Baseline Characteristics Predicting Very Good Outcome of Allogeneic Hematopoietic Cell Transplantation in Young Patients With High Cytogenetic Risk Chronic Lymphocytic Leukemia - A Retrospective Analysis From the Chronic Malignancies Working Party of the EBMT

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Abstract

Patients with chronic lymphocytic leukemia with del(17p) or del(11q) have poor long-term prognosis with targeted therapies. Conversely, this retrospective European Society for Blood and Marrow Transplantation registry study shows that young high cytogenetic risk responsive patients with human leukocyte antigen-matched donors have a high 8-year progression-free survival and low 2-year non-relapse mortality after allogeneic stem cell

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transplantation. This treatment then may compare favorably with targeted therapies for younger high cytogenetic risk patients.

Background: Patients with genetically high-risk relapsed/refractory chronic lymphocytic leukemia have shorter median progression-free survival (PFS) with kinase- and BCL2-inhibitors (KI, BCL2i). Allogeneic hematopoietic stem cell transplantation (alloHCT) may result in sustained PFS, especially in younger patients because of its age-dependent non-relapse mortality (NRM) risk, but outcome data are lacking for this population. **Patients and Methods:** Risk factors for 2-year NRM and 8-year PFS were identified in patients < 50 years in an updated European Society for Blood and Marrow Transplantation registry cohort (n = 197; median follow-up, 90.4 months) by Cox regression modeling, and predicted probabilities of NRM and PFS of 2 reference patients with favorable or unfavorable characteristics were plotted. **Results:** Predictors for poor 8-year PFS were no remission at the time of alloHCT (hazard ratio [HR], 1.7; 95% confidence interval [CI], 1.1-2.5) and partially human leukocyte antigen (HLA)-mismatched unrelated donor (HR, 2.8; 95% CI, 1.5-5.2). The latter variable also predicted a higher risk of 2-year NRM (HR, 4.0; 95% CI, 1.4-11.6) compared with HLA-matched sibling donors. Predicted 2-year NRM and 8-year PFS of a high cytogenetic risk (del(17p) and/or del(11q)) patient in remission with a matched related donor were 12% (95% CI, 3%-22%) and 54% (95% CI, 38%-69%), and for an unresponsive patient with a female partially HLA-matched unrelated donor 37% (95% CI, 12%-62%) and 38% (95% CI, 13%-63%). **Conclusion:** Low predicted NRM and high 8-year PFS in favorable transplant high cytogenetic risk patients compares favorably with outcomes with KI or BCL2i. Taking into account the amount of uncertainty for predicting survival after alloHCT and after sequential administration of KI and BCL2i, alloHCT remains a valid option for younger patients with high cytogenetic risk chronic lymphocytic leukemia with a well-HLA-matched donor.

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Introduction

Patients with chronic lymphocytic leukemia (CLL) that are refractory or early relapsing to purine analogue-containing therapies can currently be treated effectively with targeted therapies (kinase inhibitors [KI] or BCL2 inhibitors [BCL2i]). First-in-class ibrutinib, a BTK-inhibitor, and idelalisib, a PI3K-inhibitor, were approved in the United States and in Europe in 2014, and the BCL2i venetoclax has been recently approved in the United States and is expected to be approved at the end of 2016 in Europe; second-generation drugs are already tested in clinical trials. All these drugs are orally available and have a rather good safety profile.[1-3] Maturing data with ibrutinib show that many patients enjoy long progression-free survival (PFS), but measurable residual disease (MRD)-negativity is rarely reached, and especially patients with del(17p) and to a lesser extent with del(11q) have an increased risk of early disease progression. The median PFS on ibrutinib for relapsed/refractory (R/R) patients with CLL with del(17p) is 26 months (95% confidence interval [CI], 18-37 months), 55 months (95% CI, 33-not estimable) for those with del(11q), and not reached (95% CI, 40 months-not estimable) for all others,[4] whereas the median PFS under venetoclax is approximately 2 years.[3] In case of failure on ibrutinib with progressive CLL, subsequent treatment with venetoclax results in approximately 70% overall response, an estimated 1-year PFS of 80% (95% CI, 67%-89%), and a median PFS that had not been reached yet in 2 studies, but the follow-up was very short (< 12-14 months), and it is expected that relapses will remain occurring as observed in patients treated with venetoclax without KI-pretreatment.[3,5,6] Survival for patients under treatment with a targeted drug is further compromised by the occurrence of Richter's transformation (incidence approximately 10% and 15%, respectively, under ibrutinib and venetoclax)[3,5,7-11] that results in similarly dismal survival as in the days before the targeted therapy era.[11-14] These observations justify the exploration of alternative treatments for very high-risk patients with CLL.

