Journal of Oncology Research and Therapy
Alasfour M, et al. Oncol Res Ther 9: 10207.
www.doi.org/10.29011/2574-710X.10207
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Review Article

Richter's Syndrome (RS): Emerging Therapeutic Horizons

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Citation: Alasfour M, Jones SR, Pongas G (2024) Richter's Syndrome (RS): Emerging Therapeutic Horizons. J Oncol Res Ther 9: 10207. DOI: 10.29011/2574-710X.10207.

Received Date: 23 March, 2024; **Accepted Date:** 04 April, 2024; **Published Date:** 08 April, 2024

Abstract

Purpose of Review: Richter's syndrome (RS) is an aggressive lymphoma that arises from pre-existing chronic lymphocytic leukemia (CLL). Despite significant advancements in CLL treatments over the last decade, including the emergence of novel therapies, RS continues to be associated with poor outcomes. In this review, we examine the current literature on RS and discuss the future research direction. **Recent Findings:** Traditional chemoimmunotherapy regimens in RS have been associated with generally poor outcomes. However, encouraging data emerged with the CAR-T cellular therapies, the CD20/CD3 bispecific antibodies and the combination of novel agents with chemoimmunotherapy. **Summary:** Richter's syndrome remains a therapeutic challenge with limited standard-of-care options. Advances in understanding its pathogenesis and the development of novel therapies hold promise for improving outcomes. Collaboration and ongoing clinical trials are essential to enhance treatment strategies for this aggressive complication of CLL.

Keywords: Chronic lymphocytic leukemia; Diffuse large B-cell lymphoma; Hodgkin lymphoma; Richter's transformation; Transformation; Richter's Syndrome.

Introduction

Richter's syndrome (RS), also known as Richter's transformation, is a rare and aggressive complication of chronic lymphocytic leukemia (CLL). RS was first recognized by Maurice Richter in 1982 when he described a case of a "reticular cell sarcoma" in lymph nodes that had developed from a pre-existing, slowly growing leukemia [1]. While CLL is typically a slow-growing and indolent disease, RS represents a significant and sudden transformation into a more aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL). The exact incidence of RS is not well-defined, but it is estimated to affect approximately 2-10% of patients with CLL and has an annual incidence rate of 0.7% per recent data from the Surveillance, Epidemiology and End Results (SEER) database [2]. It typically presents in individuals who have had CLL for several years, with a median time to transformation of 4.7 years, and its rarely the initial presentation of CLL [3]. Much like CLL, the pathological and clinical nature of RS is heterogeneous, with approximately 80% of cases being clonally related to the underlying CLL. Within RS, two distinct pathologic subtypes exist: diffuse large B-cell lymphoma RS (DLBCL-RS) and Hodgkin lymphoma RS (HL-RS). DLBCL-RS, the more prevalent variant, constitutes about 90% of all RS cases [4]. Despite advancements in CLL treatments, RS outcomes remain poor, as complete responses are achieved in only 20% of patients, and less than 20% experience long-term survival with chemoimmunotherapy (CIT) [5]. Understanding the development, pathogenesis, and treatment of RS is crucial in improving outcomes for these patients. This article will provide an overview of RS, including its risk factors, clinical presentation, and diagnosis, while focusing on the latest treatment strategies.

Richter's Syndrome Variants and Morphology

Diffuse Large B-Cell Variant

DLBCL-RS, the more prevalent RS variant, is characterized by sheets, as opposed to focal sites, of malignant large B lymphocytes resembling centroblasts or immunoblasts, and the presence of large B cells with a nucleus size that is at least twice that of a normal lymphocyte or even larger than a macrophage nucleus

[6]. Furthermore, RS is often characterized by the expression of PD-1, which is observed in up to 80% of cases, but is rarely seen in CLL and de novo DLBCL. RS cells typically express CD20, while a common feature is the loss of CD5 and CD23 in 70% and 85% of the time, respectively [7]. Most DLBCL-RS, approximately 90-95%, exhibit a post-germinal center phenotype, as indicated by IRF4 positivity. In contrast to HL-RS, most DLBCL-RS cases are negative for Epstein-Barr virus (EBV). A noteworthy consideration when managing DLBCL-RS is the phenomenon known as pseudo-RS, which may occur when Bruton's tyrosine kinase inhibitor (BTKi) treatment is temporarily interrupted for medical procedures or toxicity. In contrast to true RS, these patients experience disease regression into CLL/SLL upon resuming the BTKi [8].

Determining the clonal relationship between RS and the underlying CLL is essential, as it holds implications for both treatment and prognosis. Clonality is determined through molecular studies involving immunoglobulin heavy chain (IGHV) sequencing. In approximately 78% of DLBCL-RS cases, a clonal relationship exists with the underlying CLL. In contrast, the remaining cases represent de novo DLBCL, which tends to be associated with a more favorable prognosis [9].

