Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2018 January ; 18(1): e35–e39. doi:10.1016/j.clml.2017.10.002.

Allogeneic Hematopoietic Cell Transplantation for Richter Syndrome: A Single-Center Experience

Mohamed A. Kharfan-Dabaja¹, Ambuj Kumar², Facundo E. Stingo³, Farhad Khimani¹, Mohammad Hussaini⁴, Ernesto Ayala¹, Taiga Nishihori¹, Bijal Shah³, Frederick L. Locke¹, Javier Pinilla-Ibarz³, Julio C. Chavez³

¹Department of Blood and Marrow Transplantation and Cellular Immunotherapy, Moffitt Cancer Center, Tampa, FL

²Program for Comparative Effectiveness Research, University of South Florida, Morsani College of Medicine, Tampa, FL

³Department of Malignant Hematology

⁴Department of Hematopathology and Laboratory Medicine, Moffitt Cancer Center, Tampa, FL

Abstract

Allogeneic hematopoietic cell transplantation is an effective therapy in patients with Richter syndrome.

Background: Recent studies have shown dismal outcomes when chronic lymphocytic leukemia progresses to Richter syndrome after patients receive ibrutinib, with a median overall survival ranging from 2.6 to 3.5 months. Published data on efficacy of allogeneic hematopoietic cell transplantation in Richter syndrome are limited to single-center case series and registry data.

Patients and Methods: We evaluated the efficacy of allogeneic transplantation in 10 patients, median age of 63 (range, 50–74) years, allografted at a median of 5 (range, 4–25) months from diagnosis of Richter syndrome. All showed an objective response to therapy before transplantation (first complete remission = 7 [70%], first partial response = 2 [20%], second partial response = 1 [10%]). Most received a myeloablative conditioning regimen (n = 7, 70%). Filgrastim-mobilized peripheral blood stem cells was the preferred cell source (n = 10, 100%).

Results: Median follow-up of surviving patients was 46 (range, 15–82) months. The 4-year overall survival was 50% (95% confidence interval [CI], 19%–81%). Nonrelapse mortality at 1 year and 4 years post-transplantation were 40% (95% CI, 19%–85%) for both time points. The 4-year incidence of relapse/progression was 10% (95% CI, 2%–64%).

Conclusion: Allogeneic hematopoietic cell transplantation is an effective treatment for patients with Richter syndrome who show an objective response before allografting. Patients must be

Address for correspondence: Mohamed A. Kharfan-Dabaja, MD, MBA, Department of Blood and Marrow Transplantation and Cellular Immunotherapy, Moffitt Cancer Center, 12902 Magnolia Dr, Tampa, FL 33612, Mohamed.Kharfan-Dabaja@moffitt.org.

Disclosure

The authors declare no relevant financial conflicts of interest in relation to this work.

referred to transplant centers as soon as the diagnosis is confirmed to evaluate candidacy for the procedure and identify a suitable donor in a timely manner.

Keywords

Chronic lymphocytic leukemia transformation; Nonrelapse mortality; Objective response; Overall survival; Relapse/progression

Introduction

In 2017, it is anticipated that 20,110 cases of chronic lymphocytic leukemia (CLL) will be diagnosed in the United States.¹ Advances in the treatment of CLL have added more effective therapies to the treatment armamentarium for this disease.^{2,3} These therapies have shown efficacy across the different prognostic groups of CLL, including those cases harboring Del17p and/or mutated *TP53*.^{4–6} Ibrutinib, an inhibitor of the Bruton tyrosine kinase, is currently indicated in the relapsed/refractory setting and as front-line therapy in Del17p CLL.^{2,4,7} Venetoclax, an inhibitor of B-cell lymphoma 2 (*BCL-2*), is approved for treatment of CLL patients with Del17p in whom at least 1 previous line of therapy has failed.⁵ Unfortunately, approximately 10% of CLL cases eventually transform into a more aggressive disease, also known as Richter syndrome (RS), typically a diffuse large B-cell (DLBCL) or less often classical Hodgkin lymphoma (HL).^{8–12} Published literature estimates an annual rate of CLL transformation ranging from 0.5% to 1%.^{9,10,12,13} Several risk factors have been described to be associated with development of RS, namely presence of bulky extensive adenopathy, Del17p, Del11q, *IGHV*-unmutated CLL, and *NOTCH 1* mutations, among others.^{11,13,14} Additionally, Rossi et al showed that stereotyped B-cell receptor (BCR) is an independent risk factor for transformation to RS¹⁵; and combining IGVH4–39 usage and stereotyped BCR in the same subject carries a risk of transformation of approximately 70% 5 years later.¹⁵

