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Allogeneic transplantation provides durable remission in a subset of DLBCL patients relapsing after autologous transplantation

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Summary

For diffuse large B-cell lymphoma (DLBCL) patients progressing after autologous haematopoietic cell transplantation (autoHCT), allogeneic HCT (alloHCT) is often considered, although limited information is available to guide patient selection. Using the Center for International Blood and Marrow Transplant Research (CIBMTR) database, we identified 503 patients who underwent alloHCT after disease progression/relapse following a prior autoHCT. The 3-year probabilities of non-relapse mortality, progression/relapse, progression-free survival (PFS) and overall survival (OS) were 30, 38, 31 and 37% respectively. Factors associated with inferior PFS on multivariate analysis included Karnofsky performance status (KPS) <80, chemoresistance, autoHCT to alloHCT interval <1-year and myeloablative conditioning. Factors associated with worse OS on multivariate analysis included KPS<80, chemoresistance and myeloablative conditioning. Three adverse prognostic factors were used to construct a prognostic model for PFS, including KPS<80 (4 points), autoHCT to alloHCT interval <1-year (2 points) and chemoresistant disease at alloHCT (5 points). This CIBMTR prognostic model classified patients into four groups: low-risk (0 points), intermediate-risk (2-5 points), high-risk (6-9 points) or very high-risk (11 points), predicting 3-year PFS of 40, 32, 11 and 6%, respectively, with 3-year OS probabilities of 43, 39, 19 and 11% respectively. In conclusion, the CIBMTR prognostic model identifies a subgroup of DLBCL patients experiencing long-term survival with alloHCT after a failed prior autoHCT.

Keywords: DLBCL, prognostic score, allogeneic transplantation, prior autologous transplan.

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Diffuse large B-cell lymphoma (DLBCL) accounts for 30% of non-Hodgkin lymphoma (NHL) cases diagnosed in the United States annually. Following the incorporation of rituximab into treatment regimens, approximately 60% of DLBCL

cases are now cured with frontline therapy. Despite overall improvements in the outcomes of DLBCL, about 30-40% of patients develop relapsed or refractory disease. Autologous haematopoietic cell transplantation (autoHCT) became the standard-of-care for chemosensitive relapsed or refractory DLBCL after the PARMA trial showed a benefit for autoHCT over conventional second-line therapy (Philip *et al*, 1995). More recently, the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study provided important information regarding outcomes of relapsed or refractory DLBCL in the rituximabera. In this study, 53% of patients who underwent an autoHCT were event-free at 3-years (Gisselbrecht *et al*, 2010). Contemporary registry data confirm these observations, reporting 3-year progression-free survival (PFS) rates of 45–50% following autoHCT (Fenske *et al*, 2009; Mounier *et al*, 2012; Hamadani *et al*, 2014). These data underscore the fact that a significant subset of DLBCL patients who undergo autoHCT will eventually relapse.

The prognosis for patients with recurrent disease following autoHCT is poor, with no consensus on the optimal therapy. There is evidence to support a graft-versus-lymphoma (GVL) effect in DLBCL (Bishop *et al*, 2008; Rezvani *et al*, 2008; Hamadani *et al*, 2013), and an allogeneic (allo-) HCT is generally considered to be the only potentially curative option for DLBCL patients who relapse after an autoHCT. (Thomson *et al*, 2009; Sirvent *et al*, 2010; Bacher *et al*, 2012; Hamadani *et al*, 2013; Klyuchnikov *et al*, 2014). However, the literature is limited regarding the outcomes of alloHCT, specifically in DLBCL patients who have relapsed after an autoHCT.

With many patients undergoing autoHCT for DLBCL each year, and with approximately 40-50% of those transplants ultimately failing, the decision of whether to pursue an alloHCT for a DLBCL patient who has progressed after an autoHCT is, unfortunately, a common clinical dilemma. No prognostic models are currently available to counsel such patients regarding their expected survival outcomes following alloHCT. We therefore sought to develop a prognostic model for DLBCL patients undergoing allografting after a failed prior autoHCT, utilizing clinical factors readily available immediately before alloHCT.

Materials and methods

Data sources

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a working group of more than 500 transplantation centres worldwide that contribute detailed data on HCT to a statistical centre at the Medical College of Wisconsin. Participating centres are required to report all transplantations consecutively; patients are followed longitudinally and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data and on-site audits of participating centres ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants.

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-HCT disease stage and chemotherapy-responsiveness, date of diagnosis, graft type (bone marrow- and/or blood-derived stem cells), conditioning regimen, post-transplant disease progression and survival, development of a new malignancy and cause of death. All CIBMTR centres 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 6 months post-HCT and annually thereafter or until death. Data for the current analysis were retrieved from CIBMTR (TED and CRF) report forms.

Patients

Adult (≥18 years) patients with relapsed/refractory DLBCL, undergoing alloHCT between 2000 and 2012 after experiencing a relapse or progression following a prior autoHCT were included in this study. Eligible donors included human leucocyte antigen (HLA)-identical siblings or adult unrelated donors (URD). Patients undergoing syngeneic or alternative donor HCT (e.g. umbilical cord blood or haploidentical) and those receiving *ex vivo* graft manipulation (T-cell depleted or CD34 selected grafts) were not included in the analysis. Patients undergoing a planned tandem auto-alloHCT ($n = 98$) were not eligible. Patients receiving the prior autoHCT for indications other than DLBCL ($n = 275$) were not included. Similarly, patients undergoing a post-autoHCT, allograft for indications other than relapsed or refractory DLBCL (e.g. graft failure, indolent NHL, therapy-related haematological malignancies etc.) were excluded.

