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Allogeneic hematopoietic stem-cell transplantation for patients with Richter transformation: a retrospective study on behalf of the Chronic Malignancies Working Party of the EBMT

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Management of Richter transformation (RT) is particularly challenging, with survival estimates <1 year. We report on outcomes of 66 RT patients undergoing allogeneic-HCT (allo-HCT) between 2008 and 2018 registered with the EBMT. Median age at allo-HCT was 56.2 years (interquartile range (IQR), 51.3–63.1). Median time from RT to allo-HCT was 6.9 months (IQR, 4.9–11) and 28 (42.4%) were in complete remission (CR). The majority underwent reduced intensity conditioning (66.2%) using peripheral blood derived stem cells. Eighteen (27.3%) patients had a matched sibling donor, 24 (36.4%) a matched unrelated donor and the remaining were mismatched. Median follow-up was 6.6 years; 1- and 3- year overall and progression free survival (PFS) (95% CI) was 65% (54–77) and 39% (27–51) and 53% (41–65) and 29% (18–40), respectively. Patients in CR at time of allo-HCT had significantly better 3-year PFS (39% *vs.* 21%, $p = 0.032$). Cumulative incidences of grade II–IV acute graft versus host disease (GVHD) at day +100 was 41% (95% CI 29–53) and chronic GVHD at 3 years was 53% (95% CI 41–65). High rates of non-relapse mortality (NRM) were observed; 38% (95% CI, 26–50) at 3 years. Although potentially curative, approaches to reduce considerable NRM and chronic GVHD rates are required.

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INTRODUCTION

Chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) frequently have an indolent course, but in a significant proportion of patients (estimated between 2 and 10%) development of an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL) can occur; so called Richter transformation (RT) [1–3]. In the past decade, advent of novel therapies such as those targeting Bruton tyrosine kinase (BTK), or the B-cell lymphoma 2 protein (BCL2) have revolutionised the therapeutic landscape and considerably improved overall outcome of patients with CLL [4–6]. However, relapse still remains the rule and resistance to these agents can arise through multiple mechanisms [7–10]. Importantly, a significant proportion of patients with CLL will demonstrate 'escape' from these modern strategies by developing RT [11]. Of note, the risk of RT in the current era of novel agents remains much the same despite such major therapeutic advances. In the vast majority of cases (approximately 80%), RT results from a transformation process of the prior CLL (clonally related RT) whereas in the remainder RT may develop from a separate B cell population unrelated to the CLL clone [11]. Clonally related RT have a particularly dismal prognosis with an overall survival (OS), in general, of less than one year [1, 12]. The pathogenesis of RT is complex; a multi-step process characterised by genomic instability, with frequent *TP53* and *NOTCH1* pathway disruption, leading to dysregulation of cell cycle and several other key pathways underlies RT development [10]. Recent work analysing 19 cases of CLL transforming to RT has also highlighted that minute clones with genomic, immunogenetic and transcriptional features of RT cells could actually be detected at the time of CLL diagnosis and lay 'dormant' until later in the disease course [13].

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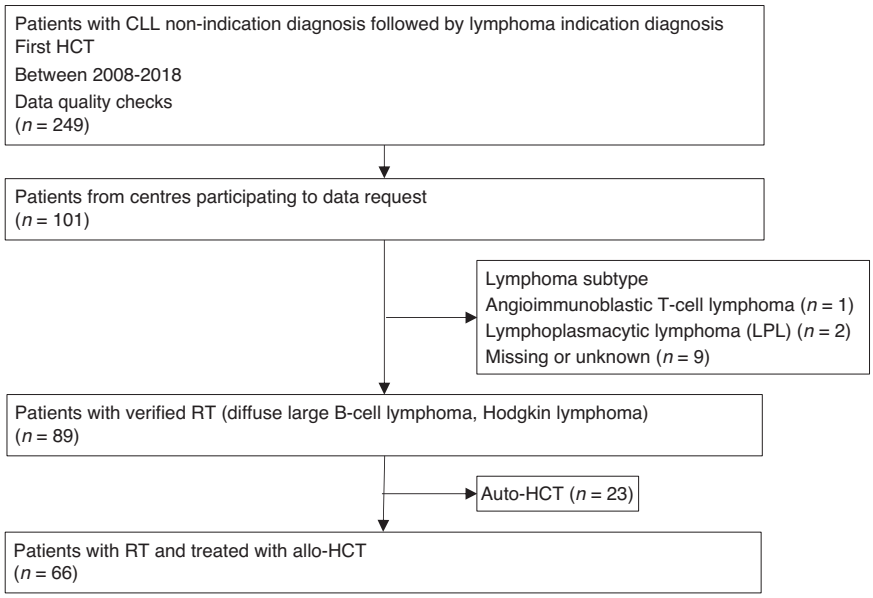

