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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Reduced intensity conditioning regimens including alkylating chemotherapy do not alter survival outcomes after allogeneic hematopoietic cell transplantation in chronic lymphocytic leukemia compared to low-intensity non-myeloablative conditioning

Niels Smedegaard Andersen[1] · Martin Bornhäuser[2,3] · Martin Gramatzki[4] · Peter Dreger[5] · Antonin Vitek[6] · Michal Karas[7] · Mauricette Michallet[8] · Carol Moreno[9] · Michel van Gelder[10] · Anja Henseler[11] · Liesbeth C. de Wreede[11] · Stefan Schönland[5] · Nicolaus Kröger[12] · Johannes Schetelig[2,3] on behalf of the CLL subcommittee, Chronic Malignancies Working Party

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Abstract

Purpose The optimal dose intensity for conditioning prior to allogeneic hematopoietic stem cell transplantation (alloHSCT) for chronic lymphocytic leukemia (CLL) is unknown.

Methods We retrospectively compared outcomes of patients who received a first alloHCST after non-myeloablative (NMA) and reduced intensity conditioning (RIC). Data of 432 patients with a median age of 55 years were included, of which 86 patients underwent NMA and 346 RIC.

Results The median follow-up after alloHSCT was 4.3 years. Compared to the RIC group, more NMA patients had purine-analog-sensitive disease, were in complete remission and received matched related donor transplantation. After RIC, the probabilities for 5-year OS, EFS, CIR, and NRM were 46%, 38%, 28%, and 35% and after NMA the respective probabilities were 52%, 43%, 25%, and 32%. In multivariate analysis, remission status prior to conditioning but not RIC versus NMA conditioning had a significant impact on CIR, EFS, and OS.

Conclusion Presumed higher anti-leukemic activity of RIC versus NMA conditioning did not translate into better outcomes after alloHSCT, but better remission status prior to conditioning did. Effective pathway inhibitor-based salvage therapies combined with NMA conditioning might thus represent the most attractive contemporary approach for alloHSCT for patients with CLL.

Keywords Relapsed/refractory chronic lymphocytic leukemia · Allogeneic hematopoietic stem cell transplantation · Nonmyeloablative/reduced intensity conditioning

✉ Johannes Schetelig
Johannes.schetelig@uniklinikum-dresden.de

[1] BMT Unit Department of Hematology, Rigshospitalet, Copenhagen, Denmark

[2] Medical Department I, University Hospital Dresden, Technische Universität Dresden, Fetscherstraße 74, 01307 Dresden, Germany

[3] DKMS gGmbH, Dresden, Germany

[4] Division of Stem Cell Transplantation and Immunotherapy, University Hospital Schleswig-Holstein, Kiel, Germany

[5] Medizinische Klinik u. Poliklinik V, University of Heidelberg, Heidelberg, Germany

[6] Department of Haematology, Institute of Hematology and Blood Transfusion, Prague, Czech Republic

[7] Department of Hematology/Oncology, Charles University Hospital, Pilsen, Czech Republic

[8] Centre Hospitalier Lyon-Sud-Hématologie, Lyon, France

[9] Hematologia, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[10] Department of Internal Medicine Hematology, University Hospital Maastricht, Maastricht, The Netherlands

[11] Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands

[12] Bone Marrow Transplantation Centre, University Hospital Eppendorf, Hamburg, Germany

Introduction

The role of allogeneic hematopoietic cell transplantation (alloHSCT) for the treatment of patients with high-risk chronic lymphocytic leukemia (CLL) has changed since the approval of ibrutinib, idelalisib, and venetoclax. These pathway inhibitors are highly active in chemoimmunotherapy-refractory and *TP53*-mutated CLL and have a favorable risk–benefit profile. Yet, none of these drugs has the potential to cure CLL and a considerable proportion of patients has to stop these drugs early due to intolerable side effects (Davids 2017; Mato et al. 2016). With the availability of these new drugs, the definition of high-risk CLL which justifies the high risk of procedure-related mortality and morbidity of alloHSCT was redefined (Dreger et al. 2018a).

Nowadays, many patients with CLL refractory to at least one pathway inhibitor refractory CLL are referred for alloHSCT. These patients may be in remission on a second pathway inhibitor or after salvage chemoimmunotherapy or have active disease. For these patients, the question is which conditioning regimen might be most promising.

Several retrospective studies have addressed the issue of conditioning prior to alloHSCT in CLL (Dreger et al. 2005; Schetelig et al. 2017b; Sobecks et al. 2014). Long-term survival was first observed after myeloablative conditioning (MAC), but the high 2-year non-relapse mortality (NRM) of 40–50% reported from early studies and the elderly patient population turned the interest toward reduced intensity conditioning (RIC) regimes (Dreger et al. 2005; Michallet et al. 1996; Sobecks et al. 2014). More recent studies showed lower NRM after MAC, but results still favored RIC (Schetelig et al. 2017b; Sorror et al. 2008a). RIC regimens were associated with less NRM and long-term disease control was retained for a significant part of the patients, with 5-year event-free survival (EFS) ranging from 32 to 46% (Brown et al. 2013; Kramer et al. 2017; Michallet et al. 2013; Schetelig et al. 2017b; Sorror et al. 2008b). MAC regimens have been compared extensively to RIC regimens, but no data exist for the comparison of fludarabine plus alkylator-based RIC to NMA based on 2 Gray total body irradiation (TBI). Several large transplant centers use this NMA regimen, whereas the majority of centers administer combinations of fludarabine and alkylating drugs for conditioning. Whether the supposed difference in intensity and short-term toxicity between these approaches affects survival outcomes and the cumulative incidence of relapse has not been studied for patients with CLL.

