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bjh research paper

Centre characteristics and procedure-related factors have an impact on outcomes of allogeneic transplantation for patients with CLL: a retrospective analysis from the European Society for Blood and Marrow Transplantation (EBMT)

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Summary

The best approach for allogeneic haematopoietic stem cell transplantations (alloHCT) in patients with chronic lymphocytic leukaemia (CLL) is unknown. We therefore analysed the impact of procedure- and centre-related factors on 5-year event-free survival (EFS) in a large retrospective study. Data of 684 CLL patients who received a first alloHCT between 2000 and 2011 were analysed by multivariable Cox proportional hazards models with a frailty component to investigate unexplained centre heterogeneity. Five-year EFS of the whole cohort was 37% (95% confidence interval [CI], 34–42%). Larger numbers of CLL alloHCTs (hazard ratio [HR] 0·96, $P = 0·002$), certification of quality management (HR 0·7, $P = 0·045$) and a higher gross national income per capita (HR 0·4, $P = 0·04$) improved EFS. *In vivo* T-cell depletion (TCD) with alemtuzumab compared to no TCD (HR 1·5, $P = 0·03$), and a female donor compared to a male donor for a male patient (HR 1·4, $P = 0·02$) had a negative impact on EFS, but not non-myeloablative versus more intensive conditioning. After correcting for patient-, procedure- and centre-characteristics, significant variation in centre outcomes persisted. In conclusion, further research on the impact of centre and procedural characteristics is warranted. Non-myeloablative conditioning appears to be the preferable approach for patients with CLL.

Keywords: chronic lymphocytic leukaemia, allogeneic stem cell transplantation, risk factor analysis, centre effects, frailties.

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Despite fundamental changes in the treatment of chronic lymphocytic leukaemia (CLL) with the introduction of the Bruton tyrosine kinase (BTK)-inhibitors, such as ibrutinib and acalabrutinib, phosphoinositide 3-kinase (PI3K)-inhibitors, such as idelalisib, and B-cell lymphoma 2 (BCL2)-inhibitors like venetoclax, some patients demonstrate only short lasting responses (Byrd *et al*, 2014; Furman *et al*, 2014; Roberts *et al*, 2015). Synergistic effects by combinations of pathway inhibitors and antibodies are currently under investigation (Cervantes-Gomez *et al*, 2015; Deng *et al*, 2015; Thijssen *et al*, 2015). Data on combinations or sequential therapies of these new drugs demonstrate promising activity but are still preliminary (Jain *et al*, 2015; Jones *et al*, 2015; Maddocks *et al*, 2015; Mato *et al*, 2015). However, restricted reimbursement of these expensive new drugs by national health care systems might limit the treatment choices for patients with CLL in many countries. For this reason, and considering its curative potential, alloHCT will remain an important salvage option for medically fit patients with high risk CLL (Dreger *et al*, 2014; Kharfan-Dabaja *et al*, 2016).

For those patients in need of alloHCT, the question remains as to which procedural choices are most promising. With declining numbers of patients, randomized controlled trials on procedural issues of alloHCT for patients with CLL will hardly be feasible. It is therefore justified to exploit registry data in order to gain insights into the most promising strategies for alloHCT. We took advantage of an extensive retrospective survey of patients who were transplanted between January 2000 and December 2011 in many different centres across Europe, thus allowing a broad overview of real-life practice. We set out to study the impact of conditioning intensity, stem cells source and different methods of graft-versus-host disease (GvHD) prophylaxis by T-cell depletion (TCD) on several survival outcomes. Given that procedural factors are closely linked to centre preferences, we aimed at correcting the estimates for potential centre differences and at quantifying and explaining the variability in outcomes between centres.

Methods

Approach

Data were extracted from the European Society for Blood and Marrow Transplantation (EBMT) registry and upgraded and updated through a Data Quality Initiative (for details see Data S1). The two countries contributing the fewest patients (10 in total) were excluded to restrict heterogeneity in the sample. Data on first alloHCTs for CLL between January 2000 and December 2011 were utilized. Patients were

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excluded if they had experienced Richter transformation prior to transplantation, or if they had received cord blood or a graft from a mismatched related or syngeneic donor.

Definitions

Remissions were assessed according to effective guidelines of the International Working Group for CLL (Cheson *et al*, 1996; Hallek *et al*, 2008). Purine analogue refractory disease was defined as non-response to purine analogue-containing chemotherapy or relapse within 6 months. Patients with re-treatment of CLL within 24 months after purine analogue combination chemotherapy were considered as having early relapse.

Conditioning intensity was classified according to the working definitions published by Bacigalupo *et al* (2009). Examples for non-myeloablative conditioning (NMA) regimens are 2 Gray total body irradiation (TBI) in combination with fludarabine or cyclophosphamide in combination with fludarabine. Examples for myeloablative conditioning (MAC) regimens are TBI at a cumulative dose of more than 8 Gray or doses of busulphan exceeding 8 mg/kg of the oral drug or 6·4 mg/kg of the i.v. formulation. Reduced-intensity (RIC) regimens represent the intermediate category.

