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RESEARCH ARTICLE

Outcomes of Patients Diagnosed With Chronic Lymphocytic Leukemia After Allogeneic Hematopoietic Stem Cell Transplantation: Results From a Tertiary Care Center

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Abstract

Background: **Allogeneic hematopoietic stem cell transplantation (allo-HCT) is currently the only curative treatment for patients with chronic lymphocytic leukemia (CLL).**

Methods: **We analyzed the outcomes of 93 patients (median age: 52 years) who underwent allo-HCT at our center between 1989 and 2019.**

Results: **After a median follow-up of 35 months, relapse was observed in 15.1% ($n = 14$) patients. The estimated 2-year non-relapse mortality, relapse-free survival, and overall survival (OS) were 38.1%, 54.2%, and 58.7%, respectively. The ECOG performance status ≥ 2 (hazard ratio [HR]: 4.1; $p = .001$) and use of total body irradiation (in a myeloablative conditioning regimen; HR: 2.64; $p = .005$) were predictive of poor OS after multivariable analysis. The occurrence of sinusoidal obstruction syndrome/veno-occlusive disease post-transplant was associated with poor survival ($p = .001$).**

Conclusion: **Although the use of kinase and bcl2 inhibitors may result in a decrease in the number and need of transplants, allo-HCT remains a viable option in selected patients with high-risk CLL and good performance status.**

Keywords: Allogeneic stem cell transplantation, Chronic lymphocytic leukemia, Outcome analysis, Predictors of outcomes

1. Introduction

Chronic lymphocytic leukemia (CLL) is the most prevalent leukemia among adults in the Western hemisphere [1]. With the introduction of novel, highly active drugs targeting multiple kinases in the B-cell receptor pathway and newer monoclonal antibodies, there has been great improvement in the outcomes in CLL [2–8]. With time, there has also been advancements in the biologic, molecular, and genetic aspects of the disease, which has resulted in better prognostic risk stratification [9–14].

Although the emergence of novel therapies has altered the therapeutic landscape of CLL because of improved efficacy and better tolerability, the disease remains incurable with pharmacologic therapy. Allogeneic hematopoietic stem cell transplantation (allo-HCT) is still the only curative option for patients with CLL [15] and may lead to long-lasting relapse-free survival (RFS) especially in patients who achieve undetectable levels of measurable

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residual disease (MRD) [16]. Currently, allo-HCT is considered a valid option for physically fit and high-risk patients with CLL [del (17p) or *TP53* mutation] or when refractory to one or more novel agents [8,15]. The effects of certain adverse prognostic factors like mutational status of *TP53*, *SF3B*, *NOTCH1*, VH gene, ZAP70 expression, and 11q− or 17p− chromosomal abnormalities are mitigated after allo-HCT [17–21].

Our study describes our experience on the outcomes of allo-HSCT in patients with CLL treated with multiple lines of treatment and examines prognostic factors affecting outcomes.

2. Patients and methods

Adult patients with CLL who underwent allo-HCT at the Princess Margaret Cancer Centre, Toronto, ON, Canada, from 1989 to 2019 were included. The study was approved by the Research Ethics Board at the University Health Network. Disease and treatment characteristics including symptoms at presentation, chemotherapy received, disease stage at presentation, cytogenetic and molecular abnormalities, as well as transplantation details were collected from electronic patient records.

