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## IMPACT OF PRETRANSPLANT CONDITIONING REGIMENS ON OUTCOMES OF ALLOGENEIC TRANSPLANTATION FOR CHEMOTHERAPY-UNRESPONSIVE DIFFUSE LARGE B-CELL LYMPHOMA AND GRADE-III FOLLICULAR LYMPHOMA

Mehdi Hamadani, MD<sup>1</sup>, Wael Saber, MD, MS<sup>2</sup>, Kwang Woo Ahn, PhD<sup>2</sup>, Jeanette Carreras, MPH<sup>2</sup>, Mitchell S. Cairo, MD<sup>3</sup>, Timothy S. Fenske, MD, MS<sup>4</sup>, Robert Peter Gale, MD, PhD<sup>5</sup>, John Gibson, MBBS, PhD<sup>6</sup>, Gregory A. Hale, MD<sup>7</sup>, Parameswaran N. Hari, MD, MS<sup>2</sup>, Jack W. Hsu, MD<sup>8</sup>, David J. Inwards, MD<sup>9</sup>, Rammurti T. Kamble, MD<sup>10</sup>, Anderas Klein, MD<sup>11</sup>, Dipnarine Maharaj, MD<sup>12</sup>, David I. Marks, MD, PhD<sup>13</sup>, David A. Rizzieri, MD<sup>14</sup>, Bipin N. Savani, MD<sup>15</sup>, Harry C. Schouten, MD, PhD<sup>16</sup>, Edmund K. Waller, MD, PhD<sup>17</sup>, Baldeep Wirk, MD<sup>8</sup>, Ginna G. Laport, MD<sup>18</sup>, Silvia Montoto, MD<sup>19</sup>, David G. Maloney, MD, PhD<sup>20</sup>, and Hillard M. Lazarus, MD

<sup>1</sup>West Virginia University Hospitals, Morgantown, WV

<sup>2</sup>Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI

<sup>3</sup>New York Presbyterian Hospital at Cornell, New York, NY

<sup>4</sup>Froedert Memorial Lutheran Hospital, Milwaukee, WI

<sup>5</sup>Imperial College, London, UNITED KINGDOM

<sup>6</sup>Royal Prince Alfred Hospital Institute of Haematology, Camperdown, AUSTRALIA

<sup>7</sup>All Children's Hospital, ST. Petersburg, FL

<sup>8</sup>Shands Healthcare and University of Florida, Gainesville, FL

<sup>9</sup>Mayo Clinic Rochester, Rochester, MN

<sup>10</sup>Baylor College of Medicine Center for Cell and Gene Therapy, Houston, TX

<sup>11</sup>Tufts Medical Center, Boston, MA

<sup>12</sup>Bethesda Health City, Boynton Beach, FL

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**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. .

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<sup>13</sup>Bristol Children's Hospital, Bristol, UNITED KINGDOM

<sup>14</sup>Duke University Medical Center, Pediatric Blood and Marrow Transplant, Durham, NC

<sup>15</sup>Vanderbilt University Medical Center, Brentwood, TN

<sup>16</sup>Academische Ziekenhuis Maastricht, Maastricht, NETHERLANDS

<sup>17</sup>Emory University Hospital, Atlanta, GA

<sup>18</sup>Stanford Hospital & Clinics, Stanford, CA

<sup>19</sup>Royal London Hospital Whitechapel, St. Bartholomew's, London, UNITED KINGDOM

<sup>20</sup>Fred Hutchinson Cancer Research Center, Seattle, WA; University Hospitals Case Medical Center, Cleveland, OH

## Abstract

Patients with chemorefractory non-Hodgkin lymphomas (NHL) generally have a poor prognosis. We used the observational database of the CIBMTR to study the outcome of 533 patients with refractory diffuse large B-cell lymphoma (DLBCL) or grade-III follicular lymphoma (FL-III) who underwent allogeneic transplantation (allo-HCT) using either myeloablative (MA; N=307) or reduced intensity/non-myeloablative conditioning (RIC/NST; N=226), between 1998-2010. We analyzed non-relapse mortality (NRM), relapse/progression, progression-free survival (PFS), and overall survival (OS). Only 45% of the patients at transplant had a Karnofsky performance score of 90%. Median follow-up of surviving patients after MA and RIC/NST allo-HCT is 35 months and 30 months, respectively. At 3years, MA allo-HCT was associated with a higher NRM compared to RIC/NST (53% vs. 42%; p=0.03), similar PFS (19% vs. 23%; p=0.40), and lower OS (19% vs. 28%; p=0.02), respectively. On multivariate analysis, FL-III histology was associated with lower NRM (relative-risk [RR]=0.52), reduced risk of relapse/progression (RR=0.42), superior PFS (RR=0.51) and OS (RR=0.53), while MA conditioning was associated with reduced risk of relapse/progression (RR=0.66). Despite a refractory state, a small subset of DLBCL and FL-III patients can attain durable remissions after allo-HCT. Conditioning regimen intensity was not associated with PFS and OS despite a higher risk of relapse/progression with RIC/NST allo-HCT.