T-cell depleting treatments were classified in four categories, patients receiving no TCD, patients receiving anti-thymocyte-globulin (ATG) of any brand and dose, patients receiving alemtuzumab given within 2 weeks prior to alloHCT and patients who received *ex vivo* T-cell depleted grafts. Donor type was classified according to the definition of Weisdorf *et al* (2008). Experience in alloHCT in general and in CLL in particular was measured by counting the number of CLL alloHCTs performed at the respective centre in the two calendar years before the patient was transplanted. The impact of implementation of a quality management system was assessed by considering accreditation with the Joint Accreditation Committee-International Society for Cellular Therapy& EBMT (JACIE) from 2 calendar years before it was granted (Gratwohl *et al*, 2011, 2014). Data were delivered by the JACIE office (Barcelona). Gross National Income (GNI) per capita, based on purchasing power parity (PPP) in the country and year in which a patient was transplanted, was used as a proxy to macro-economic factors (Gratwohl *et al*, 2015). Data available at www.worldbank.org were used.

Statistical analysis

The outcome of primary interest was event-free survival (EFS) up to 5 years after alloHCT as a surrogate for long-term disease control. Secondary outcomes were the cumulative incidences of relapse or progression (CIR) and of non-relapse mortality (NRM) up to 5 years after alloHCT, overall survival (OS) in the first 100 days after alloHCT, OS after the first relapse/progression after alloHCT and the cumulative incidences of acute GvHD (aGvHD) and chronic GvHD (cGvHD).

Cox multivariate regression models for (cause-specific) hazards were fitted for the respective endpoints to evaluate a potential clinical impact of risk factors on different transplant outcomes. The focus was on procedure-related factors: donor type, donor-patient sex match, type of conditioning, stem cell source and TCD. Patient-related factors were included in the models to adjust for confounding caused by differences in patient mix between different treatment strategies and centres. These factors have been selected on the basis of their significance and relevance in our previous analysis of this cohort (Schetelig *et al*, 2017): age, Karnofsky performance status, prior autologous HCT, remission status at alloHCT and cytogenetic abnormalities (omitted for EFS). Year of alloHCT was included as another adjustment factor. Centres were characterized by experience in alloHCT in general and for CLL specifically, JACIE accreditation and GNI/cap.

The Cox models were extended with a frailty component (a random effect), shared by all patients in the same centre, to model heterogeneity between centres not explained by these four factors or measured differences in patient mix (Therneau & Grambsch, 2000). These models attempt to separate true differences between centres and random fluctuation. They yield (Empirical Bayes) estimates of the residual centre effects that are reduced with respect to crude estimates. These estimates were used to quantify centre variability in outcome, expressed as a 'centre HRs' with respect to the average centre.

To visualize the impact of the centre HRs on EFS probabilities, we plotted predicted EFS curves of reference patients with mean values for all covariates, including centre characteristics, treated in three centres with the best, worst and an average centre HR.

All analyses were performed in SPSS Version 23 (IBM Statistics, IBM corporation, Armonk, NY, USA) and R 3.1.0 with the packages 'mice'(Buuren, 2012), 'survival'(Therneau, 2015), and 'cmprsk' (Gray, 2014). Further details regarding the statistical analysis are given in Data S1.

Results

Centre and patient characteristics

Thirty centres from Germany, the Czech Republic, France, Spain, Denmark, Switzerland, the Netherlands, Finland, Sweden and Norway contributed data (Table IA). In total, data on 684 patients met the selection criteria for this analysis. The annual number of transplantations evaluated in this analysis increased from 22 patients in 2000 to 64 patients in 2011. The average annual number of transplants for patients with CLL ranged from 0·9 (in 2000) to 4·2 (in 2011) per transplant centre during this period. The average annual numbers of overall alloHCTs ranged from 37·9 (in 2000) to 67·6 (in 2011) transplantations per centre.

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Table IA. Transplant centre characteristics. (total $n = 30$)

Parameter	Classification	*N* (%)
Number of all alloHCTs per centre per year	Median (range)	45 (0–169)
Total alloHCT volume (2000–2011)	Low volume (≤450 patients)	10 (33) median 334 patients (range 192–448)
	Intermediate volume (451–700)	10 (33) median 516 patients (range 452–589)
	Large volume (>700 patients)	10 (33) median 822 patients (range 701–1690)
Number of CLL alloHCTs per centre per year	Median (range)	2 (0–19)
Total CLL alloHCT volume (2000–2011)	Low volume (<20 patients)	12 (40) median 15 patients (range 7–18)
	Intermediate volume (20–34)	10 (33) median 29 patients (range 20–31)
	Large volume (≥35 patients)	8 (27) median 52 patients (range 35–128)
JACIE accreditation	No	11 (37%)
	Yes	19 (63%)
Year of first JACIE accreditation ($n = 19$)	Median (range)	2008 (2001–2011)
GNI/cap PPP per year current international $	Median (range)	32 535 (15 990–63 330)
Number (%) of centres using the respective Conditioning Regimens*	NMA	23 (77)
	RIC	28 (93)
	MAC	17 (57)
Number (%) of centres using the respective source of stem cells*	Bone marrow	22 (73)
	Peripheral blood	30 (100)
Number (%) of centres using TCD*	No TCD	25 (83)
	In vivo TCD with ATG	23 (77)
	In vivo TCD with alemtuzumab	11 (37)
	Ex vivo TCD	7 (23)

*Numbers add up to more than 100% because most centres offered more than one approach

Experience with the use of ATG was most common among the centres ($N = 23$) while only 11 centres reported experience with alemtuzumab administered for *in vivo* TCD and only 7 centres (of which 4 had a single patient) used *ex vivo* TCD.

