836
I–II	2 (11)	5 (8)	
III–IV	14 (78)	52 (84)	
Missing	*2 (11)*	*5 (8)*	
Extranodal involvement at any time prior to transplant *			0.616
No involvement	2 (11)	11 (18)	
Involvement	14 (78)	51 (82)	
Missing	*2 (11)*	*0*	
CNS involvement at any time prior to transplant *			0.467
No CNS	16 (89)	60 (97)	
CNS	0	2 (3)	
Missing	*2 (11)*	*0*	
Bulky disease *			0.414
<5 cm	3 (17)	12 (19)	
≥5 cm	3 (17)	19 (31)	
Missing	*12 (66)*	*31 (50)*	
Disease status prior to transplant			0.453
PIF-resistant	37 (50)	57 (45)	
REL-resistant	37 (50)	71 (55)	
Transplant related:			
Interval from diagnosis to transplant, months	15 (4–184)	29 (5–135)	0.001
Interval from autoHCT to alloHCT, months	32 (7–69)	22 (8–77)	0.501
Number of prior chemotherapy lines, median (range)	3 (2–5)	4 (1–5)	0.024
Rituximab prior to transplant *			0.013
Rituxan	11 (52)	52 (80)	
No Rituxan	10 (48)	13 (20)	
Conditioning regimens *			NA
CY/TBI	25 (53)	0	
BU/CY	13 (28)	0	
TBI Low dose <500cGY-single-	0	5 (7)	

Variable	Myeloablative	RIC/NST	P-value
TBI<800cGY-fract			
Fludarabine/Melphalan	0	23 (31)	
Fludarabine/BU	0	10 (13)	
TBI =200cGY	0	11 (15)	
Fludarabine+TBI=200cGY	0	15 (20)	
Fludarabine+CY	0	10 (13)	
TBI≥500cGY-single-	2 (4)	0	
TBI≥800cGY-fract			
BU>9 mg/kg	6 (13)	0	
BU+Melphalan	1 (2)	0	
CBV/Similar	0	1 (1)	
D-R sex match			0.351
M-M	30 (41)	61 (48)	
M-F	5 (7)	18 (14)	
F-M	25 (34)	36 (28)	
F-F	4 (5)	11 (9)	
Missing	*10 (14)*	*2 (2)*	
Graft type			0.719
Bone marrow	13 (18)	20 (16)	
Peripheral blood	61 (82)	108 (84)	
Type of donor *			<0.001
HLA-identical sibling	47 (64)	37 (29)	
Other relative	3 (4)	4 (3)	
URD well-matched	12 (16)	57 (45)	
URD partially matched	5 (7)	12 (9)	
URD mismatched	1 (1)	4 (3)	
URD degree of HLA match unknown	*6 (8)*	*14 (11)*	
Year of transplant			0.103
1998–2001	25 (34)	26 (20)	
2002–2005	22 (30)	44 (34)	
2006–2010	27 (36)	58 (45)	
GVHD prophylaxis			0.123
Ex vivo T-cell depletion	5 (7)	1 (1)	
Tacrolimus +/− others	32 (43)	67 (52)	
Cyclosporine +/− others	29 (39)	51 (40)	
CD34 selection	2 (3)	2 (2)	
Others-not specified	6 (8)	7 (5)	
Median FU of survivors (range), months	35 (3–124)	43 (4–96)	

Abbreviations: ATG = antithymocyte globulin; BU = busulfan; CMV = cytomegalovirus; CNS = central nervous system; CY = cyclophosphamide; D = donor; F = female; HLA-id = Human leukocyte antigen-identical; R = recipient; RIC = reduced intensity conditioning; NST = non-myeloablative; PIF = primary induction failure; REL = relapse; GVHD = graft-vs-host disease; M = male; MTX = methotrexate; TBI = total body irradiation; EVAL = evaluable; URD = unrelated donor.

*Research level patients only

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2014 April 01.