Fig. 1 Consort diagram of patient disposition. CLL chronic lymphocytic leukemia, HCT hematopoietic transplantation, RT Richter transformation, allo-HCT allogeneic HCT, auto-HCT autologous HCT.

Therapeutic strategies for RT are currently similar to that of de novo DLBCL but remain particularly challenging due to chemoresistance and short response duration [3]. Allogeneic hematopoietic stem-cell transplantation (allo-HCT) has been suggested as a recommended strategy in 'transplant eligible' patients with clonally related RT [1, 14]. Reported experience, however, remains somewhat limited and data on the role of transplant approaches reflecting European practice in the era of novel agents is lacking [15–18]. We hereby report on the characterisation and outcomes of patients with RT undergoing allo-HSCT in a contemporaneous period overlapping the advent of novel agents in the CLL arena, registered with the European Group for Blood and Marrow Transplantation (EBMT).

METHODS

Patients and data collection

This was a retrospective, multicentre, registry-based analysis approved by the Chronic Malignancies Working Party of the EBMT. The EBMT is a non-profit, scientific society representing more than 600 transplant centres mainly in Europe. Data are entered, managed, and maintained in a central database with internet access; each EBMT centre is represented in this database. EBMT centres commit to obtain informed consent according to the local regulations applicable at the time of transplantation in order to report pseudonymised data to the EBMT. The study was approved by the EBMT institutional review board in accordance to the *Declaration of Helsinki* and Good Clinical Practice guidelines.

Patients undergoing a first allo-HCT for RT between 2008 and 2018, using either Reduced Intensity Conditioning (RIC) or Myeloablative conditioning (MAC), as defined by standard EBMT criteria [19], were included in the study. All cases of bone marrow (BM), peripheral blood (PB) and umbilical cord blood as the source of stem cell source were included, as were all donor types.

This analysis focused on patients for whom a diagnosis of RT was confirmed by local centre investigators based on (i) existence of a prior or simultaneous phase of CLL or SLL and (ii) the histology of DLBCL or Hodgkin lymphoma as defined by the World Health Organization (WHO) 2016 classification. Relevant EBMT centre members were invited to participate a data initiative - follow up questionnaires (MED-C forms) were generated for centres to improve data completeness. Based on these criteria and data return, a total of 66 patients with validated RT undergoing allo-HCT were included in the final analysis from an initial cohort of 249 patients (Fig. 1).

Neutrophil engraftment was defined as the first day of an absolute neutrophil count (ANC) of 0.5 × 10^9/L lasting for three consecutive days. Platelet engraftment was defined as the first day of a platelet count of 20 × 10^9/L or higher, without transfusion support for seven consecutive days. Acute GVHD (aGVHD) was graded using established criteria, and chronic GVHD (cGVHD) was classified as limited or extensive according to published standards [20–22]. Performance status was assessed via the reported Karnofsky Performance Status (KPS) and co-morbidities via the haematopoietic cell transplantation-specific comorbidity index (HCT-CI). Remission, progression and relapse of RT were defined according to the Lugano classification for treatment response [23].

Statistical considerations

Progression-free survival (PFS) was defined as the time from transplant to disease progression evocative of RT or death from any cause. Overall Survival (OS) was defined as the time from transplant to death from any cause or last follow up. OS and PFS were estimated using the Kaplan-Meier product limit estimation method, and differences in subgroups were assessed by the Log-Rank test. Median follow-up was determined using reverse Kaplan-Meier method. The cumulative incidences of relapse/NRM, aGvHD II–IV and III–IV, overall cGvHD and limited and extensive cGvHD were analysed separately in a competing risks framework. In all GvHD related outcomes, relapse and death were considered competing events. Relapse and death were competing events for NRM and relapse incidence respectively. Competing risks analyses were also used to analyse the cumulative incidences of neutrophil engraftment and platelet engraftment, each with competing event death. Subgroup differences in cumulative incidences were assessed using Gray's test.