Recent studies showed dismal outcomes when CLL cases progress to RS even during ibrutinib treatment, with a median overall survival (OS) typically ranging from 2.6 to 3.5 months.^{16,17} RS has a unique genomic landscape different from de novo DLBCL and more complex than CLL without RS, which could explain its chemorefractoriness and poor outcomes.^{18,19} Recognizing the limited efficacy of traditional^{20,21} and newer therapies^{16,17} in patients with RS, the American Society for Blood and Marrow Transplantation issued clinical practice recommendations offering an allogeneic hematopoietic cell transplantation (allo-HCT) to these patients after evidence of an objective response to anthracycline-based chemotherapy.²²

Published data on the efficacy of allo-HCT in patients with RS is limited to single-center case series of 17 patients and registry data from the European Society for Blood and Marrow Transplantation (EBMT), which reported outcomes of 25 patients who received an allo-HCT (Table 1).^{23–25} In this report, we describe a single-center experience using allo-HCT in patients with RS.

Patients and Methods

We identified a total of 10 consecutive patients with RS who received an allo-HCT between April 1, 2008 and March 31, 2016 at the Moffitt Cancer Center. Most of these cases were referred to our transplant program from other medical facilities and the diagnosis of RS was reviewed for accuracy by an experienced hematopathologist at our center. This study was approved by the institutional review board of the University of South Florida and was conducted in accordance with the Declaration of Helsinki. There were no restrictions pertaining to patient's age, remission status at time of transplantation, donor source (human leukocyte antigen-matched-related, matched unrelated, mismatched unrelated, or haploidentical donors), or cell source (bone marrow or peripheral blood stem cells [PBSC]).

Response to RS therapy was assessed using the 2007 International Working Group response criteria.²⁶ Acute graft versus host disease (GVHD) was graded according to 1994 consensus criteria²⁷ and chronic GVHD using National Institutes of Health consensus development published in 2005.²⁸ Intensity of the conditioning regimen was classified according to established criteria.²⁹

Study Objectives, Definition of End Points, and Statistical Methodology

The primary end point of the study was OS. Secondary end points included relapse/progression, progression-free survival (PFS), non-relapse mortality (NRM), and causes of death. We also evaluated cumulative incidence of acute GVHD (by day +100) and chronic GVHD (all grades or moderate/severe) by 1 year. Time to neutrophil engraftment was defined as the first of 3 consecutive days of achieving an absolute neutrophil count of 500/ μ L after the post-transplant nadir. Time to platelet engraftment entailed the first of 3 consecutive days with a platelet count of 20,000/ μ L or higher in the absence of platelet transfusion for 7 consecutive days. OS was defined as time from allo-HCT (day 0) to death from any cause and censored at time of last follow-up. Relapse/progression was defined as recurrence or progression compared with baseline remission status at the time of allo-HCT. PFS was defined from allo-HCT to time of progression, relapse, or death. NRM was defined as time from transplantation to death without relapse or progression.

Baseline characteristics related to patient, disease, and the transplant procedure are summarized using descriptive statistics such as median, SD, and range for continuous measures. Frequencies and proportion were used for categorical measures. Probability of OS was calculated using the Kaplan-Meier estimate. Cumulative incidence of relapse/progression was evaluated using a competing risks model by Gray, which accounts for NRM as a competing risk.³⁰ Conversely, cumulative incidence of NRM was evaluated accounting for relapse/progression as a competing risk.³⁰ The cumulative incidence of Grade 2 to 4 acute GVHD (by day +100) and chronic GVHD (all Grades and moderate/severe) by 1 year were estimated accounting for death and relapse/progression as competing events. All data analyses were performed using NCSS 11 (NCSS, LLC, Kaysville, UT) statistical analysis software.