The median age of the cohort of patients was 55 years (range, 19–74 years) (Table IB). Most patients fulfilled criteria for high-risk CLL. Only 10% of patients had never received purine-analogues during their treatment history. Deletion 17p had been diagnosed in 28% of patients and overall 63% of patients met EBMT consensus indications (Dreger *et al*, 2007).

Outcomes for the whole cohort and for subgroups of patients

The median follow-up of surviving patients was 41 months (range, 1–148 months). The probability of EFS and OS at 5 years was 37% (95% confidence interval (CI), 34–42%) and 47% (95% CI, 43–52%), respectively. At 5 years after alloHCT the cumulative incidence of NRM was 35% (95% CI, 31–39%) and CIR was 28% (95% CI, 24–31%). Given that the patients whose registry data were reviewed for the Data Quality Initiative represent a subset of all EBMT-registered patients with CLL, we compared point estimates for OS, EFS, NRM and CIR of both datasets. No significant differences were found. At day 100 after alloHCT, the cumulative incidence of aGvHD grades II–IV was 39% (95% CI, 35–42%) and that of grades III–IV was 15% (95% CI, 13–18%) for the whole cohort. The cumulative incidence of cGvHD (limited and extensive combined) at 1 year after HCT was 52% (95% CI, 48–56%).

Outcomes by type of conditioning and TCD are shown in Table II and Fig 1. As there were significant differences in the risk profile at baseline among these groups, the results of the subsequent multivariate analyses are more informative.

Results of multivariate analyses of 5-year outcomes

The main goal of the Cox regression models extended with a frailty term was to describe the impact of procedure- and centre-related characteristics of alloHCT for patients with CLL on 5-year outcomes. Details on the multivariate models for EFS, CIR and NRM are given in Table III. Among patient and disease-related baseline risk factors, age, performance status, a history of autologous transplantation and remission status had a significant impact on EFS. Female donor to male recipient alloHCTs were significantly associated with worse EFS (HR 1·4, 95% CI 1·1–1·8, $P = 0·02$). After adjusting for baseline patient-related factors, donor-related factors, year of transplantation, and measured and

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Table IB. Patient characteristics.

Parameter*	Classification	*N* (%) (total *n* = 684)
Patient sex	Male	503 (74)
	Female	181 (26)
Age at alloHCT [years]	Median (range)	55 years (19–74 years)
	age <45 years [%]	79 (12)
	age ≥45 to <55 years [%]	250 (37)
	age ≥55 to <65 years [%]	306 (45)
	age >65 years [%]	49 (7)
Karnofsky Index [%] (*N* = 623)	100	185 (30)
	90	303 (49)
	80	112 (18)
	≤70	23 (4)
Interval CLL diagnosis – alloHCT	<2 years	134 (20)
	≥2 years to <5 years	245 (36)
	≥5 years to <10 years	248 (36)
	≥10 years	57 (8)
Previous autoHCT [%]	Yes	72 (11)
	autoHCT within 2 years prior to alloHCT	9 (1)
PA Sensitivity [%] (*N* = 574)	PA-refractory disease	240 (42)
	Relapse <24 months after PA-combination	123 (21)
	PA-sensitive disease	156 (27)
	PA-sensitivity not tested	55 (10)
Pre-treatment with alemtuzumab [%] (*N* = 547)	Yes	180 (33)
	No	367 (67)
Number of lines of pre-treatment (*N* = 622)	Median (range)	3 (0–15)
	0 to 2 lines of prior therapy	196 (32)
	3 lines of prior therapy	143 (23)
	4 lines of prior therapy	122 (20)
	≥5 lines of prior therapy	161 (26)
Cytogenetic Abnormalities [%] (*N* = 522)	Deletion 17p	144 (28)
	Deletion 11q (no deletion 17p)	142 (27)
	Other abnormalities	166 (32)
	No abnormalities detected	70 (13)
Remission Status at alloHCT [%] (*N* = 645)	Complete Remission	83 (13)
	Partial Remission	342 (53)
	Stable disease/Progressive disease	220 (34)
Conditioning Regimen [%] (*N* = 675)	NMA	223 (33)
	NMA based on 2 Gy TBI	100 (15)
	NMA based on Flu/Cy	123 (18)
	RIC	353 (52)
	RIC based on dose-reduced Busulfan	145 (21)
	RIC based on Melphalan	84 (12)
	RIC based on BCNU	18 (3)
	RIC based on dose-reduced Bu/Cy	20 (3)
	RIC, other regimens	86 (13)
	MAC	99 (15)
	MAC based on TBI	64 (10)
	MAC based on high-dose Busulfan	35 (5)
Donor Type [%]	HLA-identical sibling	279 (41)
	HLA-matched unrelated donor	322 (47)
	Partially matched unrelated donor	83 (12)
Recipient-Donor sex-match [%] (*N* = 676)	Patient male – Donor male	355 (53)
	Patient male – Donor female	143 (21)
	Patient female – Donor male	98 (14)
	Patient female – Donor female	80 (12)

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Table IB. (*Continued*)