Hodgkin lymphoma variant

The Hodgkin lymphoma subtype constitutes the second most common variant of RS, accounting for approximately 5-10% of RS cases [4, 10]. This subtype is characterized histologically by the presence of Reed-Sternberg cells, accompanied by the expression of CD30 and CD15, and the absence of CD20, all within a backdrop of polymorphous small T-cells, epithelioid cells, histiocytic cells, eosinophils, and plasma cells [6]. Moreover, most of these cases are positive for EBV. Unlike DLBCL-RS, HL-RS is usually not clonally related to the underlying CLL, indicating de novo lymphoma development in CLL patients [7]. Retrospective analyses had demonstrated that a substantial proportion of patients with HL-RS exhibit a favorable response to therapy. This is particularly true for those who underwent chemotherapy with doxorubicin hydrochloride, bleomycin sulfate, vinblastine sulfate, and dacarbazine (ABVD), where the median overall survival (mOS) reached 13.2 years [11].

Pathogenesis

The molecular pathway of clonally related DLBCL-RS exhibits heterogeneity and distinct characteristics compared to de novo DLBCL-RS as demonstrated in figure 1. Among the most frequently altered genes in RS are TP53, MYC, CDKN2A and NOTCH1, all of which play well-characterized roles in tumor suppression, cell cycle regulation, and cell proliferation inhibition [12-14]. The most prevalent isolated aberration in RS is del(17p), detected in 40% of RS cases. TP53 mutations could occur with or without del(17p) and occur in over 40% of RS cases [14, 15]. MYC activating events, which include translocations, amplifications, and mutations, occur in approximately 30% of RS, while NOTCH-1 mutations are found in around 40% of RS cases [13-15]. CDKN2A loss is present in roughly 30% of RS and often co-occurs with TP53 disruption and NOTCH-1 mutation [14]. In contrast, de novo DLBCL-RS exhibits a lower rate of TP53 mutations (~20%), similar to the rate observed in de novo DLBCL [16]. Additionally, clonally related DLBCL-RS expresses stereotyped immunoglobulin genes, particularly IGHV4-39/IGHD6-13/IGHJ5, in approximately 50% of cases, whereas this expression is rare in de novo DLBCL-RS [12]. Finally, there is evidence suggesting involvement of the stereotyped B-cell receptor (BCR) immunoglobulin in CLL transformation [17].

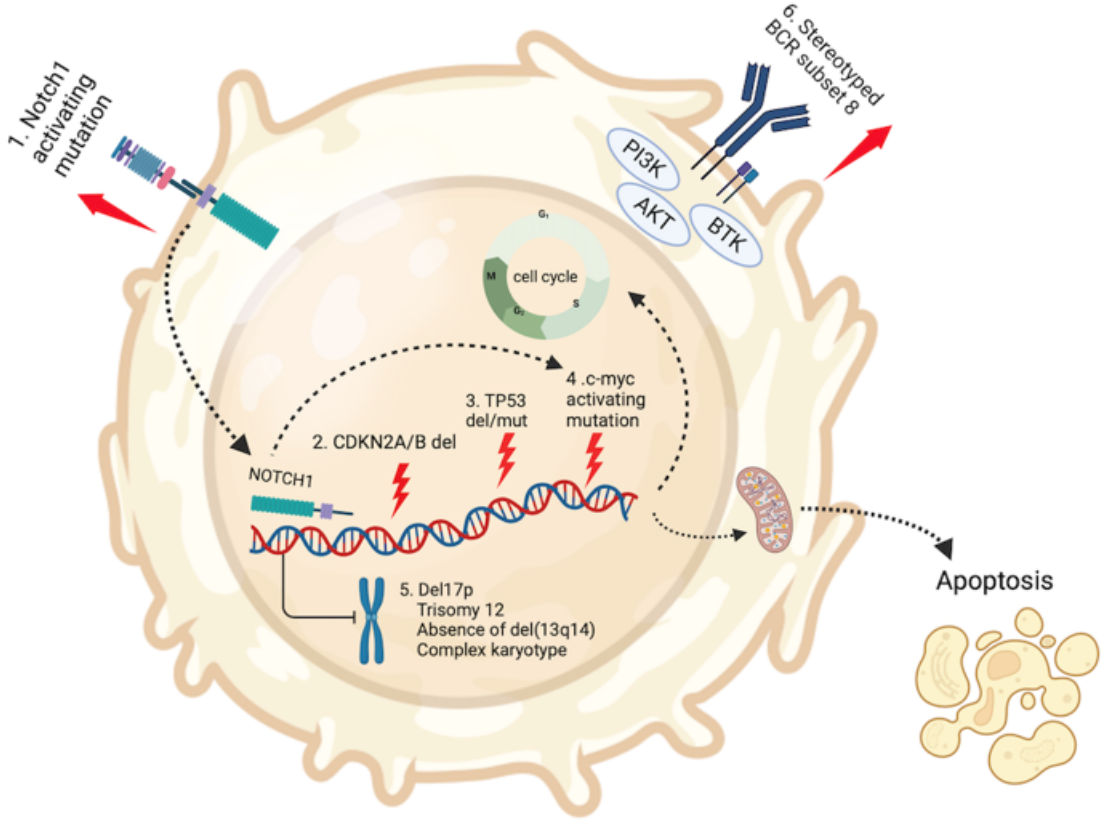

Figure 1: Molecular alterations in clonally related DLBCL-RS.