Results

The median age of 10 patients (male = 5; 50%) was 63 (range, 50–74) years. Most patients (n = 8, 80%) had good-risk karyotype at the time of original diagnosis of CLL. Six [60%] patients reported B-symptoms at the time of symptomatic disease. Nine [90%] RS patients were diagnosed as DLBCL and one [10%] as HL. All patients showed objective responses (first complete remission [CR1] 7 [70%], first partial response [PR1] = 2 [20%], second partial response [PR2] = 1 [10%]) to RS therapy consisting mainly of anthracycline-based regimens (n = 9, 90%). Most received a myeloablative conditioning (MAC) regimen (n = 7, 70%) using PBSC (n = 10, 100%) as the preferred donor source. Median time from RS diagnosis to allo-HCT was 5 (range, 4–25) months. These and other characteristics are summarized in Table 2.

Neutrophil and Platelet Engraftment

The median time to neutrophil engraftment was 17 (range, 13–28) days. For platelets, the median time to engraftment in 9 evaluable cases was 11 (range, 9–27) days. In 1 patient, platelet count never reached > 20,000/ μ L.

Response After Allo-HCT

At 6 months post-transplantation, 7 evaluable patients were in complete remission (CR). Two of those 7 cases were in PR1 or PR2 before allo-HCT. One patient who was in CR at the 6-month response assessment relapsed at 7 months postallografting and died 2 months later. At 1 year, 5 evaluable patients remained in CR.

Overall Survival and PFS

The median follow-up for surviving patients was 46 (range, 15–82) months. The median OS was 9 months (95% confidence interval [CI], 3–9 months). The 4-year OS was 50% (95% CI, 19%–81%; Figure 1A).

The median PFS was 9 months (95% CI, 3–9 months). The 4-year PFS was 50% (95% CI, 19%–81%; Figure 1B).

Acute and Chronic GVHD and NRM

The median time to onset of acute GVHD was 34 (range, 13–76) days. The cumulative incidence of Grade 2 to 4 acute GVHD was 49% (95% CI, 21%–84%). The cumulative incidence of all Grades and moderate/severe chronic GVHD were both 14% (95% CI, 2%–66%), respectively.

Allo-HCT in Patients With RS

The cumulative incidence of NRM at day +100, 1 year, and 4 years post-transplantation were 30% (95% CI, 12%–67%), 40% (95% CI, 19%–85%), and 40% (95% CI, 19%–85%), respectively.

Relapse/Progression

The cumulative incidence of relapse/progression at 4 years postallografting was 10% (95% CI, 2%–64%). Relapse was documented in 1 patient 7 months after receiving an allo-HCT from a haploidentical donor.

Causes of Death

There were a total of 5 deaths. One patient died from relapsed disease at 9 months post-transplantation. Four patients died from causes other than relapse (steroid-refractory acute GVHD = 2, chronic GVHD and infection = 1, diffuse alveolar hemorrhage = 1) at a median of 3 (range, 2–9)=months.

Discussion

These results show the efficacy of allo-HCT in patients with RS showing a 4-year OS of 50%. Our findings are consistent with those published by the EBMT, which reported a 3-year OS of 41% when patients received a transplant in CR or partial response (PR).²³ The high NRM in our study of 40% at 1 year is explained by several reasons, namely the advanced age of patients (median of 63 years; and 60% were older than 60 years), use of MAC regimens in most cases (70%), and increased use of unrelated donors (80%). Three of 4 patients who died from nonrelapse causes received a MAC allo-HCT. In contrast, in the EBMT series, which reported a 3-year NRM of 26%, patients were relatively younger (median age of 57 years, and only 40% were older than 60 years), reduced intensity conditioning (RIC) regimens were more commonly used (72%) and 44% were allografted from sibling donors.²³ In the EBMT study, a multivariate analysis identified RIC allo-HCT as a favorable predictor of superior relapse-free survival, probably explained by a lower 3-year NRM in these patients (MAC = 43% vs. RIC = 19%; $P = .06$; Table 1).²³ Use of MAC regimens is a known risk factor for worse NRM in patients who receive an allo-HCT for lymphomas.^{31–33} However, as published in the literature for chemorefractory DLBCL and Grade 3 follicular lymphomas a higher rate of relapse occurs with RIC allo-HCT regimens.^{32,33} This highlights opportunities to incorporate post-transplant strategies to mitigate the higher risk of disease relapse when using RIC allo-HCT.

