



Published in final edited form as:

Cancer. 2018 April 15; 124(8): 1733–1742. doi:10.1002/cncr.31264.

Allogeneic Hematopoietic Stem Cell Transplantation for Relapsed Follicular Lymphoma. A Combined Analysis on Behalf of the Lymphoma Working Party of the EBMT and the Lymphoma Committee of the CIBMTR

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Conflicts of Interest: The authors of the manuscript declare no conflicts of interest.

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Abstract

Background—Allogeneic hematopoietic stem cell transplantation (allo-HCT) remains the only potentially curative treatment option for relapsed follicular lymphoma (FL), yet questions remain on the optimal timing. We have analysed long-term outcomes and associated factors among recipients of allo-HCT with FL.

Patients and Methods—Patients with relapsed FL who received an allo-HCT from 2001 to 2011 from an HLA-matched donor were included. Outcome analyses for overall (OS) and progression-free survival (PFS), transplant related mortality (TRM) and disease relapse/progression were calculated. Multivariate analysis was performed to determine factors associated with outcomes and a prognostic score for treatment failure was developed in a subset analysis of patients.

Results—1,567 patients with relapsed FL were included; median follow up was of 55 months. Five-year probabilities of OS and PFS were 61% and 52%. Five-year cumulative incidences of disease progression/relapse and TRM were 29% and 19%. Chemoresistant disease, older age, heavily pre-treated patients, poor performance status and myeloablative protocols were predictors for worse survival. Prognostic score using age, lines of prior therapy, disease status and performance status stratified three groups with 5-year PFS of 68%, 53% and 46% and 5-year OS of 80%, 62% and 50% for low, intermediate and high risks respectively.

Conclusions—Allo-HCT should be considered in patients with relapsed FL and available HLA matched donors. Outcomes are better in earlier phases of the disease and reduced intensity conditionings should be preferred. The prognostic score presented here can assist in counselling patients and deciding the timing to proceed to transplant.

Keywords

Follicular Lymphoma; Allogeneic Hematopoietic Stem Cell Transplantation; Prognostic Risk Score; Unrelated Donors; Reduced Intensity Conditioning Protocols

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HCT) remains the only potentially curative therapy for patients with relapsed follicular lymphoma (FL) in spite of the introduction of novel agents. Allo-HCT is often associated with lower disease relapse compared to autologous transplant (auto-HCT), but transplant related mortality (TRM) offsets this benefit.¹ Retrospective analyses²⁻⁴ that compared auto-HCT vs allo-HCT as first transplant indicate that long-term disease control might favour allo-HCT because of a higher relapse risk in the autografted population not compensated by the well described higher TRM of the allogeneic procedure. Advances in supportive care, use of reduced intensity conditioning regimens (RIC) and better unrelated donor selection have resulted in an increasing use of allo-HCT in FL. The use of RIC⁵⁻⁷ has yet to be shown superior to myeloablative regimens (MAC),⁸ however it allows patients who are otherwise not candidates for allo-HCT to undergo this procedure. Further expansion in the number of candidates for allo-HCT is limited by the availability of HLA-matched donors. Unrelated donor allo-HCT (URD-HCT) in lymphomas is also associated with long-term disease

control. Recipients of URD-HCT often have more advanced disease at time of transplantation.^{9,10} In spite of all that, timing of transplantation and the optimal patient population still remain to be defined; moreover, prognostic models able to predict allo-HCT outcomes for this histology are not currently available.

In order to better ascertain the role of allo-HCT in patients with relapsed FL, we have conducted a retrospective analysis that includes the largest cohort of patients ever studied from both international registries, the European Blood and Marrow Transplantation (EBMT) and the Center for International Bone Marrow Transplantation Research (CIBMTR); a prognostic score for treatment failure has also been developed in order to guide clinical decisions in our daily medical practice.

Patient and Methods

Data Sources

The study was performed through collaboration between EBMT and CIBMTR lymphoma disease committees. EBMT is a voluntary organization comprising 640 transplant centres mainly from Europe. Accreditation as a member centre requires submission of minimal essential data (MED-A form) from all consecutive patients to a central registry. Since 1996, accredited EBMT centres are subject to on-site audits. Informed consent was obtained locally according to regulations applicable at the time of transplantation. Since January 2003, all transplant centres have been required to obtain written informed consent prior to data registration following the Helsinki Declaration 1975. CIBMTR is a voluntary working group of more than 450 transplant centers worldwide that contribute detailed data on consecutive HCT to a Statistical Center located at the Medical College of Wisconsin in Milwaukee and at the National Marrow Program Coordinating Center in Minneapolis. The CIBMTR collects data at two levels, transplant essential data in all patients and more comprehensive data (CRF) in a subset of patients. The CIBMTR-CRF dataset was chosen to be used in the study in order to have more disease specific information for analysis. Among 1112 patients who fulfilled eligibility for this study from the CIBMTR, 452 patients reported in CRF were included in this study.

Patient Eligibility

Patients with relapsed FL who received an HLA-matched sibling or URD-HCT from January/2001 to December/2011 and reported to the EBMT or CIBMTR-CRF were included. Patients with transformed FL, umbilical cord blood, haploidentical stem cell transplantation or *ex vivo* T-cell depleted grafts and those where a tandem HCT was pre-planned were excluded.