2.1. Statistical analysis

We calculated survival statistics using the Kaplan–Meier method and used the log-rank test to compare survival outcomes between groups. We used the Cox proportional hazards model to identify predictors of survival outcomes. A univariate regression model was initially used with a p value < 0.1 as a cut-off to include variables in the multivariable Cox regression model. Overall survival (OS) was defined as the time from transplant to date of death from any cause or date of the last follow-up. RFS was defined as the time from transplant to date of CLL relapse or death from any cause. Non-relapse mortality (NRM) was measured from the time of transplant to death from any cause in the absence of relapse. CLL relapse was treated as a competing event for NRM. Cumulative incidence of relapse (CIR) was measured as the time from transplant to relapse with death from any cause other than relapse as a competing event. All analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

During the study period from January 1989 to December 2019, 101 adult patients with CLL underwent allo-HCT at our center. Eight patients who progressed to Richter's syndrome before transplant were excluded from the final analysis. Males were 66.7% ($n = 62$) and the median age at the time of allo-HCT was 52 (range: 26–69) years. At the diagnosis of CLL, patients were staged with both the Rai and Binet staging systems. Rai staging was 0 in 13.7% ($n = 10$) patients, 1 in 43.8% ($n = 32$) patients, and 2–4 in 42.5% ($n = 31$) patients, whereas Binet staging was Binet A in 44.4% ($n = 32$) patients, Binet B in 33.3% ($n = 24$) patients, and Binet C in 22.2% ($n = 16$) patients. Baseline cytogenetic analysis was available for 53% of patients. The most frequent cytogenetic abnormality was 13q− in 46.9% ($n = 23$) patients followed by 17p− in 40.8% ($n = 20$) patients. Other detected abnormalities were trisomy 12 (22.4%; $n = 11$) and 11q− (34.7%; $n = 17$). More than one chromosomal abnormality was found in 53.1% ($n = 26$) patients. A median of four different lines of treatment (range: 1–9) was received by the patients prior to allo-HCT. Fludarabine–cyclophosphamide–rituximab regimen (36.8%; $n = 28$) was the most common chemotherapy regimen received by the patients, followed by ibrutinib (27.6%; $n = 21$).

The median time from diagnosis to allo-HCT was 71 (range: 6–201) months. Disease stage prior to transplant was more partial remission or better in 78.1% ($n = 57$) patients and stable disease in 5.5% ($n = 4$) patients. Donor type was matched sibling donor in 56.8% ($n = 54$) patients, matched unrelated donors in 32.6% ($n = 31$), and nine out of 10 mismatched unrelated or haploidentical donors in 10.8% ($n = 10$) patients. Myeloablative conditioning (MAC) was used in 66.7% ($n = 62$) and reduced-intensity conditioning (RIC) was used in 33.3% ($n = 31$) patients. The most common regimens used were busulfan–cyclophosphamide (39.8%; $n = 37$ patients) followed by RIC fludarabine–busulfan–total body irradiation (TBI) (200) regimens (25.8%; $n = 24$). TBI was administered to 50.5% ($n = 47$) patients, with 51.1% ($n = 24$) of them receiving TBI of 200 cGy, whereas the rest 48.9% ($n = 23$) were administered ≥ 400 cGy TBI. The most common graft-versus-host disease (GVHD) prophylaxis used were cyclosporine–methotrexate in 47.3% ($n = 44$) patients followed by cyclosporine–mycophenolate in 18.9% ($n = 18$) patients. Stem cell source was peripheral blood in 72% ($n = 67$) of patients and bone marrow in 28% ($n = 26$) of patients. Transplant-related parameters are mentioned in Table 1.

Early post-transplant complications included sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) (any severity based on modified

Table 1. Pre-Transplant Donor and Recipient Characteristics and Post-Transplant Complications in Patients with Chronic Lymphocytic Leukemia.