Our retrospective study suggests that survival outcomes including the cumulative incidences of relapse and NRM are comparable after NMA versus RIC-based alloHSCT, thus providing rationale to use the least toxic approach, especially for patients with CLL in remission.

Methods

Approach

Data were extracted from the EBMT registry. All consecutive patients who received a first alloHSCT for CLL between January 2000 and December 2011 and whose registry data had been updated and extended during the CLL data quality initiative were eligible for inclusion (Schetelig et al. 2017c). Patients were selected for this study if they had received either NMA or RIC conditioning based on cyclophosphamide, melphalan, or busulphan. Patients with Richter's Transformation prior to transplantation and patients who had received cord blood or a graft from a mismatched or syngeneic-related donor were excluded from the study.

Definitions

NMA was defined as conditioning based on 2 Gray TBI with or without fludarabine (FLU) and/or rituximab. No additional chemotherapy was allowed as part of NMA conditioning. RIC was defined as a combination of FLU and cyclophosphamide (CY), melphalan (MEL), or busulphan (BU) at non-myeloablative doses. Non-myeloablative doses were defined as < 10 mg/kg oral BU or < 8 mg/kg intravenous BU and < 150 mg/sqm MEL, whereas no maximum doses for cyclophosphamide (CY) were defined. Combinations of two or more alkylating agents and regimens containing TBI were not considered as RIC.

Patients were grouped according to the EBMT consensus indications except for considering time to re-treatment instead of time to relapse (Dreger et al. 2007). Purine-analog (PA) sensitivity was defined as non-response to PA containing chemotherapy or relapse within 6 months. Patients with re-treatment of CLL within 24 months after PA combination chemotherapy were considered as having early relapse. Patients who had a time to re-treatment 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 having PA-sensitive treatment.

Cytogenetic abnormalities were classified hierarchically according to Döhner et al. (2000) and donor type was grouped according to the definitions of Weisdorf et al. (2008).

Statistical analysis

The primary goal of this study was to analyze the impact of the conditioning regimen on EFS after alloHSCT. Baseline characteristics of patients treated with NMA and RIC were compared by the *t* test and Chi-square test. Median follow-up was calculated by means of the reverse Kaplan–Meier

estimator (Schemper and Smith 1996). EFS was defined as being alive without relapse/progression. The cumulative incidence of relapse/progression (CIR) and NRM was analyzed as competing risks. Point estimates for overall survival (OS) and EFS were calculated by the method of Kaplan and Meier. Estimates are reported together with 95% linear confidence intervals.

The impact of conditioning on OS, EFS, CIR and NRM was analyzed in cause-specific multivariate Cox regression models, in which age by decade and year of HSCT as continuous variables, Karnofsky performance status, cytogenetic risk, purine-analog sensitivity, remission status prior to start of the conditioning regimen, donor type, donor–recipient sex match, previous autoHSCT and information on in vivo or ex vivo T-cell depletion were included as potential confounders. Outcome information was censored at 2 years after alloHSCT for these analyses to have acceptable numbers of events for all endpoints and major subgroups during the analysis period. Since performance status, cytogenetic risk and purine-analog sensitivity had more than 5% missing data, a separate category for patients with missing information was added to these variables to keep them in the Cox models. For OS and EFS, none of the regression coefficients differed in clinically meaningful orders of magnitude between complete case analyses and analyses with separate categories for these three variables. We report the multivariate analyses performed on the full dataset with additional categories for missing information for performance status, cytogenetic risk, and purine-analog sensitivity. All hazard ratios represent time-averaged optimal estimates for the first 2 years after transplantation.

All analyses were performed in IBM SPSS Statistics version 23 and in R 3.1.0 using the packages 'survival', and 'cmprsk'.

Results

Patient characteristics

30 centers contributed data to this study. Altogether data on 432 patients met the selection criteria for this analysis. Patient characteristics are given in Table 1. The median age of the whole cohort of patients was 56 years (25–74 years) with only 5% of patients who were older than 65 years at the time of transplantation. Overall, the performance status at alloHSCT was good. Only very few patients (1% in the NMA-group and 3% in the RIC group) had serious restrictions in daily activities and needed a varying amount of assistance, indicated by a Karnofsky performance status of 70% or lower. For no patients, severe restrictions in self-care were reported and the lowest performance status prior to the start of the conditioning regimen was 60%.

The majority of patients had relapsed or refractory CLL after multiple lines of pretreatment. The median interval between diagnosis of CLL and alloHSCT was 56 months (range 1–308 months) and prior to admission for alloHSCT the patients had received a median of 3 prior therapies (range 0–13 lines of therapy). The EBMT consensus indications for allogeneic HSCT were met in 81% of the patients. Purine-analog refractory disease was documented in 42% of the patients, early relapse after purine analog containing chemotherapy in 17% of the patients and a deletion 17p was detected in 22% of CLL patients. Still, prior to conditioning the majority of patients (65%) had achieved a CR or PR after a broad range of chemoimmunotherapy regimens including alemtuzumab in 37% of patients.