Outcomes and Definitions

Histology was based on data reported to both registries. Conditioning regimens were defined as MAC or RIC according to previously established definitions.¹¹ Disease response was evaluated following Cheson's criteria.¹² Relapse or progression was considered to be chemosensitive if at least partial remission was achieved following the last course of chemotherapy before allo-HCT.

Grades II-IV acute GVHD (aGVHD) were defined according to standard criteria.¹³ Chronic GVHD (cGVHD) was determined by the treating physician. Performance status (PS) was defined according to the Karnofsky score criteria (Karnofsky PS).

In the URD-HCT group, donor-recipient pairs in the well-matched category according to Weisdorf et al¹⁴ were selected, which include high-resolution matching at HLA-A, -B, -C and -DRB1 (8/8).

The primary outcomes after allo-HCT included: incidences of acute and chronic GVHD; transplant-related mortality (TRM), defined as any death within the first 28 days of transplant or any death occurring after day 28 in the absence of overt disease progression; relapse/progression, the events were defined as progression or recurrence of FL; progression-free survival (PFS), defined as survival without recurrence or tumour progression; and overall survival (OS), where death of any cause is an event.

Statistical Analysis

Probabilities of PFS and OS were calculated using the Kaplan-Meier estimator. Values for relapse/progression, TRM and GVHD were generated using cumulative incidence (CI) estimates to account for competing risks. The EBMT and CIBMTR cohorts were combined for all the analyses after confirming that all survival outcomes, TRM and disease progression were not statistically different.

Multivariate analyses using Cox proportional hazards models for overall mortality and treatment failure (1-PFS) were built using a forward stepwise approach. Among the 1,567 patients included in the primary analysis, after exclusion of patients without information on disease progression/relapse or death, 1,523 patients were tested in the multivariate analysis. Covariates analysed were: data source (CIBMTR vs EBMT), age, gender, Karnofsky PS at transplant (<80% vs 80%), disease stage at diagnosis (I/II vs III/IV), numbers of previous chemotherapy regimens (1-2 vs 3-4 vs 5 lines), prior auto-HCT, disease status at transplant [complete remission (CR2) vs Relapse vs Never in CR vs never in CR resistant vs unknown status], prior exposure to rituximab, intensity of the conditioning regimen (MAC vs RIC), donor type (HLA matched sibling vs URD), year of transplant and use of antithymocyte globulin (ATG) or alemtuzumab (yes vs no). Variables significantly associated with each outcome event were included as covariate factors in the subsequent comparisons. Proportionality assumptions were tested by adding a time-dependent variable.

The development of a model for prediction of treatment failure (1-PFS) was based on final Cox model and included a dataset with complete data on all significant covariates, all missing or unknown status were excluded. Cox regression analysis was repeated in this subset cohort and the covariates that maintained the association with the outcome were kept in the model. The cohort included 573 patients with complete information on all significant covariates: age (continuous), number of prior lines of chemotherapy (<3, 3-4 vs 5), disease status at time of allo-HCT (chemotherapy resistance) and Karnofsky PS (<80% vs 80%). The score was computed according to the magnitude of the effect between each significant covariate and treatment failure and three risk levels were developed: low, intermediate and

high risk. Final probabilities by three risk groups were calculated by Kaplan-Meier estimate for OS and PFS, and cumulative incidence function for TRM and relapse/progression.

Results

Patients

Patient characteristics are shown in Table 1.

Transplant Related Mortality

Three- and five-year cumulative incidence of TRM were 25% (95% CI, 23-27%) and 29% (95% CI, 26-31%), respectively (Figure 1). Age, chemoresistant disease, heavily pre-treated patients, low Karnofsky PS and the use of MAC regimens were associated to a higher TRM in the multivariate analysis (Table 2, Supplemental Materials Figure A).

Relapse/Progression

Three- and five year cumulative incidence of progression/relapse were 17% (95% CI, 15-19%) and 19% (95% CI, 17-22%), respectively (Figure 1). Chemoresistant disease and grade 3 histology were associated to a significantly higher relapse rate after the procedure (Table 2).

Progression Free Survival

Adjusted three- and five year probabilities of PFS were 58% (95% CI, 55-60%) and 52% (95% CI, 49-55%), respectively (Figure 1). Age, grade 3 histology, chemorefractory disease, number of prior lines of therapy before transplant, inadequate Karnofsky PS and MAC protocols were independent adverse prognostic factors (Table 2, Supplemental Materials Figure B).

Overall Survival

Adjusted three- and five-year probabilities of OS were 66% (95% CI, 64-68%) and 61% (95% CI, 59-64%, $p = 0.13$), respectively (Figure 1). Grade 3 histology, age at transplantation, chemotherapy burden before transplantation, chemorefractory disease, poor PS and the use of MAC protocols were adverse prognostic factors (Table 2, Supplemental Materials Figure C).

GVHD

Cumulative incidence of grade 2-4 aGVHD at day 100 was 20% (95% CI, 18-22%). Corresponding incidence for cGVHD at 1 year was 45% (95% CI, 42-48%). Cumulative incidence of both acute and cGVHD was higher in the CIBMTR cohort in comparison to the EBMT cohort in the univariate analysis (Supplemental Table A).

Risk Score

The population used to generate the score was a subset of all patients with complete information on all significant variables tested in multivariate analyses. In order to assess the

representativeness of this subset, the cohort (N=573) was compared to the excluded population and there were no differences in OS (N=994, p=0.43) or PFS (N=950, p=0.13).