Donors	
6/6 or 10/10 Matched sibling donor	53 (57)
10/10 or 6/6 Matched unrelated donor	30 (32.3)
5/6 or 9/10 Mismatched or haploidentical donor	10 (10.8)
Blood group match	
Matched blood group	31 (51.7)
Major or bidirectional mismatch	16 (26.7)
Minor mismatch	13 (21.7)
CMV serology matching	
CMV serology matched	47 (60.3)
CMV serology mismatch	31 (33.3)
Pre-HCT ECOG performance status	
Score 0–1	30 (61.2)
Score ≥ 2	19 (38.8)
Conditioning regimens received	
Bu–cyclophosphamide	37 (39.8)
Flu(4) + Bu(2) + TBI(200)	24 (25.8)
Flu(4) + Bu(4)+/–TBI(400)	16 (17.2)
Cy-TBI(1200)	9 (9.7)
Others	7 (7.5)
GVHD Prophylactic regimens used	
CSA–methotrexate	44 (47.3)
Alemtuzumab-CSA	15 (16.1)
ATG-PTCy-CSA	11 (11.8)
CSA–mycophenolate	18 (19.4)
Others	5 (5.4)
Post-HCT complications	
SOS/VOD	14 (15.1)
Acute GVHD	74 (79.6)
Maximum GVHD grade	
Grade I	11 (11.8)
Grade II	26 (28)
Grade III	35 (37.6)
Grade IV	3 (3.2)

Note. Data are presented as *n* (%). ATG = antithymocyte globulin; Bu = busulfan; CMV = cytomegalovirus; CSA = cyclosporine A; ECOG = Eastern Cooperative Oncology Group; Flu = fludarabine; GVHD = graft-versus-host disease; HCT = hematopoietic stem cell transplantation; PTCy = post-transplant cyclophosphamide; SOS/VOD = sinusoidal obstruction syndrome/veno-occlusive disease; t-AML = therapy-related acute myeloid leukemia; TBI = total body irradiation.

Seattle criteria) in 15.1% ($n = 14$) of patients and graft failure in 6.5% ($n = 6$) of patients. Median (range) neutrophil engraftment, platelet engraftment, and length of hospital stay were 17 (5–45), 12 (5–76), and 23 (1–103) days, respectively. Early transplant-related mortality (TRM; before D + 100 post-transplant) occurred in 11.6% ($n = 11$) patients. Causes of early death were SOS/VOD in 36.3% ($n = 4$) patients, severe sepsis in 27.3% ($n = 3$) patients, and relapse of disease and acute GVHD each in 18.2% ($n = 2$) patients. Grade II–IV acute GVHD was observed in 68.4% ($n = 65$) patients, and chronic GVHD (all grades) was observed in 58.9% ($n = 56$) patients. After a median follow-up of 35 months (>D + 100 post-HSCT), relapse of CLL was observed in 14% ($n = 13$) patients. The estimated 2-year NRM, RFS, and OS were 38.1%, 54.2%, and 58.7%, respectively (Fig. 1).

We examined categorical and continuous variables like age, sex, presence of 17p rearrangements or more than one cytogenetic abnormalities, performance status prior to transplant, donor type, conditioning regimen intensity, GVHD prophylaxis regimens, and other parameters for factors predictive for better OS post allo-HCT in patients with CLL (excluding Richter's syndrome). The absence of 11q deletion, transplant after 2005, and mild or no GVHD were some of the factors associated with favorable outcomes after univariate analysis. Factors predictive of better OS on univariate analysis are listed in Table 2. After multivariable Cox regression analysis (Table 3), Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 (hazard ratio [HR]: 4.1; $p = .001$), and use of TBI (in a MAC regimen) (HR: 2.64; $p = .005$) were predictive of poor OS after allo-HCT (Fig. 2). The occurrence of SOS/VOD post-transplant was significantly associated with poor OS and higher NRM ($p = .001$).

4. Discussion

We studied the outcomes and predictors of outcomes in patients with CLL undergoing allo-HCT after multiple (median = 4) lines of treatment. Our outcomes after allo-HCT in CLL patients with a 2-year OS and RFS of 58.7% and 54.2%, respectively, are comparable with previously published literature [22–25]. Sorror et al. [25] reported a 2-year OS of 60% and event-free survival (EFS) of 52% in 64 patients with advanced CLL treated with non-myeloablative HCT. The largest available data is from the EBMT registry that includes 2,589 patients who underwent HCT between 2000 and 2010 and showed 2-year OS and EFS of 62% and 49%, respectively [26].

The NRM in our study was 38.2% at 2 years. This is higher than that in published literature of allo-HCT in CLL patients where mostly HLA-identical donors were used [27,28], but comparable with the results of publications which include haploidentical, umbilical cord blood, and mismatched unrelated donor allo-HCT [15,29]. Higher NRM in our cohort was likely due to our heavily pretreated population prior to allo-HCT and a high proportion of patients receiving MAC regimens. Higher NRM after allo-HCT is expected when patients become refractory or intolerable to two or more lines of therapy as the response rate and RFS seems lower when applied sequentially [15,30]. Available literature on outcomes of allo-HCT in CLL is summarized in Table 4.

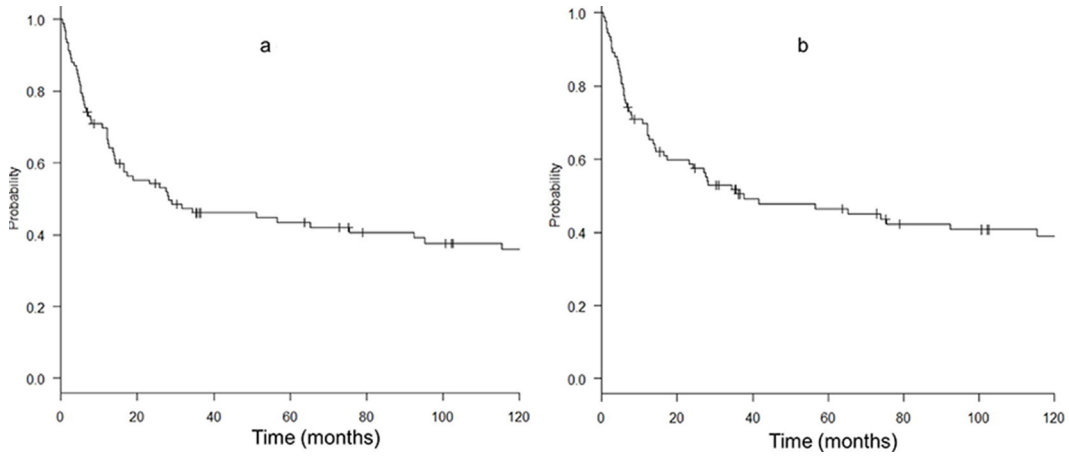

Fig. 1. Kaplan–Meier curves showing (a) relapse-free survival and (b) overall survival of patients with chronic lymphocyte leukemia after allogeneic hematopoietic stem cell transplantation.

Table 2. Factors Associated with Poor Overall Survival after Univariate Analysis.

Factor		Median estimated survival (months)	*p*
Time of transplant	HCT before 2005	24.2	0.1
	HCT after 2005	65.3	
Deletion 11q	Presence of deletion	7.97	0.1
	Absence of deletion	56.63	
Binet staging	Binet A	73.9	0.1
	Binet B	NR	
	Binet C	14.03	
FCR chemotherapy	FCR received	12.1	0.01
	No Previous FCR	138.5	
Performance status at HSCT	ECOG 0–1	NR	0.017
	ECOG 2	23.2	
Conditioning regimens	TBI ≥ 400 cGy (Cy-TBI/FBT400)	10.8	0.002
	Non-TBI–based conditioning and TBI-based RIC	75.6	
GVHD prophylaxis	CSA–methotrexate prophylaxis	37.8	0.001
	CSA–Mycophenolate	56.6	
	ATG–CSA–PTCy	NR	
	CSA–Alemtuzumab and others	5.8	
Post-transplant SOS/VOD	Patients with SOS/VOD (any severity)	6.3	0.03
	Patients without VOD	52.5	
Acute GVHD	No acute GVHD	NR	0.06
	Acute GVHD Grade I-II	130.17	
	Acute GVHD Grade III-IV	27.53	

Note. ATG = antithymocyte globulin; CSA = cyclosporine A; ECOG = Eastern Cooperative Oncology Group; FCR = fludarabine, cyclophosphamide, rituximab; GVHD = graft-versus-host disease; HCT = hematopoietic stem cell transplantation; NR = not reached; PTCy = post-transplant cyclophosphamide; RIC = reduced-intensity conditioning; SOS/VOD = sinusoidal obstruction syndrome/veno-occlusive disease; TBI = total body irradiation.