Continuous pre-transplant variables were summarised by median and interquartile range (IQR) and categorical pre-transplant variables are summarised as percentages within the group of patients with available data. All p-values were two-sided and $p < 0.05$ was considered significant. Statistical analyses were performed in R version 3.6.0 (R Development CoreTeam), using packages"survival," "prodlim" and "cmprsk".

RESULTS

Patient and disease characteristics

Patient, disease and responses to pre-allo-HCT therapy are displayed in Table 1. A total of 66 (CLL = 62; SLL = 4) patients with a confirmed diagnosis of RT who underwent allo-HCT from 39 centres were included in the final analysis. Median age at transplant was 56.2 years (interquartile range (IQR), 51.3–63.1) and 49 (74.2%) were male. Most patients had a KPS > 80 (68.3%) and either a low (51.1%) or intermediate (33.3%) HCT-CI score, where data was available. Regarding therapy for the pre-existing CLL/SLL, 10 (15.5%) had received no treatment before

Table 1. Patient characteristics.

	allo-HCT recipients	
	***n* = 66**	
Age at transplant (years), median [IQR]	56.2 [51.3–63.1]	
Patient sex, *n* (%)		
Male	49 (74.2)	
Female	17 (25.8)	
HCT-CI risk score, *n* (%), *missing for 21 (31.8%)*		
Low	23 (51.1)	
Intermediate	15 (33.3)	
High	7 (15.6)	
Karnofsky score, *n* (%), *missing for 3 (4.5%)*		
> 80	43 (68.3)	
≤ 80	20 (31.7)	
Underlying disease, *n* (%)		
CLL	62 (93.9)	
SLL	4 (6.1)	
Number of prior therapeutic lines for CLL/SLL, *missing for 2 (3%)*		
0	10 (15.6%)	
1 or 2	42 (65.6%)	
> 2	12 (18.8%)	
RT histology, *n* (%)		
Diffuse large B-cell lymphoma - NOS	57 (86.4)	
Hodgkin lymphoma	3 (4.5)	
Other	6 (9)	
Number of prior therapeutic lines for RT		
0	2 (3.0%)	
1	30 (45.5%)	
2 or more	34 (51.5%)	
Prior exposition to targeting therapies, *n* (%)	**CLL/SLL**	**RT**
	Missing for 29 (43.9%)	
Ibrutinib or other BTKi		
Yes	2 (5.4%)	13 (20%)
No	35 (94.6%)	53 (80%)
Idelalisib		
Yes	0	0
No	37 (100%)	66 (100%)
Venetoclax		
Yes	1 (2.7%)	3 (4.5%)
No	36 (97.3%)	63 (95.5%)
Prior autologous HSCT for RT	2 (3)	
Disease status at transplant, *n* (%)		
CR	28 (42.4)	
PR or SD	29 (44.0)	
PD	9 (13.6)	

Patient characteristics in the cohort of 66 patients receiving a first allogeneic hematopoietic transplant (allo-HCT) for Richter transformation (RT).
HCT-CI Hematopoietic Cell Transplantation-specific Comorbidity Index, *IQR* interquartile range, *CLL* chronic lymphocytic leukaemia, *SLL* small lymphocytic lymphoma, *NOS* not otherwise specified, *BTKi* Bruton Tyrosine kinase inhibitors, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease.