The proposed risk score used the model for treatment failure (1-PFS) included the following covariates: age at HCT, number of prior chemotherapy lines, chemotherapy sensitivity and Karnofsky PS. The score was computed using the formula in Table 3 and defined three distinct groups: 1) low risk (n=190) score range from 0.03-0.069 (mean=0.47), intermediate risk (n=191) score range from 0.70-1.05 (mean=0.87) and 3) high risk (n=192) score range from 1.06-2.29 (mean=1.36). The hazard ratio for treatment failure of patients with intermediate risk was 1.72 (95% CI, 1.24 to 2.43, p=0.0014) compared to patients with low risk; and patients with high risk was 1.40 (95% CI, 1.05-1.85, p=0.019) compared to intermediate risk. Corresponding hazard ratios for overall mortality were 2.10 (95% CI, 1.41-3.14, p=0.0003) and 1.66 (95% CI, 1.22-2.25, p=0.001); for TRM were 2.56 (95% CI, 1.57-4.16, p=0.002) and 1.74 (95% CI, 1.23-2.44, p=0.0015); and for disease progression/relapse were 1.14 (95% CI, 0.70-1.84, p=0.60) and 0.84 (95% CI, 0.50-1.41, p=0.51) (Figure 2A-D).

Discussion

The present analysis combining the EBMT and the CIBMTR experiences for a period of 10 years represents the largest study published to date that evaluates the long-term outcome of heavily pretreated FL patients receiving an allo-HCT. The therapeutic landscape of relapsed FL is undergoing rapid evolution with the development of several novel agents including phosphoinositide 3-kinase inhibitors,¹⁵ Bruton's tyrosine kinase inhibitors,¹⁶ and ABT-199 (NCT02187861).¹⁷ Although auto-HSCT as consolidation therapy at first chemosensitive relapse/progression is able to provide long-term durable remissions in the rituximab era, a significant proportion of patients will eventually relapse.¹⁸ Although allo-HCT is the only treatment strategy demonstrated to be curative in relapsed FL patients, its precise role and timing with the progressive incorporation of all these agents in clinical practice in the coming years needs to be reevaluated.

There are significant differences in clinical practice between European and US transplant centres; the more frequent use of MUD in the CIBMTR setting might account for the higher incidence of both acute and cGVHD in this cohort of patients. In spite of that, the four major post-transplant outcomes were super imposable between both registries (Supplemental Table A). Adjusted 5-year probabilities for PFS were 52% and 52% and for OS of 62% and 61% for EBMT- and CIBMTR-reported patients, respectively. These results are in line with what has already been published.¹⁹⁻²⁴

Long-term outcome of patients allografted from well-matched URD is comparable to that of HLA-matched sibling. A review from the literature gives somewhat conflicting results; while the retrospective EBMT analysis²² does not show any significant difference between the two donor sources, both the UK study²⁵ as well as the FHCRC experience²¹ indicate that URDs are associated with a poorer outcome due to a higher TRM. Number of HLA mismatches may account for these differences.

Of note, the disease control achieved in this high-risk group of patients was impressive with a relapse rate of 19% at 5-years. Later relapses may yet occur, but the *plateau* observed in the relapse curve in this and other studies^{9,19,20,23-27} is suggestive that these procedures are a curative treatment. Chemorefractoriness as well as initial diagnosis being grade 3 FL were associated to an increased relapse / progression rate after the procedure. Reason for the later might have been the inclusion of grade 3b FL patients in this series. Long-term outcome is worse in those patients that had received more lines of therapy, with chemoresistant disease, poor KS status at the time of transplant and in whom a MAC protocols were used. These results are also in line with what has been published before¹⁹⁻²³ and indicate that patients with relapsed FL should be allografted earlier in the course of the disease. The intensity of the conditioning regimen is still a matter of debate. While in a prior CIBMTR analysis,⁸ RIC protocols were associated to a higher relapse rate and a lower PFS, in our analysis, MAC protocols are associated to a higher TRM and a lower PFS and OS. In FL and in light of the low relapse rate seen, one might favour less intense conditioning protocols allowing disease cure on the basis of the clinically beneficial GVL effect.

Toxicity of allo-HCT remains significant with one-quarter of patients dying from a transplant-related complication at 3 years. The TRM rate in this study appears comparable with that reported in other studies.^{19,20,23,25} Strategies to further improve the prevention and management of allo-HCT-related complications are clearly required. The use of the transplant-related comorbidity index may help to identify patients where the risk of the allo-HCT is excessive and that alternative therapies may be more appropriate.²⁸

Finally and most importantly, the large number of patients included in the study has allowed us to construct a score that identifies clearly distinct groups of patients in terms of long-term outcome. It is always challenging to assess the procedure-related risk of a given patient before an allo-HCT taking into consideration the existence of other effective and less toxic treatment options in this histology; there are no prognostic indexes validated in this setting. The proposed score includes age, number of prior chemotherapy lines, chemotherapy sensitivity and performance score into a 3-level risk model. Although not all these factors are modifiable, the score may assist in the clinical decision to offer an allo-HCT to a given patient. Of note, allo-HCT is able to achieve an OS of 80% and a PFS higher than 60% with a 10% TRM in the low risk group of patients; these results compare favorably with those of other non-transplant therapeutic strategies. The efficacy of allo-HCT and its place in the treatment armamentarium in relation to more conventional salvage therapies and to targeted therapy remains to be elucidated. Strategies employing such agents as a bridge to transplant or alternatively as a maintenance therapy following transplantation also require further studies.