When grouped by type of conditioning (RIC versus NMA), significant differences were found with respect to patient- and disease-related characteristics. More patients in the RIC group compared to the NMA group exposed disadvantageous risk factors at alloHSCT (see Table 1). In detail, in the RIC group less patients had a very good performance status (Chi-square test, $p = 0.001$). Moreover, in the RIC group more patients had a history of autologous HSCT (Chi-square test, $p = 0.001$), more patients had purine-analog refractory CLL (Chi-square test, $p = 0.012$), more patients had received pretreatment with alemtuzumab (Chi-square test, $p = 0.043$), and less patients had CLL in remission prior to alloHSCT (Chi-square test, $p = 0.001$). Also, less patients in the RIC group had HLA-matched related donors (Chi-square test, $p = 0.002$) compared to the NMA group.

Outcomes for the whole cohort and for subgroups of patients

The median follow-up was 42 months (range 1–147 months) at the time of database lock. Time to event outcomes after 2 and 5 years are displayed in Table 2. The survival probability at 8 years after alloHSCT was 34% (95% CI 26–43%) in the RIC group and 45% (95% CI 33–58%) in the NMA group. The probability of EFS decreased from 50% (95% CI 45–56%) at 2 years after alloHSCT to 29% (95% CI 22–36%) at 8 years after alloHSCT in the RIC group and from 58% (95% CI 47–69%) at 2 years after alloHSCT to 39% (95% CI 26–51%) at 8 years in the NMA group. Kaplan–Meier plots for OS and EFS and cumulative incidence curves for relapse/progression and NRM are shown for both groups of patients in Fig. 1.

Patients whose CLL is not in remission prior to alloHSCT must be considered as high-risk transplant candidates. EFS and OS at 2 years were 42% (95% CI 33–50%) and 57% (95% CI 49–65%) in this subgroup of patients. Even in this subgroup of patients, the intensity of conditioning (NMA versus RIC) did not have a statistically significant impact on EFS and OS (p values for the log-rank tests were 0.3

Table 1 Patient characteristics

Parameter	Classification	NMA (%) (total, $N=86$)[a]	RIC (%) (total, $N=346$)[a]
Patient gender	Male	64 (74)	252 (73)
	Female	22 (26)	94 (27)
Age at HSCT (years)	Median [range]	55 [32–74]	56 [25–73]
	Age < 45 years (%)	10 (12)	31 (9)
	Age ≥ 45 to < 55 years (%)	31 (36)	108 (31)
	Age ≥ 55 to < 65 years (%)	36 (42)	178 (51)
	Age ≥ 65 years (%)	9 (11)	29 (8)
Year of HSCT (calendar years)	2000–2001	7 (8)	29 (8)
	2002–2003	14 (16)	53 (15)
	2004–2005	15 (17)	54 (16)
	2006–2007	14 (16)	60 (17)
	2008–2009	17 (20)	82 (24)
	2010–2011	19 (22)	68 (20)
Karnofsky performance status	100	42 (52)	92 (29)
	90	28 (35)	161 (51)
	80	10 (12)	55 (17)
	≤ 70	1 (1)	10 (3)
Age at CLL diagnosis (years)	Median [range]	49 [19–67]	51 [24–70]
Interval CLL diagnosis–HSCT (months)	Median [range]	61 [6–308]	55 [1–232]
Previous auto HSCT	Yes	–	51 (15)
	Within 2 years prior to allo HSCT	–	6 (2)
Purine-analog sensitivity	Refractory disease	22 (27)	131 (44)
	Relapse < 24 months after PA combination therapy	25 (31)	55 (19)
	Sensitive disease	29 (35)	82 (28)
	Sensitivity not tested	6 (7)	30 (10)
Pretreatment with alemtuzumab	Yes	22 (27)	112 (39)
	No	59 (73)	172 (61)
Number of lines of pretreatment	Median [range]	3 [1–9]	3 [0–13]
	0–2 lines of prior therapy	32 (39)	104 (31)
	3 lines of prior therapy	15 (18)	86 (26)
	4 lines of prior therapy	16 (20)	66 (20)
	≥ 5 lines of prior therapy	19 (23)	77 (23)
Cytogenetic abnormalities	Deletion 17p	13 (22)	68 (27)
	Deletion 11q (no del 17p)	13 (22)	58 (23)
	Other abnormalities	19 (33)	88 (34)
	No abnormalities detected	13 (22)	42 (16)
EBMT consensus criteria	Criteria met	58 (82)	212 (80)
	Criteria not met	13 (18)	52 (20)
Remission status at alloHSCT	Complete remission	21 (25)	39 (11)
	Partial remission	45 (53)	174 (51)
	Stable/progressive disease	19 (22)	129 (38)

Table 1 (continued)

Parameter	Classification	NMA (%) (total, $N=86$)[a]	RIC (%) (total, $N=346$)[a]
Conditioning regimen	NMA		
	2 Gy TBI ± flu	86 (100)	–
	RIC		
	Flu/Cy	–	122 (35)
	Busulfan based	–	153 (44)
	Melphalan based	–	58 (17)
	FluBuCy	–	13 (4)
Monoclonal antibodies as part of conditioning	Rituximab	16 (19)	4 (1)
	Alemtuzumab	–	28 (8)
T-cell depletion	No ex vivo or in vivo TCD	86 (100)	185 (54)
	ATG in vivo	–	117 (34)
	Alemtuzumab in vivo	–	28 (8)
	Ex vivo TCD	–	16 (5)
Donor type	HLA-matched related donor	49 (57)	127 (37)
	HLA-compatible UD	28 (33)	180 (52)
	Partially matched UD	9 (11)	39 (11)
Graft source	PBSC	84 (98)	325 (94)
	Bone marrow	2 (2)	21 (6)
GVHD prophylaxis	CSA + MTX	2 (2)	188 (55)
	CSA + MMF	62 (72)	68 (20)
	Tacro + MMF	22 (26)	7 (2)
	CSA monotherapy	–	58 (17)
	Other	–	21 (6)
Recipient–donor gender match	Patient and donor male	48 (56)	181 (53)
	Patient male–donor female	16 (19)	69 (20)
	Patient female–donor male	10 (12)	56 (16)
	Patient and donor female	12 (14)	38 (11)
Recipient–donor CMV match	Patient neg–donor neg	14 (17)	79 (23)
	Patient neg–donor pos	13 (15)	29 (9)
	Patient pos–donor neg	28 (33)	91 (27)
	Patient pos–donor pos	29 (35)	141 (42)