## Keywords

DLBCL; grade III follicular lymphoma; allogeneic transplantation; refractory; relapsed; graft-versus-host disease

## INTRODUCTION

High dose chemo- and/or radiation-therapy and autologous hematopoietic cell transplantation (auto-HCT) is considered a standard therapy for patients with relapsed, chemosensitive diffuse large B-cell lymphoma (DLBCL), and appears to be curative for 40-45% of the patients [1-3]. However, the results of auto-HCT in the high-risk group of patients with relapsed aggressive non-Hodgkin lymphomas (NHL) with chemorefractory disease at the time of autografting have been uniformly disappointing. Allogeneic hematopoietic cell transplantation (allo-HCT) potentially is a curative modality for a variety of hematologic malignancies including indolent and aggressive lymphomas [4-7]. The advantages of an allo-HCT include a tumor-free graft, as well as an 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, aggressive NHL patients, especially the subgroup with chemosensitive disease, can achieve long-term remissions after allo-HCT [6,8-10]. Patients with aggressive NHL refractory to salvage chemotherapy, however, have a poor prognosis and there are only limited data available regarding the outcomes after allo-HCT for this extremely high-risk group. Moreover, the effects of regimen intensity, e.g. myeloablative (MA) conditioning versus reduced-intensity conditioning (RIC) or non-myeloablative conditioning (NST) regimens, are not known. We report herein the outcomes of allo-HCT in patients with chemorefractory, aggressive B-cell NHL 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 refractory, aggressive NHL patients undergoing allo-HCT.

## Subjects 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.

### Subjects

The study population included all patients with aggressive, chemo-refractory B-cell NHL receiving an allo-HCT reported to the CIBMTR between 1998 and 2010. Eligible histologies included WHO grade III follicular lymphoma (FL-III), and DLBCL. Subjects included in our analysis with primary refractory disease (i.e. the patients who never achieved a complete remission [CR] or partial remission [PR] in response to any of the pre-HCT therapies) at the time of allo-HCT were labeled as primary induction failure (PIF)-resistant, while the patients with chemorefractory disease at the time allo-HCT, following a relapse from a prior remission were labeled as relapsed (REL)-resistant. Patients with indolent histologies (including grade I-II FL), and ones with transformed large cell lymphomas were not

included. Patients with evidence of chemosensitive disease (i.e. patients achieving a CR or PR) in response to the last line of chemotherapy administered before 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 were categorized as MA or RIC/NST using established consensus criteria [11]. Previously established criteria for categorizing the degree of HLA matching were used [12] 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 [13]. Chronic GVHD was defined as the development of any evidence of chronic GVHD based on clinical criteria [14]. Neutrophil engraftment was defined as 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  $20 \times 10^9/L$  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 product limit estimate. Probabilities of NRM, lymphoma progression/relapse, acute and chronic GVHD, and engraftment were calculated using cumulative incidence curves to accommodate for competing risks. 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, histology (DLBCL vs. FL-III), disease status at allo-HCT, conditioning regimen intensity, 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, 533 patients received allo-HCT for refractory FL-III (n=80) and DLBCL (n=453); 307 patients received a MA allo-HCT and 226 received a RIC/NST allo-HCT. Twelve DLBCL patients in the MA cohort were included in a prior CIBMTR analysis [15]. Median follow up of survivors for the MA and the RIC/NST groups was 35 months and 30 months, respectively. Completeness of follow up at 3 years was 80% in both groups reflecting good follow up to this time point [16]. Table 1 describes patient-, disease- and transplant related variables of two cohorts (MA vs. RIC/NST) analyzed. The RIC/NST cohort was older compared with MA cohort (median age 53 years vs. 46 years,  $p < 0.001$ ). Only 242 patients (45%) had a pre-transplant KPS of 90 or higher. Median time from diagnosis to transplant was significantly longer in RIC/NST groups compared to MA cohort (24 months vs. 15 months,  $p\text{-value} < 0.001$ ).