Our analysis has important limitations. During the era of this analysis EBMT/CIBMTR case reports forms did not distinguish between grade 3a vs. 3b histologies, but considering that fact that grade 3b is a rare histology, we anticipate grade 3b numbers to be low in the current dataset. But using the current dataset we cannot predict if outcomes of grade 3a FL are different from grade 3b. We excluded transformed histologies from this analysis, as determined by reporting center (based on either histological or clinical grounds). However, we cannot exclude the possibility that a few transformed cases, not recognized by reporting

center might have been included in current analysis. Since this analysis included cases reported to CIBMTR at TED level and EBMT at Med-A level (where elaborate pre and post transplant therapy data are not collected) we are not able to assess the impact of pre-transplant therapies, post alloHCT maintenance/consolidation treatments or chimerism kinetics on HCT outcomes. The fact that the EBMT and CIBMTR do not collect data on patients not undergoing HCT, means cost-effectiveness type analysis are not possible utilizing registry datasets.

In conclusion, the present analysis albeit retrospective in nature indicates an excellent long-term outcome of patients with relapsed FL being treated with allo-HCT, especially for those patients belonging to the low risk group. If allo-HCT is considered a treatment option and no HLA-matched sibling donor is available, an URD search should be started in a timely manner, it has to be considered earlier in the course of the disease, before the patient fails multiple lines of chemotherapy, his performance status deteriorates and the disease demonstrates to be chemorefractory. MAC protocols should be avoided due to the excess of toxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

CIBMTR Support List: The CIBMTR is supported primarily by Public Health Service Grant/Cooperative Agreement 5U24-CA076518 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 5U10HL069294 from NHLBI and NCI; a contract HSH250201200016C with Health Resources and Services Administration (HRSA/DHHS); two Grants N00014-15-1-0848 and N00014-16-1-2020 from the Office of Naval Research; and grants from *Actinium Pharmaceuticals, Inc.; Alexion; *Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; Astellas Pharma US; AstraZeneca; Atara Biotherapeutics, Inc.; Be the Match Foundation; *Bluebird Bio, Inc.; *Bristol Myers Squibb Oncology; *Celgene Corporation; Cellular Dynamics International, Inc.; Cerus Corporation; *Chimerix, Inc.; Fred Hutchinson Cancer Research Center; Gamida Cell Ltd.; Genentech, Inc.; Genzyme Corporation; Gilead Sciences, Inc.; Health Research, Inc. Roswell Park Cancer Institute; HistoGenetics, Inc.; Incyte Corporation; Janssen Scientific Affairs, LLC; *Jazz Pharmaceuticals, Inc.; Jeff Gordon Children's Foundation; The Leukemia & Lymphoma Society; Medac, GmbH; MedImmune; The Medical College of Wisconsin; *Merck & Co, Inc.; *Mesoblast; MesoScale Diagnostics, Inc.; *Milenyi Biotech, Inc.; National Marrow Donor Program; Neovii Biotech NA, Inc.; Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals; Optum Healthcare Solutions, Inc.; Otsuka America Pharmaceutical, Inc.; Otsuka Pharmaceutical Co, Ltd. – Japan; PCORI; Perkin Elmer, Inc.; Pfizer, Inc.; *Sanofi US; *Seattle Genetics; *Spectrum Pharmaceuticals, Inc.; St. Baldrick's Foundation; *Sunesis Pharmaceuticals, Inc.; Swedish Orphan Biovitrum, Inc.; Takeda Oncology; Telomere Diagnostics, Inc.; University of Minnesota; 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, Health Resources and Services Administration (HRSA) or any other agency of the U.S. Government.

*Corporate Members

Funding Sources: None.

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Key Message

Allogeneic stem cell transplantation (allo-HCT) from HLA matched donors is a curative therapy for patients with follicular lymphoma. Allo-HCT should be considered early in the course of the disease and myeloablative conditioning protocols should be avoided. A prognostic score based on easy to collect clinical data can be used to optimize the candidate and best timing for the procedure.