Parameter*	Classification	*N* (%) (total *n* = 684)
Recipient-Donor CMV-Match [%] (*N* = 641)	Patient negative – Donor negative	157 (24)
	Patient negative – Donor positive	67 (10)
	Patient positive – Donor negative	169 (26)
	Patient positive – Donor positive	248 (39)
Source of stem cells [%]	Bone marrow	48 (7)
	Peripheral blood	636 (93)
TCD [%] (*N* = 676)	No TCD	354 (52)
	In vivo TCD with ATG	204 (30)
	In vivo TCD with alemtuzumab	74 (11)
	Ex vivo TCD	44 (7)
Year of allogeneic HCT	2000–2001	64 (9)
	2002–2003	102 (15)
	2004–2005	114 (17)
	2006–2007	123 (18)
	2008–2009	147 (21)
	2010–2011	134 (20)
GNI/cap PPP per year [current international $]	Low GNI (15 990–30 000)	222 (32)
	Intermediate GNI (30 000–40 000)	307 (45)
	High GNI (40 000–63 330)	155 (23)

alloHCT, allogeneic haematopoietic cell transplantation; ATG: anti-thymocyte globulin; autoHCT, autologous haematopoietic cell transplantation; CLL, chronic lymphocytic leukaemia; CMV, cytomegalovirus; Cy, cyclophosphamide; Flu, fludarabine; GNI/cap PPP, Gross National Income per capita based on purchasing power parity; HCT, haematopoietic cell transplantation; HLA, human leucocyte antigen; JACIE, Joint Accreditation Committee-International Society for Cellular Therapy and European Society for Blood and Marrow Transplantation; MAC, myeloablative conditioning; N, number; NMA, non-myeloablative; PA, purine-analogue; RIC, reduced-intensity conditioning; TBI, total body irradiation; TCD, T-cell depletion.

*The number of patients with available information is given in brackets if this deviates from the total number.

unmeasured centre characteristics, TCD retained a significant impact on 5-year outcomes: according to the model, the administration of ATG protected against NRM but entailed a greater risk of relapse or progression. Alemtuzumab administered for *in vivo* TCD was associated with a greater risk of relapse but no significant impact on NRM. The net impact on EFS of TCD with alemtuzumab compared to no TCD thus was negative (HR 1·5, 95% CI 1·04–2·1, $P = 0·03$). *Ex vivo* TCD did not show a significant negative or positive impact on EFS, CIR or NRM.

RIC was associated with a greater risk of NRM compared to NMA conditioning (HR 1·6, 95% CI 1·1–2·3, $P = 0·009$) and MAC had a protective impact against relapse compared to NMA conditioning (HR 0·4, 95% CI 0·2–0·8, $P = 0·009$). Despite this, neither RIC nor MAC was associated with improved EFS, because the reduction of the CIR was counterbalanced by an increased NRM. Peripheral blood stem cells as graft source compared to bone marrow also reduced the CIR (HR 0·5, 95% CI 0·3–0·8, $P = 0·006$) but did not significantly impact EFS (HR 0·8, 95% CI 0·5–1·1, $P = 0·2$) due to a negative impact on NRM. The same pattern applied for human leucocyte antigen (HLA)-matched unrelated donor *versus* HLA-identical sibling donor alloHCT, where a significantly lower risk of relapse (HR 0·5, 95% CI 0·3–0·7, $P < 0·001$) was counterbalanced by a higher risk of NRM (HR 2·2, 95% CI 1·5–3·2, $P < 0·001$).

Table II. Time-to-event outcomes in patients with chronic lymphocytic leukaemia at 5 years after allogeneic haematopoietic cell transplantation by Conditioning intensity and TCD.

Risk factor	Event-free survival % (95% CI)	Cumulative incidence of relapse/ progression % (95% CI)	Non-relapse mortality % (95% CI)
Conditioning intensity			
Non-myeloablative	43% (36–51%)	30% (23–37%)	27% (20–33%)
Reduced intensity	32% (26–38%)	28% (23–33%)	40% (35–46%)
Myeloablative	46% (36–58%)	23% (13–32%)	32% (22–42%)
TCD			
None	42% (36–48%)	23% (18–28%)	36% (30–41%)
ATG	37% (30–45%)	31% (23–38%)	33% (26–40%)
Alemtuzumab	14% (8–27%)	46% (34–58%)	40% (28–52%)
Ex vivo TCD	50% (36–69%)	26% (12–41%)	23% (10–36%)

The *P*-value for event-free survival is derived from the log-rank test; it compares the event-free survival of the groups during the first 5 years after alloHCT. The *P*-values for cumulative incidence of relapse/progression and non-relapse mortality are derived from Gray's test; it compares the cumulative incidence curves of the groups during the first 5 years after alloHCT.

ATG, anti-thymocyte globulin; CI, Confidence Interval; TCD, T-cell depletion.