development of RT, 42 (65.6%) had received between 1 and 2 lines of therapy and 12 (18.8%) > 2 lines of treatment; this data was not available for 2 patients. Regarding histological characterisation, the majority ($n = 57$ (86.4%)) were reported as DLBCL, not otherwise specified (NOS) with 3 (5.4%) cases of RT presenting as Hodgkin Lymphoma. The majority of patients (34 (51.5%)) received 2 or more therapeutic lines for RT while 30 (45.5%) received one line. Heterogeneous approaches were taken for treatment, reflective of local practices, between the diagnosis of RT and allo-HCT. R-CHOP-based regimens were the most frequent (45%), followed by platinum derivative combination chemoimmunotherapy (14%) and 12% received fludarabine-based regimens. With regard to integration of BTKi or BCL2i for the treatment of RT, a total of 12 (20%) patients had treatment with ibrutinib, 1 patient had acalabrutinib and 3 (4.5%) patients had exposure to venetoclax (agents either used alone or in combination/sequential). A total of 28 (42.4%) of patients were in complete remission (CR) at the time of allo-HCT whereas 29 (43.9%) were <CR and 9 (13.6%) were classified as relapsed or progressive disease.

Transplant characteristics

Median time from RT to allo-HCT was 6.9 months (IQR, 4.9–11) (Table 2). Stem cell source was peripheral blood in the vast majority of cases (90.9%) and a majority underwent RIC (66.2%). Regarding donor type, 18 (27.3%) patients had a matched sibling donor (MSD), 24 (36.4%) a matched unrelated donor (MUD), 17 (25.8%) a mismatched UD and for 5 cases an UD was used with number of matches unknown. A mismatched related donor (MMRD) was used for 2 (3%) patients. Conditioning regimens were markedly heterogeneous but the most frequent reported were fludarabine-busulfan, fludarabine- melphalan and fludarabine-cylcophophamide based.

Outcomes

Engraftment and GVHD. The incidence of neutrophil and platelet engraftment by day +28 was 92% (95% CI 84–99) and 84% (95% CI 74–94), respectively. Of note, 7 patients had a neutrophil count that was reported as never < 1×10^9/L during the allo-HCT and 14 patients had a platelet reported as never below 20×10^9/L. Where evaluated, median time to neutrophil and platelet engraftment was 16 days (95% CI, 14–18) and 15 days (95% CI, 13–18), respectively. As shown in Fig. 2a, the day +100 cumulative incidences of aGvHD II, III and IV were 22% (95% CI 12–32%), 11% (95% CI 3–19%) and 8% (95% CI 1–15%), respectively. The cumulative incidence of cGVHD at 1 and 3- years was 52% (95% CI 39–64) and 53% (95% CI 41–65), respectively (Fig. 2b). Incidence of extensive cGVHD was reported as 29% (95% CI 19–40%) and 31% (95% CI 20–42%) at 1- and 3- years.

Survival outcomes and relapse incidence. Median follow-up was 6.6 years (95% CI, 5.5–8.7). The 1–3-and 5-year PFS was 53% (95% CI, 41–65), 29% (95% CI, 18–40) and 24% (95% CI, 14–34), respectively (Fig. 3a). The 1–3-and 5-year OS was 65% (95% CI, 54–77), 39% (95% CI, 27–51) and 30% (95% CI, 19–42) respectively (Fig. 3b). Patients in CR at time of allo-HCT had a significantly better 3-year PFS (39% (21–57%) vs. 21% (8–34%), $p = 0.032$) (Fig. 3c) and better 3-year OS, although not statistically significant (46% (28–65%) vs. 33% (18–48%), $p = 0.09$). Furthermore, patients with more than 1 prior therapeutic lines for RT at time of allo-HCT had a significantly shorter 3-year PFS (18% (5–30%) vs. 41% (24–58%), $p = 0.043$) (Fig. 3d) as well as a trend for higher 3-year NRM, although not statistically significant (47% (30–64%) vs. 29% (14–45%), $p = 0.09$). HCT-CI score had no significant impact on either PFS or OS. KS, when comparing >80 versus ≤ 80, had no significant effect on OS but those with a lower KS had a trend to worse PFS (1 -year PFS 63% (48–77%)) for >80 versus 35% (14–56%) for ≤ 80, $p = 0.05$.

The 1-year, 3-year and 5-year NRM was 23% (95% CI, 13–33), 38% (95% CI, 26–50) and 41% (95% CI, 29–53), respectively (Fig. 4a). Lastly, with regard to the cumulative incidence of relapse (CIR) the 1-,3- and 5-year CIR was 24% (95% CI, 14–35%), 33% (95% CI, 22–45%) and 35% (95% CI, 23–46%), respectively (Fig. 4b). Patients with low KPS (≤ 80) had a higher 1-year relapse (45% (23–67%)) compared to those with a

Table 2. Transplantation modalities.

	allo-HCT recipients $N = 66$
Time from RT diagnosis to allo-HCT (months), median [IQR]	6.9 [4.8–11]
Year of allo-HSCT	
2008–2013	30 (45.5)
2014–2018	36 (54.5)
Conditioning, *n* (%), *missing for 1 (1.5%)*	
Myeloablative	22 (34)
Reduced intensity	43 (66)
Fludarabine + Melphalan	12 (28)
Fludarabine + Busulfan	10 (23)
Stem-cell source, *n* (%)	
Bone marrow	2 (3)
Peripheral blood	60 (91)
Bone marrow + peripheral blood	1 (1.5)
Cord blood	3 (4.5)
Donor type, *n* (%)	
Identical sibling	18 (27.3)
Mismatched relative	2 (3)
Matched unrelated	24 (36.4)
Mismatched unrelated	17 (25.8)
Unrelated mismatch unknown	5 (7.6)
Graft-versus-host disease prophylaxis	
Ciclosporine, *n* (%), *missing for 2 (3%)*	52 (81.3)
Ciclosporine + Mycophenolate mofetil, *n* (%), *missing for 2 (3%)*	23 (36)
Anti-thymocyte globulin, *n* (%), *missing for 2 (3%)*	4 (6.3)
Alemtuzumab, *n* (%), *missing for 2 (3%)*	8 (12.5)
CMV serostatus in patient and donor, missing for 4 (6.1%)	
−/−	15 (24.2)
−/+	4 (6.5)
+/−	16 (25.8)
+/+	27 (43.5)

Transplant characteristics in the cohort of 66 patients receiving a first allogeneic hematopoietic transplant (allo-HCT) for Richter transformation (RT).
allo-CT allogeneic hematopoietic transplant, *RT* Richter transformation, *CMV* cytomegalovirus.

better performance score, although not statistically significant (16% (5–27%)) ($p = 0.1$) (Supplementary Table 1).

Main causes of death were reported as: GVHD (30.4%); grade III-IV aGVHD ($n = 3$) and chronic GVHD ($n = 11$), infection (28.3%), relapse or progression (19.6%), organ damage or failure (8.7%), secondary malignancies including post-transplant lymphoproliferative disorders (4.3%) and other (8.7%).

DISCUSSION

Therapies targeting BTK or BCL2 have been transformative in managing patients with CLL/SLL but have failed to prevent the inherent risk of transformation. RT, in particular clonal related RT, remains one of the main obstacles to long term CLL 'cure', and reflects underlying aggressive disease biology. Significant progress allowing long-term disease control is lacking for patients following RT, even in the era of novel agents, and remains a major unmet need in the field. Allo-HCT may be a valid option for selected patients to prolong response and improve survival, but as highlighted by Thompson and Siddiqi, is limited by a lack of prospective trials and the inherent bias of comparing those deemed 'transplant eligible' and being positioned for a transplant option versus those who are not [3]. We hence aimed to retrospectively evaluate the role of allo-HCT for patients with RT from a large European registry.

RT refers to the onset of an aggressive lymphoma in patients with underlying CLL/SLL. Pivotal to this study was an avoidance of 'misuse' of the term 'RT' following transformation of other lymphoproliferative disorders such as marginal zone lymphoma or even follicular lymphoma in registry reporting from centres. For such reasons, we only selected patients with a validated RT diagnosis after centre verification during the data request follow up which required histological confirmation. We hence focused our analyses on 66 patients from an initial cohort of 249 patients. This study confirmed that for patients who engrafted, there was timely neutrophil and platelet engraftment. Cumulative incidence of aGVHD grade II–IV by day +100 was 41% (95% CI 29–53). A previous report from the EBMT evaluated outcomes in 25 patients undergoing allo-HCT between 1997 and 2007, prior to the introduction of novel agents [15]. Of note, in this larger and more contemporaneous study (2008–2018), we actually highlight similar 3-year rates for both PFS (29% vs. 27%) and OS (39% vs. 36%), respectively for the current study versus the earlier cohort, demonstrating no real improvement in allo-HCT survival outcomes for RT over time. Moreover, our current cohort reveals an impact of disease status at time of allo-HCT on PFS, whereby those in CR had a better PFS. This suggests that optimising bridging therapy to gain maximal response and selecting patients with CR for allo-HCT could lead to better outcomes.

