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ORIGINAL REPORT

Outcomes of Patients With Chronic Lymphocytic Leukemia and Richter's Transformation After Transplantation Failure

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ABSTRACT

Purpose
Allogeneic stem-cell transplantation (SCT) induces long-term remission in a fraction of patients with high-risk chronic lymphocytic leukemia (CLL) or Richter's transformation (RT). Our purpose was to determine the outcomes of patients whose disease progressed after allogeneic SCT.

Patients and Methods
We retrospectively analyzed the outcomes of 72 patients (52 with CLL and 20 with RT) who underwent allogeneic SCT between 1998 and 2011 and had documented progression after transplantation. Twenty-two (31%) never had a response, and 50 (69%) had a response but experienced relapse after a median of 7 months (range, 2 to 85 months). Forty-eight patients who were receiving or were candidates to receive post-SCT cell-based therapies were not included in this analysis.

Results
The median age at time of transplantation was 58 years (range, 30 to 72 years). Sixty-two patients (86%) received more than two treatment regimens and 37 (51%) received more than three treatment regimens before SCT. Sixty-six patients (92%) had active disease at the time of transplantation. The 2- and 5-year survival rates were 67% and 38% (patients with CLL) and 36% and 0% (patients with RT). The patients who developed acute or chronic graft-versus-host disease had a longer overall survival (OS; $P = .05$). In a multivariable analysis, RT or low hemoglobin at the time of SCT predicted shorter OS. Chronic graft-versus-host disease and an initial response to SCT predicted longer OS.

Conclusion
Patients with CLL in whom allogeneic SCT fails may have a response to and benefit from salvage therapies, and their prognosis is relatively good.

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INTRODUCTION

The majority of patients with chronic lymphocytic leukemia (CLL) who receive a combination of chemotherapy and immunotherapy will experience a response.[1,2] In most cases, however, the disease will ultimately relapse and, with time, will become refractory. The prognosis of patients with refractory CLL is dismal, and the median survival is measured in months.[3]

Allogeneic hematopoietic stem-cell transplantation (SCT) is a treatment option offered to selected patients with CLL on the basis of risk-benefit assessment and the patient's preferences. Most patients who undergo allogeneic SCT for CLL have refractory disease or Richter's transformation (RT), and many of them are heavily pretreated.[4]

Early myeloablative SCT studies established that long-term remission or cure is attainable in CLL. However, a myeloablative preparative regimen has limited benefits because the rates of treatment-related mortality have been as high as 50%.[5-10] High response rates and long-term remissions have also been attained with reduced-intensity conditioning (RIC) regimens. These regimens significantly reduce treatment-related mortality[11] and have increased the 5-year survival rate to 50% to 70%.[12-16] However, the nonrelapse mortality within the first 2 years amounts to 15% to 25%,[6,12-14,17] and approximately half the surviving patients develop chronic graft-versus-host disease (GVHD), which contributes to debilitating morbidity and nonrelapse mortality.[18]

The efficacy of RIC-SCT has been attributed to a graft-versus-leukemia (GVL) effect.[19,20] We

previously reported an effective GVL response in patients who experienced relapse after RIC-SCT and were treated with a combination of donor lymphocyte infusions (DLIs) and rituximab.[21] Whether GVL also contributed to a favorable outcome in patients who were not in remission after SCT is not known.

Our purpose was to characterize the outcomes of patients with CLL or RT whose disease progressed after SCT. Retrospective review and analysis of patient records revealed 2- and 5-year survival rates from time of progression of 73% and 29%: for patients with CLL, the rates were 67% and 38%, respectively; for those with RT, 38% and 0%. Patients who developed chronic GVHD had a more favorable outcome.