1. NOTCH1 activating mutation leads to NOTCH1 overexpression on the cell surface leading to transcriptional activation via the NOTCH1 intracellular domain, which subsequently induces MYC expression leading to growth and survival advantage of tumor cells. 2-3. Bi-allelic loss of CDKN2A, CDKN2A and TP53 lead to cellular proliferation, however, this proliferation is dependent on BCR signaling [18]. 4. C-MYC activation is mostly found in a subset of RS that also harbors a TP53 mutation [19]. 5. Del17p, trisomy 12, absence of del (13q14) and complex karyotype are associated with increased risk of transformation. 6. Mutations in BCR signaling components, such as CD79A, CD79B and CARD11 lead to BCR activation and proliferative signals [17].

Risk factors

Currently, there are no standardized models for predicting the risk of RS at the time of CLL diagnosis. However, several studies have identified independent risk factors that may contribute to predicting RS development. One study highlighted CD38 expression ≥ 30%, IGHV 4-39, lymph node size =3 cm, and the absence of del(13q14) as independent risk factors for progression to RS [20]. In a separate retrospective study conducted in a Danish cohort, advanced Binet stage (B-C), del(17p), and unmutated IGHV were identified as independent risk factors for the development of RS [21]. In the era of ibrutinib treatment, a rapid rise in serum lactate dehydrogenase (LDH) and lymphadenopathy without lymphocytosis were recognized as independent prognostic variables for RS development at the time of disease progression [22]. Additionally, Visentin et al. identified the presence of a complex karyotype as being associated with an increased risk of RS. Specifically, individuals with five or more chromosomal abnormalities or those with major structural abnormalities are at higher risk, suggesting that the latter be monitored closely for the development of RS [23]. Recent data emerged from a large international multicenter retrospective study that included 242 patients regarding the relationship between prior CLL treatments and survival outcomes in RS. Patients who developed RS without any prior CLL therapy exhibited a significantly higher mOS of approximately 5 years, compared to patients who had received previous CLL therapies, particularly those treated with small molecule inhibitors such as BTKis and BCL-2 inhibitors (BCL2i). The latter group had much lower survival outcomes, with a mOS of 8.2 months [24].

Clinical Presentation and Diagnosis

The possibility of transformation to RS should be considered when patients with CLL present with specific clinical manifestations. These include new-onset fevers, rapidly progressive lymphadenopathy (particularly if localized or with disproportionate growth in one lymph node cluster), hepatosplenomegaly, drenching night sweats, unintended weight loss, and sudden physical deterioration [25]. Laboratory findings showing persistent elevations or rapid increases in LDH, hypercalcemia or the absence of lymphocytosis in the presence of lymphadenopathy can raise clinical suspicion of RS [25].

Many conditions, such as infections, inflammatory states, and secondary malignancies can mimic RS and require the clinician to consider a broad differential diagnosis. To improve diagnostic accuracy, a comprehensive evaluation should be performed. While RS typically presents as a variant of DLBCL, it can rarely manifest as an HL variant. Furthermore, distinguishing RS from accelerated CLL or even pseudo-RS can be challenging. Given the complexity of these differential diagnoses and the need to identify specific RS variants, consultation with an experienced hematopathologist is essential to ensure an accurate diagnosis [26].

Since RS transformation is often localized to a single lesion, the biopsy should be targeted to the lesion with the highest SUV activity if anatomically accessible. A modified outline of the diagnostic workup of RS by Condoluchi & Rossi is shown in Figure 2 [27]. The convention of using SUVmax =5 as a threshold for proceeding with biopsy was employed due to its high negative and positive predictive value (97% and 53%, respectively) [28, 29]. While an SUV max =10 has a high sensitivity (91%) and a specificity (95%) for identifying RS, the same observation does not apply for patients following kinase inhibitor discontinuation, where an SUV =10 lacked sensitivity and specificity to differentiate between RS and CLL progression [30, 31]. After determining the SUVmax threshold, targeting that area for excisional lymph node biopsy is advisable for histopathologic testing, followed by molecular characterization and IGHV testing [32]. Notably, emerging diagnostic tools, including AI-based approaches designed to enhance accurate histopathologic diagnosis of RS, are on the horizon [33].

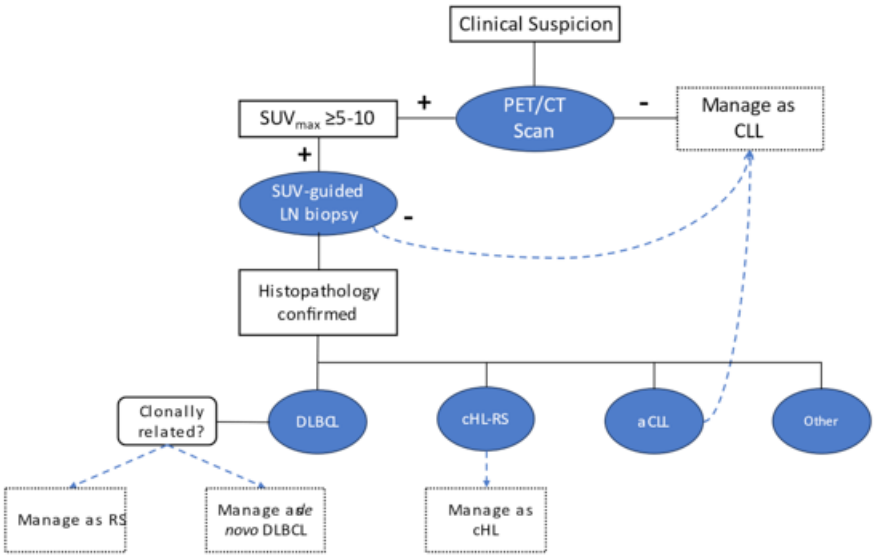

Figure 2: Algorithm for the diagnostic work up of RS.

Treatment of DLBCL-RS

Chemotherapy

Frontline therapy for RS, when parallels the approach of de novo DLBCL, yields particularly unfavorable outcomes for DLBCL-RS patients, as outlined in Table 1. The R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) showed a poor overall response rate (ORR) of 67%, a complete response (CR) of 7%, median progression-free survival (mPFS) of 10 months, and a median overall survival (mOS) of 21 months, which is significantly inferior to the outcomes of de novo DLBCL (34). Similarly, R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) had a low ORR of 39%, mPFS of 3 months and a mOS of 6 months [35].

Platinum-based chemotherapy regimens proved to be equally suboptimal against DLBCL-RS. The OFAR regimen (oxaliplatin, fludarabine, ara-C, and rituximab) achieved an ORR of 38% to 50%, including a CR in 6% to 20% of cases, with a mPFS of 3 months and a mOS of 6 to 8 months [36]. Additionally, DHAP (Dexamethasone, cytarabine, and cisplatin) or ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin) displayed an ORR of 43%, with 25% CR, and an 8-month mOS [37]. Notably, these regimens were associated with higher rates of hematologic toxicities, offering only marginal improvement in OS and PFS [37, 38].

Treatments developed for more aggressive lymphomas were particularly toxic in DLBCL-RS. Hyper-CVAD (fractioned cyclophosphamide, vincristine, doxorubicin, and dexamethasone) elicited a response in 41% (with 38% achieving CR), but the mOS is limited to 10 months [39]. Notably, severe hematologic toxicity occurred in all patients, with infectious complications affecting 50% and a treatment-related mortality (TRM) of 14% [40]. Similarly, a combination of rituximab plus hyper-CVAD alternating with methotrexate and cytarabine resulted in an ORR of 43%, with 27% achieving CR and a mOS of 8 months. This regimen was highly toxic, causing severe hematologic toxicity in all studied patients and a TRM of 22% [40]. While the available evidence comparing the superiority of a particular chemotherapy regimen is limited by small sample sizes or retrospective study design, R-CHOP and R-EPOCH are the most employed first-line regimens for DLBCL-RS.

	Author (move to Left)	Regimen	Study design	Number of patients	ORR (%)	CR (%)	Median OS (mo)	PFS (mo)	TRM (%)	AEs grade ≥3
Fludarabine-based	Giles, et al (41)	PFA or CFA	Single-arm, prospective Phase II	12	19	0	6	NR	NR	TLS (7%), neutropenia (55%), thrombocytopenia (76%).
	Tsimberidou et al (42)	FACP-GM	Single-arm, prospective phase II	15	5	5	2.2	1.5	18	granulocytopenia (90%), anemia (62%), thrombocytopenia (83%), Neutropenic fever (55%) - (fungal31%; bacterial 57%; HSV 6%; VZV 6%), hyperbilirubinemia in 14%, cardiac failure (3%)
Anthracycline-based	Tsimberidou et al (40)	R-GM-CSF +	Single-arm, prospective	30	43	27	8	NR for RS cohort	22	Neutropenia (100%), thrombocytopenia (40%), sepsis (39%), neurotoxicity (mainly steroid-related mood lability or depression; 8%), peripheral neuropathy (4%), oral mucositis/esophagitis (10%), diarrhea (3%), renal failure (4%)
		R-Hyper-CVAD alternating with HD-MTX/cytarabine	Phase II							
	Dabaja et al (39)	Hyper-CVAD	Single-arm, prospective Phase II	29	41	38	10	NR	20	Granulocytopenia 100%, thrombocytopenia (79%), sepsis 8%, fungal pneumonia (6%)

	Langerbeins et al (34)	R-CHOP	Single-arm, prospective Phase II	15	67	7	21	10	3	Anemia (75%), neutropenia (55%), thrombocytopenia (65%), Infections (28%), neurotoxicity (36%), polyneuropathy (1%)
	Rogers et al (35)	R-EP-OCH	Retrospective	46	39	NR	5.9	3.5	30	Neutropenic fever (17%), infections (21%), ICU stay (4%)
	Eyre et al (43)	O-CHOP + O maintenance	Single-arm, prospective Phase II	37	46	27	11.4	6.2	0	Anemia (3%), thrombocytopenia (11%), neutropenic fever (2%), vomiting (1%), infusion related reaction (1%), pneumonia (3%), sepsis (7%), rash (2%)
Platinum-based	Durot et al (37)	DAHP/ ESHAP	Retrospective	28	43	25	8.3	6.9	18	Neutropenia (83%), thrombocytopenia (82%), anemia (72%), acute renal insufficiency (AKI) (12%), TLS (12%)
	Tsimberidou et al (38)	OFAR2	Prospective I/II	31	38	6	6	3	8	Neutropenia (89%), neutropenic fever (20%), anemia (50%), thrombocytopenia (77%), infection (17%), nausea/ vomiting (6%)
	Tsimberidou et al (36)	OFAR1	Prospective I/II	20	50	20	8	3	5	Neutropenia (85%), neutropenic fever (8%), anemia (54%), thrombocytopenia (95%)

Abbreviations: AEs = adverse effects; CFA = cyclophosphamide, fludarabine, cytarabine; CR = complete response; DAHP = dexamethasone, cytarabine, and cisplatin; ESHAP = etoposide, methylprednisolone, cytarabine, and cisplatin; FACPGM = fludarabine, cytarabine, cyclophosphamide, cisplatin, and granulocyte– macrophage colony-stimulating factor; R-GM-CSF = Rituximab, granulocyte– macrophage colony-stimulating factor; HD-MTX = high-dose methotrexate; R-HyperCVAD = rituximab, fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone; NR = not reported; O = ofatumumab; OFAR = oxaliplatin, fludarabine, cytarabine and rituximab; ORR = overall response rate; OS = overall survival; PFA = cisplatin, fludarabine, cytarabine; PFS = progression-free survival; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-EPOCH = rituximab, etoposide, prednisolone, vincristine, and doxorubicin; RT = Richter transformation; TLS = tumor lysis syndrome; TRM = treatment-related mortality.

Table 1: Treatment of DLBCL-RS.

Novel targeted therapies

BTK inhibitors

Given the suboptimal response rates and poor survival outcomes achieved with conventional chemotherapies, the utilization of novel therapies is urgently needed. BTK inhibitors (BTKis) showed promise in treating DLBCL-RS, as summarized in Table 2. Ibrutinib, a first-generation BTKi, demonstrated an ORR of 75%, with a CR observed in 25% of patients with DLBCL-RS who were treatment-naïve to novel agents [44]. Acalabrutinib, a second-generation BTKi, was evaluated in 25 patients with treatment-naïve or relapsed/refractory (R/R) DLBCL-RS and achieved an ORR of 40%, with a CR rate of 8% and a mPFS of 3.2 months [45]. Additionally, findings from the phase I BELLWAVE-001 trial, which assessed the safety and effectiveness of the non-covalent BTKi, nemtabrutinib, revealed an ORR of 50% among six DLBCL-RS patients, all of whom achieved a PR [46]. Non-covalent BTKis were also explored as an alternative to covalent BTKis, particularly when acquired resistance is suspected. The BRUIN study, a phase 1/2 clinical trial, recently reported updated results with an 18-month median survival follow up, where it assessed pirtobrutinib in 82 patients with DLBCL-RS. It demonstrated an encouraging OS and a manageable safety profile, with an ORR of 50%, a CR rate of 13.4%, a mPFS of 3.7 months, and a mOS of 12.5 months [47].

Resistance to non-covalent BTKis was associated with secondary BTK mutations and downstream PLCγ2 mutations, which can also confer resistance to covalent BTKis [48]. One novel strategy to overcome BTKi acquired mutations is the degradation of the BTK by the proteasome machinery. NX-2127 is a novel small molecule that causes BTK degradation and immunomodulatory drug mimicry by inducing ubiquitination of proteasome complexes and has activity against both wild-type BTK and drug-resistant mutant BTKis [49]. Current trials with the various BTK degraders are underway and the results are anticipated to change the management landscape of RS refractory to conventional BTKi.

BCL2 inhibitor

Another important pathway for the survival of CLL is the intrinsic pathway of apoptosis, regulated by BCL2. Venetoclax, a BCL2 inhibitor, showed high efficacy in CLL but limited activity as monotherapy in RS, yielding an ORR of 43% with no CR [50]. Although these responses were short-lived, this served as a proof of principle for future studies exploring BCL2 inhibition in combination strategies, which will be discussed further in this article.