No significant difference at baseline was observed between the two groups in terms of disease stage at diagnosis, B-symptoms, number of lines of prior therapy, bone marrow or extranodal involvement, disease bulk, central nervous system involvement, prior rituximab use, and donor type. Significantly more patients in the RIC/NST group had a prior history of undergoing an auto-HCT (38% vs. 15%;  $p\text{-value} < 0.001$ ) and received a peripheral blood allograft (88% vs. 79%;  $p\text{-value} = 0.008$ ). More patients in the MA group had primary refractory disease (PIF-resistant) (52% vs. 39%,  $p = 0.005$ ). The commonest conditioning regimens prior to MA allo-HCT were CY/TBI (cyclophosphamide/total body irradiation) and Bu (busulfan)/CY. The majority of the patients (~90%) in both cohorts received calcineurin inhibitor-based GVHD prophylaxis.

### Outcomes

Univariate analysis of patient outcomes after HCT is shown in Table 2, while multivariate analysis for NRM, relapse/progression, PFS and OS are summarized in Table 3.

### Engraftment and GVHD

The cumulative incidence of neutrophil engraftment at day +28 was 85% in the MA cohort and 90% in the RIC/NST cohort ( $p\text{-value} = 0.08$ ) (Table 2). The cumulative incidence of platelet recovery at day +28 was significantly higher after RIC/NST compared to MA conditioning (79% vs. 54%;  $p\text{-value} < 0.001$ ). Cumulative incidence of grade II-IV acute GVHD at day +100 was 29% and 31% in MA and RIC/NST groups ( $p\text{-value} = 0.68$ ), respectively (Table 2). Cumulative incidence of chronic GVHD at 1 year post transplantation in similar order was 33% and 38%, respectively ( $p\text{-value} = 0.27$ ).

### Non relapse mortality

Cumulative incidence of NRM was significantly lower in RIC/NST cohort vs. MA cohort, both at 100 days (RIC/NST 25% [95% CI 20-31] vs. MA 38% [95% CI 32-43],  $P\text{-value} = 0.004$ ) and at 3 years (RIC/NST 42% [95% CI 35-49] vs. MA 53% [95% CI 46-59],  $P\text{-value} = 0.03$ ) However, on multivariate analysis conditioning regimen intensity was no



longer associated with NRM (MA vs. RIC/NST, RR 1.25, 95% CI 0.94-1.65) (Table 3). FL-III histology (RR=0.52, 95% CI 0.35-0.79; p-value=0.002) and matched related donor (MRD) allo-HCT (RR=0.64, 95% CI 0.48-0.86; p-value=0.003) were associated with a reduced risk of NRM in multivariate analysis. Separate multivariate analysis for patients previously not undergoing an auto-HCT similarly showed reduced risk of NRM with FL-III (RR 0.44, 95% CI 0.27-0.74) and MRD transplantation (RR 0.72, 95% CI 0.51-1.00). Multivariate analysis of DLBCL patients only (by excluding FL-III) also showed association of MRD with reduced risk of NRM (RR=0.65, 95% CI 0.48-0.89).

### 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 28% in the MA cohort (95% CI 23-34) and 35% (95% CI 28-42) in the RIC/NST cohort (p-value=0.12). On multivariate analysis, MA conditioning (RR=0.66, 95% CI 0.47-0.92; p-value=0.02), FL-III histology (RR=0.42, 95% CI 0.25-0.73; p-value=0.002) and a prior auto-HCT more than 12 months before the allo-HCT compared to no prior auto-HCT (RR=0.30, 95% CI 0.15-0.63; p-value=0.001) were associated with a reduced risk of relapse/progression (Table 3). Separate multivariate analysis for patients previously not undergoing an auto-HCT similarly showed reduced risk of relapse/progression with FL-III (RR=0.39, p-value=0.002). Multivariate analysis of DLBCL patients only, showed an association of a prior auto-HCT more than 12 months before the allo-HCT, with reduced risk of relapse/progression (RR=0.27, p-value=0.002).