PATIENTS AND METHODS

We searched the clinical databases of the Department of Leukemia and of the Bone Marrow Transplantation Program at The University of Texas MD Anderson Cancer Center to identify patients who underwent allogeneic SCT at the center and who, at the time of post-transplantation response assessment, had had no response (refractory disease) or had experienced relapse after an initial documented response and were referred to the Leukemia Clinic for further treatment. Patients with progressive or residual disease were usually treated with step-wise DLI. DLI was not administered to patients with acute GVHD or rapidly progressing disease. In this analysis, we excluded patients with documented post-SCT relapsed/refractory disease who were undergoing, or were candidates to undergo, treatment with DLI as their sole therapy and considered them to be on an ongoing cell therapy regimen.

All patients included in this study had provided written informed consent for treatment in various clinical trials that had been approved by the institutional review board. Separate institutional review board approval was obtained, which allowed us to retrospectively collect and analyze data from the patients' electronic medical records. Some of the patients' data were previously reported.[15,21] However, the post-transplantation follow-up and long-term outcomes of these patients are provided here for the first time.

Patient characteristics were analyzed as frequencies (percentages) for categorical variables and as median and range for continuous variables. The response criteria were those defined by the National Cancer Institute's Sponsored Working Group on CLL.[22] Before transplantation, all patients underwent computed tomography scans of the chest, abdomen, and pelvis and a gallium or positron emission tomography scan. Biopsies were performed when RT was suspected. The patients with RT reported here are those who had histologically confirmed RT.

Overall response rates included partial response (PR) or complete response (CR). Refractory disease was defined as failure to achieve CR or PR. Relapsed disease was defined as disease progression 6 months or more after attaining CR or PR, and progressive disease was defined as disease progression within 6 months after completion of a given therapy.[23] Overall survival (OS) was demarcated as the time between the date of progression and the date of death or last follow-up contact, whichever occurred first. Patients who were alive at last follow-up contact were censored at that time.

To compare groups of patients on the basis of categorical variables, we used the χ^2 test. For categorical time-dependent (paired) variables, we used the McNemar's test. The probability of OS was estimated by the Kaplan-Meier method. The log-rank test was used to compare survival distributions. To determine whether resistant disease before transplantation predicts poor response to SCT, we estimated the odds ratio of the pretransplantation immunotherapy and chemotherapy sensitivity by the exp(β) in a logistic regression model with the post-transplantation response as a dichotomous dependent variable. Univariable and multivariable Cox proportional hazards regression models were fit to assess association between OS and the following variables: age, Eastern Cooperative Oncology Group performance status, hemoglobin level, platelet count, WBC count, cytogenetic abnormalities, p53 deletion or mutation, the diagnosis at time of transplantation (CLL or RT), the type of SCT (myeloablative *v* nonmyeloablative), presence of acute GVHD or chronic GVHD, best chimerism response, post-transplantation response assessment, and response to first post-transplantation treatment. For the multivariable model, we used a backwards stepwise elimination of nonsignificant covariates on the basis of the likelihood ratio. Significance levels were set at 0.05. Statistical analyses were performed by using SPSS version 21 software (SPSS, Chicago, IL) and GraphPad Prism version 6.0 software (GraphPad Software, San Diego, CA).

RESULTS

Patient Characteristics

Our retrospective review of the Bone Marrow Transplantation Program database identified 358 patients who underwent allogeneic SCT between 1998 and 2011 (159 months). From those patients, we identified 72 who had been referred to the Leukemia Clinic for further treatment for active disease after a median of 74 months (range, 13 to 196 months) from diagnosis and a median of 7 months (range, 7 to 87 months) after transplantation. Forty-eight patients with documented post-SCT relapsed/refractory disease who were undergoing, or were candidates to undergo, cell-based therapies such as DLI were excluded from this analysis. The median time from progression to last follow-up was 30 months (range, 13 to 137 months) and 23 patients (32%) were still alive at time of last follow-up. The patient and disease characteristics at time of diagnosis are summarized in Table 1.