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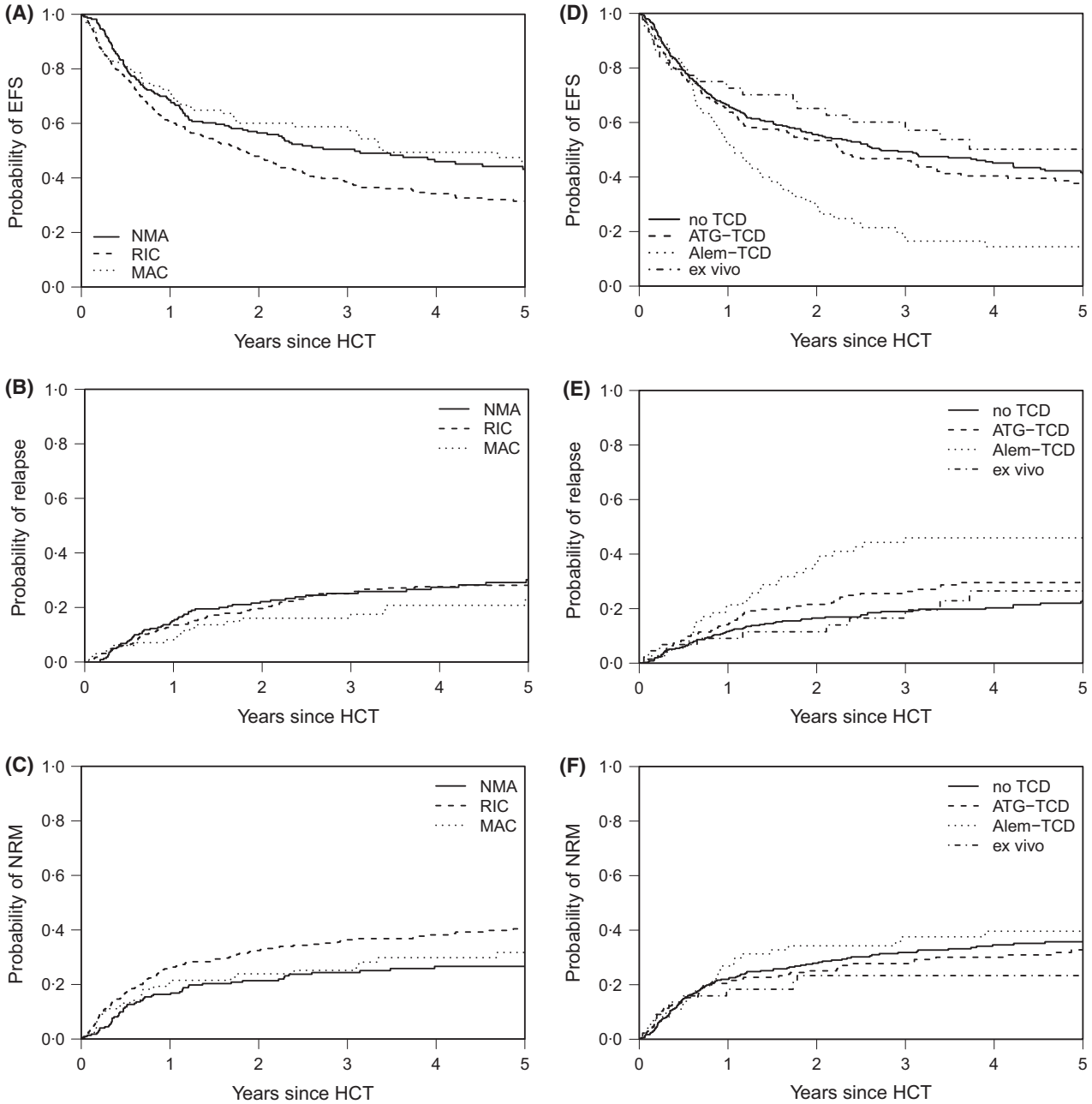

Fig 1. Event-free survival, cumulative incidence of relapse/progression and non-relapse mortality by type of conditioning (A–C) and T-cell depletion (D–F). Panels A, D: Kaplan–Meier plots for event-free survival from haematopoietic cell transplantation. Panels B, E: Cumulative incidence plots for relapse/progression. Panes C, F: Cumulative incidence plots for non-relapse mortality. EFS, event-free survival; HCT, haematopoietic cell transplantation.

In order to study differences in transplant centre outcome, the model also included variables capturing disease-specific experience, provision of quality management and the economic situation. We found a trend for less relapse/progression (HR 0·96 per additional transplantation, 95% CI 0·9–1·002, $P = 0·06$) and a significant lower risk of NRM (HR 0·96, 95% CI 0·93–0·99, $P = 0·005$) in centres with higher numbers of alloHCTs for patients with CLL. Quality management was associated with a significantly lower risk of relapse/progression (HR 0·5, 95% CI 0·3–0·8, $P = 0·003$). Higher GNI per capita showed a strong positive association with better EFS (HR 0·4, 95% CI 0·2–0·96, $P = 0·04$). However, even when including these variables to the regression model, residual variation between centres in 5-year EFS due to unmeasured centre differences was still present (test for variance of the centre effects: $P = 0·02$). The hazard ratios for 5-year EFS ranged between 0·6 (transplant centre with best outcome) and 1·2 (worst outcome) in the dataset.

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Table III. Risk factors for event-free survival, non-relapse mortality and relapse/progression within the first 5 years after alloHCTin patients with CLL. Models with factors describing centre characteristics.