Allogeneic hematopoietic stem cell transplantation (alloHCT) is considered a treatment able to achieve longer lasting PFS, especially in the patients who achieve MRD-negativity.[15-18] The effect of alloHCT is better when performed in patients with responsive disease,[19] although most studies report that outcome is not influenced by the presence of high-risk cytogenetic or molecular abnormalities including del(17p) and TP53 mutations.[15,16,20-22] The main drawback of alloHCT is the occurrence of non-relapse mortality (NRM), which is highest within the first 2 years. NRM after alloHCT is mainly owing to infection or the occurrence of graft-versus-host-disease. Well-known factors that are associated with NRM after alloHCT are higher age, poor performance status, comorbidity, the use of human leukocyte antigen (HLA)-mismatched donors, and a female donor for a male patient.[23]

As, generally speaking, drawbacks of a given therapy in terms of toxicity must outweigh the benefits, alloHCT in CLL is particularly considered in younger patients with either a high risk of refractoriness or actual refractory disease to targeted therapy and relatively few factors that predict high NRM. The outcome of such a transplant policy in younger patients with CLL, however, had never been studied neither prospectively nor retrospectively.

In this study, we aimed to evaluate and illustrate the relevance of known predictors for NRM and relapse retrospectively in an updated registry cohort of the European Society for Blood and

Marrow Transplantation (EBMT) of young patients with CLL less than 50 years old who were transplanted between January 2000 and December 2011. Based on the risk-factor models from our analysis, we created good- and poor-risk transplant risk reference patients to illustrate the predicted outcomes that can be helpful when counseling younger fit high-risk patients with CLL in case the option of alloHCT is considered.

Methods

Approach

The study population consisted of all patients below the age of 50 who received a first alloHCT for CLL between January 2000 and December 2011, who were registered in the EBMT database and whose data were improved and extended in a Data Quality Initiative (for details, see Supplemental Material in the online version). Updated outcome data were extracted from the EBMT registry on December 4, 2015.

Statistical Analysis

The main objective of this analysis was to identify risk factors for NRM within the first 2 years after alloHCT and to estimate their effect size. We selected 2 years as a time horizon because treatment-related mortality after alloHCT mainly occurs within the first 2 years. Further, 2-year outcomes can easily be compared with published results of targeted therapies with currently limited follow-up. Additionally, PFS up to 8 years after alloHCT was analyzed as a surrogate for long-term disease control. PFS was calculated as time to death, relapse, or disease progression, whatever occurred first, and patients were censored if alive and relapse-/progression-free at moment of last follow-up. A secondary analysis dealt with the cumulative incidence of relapse or progression (CIR).

In order to assess a possible influence of risk factors on outcomes after alloHCT, we fitted Cox regression models for (cause-specific) hazards for all the aforementioned endpoints. Our emphasis was in gaining insight into the most relevant risk factors and their effect on transplant outcome, hence the parsimony of our models was not an end in itself. An initial set of baseline variables eligible for selection was predefined, based on clinical grounds, which included: age, donor type, donor-recipient gender match, calendar year of alloHCT, Karnofsky index, cytogenetic abnormalities, remission status at alloHCT, purine analogue sensitivity, treatment with alemtuzumab prior to start of conditioning regimen, history of prior autologous HCT, donor-recipient cytomegalovirus match, graft type, conditioning regimen, and type of T-cell depletion. Next, we applied a 2-step selection procedure among this initial set while keeping age, donor type, and donor-recipient gender match into all models, reflecting their importance in the EBMT risk score.[23] Cytogenetics was also maintained in all models because the focus of this research is to predict outcome for patients with high-risk cytogenetics (ie, del(17p) and del(11q)). Because of the relatively low numbers of patients in these 2 cytogenetic categories, and because both are a current indication for alloHCT, they were combined in 1 high-risk cytogenetic category "del(17p) and/or del(11q)." With the goal to visualize the outcomes of a "good transplant risk" and a "poor transplant risk" patient, we plotted the model-based predicted probabilities of NRM, CIR, and PFS of 2 46-year-old (the median age of this cohort) reference patients with high-risk cytogenetics who had favorable and unfavorable characteristics, respectively, according to the fitted models. All analyses were performed in SPSS and R 3.0.3 using the packages 'mice', 'prodlim', 'mstate', and 'cmprsk'.[24,25] Further details about the statistical analysis are given in the Supplemental Material (in the online version).

Results

Description and Outcome of the Whole Cohort

A total of 197 patients with CLL who had been treated with alloHCT when younger than 50 years were identified in the Data Quality Initiative (Table 1). The median age was 46 years; 81% were older than 40 years. Seventeen percent had a del(17p) and 35% a del(11q) without del(17p), 12% had had an autologous HCT (autoHCT) as part of their preteatment prior to alloHCT, mainly in the context of an intergroup trial between 2001 and 2007,[26] all but one > 2 years before, and 38% were in remission at the time of alloHCT. Seventy-six percent received non-myeloablative conditioning, 42% had a HLA-identical sibling donor, and 20% were males with a female donor. The median follow-up of all patients was 90.4 months.

Two- and 8-year PFS of the whole cohort were 55% (95% CI, 48%-62%) and 38% (95% CI, 31%-46%) respectively (Figure 1A); 2- and 8-year cumulative incidence of relapse/progression were 25% (95% CI, 18.6%-30.7%) and 39% (95% CI, 31.6%-44.7%), and 2- and 8-year NRM were 20% (95% CI, 14.8%-26.1%) and 23% (95% CI, 16.8%-28.7%), respectively (Figure 1B). Overall survival was 72% (95% CI, 65%-78%) and 52% (95% CI, 44%-59%) at 2 and 8 years after alloHCT.

PFS was not statistically different between the 3 different cytogenetic subgroups in univariate analysis (Figure 2).

