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ARTICLE

Rituximab-based allogeneic transplant for chronic lymphocytic leukemia with comparison to historical experience

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Abstract

Relapse of chronic lymphocytic leukemia (CLL) after allogeneic hematopoietic cell transplantation (HCT) remains a clinical challenge. We studied in a phase II trial whether the addition of peri-transplant rituximab would reduce the relapse risk compared with historical controls ($n = 157$). Patients ($n = 55$) received fludarabine and low-dose total body irradiation combined with rituximab on days −3, + 10, + 24, + 36. Relapse rate at 3 years was significantly lower among rituximab-treated patients versus controls (17% versus 31%; $P = 0.04$). Overall survival (OS), progression-free survival (PFS) and nonrelapse mortality (NRM) were statistically similar: (53% versus 50%; $P = 0.8$), (44% versus 42%; $P = 0.63$), and (38% versus 28%; $P = 0.2$), respectively. In multivariate analysis, rituximab treatment was associated with lower relapse rates both in the overall cohort [hazard ratio (HR): 0.34, $P = 0.006$] and in patients with high-risk cytogenetics (HR: 0.21, $P = 0.0003$). Patients with no comorbidities who received rituximab conditioning had an OS rate of 100% and 75% at 1 and 3 years, respectively, with no NRM. Peri-transplant rituximab reduced relapse rates regardless of high-risk cytogenetics. HCT is associated with minimal NRM in patients without comorbidities and is a viable option for patients with high-risk CLL. Clinical trial information: NCT00867529.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) remains the only potentially curative treatment for chronic lymphocytic leukemia (CLL), but it is complicated by nonrelapse mortality (NRM) [1]. In recent years, novel agents like B-cell receptor inhibitors (ibrutinib, idelalisib, and duvelisib) and a BCL-2 antagonist (venetoclax) have extended survivals for CLL patients in general and in particular for those with high-risk features for whom

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conventional chemoimmunotherapy regimens are not effective [2–4]. As a result, a decreasing number of CLL patients are offered HCT nationwide per the Center for International Blood and Marrow Transplant Research [5]. Despite the promising results from the novel agents, their efficacy is limited in high-risk CLL patients and sequential therapy is often required for these patients [6–10]. In addition, most of the current agents require an indefinite duration of treatment that can increase the cost and carries the risk of poor drug adherence [11, 12]. Therefore, and while newer agents and combinations are being studied, exclusive use of novel agents as the only therapeutic strategy in high-risk CLL patients seems to be premature and incorporation of HCT in selected patients with a reasonable risk/benefit ratio is still part of the standard approach to high-risk CLL patients [13–16]. In the meantime, interventions to improve the efficacy of allogeneic HCT for CLL are required.

CLL predominantly affects the elderly [17], Patients are referred to allogeneic HCT only after they have become unresponsive to other therapies, which usually occurs many years after diagnosis. Given their age and frequent comorbidities, patients with CLL are generally conditioned for HCT with reduced intensity regimens in order to minimize associated toxicities. Therefore, eradication of CLL cells relies largely on graft-versus-leukemia (GVL) effects. While GVL effects begin immediately after HCT, they are initially attenuated both by the need of the donor immune system to establish itself and by the broad immunosuppression from drugs given to control graft-versus-host disease (GVHD). Given the reliance on GVL effects and their initial impairment, relapse of CLL has been the most pressing problem after allogeneic HCT, especially in patients with bulky disease or unfavorable-risk cytogenetics. This has affected long-term outcomes after HCT. Clinical efficacy and safety of anti-CD20 therapy for CLL in the pre-HCT setting has been shown where high-quality remissions were reported [18, 19]. In order to reduce the relapse risk, we evaluated the use of peri-transplant rituximab in a phase II trial. The trial was based on the hypothesis that rituximab could enhance early direct cell kill through antibody-dependent cytotoxicity [16]. Moreover, by inducing apoptosis, rituximab can promote uptake and cross-presentation of cell-derived peptides by antigen-presenting dendritic cells, resulting in a cross-priming and generation of donor-derived cytotoxic cells that might result in an earlier switch-on of GVL effects [20–22]. Safety and efficacy of a rituximab-based regimen using a different conditioning backbone had been shown in the clinical setting [20]. Here, we compare the results of the phase II trial to historical patients not given rituximab. The initial report of the historical experience has been previously published, and the outcomes have been updated for the purpose of this analysis [23].