In our study, the cumulative incidence of relapse/progression was 10%. Only 1 patient, 56 years old, relapsed 7 months after being allografted in CR1 from a haploidentical donor using a RIC regimen; the patient declined further treatment and died from fulminant relapse 2 months later. In the EBMT series, remission status at time of transplantation was a significant predictor of post-transplant outcomes; for instance, the 3-year OS was better when patients received a transplant in CR or PR versus in the relapsed-refractory or progressive disease state (41% vs. 21%).²³ This was also the case in a series of 17 patients from the M.D. Anderson Cancer Center, which described superior 3-year OS in patients allografted in CR/PR (75% vs. 21%).²⁴ These highlight the importance of performing allo-HCT in RS patients who show an objective response to treatment before the procedure.

We acknowledge several limitations in our study including its retrospective nature, a small sample size, and single-center data. Another limitation was the inability to confirm the

clonal relationship between CLL and RS. This is explained by the fact that these patients were referred from other medical facilities and the tissue source was obtained for the sole purpose of confirming the diagnosis of RS. Of note, this limitation was also acknowledged in the EBMT study.²³ Notwithstanding this limitation, it is important to note that in approximately 80% of RS cases the DLBCL is clonally related to CLL.^{10,34}

Future research should focus on developing more effective models to better predict CLL patients at high risk of transformation to RS. This is of utmost importance considering the dismal survival of patients who transform while receiving ibrutinib.^{16,17} In our series, only 1 patient had received ibrutinib and later idelalisib for treatment of CLL before transformation to RS occurred; and was allografted in CR from a haploidentical donor. This patient ultimately relapsed and died 9 months after her allo-HCT.

A recently published phase II study described the efficacy of pembrolizumab, a humanized programmed death 1 (PD-1)-blocking antibody, showing objective responses in 4 (44%) of 9 RS cases.³⁵ Interestingly, the authors describe that all responses occurred in RS patients whose disease progressed after ibrutinib treatment.³⁵ Although these data are encouraging the findings beg validation in a larger study.³⁵ Also, it is of paramount importance to show the safety and feasibility of using PD-1 inhibitors in patients who are being considered for future allo-HCT. A recent multicenter study showed that use of PD-1 blockade in patients with classical HL whose disease relapsed after an allo-HCT was complicated by rapid onset of severe and treatment-refractory GVHD.³⁶ Other studies using a different checkpoint inhibitor showed GVHD exacerbation in patients who received allograft for relapsed HL who had previous acute GVHD.³⁷

Conclusion

Allo-HCT is an effective treatment option for patients with RS who show an objective response before allografting. In this setting, long-term OS is anticipated in 41% to 75% of cases. Patients with RS must be referred to transplantation centers as soon as the diagnosis is confirmed to evaluate their candidacy for allo-HCT and identify a suitable human leukocyte antigen-compatible donor in a timely manner. Although there are no randomized controlled studies that have compared the efficacy of the conditioning regimen intensity (RIC vs. MAC), findings from the published literature favor using an RIC allo-HCT because of a lower NRM rate.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017; 67:7–30. [PubMed: 28055103]
2. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2013; 369:32–42. [PubMed: 23782158]
3. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. *Blood* 2015; 125:2497–506. [PubMed: 25700432]
4. Farooqui MZ, Valdez J, Martyr S, et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: a phase 2, single-arm trial. *Lancet Oncol* 2015; 16:169–76. [PubMed: 25555420]

5. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. *Lancet Oncol* 2016; 17:768–78. [PubMed: 27178240]
6. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2014; 370:997–1007. [PubMed: 24450857]
7. Burger JA, Keating MJ, Wierda WG, et al. Safety and activity of ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: a single-arm, phase 2 study. *Lancet Oncol* 2014; 15:1090–9. [PubMed: 25150798]
8. Thornton PD, Bellas C, Santon A, et al. Richter transformation of chronic lymphocytic leukemia. The possible role of fludarabine and the Epstein-Barr virus in its pathogenesis. *Leuk Res* 2005; 29:389–95. [PubMed: 15725472]
9. Maddocks-Christianson K, Slager SL, Zent CS, et al. Risk factors for development of a second lymphoid malignancy in patients with chronic lymphocytic leukaemia. *Br J Haematol* 2007; 139:398–404. [PubMed: 17910629]
10. Rossi D, Spina V, Deambrogi C, et al. The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation. *Blood* 2011; 117: 3391–401. [PubMed: 21266718]
11. Rossi D, Spina V, Forconi F, et al. Molecular history of Richter syndrome: origin from a cell already present at the time of chronic lymphocytic leukemia diagnosis. *Int J Cancer* 2012; 130:3006–10. [PubMed: 21796624]
12. Parikh SA, Rabe KG, Call TG, et al. Diffuse large B-cell lymphoma (Richter syndrome) in patients with chronic lymphocytic leukaemia (CLL): a cohort study of newly diagnosed patients. *Br J Haematol* 2013; 162:774–82. [PubMed: 23841899]
13. Rossi D, Cerri M, Capello D, et al. Biological and clinical risk factors of chronic lymphocytic leukaemia transformation to Richter syndrome. *Br J Haematol* 2008; 142:202–15. [PubMed: 18492108]
14. Harousseau JL, Flandrin G, Tricot G, Brouet JC, Seligmann M, Bernard J. Malignant lymphoma supervening in chronic lymphocytic leukemia and related disorders. Richter syndrome: a study of 25 cases. *Cancer* 1981; 48:1302–8. [PubMed: 7023653]
15. Rossi D, Spina V, Cerri M, et al. Stereotyped B-cell receptor is an independent risk factor of chronic lymphocytic leukemia transformation to Richter syndrome. *Clin Cancer Res* 2009; 15:4415–22. [PubMed: 19509140]
16. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. *JAMA Oncol* 2015; 1:80–7. [PubMed: 26182309]
17. Jain P, Keating M, Wierda W, et al. Outcomes of patients with chronic lymphocytic leukemia after discontinuing ibrutinib. *Blood* 2015; 125:2062–7. [PubMed: 25573991]
18. Fabbri G, Khiabanian H, Holmes AB, et al. Genetic lesions associated with chronic lymphocytic leukemia transformation to Richter syndrome. *J Exp Med* 2013; 210: 2273–88. [PubMed: 24127483]
19. Chigrinova E, Rinaldi A, Kwee I, et al. Two main genetic pathways lead to the transformation of chronic lymphocytic leukemia to Richter syndrome. *Blood* 2013; 122:2673–82. [PubMed: 24004666]
20. Langerbeins P, Busch R, Anheier N, et al. Poor efficacy and tolerability of R-CHOP in relapsed/refractory chronic lymphocytic leukemia and Richter transformation. *Am J Hematol* 2014; 89:E239–43. [PubMed: 25196783]
21. Rogers KA, Salem G, Stephens DM, et al. A single-institution retrospective cohort study of patients treated with R-EPOCH for Richter transformation of chronic lymphocytic leukemia. *Blood* 2015; 126:2951.
22. Kharfan-Dabaja MA, Kumar A, Hamadani M, et al. Clinical practice recommendations for use of allogeneic hematopoietic cell transplantation in chronic lymphocytic leukemia on behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant* 2016; 22:2117–25. [PubMed: 27660167]