Patient Clinical Characteristics at the Time of SCT and Transplantation Procedure

Patient clinical characteristics and treatment history at the time of transplantation are summarized in Table 2. Details of the SCT

Table 1. Patient and Disease Characteristics at Time of Diagnosis

Characteristic	No./Total Available	%
Total No. of patients	72	
Age, years		
Median	51	
Range	28-70	
Sex		
Male	54	75
Female	18	25
Rai staging		
0	6	8
1	37	51
2	5	7
3	6	8
4	18	25
Cytogenetics by FISH		
Normal karyotype	15/51	29
del(13q)	6/51	12
T12	3/51	6
del(11q)	12/51	24
del(17p)	15/51	29
V_H mutation status		
Mutated	6/38	16
Unmutated	32/38	84
Mean β_2 microglobulin, mg/L	4.0	

Abbreviations: FISH, fluorescent in situ hybridization; V_H, immunoglobulin heavy chain.

Table 2. Patient Clinical Characteristics at Time of SCT

Characteristic	Primary Diagnosis at Time of SCT: CLL No.	CLL %	RT No.	RT %	*P*
Total No. of patients	52	72	20	28	
Age at time of transplantation, years					.94
Median	58		58		
Range	30-72		32-72		
< 50	6	11	4	20	
≥ 50 to < 65	39	75	11	55	
≥ 65	7	14	5	25	
ECOG performance status					
0	4	20	16	31	.59
1	13	65	31	60	
2 or more	3	15	5	9	
No. of prior treatments					
1	9	17	1	5	.30
2	16	31	9	45	
3 or more	27	52	10	50	
Response to last treatment					
CR	3	6	0		.48
PR	21	43	8	40	
Refractory	25	51	12	60	
Time from diagnosis of CLL to SCT, months					.43
Median	70		45		
Range	11-167		12-161		
Bone marrow cellularity					.9
Percent	50		45		
Range	15-100		20-95		
Fludarabine refractory	13	26	6	32	.7

Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete response; ECOG, Eastern Cooperative Oncology Group; PR, partial response; RT, Richter's transformation; SCT, stem-cell transplantation.

Table 3. SCT Conditioning and Outcome Data

SCT Parameters	Primary Diagnosis at Time of SCT: RT (n = 20) No.	RT %	CLL (n = 52) No.	CLL %
Donor				
Matched related	7	35	28	54
Matched unrelated	11	55	23	44
Haplo-identical	2	10	1	2
Stem-cell source				
Peripheral blood	14	70	36	69
Bone marrow	6	30	11	21
Cord blood	0		5	10
Conditioning regimen				
Myeloablative	6	30	14	27
Nonmyeloablative	14	70	38	73
Engraftment				
Yes	20	100	48	92
No	0		4	8
Acute GVHD				
Yes	12	60	25	48
No	8	40	27	52
Chronic GVHD	11	51	24	46
Limited	3	27	4	17
Extensive	8	73	20	83
Best donor/recipient chimerism				
Only recipient	0		2	4
Mixed donor/recipient	12	63	24	51
Only donor	7	37	21	45
Post-transplantation response				
Response	13	65	37	71
CR	7	54	18	49
PR	6	46	19	51
No response	7	35	15	29

Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete response; GVHD, graft-versus-host disease; PR, partial response; RT, Richter's transformation; SCT, stem-cell transplantation.

procedures are summarized in Table 3. Specifics of the SCT preparative regimens, infection and GVHD prophylaxis, and supportive care were previously published.[21,24,25] The most common preparative regimen comprised fludarabine 30 mg/m^2 and cyclophosphamide 750 mg/m^2 on days −5 to −3 and rituximab 375 mg/m^2 on day −13 and 1,000 mg/m^2 on days −6, +1, and +8.