Patients and methods

Between 2009 and 2014, 55 CLL patients were given HCT after conditioning with a rituximab-based conditioning regimen. Of these patients, 50 were diagnosed with CLL and were treated on a single-arm phase II clinical trial for CLL (NCT00104858), and the other five were diagnosed with small lymphocytic lymphoma (SLL) and were treated on a separate phase II study focused on lymphoma patients (NCT00867529). Both cohorts are collectively included in this analysis (rituximab cohort). We compared the outcome of the 55 patients with that of 157 patients who were transplanted at our institutions between 1997 and 2014 and did not receive rituximab (historical control) [17]. Protocols were approved by the institutional review boards of the Fred Hutchinson Cancer Research Center and the collaborating sites. All patients signed consent forms.

Phase II trial patients (rituximab cohort)

Patients with a diagnosis of CLL and SLL were included if they: (1) failed to achieve at least partial response after at two cycles of treatment with a fludarabine-containing regimen (or another nucleoside analog); (2) experienced relapse within 12 months after completing a fludarabine-containing regimen; (3) failed FCR (fludarabine, cyclophosphamide, and rituximab) regimen at any time; or (4) had a deletion on the short arm of chromosome 17 (del17p) and were treated with at least one line of treatment. Patients with active infections, CNS involvement, or significant limitations in organ functions were excluded.

Donors

Both HLA-matched related and unrelated donors were allowed. All donors were HLA-matched at the allele level at HLA-A, -B, -C, -DRB1, and -DQB1. For unrelated donors, a single allele disparity was allowed for HLA-A, -B, or -C as defined by high resolution typing. Only G-CSF mobilized peripheral blood mononuclear cells (PBMCs) were used as a hematopoietic cell source.

Study design and treatment

In the single-arm phase II study, transplants were performed in the outpatient setting, and patients were only admitted to inpatient services if medically indicated for the control of complications or for the infusion of donor PBMC if overnight infusion was logistically required. Conditioning began 4 days before HCT. From days −4 to −2, patients received fludarabine (30 mg/m^2/day i.v.). On day 0, 200 cGy of total body irradiation (TBI) was administered at 6–10 cGy/min from a linear accelerator. PBMCs were infused as soon as possible following TBI. Patients received rituximab at a dose of 375 mg/m^2 on day −3 before and days +10, +24, and +38 after HCT. GVHD prophylaxis included cyclosporine (CSP) and mycophenolate mofetil (MMF). CSP was started on day −3 at 5.0 mg/kg orally every 12 h. In the absence of acute GVHD, CSP was continued until day +56 for related and until day +100 for unrelated recipients followed by taper to day +180. The CSP trough levels were kept at 400 ng/ml until day 28 and 120–360 ng/ml after day 28. MMF was started within 4–6 h HCT at a dose of 15 mg/kg orally. In patients with related donors, MMF was stopped abruptly on day +27, while for unrelated recipients it was tapered from day +40 until day +96.

Historical controls

For historical comparison, we included data from all patients who underwent HCT for CLL or SLL on previous prospective and registered trials between 1997 and 2014 [17]. The conditioning regimen consisted of fludarabine 30 mg/m^2/d days −4 to −2 followed by TBI (200 or 300 cGy) on day 0. GVHD prophylaxis consisted of a calcineurin inhibitor in addition to MMF as described above. These patients will be referred to as historical cohort.

Statistical analysis

The phase II study was designed to enroll 80 patients, in order to provide 89% power to detect improvement in an assumed historical 18-month overall survival (OS) rate of 45%, assuming a true survival rate of 60% and 1-sided 0.10 significance level. Enrollment to the study was terminated after 55 patients, due to slow accrual. In fact, 18-month overall survival exceeded 60% for both protocol patients and the historical control group described above. The statistical comparison used all available patients and was not based on specific power considerations.