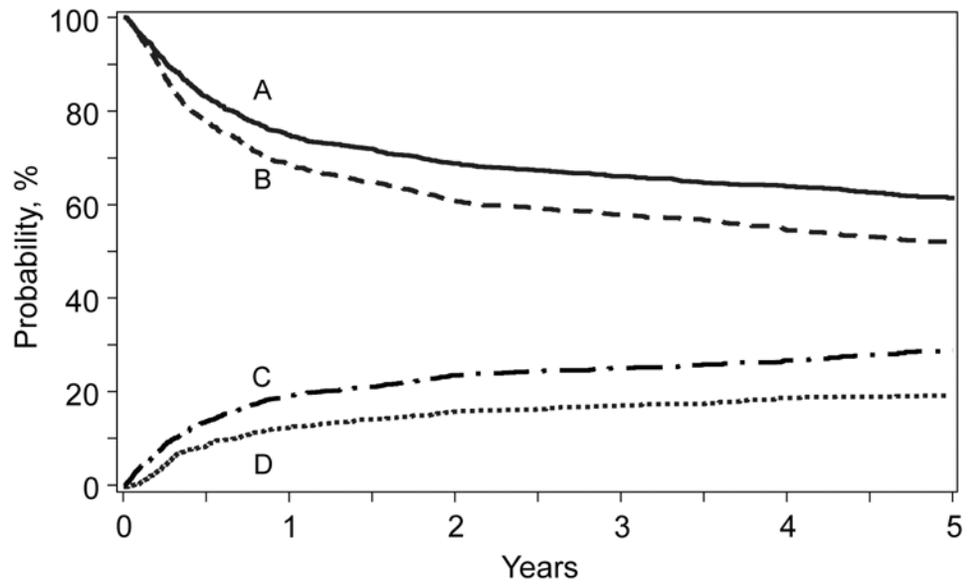
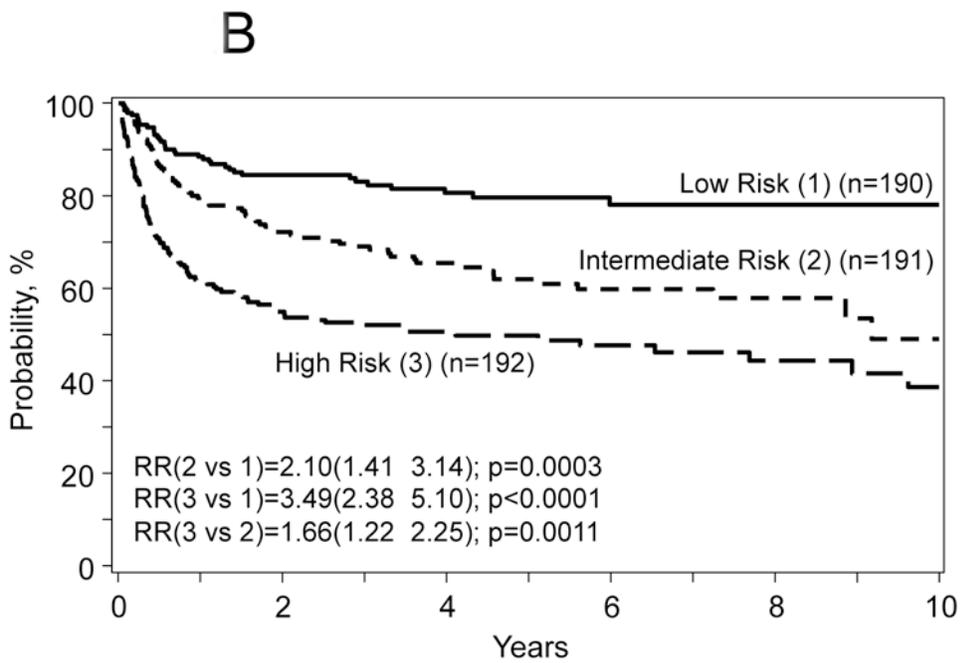
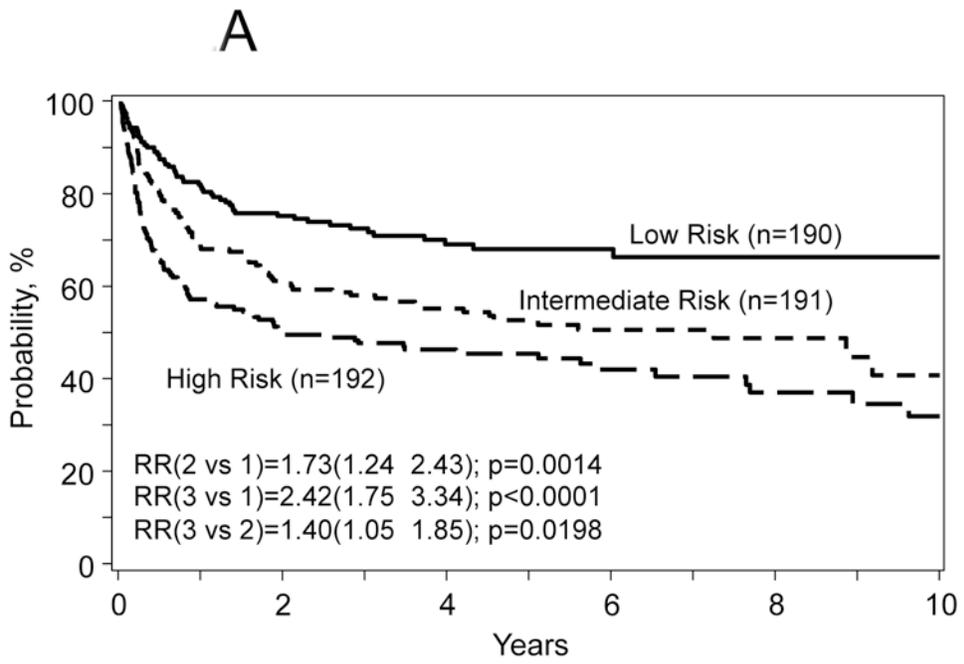


Figure 1. Probabilities for overall survival (A) and progression free survival (B) and cumulative incidences for transplant related mortality (C) and disease progression/relapse (D) for patients with FL who received an allogeneic hematopoietic cell transplantation from 2001-2011.



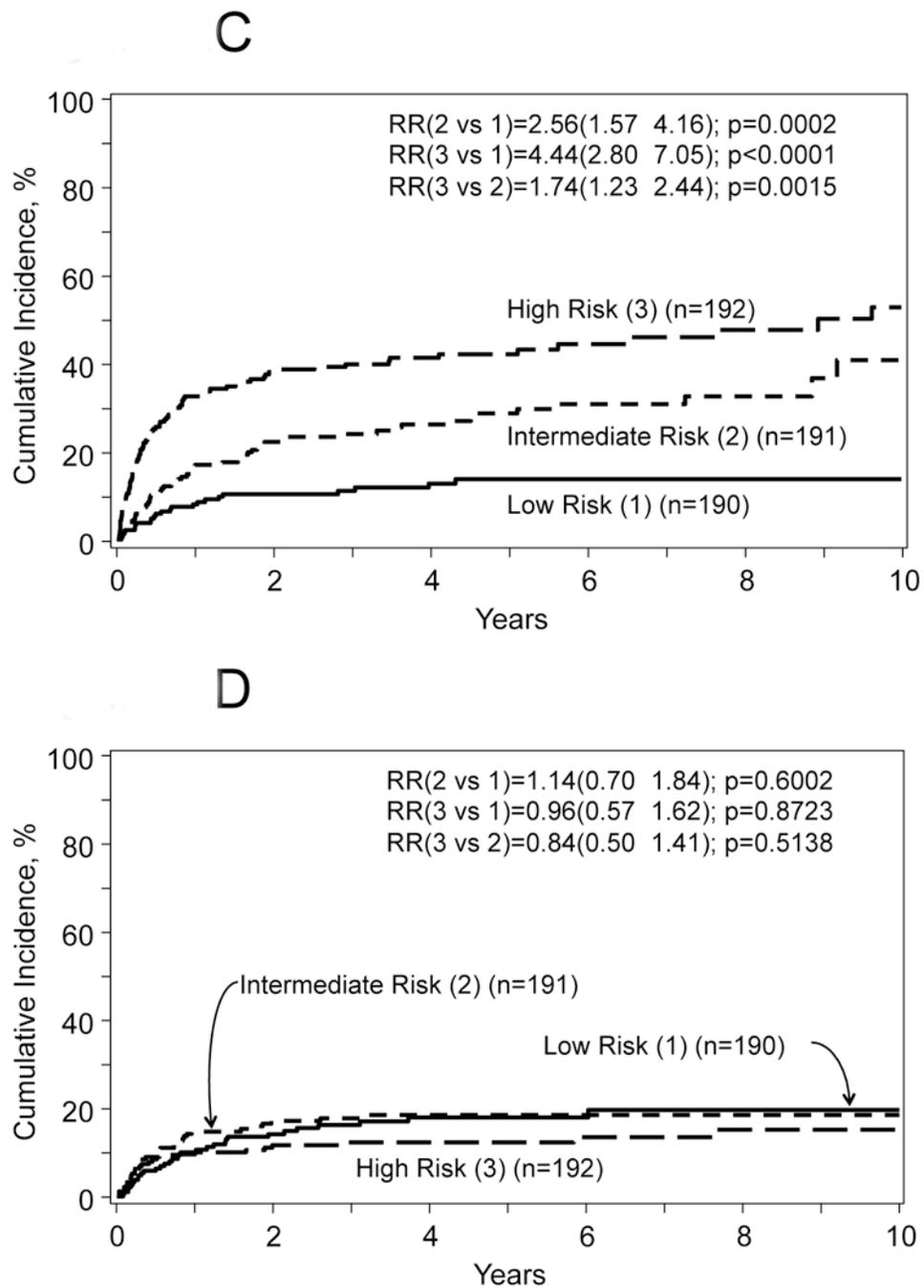


Figure 2. Probabilities for progression free survival (A) and overall survival (B), transplant related mortality (TRM) (C) and disease progression/relapse (D) according to prognostic score.

Table 1
Characteristics of patients who underwent HLA identical sibling allogeneic transplant or HLA matched unrelated donor allogeneic transplant for follicular lymphoma from 2001-2011, by registry

	Total N (%)	CIBMTR N (%)	EBMT N (%)	P-value
Number of patients	1567	452	1115	
Patient age at transplant, years				0.062
Median	51 (21-74)	50 (21-74)	51 (24-72)	
21-30	24 (2)	12 (3)	12 (1)	
31-40	204 (13)	67 (15)	137 (12)	
41-50	586 (37)	155 (34)	431 (39)	
51-60	592 (38)	175 (39)	417 (37)	
61	161 (10)	43 (10)	118 (11)	
Gender				0.064
Male	935 (60)	286 (63)	649 (58)	
Female	632 (40)	166 (37)	466 (42)	
Karnofsky score				<0.001
<80	56 (4)	35 (8)	21 (2)	
80	1005 (64)	392 (87)	613 (55)	
Missing	506 (32)	25 (6)	481 (43)	
Disease-related				
Histology				<0.001
Grade 1	455 (29)	187 (41)	268 (24)	
Grade 2	389 (25)	163 (36)	226 (20)	
Grade 3	319 (20)	84 (19)	235 (21)	
Unknown grade	404 (26)	18 (4)	386 (35)	
Number of prior chemotherapy regimens				<0.001
1-2	291 (19)	102 (23)	189 (17)	
3-4	397 (25)	225 (50)	172 (15)	
5	172 (11)	97 (21)	75 (7)	
Missing number of previous regimens	707 (45)	28 (6)	679 (61)	
Previous ASCT	456 (29)	53 (12)	403 (36)	<0.001
Interval ASCT-allo-HCT, median (range), months	26 (1-249)	19 (1-101)	27 (6-249)	0.001
Disease stage at diagnosis				<0.001
I-II	121 (8)	61 (13)	60 (5)	
III-IV	816 (52)	359 (79)	457 (41)	
Not available	630 (40)	32 (7)	598 (54)	
Disease status at HCT				<0.001
PIF sensitive	63 (4)	63 (14)	0	
PIF resistant	138 (9)	43 (10)	95 (9)	