Definitions

The intensity of alloHCT conditioning regimens was categorized as myeloablative or reduced intensity conditioning/non-myeloablative conditioning (RIC/NMA) using consensus criteria (Bacigalupo *et al*, 2009). Previously established criteria for categorizing the degree of HLA matching were used for URDs (Weisdorf *et al*, 2008). Complete remission (CR) to last therapy line before HCT on CIBMTR forms is defined as complete resolution of all known areas of disease on radiographic [computerized axial tomography (CAT) scan) assessments, while partial remission (PR) is defined as ≥50% reduction in the greatest diameter of all sites of known disease and no new sites of disease. Resistant disease is defined as <50% reduction in the diameter of all disease sites, or development of new disease sites.

Study endpoints

Primary outcomes were non-relapse mortality (NRM), progression/relapse, PFS and overall survival (OS). NRM was defined as 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. 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. Acute (Przepiorka *et al*, 1995) and chronic (Shulman *et al*, 1980) graft-versus-host disease (GVHD) was defined and graded using established criteria. Neutrophil recovery was defined as the first of 3 successive days with absolute neutrophil count (ANC) $\geq 0{\cdot}5 \times 10^9$/l after post-transplantation nadir. Platelet recovery 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 neutrophil and platelet recovery, death without the event was considered a competing risk.

Statistical analysis

Probabilities of PFS and OS were calculated as described previously (Zhang *et al*, 2007). Cumulative incidence of NRM, lymphoma progression/relapse and haematopoietic recovery were calculated to accommodate for competing risks (Zhang & Zhang, 2011). Associations among patient-, disease- and transplantation-related variables and outcomes of interest were evaluated using Cox proportional hazards regression. Backward elimination was used to identify covariates that influenced outcomes. Covariates with a $P < 0{\cdot}05$ were considered significant. The proportional hazards 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 added as time-dependent covariates in the Cox regression model. Interactions between the main effect and significant covariates were examined. Results are expressed as hazard ratio (HR). The variables considered in multivariate analysis are shown in Table SI. To evaluate the impact of GVHD on transplantation outcomes, multivariate analyses were performed using Cox proportional hazards models, where the main-effect variable was defined as the time-dependent occurrence of acute grade II–IV GVHD or chronic GVHD versus neither. Each step of model building included the main-effect. Factors with a $P < 0{\cdot}05$ were kept in the final model. The potential interactions between the main effect and all significant risk factors were tested. All statistical analyses were performed using SAS version 9·3 (SAS Institute, Cary, NC, USA).

Prognostic model for PFS

To develop a prognostic model able to predict PFS of DLBCL patients undergoing an alloHCT after a failed prior autoHCT, a Cox regression method was used to identify potential patient- and disease-related risk factors associated with treatment failure (failure event of PFS), using backward elimination with $P < 0{\cdot}05$ to enter and remove factors from the model. The results were then confirmed using a stepwise selection procedure and a forward selection. The risk factors considered in the model-building procedure are shown in Table S1. Risk scores between 0 and 5 were assigned based on the ratios of log HRs. The risk scores were then plotted using the Kaplan–Meier (KM) curves and fitted in the Cox proportional hazards model to classify risk scores into different risk groups based on their distribution of the KM curves and HRs of the Cox model. PFS probabilities of the developed risk groups were calculated using the KM estimates.

Results

Patient characteristics

Between 2000 and 2012, 503 DLBCL patients undergoing an alloHCT after experiencing disease relapse or progression following a prior autoHCT were reported to the CIBMTR. Patient characteristics are described in Table I. Briefly, median age at alloHCT was 52 years, with the majority of patients being Caucasian/white (88%). Fifty-four per cent had advanced stage disease at diagnosis and at the time of alloHCT, 10% had bulky disease and 32% had extranodal involvement. The median number of prior therapies before alloHCT was 4. Prior to alloHCT, 74% had chemosensitive disease. RIC/NMA conditioning regimens were used in 376 subjects (75%) and peripheral blood was the most common graft source (91%). Donors were balanced between related (50%) and unrelated (50%). Median **t**ime **i**nterval **b**etween **a**utoHCT and **a**lloHCT (TIBAA) was 15 months.

Univariate outcomes

The probabilities of neutrophil recovery at day 28 and at day 100 were 94% (95% confidence interval; [CI]: 92-96) and 96% (95% CI: 94-98), respectively. The probabilities of platelet recovery at day 28 and day 100 were 83% (95% CI: 78-86) and 89% (95% CI: 86-92), respectively (Table II). The cumulative incidence of grade II-IV acute GVHD at day +100 was 36% (95% CI = 28-44) and chronic GVHD at 1 year was 40% (95% CI = 35-44).

Median follow-up of survivors was 55 months (range 11-49). The probabilities of NRM at 1, 3 and 5 years were 23% (95% CI: 19-27), 30% (95% CI: 26-34) and 31% (95% CI: 27-36), respectively (Fig 1A). The probabilities of disease progression/relapse at 1, 3 and 5 years were 33% (95% CI: 29-37), 38% (95% CI: 34-43) and 40% (95% CI: 36-45) (Fig 1B). The probabilities of PFS at 1, 3 and 5 years were 44% (95% CI: 40-48), 31% (95% CI: 27-36) and 29% (95% CI: 24-33), respectively (Fig 1C), and those for OS were 54%

Table I. Characteristics of patients who underwent an allogeneic transplant after a failed autologous transplant for DLBCL from 2000–2012 reported to the CIBMTR. (Italicized text indicates variables available in CRF-level data patients).