Cumulative incidences of relapse and NRM and Kaplan–Meier estimates of OS and progression-free survival (PFS) were calculated at 3 years for the rituximab cohort and historical cohort separately. This cutoff was chosen because of the shorter follow-up for the rituximab cohort. Associations between clinically relevant factors and clinical outcomes were assessed using univariate and multivariate cox proportional hazard models. All patients from both the rituximab and the historical cohorts were included and contributed to the model ($n = 215$). Factors associated with at least one endpoint at the level of significance of 0.05 from the univariate models were included in the multivariate analysis. These models tested the following factors: age, donor type, CD34 +and CD3 +doses, disease status, diagnosis to transplant interval, numbers of prior treatments, HCT comorbidity index (HCT-CI), presence of bulky lymph nodes (>5 cm), fludarabine-refractory disease, peritransplant rituximab, and high-risk cytogenetics. High-risk cytogenetics were defined as the presence of either del17p (detected by either analysis of G-banded chromosomes or by fluorescent in site hybridization) or a complex karyotype (defined as three or more abnormalities in metaphase karyotype) at any time from diagnosis to transplant. Multivariable models were done separately for patients with high-risk cytogenetics. Response criteria were based on NCI-working group and the international workshop joint formal criteria for evaluating disease response for CLL [24, 25]. Progressive disease was defined as new lymphadenopathy or ≥50% increase in size of nodes, spleen, liver, or circulating lymphocytes. Relapse was defined as meeting criteria of progression occurring 6 months after achievement of complete or partial remission.

All cited p-values associated with time-to-event comparisons are derived from hazard ratio analysis and do not refer to specific time points. All p-values are 2-sided and are unadjusted for multiple comparisons. Statistical analysis was performed using SAS v.8.0.

Results

Patient characteristics

Pretransplant characteristics are summarized in Table 1. Rituximab-treated patients and historical patients had the following statistically significant differences at baseline: The rituximab cohort more frequently had del17p (54% versus 18%, $P < 0.001$) or complex cytogenetics (37% versus 18%, $P = 0.004$) and more frequently received grafts from unrelated donors (69% versus 48%, $P = 0.008$). In addition, there was a suggestion that they had higher incidences of bulky lymph nodes (26% versus 14%, $P = 0.07$) and of HCT-CI scores of ≥3 (47% versus 34%, $P = 0.08$), respectively. Fifty-one patients (93%) from the rituximab-treated group were previously treated with a purine analog and 38 (69%) had FCR. All these patients were previously treated with rituximab at some point before allo-HCT. Focusing on the immediate treatment before transplant, rituximab-treated patients received CLL-directed therapy at median 283 days (range 26–539) before allo-HCT. For 50 of 55 pts (91%), treatment included an anti-CD20 antibody: FCR ($n = 10$), bendamustine and rituximab ($n = 12$), oxaliplatin, fludarabine, ara-C, and rituximab ($n = 8$), single-agent ofatumumab ($n = 7$), high-dose methylprednisone (HDMP) ($n = 4$), single-agent rituximab ($n = 4$), ofatumumab and HDMP ($n = 1$), bendamustine and ofatumumab ($n = 1$), and other rituximab-based chemoimmunotherapy regimens ($n = 3$). Other patients received alemtuzumab ($n = 3$), HDMP ($n = 1$), and clofarabine ($n = 1$).

Table 1 Patient characteristics

	Rituximab ($n = 55$)	Historical cohort ($n = 157$)	P-value	All patients ($n = 212$)
Male gender, n (%)	39 (71)	119 (76)	0.47	158 (75)
Race, n (%)				
Caucasian	53 (100)	148 (95)		201 (97)
Others		7 (5)	0.12	7 (3)
Age, median (range) years	59 (35–74)	57 (38–72)	0.06	58 (35–74)
Diagnosis, n (%)				
CLL	53 (96)	140 (89)		193 (91)
SLL	1 (2)	10 (6)		11 (5)
PLL	1 (2)	2 (1)		3 (1)
Richter's syndrome		5 (3)	0.30	5 (2)
Years from diagnosis to HCT; median (range)	5.8 (0.3–21.4)	4.9 (0.4–26.9)	0.21	5.0 (0.3–26.9)
Number of prior treatments;				
median (range)	4 (1–10)	4 (0–12)	0.92	4 (0–12)
≥5 prior treatments, n (%)	19 (35)	51 (33)	0.80	70 (33)
Disease status at transplant, n (%)				
Complete remission	5 (10)	10 (6)		15 (7)
Partial remission	10 (20)	56 (36)		66 (32)
Unresponsive	30 (59)	75 (49)		105 (51)
Untreated relapse	6 (12)	13 (8)	0.14	19 (9)
Cytogenetics, n (% of tested patients)				
del (17p)	29 (54)	26 (18)	< 0.0001	55 (27)
del (11q)	11 (20)	28 (19)	0.82	39 (19)
trisomy 12	6 (11)	23 (16)	0.43	29 (14)
del (13q)	18 (33)	61 (41)	0.31	79 (39)
complex	20 (37)	26 (18)	0.004	46 (23)
Donor type, n (%)				
Related	17 (31)	81 (52)		98 (46)
Unrelated	38 (69)	76 (48)	0.008	114 (54)
HCT-CI				
Median (range)	2 (0–6)	2 (0–9)	0.006	2 (0–9)
HCT-CI ≥ 3, n (%)	26 (47)	51 (34)	0.08	77 (38)
Conditioning regimen, n (%)				
Fludarabine, TBI 2 Gy	52 (95)	128 (82)		180 (85)
Fludarabine, TBI 3 Gy	3 (5)	7 (4)		10 (5)
TBI 2 Gy	0	22 (14)	0.01	22 (10)
Cell transplanted, median (range)				
CD34+ × 10^6/kg	7.8 (1.5–28.4)	8.1 (1.1–37.8)	0.79	8.0 (1.1–37.8)
CD3+ × 10^6/kg	2.9 (0.0–42.3)	2.9 (0.0–6.7)	0.77	2.9 (0.0–42.3)
Fludarabine-refractory disease, n (%)	18 (33)	48 (31)	0.77	66 (31)
Lymph node size ≥5 cm, n (%)	14 (26)	20 (14)	0.07	34 (18)

Outcomes

The median duration of follow-up for rituximab-treated, historical, and all patients was 35 months (range: 7–63), 86 months (range: 3–181), and 60 months (range: 3–181), respectively. Rituximab-treated patients had a comparable complete remission rate of 44% compared with 48% among historical patients ($p = 0.59$). However, the rate of relapse at 3 years was statistically significantly lower among the rituximab cohort than historical patients (17% [95% CI, 7–27%] versus 31% [95% CI, 23–38%], $p = 0.04$). There were no statistically significant differences in the unadjusted rates of OS (53% [95% CI, 38–67%] versus 50% [95% CI, 42–58%], $p = 0.85$), PFS (44% [95% CI, 31–58%] versus 42% [95% CI, 34–50%], $p = 0.63$), or NRM (38% [95% CI, 25–52%] versus 28% [95% CI, 20–35%]; $p = 0.20$) between the two groups of patients (Fig. 1a–d).

Given the strong association between the HCT-CI and the clinical outcomes, we separately analyzed the outcomes among patients without comorbidities (HCT-CI = 0; $n = 55$). The 1- and 3-year OS rates were 100 and 75% [95% CI, 33–100%] among rituximab-treated patients ($n = 8$) versus 77 % [95% CI, 64–89%] and 63% [95% CI, 49–77%], respectively, among the historical patients ($n = 47$). NRM rates were 0 and 13% [95% CI, 3–23%] for rituximab-treated and historical patients with no comorbidities, respectively.

Toxicities

Severe neutropenia (<500 cells/μl) was more common in the rituximab cohort (15.1% versus 10.4%; $P = 0.01$), but incidence of severe thrombocytopenia (<20,000 cells/μl) was similar between the two groups (0.5% versus 2.5; $P = 0.49$). There was also no difference in rate of colony-stimulating growth factor use (4.9% versus 3.0%; $P = 0.20$), blood (RBC) transfusion (6.3% versus 6.3%; $P = 0.97$) or platelet transfusion (2.5% versus 5.1%; $P = 0.06$) between the rituximab and historical cohorts. Nonhematologic adverse events (AEs) were similar between the two cohorts, with hyperbilirubinemia (13% versus 13%; $p = 0.9$), hypoxia (9% versus 11%; $p = 0.71$), and elevated creatinine (9% versus 5%; $p = 0.28$) as the most common AEs. Table 2 summarizes details of nonhematologic events in the two groups of patients.

GVHD

The incidences of grade 2–4 acute GVHD (69% versus 58%; $P = 0.53$) and grade 3–4 acute GVHD (18% versus 18%; $P = 0.98$) were not statistically significantly different between rituximab and historical patients. There was also no difference in the incidence of chronic GVHD at 3 years between the two groups (66% versus 55%; $P = 0.68$).

Causes of death

Fifty percent of the rituximab patients died. Causes of death included infections (18%), acute GVHD complications (12%), disease relapse or progression (10%), complications of chronic GVHD (6%), and other causes (4%). Among the historical patients, 62.5% died. Causes of death included disease relapse or progression (27%), infections (13%), and complications from acute (6%) or chronic (3%) GVHD. Other deaths were from neurologic events (2.5%), secondary malignancies (2.5%), or other causes (8%). The cause of death was unknown in one patients.

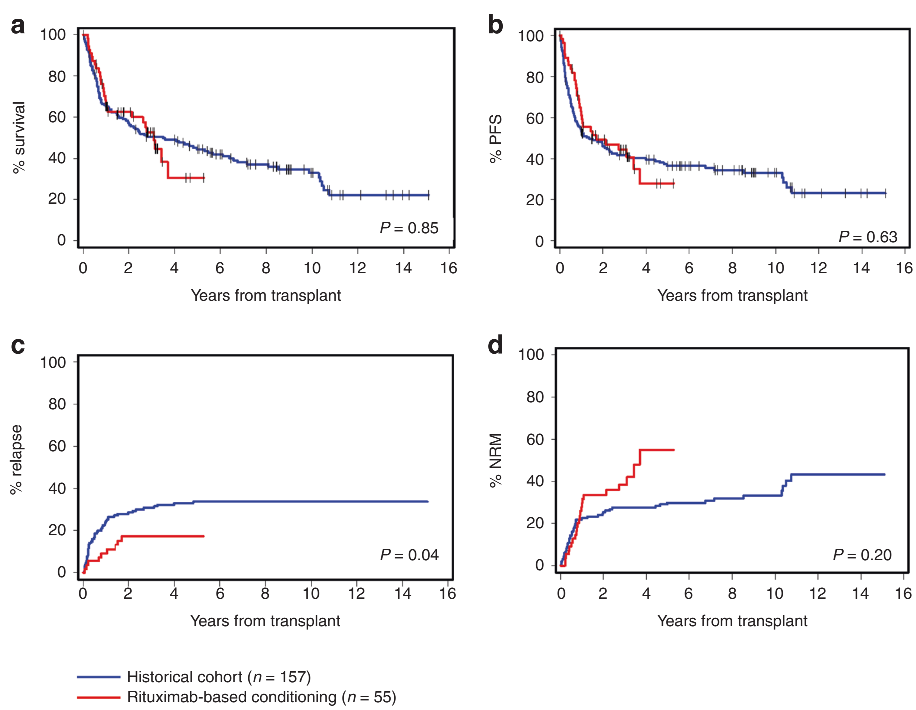

Fig. 1 Kaplan–Meier curves for **a** overall survival, **b** progression-free survival, **c** relapse, and **d** nonrelapse mortality comparing patients who were treated with rituximab-based conditioning on the phase II clinical trial (red) and historical cohort patients (blue). P-values are by log-rank test

Table 2 Patients with grade 3–4 adverse events[a]

Event	Rituximab (total $n = 55$), n (%)	Historical cohort (total $n = 157$), n (%)	P-value
Hepatic			
Hyperbilirubinemia	7 (13)	21 (13)	0.9
Renal			
Elevated creatinine	5 (9)	8 (5)	0.28
Tumor lysis syndrome	0	3 (2)	0.30
Cardiovascular			
Hypertension	3 (5.5)	1 (0.5)	0.02
Hypotension	2 (3.5)	6 (4)	0.95
Atrial fibrillation	1 (2)	3 (2)	0.96
Venous thromboembolism	1 (2)	2 (1)	0.76
Cardiopulmonary arrest	1 (2)	1 (0.5)	0.43
Congestive heart failure	0	3 (2)	0.30
Acute coronary syndrome	0	3 (2)	0.30
Infectious			
Hepatitis C	1 (2)	0	0.09
Encephalitis	1 (2)	0	0.09
Pneumonia	1 (2)	0	0.09
Febrile neutropenia	1 (2)	6 (4)	0.47
SEPSIS/septic shock	0	5 (3)	0.18
Disseminated/invasive fungal infection	0	4 (2.5)	0.23
Pulmonary			
Pleural effusion	1 (2)	4 (2.5)	0.75
Dyspnea	1 (2)	2 (1)	0.76
Diffuse alveolar hemorrhage	1 (2)	1 (0.5)	0.43
Hypoxia	5 (9)	17 (11)	0.71
Gastrointestinal[b]			
Diarrhea	1 (2)	2 (1)	0.76
Bleeding	2 (3.5)	2 (1)	0.26
Anorexia	1 (2)	0	0.09
Colitis	0	5 (3)	0.18
Nausea and vomiting	1 (2)	3 (2)	0.96
Neurological			
Neuropathy	1 (2)	1 (0.5)	0.43
Insomnia	0	1 (0.5)	0.55
Depression	1 (2)	0	0.09
Seizure	1 (2)	1 (0.5)	0.43
Syncope	0	3 (2)	0.30
Cerebrovascular accident	1 (2)	0	0.09

[a]Occurring in ≥1% of patients

[b]Unrelated to GVHD

Predictors of clinical outcomes

In order to identify independent prognostic factors for clinical outcomes, we developed univariate and multivariate models using data from the entire cohort of patients ($n = 212$). In the multivariable models (Table 3), peri-transplant rituximab (HR 0.34, $P = 0.006$) and unrelated grafts (HR 0.37, $P = 0.0007$) were significantly associated with a lower relapse rate, while high-risk cytogenetics increased the risk of relapse (HR: 4.61, $P < 0.0001$). HCT-CI scores of ≥3 were the only predictor for increased NRM (HR 3.63, $P = 0.001$). None of these factors significantly predicted OS with the exception for a suggestive association with HCT-CI scores of ≥3 (HR: 1.62, $p = 0.06$). Unrelated grafts predicted improved PFS (HR: 0.69, $P = 0.05$), while high-risk cytogenetics predicted worse PFS (HR: 1.84, $P = 0.004$).

We looked specifically for prognostic markers in patients with high-risk cytogenetics as they are more likely to be offered HCT in the era of novel agents. Among those patients (Table 4), having an unrelated donor was associated with both better PFS (HR: 0.38, $P = 0.003$) and lower relapse (HR: 0.21, $P = 0.0003$). Peri-transplant rituximab was associated with a lower relapse rate (HR: 0.42, $P = 0.04$). Higher HCT-CI was associated with higher NRM.

Discussion

CLL patients with high-risk cytogenetics continue to have relatively poor outcomes with elusive chances of cure. In this phase II study, we showed that the addition of four doses of peri-transplant rituximab to our traditional minimal-intensity conditioning regimen before HCT resulted in a threefold decrease in relapse rates. This benefit was also present among patients with high-risk cytogenetics. Our study confirms previous reports by us and others indicating high long-term PFS and OS rates in patients with high-risk CLL after HCT [1, 23, 26–28]. Likewise, unrelated grafts achieved better disease control, supporting the use of such grafts to treat high-risk CLL. In addition, CLL patients with no comorbidities experienced a threefold lower incidence of NRM compared with those with multiple comorbidities. While patient numbers were relatively small, 75% of those CLL patients without comorbidities given rituximab-based conditioning regimen were disease free at 3 years. This suggests that HCT should strongly be considered as treatment of choice for high-risk CLL patients without comorbidities. Recent clinical practice guidelines by the American Society of Blood and Marrow Transplantation, the International Workshop on CLL, and the European Society for Blood and Marrow Transplantation

Table 3 Multivariable model of association between relevant clinical factors and outcomes in all patients*

	Overall Mortality (114 events)		PFS (121 events)		Relapse (55 events)		NRM (66 events)	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Donor								
Related	1.0		1.0		1.0		1.0	
Unrelated	0.87 (0.6–1.3)	0.49	0.69 (0.5–1.0)	0.05	0.37 (0.2–0.7)	0.0007	1.13 (0.7–1.9)	0.66
HCT-CI								
0	1.0		1.0		1.0		1.0	
1–2	1.21 (0.7–2.0)	0.45	1.28 (0.8–2.1)	0.32	0.78 (0.4–1.5)	0. 46	2.24 (1.0–5.1)	0.05
3+	1.62 (1.0–2.6)	0.06	1.52 (0.9–2.5)	0.09	0.59 (0.3–1.2)	0.13	3.63 (1.6–8.0)	0.001
High risk CG**								
No	1.0		1.0		1.0		1.0	
Yes	1.40 (0.9–2.1)	0.13	1.84 (1.2–2.8)	0.004	4.61 (2.5–8.6)	<0.0001	0.89 (0.5–1.6)	0.68
Rituximab								
No	1.0		1.0		1.0		1.0	
Yes	0.94 (0.6–1.5)	0.81	0.78 (0.5–1.2)	0.27	0.34 (0.2–0.7)	0.006	1.42 (0.8–2.5)	0.23

*Following factors were included in the univariate models and only moved to the multivariable model if reached statistical significance ($p < 0.05$) for any endpoint in the univariate models: age, donor type, disease status, CD34+ and CD3+ doses, number of prior treatments, diagnosis to transplant interval, high-risk CG, HCT comorbidity index (HCT-CI), presence of bulky lymph nodes (>5 cm), fludarabine refractory disease, and rituximab-containing conditioning

**del17p or complex CG (defined as three or more abnormalities)

Table 4 Multivariable model of association between relevant clinical factors and outcomes in patients with high-risk CG (del 17p or complex)*

	Overall Mortality (42 events)		PFS (49 events)		Relapse (27 events)		NRM (22 events)	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Donor								
Related	1.0		1.0		1.0		1.0	
Unrelated	0.63 (0.3–1.2)	0.18	0.38 (0.2–0.7)	0.003	0.21 (0.1–0.5)	0.0003	0.84 (0.3–2.4)	0.74
CD34 dose/kg								
<7.80	1.0		1.0		1.0		1.0	
≥7.80	1.59 (0.8–3.0)	0.16	1.63 (0.9–2.9)	0.10	1.12 (0.5–2.5)	0.79	2.47(1.0–6.4)	0.06
Number of regimens								
0–4	1.0		1.0		1.0		1.0	
5+	1.39 (0.7–2.7)	0.33	1.30 (0.7–2.4)	0.41	1.26 (0.5–2.9)	0.59	1.20 (0.5–3.0)	0.70
HCT-CI								
0	1.0		1.0		1.0		1.0	
1–2	0.96 (0.4–2.3)	0.93	0.76 (0.3–1.7)	0.51	0.27 (0.1–0.8)	0.01	*	0.005
3+	0.88 (0.4–2.0)	0.75	0.72 (0.3–1.5)	0.38	0.31 (0.1–0.8)	0.01	†	0.009
Rituximab								
No	1.0		1.0		1.0		1.0	
Yes	0.94 (0.5–1.8)	0.86	0.80 (0.4–1.4)	0.46	0.42 (0.2–1.0)	0.04	1.64 (0.6–4.2)	0.31

*Following factors were included in the univariate models and only moved to the multivariable model if reached statistical significance ($p < 0.05$) in the univariate models: age, donor type, disease status, CD34+ and CD3+ doses, number of prior treatments, diagnosis to transplant interval, HCT comorbidity index (HCT-CI), presence of bulky lymph nodes (>5 cm), fludarabine-refractory disease and rituximab-containing conditioning

†HR not estimable due to 0 events in reference category

(EBMT), and European Research Initiative on CLL (ERIC) recommend allogeneic HCT for high-risk CLL patients with refractory disease while they are still responding to either BCR inhibitors or venetoclax [13–16]. Our finding supports that recommendation from the safety standpoint, especially for patients with no comorbidity.

Addition of rituximab was feasible, improved clinical efficacy, and was independently associated with a lower relapse rate both in the entire cohort and in patients with high-risk cytogenetics. More than half of the patients were alive at 3 years, and more than 40% were alive without disease progression. Rituximab-treated patients had more comorbidities than historical patients, which might explain their slightly higher NRM and comparable OS despite the lower relapse rate seen with rituximab. Khoury et al. reported excellent 2-year OS and PFS (90% and 75%, respectively) with rituximab-containing conditioning regimen [29]. Also, Montesinos et al. also observed a lower relapse rate but higher NRM when they added ofatumumab to the conditioning regimen [30]. Our findings are in line with recent reports indicating an independent association between high-risk cytogenetics (del17p or complex karypote) and a higher relapse rate and shorter PFS, although we did not find an association with OS confirming the findings from the German group [26, 27]. It should be noted that given the shorter follow-up for rituximab-treated patients, true estimate of relapse—especially late ones—may be different with longer follow-up. Also, rituximab cohort was transplanted in more recent years, and these patients have potentially benefited from improved post-HCT care in this era.

We believe that HCT remains a viable treatment option for CLL in the era of novel agents. Despite the introduction of new drugs, CLL remains incurable, and the duration of response to the novel agents is limited. Ibrutinib—the most effective drug for high-risk CLL to date—provides a median PFS duration of 26 months in patients with del17p based on the longest published follow-up in the relapsed setting [8]. Similar PFS (27 months) has recently been reported in CLL patients with del17p who were treated with venetoclax in the relapsed setting [9, 31]. While these results are significantly better than the historical treatments [32], they also indicate that cure of high-risk CLL using nontransplant approaches remains an unmet need. Also, drug tolerability remains an issue in a number of patients and has resulted in treatment discontinuation in 30–40% of patients taking ibrutinib or venetoclax based on the "real-world" data [12, 33].

Immunotherapy using chimeric antigen receptor T cells (CAR-T) is another novel approach that has shown promising results in extremely high-risk CLL patients. Admittedly, the follow-up for this experimental treatment is still very limited, hampering head-to-head comparisons with allogeneic HCT or even with novel agents. Further, long-term remissions were only observed in patients in a fraction of patients who achieved deep molecular responses [34]. In the future, CLL investigators could be interested in comparing these two immunologically based treatment approaches (CAR-T versus nonmyeloablative allogeneic HCT) in a randomized clinical trial and/or explore the approach of using CAR-T as a debulking treatment before allogeneic HCT to enhance long-term remissions particularly in high-risk CLL. Our current institutional approach to high-risk CLL patients is mainly in line with EBMT/ERIC guidelines [16] and involves using novel therapeutic agents in the first- and second-line settings. Patients who show disease progression after first novel agent (usually a BTKi or venetoclax), will be counselled about cellular therapy and depending on availability of CAR-T option (currently only available on a clinical trial), donor status and medical comorbidities, CAR-T or allo-HCT is recommended. With this approach, majority of patients receive CAR-T before allo-HCT. In patients with detectable disease after CAR-T, allo-HCT remains the most important treatment modality.

Despite robust efficacy data for HCT, the higher incidence of NRM compared with nontransplant approaches is the main clinical concern. It is therefore critically important to investigate novel strategies to reduce NRM after HCT. In this context, very encouraging data on statistically significant reductions in both serious acute GVHD and NRM among unrelated HCT recipients have recently been reported using triple GVHD prevention with MMF, CSP, and sirolimus [35]. In addition, and as alternative treatments for high-risk CLL become more effective and safer, it is important to identify patients with a low comorbidity burden for whom an earlier utilization of HCT with the intent of cure should be considered.

Our study has number of limitations. First, the treatment landscape of CLL has changed dramatically and we acknowledge that in the current era, transplant outcomes can be affected by pre or post HCT use of novel agents (BTKi, venetoclax or PI3 Kinase inhibitors). Second, given the likelihood of later relapse in CLL patients, longer follow-up of our rituximab-treatment patient in necessary to provide more accurate estimate of disease control.

In conclusion, incorporation of rituximab to the conditioning regimen was feasible and effective. Our results encourage future utilization of newer anti-CD20 monoclonal antibodies that have been shown to be superior to rituximab for CLL [36]. Our findings support early utilization of HCT for patients with high-risk CLL with no comorbidities to avoid clinical and financial toxicities of non-HCT therapies that do not necessarily promise cure. This approach has the potential to provide prolonged disease control with an acceptable risk of treatment-related mortality.

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Author contributions MS, DGM, BS, BMS, RS, and MLS designed the study; MS, BS, and MLS performed the data analysis and interpretation, all authors contributed to data collection, writing and final approval of the paper.

Compliance with ethical standards

Conflict of interest MS provided consultancy for Abbvie, Genentech, Astra Zeneca and Sound Biologics; has been on the advisory board for Abbvie, Genentech, Pharmacyclics, Astra Zeneca, ADC Therapeutics, Atara, and Verastem; and receives research funding from Mustang Biopharma, Pharmacyclics, Gilead, Genentech, TG Therapeutics, Bigene, Celgene, Acerta, Emergent, Sunesis and Merck. Otherwise, the authors declare that they have no conflict of interest.

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