N number, *HSCT* hematopoietic stem cell transplantation, *CLL* chronic lymphocytic leukemia, *PA* purine-analog, *EBMT* European Society for Blood and Marrow Transplantation, *NMA* non-myeloablative, *RIC* reduced intensity conditioning, *del* deletion, *NA* not applicable, *ATG* anti-thymocyte globulin, *TCD* T-cell depletion, *HLA* human leukocyte antigen, *UD* unrelated donor, *GVHD* graft-versus-host disease, *CSA* cyclosporine, *MTX* methotrexate, *Tacro* tacrolimus, *MMF* mycophenolate mofetil, *CMV* cytomegalovirus, *neg* negative, *pos* positive

[a]Percentages were calculated for the number of patients with available information. Due to rounding percentages may add up to more or less than one hundred percent

and 0.6). Point estimates for OS, EFS, CIR and NRM at 2 and 5 years post-allo HSCT by remission status and type of conditioning are provided in Table 2 and shown in Fig. 2.

After RIC-versus NMA-based alloHSCT, the probability of NRM was 10% (95% CI 6–13%) and 3% (95% CI 0–7%) at day + 100, 27% (95% CI 23–32%) and 29% (95% CI 19–38%) at 2 years and 35% (95% CI 29–40%) and 37% (95% CI 25–48%) at 8 years, respectively. The CIR was 22% (95% CI 18–27%) and 13% (95% CI 6-21%) at 2 years and 37% (95% CI 29–44%) and 25% (95% CI 14–36%) at 8 years after RIC-versus NMA-based alloHSCT, respectively.

Results of multivariate analyses

Results of multivariate Cox regression analyses for EFS, OS, CIR, or NRM in the first 2 years are shown in Table 3. Conditioning intensity (RIC versus NMA) did not have a significant impact on EFS, OS, CIR, or NRM. Factors

Table 2 Outcomes in patients with CLL at 2 and 5 years after alloHSCT

Subgroups	Patient number	Overall survival % (SE)		Event-free survival % (SE)		Cumulative incidence of relapse/progression % (SE)		Non-relapse mortality % (SE)	
Time from HSCT		2 years	5 years	2 years	5 years	2 years	5 years	2 years	5 years
RIC	346	63 (3)	46 (3)	50 (3)	38 (3)	22 (2)	28 (3)	27 (2)	35 (3)
NMA	86	68 (5)	52 (6)	58 (5)	43 (6)	13 (4)	25 (6)	29 (5)	32 (5)
RIC									
Age < 55 years	139	75 (4)	56 (5)	55 (4)	48 (5)	30 (4)	32 (4)	14 (3)	20 (4)
Age ≥ 55 years	207	54 (4)	39 (4)	47 (4)	31 (4)	17 (3)	25 (3)	36 (3)	45 (4)
NMA									
Age < 55 years	41	75 (7)	59 (8)	60 (8)	41 (9)	18 (6)	36 (9)	22 (7)	22 (7)
Age ≥ 55 years	45	61 (7)	46 (9)	56 (8)	46 (8)	9 (5)	12 (5)	35 (7)	42 (8)
RIC: del(17p)	68	56 (7)	40 (7)	46 (7)	38 (7)	26 (6)	28 (6)	29 (6)	34 (7)
NMA: del(17p)	13	45 (17)	45 (17)	45 (17)	45 (17)	8 (8)	8 (8)	47 (19)	47 (19)
RIC									
CR at HSCT	39	69 (8)	56 (9)	69 (7)	53 (9)	5 (4)	12 (6)	26 (7)	34 (9)
PR at HSCT	174	67 (4)	49 (5)	54 (4)	42 (4)	21 (3)	25 (4)	25 (3)	33 (4)
SD/PD at HSCT	129	55 (4)	39 (5)	40 (4)	28 (4)	29 (4)	35 (4)	31 (4)	36 (4)
NMA									
CR at HSCT	21	60 (11)	52 (12)	60 (11)	35 (13)	0 (0)	17 (12)	40 (11)	48 (13)
PR at HSCT	45	71 (7)	56 (9)	61 (7)	50 (8)	14 (5)	22 (7)	25 (7)	28 (7)
SD/PD at HSCT	19	68 (11)	46 (12)	53 (11)	38 (12)	21 (10)	36 (13)	26 (10)	26 (10)
RIC									
HLA-ident SIB	127	65 (4)	49 (5)	53 (5)	42 (5)	24 (4)	30 (4)	23 (4)	28 (4)
Matched UD	180	63 (4)	46 (4)	50 (4)	36 (4)	21 (3)	26 (4)	28 (3)	38 (4)
NMA									
HLA-ident SIB	49	78 (6)	56 (8)	63 (7)	43 (8)	18 (6)	34 (8)	18 (6)	23 (6)
Matched UD	28	61 (10)	61 (10)	57 (10)	57 (10)	7 (5)	7 (5)	36 (10)	36 (10)