Number of patients	503
Number of CRF-level data patients	155
Number of centres	133
Median age at transplant, years (range)	52 (19–72)
Male gender	305 (61)
Race	
Caucasian/White	444 (88)
Black	17 (3)
Others*	33 (7)
Missing	9 (2)
Karnofsky performance score	
80–100%	393 (78)
<80%	52 (10)
Missing	58 (12)
Stage III/IV at Diagnosis	*83 (54)*
Remission status at HCT	
Complete remission	175 (35)
Partial remission	197 (39)
Chemorefractory	106 (21)
Untreated	12 (2)
Unknown	13 (3)
Rituximab prior to HCT	*112 (72)*
Radiation therapy prior to HCT	*98 (63)*
Lines of therapy prior to alloHCT	
Median (range)	*4 (1–7)*
History of transformation from indolent histology	*25 (16)*
Elevated lactate dehydrogenase at HCT	*52 (34)*
Active extranodal disease at HCT	49 (32)
Bone marrow involvement at HCT	
No bone marrow involvement	*141 (91)*
Bone marrow involvement	*7 (5)*
Missing	*7 (5)*
Bulky Disease (>5 cm) at HCT	15 (10)
Conditioning regimen intensity	
Myeloablative	127 (25)
Reduced intensity conditioning	376 (75)
TBI in conditioning regimens	
Myeloablative doses of TBI	41 (8)
Graft type	
Bone marrow	47 (9)
Peripheral Blood	456 (91)
Type of donor	
HLA-identical sibling	253 (50)
Unrelated well-matched	118 (23)
Unrelated partially matched	132 (26)
Donor-Recipient CMV status	
−/+	102 (20)
Other	226 (45)
Missing	175 (35)
GVHD Prophylaxis	
CNI + MMF +- others	180 (36)
CNI + MTX +-others (except MMF)	219 (43)
CNI + others (except MTX, MMF)	64 (13)
Other GVHD prophylaxis†	7 (1)
Missing GVHD prophylaxis	33 (7)
Antithymocyte globulin in conditioning	110 (22)
Alemtuzumab in conditioning	7 (1)
Year of Transplant	
2000–2003	111 (22)
2004–2007	154 (31)
2008–2012	238 (47)
Time from autoHCT to alloHCT	
Median (range)	15 (1–198)
≤12 months	201 (40)
>12 months	302 (60)
Median follow-up of survivors (range), months	55 (1–149)

HCT, haematopoietic cell transplantation; alloHCT, allogeneic haematopoietic cell transplantation; autoHCT, autologous haematopoietic cell transplantation; TBI, total body irrdation; CMV, Cytomegalovirus; GVHD, graft-versus-host disease; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; MTX, methotrexate.

*Asian (n = 25), Native American (n = 1), Pacific Islander (n = 1), other (n = 6).

†MMF/Campath (n = 1), MMF/Sirolimus (n = 1), MTX (n = 3), MMF/MTX (n = 1), MMF/MTX/Sirolimus (n = 1).

(95% CI: 49-58), 37% (95% CI: 32-41) and 34% (95% CI: 30-39), respectively (Fig 1D).

Multivariate outcomes

On multivariate analysis, chemoresistant disease before HCT (HR = 1·86, 95% CI:1·23-2·81; P = 0·003) and URD transplantation (HR = 1·44, 95% CI:1·04-2·00; P = 0·03) were associated with a higher risk of NRM (Table III). Use of myeloablative conditioning displayed a time-varying effect on the risk of NRM. During the first 10 months post-transplant it was associated with a higher NRM (HR = 1·99, 95% CI:1·34-2·95; P = 0·001), but not beyond 10 months post-alloHCT (HR = 0·59; P = 0·23). Multivariate analysis for disease progression/relapse demonstrated that KPS <80 (HR = 1·81, 95%CI:1·18-2·77; P = 0·006) and chemoresistant disease (HR = 2·25, 95% CI:1·51-3·36; P < 0·0001) were associated with a higher risk of progression/relapse post-alloHCT (Table III). TIBAA displayed a time-varying effect on the risk of disease progression/relapse. During the first year post-alloHCT, a short (<12 months) TIBAA was associated with a higher progression/relapse risk (HR = 2·28, 95% CI:1·66-3·14; P < 0·0001), but not beyond first year post-alloHCT (HR = 0·51; P = 0·14).

Patients with KPS <80 (HR-1·79, 95% CI:1·29-2·48; P = 0·0005), chemoresistant disease (HR = 2·04, 95% CI:1·53-2·73; P < 0·0001), short TIBAA (<12 months) (HR-1·32, 95% CI:1·06-1·64: P = 0·01) and use of use of myeloablative conditioning (HR-1·29, 95% CI:1·09-1·63; P = 0·03) had a higher risk of therapy failure (i.e. inferior PFS) (Table III).

Table II. Haematopoietic recovery, graft-versus-host disease and survival outcomes.