23. Cwynarski K, van Biezen A, de Wreede L, et al. Autologous and allogeneic stem-cell transplantation for transformed chronic lymphocytic leukemia (Richter syndrome): a retrospective analysis from the chronic lymphocytic leukemia subcommittee of the chronic leukemia working party and lymphoma working party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol* 2012; 30:2211–7. [PubMed: 22547610]
24. Tsimberidou AM, O'Brien S, Khouri I, et al. Clinical outcomes and prognostic factors in patients with Richter syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. *J Clin Oncol* 2006; 24: 2343–51. [PubMed: 16710033]
25. El-Asmar J, Kharfan-Dabaja MA. Hematopoietic cell transplantation for Richter syndrome. *Biol Blood Marrow Transplant* 2016; 22:1938–44. [PubMed: 27375122]
26. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; 25:579–86. [PubMed: 17242396]
27. Przepiorka D, Weisdorf D, Martin P, et al. 1994 consensus conference on acute GVHD grading. *Bone Marrow Transplant* 1995; 15:825–8. [PubMed: 7581076]
28. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant* 2005; 11:945–56. [PubMed: 16338616]
29. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant* 2009; 15:1628–33. [PubMed: 19896087]
30. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988; 16:1141–54.
31. Fenske TS, Ahn KW, Graff TM, et al. Allogeneic transplantation provides durable remission in a subset of DLBCL patients relapsing after autologous transplantation. *Br J Haematol* 2016; 174:235–48. [PubMed: 26989808]
32. van Kampen RJ, Canals C, Schouten HC, et al. Allogeneic stem-cell transplantation as salvage therapy for patients with diffuse large B-cell non-Hodgkin lymphoma relapsing after an autologous stem-cell transplantation: an analysis of the European Group for Blood and Marrow Transplantation Registry. *J Clin Oncol* 2011; 29:1342–8. [PubMed: 21321299]
33. Hamadani M, Saber W, Ahn KW, et al. Impact of pretransplantation conditioning regimens on outcomes of allogeneic transplantation for chemotherapy-unresponsive diffuse large B cell lymphoma and grade III follicular lymphoma. *Biol Blood Marrow Transplant* 2013; 19:746–53. [PubMed: 23380340]
34. Mao Z, Quintanilla-Martinez L, Raffeld M, et al. IgVH mutational status and clonality analysis of Richter transformation: diffuse large B-cell lymphoma and Hodgkin lymphoma in association with B-cell chronic lymphocytic leukemia (BCLL) represent 2 different pathways of disease evolution. *Am J Surg Pathol* 2007; 31:1605–14. [PubMed: 17895764]
35. Ding W, LaPlant BR, Call TG, et al. Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. *Blood* 2017; 129:3419–27. [PubMed: 28424162]
36. Haverkos BM, Abbott D, Hamadani M, et al. PD-1 blockade for relapsed lymphoma post-allogeneic hematopoietic cell transplant: high response rate but frequent GVHD. *Blood* 2017; 130:221–8. [PubMed: 28468799]
37. Herbaux C, Gauthier J, Brice P, et al. Efficacy and tolerability of nivolumab after allogeneic transplantation for relapsed Hodgkin lymphoma. *Blood* 2017; 129: 2471–8. [PubMed: 28270452]

Clinical Practice Points

- The findings of our study show that allo-HCT is capable of inducing durable responses in patients with RS, provided that an objective response is attained before allografting.
- Use of MAC results in a high incidence of NRM of 40%. Thus, a RIC allo-HCT might be preferable, whenever indicated, considering the relatively advanced age of these patients.

Figure 1.

(A) Overall (OS) and (B) Progression-Free Survival (PFS)

Abbreviation: allo-HCT = allogeneic hematopoietic cell transplantation.

Table 1

Studies Reporting Outcomes of Allo-HCT in Patients With RS (10 Patients)

Reference	Study	n	Median Age (Range), y	Remission Status at Time of Allo-HCT	Regimen Intensity	Outcomes
Cwynarski et al ²³	EBMT registry data	25	57 (31–70)	CR = 1 PR, n = 15 Refractory = 9 Unknown = 1	RIC = 18 MAC = 7	Allo-HCT in CR/PR OS = 41% (3-y) Allo-HCT in refractory disease OS = 17% (3-y) NRM = 26% all patients (3-y) NRM (RIC) = 19% NRM (MAC) = 43% (3-y), <i>P</i> = .06
Tsimberidou et al ²⁴	Retrospective	17	60 (35–72)	CR/CRu = 2 PR = 10 Refractory = 4 Untreated = 1	RIC = 15 MAC = 2	Allo-HCT in CR/CRu/PR ^a OS = 75% (3-y) Allo-HCT in refractory disease ^a OS = 21% (3-y)

Abbreviations: Allo-HCT = allogeneic hematopoietic cell transplantation; CRu = complete remission undetermined; EBMT = European Society for Blood and Marrow Transplantation; MAC = myeloablative conditioning; NRM = nonrelapse mortality; OS = overall survival; RIC = reduced intensity conditioning; RS = Richter syndrome.

^aOutcomes reported as cumulative for 20 patients (allo-HCT = 17; auto-HCT = 3).