Table 3. Predictive Factors for Poor Overall Survival after Multivariable Cox Regression Analysis.

Factor	HR (95% CI)	*p*
ECOG performance status score ≥ 2	4.1 (1.8–9.3)	0.001
Conditioning regimen with TBI ≥ 400 cGy	2.64 (1.1–6.2)	0.025

Note. CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; TBI = total body irradiation.

The effect of cytogenetic abnormalities on post–allo-HCT outcomes is still unclear. Several studies reported that cytogenetic risk did not affect survival after-HCT in CLL patients [22,27], whereas Chavez et al. [24] showed significantly worse outcomes after allo-HCT, with a median survival of 5.5 months in patients with 11q− as well as 17p−. The presence of 11q− is associated with bulky lymphadenopathy as

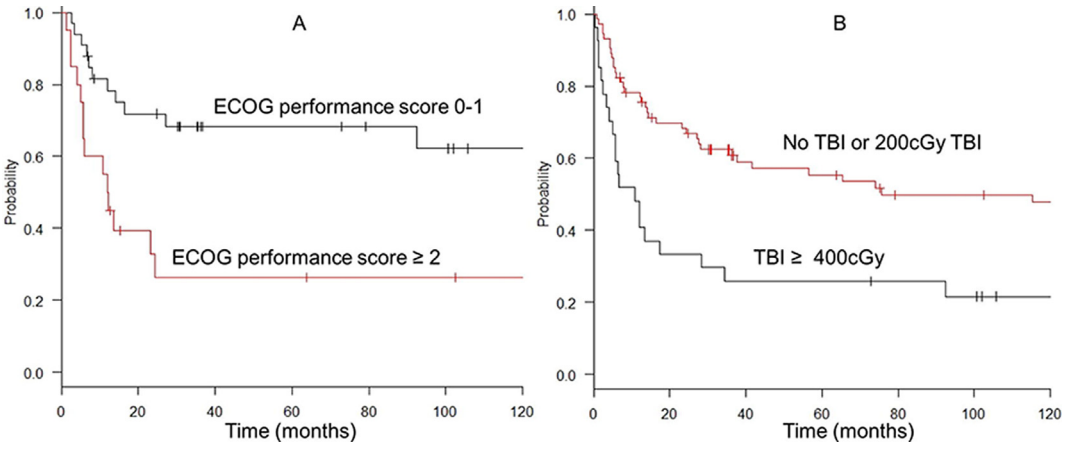

Fig. 2. Kaplan–Meier curves showing predictors of poor overall survival that is (A) Eastern Cooperative Oncology Group (ECOG) performance score and (B) use of total body irradiation (TBI) in myeloablative conditioning in patients with chronic lymphocyte leukemia after allogeneic hematopoietic stem cell transplantation.

well as a more aggressive disease course and poor response to therapy [31–33]. In our study, the median OS was 8 months in the group of patients with deletion 11q, while it was 56 months in patients without the deletion. However, since cytogenetic information was only available for 52% of the patients and additional cytogenetic abnormalities were present in most of the patients, this difference was not statistically significant.