Post-Transplantation Response Assessment

RT is a major risk in patients who are undergoing SCT, and RT was diagnosed in 16 patients with CLL (31%) after transplantation. Conversely, CLL was diagnosed in four (20%) of the 20 patients who had RT before SCT but were without evidence of RT at post-transplantation response assessment. In all these patients, the same immunoglobulin light chain, fluorescent in situ hybridization, and *p53* gene abnormalities were detected before and after transplantation. These tests did not detect an unrelated clone or clonal evolution during post-transplantation follow-up. One patient with pretransplantation CLL developed treatment-related acute myeloid leukemia (AML) 6 months after allogeneic SCT. His bone marrow (BM) cytogenetic analysis before transplantation revealed del(7). When AML was diagnosed, the patient's BM analysis showed mixed chimerism and del(7), suggesting that the AML clone was of recipient's origin.

Twenty-two patients (30%) had refractory disease. Fifty (70%) of the patients who had an initial response to SCT (25 with CR and 25 with PR) subsequently experienced relapse, and the median time from transplantation to relapse was 11 months (range, 2 to 85 months). The response rates in patients with CLL and RT were similar (Table 3). To determine whether any of the factors tested were associated with post-transplantation failure, we performed a match-paired analysis. We identified in our database patients with CLL or RT who underwent SCT about the same time, attained CR, and did not relapse. For 47 of our analyzed patients, we identified a match within the same calendar year and for 61 patients within two calendar years. The matched patients who remained in CR following SCT had higher rates of acute GVHD (60% [n = 41] *v* 40% [n = 27]; $P = .004$) and/or chronic GVHD (59% [n = 41] *v* 41% [n = 28]; $P = .011$). The estimated median BM cellularity of patients for whom SCT failed was 50% (range, 15% to 100%) whereas the BM cellularity of patients who remained in remission was 35% (range, 5% to 90%; $P < .001$).

Post-Transplantation Treatments

Most patients who experienced relapse after transplantation received additional treatments. Patients with pre-SCT RT and those who transformed to RT after SCT (n = 16) underwent

Table 4. Post-Transplantation Treatment Regimens

Treatment Regimen	Post-Transplantation Diagnosis							
	CLL (n = 40)				RT (n = 32)			
	Given First		Given		Given First		Given	
	No.	%	No.	%	No.	%	No.	%
Rituximab*	13	33	17	43	5	20	8	25
Thalidomide or lenalidomide with or without rituximab	3	8	10	25	3	9	8	25
Alemtuzumab with or without rituximab	5	13	10	28	1	3	3	9
Ofatumumab	3	8	11	28	2	6	6	19
Purine analog-based regimen†	3	8	8	20	0		3	9
BR/FBR	1	3	6	15	0		2	6
R-hyperCVAD/OFAR	2	5	11	28	9	28	30	94
R-ICE/R-EPOCH/R-DHAP/R-ESHAP	0		0		4	13	6	19
R-CHOP/R-COP	1	3	2	5	1	3	1	3
Ibrutinib	1	3	5	13	0		0	
Radiation	0		3	8	0		6	19
Donor lymphocyte infusion‡	NA		16	40	NA		17	53
Second allogeneic SCT	0		2	5	0		2	6
Other treatment	2	5	4	10	2	6	14	44
No treatment§	0		4	10	0		1	3

Abbreviations: BR, bendamustine, rituximab; CLL, chronic lymphocytic leukemia; FBR, cyclophosphamide, bendamustine, rituximab; NA, not available; R-hyperCVAD, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; OFAR, oxaliplatin, fludarabine, cytarabine, rituximab; R-ICE, rituximab, ifosfamide, cisplatin, etoposide; R-EPOCH, rituximab, etoposide, prednisone, vincristine, doxorubicin; R-DHAP, dexamethasone, doxorubicin, cytarabine, cisplatin; R-ESHAP, rituximab, etoposide, methylprednisolone, cytarabine, cisplatin; R-CHOP, rituximab, cyclophosphamide, vincristine, prednisone, doxorubicin; R-COP, rituximab, cyclophosphamide, vincristine, prednisone; RT, Richter's transformation.