Table 2

Patient, Disease, and Treatment Characteristics

Variable	Allo-HCT (n = 10)
Median Age of Patients (Range), y	63 (50–74)
Median Age of Donors (Range), y	27 (21–66)
Patient Sex	M = 5 (50%) F = 5 (50%)
Donor Sex	M = 7 (70%) F = 3 (30%)
Rai Stage at CLL Diagnosis	0 = 3 (30%) 1 = 2 (20%) 2 = 0 3 = 1 (10%) 4 = 1 (10%) Unknown/not available = 3 (30%)
Karyotype at Time of CLL Diagnosis	Normal = 5 (50%) Trisomy 12 = 2 (20%) Del13q = 1 (10%) Del17p = 1 (10%) Unknown/not available = 1 (10%)
CD38 Expression >30% at Time of CLL Diagnosis	Yes = 5 (50%) No = 1 (10%) Unknown/not available = 4 (40%)
Expression of ZAP-70 >20% at Time of CLL Diagnosis	Yes = 4 (40%) Unknown/not available = 6 (60%)
Presence of B Symptoms at Time of CLL Symptoms	Yes = 6 (60%) No = 3 (30%) Unknown/not available = 1 (10%)
Median Number of Lines of Therapies to Treat CLL	1 (0–3)
Histology Subtype of RS	DLBCL = 9 (90%) cHL = 1 (10%)
Therapy for RS	CHOP-R = 6 (60%) DA-EPOCH = 1 (10%) Other = 3 (30%) ^a
Median Number of Lines of Therapies to Treat RS	1 (1–2)
Remission Status at Time of Transplantation for RS	CR1 = 7 (70%) PR1 = 2 (20%) PR2 = 1 (10%)
Donor Source	MRD = 1 (10%) MUD = 8 (80%) Haploidentical = 1 (10%)
Cell Source	PBSC = 10 (100%)
Median CD34 × 10 ⁶ /kg Recipient Body Weight (Range), Cells	7.88 (3.07–10.00)
Regimen Intensity	MAC = 7 (70%) RIC/NMA = 3 (30%)
Acute GVHD Prophylaxis	TAC-SRR = 5 (50%) TAC-MTX = 2 (20%) TAC-MMF = 1 (10%) TAC-MMF-PTCY = 1 (10%) SIR-PTCY = 1 (10%)
Median Time From Diagnosis of CLL to Diagnosis of RS (Range), mo	27 (0–104)
Median Time From Diagnosis of RS to Transplantation (Range), mo	5 (4–25)

Myeloablative conditioning regimens were: FLU and intravenous BU (AUC, 3500) with R = 2; FLU-BU (AUC, 5300) = 2; FLU-BU (AUC, 5300)-R = 2; pentostatin-BU-R = 1; RIC regimens: FLU-CY-total body radiation 2 Gy = 1; FLU-CY-R = 1; FLU-melphalan = 1.

Abbreviations: Allo-HCT = allogeneic hematopoietic cell transplantation; AUC = area under the curve; BR = bendamustine plus rituximab; BU = busulfan; cHL = classical Hodgkin lymphoma; CHOP = cyclophosphamide, adriamycin, vincristine, prednisone; CLL = chronic lymphocytic leukemia; CR1 = first complete remission; CY = cyclophosphamide; DA-EPOCH = dose-adjusted etoposide, prednisone, vincristine, and adriamycin; DLBCL = diffuse large B-cell; F = female; FLU = fludarabine; GVHD = graft versus host disease; HLA = human leukocyte antigen; M = male; MAC = myeloablative conditioning; MMF = mycophenolate mofetil; MRD = HLA-matched related donor; MTX = methotrexate; MUD = HLA-matched unrelated donor; NMA = nonmyeloablative conditioning; PBSC = filgrastim mobilized peripheral blood stem cells; PR1 = first partial response; PR2 = second partial response; PTCY = post-transplant cyclophosphamide; R = rituximab; RIC = reduced intensity conditioning; RS = Richter syndrome; SIR = sirolimus; TAC = tacrolimus; ZAP-70 = zeta-chain-associated protein kinase 70.

^aCHOP-R and BR = 1; HyperCVAD and alemtuzumab = 1; alemtuzumab = 1.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript