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Hematopoietic Cell Transplantation for Richter Syndrome

Jessica El-Asmar [1], Mohamed A. Kharfan-Dabaja [2,3,*]

[1] Department of Internal Medicine, Cleveland Clinic, Cleveland, Ohio
[2] Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida
[3] Department of Oncologic Sciences, University of South Florida College of Medicine, Tampa, Florida

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Treatment combining chemotherapy with immunotherapy as well as novel targeted therapies have shown limited efficacy in Richter syndrome. Overall response rates after chemoimmunotherapy range from 43% to 67%, but remissions are generally short-lived. In chronic lymphocytic leukemia (CLL), allogeneic hematopoietic cell transplantation (all-HCT) is considered a potentially curative treatment modality, yielding 3-year overall survival rates exceeding 50% and a plateau in survival curves. In Richter syndrome, efficacy of allo-HCT depends on demonstrating an objective response (complete remission or partial response) before allografting, with resulting 3-year survival rates of 41% to 75%. On the other hand, the efficacy of autologous HCT is limited, especially when considering that patients autografted for Richter syndrome might relapse with CLL in 35% of cases. Notwithstanding the scarcity of published data, we recommend that patients with Richter syndrome should be referred to transplant centers as soon as the diagnosis is confirmed to evaluate their candidacy for allo-HCT. Establishing a clonal relationship to CLL is important considering the more aggressive disease course in clonally related Richter syndrome. Moreover, achievement of a complete remission or partial response to salvage therapy must be a prerequisite before moving forward with allografting for Richter syndrome. Patients who fail to demonstrate an objective response to salvage therapy should be considered for enrollment in clinical trials.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) represents the most common leukemia in the Western hemisphere and is generally considered a low-grade lymphoproliferative neoplasm. Over 18,000 patients will be diagnosed with CLL in the United States in 2016, and it is anticipated that a proportion of them (up to 10%) will transform into a more aggressive disease entity, typically a diffuse large B cell lymphoma (DLBCL) or so-called Richter syndrome (RS), first described in 1928 [1-7]. Many published studies estimate an annual rate of transformation of .5% to 1% [3-5]. In most cases (~80%) the DLBCL is clonally related to CLL, whereas in the remaining 20% a clonal relationship to CLL cannot be confirmed [4,8]. Establishing a clonal relationship to CLL has prognostic implications. For example, Rossi et al. [4] reported that clonally related RS has a median overall survival (OS) of 14 months but RS without a clonal relationship to CLL has a better OS of approximately 63 months. Fabbri et al. [9] demonstrated that clonally related RS is pathogenetically different from de novo DLBCL. For instance, in contrast to de novo DLBCL, typical features present in RS-DLBCL include the common activation of *NOTCH* and inactivation of *TP53* pathways [9]. RS-DLBCL lacks lesions commonly seen in de novo DLBCL such as inactivation of acetyltransferase genes *CREBBP/EP300* and of the *B2M* gene, among others [9]. Moreover, translocations in genes such B cell lymphoma 2 (*BCL-2*) and *BCL-6* are more commonly associated with de novo DLBCL [9,10]. These differences clearly indicate that RS-DLBCL and de novo DLBCL represent distinct disease entities [9].

Several risk factors have been associated with development of RS, including presence of bulky extensive adenopathy, immunoglobulin heavy chain variable region genes (*IGHV*)-unmutated CLL, Del17p or Del11q, or *NOTCH 1* mutations, among others [4,5,11-13]. When deciding on the most adequate therapeutic plan for patients with RS, it is crucial to distinguish between clonally related and clonally unrelated RS. In this review we summarize the published literature pertaining to the front-line treatment of RS with conventional chemoimmunotherapy or novel therapies and also review the role of autologous (auto) or allogeneic (allo) hematopoietic cell transplantation (HCT) as consolidation or for treatment of relapsed or refractory (R/R) RS.

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* Correspondence and reprint requests: Mohamed A. Kharfan-Dabaja, MD, MBA, FACP, Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, FOB-3, Tampa, FL 33612.
E-mail address: Mohamed.Kharfan-Dabaja@Moffitt.org (M.A. Kharfan-Dabaja).

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TREATMENT OF RS

Chemoimmunotherapy Combinations

It is common practice to treat patients with RS with established chemoimmunotherapy regimens commonly used to treat other B cell non-Hodgkin lymphomas [14]. For instance, a chemoimmunotherapy regimen combining cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (CHOP-R) is commonly prescribed for treatment of RS [14]. A phase II study of the German CLL Study Group evaluated the efficacy of CHOP-R in 15 patients (median age, 69 years) with RS [15]. Responses were reported as follow: complete remission (CR) of 7% and partial response (PR) of 60%. The remaining patients achieved a stable disease of 13% or progressive disease of 20% [15]. Responses, however, were relatively short-lived, with a reported median progression-free survival of only 10 months and a dismal OS at 21 months [15]. In the end, authors reported that 67% of treated patients died from disease progression [15]. Rogers et al. [16] reported outcomes of 46 patients with RS (median age, 67 years) treated with the combination of rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin, or R-EPOCH, and showing an overall response rate (ORR) of only 38% (CR = 20%) and a median survival of only 5.9 months. The authors reported that these patients had received a median of 3 prior CLL treatments including ibrutinib in 22% of cases [16]. These findings highlight the limited efficacy of R-EPOCH and ibrutinib in RS [16].

Investigators from the MD Anderson Cancer Center evaluated a more intensive regimen that combined fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone plus rituximab and granulocyte-macrophage colony-stimulating factor alternating with methotrexate and cytarabine plus rituximab and granulocyte-macrophage-colony stimulating factor in 30 patients with RS and 19 with refractory CLL [17]. Specific to RS cases, ORRs were observed in 43% (CR = 27%), and the 1-year survival rate was 28% [17]. Early treatment mortality, defined as death occurring within the first 2 cycles of therapy, was 22% (18% during cycle 1 and 4% during cycle 2). This regimen appears to yield slightly higher CR rates in RS cases, vis-à-vis CHOP-R, but at the expense of a high treatment-related mortality [15,17].

A phase I/II study evaluated a combination of oxaliplatin, fludarabine, cytarabine, and rituximab (OFAR-1) in 20 patients with RS and 30 with fludarabine-refractory CLL [18]. The ORR was 50% (CR = 20%) [18]. However, none of the RS patients who harbored Del17p (0/5) or Del11q (0/2) achieved a CR [18]. At 6 months, the failure-free survival rate was 47% for all RS patients, but RS harboring the Del17p mutation had a lower 6-month failure-free survival rate of 27% [18]. Moreover, the reported 6-month OS rate for all RS patients was 59% (53% for RS with Del17p mutation) [18]. These findings suggest that RS, especially when associated with Del17p mutation, represents an adverse prognostic predictor for achieving CR and results in inferior failure-free survival when treated with OFAR [18]. Another phase I/II study using a modified OFAR-1 regimen that consisted of a lower dose of cytarabine (from 1 to .5 g/m^2) and, alternatively, a higher dose of oxaliplatin (from 25 to 30 mg/m^2) per cycle, namely OFAR-2, was conducted by the MD Anderson group [19]. A total of 102 (RS, 35; relapsed/refractory CLL, 67) patients received OFAR-2. Six of 35 RS patients (23%) harbored Del17p [19]. ORR for all RS patients was 43% (CR = 9%); only 1 of 5 assessable RS patients (20%) with Del17p demonstrated an objective response. At 2 years, only 19.7% of RS patients were alive [19]. These data suggest that OFAR-1 and OFAR-2 are acceptable induction strategies for patients with RS, but further consolidative strategies must be considered because of poor OS [18,19].

Although these studies described treatment outcomes within the broad rubric of RS, a major limitation is the absence of molecular data to help discern outcomes of clonally related RS from those with de novo DLBCL. These studies are summarized in Table 1.

Outcomes Using Novel Therapies

Ibrutinib

Ibrutinib is a B cell receptor inhibitor that targets the Bruton's tyrosine kinase. It has been recently added to the therapeutic armamentarium of CLL, including those harboring Del17p [20-22]. Tsang et al. [23] described a small series of 4 patients, ages 62 to 74 years, who received ibrutinib for treatment of RS. Two of 4 had received 3 prior lines of therapy, 1 had received 2, and the fourth received no prior therapies for RS before ibrutinib [23]. Median duration of ibrutinib therapy was 6.1 months (range, 2.8 to 10.8). Although 3 patients experienced objective responses (CR, 1; PR, 2), the 2 who achieved a PR eventually progressed (1 from RS, 1 from CLL) at 8 and 11 months, respectively [23].

Maddocks et al. [6] evaluated outcomes of 308 patients with CLL. Del17p was present in 113 cases (37%), and 169 patients (58%) had complex cytogenetics defined as ≥3 abnormalities [6]. Only 31 patients (10%) had to discontinue ibrutinib because of disease progression, and 18 of those 31 (58%) progressed with evidence of RS (3/18 already had

Table 1
Studies Evaluating Chemoimmunotherapy Regimens for Treatment of RS

Author [Reference]	Year of Publication	Study Type	No. of Patients	Regimen	ORR and CR	Survival
Tsimberidou et al. [17]	2003	Phase II	30	Hyper-CVXD plus rituximab and GM-CSF alternating with methotrexate and cytarabine plus rituximab and GM-CSF	ORR = 43% CR = 27%	1-year OS rate = 28%
Tsimberidou et al. [18]	2008	Phase I-II	20	OFAR-1	ORR = 50% CR = 20%	6-month FFS rate = 47% 6-month OS rate = 59%
Tsimberidou et al. [19]	2013	Phase I-II	35	OFAR-2	ORR = 43% CR = 9%	Median OS = 6.6 months 2-year OS = 19.7%
Langerbeins et al. [15]	2014	Phase II	15	CHOP-R	ORR = 67% CR = 7%	Median PFS = 10 months Median OS = 21 months
Rogers et al. [16]	2015	Retrospective	46	R-EPOCH	ORR = 38% CR = 20%	Median PFS = 3.5 months Median OS = 5.9 months

Hyper-CVXD indicates cyclophosphamide, liposomal daunorubicin, vincristine, and dexamethasone; GM-CSF, granulocyte-macrophage colony-stimulating factor; FFS, failure-free survival; PFS, progression-free survival.