	Total N (%)	CIBMTR N (%)	EBMT N (%)	P-value
REL sensitive	457 (29)	139 (31)	318 (29)	
REL resistant	73 (5)	70 (15)	3 (<1)	
CR2+	452 (29)	89 (20)	363 (33)	
REL untreated/unknown	315 (20)	16 (4)	299 (27)	
PIF unknown	3 (<1)	2 (<1)	1 (<1)	
Not available	66 (4)	30 (7)	36 (3)	
Response to therapy immediately prior to HCT				<0.001
Sensitive	1192 (76)	307 (68)	885 (79)	
Resistant	258 (16)	113 (25)	145 (13)	
Unknown	117 (7)	32 (7)	85 (8)	
Transplant-related				
Interval diagnosis to allo-HCT, median (range), months	47 (3-363)	42 (3-352)	51 (4-363)	<0.001
Rituximab at conditioning	154 (10)	92 (20)	62 (6)	<0.001
Conditioning regimens				<0.001
Myeloablative (MA)	365 (23)	145 (32)	220 (20)	
RIC/NMA	1202 (77)	307 (68)	895 (80)	
Conditioning regimens				<0.001
MAC				
TBI+Cy	155 (10)	79 (17)	76 (7)	
BEAM ± others	56 (4)	4 (1)	52 (5)	
Bu ± others	51 (3)	32 (7)	19 (2)	
Bu+Cy	40 (3)	23 (5)	17 (2)	
Fludarabine ± others	16 (1)	0	16 (1)	
TBI+Fludarabine	8 (1)	0	8 (1)	
Others	39 (2)	7 (2)	32 (3)	
RIC				
Fludarabine+Melphalan	303 (19)	46 (10)	257 (23)	
Bu ± Fludarabine	196 (13)	69 (15)	127 (11)	
Cy+Thiotepa	37 (2)	0	37 (3)	
Melphalan+Cy	19 (1)	11 (2)	8 (1)	
CCNU ± others	11 (1)	3 (1)	8 (1)	
TBI+Cy	10 (1)	9 (2)	1 (<1)	
Others	29 (2)	10 (2)	19 (2)	
NMA				
TBI+Fludarabine	226 (14)	40 (9)	186 (17)	
Fludarabine+Cy	216 (14)	113 (25)	103 (9)	
TBI +/- Cy	33 (2)	4 (1)	29 (3)	
Others	122 (8)	2 (<1)	120 (11)	
Donor type				<0.001

	Total N (%)	CIBMTR N (%)	EBMT N (%)	P-value
HLA-matched siblings	1148 (73)	285 (63)	863 (77)	
Unrelated well matched	419 (27)	167 (37)	252 (23)	
D-R CMV status				<0.001
Any Positive	885 (56)	302 (67)	583 (52)	
All negative	381 (24)	137 (30)	244 (22)	
Missing	301 (19)	13 (3)	288 (26)	
D-R sex match				0.427
M-M & F-F	847 (54)	248 (55)	599 (54)	
M-F	338 (22)	86 (19)	252 (23)	
F-M	365 (23)	113 (25)	252 (23)	
Missing	17 (1)	5 (1)	12 (1)	
Source of stem cells				0.767
Bone marrow	154 (10)	46 (10)	108 (10)	
Peripheral blood	1413 (90)	406 (90)	1007 (90)	
Year of transplant				<0.001
2001-2003	380 (24)	150 (33)	230 (21)	
2004-2006	411 (26)	123 (27)	288 (26)	
2007-2009	499 (32)	135 (30)	364 (33)	
2010-2011	277 (18)	44 (10)	233 (21)	
ATG-Campath				<0.001
ATG alone	4 (1)	0	4 (<1)	
Campath alone	248 (16)	60 (13)	188 (17)	
ATG+Campath	229 (14)	29 (6)	200 (18)	
None	352 (22)	352 (78)	0	
Missing	734 (47)	11 (2)	723 (65)	
GVHD prophylaxis				<0.001
CNI+MTX	360 (23)	61 (13)	299 (27)	
CNI+MMF	318 (20)	42 (9)	276 (25)	
CNI± other	608 (39)	334 (74)	274 (24)	
Others/missing	281 (18)	15 (3)	266 (24)	
Follow-up of survivors, median (range), months	55 (3-160)	58 (3-130)	54 (3-160)	

EBMT = European Group for Blood and Marrow Transplantation; CIBMTR = Center for International Blood and Bone Marrow Transplant Research; ASCT = Autologous stem Cell Transplantation; Allo-HCT = Allogeneic Hematopoietic Transplantation; BuCy = Busulfan Cyclophosphamide; BEAM = BCNU, etoposide, cytarabine, melphalan; CBV = Cyclophosphamide, BCNU, etoposide; TBI = Total Body Irradiation; RIC = reduced intensity conditioning; NST = non-myeloablative transplant; Mel = Melphalan; M = Male; F = Female; CMV = Cytomegalovirus; GVHD = graft versus host disease; MTX = methotrexate; CsA = cyclosporine; MMF = Mycophenolatemofetil; FK506 = tacrolimus.