SE standard error, *HSCT* hematopoietic stem cell transplantation, *NMA* non-myeloablative, *RIC* reduced intensity conditioning, *Del* Deletion, *CR* complete remission *PR* partial remission, *SD* stable disease, *PD* progressive disease, *HLA-ident* human leukocyte antigen identical, *SIB* sibling, *UD* unrelated donor

with a significant impact on overall mortality within the first 2 years were age (HR 1.3 per decade, $p = 0.05$), performance status (e.g., Karnofsky performance status of 80% versus 100% HR 1.8, $p = 0.03$), remission status (e.g., SD/PD versus CR HR 1.6, $p = 0.1$), and sex match (female donor–male recipient compared to male donor–male recipient HR 1.8, $p = 0.009$). The pattern of significant risk factors was comparable for EFS and NRM in the first 2 years, apart from age which had a profound impact on NRM (HR 1.4 per decade, $p = 0.02$) but no significant impact on EFS, and the history of prior autologous HSCT which had a significant impact on EFS (HR 1.6, $p = 0.04$) but not on OS and NRM.

With respect to the CIR within the first 2 years, prior autologous HSCT had a negative impact (HR 2, $p = 0.03$). Also, poor disease control at alloHSCT had a strong negative impact (e.g., SD/PD versus CR HR 12.3, $p = 0.001$), while unrelated donor HSCT had a protective effect on this endpoint.

Discussion

The curative potential of alloHSCT for patients with CLL comes at a substantial risk of morbidity and mortality. With the better risk–benefit ratio of orally available pathway inhibitors such as ibrutinib, venetoclax and idelalisib compared to alloHSCT for patients with high-risk relapsed or refractory CLL, the timing of alloHSCT has changed (Dreger et al. 2007, 2018a). Despite the advances in targeted therapies, alloHSCT still has a role for selected good-risk transplant candidates with very high-risk CLL, who ask for a potentially curative treatment, for patients with chemoimmunotherapy-refractory disease without access to pathway inhibitors, and for patients with chemoimmunotherapy-refractory disease, who failed one or more pathway inhibitors.

Due to the low number of alloHSCT for CLL, prospective multicenter trials which aim at a disease-specific improvement of the procedure are difficult to set up and complete

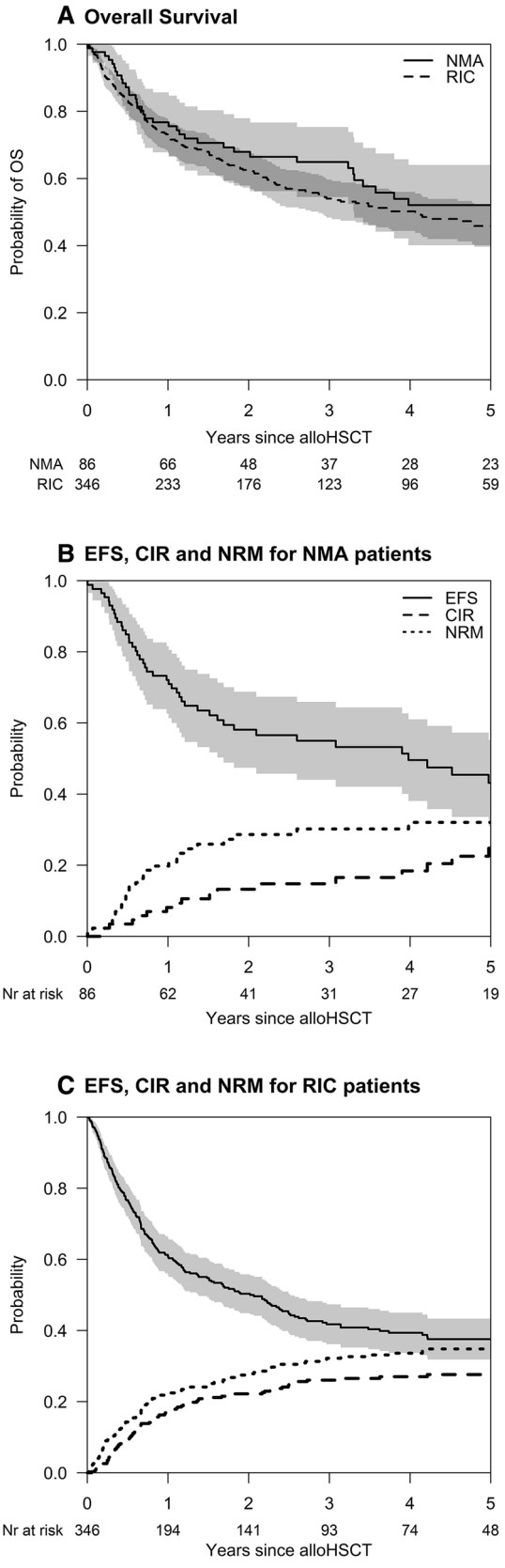

Fig. 1 Overall survival, event-free survival, cumulative incidence of relapse/progression and non-relapse mortality by conditioning with NMA or RIC. **a** Kaplan–Meier plots for overall survival for both types of conditioning. Panels B and C show Kaplan–Meier plots for event-free survival and cumulative incidence plots for relapse (broken lines) and non-relapse mortality (dotted lines) after NMA (**b**) and RIC (**c**) conditioning. The gray areas around the survival curves show the 95%-confidence interval

(Schetelig et al. 2018). Therefore, information for the procedural choices must be taken from trials which were conducted in other indications and from retrospective studies, such as the one presented here. We asked the question whether dose intensity of the conditioning regimen prior to alloHSCT impacts on disease control in patients with CLL by comparing RIC based on a combination of fludarabine plus an alkylating agent and NMA conditioning based on 2 Gray TBI (Bacigalupo et al. 2009). We used registry data which were upgraded and updated in a data quality initiative which focused on collecting comprehensive disease-specific baseline characteristics and long-term follow-up. This enabled us to correct comparison of these two conditioning regimens for the most relevant risk factors.