Outcomes	Evaluated (*n*)	Probability (95% CI)
Neutrophil recovery >0·5 × 10^9/l		
28-day	478	94 (92–96)%
100-day		96 (94–98)%
Platelet recovery ≥ 20 × 10^9/l		
28-day	374	83 (78–86)%
100-day		89 (86–92)%
Acute GVHD (II–IV)*		
100-day	151	36 (28–44)%
Acute GVHD (III–IV)*		
100-day	151	15 (10–21)%
Chronic GVHD		
6 month	454	26 (22–30)%
1-year		40 (35–44)%
3-year		47 (42–51)%
Extensive chronic GVHD		
1-year	454	33 (28–37)%
NRM		
1-year	494	23 (19–27)%
3-year		30 (26–34)%
5-year		31 (27–36)%
Relapse/Progression		
1-year	494	33 (29–37)%
3-year		38 (34–43)%
5-year		40 (36–45)%
Progression-free survival		
1-year	494	44 (40–48)%
3-year		31 (27–36)%
5-year		29 (24–33)%
Overall survival		
1-year	503	54 (49–58)%
3-year		37 (32–41)%
5-year		34 (30–39)%

GVHD, graft-versus-host disease; NRM, non-relapse mortality; CI, confidence interval.
*Applies to patients with CRF-level data.

On multivariate analysis a higher risk of mortality (i.e. inferior OS) was associated with with KPS <80 (HR-1·86, 95%CI:1·33-2·60; $P = 0·0003$), chemoresistant disease (HR = 1·94, 95% CI:1·44-2·61; $P < 0·0001$) and myeloablative conditioning (HR = 1·39, 95% CI:1·09-1·78; $P = 0·008$). Graft type displayed a time-varying effect on the risk of mortality. During the first 3 months post-transplant, peripheral blood grafts were associated with a lower risk of mortality (HR = 0·37, 95% CI:0·22-0·61; $P < 0·0001$), but not beyond 3 months post-alloHCT (HR = 1·43; $P = 0·25$). (Table III).

Development of acute GVHD (HR = 2·24, 95% CI:1·24-4·04; $P = 0·007$) and chronic GVHD (HR = 1·72, 95% CI:1·06-2·82; $P = 0·03$) was associated with higher risk of NRM. Neither acute, nor chronic GVHD were associated with risk of disease relapse/progression (data not shown). Acute GVHD was associated with a higher risk of mortality (HR = 1·85, 95% CI:1·27-2·69; $P = 0·001$). Chronic GVHD was not associated with mortality risk ($P = 0·54$).

CIBMTR prognostic model for PFS

Three significant prognostic factors were included in the final model predicting post-alloHCT PFS: KPS, chemosensitivity status and TIBAA. The final model only included those patients who had no missing data regarding KPS, chemosensitivity and TIBAA ($n = 417$). Based on the ratios of log HRs in the final model, chemoresistant disease was assigned 5 points, KPS of <80 was assigned 4 points and TIBAA <12 months was assigned 2 points (Table IV). Therefore, the total risk score for any individual patient using the 3 significant prognostic factors ranged from 0 to 11. Table IV summarizes the performance of the prognostic model. Distribution of patients by total risk score was as follows: 194 patients had a total risk score of 0 (reference category), 103 patients had a total risk score of 2 (HR = 1·30 range, 0·97 to 1·76), 14 patients had a total risk score of 4 (HR = 1·41 range, 0·76 to 2·62), 38 patients had a total risk score of 5 (HR = 1·66 range, 1·13 to 2·46), 12 patients had a total risk score of 6 (HR = 2·21 range, 1·19 to 4·11), 35 patients had a total risk score of 7 (HR = 2·34 range, 1·58 to 3·47), 3 patients had a total risk score of 9 (HR = 1·79 range, 0·44 to 7·24) and 18 patients had a total risk score of 11 (HR = 5·47 range, 3·26 to 9·19).

Based on the HRs and the distribution of the KM curves across the total risk score categories (Fig S1), we classified each patient into four prognostic risk groups: low-risk group (score = 0), intermediate-risk group (score = 2 to 5), high-risk group (score = 6 to 9) or very high-risk group (score = 11). Statistical significance was reached when we compared the PFS between low and intermediate group ($P = 0·01$), low and high-risk group ($P < 0·0001$) and low and very high-risk group ($P < 0·0001$) (Table IV). The 1-year PFS probabilities for the low, intermediate, high and very high-risk groups were 54% (95% CI = 47-61), 40% (95% CI = 33-48), 26% (95% CI = 14-38) and 6% (95% CI = 0-16), respectively. The probability for 3-year PFS was 40% (95% CI:32-47), 32% (95% CI = 25-40), 11% (95% CI:2-20) and 6% (95% CI:0-16) respectively, for the three prognostic groups (Fig 2A). The prognostic model also predicted OS following alloHCT (Table IV). The 1-year OS probabilities for the low, intermediate, high and very high-risk groups were 63% (95% CI = 57-70), 52% (95% CI = 44-60), 38% (95% CI = 25-51) and 17% (95% CI = 0-34), respectively. The probability for 3-year OS was 43% (95% CI:36-51), 39% (95% CI = 31-46), 19% (95% CI:8-31) and 11% (95% CI:0-26) respectively, for the three prognostic groups (Fig 2A).