A recent series on behalf of the Center for International Blood and Marrow Transplant Research (CIBMTR) evaluated response to HCT in RT and included 118 DLBCL-RT patients who underwent allo-HSCT between 2007 and 2017 [16] Here, in a cohort where a third had deletion 17p and 39% had received a novel agent at any point before allo-HCT, 3-year PFS and OS appeared slightly superior (43% and 52%, respectively) than results from our current study. However, both the 1-year NRM and CIR incidence were similar; NRM was 23% in both studies and CIR 24% and 23% in EBMT and CIBMTR cohorts, respectively. Of note, 1-year incidence of chronic GVHD appears higher in our study (52%) compared to the CIBMTR one (37%) which may result from a larger proportion of patients transplanted with MMUDs in our EBMT cohort (25.8%) compared to CIBMTR (6%). This may also explain, at least in part, the survival discrepancies between both series, given that cGVHD was the main cause of NRM in our series. The use of posttransplant cyclophosphamide combined with a short course of cyclosporine A has recently been shown as an effective approach to reduce incidence of severe GVHD and might be an interesting approach for patients with RS [24] Similar to our findings, being in CR at the time of allo-HCT significantly associated with improved 3-year PFS in the CIBMTR cohort. This observation is also in line with a recent series from the Dana-Farber Cancer Institute evaluating outcomes of 28 well-described RT patients undergoing allo-HCT in a single centre [17]. Here, where 92.8% of the cohort were in CR or PR at the time of allo-HCT, the 4-year PFS and OS were 39% and 53% respectively. This study also confirmed the adverse prognostic effect of high lactate dehydrogenase (LDH) levels and thrombocytopenia prior to allo-HCT for RT; these factors were not robustly captured in the EBMT data set. As was found in the CIBMTR study, the number of prior lines influences NRM as well as PFS in our study.

Genomic characterisation of CLL/SLL and RT is highly relevant to guide therapeutic choice. The presence of 17p deletion is a hallmark of poor prognosis in CLL/SLL and the clonal relatedness of RT to prior CLL is a hallmark of poor prognosis [10]. Because of the

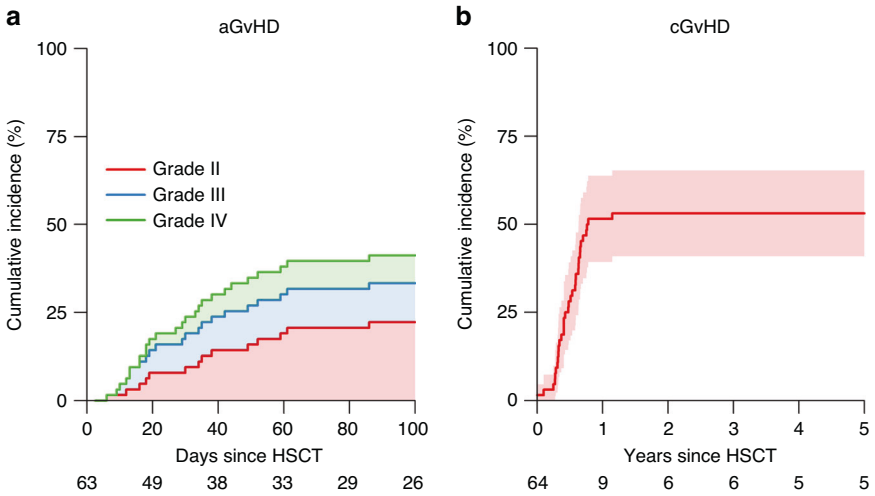

Fig. 2 Cumulative incidence curves. Cumulative incidence curves of overall **a** acute graft versus host disease (aGvHD) grade II-III-IV and **b**chronic GvHD (cGvHD) after allogeneic hematopoietic cell transplant (allo-HSCT) for Richter transformation (RT), with competing events relapse of CLL or RT and death. Cumulative incidences are represented as percentages in (**a**, **b**), with the 95% confidence intervals indicated as shaded regions in (**b**). Below the time axis are the number of patients at risk at indicated timepoints.