Table 2

Univariate analysis

	Myeloablative		RIC/NST		
Outcome event	**N**	**Prob (95% CI)**	**N**	**Prob (95% CI)**	**P-value***
Time to ANC>0.5 × 10^9/L	58		117		
@ 28 days		90 (78–95)		92 (85–96)	0.579
@ 100 days		90 (78–95)		94 (88–97)	0.343
Platelet recovery ≥ 20 × 10^9	39		91		
@ 28 days		72 (54–84)		80 (70–87)	0.337
@ 100 days		82 (66–91)		87 (78–92)	0.510
Acute GVHD (II-IV)	50		98		
@ 100 days		36 (23–50)		37 (28–46)	0.930
Chronic GVHD	49		105		
@ 1 year		35 (22–48)		43 (33–52)	0.347
@ 3 years		37 (24–51)		49 (39–58)	0.160
NRM	71		120		
@ 100 days		33 (23–45)		26 (18–34)	0.281
@ 1 year		43 (31–54)		38 (29–48)	0.561
@ 3 years		47 (35–59)		43 (34–53)	0.679
Relapse/Progression	71		120		
@ 1 year		26 (17–38)		24 (16–32)	0.664
@ 3 years		33 (22–45)		32 (23–41)	0.890
Progression free survival	71		120		
@ 1 year		31 (20–42)		38 (29–48)	0.316
@ 3 years		20 (11–32)		25 (17–34)	0.531
Overall survival	74		128		
@ 1 year		33 (22–44)		46 (37–54)	0.066
@ 3 years		25 (16–36)		30 (22–39)	0.455

Abbreviations: ANC = neutrophil recovery; NRM = non-relapse mortality; PFS = progression-free survival; PROB = probability; CI = confidence interval.

* Probabilities of neutrophil and platelet recovery, platelet recovery, acute GVHD, chronic GVHD, treatment-related mortality and progression/relapse were calculated using the cumulative incidence estimate. Progression-free survival and overall survival was calculated using the Kaplan-Meier product limit estimate.

Table 3

Causes of death

Cause of death	Myeloablative	RIC/NST
Total number	56	93
Graft rejection	2 (4)	1 (1)
Infection	8 (14)	11 (12)
Pulmonary syndrome	0	2 (2)
ARDS	0	1 (1)
GVHD	3 (5)	12 (13)
Primary disease	22 (39)	39 (42)
Organ failure	7 (13)	8 (9)
2nd malignancy	0	2 (2)
Hemorrhage	3 (5)	2 (2)
Accidental death	0	1 (1)
Vascular	0	1 (1)
Toxicity	2 (4)	3 (3)
Other cause-not specified *	9 (16)	10 (11)

* 6 cases reported “other HSCT related cause”

Abbreviations: ARDS=adult respiratory distress syndrome; GVHD=graft-versus-host disease.

Table 4

Studies reporting outcomes of allogeneic transplantation in (at least 30) mantle cell lymphoma patients

Author	No of patients	No with RD	Conditioning	RR (year)	NRM (year)	PFS (year)	OS (year)	PFS of RD patients (year)	OS of RD patients (year)
Maris (19)	33	13	NST	9%*(2yrs)	24%*(2yrs)	60%*(2yrs)	65%*(2yrs)	NR	NR
Tam (27)	35	6	NST	NR	9%*(1yr)	46%*(6yrs)	53%*(6yrs)	NR	NR
Cook (28)	70	12	RIC	65%*(5yrs)	21%*(5yrs)	37%*(5yrs)	14%*(5yrs)	0% (3yrs)	38% (3yrs)
Le Gouill (29)	70	15	RIC	NR	32%*(2yrs)	50%*(2yrs)	53%*(2yrs)	11% (2yrs)	31% (2yrs)
CIBMTR (current)	202	202	RIC/NST & MA	33–32% (3yrs)	43–47% (3yrs)	N/A	N/A	20–25% (3yrs)	25–30% (3yrs)

Abbreviations: MA=myeloablative; NRM=non-relapse mortality; N/A=not applicable; No=number; NR=not reported; NST; non-myeloablative conditioning; OS=overall survival, PFS=progression free survival; RD=refractory disease; RIC=reduced intensity conditioning; RR=relapse rate.

*data includes chemosensitive patients.