	Event-free survival up to 5 years			Risk of relapse/progression up to 5 years			Risk of non-relapse mortality up to 5 years		
Risk factors	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age by decade	1·2	1·01–1·36	0·03	0·9	0·7–1·1	0·4	1·4	1·2–1·8	<0·001
Karnofsky Index			0·02			0·3			0·04
90–100%	1			1			1		
80%	1·5	1·1–1·9	0·009	1·4	0·9–2·2	0·1	1·5	1·1–2·2	0·02
≤70%	1·7	0·9–3·2	0·07	1·3	0·5–3·6	0·5	1·9	0·9–3·9	0·08
Prior autologous HCT			0·003			<0·00			0·3
No	1			1		1	1		
Yes	1·7	1·2–2·4		2·4	1·5–3·8		1·2	0·8–1·9	
Remission Status at alloHCT			0·01			<0·001			0·4
Complete Remission	1			1			1		
Partial Remission	1·3	0·9–1·9	0·1	3·5	1·6–7·7	0·002	0·8	0·5–1·2	0·3
SD/PD	1·7	1·2–2·6	0·007	4·9	2·2–11·2	<0·001	0·9	0·6–1·5	0·8
Cytogenetic abnormalities	–	–	–			0·3			0·6
Deletion 17p				1			1		
Deletion 11q (no del 17p)				0·9	0·5–1·5	0·7	0·9	0·6–1·3	0·6
Other/no abnormalities				0·7	0·4–1·1	0·1	0·8	0·6–1·2	0·4
Donor Type			0·6			0·002			<0·001
HLA-identical Sibling	1			1			1		
Matched UD	1·1	0·8–1·5	0·5	0·5	0·3–0·7	<0·001	2·2	1·5–3·2	<0·001
Partially matched UD	1·2	0·8–1·8	0·3	0·6	0·3–1·0	0·06	2·3	1·5–3·8	<0·001
Donor-Patient Sex Match			0·01			0·09			0·03
Male into Male	1			1			1		
Female into Male	1·4	1·1–1·8	0·02	1·1	0·7–1·7	0·6	1·6	1·2–2·3	0·005
Male into Female	0·9	0·7–1·3	0·6	0·6	0·4–1·1	0·1	1·2	0·8–1·8	0·4
Female into Female	0·8	0·5–1·1	0·1	0·6	0·3–1·1	0·08	0·9	0·6–1·5	0·7
Year of Transplantation	1·1	1·04–1·18	0·002	1·2	1·1–1·3	<0·001	1·0	0·9–1·1	0·9
Conditioning Intensity			0·3			0·03			0·04
Non-myeloablative	1			1			1		
Reduced intensity	1·1	0·9–1·5	0·3	0·7	0·5–1·1	0·1	1·6	1·1–2·3	0·009
Myeloablative	0·9	0·6–1·3	0·5	0·4	0·2–0·8	0·009	1·3	0·8–2·2	0·3
Stem cell source									
Bone marrow	1			1			1		
PBSC	0·8	0·5–1·1	0·2	0·5	0·3–0·8	0·006	1·1	0·6–1·9	0·7
TCD			0·09			0·003			0·06
None	1			1			1		
Anti-Thymocyte-Globulin	0·9	0·7–1·3	0·6	1·7	1·003–2·7	0·048	0·6	0·4–0·9	0·007
Alemtuzumab	1·5	1·04–2·1	0·03	2·7	1·6–4·5	<0·001	0·8	0·5–1·4	0·5
Ex vivo TCD	0·9	0·5–1·6	0·8	1·3	0·5–3·3	0·5	0·8	0·4–1·6	0·5
alloHCT Volume of TC per alloHCT in 2 prior years	1·00	1·00–1·00	0·2	1·00	1·00–1·01	0·2	1·00	1·00–1·00	0·7
CLL alloHCT Volume of TC per alloHCT in 2 prior years	0·96	0·93–0·98	0·002	0·96	0·9–1·00	0·06	0·96	0·93–0·99	0·005
JACIE accreditation			0·045			0·003			0·9
No	1			1			1		
Yes	0·7	0·5–0·99		0·5	0·3–0·8		0·98	0·7–1·4	
Logarithm of GNI per cap PPP/1000	0·4	0·2–0·96	0·04	0·4	0·1–1·5	0·2	0·5	0·2–1·1	0·08

Coefficients and their Confidence Intervals and *P*-values have been estimated in (cause-specific) multivariate Cox proportional hazards models after a Multiple Imputation procedure.

alloHCT, allogeneic HCT, haematopoietic cell transplantation; ATG, anti-thymocyte globulin; CI, confidence interval; GNI per cap PPP, Gross National Income per capita based on purchasing power parity in current international $; HLA, human leucocyte antigen; HR, hazard ratio; JACIE, Joint Accreditation Committee- International Society for Cellular Therapy and European Society for Blood and Marrow Transplantation; PBSC, peripheral blood stem cells; PD, progressive disease; SD, stable disease; TC, transplant centre; TCD, T-cell depletion; UD, unrelated donor.

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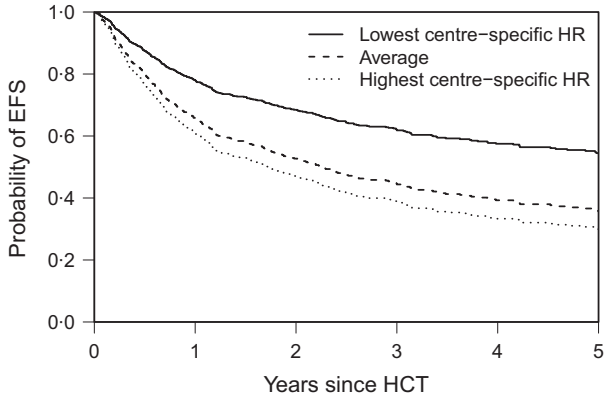

Fig 2. Impact of centre-effects on event-free survival. The impact of unmeasured characteristics of centres on EFS is shown in a model-based plot after adjusting for known patient-, procedure- and measured centre-related factors. Outcomes are shown for three reference patients who share the same values for all predictors in the model (the mean values in the dataset) who would be transplanted in centres with the highest, lowest and average frailty (centre HR) in the dataset. Unmeasured centre effects may represent patient selection, external factors or centre-specific factors that have an influence on outcome not accounted for in the model. EFS, event-free survival; HCT, haematopoietic cell transplantation; HR, hazard ratio.

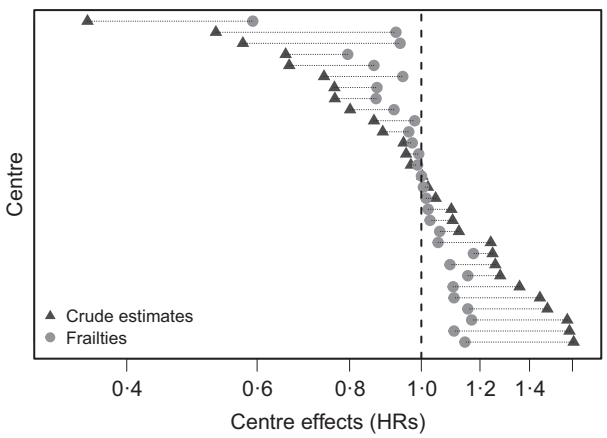

Fig 3. Model-based shrinkage of centre effects. The figure illustrates the impact of unmeasured centre characteristics on 5-year event-free survival for the 30 centres in the sample. Triangles indicate crude estimates of centre effects, calculated as the ratio of the observed and expected number of events in a centre. The expected number of events is based on measured patient and centre characteristics. Dots indicate the estimates of residual centre effects (HRs) taken from the Cox models with a frailty component as described in the methods section. These estimates take into account measured patient and centre characteristics. The centre effects (frailties) derived from this model are always smaller compared to the crude estimates, thereby accounting for chance fluctuations between centres. Points to the right of the vertical broken line indicate centres with a higher than average incidence of relapse and death and points on the left of the line indicate centres with a lower than average incidence of relapse and death. A frailty of one indicates no deviation from the average outcome.

Figure 2 shows the corresponding range of model-based EFS curves (indicating the average centre and the centres with best and worst outcome, adjusting for known factors) for a reference patient. Figure 3 illustrates how the Cox model with a frailty component shrinks the estimates of the centre effects with respect to crude estimates.

Mortality within the first 100 days and after relapse/progression

We also investigated the impact of procedure- and centre-related risk factors on mortality in the first 100 days after alloHCT. Day 100 mortality was not significantly different among transplant centres and none of the centre-related factors had a significant impact on outcome. After adjusting for patient-related risk factors, patients who received NMA conditioning had the lowest day 100 mortality. The HR comparing RIC versus NMA was 2·2 (95% CI 1·1–4·6, $P = 0·03$) and the HR comparing MA *versus* NMA was 2·3 (95% CI 0·9–5·6, $P = 0·08$).

Data of 170 patients who experienced relapse or progression after alloHCT were available (characteristics of these patients are provided in Table SI). Two-year OS after relapse/progression from first alloHCT was 42% (95% CI 31–57%) after NMA conditioning, 41% (95% CI, 31–54%) after RIC, and 30% (95% CI, 14–62%) after MA conditioning for first alloHCT, respectively (Figure S1A). Two-year OS of patients with *ex vivo* TCD for first alloHCT was 57% (95% CI, 35–94%), with alemtuzumab 45% (95% CI, 29–68%), with ATG 39% (95% CI, 27–56%) and without either type of TCD 36% (95% CI, 25–50%), respectively (Figure S1B). No significant centre variability or impact of centre-related factors was found for mortality after relapse/progression.

Discussion

Chronic lymphocytic leukaemia represents a rare indication for alloHCT. During the study period the median annual number of alloHCTs per centre for patients with CLL was only 2, ranging from 0 to 19 transplantations. For such rare transplant indications it is difficult to set up local disease-specific guidelines for alloHCT. Even for study alliances it is almost impossible to conduct prospective clinical trials on alloHCT for patients with CLL in order to evaluate procedural factors. This setting justifies well-conducted international registry-based retrospective studies. However, centres often have preferences on how to deliver alloHCT in certain diseases and thus the challenge arises to distinguish between the impact of variations in procedures, and of known and unmeasured centre characteristics on different outcomes. The issue of potential centre effects has only been addressed in a minority of published studies, and more advanced statistical methodology has rarely been applied for this specific purpose (Andersen *et al*, 1999; Loberiza *et al*, 2003; Katsahian *et al*, 2006; Logan *et al*, 2008). Frailty models, as utilized for this

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study, allow for separation of observed centre effects into explained variation by case mix and centre characteristics, unexplained differences between centre outcomes and random fluctuations (Glidden & Vittinghoff, 2004). These models have been investigated and their use recommended in statistical literature, however, they have been very rarely used for studies in the medical context.

We present data of a large cohort of patients who were well characterized with respect to their treatment history and disease biology as reported by the transplant centres that participated in a data quality initiative to upgrade and update baseline and outcome data. Owing to the retrospective nature, some important limitations also had to be accepted: detailed information on monitoring of minimal residual disease (MRD) and MRD-triggered interventions after alloHCT and data on comorbidity was not available. Further, the contributing centres are not a random sample of all transplant centres reporting to the EBMT. The fact that these centres contributed to the data quality initiative could indicate a special commitment for patients with CLL. Moreover, distribution of risk factors and treatment choices might also differ somewhat from that of all transplanted CLL patients. The results of this study may therefore not display the full range of variation in outcome.