### Progression free survival

PFS estimates were not significantly different between MA and RIC/NST groups, neither at one year (26% [95% CI 20-31] vs. 32% [95% CI 25-38], p=0.13) nor at three years (19% [95% CI 15-25] vs. 23% [95% CI 17-30], p=0.40) (Figure 1 and Table 2). On multivariate analysis, FL-III (RR=0.51, 95% CI 0.37-0.70; p-value<0.0001) was associated with a superior PFS compared to DLBCL (Table 3). Separate multivariate analysis for patients previously not undergoing an auto-HCT also showed that only FL-III was associated with superior PFS (RR=0.43, p-value<0.0001), while in the multivariate analysis for DLBCL patients only, none of the variables were significant.

### Overall survival

In univariate analysis, RIC/NST group had superior OS at one year (41% [95% CI 34-47] vs. 31% [95% CI 25-36], p=0.01) and at three years (28% [95% CI 22-35] vs. 19% [95% CI 15-24], p=0.02) compared to the MA group (Table 2). On multivariate analysis only FL-III (RR=0.53, 95% CI 0.39-0.72; p-value<0.0001) was associated with a reduced risk of death after allo-HCT (Figure 1 and Table 3). Separate multivariate analysis for patients previously not undergoing an auto-HCT also showed that only FL-III was associated with reduced risk of death (RR=0.40, p-value<0.0001), while in the multivariate analysis for DLBCL patients only, none of the variables were significant.

### Causes of death

The majority of deaths, 104 in the MA cohort and 77 in the RIC/NST cohort, were attributed to disease relapse and/or progression. Causes of death are summarized in Table 4.

## DISCUSSION

The aims of the present study were to define outcomes of chemorefractory DLBCL and FL-III 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

aggressive lymphoma patients gleaned from multiple centers provides several important observations. First, despite refractory disease at baseline, approximately a quarter of aggressive NHL patients undergoing allo-HCT are alive and in remission three years post transplantation. Second, although use of MA allo-HCT in this poor prognosis group reduced the relapse risk, OS (on univariate analysis) was inferior likely due to the unacceptably high rates of NRM. Third, histologic subtype emerges as a major predictor of transplantation outcomes, with refractory FL-III consistently showing better outcomes compared to DLBCL; this finding emphasizes the importance of different disease biology of these subtypes. Fourth, high NRM rates after allo-HCT in this high-risk group will continue to be the main barrier towards wider application of this modality.

There is limited published data on the role of allo-HCT in patients with refractory aggressive B-cell NHL. Registry data from EBMT (European Group for Blood and Bone Marrow Transplantation) on outcomes of RIC allo-HCT in patients with NHL (including indolent and aggressive histologies) identified aggressive histology and chemorefractory disease as predictors of inferior outcomes, but included only 13 refractory aggressive lymphoma patients [17]. French [10] and Japanese [8] registry data reported OS rates of ~40% with allografting in aggressive NHL, but these studies included a small number of patients with refractory disease (n=27 in French study and number of B-cell aggressive NHL not reported in Japanese study), whose outcomes were not reported separately. Further, a single institution reported 5 year survival rates of approximately 35% in 46 refractory aggressive NHL patients undergoing allo-HCT; most of these subjects received MA conditioning [18]. Finally, a retrospective analysis from United Kingdom of 17 refractory DLBCL patients receiving RIC allo-HCT showed a disappointing 3 year OS/PFS of only 12% [7]. Our study, the largest report to date, indicates that a small subset of refractory FL-III/DLBCL patients (~25%) can survive long-term post allo-HCT. It is however; important to interpret these numbers in the context of dismal long-term prognosis of these patients with standard chemotherapies, and in light of the fact, that only a minority of patients in our study at transplant had good KPS.

Despite the reduced risk of relapse/progression, we note that MA allo-HCT was not associated with improved survival outcomes, potentially due to high NRM rate of 53% at 3 years. Our report is not 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' or primary-refractory disease. Time interval between diagnosis and allo-HCT was shorter in the MA cohort, compared to RIC/NST cohort, which might be a surrogate marker of more aggressive disease biology of patients included in the former group. However, the distribution of other potentially adverse prognostic factors, e.g. bulky disease, bone marrow involvement, extranodal disease, and lines of prior therapy across these two cohorts, appear balanced at baseline in our study. Hematologic engraftment in RIC/NST cohort appears more robust, likely reflecting more frequent use of peripheral blood rather than bone marrow as an allogeneic graft source in this setting. Our data indicate that in patients with aggressive B-cell NHL who are refractory to conventional therapies, escalating the intensity of conditioning regimens is unlikely to improve patient outcomes. The RIC/NST group in our study is heterogeneous and represents a spectrum of conditioning regimens ranging from truly NST approaches to nearly ablative regimens. However, the relatively small number of patients receiving a truly NST allo-HCT (2Gy-TBI=14, fludarabine/2Gy-TBI=9) in our study, precludes us from assessing the relative risk and benefits of NST versus RIC allo-HCT in refractory B-cell NHL.

The NRM rates we observed for the RIC/NST cohort are higher than the rates generally reported for indolent lymphomas [19,20]; however, in the subset of chemorefractory

indolent lymphomas NRM rates approaching 50-60% have been previously reported [21,22]. One-third of the RIC/NST patients in our study previously received an auto-HCT, a potential reason for high NRM. On multivariate analysis, however, a prior auto-HCT was not associated with higher NRM, and other investigators also have not consistently found a prior auto-HCT to significantly influence NRM after the allogeneic procedure in DLBCL [6,7]. Moreover separate multivariable analyses in our study performed by excluding patients who underwent prior auto-HCT, showed findings in line with the multivariable analyses of entire study population. Nonetheless it is clear that mitigating NRM rates via development of novel conditioning approaches in this high-risk group, designed to provide better disease control and acceptable NRM rates, while permitting the GVL effect to emerge post transplantation, are urgently needed. Along these lines Gopal et al. [23] 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 [24]. Our data also hint that in the context of refractory lymphoma patients, availability of a MRD might be predictive of reduced rates NRM post allo-HCT.

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 DLBCL and FL-III patients. Missing variables in registration-level patients include disease stage at diagnosis, bulky disease status, B-symptoms, LDH level, bone marrow involvement, and extranodal involvement at *any* time point before allo-HCT. While some of these variables (e.g. LDH level before allo-HCT) are prognostic [9,25], 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 patients is not known. The fact that data about key variables of interest, such as; disease status at transplantation, intensity of conditioning regimens, donor type, graft source, KPS, history of prior autografting and all post-transplantation outcomes of interest (engraftment, GVHD, NRM, OS, PFS etc.) were available on both registration- and research-level patients, supported our decision to include both patient populations. Another possible limitation of our report is the lack of information about functional imaging (i.e. PET or PET/CT scan results) before allo-HCT. Some of the patients included in this study were transplanted in the pre PET-era. Even in patients transplanted in the time period when PET scans became widely available; this imaging modality was likely not uniformly performed in all patients before allo-HCT. Moreover, information about functional imaging is not available for registration-level patients, and the criteria used to uniformly report and interpret response rates using PET scans were not purposed until 2007 [26]. However; wherever available, patients with a negative PET scan before allo-HCT are considered chemosensitive for CIBMTR reporting purposes and were not included in the current study.

A noteworthy finding of our study is the relatively encouraging outcomes of FL-III patients after allo-HCT despite refractory disease. The 3 year PFS of FL-III patients in our study after MA and RIC/NST was 41% and 40% respectively (Figure 2). The 3 year OS in similar order was 42% and 51% respectively. Vose and colleagues [27] previously have reported that this population is not likely to achieve long-term remissions with auto-HCT. We decided to include FL-III patients in addition to DLBCL in our report, to highlight the fact that while these patients may not achieve durable remissions with auto-HCT, this is not necessarily true following allo-HCT. Our encouraging data support examining the role of allo-HCT in refractory FL-III, prospectively. Whether the outcomes of refractory grade IIIa FL are different from grade IIIb FL following allo-HCT is not known. This data is unfortunately not captured in CIBMTR reporting forms. RIC/NST allo-HCT in aggressive histologies has been associated with a higher risk of relapse compared to more indolent varieties [9]. Within the context of refractory aggressive histologies, the lower relapse rates



of FL-III compared to DLBCL is intriguing and illustrates the different disease biologies of these two subtypes.

In order to utilize our data for decision making in the *clinic*, it is important to interpret these results in the context of outcomes of relapsed DLBCL with other available treatment modalities. In general consolidation with auto-HCT clearly remains the standard option for relapsed and chemosensitive DLBCL, even in the chemoimmunotherapy (CIT)-era [3]. For those DLBCL patients, who relapse following an auto-HCT but remain sensitive to salvage chemotherapies, RIC/NST allo-HCT is routinely offered by many centers based on encouraging outcomes (OS, 45%-50%; PFS, 35%-45%) reported by many groups [5-7,28]. The best therapeutic option for chemorefractory DLBCL patients is more controversial. In the pre CIT-era, van Besien et al [29] initially showed that a small subset of such refractory aggressive NHL patients (~20%) could survive disease-free post allo-HCT. Observations by others [30]; however, suggested that a similar degree of disease control in refractory DLBCL patients could potentially be achieved with auto-HCT (3year PFS=19.4%). It is however important to point out that the outcomes of chemorefractory DLBCL following auto-HCT in a large CIBMTR study were disappointing; with only seven of 52 chemotherapy-resistant patients (13%) surviving disease-free 2 years post HCT [31]. Similarly the outcomes of chemorefractory DLBCL patients in the CIT-era with [3,32], or without [3] auto-HCT have been generally poor (3 year PFS <10-15%). In contrast, the 20-25% 3 year PFS of refractory aggressive NHL patients in our study, has been consistently seen in other reports that included a small subset of refractory patients [7,15,33]. Hence it appears unlikely that in the CIT-era, salvage chemotherapies with or without auto-HCT can provide durable disease control in refractory DLBCL. For such refractory DLBCL patients, especially for the subset with an available MRD consideration of a RIC/NST allo-HCT should be considered a valid option.

In conclusion, our analysis of this large set of registry data show that a subset of chemorefractory FL-III/DLBCL patients can have durable remissions after allo-HCT. MA conditioning does not provide superior survival outcomes, compared to RIC/NST allo-HCT. While refractory, aggressive NHL patients are best managed on a clinical trial, in the absence of a protocol therapy option, consideration of an allograft appears to be a viable option for NHL patients who have disease refractory to conventional therapies.

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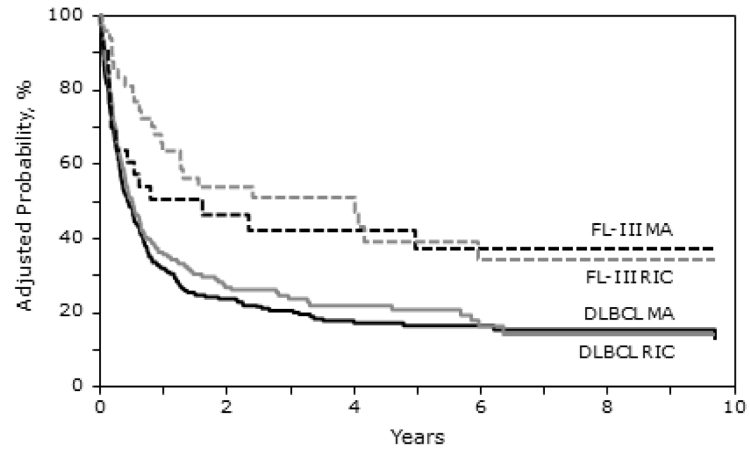
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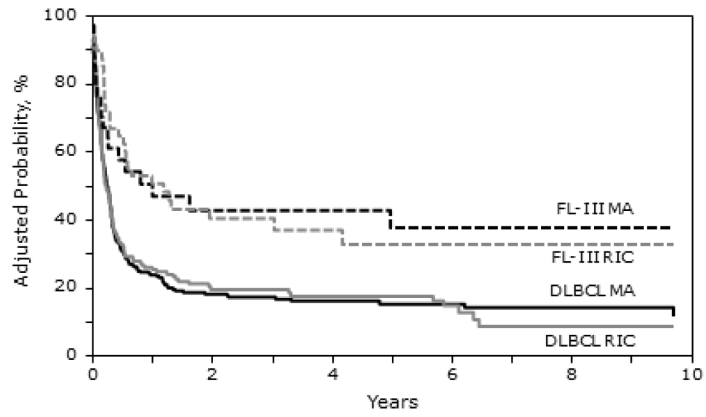
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**Figure 1.** Kaplan-Meier estimates of adjusted overall survival following allogeneic transplantation for FL-III and DLBCL





**Figure 2.** Kaplan-Meier estimates of adjusted progression free survival following allogeneic transplantation for FL-III and DLBCL

**Table 1**

Characteristics of patients that underwent an allogeneic transplant for chemorefractory aggressive FL-III and DLBCL reported to the CIBMTR between 1998 and 2010

Variable	Myeloablative	RIC/NST	P-value
Number of patients	307	226	
Number of centers	85	59	
Age, median (range), years	46 (19-66)	53 (20-70)	<0.001
Sex			0.293
Male	185 (60)	126 (56)	
Karnofsky score			0.590
<90%	156 (51)	135 (60)	
Histology			0.001
Follicular Lymphoma (grade 3)	32 (10)	48 (21)	
DLBCL	275 (90)	178 (79)	
Prior auto-HCT	48 (15)	86 (38)	<0.001
Interval from auto-HCT to allo-HCT, months	13 (6-136)	17 (6-198)	0.149
Interval from diagnosis to transplant, months	15 (1-238)	24 (5-340)	<0.001
Disease stage at diagnosis*			0.940
I-II	30 (34)	33 (34)	
III-IV	54 (62)	58 (60)	
Missing	3 (4)	6 (6)	
B-symptoms at any time prior to transplant*			0.424
A	41 (47)	50 (52)	
B	34 (39)	32 (33)	
Missing	12 (14)	15 (15)	
LDH at any time prior to transplant*			0.986
Normal	32 (37)	34 (35)	
Abnormal	53 (61)	56 (58)	
Unknown	2 (2)	7 (7)	
Number of prior chemotherapy lines, median (range)	3 (1-5)	4 (1-5)	0.253
Bone marrow involvement at any time prior to transplant*			0.900
No BM involvement	46 (53)	46 (47)	
BM involvement	21 (24)	22 (23)	
Missing	20 (23)	29 (30)	
Extranodal involvement at any time prior to transplant*			0.507
No involvement	19 (22)	25 (26)	
Involvement	68 (78)	71 (73)	
Missing	0	1 (1)	
Conditioning regimens*			NA
CY/TBI	103 (50)	0	
BU/CY	65 (31)	0	

Variable	Myeloablative	RIC/NST	P-value
TBI Low dose <500cGY-single-TBI<800cGY-fract	0	7 (6)	
Fludarabine/Melphalan	0	30 (28)	
Fludarabine/BU	0	21 (19)	
TBI =200cGY	0	14 (13)	
Fludarabine+TBI=200cGY	0	9 (8)	
Fludarabine+CY	0	17 (16)	
Fludarabine +Ara-C+ida	0	1 (1)	
TBI 500cGY-single-TBI 800cGY-fract	17 (8)	0	
Melphalan>150 mg/m <sup>2</sup>	7 (3)	0	
BU>9 mg/kg	11 (5)	0	
BU+Melphalan	5 (3)	0	
CBV/Similar	0	10 (9)	
CNS involvement at any time prior to transplant *			0.381
No CNS	84 (97)	90 (93)	
CNS	3 (3)	6 (6)	
Missing	0	1 (1)	
Bulky disease *			0.571
<5 cm	18 (21)	22 (23)	
5 cm	26 (30)	25 (26)	
Missing	43 (49)	50 (51)	
Radiation prior to transplant *			0.244
No	20 (23)	19 (20)	
Yes	32 (37)	48 (49)	
Missing	35 (40)	30 (31)	
Rituximab prior to transplant *			0.122
Rituximab	57 (59)	80 (70)	
No rituximab	39 (41)	35 (30)	
Disease status			0.005
PIF-resistant	159 (52)	89 (39)	
REL-resistant	148 (48)	137 (61)	
Graft type			0.008
Bone marrow	65 (21)	28 (12)	
Peripheral blood	242 (79)	198 (88)	
Type of donor *			0.090
HLA-id sibling	162 (60)	94 (47)	
Other relative	16 (6)	13 (7)	
URD well-matched	64 (23)	62 (31)	
URD partially matched	20 (7)	23 (12)	
URD mismatched	10 (4)	8 (4)	
Year of transplant			0.002
1998-2001	86 (28)	35 (15)	