*Rituximab given as single treatment or in combination with a steroid and/or granulocyte-macrophage colony-stimulating factor.

†Purine analog–based regimens included fludarabine, cyclophosphamide, and rituximab (FCR); cyclophosphamide, fludarabine, cytarabine, and rituximab (CFAR); or pentostatin, cyclophosphamide, and rituximab (PCR).

‡Patients who received only donor lymphocyte infusion are not included.

§Other treatments included IPI-145; chimeric antigen receptor T cells; cytarabine with cladribine; flavopiridol; bafetinib; anti-CD23 antibodies; 8-chloroadenosine; 6-mercaptopurine, vincristine, methotrexate, and prednisone (POMP); azacitidine; and clofarabine.

post-transplantation treatments. Patients with post-transplantation progressive disease were treated for constitutional symptoms and/or severe fatigue (20 patients), granulocytopenia with recurrent infections (two patients), and anemia and/or thrombocytopenia (nine patients). Twenty-one patients were treated for worsening lymphadenopathy (eight patients), massive BM involvement (five patients), or both (eight patients). Five patients did not receive treatment. Four patients had stable disease and did not require treatment, and one patient died before treatment was initiated. The patient who developed secondary AML was treated accordingly but died soon thereafter.

Because there is no consensus on treatment for relapsed/refractory disease after transplantation, the post-transplantation treatment these patients received varied. These treatments are summarized in Table 4. Thirty-two patients (44%) received DLIs and most patients with CLL received an anti-CD20 antibody–based regimen with either rituximab (40%; n = 16) or ofatumumab (28%; n = 11). Five patients received the Bruton tyrosine kinase inhibitor ibrutinib, which did not become available until 2010. Most patients with post-SCT RT received chemoimmunotherapy with either hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine (modified hyperCVAD)[26] or oxaliplatin, fludarabine, rituximab, and pegfilgrastim (OFAR).[27] Four patients who had a response to the first post-transplantation treatment regimen underwent a second allogeneic SCT.

The overall rate of response to the first post-transplantation treatment protocol was 45% (n = 34). The response was CR in four patients (6%; three with CLL, one with RT) and PR in 26 (36%; 18 with CLL, eight with RT). Patients who did not respond to post-SCT failure first-line salvage therapy could still be given salvage therapy. Twenty-nine patients for whom first-line therapy failed received additional treatments, and 12 (41%) of those patients responded. Overall, the patients received a median of two different post-transplantation treatments (range, 0 to 8 treatments; Table 4).

Survival

The median OS from time of progression of the 72 patients in the study was 35 months (95% CI, 30 to 40 months; Fig 1A). The strongest predictor of OS was the diagnosis at time of SCT. OS duration was 36 months (95% CI, 24 to 48 months) in patients with CLL (n = 52) and 15 months (95% CI, 2 to 28 months) in patients with RT (n = 20; $P < .001$; Fig 1B). The 2- and 5-year OS rates were 67% and 38% in patients with CLL and 36% and 0% in patients with RT. Patients with CLL for whom the first post-transplantation regimen failed and who received additional treatment(s) had a relatively good survival expectancy; the post second-line treatment OS in these patients was 21 months (95% CI, 12 to 30 months).

Patients who had a response to SCT had longer OS than those who did not have a response ($P = .003$; Fig 1C), and GVL likely contributed to favorable survival outcome as evinced by the significantly longer OS in patients who experienced acute (Fig 1C) or chronic (Fig 1D) GVHD following SCT than in those who did not have GVHD ($P = .04$ and $P = .05$, respectively).