Impact of conditioning intensity

Compared to RIC/NMA conditioning, the patients receiving myeloablative alloHCT were younger (median age 53 years

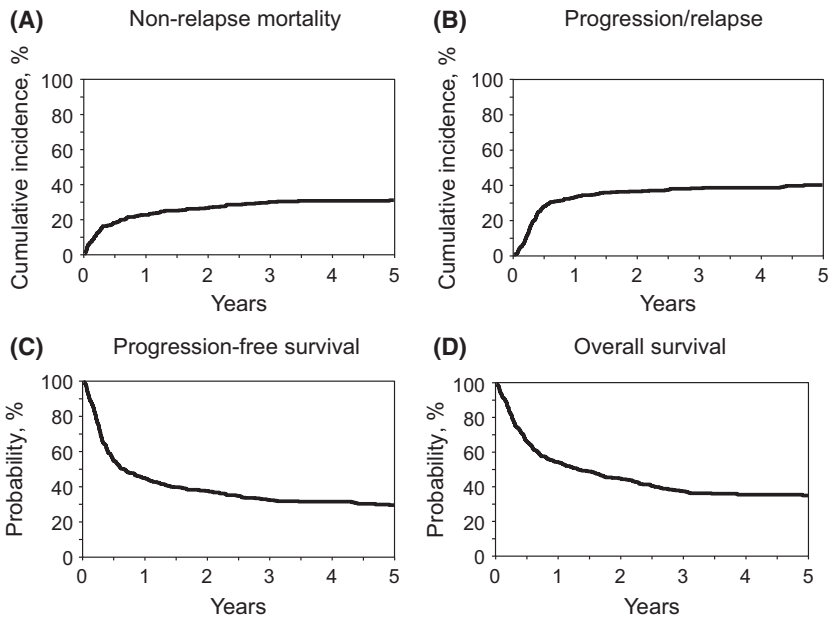

Fig 1. Outcomes for DLBCL patients undergoing allogeneic HCT after a prior failed autologous HCT. Cumulative incidence of (A) non-relapse mortality, (B) disease progression/relapse, (C) progression-free survival and (D) overall survival.

vs. 48 years; $P = 0{\cdot}0001$), more likely to have chemoresistant disease [19% ($n = 71$) vs. 28% ($n = 35$); $P = 0{\cdot}04$] and similar KPS ($P = 0{\cdot}54$). Table V summarizes survival outcomes of the study population stratified according conditioning intensity. In patients receiving myeloablative conditioning compared to RIC/NMA, the 5-year adjusted probabilities of PFS (27% vs. 30%; $P = 0{\cdot}47$, Fig 3A) and OS (28% vs. 37%; $P = 0{\cdot}055$, Fig 3B) were not significantly different. Restricting analysis to chemoresistant patients, the 5-year adjusted probabilities of PFS (13% vs. 18%; $P = 0{\cdot}47$, Fig 3C) and OS (15% vs. 25%; $P = 0{\cdot}22$, Fig 3D) in similar order, were not significantly different.

Causes of death

At a median follow-up of 55 months, 325 patients were no longer alive. The most common cause of death post-alloHCT was relapsed DLBCL ($N = 142$, 44% of all deaths). GVHD accounted for 9% ($n = 28$) of deaths, while infections were responsible for 19% of mortality ($n = 61$). For details please see Table S2.

Discussion

Prognostic models predicting outcomes of alloHCT in DLBCL failing a prior autoHCT are currently not available. Here, we have performed a registry analysis of DLBCL patients undergoing alloHCT after a failed prior autograft. This analysis provides several important observations: (i) NRM (23% at 1-year, 30% at 3-years) remains significant following alloHCT, (ii) a prognostic model based on factors readily available prior to alloHCT (TIBAA, chemosensitivity status, KPS) was developed for pre-transplant patient counseling, (iii) GVHD increased risk of non-relapse and overall mortality without reducing risk of relapse/progression and (iv) myeloablative conditioning provides no benefit in this setting, including in the subset of patients with chemoresistant disease.

There is evidence to support a possible GVL effect in DLBCL, including long-term responses in chemoresistant patients undergoing RIC alloHCT (Hamadani *et al*, 2013). and responses to donor lymphocyte infusion and/or withdrawal of immune suppression (Bishop *et al*, 2008; Thomson *et al*, 2009). Because of the potential for a GVL effect in DLBCL, combined with the poor prognosis associated with relapse after autoHCT, such patients are often considered for alloHCT. Notably, in the current analysis no benefit of acute or chronic GVHD was seen, in terms of reducing the risk of disease progression/relapse. These observations are in line with another recent large CIBMTR analysis (Urbano-Ispizua *et al*, 2015).

The decision to proceed with alloHCT in DLBCL after a failed autograft is complex because many of these patients have advanced age, impaired performance status or comorbid conditions that may limit their candidacy for alloHCT. For example, in one study, only 19% of patients who relapsed or progressed after autoHCT ultimately underwent an alloHCT (Rigacci *et al*, 2012). Among DLBCL patients undergoing alloHCT after a failed autograft, no tools are available to estimate HCT survival outcomes for patient counseling. The CIBMTR prognostic score reported in this study is not only easy to use, but utilizes information readily available prior to alloHCT (response to last therapy before alloHCT, KPS at HCT and TIBAA). This prognostic model is not designed to be applied to DLBCL patients at the time of their initial relapse after autoHCT (e.g. to determine their candidacy for

Table III. Multivariate analysis results.