Multivariate Risk Factor Analysis for 2-Year NRM, CIR, and PFS

During the first 2 years, 40 NRM and 48 CIR events were observed. For NRM only, the use of an unrelated donor had a significant negative impact on the risk of NRM (HR, 2.5; 95% CI, 1.1-5.4 and HR, 4.0; 95% CI, 1.4-11.6 for HLA-matched and partially HLA-matched unrelated donors, respectively) (Table 2). Two risk factors had a significant impact on the risk of CIR: a prior autoHCT (HR, 3.1; 95% CI, 1.4-7.0) and no remission (HR, 2.7; 95% CI, 1.5-5.1) (Table 2). For PFS, 3 factors had a significant negative impact: prior autoHCT (HR, 2.3; 95% CI, 1.2-4.1), no remission (HR, 1.9; 95% CI, 1.2-2.9), and a partially HLA-matched unrelated donor (HR, 3.0; 95% CI, 1.5-6.2) (Table 2). Unfavorable cytogenetics had no statistically significant negative impact on relapse/progression or PFS (HR for PFS, 1.4; 95% CI, 0.9-2.4) (Table 2).

Multivariate Risk Factor Analysis for 8-Year PFS

In order to identify predictive risk factors for long-term disease control, a Cox model was fitted for 8-year PFS. The following 3 risk factors had a significant negative impact on 8-year PFS (Table 3): prior autoHCT (HR, 1.9; 95% CI, 1.1-3.3), no remission at the time of alloHCT (HR, 1.7; 95% CI, 1.1-2.5), and the use of a partially HLA-matched unrelated donor (HR, 2.8; 95% CI, 1.5-5.2). Unfavorable cytogenetics did not significantly predict for inferior 8-year PFS (HR, 1.3; 95% CI, 0.9-2.1).

Table 1 Characteristics of 197 Patients Who Underwent Allogeneic HCT Below the Age of 50

Factors	No. Patients (%)
Age, y	
<45	80 (41)
45-50	117 (59)
Median	46
Chemosensitivity prior to alloHCT (n = 166)	
PA refractory	67 (40)
Relapse after chemo-immunotherapy	32 (19)
Cytogenetics (n = 137)	
del(17p)	23 (17)
del(11q) and no del(17p)	48 (35)
No del(17p) nor del(11q)	67 (48)
Median number of prior lines of therapy (range)	3 (0-10)
Previous autologous HCT	
No	153 (88)
Yes	24 (12)[a]
Remission status at the time of alloHCT	
CR/PR	71 (38)
No remission	114 (62)
Karnofsky score at the time of alloHCT (n = 181)	
90-100	152 (84)
≤80	29 (16)
Conditioning (n = 194)	
Non-myeloablative	58 (30)
Reduced-intensity	89 (46)
Myeloablative	47 (24)
Stem cell source	
Bone marrow	17 (9)
Mobilized peripheral blood	180 (91)
TCD (n = 195)	
No in or ex vivo TCD	82 (42)
In vivo TCD with ATG	71 (36)
In vivo TCD with alemtuzumab	23 (12)
Ex vivo TCD	19 (10)
Donor type	
HLA-matched related	83 (42)
HLA-matched unrelated	97 (49)
Partially HLA-matched unrelated	17 (9)
Donor-patient gender match (n = 194)	
All other combinations	155 (80)
Female donor for male patient	39 (20)
CMV-serostatus of patient (n = 180)	
Positive	69 (38)
Negative	111 (62)

The number of patients with available information is given in brackets if deviating from total number.
Abbreviations: alloHCT = allogeneic hematopoietic cell transplantation; ATG = anti-thymocyte globulin; autoHCT = autologous hematopoietic cell transplantation; CLL = chronic lymphocytic leukemia; CMV = cytomegalovirus; CR/PR = complete or partial remission; del(17p) and del(11q) = deletion 17p or 11q respectively; EBMT = European Society for Blood and Marrow Transplantation; HLA = human leukocyte antigen; PA = purine analogue; TCD = T cell depletion.
[a]Twenty-three had their autoHCT > 2 years before the alloHCT.

PFS of a Model-based "Good Transplant Risk" and "Poor Transplant Risk" Patient With High Cytogenetic Risk

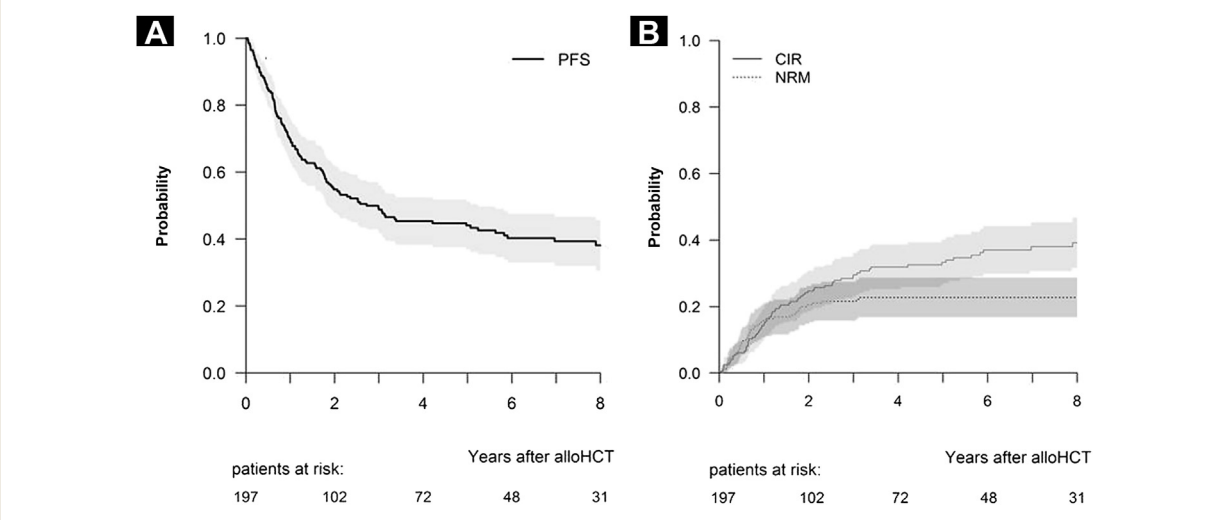
With the purpose to describe and visualize the short- and long-term outcomes of cytogenetically high-risk patients (del(17p) and/or del(11q)) with favorable or poor risk factors as identified by the models, we created a good and poor transplant risk reference patient with the following risk factors that are based on the above described risk factor analyses: the good transplant risk patient had no prior autoHCT, CLL in remission at the time of alloHCT, and an HLA-matched sibling donor with a favorable gender match (male for male patients, any donor gender for female patients); the poor transplant risk patient was male, had no prior autoHCT, no remission at the time of alloHCT, and an unrelated female donor. We choose the median age of the cohort as the age of the reference patient (ie, 46 years). The predicted 2-year NRM and CIR for the good-risk reference patient with high-risk cytogenetics were 12% (95% CI, 3%-22%) and 20% (95% CI, 7%-33%), respectively, which translated to a 2-year PFS of 68% (95% CI, 53%-83%) (Figure 3A). For the poor-risk reference patient, 2-year NRM, CIR, and PFS were 37% (95% CI, 12%-62%), 25% (95% CI, 5%-44%), and 38% (95% CI, 13%-63%), respectively (Figure 3B). Eight-year PFS for the good-risk reference patient was 54% (95% CI, 38%-69%) (Figure 4A), and for the poor-risk reference patient, 22% (95% CI, 9%-52%) (Figure 4B).

Discussion

AlloHCT is currently less frequently performed for patients with R/R CLL because of the availability of the KIs, ibrutinib and idelalisib, and the BCL2i, venetoclax. Patients with del(17p) or del(11q), however, have an increased risk of disease progression under these drugs that compromises their life expectancy (median PFS, 26 months and 16 months, respectively, under ibrutinib ad venetoclax), particularly when progression occurs with Richter's transformation (what one-third of the progressors do).[3-11] It is therefore especially relevant for younger patients to have effective alternative therapies available. AlloHCT is one such option, and the advantage for younger patients is that its accompanied risk of NRM is lower at a younger age.[21,27] As no reference for the shorter-term NRM and longer-term PFS probability for this younger population of patients with R/R CLL with high cytogenetic risk factors have been published yet, we did this study. We found that the predicted 8-year PFS in a good transplant risk patient is 54%, which seems to contrast favorably with the results with KI or BCL2i even when used sequentially.[3-11] It is unknown, but unlikely as no age effect has been demonstrated for outcome after KI or BCLi treatment, that the result of sequential use of KI and BCL2i in younger cytogenetic high-risk patients will approach the predicted good long-term result of alloHCT in a younger good transplant risk patient.

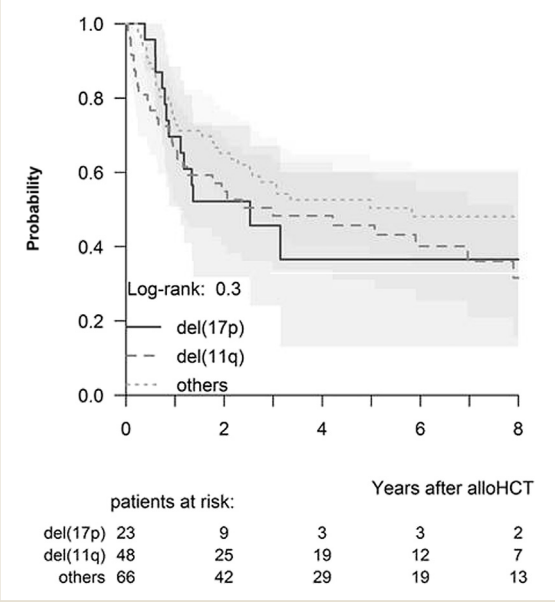
We found that donor type and HLA match are the main predictors of the risk of 2-year NRM and 8-year PFS. This risk is highest with partially HLA-matched unrelated for both endpoints when compared with HLA-matched related donors, which is similar to the results of analyses of larger cohorts of patients transplanted with peripheral blood stem cells from partially HLA-matched unrelated donors for various malignant hematologic diseases.[28-32] The use of HLA-matched unrelated donors predicted a lesser increased risk of 2-year NRM but without affecting 8-year PFS compared with HLA-matched related donors. This differential impact for the risk of TRM and PFS has also been observed in several other larger studies,[30,32-34] whereas others revealed no impact on TRM.[29,31,35]

Figure 1 PFS (With 95% Confidence Intervals), CIR, and NRM Plots for All Patients. Number of Patients at Risk at Selected Time Points After alloHCT Are Given Below the Time Scale on the X-axis



Abbreviations: alloHCT = allogeneic hematopoietic cell transplantation; CIR = cumulative incidence of relapse/progression; NRM = non-relapse mortality; PFS = progression-free survival.

Figure 2 PFS Kaplan-Meier Plots (Including 95% Confidence Intervals) for the Three Cytogenetic Subgroups: del(17p), n = 23; del(11q) and No del(17p), n = 48; and No del(17p) nor del(11q), n = 66. Number of Patients at Risk at Selected Time Points After alloHCT in the 3 Subgroups Are Given Below the Time Scale on the X-axis



Abbreviations: alloHCT = allogeneic hematopoietic cell transplantation; PFS = Progression-free survival.

For CIR, 2 risk factors were identified: no remission at the time of alloHCT and having had a previous autoHCT. The first risk factor is well-known,[15,17,19] and the second had become irrelevant as autoHCT does not result in improved OS[36,37] yet negatively affects quality of life.[38] Similarly to what has been reported in most previous reports, high-risk cytogenetics was not a statistically significant predictor for increased CIR.[15,16,20-22]

The risk factor for relapse "remission status at the time of alloHCT" was, until the era of KI and BCL2i, not easy to influence as there was no real standard remission-induction scheme. Only one prospective study with intention-to-treat analysis of a strategy with R-DHAP (rituximab, dexamethasone, high-dose cytarabine, cisplatin) remission-induction followed by alloHCT showed that R-DHAP can be applied prior to alloHCT but with a remission rate of 58%, irrespective of the presence of del(17p).[21] Sixty-seven percent proceeded to alloHCT, whereas the remainder did not, owing to toxicity or disease progression.[21] These data are in line with results from retrospective studies, where, in addition to toxicity and disease progression, refusal/non-compliance or the absence of a suitable donor were additional reasons for not making it to transplant.[39,40] It may, in current clinical practice, be appropriate to take advantage of the remission induced by either KI (or perhaps BCL2i), as alloHCT showed to be feasible, and CIR did not seemed to be compromised after use of KI for remission-induction.[41,42]

We did not report on overall survival as it is expected that the currently available salvage treatments with a KI or BCL2i will significantly improve the response rate and survival in patients with disease progression after alloHCT.[10,18,43-46]

A factor we could not study is the impact of comorbidity, known for its age-independent relevance from other transplant studies,[47,48] because information on this variable is lacking until now in the EBMT database. The fact that the predicted 2-year NRM in the good transplant risk patient is rather low may indicate that the vast

Table 2 Risk Factors for NRM, CIR, and PFS Within the First 2 Years After AlloHCT in Multivariate Analysis

	NRM		CIR		PFS	
Risk Factors	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Age (in decades)	0.8 (0.4-1.6)	.55	0.8 (0.4-1.4)	.38	0.8 (0.5-1.2)	.27
Cytogenetics						
No del(17p) or del(11q)	1		1		1	
del(17p) and/or del(11q)	1.3 (0.6-2.9)	.51	1.6 (0.8-3.4)	.18	1.4 (0.9-2.4)	.16
Prior autoHCT						
No			1		1	
Yes	—		3.1 (1.4-7.0)	<.01	2.3 (1.2-4.1)	<.01
Remission status at the time of alloHCT						
CR/PR			1		1	
No remission			2.7 (1.5-5.1)	<.01	1.9 (1.2-2.9)	<.01
Donor type						
HLA-matched sibling	1		1		1	
HLA-matched unrelated	2.5 (1.1-5.4)	.03	1.0 (0.5-1.9)	.95	1.5 (0.9-2.4)	.13
Partially HLA-matched unrelated	4.0 (1.4-11.6)	.01	2.2 (0.8-6.4)	.14	3.0 (1.5-6.2)	<.01
Donor-patient gender match						
All other combinations	1		1		1	
Female donor for male patient	1.5 (0.7-3.3)	.27	0.7 (0.3-1.7)	.42	1.1 (0.6-1.9)	.85

HRs and their associated CIs and *P* values are based on multivariate Cox regression models.
Abbreviations: alloHCT = allogeneic hematopoietic cell transplantation; autoHCT = autologous hematopoietic cell transplantation; CI = confidence interval; CIR = cumulative incidence of relapse/progression; CLL = chronic lymphocytic leukemia; CR/PR = complete or partial remission; del(17p) and del(11q) = deletion 17p or 11q respectively; HCT = hematopoietic cell transplantation; HLA = human leukocyte antigen; HR = hazard ratio; NRM = non-relapse mortality; PFS = progression-free survival.