Two main messages from this study are: first, the decision whether NMA conditioning or RIC is chosen does not have a major impact on short- and long-term disease control or NRM. Second, remission status prior to alloHSCT is a strong prognostic factor for OS and EFS. How do these findings fit into the context of modern CLL treatment?

Better anti-leukemic activity of RIC over NMA conditioning in patients suffering from refractory disease or short lasting remissions after chemoimmunotherapy which contained alkylating agents cannot be assumed. Melphalan and Busulphan have both been used for the treatment of CLL half a century ago but were not selected for further development (Dighiero et al. 1991; Turesson 1957). On the other hand, CLL is considered a radio-sensitive cancer, but little information is available on the anti-leukemic efficacy of TBI (Johnson 1970; Sabloff et al. 2014). The dilemma with supporting one's choice based on the presumed anti-leukemic efficacy of the conditioning regimen is potentiated by the high rate of proven or unproven *TP53*-mutated CLL among these patients, a molecular feature which reduces cellular sensitivity to radio- and chemotherapy (Zenz et al. 2009). Thus, anti-leukemic activity cannot be used as a strong argument for either option, RIC versus NMA. Engraftment rates are high with both approaches and depend more on the use of ex vivo or in vivo T-cell depletion (Brown et al. 2013; Delgado et al. 2008; Khouri et al. 2008; Kramer et al. 2017; Sorror et al. 2005). So, toxicity might be the best discriminator: Again, robust comparisons of treatment emerging adverse events after RIC versus NMA conditioning do not exist but it is broadly accepted that NMA conditioning is less toxic and causes less severe neutropenia, less mucositis and