	Author	Novel targeted agent	Study design	Number of patients	ORR (%)	CR (%)	OS median (mo)	PFS median (mo)	TRM (%)
BTK-inhibitors	Tsang et al. (44)	Ibrutinib	Retrospective	4	75	25	9.5	NR	0
	Eyre et al. (45)	Acalabrutinib	Single-arm, open-label Phase I/II	25	40	8	NR	3.2	0
	Tam et al. (51)	Zanubrutinib	Single-arm, open-label Phase I/II	13	61.5	15.4	29.3	17.3	0
	Tam et al. (51)	Zanubrutinib + tislelizumab	Single-arm, open-label Phase Ib	7	42.9	14.3	15.4	2.9	0
	Wierda et at. (52)	Pirtobrutinib	Single-arm, open-label phase I/II	82	50	13.4	12.5	3.7	0

	Woyach et al. (46)	Nemtabrutinib	Single-arm, open-label Phase I/II	6	50	0	NR	NR	NR
	Younes et al. (53)	Ibrutinib + nivolumab	Phase I/IIa R/R	20	65	10	10	5	0
BCL2-inhibitors	Davids et al. (50)	Venetoclax	Single-arm, open-label Phase I	7	42.9	0	NR for RS cohort	NR for RS cohort	NR
	Bouclet et al. (54)	Venetoclax	Retrospective	7	28.6	0	1.1	NR	NR
	Davids et al. (55)	VR-CHOP	Single-arm, open-label Phase II	25	68	48	19.2	7.2	4
	Davids et al. (56)	VR-EPOCH	Single-arm, open-label Phase II	26	62	50	19.6	10.1	0
	Jain et al. (57)	Venetoclax + atezolizumab + obinutuzumab	Single-arm, open-label Phase II	7	100	71	NR	NR	NR
PI3K-inhibitors	Visentin et al. (58)	Idelalisib	Retrospective	4	75	25	NR	NR	NR
	Crombie et al. (59)	Duvelisib + Venetoclax	Single-arm, open-label Phase I/II	3	0	0	NR	NR	NR

Abbreviations: BCL2 = B-cell lymphoma/leukemia 2; BTK = Bruton tyrosine kinase; CR = complete response; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PI3K = phosphoinositide 3-kinase; R/R = relapsed/refractory; RS = Richter's syndrome; TRM = treatment-related mortality; VR-CHOP = venetoclax, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VR-EPOCH = venetoclax, rituximab, dose-adjusted etoposide, prednisolone, vincristine, and doxorubicin.

Table 2: DLBCL-RS Summarized.

Immunotherapy

The high expression of PD-1 in DLBCL-RS, has provided a rationale for exploring PD-1 inhibitors as potential treatments. Several studies have investigated PD-1 inhibitors, such as pembrolizumab, in DLBCL-RS. Notably, in a phase II clinical trial, Pembrolizumab, a monoclonal antibody targeting the PD-1 receptor, showed activity in patients with DLBCL-RS. The trial achieved an ORR of 44%, including a CR rate of 11%, with a PFS of 5.4 months and an OS of 10.7 months, however it had no activity in CLL [60]. Unfortunately, such results were not reproducible in subsequent studies, including a larger phase II trial involving 23 R/R DLBCL-RS patients (18 of whom had DLBCL-RS) where it reported less favorable outcomes, with an ORR of 13%, a PFS of 2 months, and an OS of 4 months [61]. In summary, the role of PD-1 inhibition in RS will require refinement and exploration of combinational therapies as described below.

More recently, studies have explored changes in T-cell subsets in patients with RS as predictors of response to PD-1 inhibitors. A study that analyzed 20 patients with RS, showed that PD-1 responders had an increased Th17 subset and reduced Th2 T cells at baseline compared to those who progressed or had stable disease, suggesting that an increased Th17/Th2 ratio maybe a potential predictor of response to PD-1 inhibition. However further validation and exploration of the immunological landscape in RS is needed for more personalized therapies [62].

Combinational therapies of novel agents in RS

Combination therapies of novel agents with other treatments are being explored in current trials, due to suboptimal responses to chemo-immunotherapy and short-lived responses with single-agent novel therapies. In the following section, we will describe some of those studies along with ongoing clinical trials that have not yet resulted in outcome data.

Novel agents with chemoimmunotherapy

Various combinations of novel agents with chemoimmunotherapy have been explored. Promising outcomes were observed when venetoclax was used with R-EPOCH (VR-EPOCH), as evidenced by a phase II single-arm trial involving 26 DLBCL-RS patients. This combination yielded a CR rate of 50%, with 11 out of the 26 patients achieving undetectable minimal residual disease (MRD) for CLL. Additionally, the OS reached 19.6 months, and the PFS extended to 10.1 months. However, this combined therapy was accompanied by significant adverse effects, including hematological toxicity, such as neutropenia (grade 3/4 in 65% of patients) and thrombocytopenia (grade 3/4 in 50% of patients), as well as non-hematological complications like febrile neutropenia (seen in 38% of patients) and infections (reported in 20% of patients) [56]. Venetoclax was also studied in combination with R-CHOP (VR-CHOP) and found to achieve similar response rates to VR-EPOCH, but with less toxicity. A retrospective analysis of 10 patients with DLBCL-RS treated with VR-CHOP showed an ORR of 60% and CR of 50%. Additionally, the study examined 20 patients who received VR-EPOCH and found that they experienced more grade 3/4 infections and neutropenic fever, occurring in 37% and 42% respectively compared to 33% and 33% in the VR-CHOP cohort [63]. To assess whether the intensified anthracycline backbone when combined with venetoclax can preserve efficacy while mitigating toxicity, a new cohort was added to the NCT03054896 study, evaluating the combination of venetoclax with R-CHOP in DLBCL-RS.

Trials assessing the combination of BTKis with CIT have not been reported yet. The STELLAR study evaluates the combination of acalabrutinib with RCHOP and has two more arms including single agent acalabrutinib and RCHOP. Notably, this would be the first randomized study in DLBCL-RS and could change the paradigm of designing clinical trials to address those unmet needs.

PI3K inhibitors and venetoclax

PI3K inhibitors, specifically idelalisib and duvelisib, have shown some efficacy in RS. In a retrospective study involving four patients with ibrutinib-resistant DLBCL-RS who received idelalisib as monotherapy, an ORR of 75% was achieved, including a CR rate of 25% [58]. Interestingly, PI3K inhibition can promote tumor sensitivity to BCL-2 antagonism [64]. Similarly, CLL cells from patients treated with duvelisib showed increased sensitivity to venetoclax, and the combination of both drugs had a synergistic effect in Richter's syndrome patient-derived xenograft (PDX) models [65, 66]. An ongoing phase I/II trial is underway to evaluate the use of duvelisib in combination with venetoclax in patients with R/R CLL and RS. Four of the eight RS patients enrolled in the trial so far have responded, with two achieving a CR. Two of these responders subsequently underwent cellular therapies, one with CAR-T and the other with an allogeneic hematopoietic stem cell transplantation (alloHCT), resulting in durable remissions. This combination was further explored with the addition of a CD20 monoclonal antibody, ublituximab to a PI3K inhibitor, umbralisib, and venetoclax in a phase I/II trial for patients with R/R CLL (n= 46) and RS (n=5). The triplet therapy was administered in a response-adapted and time-limited strategy, demonstrating a CR in 38% of patients [67]. These findings suggest that combinations like BCL-2 and PI3K inhibitors may be a backbone for more effective therapies [68].

Novel agents with checkpoint blockade

Integrating novel therapeutic agents in conjunction with checkpoint inhibitors presents another promising avenue for treating RS. A phase II study examined the combination of

ibrutinib and nivolumab in 24 patients with DLBCL-RS and resulted in an ORR of 42%, a CR rate of 34%, and a mOS of 13 months [69]. Additionally, a phase I/IIa study examined the same combination of ibrutinib with nivolumab, yielding an ORR of 65%, and a CR rate of 10% [53]. Unfortunately, both studies demonstrated short-lived responses, with a median duration of response (mDOR) of approximately 7 and 9 months [53, 69]. More recently, zanubrutinib, in combination with the anti-PD-1 monoclonal antibody, tislelizumab, exhibited promising results in the phase 2 trial, RT1. Of the 48 patients who received at least 3 cycles of the combination, results showed an ORR of 58.3%, a CR rate of 18.8% that lasted for 6 months or more in 70% of patients, a mPFS of 10 months and a 12-month OS of 74.7% [67].

Currently, ongoing trials are exploring the combination of PI3K inhibitors with immunotherapy, such as copanlisib plus nivolumab (NCT03884998) and the triplet therapy with umbralisib, ublituximab and pembrolizumab. Preliminary results from the former showed an ORR of 27%, including one patient achieving a CR and two with partial responses (PR) [70]. Additionally, the phase 2 RT1 trial underwent a protocol amendment and is now recruiting an additional cohort to study the triplet combination therapy of tislelizumab, zanubrutinib and sonrotoclax, a second generation BCL-2 inhibitor. These ongoing investigations hold promise for advancing treatment options in RS.

Cellular therapy

Stem cell transplantation

Given the short duration of response to chemotherapy, autologous (autoHCT) and allogeneic (alloHCT) hematopoietic cell transplantation have been proposed for patients who achieve remission with initial therapy. A retrospective study by the European Group for Blood and Marrow Transplantation (EBMT) examine 59 patients with DLBCL-RS and showed a three-year relapse-free survival of 27% after alloHCT and 45% after autoHCT with an overall 3-year survival of 36% and 59% respectively [71]. The best OS benefit was seen in younger patients (<60 years), those who received an alloHCT with a reduced-intensity conditioning regimen, and those who had a favorable response to induction chemotherapy at the time of stem cell transplantation [71]. Notably, a plateau observed at the tail of the OS curve, implies a curative graft versus leukemia (GVL) effect.