Table 3 Risk Factors for 8-Year PFS After AlloHCT in Multivariate Analysis

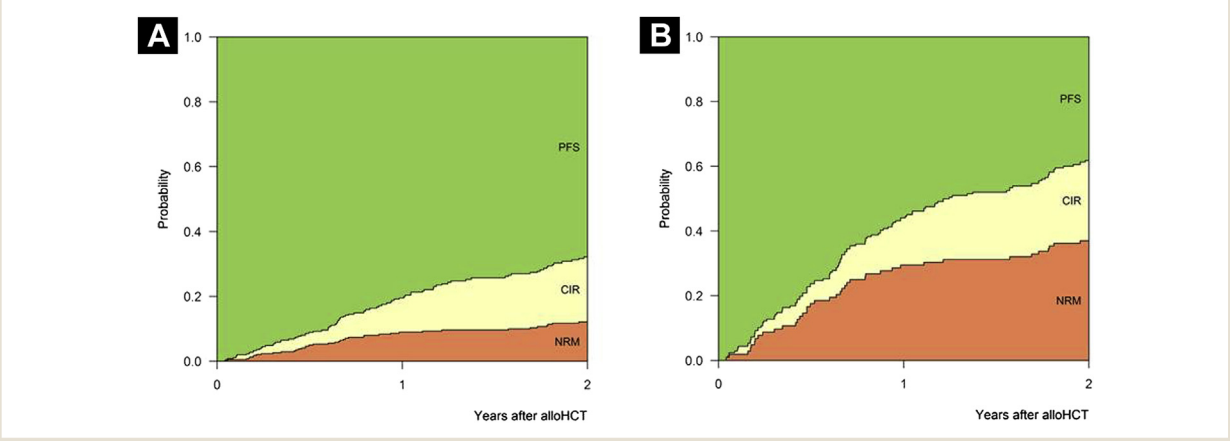
Risk Factors	**HR (95% CI)**	***P* Value**
Age (in decades)	0.80 (0.54-1.19)	.26
Cytogenetics		
No del(17p) or del(11q)	1	
del(17p) and/or del(11q)	1.3 (0.9-2.1)	.19
Previous autoHCT		
No	1	
Yes	1.9 (1.1-3.3)	.03
Remission status at the time of alloHCT		
CR/PR	1	
No remission	1.7 (1.1-2.5)	.01
Donor		
HLA-matched sibling	1	
HLA-matched unrelated	1.2 (0.8-1.8)	.41
Partially HLA-matched unrelated	2.8 (1.5-5.2)	<.01
Donor-patient gender match		
All other combinations	1	
Female donor for male patient	1.2 (0.7-1.9)	.50

Abbreviations: alloHCT = allogeneic hematopoietic cell transplantation; autoHCT = autologous hematopoietic cell transplantation; CI = confidence interval; CLL = chronic lymphocytic leukemia; del(17p) and del(11q) = deletion 17p or 11q respectively; EBMT = European Society for Blood and Marrow Transplantation; HCT = hematopoietic cell transplantation; HLA = human leukocyte antigen; HR = hazard ratio.

majority of the patients in this cohort had no or only few comorbidities, which makes sense as comorbidity incidence increases with rising age. Nevertheless, comorbidity should, of course, be considered when counseling patients for alloHCT.

The current medical dilemma in clinical decision-making for patients with high cytogenetic risk immunochemotherapy-R/R CLL, especially when young, is whether or not to propose alloHCT and its timing.[49] As discussed above, the median PFS with ibrutinib or venetoclax for high cytogenetic risk patients is 26 and 16 months, respectively,[3,4] and the effect of salvage therapy that may include alloHCT after (the sequential use of) KI and/or BCL2i failure is tempting but uncertain both in the short and longer run because data are lacking. When alloHCT is considered before exploiting KIs and/or BCL2is, only a very low NRM risk is acceptable, whereas for KI- and/or BCL2i-refractory patients, a higher NRM risk is acceptable. In this study, we found that the risk of 2-year NRM is lowest for younger patients when using a matched related donor. We subsequently illustrated that the predicted 2-year NRM in a model that created a young good transplant risk patient with high-risk cytogenetics, responsive disease, and a matched related donor is 12%. This 2-year NRM is a bit higher than the disease-progression-independent death rate reported in the prospective register trials of the KIs and BCL2is,[2,3,7] but at least similar to that reported in a recent prospective real-world observational study (9% with a median follow-up of 10.2 months).[10] It is, however, unknown whether age affects the NRM risk for KI and BCL2i, and it is therefore uncertain if the given NRM applies to younger patients. The next factor to be weighed when counseling immune-chemotherapy R/R patients is the risk of CIR and its accompanied compromised

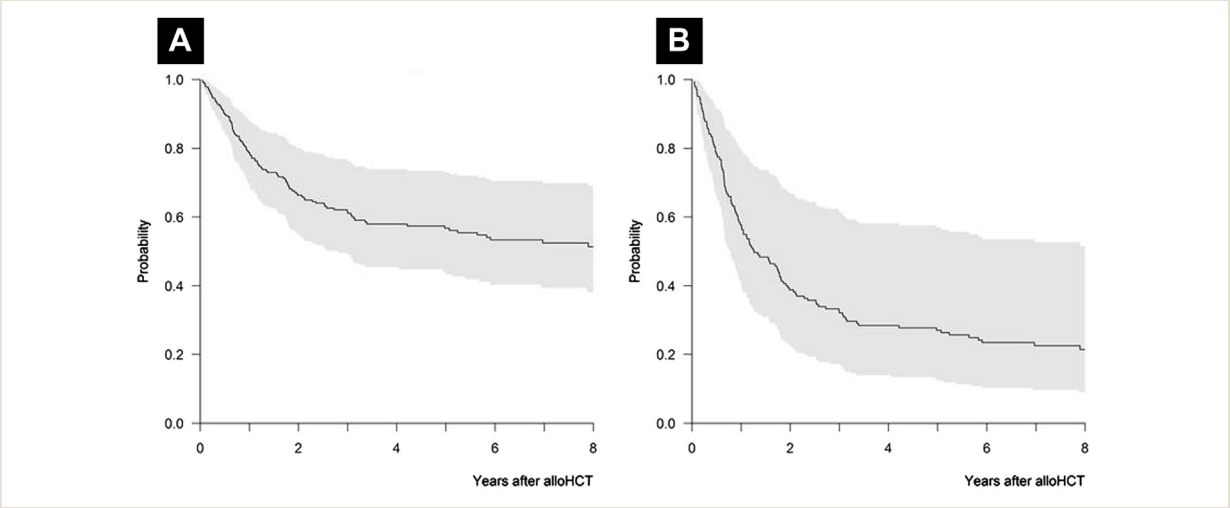
Figure 3 Model-based Prediction of 2-year NRM, CIR, and PFS of a 46-year-old Patient With del(17p) and/or del(11q) and Good Transplant Risk (A) or Poor Transplant Risk (B). The Good Transplant Risk Characteristics Are: No Prior autoHCT, Remission at the Time of alloHCT, Human Leukocyte Antigen-matched Sibling Donor, and Favorable Gender Match (Male Donor for Male Patients, Any Donor Gender for Female Patients). The Poor Transplant Risk Characteristics Are: No Prior autoHCT, No Remission at the Time of alloHCT, and Unrelated Female Donor for Male Patient



Abbreviations: alloHCT = allogeneic hematopoietic cell transplantation; autoHCT = autologous hematopoietic cell transplantation; CIR = cumulative incidence of relapse/progression; NRM = non-relapse mortality; PFS = progression-free survival.

survival, especially for the one-third progressing with Richter's transformation.[3-11] We found a 2-year CIR of 20% at 2 years for patients with high-risk cytogenetics transplanted in remission, which contrasts favorably with the results of treatment with ibrutinib (median PFS, 26 months) or venetoclax (median PFS, 16 months) in high cytogenetic risk patients.[3,4] With longer follow-up after alloHCT, the risk of NRM vanished in this patient population, but disease progression kept occurring. This is in line with our recently published study on a much larger cohort of patients with CLL who had been allo-transplanted between 2000 and 2010, where we showed that 5-year mortality in younger patients who were event-free alive at 5 years after alloHCT was limited (8% in the patients vs. 3% in the age-, gender-, and calendar year-matched general population) and was mainly owing to disease progression in contrast to a remaining high NRM in older patients.[21]

Figure 4 Model-based Prediction of 8-year Progression-free Survival of a 46-year-old Patient With del(17p) and/or del(11q) and Good Transplant Risk (A) and Poor Transplant Risk (B). The Good Transplant Risk Characteristics Are: No Prior autoHCT, Remission at the Time of alloHCT, Human Leukocyte Antigen-matched Sibling Donor, Favorable Gender Match (Male for Male Patients, Any Donor Gender for Female Patients). The Poor Transplant Risk Characteristics Are: No Prior autoHCT, No Remission at the Time of alloHCT, and Unrelated Female Donor for Male Patient



Abbreviations: alloHCT = allogeneic hematopoietic cell transplantation; autoHCT = autologous hematopoietic cell transplantation.

The very long follow-up of a large number of transplanted patients in this and the referred study adds strongly to the clinical significance of the results, especially with respect to NRM.[21] Fortunately, there is growing evidence that relapsing patients after alloHCT do respond well to ibrutinib without developing unexpected side effects,[10,43-46] which will likely prevent death owing to disease progression in many ibrutinib-naive patients and may add in tipping the balance in favor of alloHCT in good transplant risk younger patients. Finally, from an economical point of view, alloHCT may become a preferred option under circumstances that life-long treatment with KI and BCL2i cannot be afforded in younger patients with a long life-expectancy because of their very high costs.[50]

For less good transplant risk R/R patients with high-risk cytogenetics, the sequential use of KI and BCL2i seems the preferred option at first. When these patients fail 1 or 2 of these drugs, they may be brought to alloHCT when one might accept a higher NRM risk. It should be realized, however, that it is yet unknown how to salvage these KI- and/or BCL2i-refractory patients effectively before the alloHCT, especially because a substantial proportion will have relapsed with Richter's transformation.[3,5,7-11]

Conclusion

In this study, we showed that young patients with high cytogenetic risk R/R CLL have a fairly good long-term outcome after alloHCT when using well-HLA-matched donors because of a low predicted risk of NRM and a substantially higher predicted 8-year PFS than seems possible with the sequential use of KI and BCL2i. AlloHCT with HLA-matched donors may therefore, in the longer run, be superior to the results of the sequential use of KI and BCL2i in this particular group of patients.