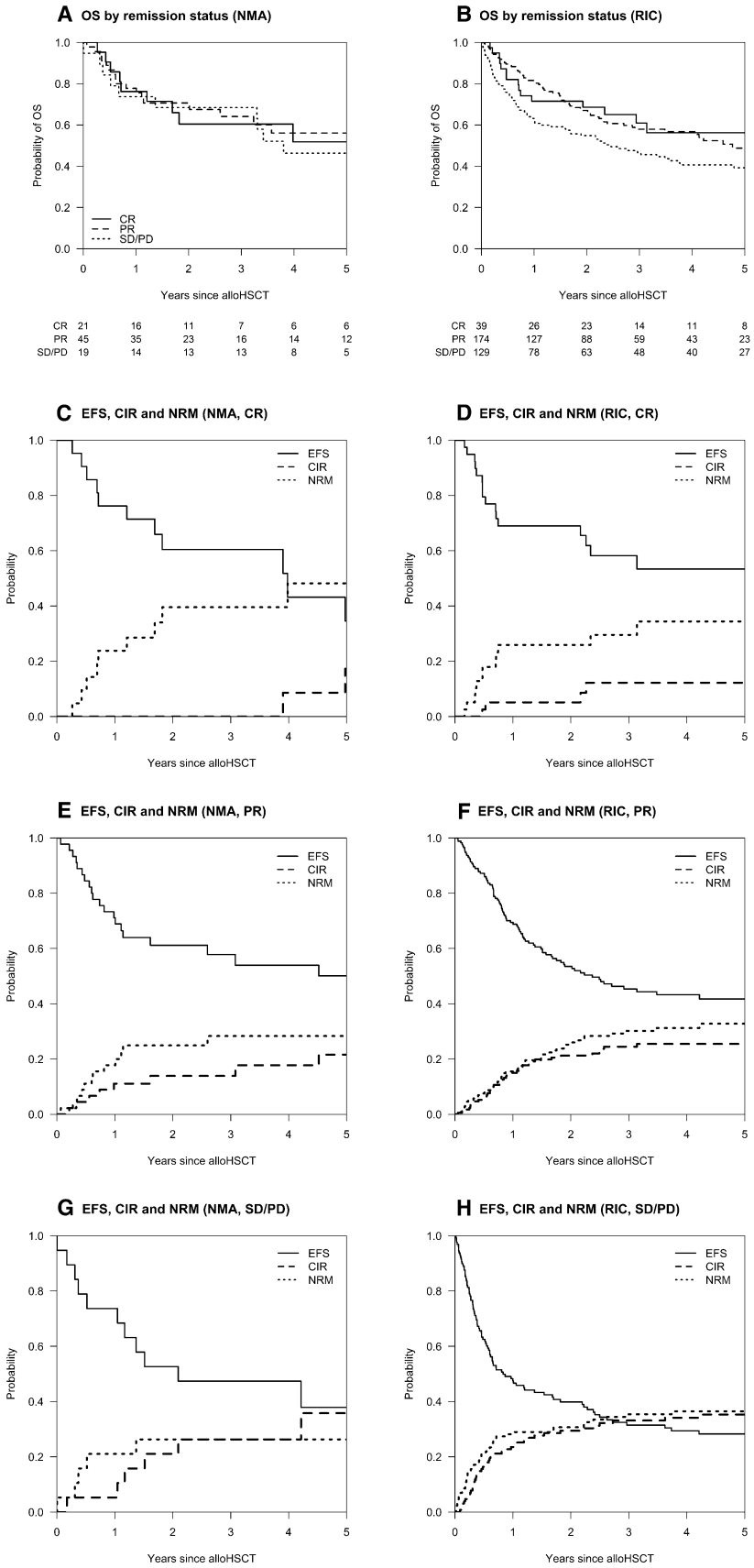

Fig. 2 Overall survival, event-free survival, cumulative incidence of relapse/progression and non-relapse mortality by RIC versus NMA conditioning and remission status prior to alloHSCT. Outcomes after RIC (right panels) and NMA (left panels) conditioning are displayed. **a**, **b** Kaplan–Meier plots for overall survival by remission status for the two groups of patients, respectively. The panels below show event-free survival, cumulative incidence of relapse/progression and non-relapse mortality for the respective groups of patients in complete remission (CR, **c**, **d**), partial remission (PR, **e**, **f**) or stable/progressive disease (SD/PD) (**g**, **h**)

Table 3 Risk factors for survival outcomes within the first 2 years after alloHSCT in patients with CLL

Risk factors	Relapse incidence			Non-relapse mortality			Event-free survival			Overall survival		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age by decade	0.8	0.6–1.04	0.08	1.4	1.1–1.9	0.02	1.1	0.9–1.3	0.6	1.3	1.01–1.7	0.04
Year of HSCT	1.1	1.00–1.2	0.06	1.0	0.9–1.03	0.2	1.0	0.95–1.1	0.8	1.0	0.9–1.05	0.6
Karnofsky performance status			0.4			0.01			0.003			0.003
100%	1			1			1			1		
90%	1.3	0.7–2.2	0.4	1.2	0.7–2.0	0.5	1.2	0.8–1.8	0.3	1.2	0.8–1.9	0.4
80%	2.0	0.97–4.0	0.06	2.1	1.2–3.7	0.01	2.0	1.3–3.1	0.002	1.8	1.1–3.0	0.02
≤ 70%	2.0	0.4–10.1	0.4	5.0	1.7–14.5	0.003	3.4	1.4–8.0	0.006	5.1	2.1–12.9	< 0.001
Unknown	1.0	0.4–2.5	0.98	0.9	0.4–2.2	0.9	0.9	0.5–1.7	0.8	0.9	0.4–1.9	0.8
Prior autologous HSCT			0.03			0.4			0.03			0.2
No	1			1			1			1		
Yes	2.0	1.1–3.7		1.3	0.7–2.6		1.6	1.05–2.5		1.5	0.9–1.9	
Cytogenetic risk categories			0.3			0.3			0.5			0.2
Deletion 17p	1			1			1			1		
Deletion 11q	0.9	0.5–1.9	0.8	0.5	0.2–1.03	0.06	0.7	0.4–1.1	0.1	0.5	0.3–0.9	0.01
Other	0.5	0.2–1.02	0.06	1.0	0.5–1.7	0.9	0.7	0.4–1.1	0.1	0.8	0.5–1.3	0.3
No abnormality	0.8	0.3–1.9	0.6	0.9	0.5–1.8	0.9	0.8	0.5–1.4	0.5	0.8	0.4–1.5	0.5
Unknown	0.8	0.4–1.7	0.6	0.7	0.4–1.4	0.3	0.7	0.5–1.2	0.2	0.7	0.4–1.1	0.2
Purine-analog sensitivity			0.4			0.03			0.06			0.02
PA-sensitive disease	1			1			1			1		
Early relapse[a]	1.7	0.8–3.6	0.2	0.8	0.4–1.5	0.5	1.1	0.7–1.7	0.8	0.8	0.5–1.5	0.6
PA-refractory disease	1.7	0.9–3.5	0.1	0.8	0.4–1.3	0.4	1.1	0.7–1.6	0.8	0.9	0.6–1.5	0.8
PA sensitivity not tested	1.4	0.5–4.2	0.5	0.9	0.4–1.9	0.8	1.0	0.6–2.0	0.9	1.0	0.5–2.0	0.96
No information	2.3	0.96–5.7	0.06	2.2	1.1–4.3	0.02	2.1	1.2–3.6	0.006	2.3	1.2–4.1	0.007
Remission status at HSCT			< 0.001			0.09			< 0.001			0.03
Complete remission	1			1			1			1		
Partial remission	5.5	1.3–23.3	0.02	0.9	0.5–1.6	0.8	1.4	0.8–2.3	0.2	1.0	0.6–1.6	0.9
SD/PD	12.3	2.8–54.1	0.001	1.5	0.8–2.9	0.2	2.5	1.5–4.4	0.001	1.6	0.9–2.9	0.09
Donor Type			0.3			0.1			0.6			0.2
HLA-identical sibling	1			1			1			1		
Matched UD	0.6	0.4–1.1	0.1	1.5	0.9–2.5	0.09	1.0	0.7–1.5	0.9	1.3	0.9–2.0	0.2
Partially matched UD	0.8	0.3–1.8	0.5	1.9	0.99–3.6	0.052	1.3	0.8–2.1	0.4	1.6	0.9–2.8	0.1
Donor–patient sex match			0.09			0.07			0.03			0.04
Male into male	1			1			1			1		
Female into male	1.2	0.6–2.1	0.6	1.9	1.1–3.1	0.01	1.5	1.02–2.1	0.04	1.8	1.2–2.7	0.009
Male into female	0.5	0.2–1.1	0.08	1.3	0.7–2.2	0.4	0.9	0.6–1.4	0.5	1.0	0.6–1.7	0.9
Female into female	0.5	0.2–1.1	0.09	0.9	0.5–1.7	0.8	0.7	0.4–1.2	0.2	0.9	0.5–1.5	0.6
T-cell depletion			0.1			0.8			0.4			0.6
No ex vivo or in vivo TCD	1			1			1			1		
In vivo TCD with ATG	1.6	0.9–2.9	0.1	0.9	0.5–1.5	0.7	1.2	0.8–1.8	0.4	0.9	0.6–1.5	0.8
In vivo TCD with alemtuzumab	2.5	1.1–5.5	0.03	0.9	0.4–2.0	0.7	1.4	0.8–2.4	0.3	1.1	0.6–2.1	0.8
Ex vivo TCD	0.7	0.2–3.4	0.7	0.3	0.0–2.6	0.3	0.5	0.2–1.7	0.3	0.3	0.03–1.9	0.2
Conditioning regimen			0.6			0.2			0.5			0.3
NMA	1			1			1			1		
RIC	1.2	0.6–2.7		0.7	0.4–1.2		0.9	0.6–1.3		0.8	0.5–1.2	