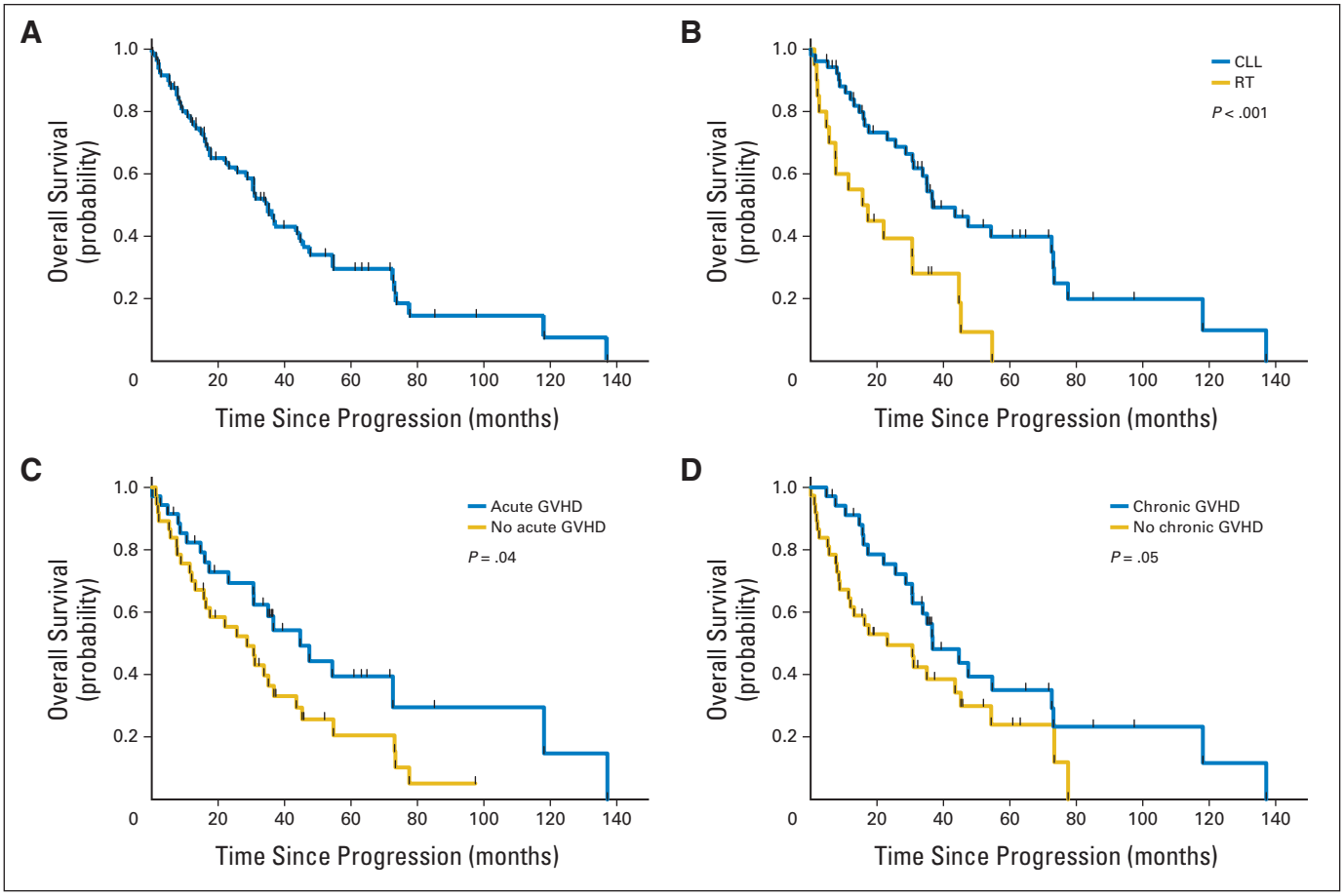

Fig 1. Survival from time of progression in patients for whom allogeneic stem-cell transplantation failed. (A) The median overall survival (OS) of the entire cohort was 35 months (95% CI, 30 to 40 months). (B) Diagnosis at the time of transplantation predicted survival: OS is shown for patients who had chronic lymphocytic leukemia (CLL; median OS, 36 months; 95% CI, 24 to 48 months) or Richter's transformation (RT) at the time of transplantation (median OS, 15 months; 95% CI, 2 to 28 months). (C) Presence of acute graft-versus-host disease (GVHD) predicted survival: OS is shown for patients who developed acute GVHD after stem-cell transplantation (median OS, 45 months; 95% CI, 28 to 61 months) and those who had no acute GVHD (median OS, 29 months; 95% CI, 17 to 41 months). (D) Presence of chronic GVHD predicted survival: OS is shown for patients who developed chronic GVHD after stem-cell transplantation (median OS, 37 months; 95% CI, 23 to 51 months) and patients who did not develop chronic GVHD (median OS, 23 months; 95% CI, 5 to 41 months).

Conversely, sensitivity to chemotherapy was not predictive of OS: patients with chemotherapy-sensitive disease before SCT had a similar OS rate to those with refractory disease before SCT. Likewise, a similar survival outcome was observed in patients who received or did not receive DLIs and in patients who did or did not have a response to the first post hematopoietic stem-cell transplantation treatment.

In a multivariable analysis, only low hemoglobin level and a diagnosis of RT at time of SCT were associated with a shorter OS, whereas chronic GVHD and response to the first post-transplantation treatment assessment predicted a longer OS (Table 5).

DISCUSSION

In CLL, allogeneic SCT is commonly perceived as a last resort, offered to patients after all other options have been exhausted. We report here that the prognosis after SCT has failed for patients with CLL is relatively good, unlike for those with acute leukemia. Similar to all other patients with relapsed/refractory CLL, post-SCT relapsed patients were treated according to our standard treatment criteria. Four of those patients (8%) did not require treatment for a median follow-up of 45 months.