	N	HR	95% CI Lower limit	95% CI Upper limit	*P*-value
Non-relapse mortality					
Chemosensitivity					
CR	173	1			
PR	192	1·01	0·69	1·48	0·97
Chemoresistant	104	1·86	1·23	2·81	0·003
Conditioning regimen (≤10 months)					
RIC/NMA	368	1			
MA	126	1·99	1·34	2·95	0·001
Conditioning regimen (>10 months)					
RIC/NMA	177	1			
MA	47	0·59	0·25	1·39	0·23
Type of donor					
HLA-identical sibling	245	1			
Well-matched/partially matched	249	1·44	1·04	2·00	0·03
Progression/Relapse					
KPS					
80–100	388	1			
<80	51	1·81	1·18	2·77	0·006
Chemosensitivity					
CR	173	1			
PR	192	1·36	0·95	1·96	0·09
Chemoresistant	104	2·25	1·51	3·36	<0·0001
Time from autoHCT to alloHCT (≤1 year from HCT)					
≥12 months between auto & allo	294	1			
<12 months between auto & allo	200	2·28	1·66	3·14	<0·0001
Time from autoHCT to alloHCT (>1 year from HCT)					
≥12 months between auto & allo	146	1			
<12 months between auto & allo	66	0·51	0·20	1·25	0·14
Progression free survival					
KPS					
80–100	388	1			
<80	51	1·79	1·29	2·48	0·0005
Chemosensitivity					
CR	173	1			
PR	192	1·14	0·88	1·49	0·31
Chemoresistant	104	2·04	1·53	2·73	<0·0001
Time from autoHCT to alloHCT					
≥12 months between auto & allo	294	1			
<12 months between auto & allo	200	1·32	1·06	1·64	0·01
Conditioning regimen					
RIC/NMA	368	1			
MA	126	1·29	1·02	1·63	0·03
Overall survival					
KPS					
80–100	393	1			
<80	52	1·86	1·33	2·60	0·0003
Chemosensitivity					
CR	175	1			
PR	197	1·16	0·88	1·52	0·30
Chemoresistant	106	1·94	1·44	2·62	<0·0001
Conditioning Regimens					
RIC/NMA	376	1			
MA	127	1·39	1·09	1·78	0·008
Graft Type (≤3 months)					

Table III. (*Continued*)

	N	HR	95% CI Lower limit	95% CI Upper limit	*P*-value
Bone marrow	47	1			
Peripheral blood	456	0·37	0·22	0·61	<0·0001
Graft Type (>3 months)					
Bone marrow	27	1			
Peripheral blood	377	1·43	0·78	2·64	0·25

N, number; HR, hazard ratio; CI, confidence interval; CR, complete response; PR, partial response; RIC, reduced intensity conditioning; NMA, non-myeloablative conditioning; MA, myeloablative conditioning; KPS, Karnofsky performance status; HLA, human leucocyte antigen; HCT, haematopoietic cell transplantation; alloHCT, allogeneic; auto,= autologous.

Table IV. Prognostic model for progression free survival and overall survival.

Prognostic score*	*N*	HR	95% CI Lower limit	95% CI Upper limit	*P*-value
0	194	1			
2	103	1·30	0·97	1·76	0·08
4	14	1·41	0·76	2·62	0·28
5	38	1·66	1·13	2·46	0·01
6	12	2·21	1·19	4·11	0·01
7	35	2·34	1·58	3·47	<0·0001
9	3	1·79	0·44	7·24	0·41
11	18	5·47	3·26	9·19	<0·0001
Progression-free survival risk groups					
Low (Score 0)	194	1			
Intermediate (Score 2,4,5)	155	1·40	1·08	1·82	0·01
High (Score 6,7,9)	50	2·28	1·61	3·22	<0·0001
Very high (Score 11)	18	5·47	3·26	9·19	<0·0001
Contrast					
Intermediate *versus* High		0·61	0·43	0·87	0·006
Intermediate *versus* Very high		0·26	0·15	0·43	<0·0001
High *versus* Very high		0·42	0·24	0·73	0·002
Overall survival risk groups					
Low (Score 0)	199	1			
Intermediate (Score 2,4,5)	156	1·34	1·02	1·76	0·03
High (Score 6,7,9)	50	2·11	1·47	3·03	<0·0001
Very high (Score 11)	18	3·94	2·32	6·68	<0·0001
Contrast					
Intermediate *versus* High		0·63	0·44	0·91	0·02
Intermediate *versus* Very high		0·34	0·20	0·58	<0·0001
High *versus* Very high		0·54	0·30	0·96	0·03

N, number; HR, hazard ratio; CI, confidence interval; CR, complete response; PR, partial response; KPS, Karnofsky performance status; alloHCT, allogeneic haematopoietic cell transplantation; autoHCT, autologous haematopoietic cell transplantation;
KPS ≥80 = 0 point, KPS <80 = 4 points.
Disease status CR or PR = 0 point, Chemoresistant = 5 points.
Time from autoHCT to alloHCT ≥12 months = 0 point, <12 months = 2 points.
*Prognostic score determined by following:

salvage therapies or for a future alloHCT), but rather as a tool to be used immediately prior to alloHCT for estimating transplantation outcomes for patient counselling.