HR hazard ratio, *HSCT* hematopoietic stem cell transplantation, *Del* deletion, *PA* purine analog, *SD* stable disease, *PD* progressive disease, *HLA* human leukocyte antigen, *UD* unrelated donor, *TCD* T-cell depletion, *NMA* non-myeloablative, *RIC* reduced intensity conditioning

[a]Early relapse is defined as re-treatment within 24 months after a purine-analog combination therapy

fewer life-threatening infections. Our data also support this rating. We observed a non-significant higher mortality at day + 100 of 10% (95% CI 6–13%) after RIC versus 3% (95% CI 0–7%) after NMA conditioning. While we could not demonstrate an advantage of the presumably more toxic RIC in terms of better disease control, our data provide a rationale to choose NMA conditioning based on 2 Gray TBI with or without fludarabine as the less toxic approach.

Remission status at the time of transplantation is a strong prognostic factor for CIR (Brown et al. 2013; Sorror et al. 2008a; van Gelder et al. 2017). Besides, donor type (unrelated donor was associated with less relapse/progression than matched related HSCT), stem cell source (less relapse after PBSC versus BM) and graft manipulation (in vivo and ex vivo T-cell depletion were associated with a greater risk of relapse compared to T-cell replete HSCT) had an impact on CIR in a recently published large risk factor analysis (Schetelig et al. 2017b). This pattern of risk factors points toward the possibility that graft-versus-leukemia reactions indeed play the major role for disease control (Ritgen et al. 2004; Schetelig et al. 2003). Yet, these immunologic reactions are incompletely understood and poorly predictable for individual patients (Gragert et al. 2014; Shah et al. 2011).

The main weakness of this study comes from the fact that the data stem from patients who had not received pathway inhibitors prior to alloHSCT. Whether or not exposure to these drugs has an impact on outcome after subsequent alloHSCT is a matter of ongoing research. First data indicate that the post-transplant course is not affected by the exposure to ibrutinib and idelalisib (Dreger et al. 2018b; Schetelig et al. 2017a). Treatment sequences, however, are currently changing. Studying the impact of previous treatments on HSCT outcome will thus remain an ongoing challenge for the next couple of years. Additional weakness comes from the lack of standardized assessments for the Hematopoietic Cell Transplantation Comorbidity Index and the lack of precise measurements of residual CLL prior to alloHSCT. Finally, we cannot exclude confounding by unmeasured risk factors and local decisions to use NMA conditioning instead of RIC for patients with more comorbidity and a poorer health status. Such bias, however, would strengthen our conclusion to prefer NMA conditioning given comparable outcomes in terms of survival.

Based on the data coming from this study, we prefer NMA conditioning based on 2 Gray TBI, especially for patients with CR or in good partial remission. For patients with poor disease control at the time of referral for alloHSCT, the most potent combinations of pathway inhibitors and antibodies should be used to induce a remission prior to alloHSCT instead of increasing the dose intensity of the conditioning regimen. Patients, who do not achieve at least a partial remission, should be offered participation in clinical trials whenever possible. This group of patients might benefit most from access to CAR-T cells (Turtle et al. 2017). Our preference for NMA conditioning does not apply for patients with suspected or proven histological Richter's transformation who were excluded from the study population and who might achieve better results with conditioning regimens designed for patients with aggressive lymphoma (Cwynarski et al. 2012; Glass et al. 2014).

In summary, our results suggest that RIC does not offer a significant advantage over NMA conditioning for patients with CLL without a history of Richter's transformation. Therefore, we recommend NMA conditioning as the least toxic approach for conditioning of patients with CLL.

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Compliance with ethical standards

Conflict of interest The authors declare to have no conflict of interest with the issue addressed with this manuscript.

Ethical approval This is a retrospective registry study of the European Society of Blood and Marrow Transplantation (EBMT). Patients were not exposed to study procedures or addional assessments. The study was approved by the internal study board of the Chronic Malignancies Working Party of EBMT. EBMT Registry data were analyzed in full compliance with the Society's institutional standards. All patients have consented in the use of their medical data to advance hematopoietic cell transplantation.

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