* Other GVHD prophylaxis: MTX alone (n=14); MMF alone (n=13) and not specified (n=254)

Table 2

Multivariate analysis of patients receiving hematopoietic cell transplantation for follicular lymphoma from 2001-2011.

Outcome/Factors	N	RR (95% CI)	P-value
Progression/Relapse			
Histologic Grade			
Grade 1	444	1.00	
Grade 2	383	1.32 (0.95 – 1.84)	0.101
Grade 3	308	1.63 (1.16 – 2.28)	0.004
Missing	388	1.20 (0.85 – 1.68)	0.294
Disease status at HCT			
Chemosensitive	1.158	1.00	
Chemorefractory	253	1.46 (1.07 – 1.97)	0.015
Missing	112	1.23 (0.79 – 1.93)	0.362
Transplant Related Mortality			
Age (Continuous)	1.523	1.04 (1.02 – 1.05)	< 0.0001
N. of prior chemotherapy lines			
1-2	285	1.00	0.008
3-4	390	1.56 (1.12 – 2.17)	
≥5	165	2.53 (1.77 – 3.62)	<0.0001
Missing	683	1.84 (1.35 – 2.51)	0.0001
KPS			
≥ 80	986	1.00	
< 80	54	2.05 (1.32 – 3.19)	0.001
Missing	483	0.94 (0.76 – 1.16)	0.556
Conditioning regimen			
RIC/NMA	1.168	1.00	-
MAC	355	1.49 (1.18 – 1.87)	0.0007
Disease status at HSCT			
Chemosensitive	1.158	1.00	
Chemoresistant	253	1.61 (1.28 – 2.03)	<0.0001
Missing	112	1.14 (0.78 – 1.66)	0.510
Progression free survival			
Histology			
Grade 1	444	1.00	
Grade 2	383	1.15 (0.94 – 1.42)	0.177
Grade 3	308	1.42 (1.15 – 1.76)	0.001

Outcome/Factors	N	RR (95% CI)	P-value
Missing	388	1.17 (0.94 – 1.44)	0.154
N. of prior chemotherapy lines			
1-2	285	1.00	
3-4	390	1.33 (1.04 – 1.70)	0.022
>=5	165	1.93 (1.46 – 2.55)	< 0.0001
Missing	683	1.56 (1.24 – 1.95)	0.0001
KPS			
>= 80	986	1.00	
< 80	54	1.78 (1.23 – 2.58)	0.002
Missing	483	0.96 (0.81 – 1.14)	0.634
Disease status at HSCT			
Chemosensitive	1.158	1.00	
Chemoresistant	253	1.54 (1.28 – 1.86)	<0.0001
Missing	112	1.15 (0.86 – 1.54)	0.336
Conditioning regimen			
RIC/NMA	1.168	1.00	
MAC	355	1.36 (1.14 – 1.63)	0.0008
Overall Survival			
Age (Continuous)	1.523	1.03 (1.02 – 1.04)	> 0.0001
Histology			
Grade 1	444	1.00	
Grade 2	383	1.17 (0.93 – 1.48)	0.180
Grade 3	308	1.44 (1.13 – 1.83)	0.003
Missing	388	1.29 (1.01 – 1.63)	0.039
N. of prior chemotherapy lines			
1-2	285	1.00	
3-4	390	1.48 (1.11 – 1.97)	0.007
>=5	165	2.41 (1.77 – 3.30)	< 0.0001
Missing	683	1.73 (1.33 – 2.26)	< 0.0001
KPS			
>= 80	986	1.00	
< 80	54	2.23 (1.52 – 3.25)	< 0.0001
Missing	483	0.89 (0.73 – 1.07)	0.219
Disease status at HCT			
Chemosensitive	1.158	1.00	<0.0001
Chemoresistant	253	1.59 (1.30 – 1.95)	0.227
Missing	112	1.20 (0.86 – 1.67)	

Outcome/Factors	N	RR (95% CI)	P-value
Conditioning regimen			
RIC/NMA	1.168	1.00	
MAC	355	1.42 (1.16 – 1.73)	0.0006

RR = Relative risk; CI = Confidence interval; HCT = Stem cell transplantation; KPS. Karnofsky performance score; ASCT = Autologous stem cell transplantation; RIC = Reduced intensity conditioning; NMA = Non-myeloablative conditioning regimen; MAC = Myeloablative conditioning regimen.

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Table 3

Prognostic score for treatment failure among patients with FL undergoing allogeneic HCT.

Risk	β (Parameter)	p-value
Age (increment of 1 year)	0.0160	0.0271
Number of prior lines of therapy = 3-4	0.3592	0.0243
Number of prior lines of therapy = 5	0.7013	<0.0001
Performance score (KPS) = <80%	0.4962	0.0213
Disease Status = Chemoresistant	0.5134	0.0002
Score = Age*0.0160 + (>5 prior lines of therapy)*0.7013 + (Chemoresistant)*0.5134 + (KPS<80%)*0.4962 + (3-4 prior lines of therapy)*0.3592 with range of (0.0331 – 2.2901)		
Risk Level	Score	
Low Risk	<0.70	
Intermediate Risk	0.70-1.05	
High Risk	>1.05	