In this study we exemplarily show the impact of disease-specific expertise on transplant outcomes in patients with a rare indication for alloHCT. More experience, measured by the number of transplants in this indication in the two preceding years, had a positive impact on EFS (HR 0·96 per alloHCT, $P = 0{\cdot}002$) and was associated with a lower risk of NRM (HR 0·96 per alloHCT, $P = 0{\cdot}005$). In contrast to Gratwohl *et al* (2015), who found an impact of the total number of alloHCTs at a centre in a large study of 37 542 alloHCTs, the total alloHCT volume of the transplant centre did not show a significant impact on EFS, CIR or NRM in our data. But, like others before, we could show that accreditation with JACIE and larger GNI per capita based on PPP had a beneficial impact on EFS (Gratwohl *et al*, 2011, 2014, 2015). Measured and unmeasured centre characteristics did not have a significant impact on 100-day mortality and survival after relapse.

When accounting for measured patient-, disease-, procedure- and centre-related characteristics, substantial variation of centre outcome in terms of EFS remained. The magnitude of unexplained centre variation is displayed by the centre-specific frailties, ranging from 0·6 to 1·2 for the centres in the dataset, equivalent to a HR of 2 for the centre with worst outcome compared to the top centre, even after adjustment for all measured covariates. The systematic shrinkage of centre effects protects against over-interpretation of extreme outcomes of small centres. In turn, some centre effects may be underestimated and the real differences may be even larger.

These unexplained centre effects probably represent a mixture of differences which could apply to the location of the transplant centre (e.g. environmental influences or buildings and structures of the hospital determining the risk of infections), unmeasured characteristics of the patient population transplanted at this centre (e.g. socio-economic status, marital status, comorbidity), selection criteria which were not reported (e.g. based on insurance status or local contraindications against alloHCT) and factors determining the success of the transplant procedure which might differ between centres (e.g. team expertise, the schema for MRD monitoring, the strategy for immune-modulation, the quality of the follow-up programme). When considering this long list of potential factors it appears unlikely that one single factor causes all unexplained variation in outcomes, but also that all information on potential risk factors will ever be collected.

How can the results then be used? The range of the frailties indicates the potential size of a bias when preferentially single-centre data from transplant centres with better outcomes are published. Our results might therefore be used as note of caution when such studies are interpreted.

A major result of our study is that, even after adjustment for these centre-related factors, some procedure-related factors retained their impact on EFS. With respect to TCD, the data suggest that *in vivo* TCD with alemtuzumab has a negative impact on EFS, which was mainly caused by an increased incidence of relapse. The British Society of Blood and Marrow Transplantation (BSBMT) reported results on 41 consecutive patients who received alemtuzumab-based RIC alloHCT for CLL and found a probability of EFS at 2 years after alloHCT of 45% (95% CI, 27–62%) (Delgado *et al*, 2006). In our larger cohort of 74 patients who received alemtuzumab-based conditioning we found a 2-year probability of EFS of only 29% (95% CI, 20–43%). Multiple reasons may account for this difference, among them specific expertise in using alemtuzumab in the BSBMT group. Dosing of alemtuzumab with the goal of *in vivo* TCD is especially challenging in patients with CLL due to the variable amount of target antigen presented by residual CLL cells (Hale *et al*, 2004). As a consequence, the depth of *in vivo* TCD can vary among patients, which may encompass differences in transplant outcomes. Moreover, the distribution of risk factors might have been different between the British and the EBMT patients.

With respect to conditioning intensity, our results suggest that dose intensity does translate into better control of CLL. However, this comes at the price of higher NRM. This pattern has been shown before for patients with CLL (Dreger *et al*, 2005). Given the full pipeline of new drugs for CLL, a rational decision would be to accept less risk of NRM but higher risk of relapse and therefore to opt for the least toxic approach for conditioning. Exemplarily, a growing body of clinical data suggests that the BTK-inhibitor ibrutinib is safe and efficacious for the treatment of relapse after alloHCT (Link *et al*, 2016; Michallet *et al*, 2016; Ryan *et al*, 2016).

In conclusion, the observation that disease-specific centre experience and JACIE accreditation have a beneficial impact

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on transplant outcomes indicates the possibility that in rare transplant indications, disease-specific transplant programmes which aim at standardization of the preparative phase, the transplant procedure, disease monitoring and immune-modulation after alloHCT could improve the outcome at transplant centres.

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Disclosures and Author Contributions

The authors declare that they have no conflict of interest in the work reported in this manuscript. JS and LCdW designed the study and wrote the manuscript. JS, NSA, CM, MvG, AV, MK, MMi, MMa, MG, DB, JF, JD, LV, JP, PD, NS, EW, MB, SOS and NK contributed patient data. AvB and AH supervised the data management. LCdW did the statistical analysis with valuable input from HP, JS and SI. All authors contributed to the discussion of the results, reviewed the manuscript and approved its final version.

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Key Points

- Event-free survival after allogeneic stem cell transplantation for patients with CLL varies significantly between centres. Differences in patient mix, procedure-related factors and centre characteristics explain part of the observed differences.
- Non-myeloablative conditioning did not have a negative impact on EFS and exposed patients to a lower risk of non-relapse mortality. For patients with CLL, the least toxic approach for conditioning should be preferred.

Supporting Information

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

Fig S1. Title: Death after relapse by previous treatment approach (conditioning intensity & TCD). The left panel (A) shows death after relapse by conditioning intensity for first transplantation. The right panel (B) shows death after relapse by T-cell depletion for first alloHCT. In these plots time zero is the day of first relapse/progression after first alloHCT.

Table SI. Characteristics of patients with relapse/progression after first alloHCT.

Data S1. Data Quality Initiative and Statistical Analysis.

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