The patients in our study tolerated one to eight lines of post-SCT therapy with a median OS of nearly 3 years from time of documented progression. Although selection of younger patients and patients who were eligible for transplantation may partly account for the unexpectedly prolonged survival in our cohort, in a multivariable analysis, age and performance status were not significantly associated with OS.

Remissions obtained in post-transplantation CLL following DLI are considered evidence for the GVL effect. The alloimmune cells are thought to play a key role in immune surveillance and suppression of the leukemic clone.[5,19-21,28-30] Nearly half our patients with active CLL after transplantation had chronic GVHD, and the association of chronic GVHD with achieving cure and its power to predict OS among patients for whom transplantation failed suggests that the GVL effect contributes to prolonged survival even in patients with a high burden of disease.

The relatively long post-transplantation survival rates were largely restricted to patients with CLL rather than RT. Case reports

Table 5. Prognostic Factor Analysis for Patients With Primary Diagnosis of CLL for Whom Allogeneic SCT Failed

Prognostic Factor	HR	95% CI	*P*
Univariable analysis			
Age ≥ 5 *v* < 55 years	1.6	0.88 to 3.0	.12
At time of transplantation			
ECOG performance status			
0	1		
1	1.6	0.78 to 3.43	.19
2 to 3	4.37	1.5 to 12.5	.006
Hemoglobin	0.74	0.63 to 0.87	< .001
Albumin	0.54	0.39 to 0.75	< .001
Bone marrow cellularity	0.99	0.98 to 1.01	.93
Diagnosis (RT *v* CLL)	2.75	1.48 to 5.11	.001
Complex cytogenetics	0.59	0.25 to 1.39	.23
del(17)/p53 mutated	0.75	0.36 to 1.52	.42
Conditioning regimen*	0.71	0.37 to 1.38	.31
After transplantation			
Acute GVHD	0.55	0.30 to 0.99	.049
Chronic GVHD	0.57	0.32 to 1.01	.055
Best chimerism response†	0.54	0.28 to 1.01	.055
Post-transplantation response‡	0.40	0.22 to 0.75	.006
Multivariable analysis			
Hemoglobin	0.76	0.64 to 0.90	.002
RT at time of transplantation	3.54	1.74 to 7.22	< .001
Response§	0.35	0.17 to 0.71	.004
Chronic GVHD	0.53	0.28 to 1.00	.05