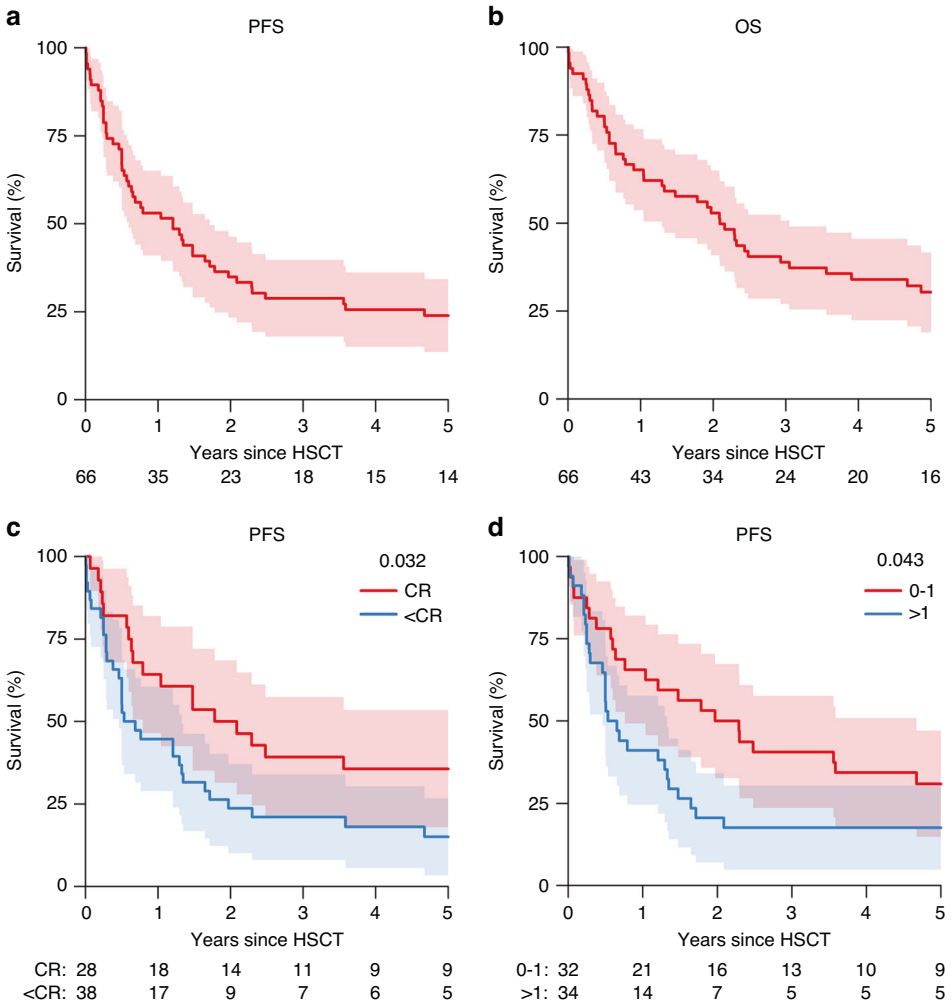

Fig. 3 Kaplan–Meier curves. Kaplan–Meier curves of overall **a** progression free survival (PFS), **b** overall survival (OS), **c** PFS stratified by complete response (CR) status before allogeneic hematopoietic stem cell transplant (allo-HSCT) and **d** PFS stratified by number of prior therapeutic lines for Richter transformation before allo-HSCT. Corresponding log-rank *p* values are indicated in the plots. Survival probabilities are represented as percentages, with the 95% confidence intervals indicated as shaded regions. The corresponding log-rank *p* value is indicated in the plot. Below the time axis are the number of patients at risk at indicated timepoints, in each group.