Clinical Practice Points

- AlloHCT may result in long-term PFS in patients with R/R CLL irrespective of the presence of high-risk cytogenetics. The downside is the risk of NRM, which depends on age and the degree of HLA-matching of patient and donor.
- In this study, we elaborated on this knowledge by focusing on young patients with high cytogenetical risk (del(17p)/del(11q)) CLL by showing the impact of HLA-matching on predicted 2-year NRM, thereby defining good- and poor-risk transplant candidates. We also show that the predicted median PFS of good transplant risk patients is more than 8 years when transplanted in remission.
- The alternative for high-risk patients with immune-chemotherapy refractory CLL is sequential treatment with new drugs: BTK, PI3K, and BCL2 inhibitors. However, in the long run, this strategy will likely result in a lower survival rate in high cytogenetic risk patients than seems possible with alloHCT in good-risk transplant candidates, because a substantial proportion (33%) of progressing patients, during the use of these new drugs, do so with Richter's transformation, which heralds poor survival, whereas the median PFS in those patients progressing with CLL will be relatively shorter on the second and/or third line.
- This scenario, with an expected lower survival rate under sequential new drugs, is especially relevant to consider in younger patients that may otherwise have a fair chance on longer survival with alloHCT when a well HLA-matched donor is available.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

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Supplemental Material

Data Quality Initiative (DQI)

The data presented in this study have been collected by means of a DQI initiated by the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation (EBMT). First, all data of patients fulfilling the inclusion criteria were extracted from the registry containing data routinely collected by EBMT. Then, all centers in which these patients had been transplanted were asked to check, update, and extend these data with relevant pretransplantation information that is not collected by the regular EBMT forms. The data presented here describe the patients who have been transplanted in the 32 centers that participated in the DQI. Patients were excluded if they had experienced Richter's transformation prior to transplantation, or if they had received cord blood or a graft from a syngeneic or mismatched related donor.

Definitions

Response and relapse/progression were defined according to the updated National Cancer Institute criteria.[1] Purine analogue (PA) refractory disease was defined as nonresponse to PA containing chemotherapy or relapse within 6 months. Patients with retreatment of chronic lymphocytic leukemia within 24 months after PA combination chemotherapy were considered as having early relapse. Patients with a time to retreatment after the last PA combination therapy of more than 2 years and patients with a remission duration of more than 6 months after PA monotherapy were considered as having PA-sensitive disease. Cytogenetic abnormalities were categorized as being either del(17p), del(11q) or neither of these 2. Conditioning intensity was classified according to the working definitions published by Bacigalupo et al.[2] Donor type was classified according to the definition of Weisdorf et al.[3]

Statistical Methods

Progression-free survival (PFS) for the whole cohort and for subgroups were estimated by means of the Kaplan-Meier product limit method, and differences between subgroups were assessed by the log-rank test; cumulative incidence of relapse or progression (CIR) and non-relapse mortality (NRM) were calculated by means of cumulative incidence curves to accommodate competing risks (CIR considered a competing risk for NRM and vice versa). Follow-up for all patients was estimated by means of the reverse Kaplan-Meier method.

The issue of missing information for some clinically relevant risk factors was addressed by multiple imputation.[4]

Before fitting Cox models to the data, all relevant outcomes were censored artificially at 2 and 8 years, respectively, to limit violations of the proportionality assumption. Predictors of interest for all Cox models were: age (as linear factor by decade), donor type, donor-recipient gender match, calendar year of allogenic hematopoietic cell transplantation, Karnofsky index, cytogenetic abnormalities, remission status at allogenic hematopoietic cell transplantation, PA sensitivity, treatment with alemtuzumab prior to start of conditioning regimen, history of prior autologous hematopoietic cell transplantation, donor-recipient cytomegalovirus match, graft type, conditioning regimen, and type of T cell depletion. The age of patients below 30 years at transplantation was truncated at 30 years because this group was too small ($n = 5$) to properly estimate the age effect. To account for missing information for some risk factors, we used multiple imputations by chained equations. In order to decide on the number of imputations, we followed the often proposed "rule of thumb" that suggests to use about as many imputations as the percentage of cases with missing information for the most incomplete covariate, generating 30 complete datasets.[5,6] Predictors used in the imputation models were the predictors mentioned above plus the center in which the patient was transplanted and outcomes (hazards and status indicators).

For the first round of selection, stepwise backward variable selection based on Akaike information criterion was performed for each imputed dataset separately, always keeping age, donor type, donor-recipient gender match, and cytogenetics (in 2 categories). Risk factors that were selected in at least 40% of the models were included into a single model. Pooled estimates based on fitting this model on all multiple imputed (MI) datasets were then derived by means of the Rubin rules. Finally, for the second round of selection, the pooled Wald test was applied, keeping in the final model all risk factors with a P-value of $< .15$, taking this more liberal cut-off to avoid missing variables relevant for outcome yet not significant at the .05 level owing to the relatively small size of the dataset.

Nintety-five percent point-wise confidence intervals for the predicted PFS probabilities were calculated by applying the Rubin rules to the patient-specific cumulative hazards; results were then transformed into CIs on the PFS scale. For the competing risks outcomes, patient-specific CIR and NRM curves based on integrating information of both cause-specific hazard models were calculated in the 30 MI datasets separately by means of functions in the 'mstate' package in R. Then, pooled outcome probabilities and their standard errors were again calculated by point wise application of the Rubin rules to the quantities of interest.

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