Abbreviations: CLL, chronic lymphocytic leukemia; ECOG, Eastern Cooperative Oncology Group; GVHD, graft-versus-host disease; HR, hazard ratio; RT, Richter's transformation; SCT, stem-cell transplantation.
*Myeloablative versus nonablative.
†Complete donor versus mixed/autologous.
‡Response versus no response.
§At post-transplantation assessment.

and small case series have suggested that allogeneic SCT might improve treatment outcome in RT.[31-33] In a recent study, the cumulative survival rate at 3 years was 75%, and remission after allogeneic SCT correlated independently with prolonged survival.[33] In our cohort, the 5-year survival rate in CLL was 36%, but none of the patients with well-documented RT survived 5 years. Our findings indicate that, in RT, like other aggressive lymphomas but not like CLL, the benefit from allogeneic SCT is restricted to patients who achieve a durable response. A recent study of whole-exome sequencing and copy number variation analysis revealed that, in most cases, RT was derived from the CLL clone.[34] By using our standard laboratory tests, we did not detect unrelated clones in patients who developed RT after transplantation or in the four patients who had RT before and CLL after BM transplantation.

After ibrutinib became available, questions were raised about the role of SCT and other immunotherapies in patients with relapsed/refractory CLL.[35] As a single agent, ibrutinib is well tolerated, induces durable responses, and prolongs progression-free survival and OS in high-risk patients, regardless of adverse cytogenetic abnormalities.[36] SCT often results in a durable eradication of minimal residual disease and offers the potential for cure.[37] Furthermore, our data suggest that SCT is beneficial, even in patients in whom a durable response is not maintained. In contrast, the rates of CR have been low with ibrutinib, and the resistance acquired by a proportion of patients[38] seems to be difficult to overcome.

The variety of salvage treatments administered to our patients limited our ability to compare the efficacies and toxicities of these regimens. Because of the favorable outcomes with ibrutinib in relapsed/refractory CLL, we believe that ibrutinib might have a role in the treatment of disease progression following transplantation failure. In our cohort, ibrutinib was administered after three to five post-transplantation treatments. Of the five patients who received ibrutinib, four responded and are alive after a median follow-up duration of 16 months.

The patients reported here received several lines of therapy that failed, including SCT. In such heavily treated patients the association between response and OS is not entirely clear. In heavily treated patients, therapeutic intervention might not be required unless clearly indicated. Among our patients for whom BM transplantation failed, four patients did not receive post-transplantation treatment. In 37 patients, treatment was administered because of progressive disease or transformation, and in 31 patients treatment was administered because of symptomatic disease. Whether a subset of these patients would do well with a watch-and-wait approach is not clear.

Allogeneic SCT was associated with a significant risk for transformation; 16 patients (30%) with CLL developed RT after transplantation. The opposite effect also occurred: four patients who had RT before transplantation had CLL but no signs of aggressive lymphoma at the post-transplantation work-up. The outcomes of these four patients were similar to those of patients with CLL rather than RT, with a median OS of 31 months. A turn in the course of the disease after transplantation was also observed in seven patients whose disease was refractory to fludarabine before transplantation but responded to regimens that included fludarabine after the transplantation. Taken together, these findings suggest that allogeneic SCT may reset the clock and dramatically change the course of the disease, either through the GVL effect or another mechanism yet to be determined.

In conclusion, whereas in acute leukemia SCT failure is associated with poor outcome, the estimated 5-year survival after SCT failure in CLL was 38%. Patients who developed chronic GVHD had significantly higher OS, suggesting that a donor GVL effect contributes to controlling the disease, even in the absence of overt response.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Outcomes of Patients With Chronic Lymphocytic Leukemia and Richter's Transformation After Transplantation Failure

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