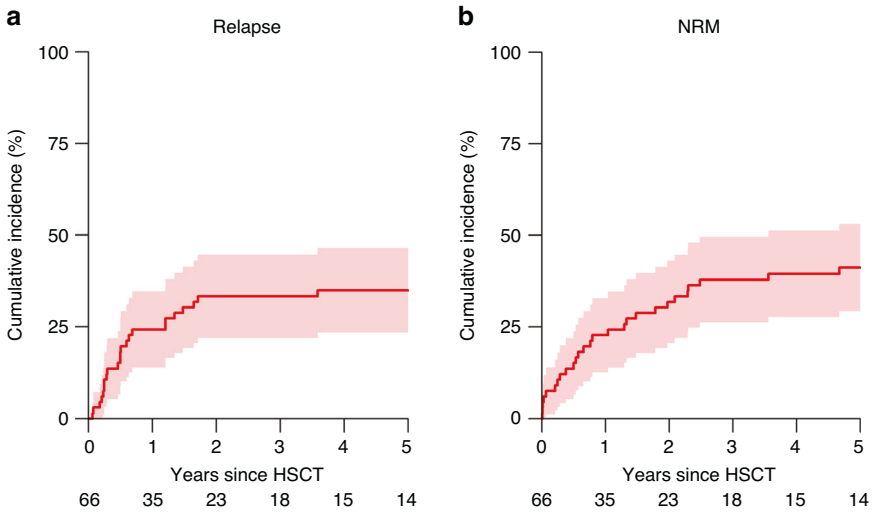

Fig. 4 Cumulative incidence curves. Cumulative incidence curves of **a** events relapse and **b** death without preceding relapse (NRM) after allogeneic hematopoietic stem cell transplant (allo-HSCT) for Richter transformation (RT). Cumulative incidences are represented as percentages, with the 95% confidence intervals indicated as shaded regions. Below the time axis are the number of patients at risk at indicated timepoints.

retrospective nature of this study, which collated allo-HCT data over a long time period from multiple centres, we did not have access to sufficient information to investigate the potential impact of genomic anomalies on outcome. However, of note, the presence of 17p deletion did not have any significant impact upon outcomes post allo-HCT in the CIBMTR study described above [16].

Considering alternative therapy approaches, bispecific antibodies and chimeric antigen receptor T-cell (CAR-T) therapies are transforming the management of patients with DLBCL but hurdles remain for the development of immunotherapies in CLL due to the well-described inherent T-cell dysfunction [25]. To date only preliminary data are reported, including use alongside BTKi, so that the use of such strategies in RT, as yet, remains unapproved [26–29]. Our present study with long term follow-up provides an important reference for further evaluating these approaches to RT.

Limitations to conclusions from our EBMT RT allo-HCT cohort are those inherent to a retrospective, registry-based study of a rare disease entity, spanning a long period of time for inclusion, with heterogeneous disease and transplant management strategies, a lack of complete data on genomic such as *TP53* alterations, clonal relationship and other prognostic markers (LDH and platelet counts prior to allo-HCT) and the selection bias of who with RT is candidate for transplant. In addition, only a minority of our cohort was pre-treated with BTK or BCL2 targeted agents so that further studies should be conducted to better depict transplant approaches in this setting. Lastly, as regards the relapse detail, we do not have discriminatory data on whether the patients relapsed with RT or CLL/SLL.

Nonetheless, it should be noted that allo-HCT can offer durable response rates and possibility of long-term cure for RT and the underlying CLL. Our findings confirm superior long-term outcomes notably for patients in best response at the time of transplant. Conversely, NRM rates remain high and the incidence of chronic GVHD and its related mortality should prompt consideration to allo-HSCT in optimal conditions, in terms of both patient performance status and donor compatibility. Prospective co-ordinated approaches are needed to evaluate which transplant platforms offers the chance of best long-term outcome.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding authors. The data are not publicly available due to privacy or ethical restrictions. No publicly available datasets are available to non-EBMT centres.

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AUTHOR CONTRIBUTIONS

RG, DJE, OT, IYA, MVG and DM designed the study, analysed data and wrote the manuscript. All other co-authors contributed data to the study, critically revised the paper and approved the submitted and final version.

COMPETING INTERESTS

R.G. declares conflicts of interest with Roche, Amgen, Janssen, Abbvie, BeiGene and AstraZeneca.

ETHICS APPROVAL

This retrospective study was approved by the Chronic Malignancies Working Party (CMWP) of EBMT.

ADDITIONAL INFORMATION

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