Variable	Myeloablative	RIC/NST	P-value
2002-2005	88 (29)	82 (36)	
2006-2010	133 (43)	109 (48)	
ATG*			<0.001
ATG alone	12 (14)	24 (25)	
Alemtuzumab alone	0	13 (14)	
No ATG or alemtuzumab	75 (26)	59 (61)	
GVHD prophylaxis			0.107
Ex vivo T-cell depletion	10 (3)	3 (1)	
Tacrolimus +/- others	168 (55)	119 (53)	
Cyclosporine +/- others	105 (34)	88 (39)	
CD34 selection	6 (2)	0	
Others-not specified	18 (6)	16 (7)	
Median FU of survivors (range), months	35 (3-122)	30 (3-110)	

**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

**Table 2**

## Univariate outcome probabilities

Outcome event	Myeloablative		RIC/NST		P-value*
	N	Prob (95% CI)	N	Prob (95% CI)	
Time to ANC > 0.5 × 10 <sup>9</sup> /L	245		189		
@ 28 days		85 (80-89)		90 (85-94)	0.085
@ 100 days		86 (81-90)		92 (87-95)	0.047
Platelet recovery 20 × 10 <sup>9</sup>	171		146		
@ 28 days		54 (46-61)		79 (71-85)	<0.001
@ 100 days		71 (63-77)		87 (80-92)	<0.001
Acute GVHD (II-IV)	225		183		
@ 100 days		29 (24-35)		31 (25-38)	0.684
Chronic GVHD	229		179		
@ 1 year		33 (27-39)		38 (31-45)	0.274
@ 3 years		37 (31-43)		39 (32-46)	0.619
NRM	289		218		
@ 100 days		38 (32-43)		25 (20-31)	0.004
@ 1 year		47 (41-53)		36 (30-43)	0.017
@ 3 years		53 (46-59)		42 (35-49)	0.034
Relapse/Progression	289		218		
@ 1 year		27 (22-33)		32 (26-39)	0.289
@ 3 years		28 (23-34)		35 (28-42)	0.124
Progression free survival	289		218		
@ 1 year		26 (20-31)		32 (25-38)	0.138
@ 3 years		19 (15-25)		23 (17-30)	0.408
Overall survival	307		226		
@ 1 year		31 (25-36)		41 (34-47)	0.016
@ 3 years		19 (15-24)		28 (22-35)	0.027

**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**

Multivariate analysis for NRM, progression/relapse, progression free survival and overall survival (*follicular/DLBCL*)

Variables	N	RR (95% CI)	P-value	
<b>TRM</b>				
Main effect				
RIC/NST	202	1	0.113	
Myeloablative	264	1.25 (0.95-1.66)		
Histology				
DLBL	393	1	0.002	
follicular	73	0.52 (0.35-0.79)		
Donor type				
Unrelated	217	1	0.003	
Related	249	0.64 (0.48-0.86)		
<b>Progression/relapse</b>				
Main effect				
RIC/NST	202	1	0.015	
Myeloablative	264	0.66 (0.47-0.92)		
Histology				
DLBL	393	1	0.002	
follicular	73	0.42 (0.25-0.73)		
Prior autologous transplant				
No prior auto	365	1	P <sub>overall</sub> =0.006	
Prior auto, 12 m	39	0.90 (0.49-1.65)		0.742
Prior auto, >12 m	62	0.30 (0.15-0.63)		0.001
<i>Contrast: 12 vs. &gt;12</i>		2.99 (1.22-7.35)		0.017
<b>Progression free survival</b>				
Main effect				
RIC/NST	202	1	0.843	
Myeloablative	264	1.02 (0.83-1.27)		
Histology				
DLBL	393	1	<0.001	
follicular	73	0.51 (0.37-0.70)		
<b>Overall survival</b>				
Main effect				
RIC/NST	226	1	0.220	
Myeloablative	307	1.14 (0.93-1.40)		
Histology				
DLBL	453	1	<0.001	
follicular	80	0.53 (0.39-0.72)		

**Table 4**

## Causes of death

Cause of death	Myeloablative	RIC/NST
Total number	241	162
Graft rejection	0	1 (1)
Infection	31 (13)	18 (11)
Pulmonary syndrome	4 (2)	4 (2)
ARDS	6 (2)	0
GVHD	13 (5)	14 (9)
Primary disease	104 (43)	77 (48)
Organ failure	26 (11)	11 (7)
Second malignancy	1 (<1)	0
Hemorrhage	4 (2)	2 (1)
Vascular	1 (<1)	1 (1)
Toxicity	5 (2)	1 (1)
Other cause-not specified*	46 (19)	33 (20)

\* 29 cases reported "other HSCT related cause"

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