To date, there have only been three previous studies that have focused specifically on alloHCT outcomes in DLBCL patients who progressed after a prior autoHCT (Table VI) (van Kampen *et al*, 2011; Rigacci *et al*, 2012; Kim *et al*, 2014). These studies (which largely focused on patients who underwent alloHCT from 1995–2008) showed approximately 30-40% PFS; however each study was limited by relatively short follow-up (median 2-3 years), and limited patient numbers (30-165 patients). Potentially partly due to these

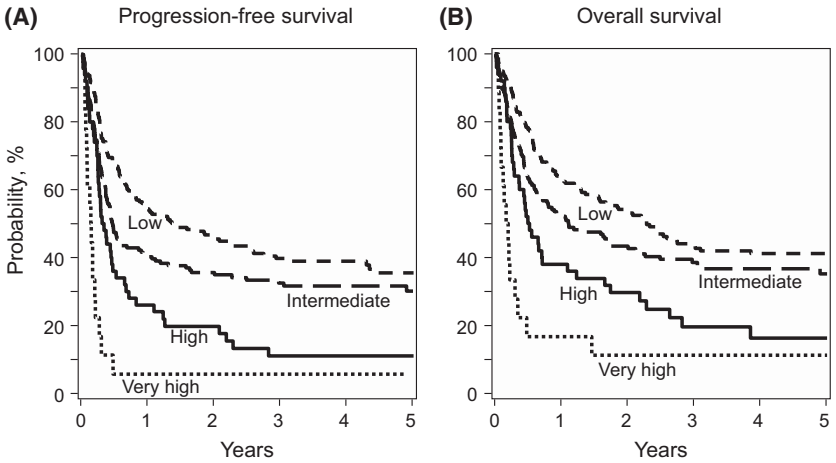

Fig 2. Prognostic index for DLBCL patients undergoing allogeneic HCT (alloHCT) after a prior failed autologous HCT (autoHCT). Three adverse prognostic factors were used to construct a prognostic model for PFS, including KPS <80 (4 points), interval between autoHCT and alloHCT of <1 year (2 points) and chemoresistant disease at alloHCT (5 points). This classified patients into four groups: low-risk (0 points), intermediate-risk (2–5 points), high-risk (6–9 points) or very high-risk (11 points). (A) Progression-free survival and (B) overall survival based on CIBMTR prognostic index.

Table V. Allogeneic transplantation outcomes stratified according to transplantation conditioning intensity

	Myeloablative conditioning Adjusted probability (95% CI)	Reduced-intensity or non-myeloablative conditioning Adjusted probability (95% CI)	*P*-value
Progression-free survival	*N* = 126	*N* = 368	
1-year	36 (26-44)%	46 (42-51)%	0·03
3-year	29 (21-36)%	33 (28-37)%	0·39
5-year	27 (19-34)%	30 (25-35)%	0·47
Overall survival	*N* = 127	*N* = 376	
1-year	44 (36-52)%	56 (52-61)%	0·01
3-year	31 (23-39)%	39 (34-44)%	0·12
5-year	28 (20-36)%	37 (32-42)%	0·055
Chemoresistant patients only			
Progression-free survival	*N* = 35	*N* = 69	
1-year	16 (4-27)%	33 (23-44)%	0·03
3-year	13 (2-24)%	20 (11-29)%	0·31
5-year	13 (2-24)%	18 (9-27)%	0·47
Overall survival	*N* = 35	*N* = 71	
1-year	23 (10-37)%	45 (33-56)%	0·02
3-year	15 (3-27)%	29 (19-39)%	0·09
5-year	15 (3-27)%	25 (15-35)%	0·22

limitations, these three studies had conflicting results regarding factors predicting improved PFS and OS after alloHCT. In contrast, the current study is strengthened by a large number of patients (n = 503), treated in a more contemporary era (2000-2012), with a median follow up of 4·6 years.

Our study found a NRM rate of 23% at 1 year and 30% at 3 years. This is in line with other studies looking at alloHCT following a failed autoHCT in DLBCL patients, in which the rate of NRM was 17-28% at 35 years (van Kampen *et al*, 2011; Rigacci *et al*, 2012; Kim *et al*, 2014). In the current study KPS <80, chemoresistant disease, a TIBAA <1-year and myeloablative conditioning were all predictive of worse survival outcomes on multivariate analysis, generally in line with predictive factors reported in prior studies (Table IV). It is worth noting that in the European Group of Blood and Marrow Transplantation (EBMT) study (van Kampen *et al*, 2011), a time from autoHCT to post-autograft relapse of <1-year was predictive of PFS. In contrast we used TIBAA in this study, since the interval between autoHCT and post-autograft relapse is not captured for all patients in the CIBMTR registry. The TIBAA is not only easily imputable immediately prior to alloHCT, but (for the patients in the CIBMTR registry for whom interval between autoHCT and post-autoHCT relapse was captured) it also correlates closely with the interval between autoHCT and post-autoHCT relapse (data not shown).

We found no benefit of myeloablative conditioning in this study, even in the subset of chemoresistant patients. In fact, myeloablative conditioning was associated with increased NRM, inferior PFS as well as OS on multivariate analysis. These observations are consistent with prior CIBMTR data showing no benefit of myeloablative conditioning in chemoresistant DLBCL (Hamadani *et al*, 2013). Our results indicate that the same holds true in the setting of DLBCL patients who have undergone a prior autoHCT.