To date, no randomized clinical trials have compared the dose intensity of the preparative regimens (MAC vs. RIC vs. non-MAC regimens) in CLL [8]. Post-transplant outcomes favoring RIC regimens were shown in the single-center retrospective study by Peres et al. [34], who showed a 5-year OS of 63% in the RIC group versus 18% in the MAC group. Dreger et al. [35], however, showed that there was no significant difference between RIC and MAC in terms of EFS and OS, but showed a significant reduction of TRM in the patients receiving RIC. Brown et al. [36] stated that RIC HCT in patients with CLL was associated with significantly improved long-term RFS (43% vs. 36%) and OS (63% vs. 49%) at 5 years compared with MAC. Kharfan-Dabaja et al. [37] concluded that RIC regimens appear to be the most desirable choice for CLL patients undergoing HCT, based on lower NRM (23% vs. 32%) and better OS rates (60% vs. 51%). The large retrospective study from the CIBMTR registry showed that the 3-year OS was significantly higher for the RIC allo-HCT group [40]. In our study, the risk of NRM declined significantly after 2005, possibly because of the increased use of RIC regimens compared with MAC regimens after 2005 (data not shown). A similar result was found in the study by Dana-Farber Cancer Institute (Boston, MA, USA), where the risk of death declined significantly starting in 2004, 5-year OS for HCT between 2004 and 2009 was 83% for RIC regimens compared with 47% for MAC regimens in patients with CLL undergoing allo-HCT [36].

Graft-versus-leukemia effect leading to lower relapse rate is frequently linked to the occurrence of GVHD in patients with CLL [35,38]. A significantly lower incidence of relapse or progression has been found in patients with acute or chronic GVHD (relative risk: 0.2, $p = .006$) compared with patients who did not have clinical signs of GVHD after HCT [17]. Therefore, different types of GVHD prophylaxis may have an impact on the outcome of allo-HCT [17]. We found a significantly longer OS in univariate analysis in patients who received novel GVHD prophylactic regimens (antithymocyte globulin–post-transplantation cyclophosphamide–cyclosporine) than in those who received other GVHD prophylaxis regimens like cyclosporine–methotrexate or alemtuzumab. The small number of patients and retrospective nature of our study prevents making definitive conclusions on the ideal GVHD prophylaxis. However, it is less likely that a head-to-head trial will be conducted to compare the GVHD prophylactic regimens in allo-HCT in patients with CLL.

The risk factors identified for poor outcomes after allo-HCT in patients with CLL according to published literature, including higher age, unrelated donor type, unfavorable sex mismatch (female donor to a male patient), prior autologous transplantation, and disease responsiveness to initial therapy [15,22,23], were not predictive of outcomes in our cohort of patients. In line with other large studies, our analysis demonstrated a significant

Table 4. Existing literature on outcome after allogeneic HCT in CLL.

Study	Site	Study period	No. of patients	Median lines of Treatment	Duration (years)	OS (%)	PFS (%)	NRM (%)	Relapse (%)
Pavletic et al. (2000)[46]	UNMC + VUBMT	1988–1997	23	2	5	62	65		5
Sorror et al. (2005) [25]	Fred Hutchison Cancer Research Center, Seattle, Washington	Dec 1997–Dec 2003	64	4	2	60	52	22	26
Pavletic et al. (2005)[47]	MDACC	1993–1999	38	3	5	33	30	38	32
Caballero et al. (2005) [20]	University of Salamanca, Spain	1999–2004	30	3	5	70	72	20	—
Schetelig et al. (2008)[22]	EBMT	March 1995–July 2006	44	3	3	44	37	44	—
Dreger et al. (2010) [28]	German CLL Study Group	2001–2007	90	4	4	65	42	23	—
Khouri et al. (2011) [26]	MDACC	1996–2007	86	—	3	53	38	—	—
Brown et al. (2013) [36]	Dana Farber Cancer Institute, Boston	1998–2009	108	—	6	63	43	16	—
Chavez et al. (2014) [24]	Moffitt Cancer Centre, Tempa, Florida	Jan 2003–Jan 2011	43	—	3	51	48	33 (1 yr)	—
van Gelder et al. (2017) [23]	EBMT	2000–2010	2589	—	2	62	49	30	21