Our study has limitations. The nature of data captured in the CIBMTR registry precludes comparison against DLBCL patients failing an autoHCT but never undergoing a subsequent alloHCT. In a recent CIBMTR study (Hamadani *et al*, 2014), among DLBCL patients undergoing autoHCT who experienced disease relapse, the 3-year post-relapse OS was 19% (unpublished data). These unpublished observations should however, be used with caution to ascertain the relative benefit of alloHCT in this setting. Other limitations of the current analysis include the lack of information regarding pre-alloHCT PET status, as well as biomarkers known to affect prognosis in DLBCL, such as cytogenetic abnormalities

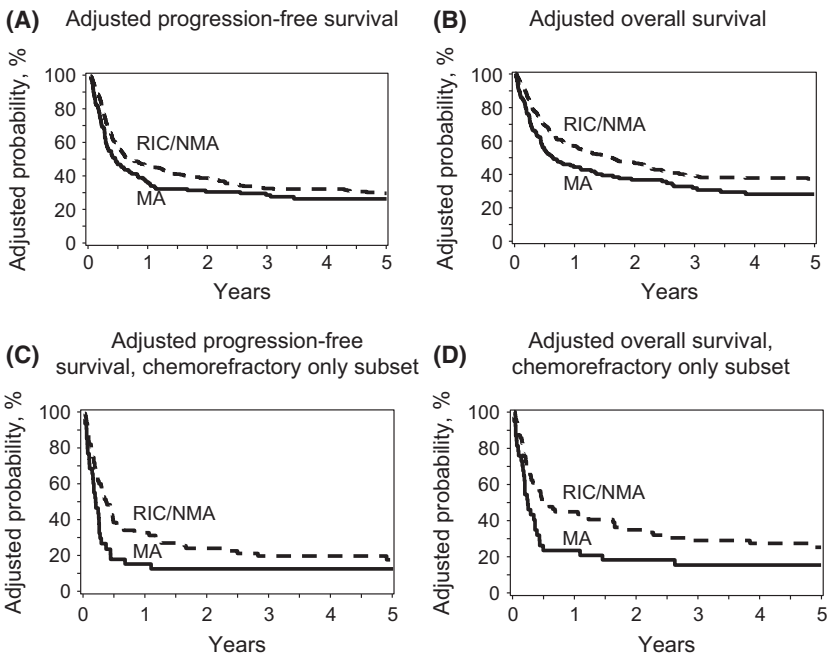

Fig 3. Overall survival (OS) and progression-free survival (PFS) of DLBCL patients undergoing allogeneic HCT after a prior failed autologous HCT, stratified by conditioning intensity. PFS of all patients (A), OS of all patients (B), PFS of chemoresistant patients (C) and OS of chemoresistant patients (D).

Table VI. Studies reporting outcomes of allogeneic transplantation in diffuse large B-cell lymphoma patients who received a prior autograft.

Study	*N*	MA vs. RIC (*N*)	NRM	PFS	OS	Factors predicting better PFS or OS
Van Kampen *et al* (2011)	101	37 vs. 64	28% (3-year)	42% (3-year)	54% (3-year)	TIBAR>1-year, normal LDH, peripheral blood graft
Rigacci *et al* (2012)	165	49 vs. 116	28% (not specified)	31% (5-year)	39% (5-year)	Chemosensitive disease, matched sibling donors
Kim *et al* (2014)	30	7 vs. 23	17% (not specified)	38% (5-year)	43% (5-year)	Chemosensitive disease, good performance status
Current analysis	503	127 vs. 376	31% (5-year)	29% (5-year)	34% (5-year)	KPS>80, chemosensitive disease, RIC, TIBAA >1-year

MA, myeloablative conditioning; RIC, reduced intensity conditioning, NRM, non-relapse mortality, PFS, progression-free survival; OS, overall survival; LDH, lactate dehydrogenase; TIBAA, time-interval between autologous and allogeneic transplantation; TIBAR, time interval between autologous transplant and post-autograft relapse; KPS, Karnofsky performance score.

(*MYC*, *BCL2*, and *BCL6* rearrangements) or 'cell-of-origin' profile (germinal centre versus activated B-cell). However it was recently reported that pre-alloHCT PET status in NHL does not predict PFS or OS (Bachanova *et al*, 2015). In addition, while the presence of *MYC* rearrangement is associated with inferior PFS and OS following HCT (Thieblemont *et al*, 2011), the available literature would indicate that 'cell-of-origin' profile fails to predict outcomes following HCT (Moskowitz *et al*, 2005; Gu *et al*, 2012).

In conclusion, we were able to construct a CIBMTR prognostic model to predict PFS after alloHCT, using KPS, TIBAA and chemoresistance at alloHCT. This tool was able to discriminate 3-year PFS, ranging from 38% down to 10%. This same prognostic tool was able to discriminate 3-year OS, ranging from 43% down to 14%. This prognostic index should help provide a more accurate estimate of risks and benefits with alloHCT, when counselling DLBCL patients before a planned alloHCT. This prognostic model requires independent validation, possibly by analysing data reported to other transplantation registries (e.g. EBMT registry). The CIBMTR prognostic model is not designed to assess suitability of DLBCL patient for a future allograft, at the time of their initial post-autograft relapse. On the other hand, these data also illustrate the shortcomings of alloHCT for this patient population. Further gains will need to be achieved in reducing NRM as well as augmenting GVL effects in order for alloHCT to achieve more widespread applicability for DLBCL patients relapsing after autoHCT. Rationally designed clinical trials that integrate novel agents (such as immune checkpoint inhibitors, antibody-drug conjugates and B-cell receptor signalling inhibitors) and/or novel cellular therapies (such as chimeric antigen receptor technology) with alloHCT may help to achieve this goal.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig S1. KM estimates of PFS stratified according to all possible combinations of total risk scores, across study population

Table S1. Variables tested in Cox proportional hazards regression models.

Table S2. Causes of death.

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