Note. CLL = chronic lymphocytic leukemia; EBMT = European Society for Blood and Marrow Transplantation; HCT = hematopoietic stem cell transplantation; MDACC = MD Anderson Cancer Center, University of Texas, Houston; NRM = non-relapse mortality; OS = overall survival; PFS = progression-free survival; UNMC = University of Nebraska Medical Center; VUBMT = Vanderbilt University Medical Center and Veterans Affairs Medical Center Bone Marrow Transplantation Program in Nashville.

impact of performance status on 2-year OS in patients with CLL undergoing allo-HCT [29,36,39]. Schetelig et al. [22] reported that performance status has a bigger impact on the CIR than on NRM, which is consistent with the concept that the performance status is mainly determined by the disease activity [40,41]. However, performance status pre-transplant is also related to NRM as seen in our study (data not shown) due to increased susceptibility to chemo toxicity and less reserve to tolerate post-transplant complications like GVHD [24]. Thus, patients of CLL with good performance status have improved survival (ECOG 0–1 median OS not reached vs. 12 months ECOG $\geq$ 2) and should be considered a predictor for favorable outcome after allo-HCT.

In our cohort, the use of TBI $\geq$ 400 cGy (in a MAC regimen, either combined with 4 days of busulfan or cyclophosphamide) was found to be a predictive factor for poor OS; however, RIC regimes with TBI (200 cGy combined with 2 days of busulfan) did not have poor outcomes. The Seattle group found that the patients who received TBI as a part of their MAC for allograft in CLL fared better than those who did not [42]. However, this was not reproduced in studies by Sabloff et al. [43] and Toze et al. [44] who found no difference in TBI-based versus non–TBI-based MAC in CLL. There is paucity of published literature on comparison of TBI in MAC versus RIC regimens in CLL.

SOS/VOD is one of the predictive factors for poor OS after multivariate analysis in our study. The occurrence of VOD correlated positively with the use of busulfan–cyclophosphamide conditioning regimen (Pearson correlation = 0.265; $p = .04$, results not shown). Similar outcomes were reported by Doney et al. [42] where VOD occurred in 11/25 CLL patients who underwent allo-HCT and correlated with the use of busulfan–cyclophosphamide regimen compared with cyclophosphamide–TBI regimen. Thus, the use of busulfan–cyclophosphamide regimen and subsequent occurrence of SOS/VOD is associated with poor outcomes in patients with CLL after allo-HCT.

We acknowledge several limitations in our study including its retrospective nature with single-center data spread over 30 years. This has led to missing data and changes in transplant procedures with time including newer GVHD prophylactic regimens and improvement in supportive care, all of which may skew the results.

In conclusion, this retrospective study shows reasonable outcomes of CLL patients who underwent allo-HCT with improving trends for survival and NRM with time. The effect of prior treatment with newer treatment modalities (e.g., venetoclax,

ibrutinib, or obinituzumab), MRD monitoring, and newer GVHD prophylactic regimens on outcomes after allo-HCT need to be studied prospectively. However, in view of the increased efficacy and tolerability of the tyrosine kinase inhibitors and BCL2 inhibitors, there has been a decrease in the number of transplants in CLL [45], and thus such data are less likely to be generated. Allo-HCT may be considered in patients with high risk / refractory CLL, with favorable outcomes in patients with good performance status, suitable donors, and when using reduced intensity conditioning regimens.

Authors' contributions

SML and RVN: data collection and initial draft preparation. CC: data collection. IP, ZA, WL, FVM, DDHK, ADL, AG, JL, RK, and JM: supervision/review and editing of the final manuscript draft. AV: validation of results, conceptualization, and final draft. All the authors contributed in the interpretation of data, drafting the article, and final approval of the version to be submitted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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