More recently, a large Center for International Blood and Transplant Research retrospective registry study evaluated the outcomes after alloHCT and autoHCT in DLBCL-RS and found a three-year PFS and OS of 43% and 52% vs 48% and 57% respectively [72]. Similar to the EBMT study, the best outcomes in alloHCT were observed in patients who achieved a CR before HCT. Collectively, these studies suggest that both autoHCT and alloHCT can be effective in DLBCL-RS, with the latter offering a curative chance.

Anti-CD19 CAR-T therapy

Given the revolutionary role of chimeric antigen receptor T-cell (CAR-T) therapy in managing relapsed and refractory DLBCL, this approach has also been explored in RS-DLBCL. In a retrospective study of 9 patients with DLBCL-RS treated with axi-cel, 8 of whom were previously treated with a BTKi, 5 achieved a CR and 3 a PR with an impressive ORR of 100% in the 8 evaluable patients [73]. A larger international multi-center retrospective study evaluated 62 patients with DLBCL-RS who received CD19 CAR-T, 84% of whom were exposed to prior BTKi or BCL2i, and showed a CR of 47%, PR of 18%, and an ORR of 65%. However, responses were short-lived, as the mOS was 8.5 months [74]. Similarly, in a smaller cohort of 19 patients with CLL, four of whom had DLBCL-RS, were treated with ibrutinib in combination with anti-CD19 CAR-T and yielded an 83% response rate, but the responses of those with DLBCL-RS were unclear [75]. In a study by Benjamini et al., six patients with DLBCL-RS were treated with anti-CD19 CAR-T cells, 4 patients achieved CR, while two of those 4 proceeded to alloHCT [76]. Additional trials supporting the role of CAR-T in RS include the study of liso-cel, which was tested in the R/R CLL setting and included five patients with DLBCL-RS , two of whom achieved a CR and one with a PR [77]. This study showed that patients with bulky lymphadenopathy were less likely to respond to CAR-T treatment. More recently, a study enrolled 20 patients to evaluate the use of the CAR-T19, varnimcabtagene autoleucel (var-cel), in patients with R/R CLL with or without DLBCL-RS. Initial outcomes presented in the 2023 American Society of Hematology (ASH) meeting showed an ORR of 83%, with 61% achieving a CR, however, 39% of patients progressed at a median of 63 days, and those were noted to be the patients with RS, suggesting that var-cel may offer more durable responses in R/R CLL compared to RS [78].

T-lymphocytes from heavily pre-treated CLL are characterized by T-cell exhaustion and impairment, which is thought to interfere with CAR-T. Recent efforts are focused on enhancing CAR-T cells by combining them with a BTKi, leading to the reversal of the exhausted T-cell phenotype [79]. Clinical trials (NCT05873712 and NCT05672173) evaluating this concept involve liso-cel combined with either zanubrutinib (NCT05873712) or nivolumab (NCT05672173) and ibrutinib, which are currently enrolling.

Bispecific antibodies

Bispecific antibodies, engaging T-lymphocytes against the tumor cells have demonstrated activity in RS. In a phase II study, patients with DLBCL-RS who did not achieve a CR after

two cycles of R-CHOP received blinatumomab, a CD19/CD3 bispecific T-cell engaging antibody. Out of 39 patients who were treated with R-CHOP, 25 switched to the blinatumomab arm and achieved an ORR of 36% [80]. These results are promising, but longer follow up is needed to assess the durability of response.

CD20/CD3 bispecific antibodies have also been explored in RS. A phase I study of glofitamab in R/R B-cell lymphomas included 6 patients with DLBCL-RS, 3 of whom achieved CR and 2 PR. The most common adverse event (AE) was cytokine release syndrome (CRS) in 50.3% of all patients, which could be reduced with initial obinutuzumab debulking [81]. Epcoritamab has equally demonstrated a high response rate, where a phase 1b/2 study showed an ORR of 60% and a CR of 50% among patients with DLBCL-RS [82]. The antitumor activity was observed in most patients at the initial 6 weeks assessment, and there was no discontinuation because of AEs. The most common AEs were CRS (40% grade 1 and 50% grade 2). Mosunetuzumab, another CD20/CD3 T-cell engaging bispecific antibody, has been investigated as fixed-duration therapy in R/R RS. Early data from the 20 enrolled patients showed an ORR of 40% and a CR of 20%[83]. Similar to other bispecific antibodies, the most common AE was CRS (20% grade 1, 40% grade 2 and 5% grade 3) after a median follow up of 8.7 months [83]. Bispecific antibodies appear to have a manageable safety profile and maybe preferable over CAR-T for rapidly growing DLBCL-RS, given the lack of manufacturing delay.

Ongoing trials of investigational and combination therapies

Various combination therapies are currently under investigation in RS, especially triplet therapies in several phase II trials that are actively enrolling patients. Among these, triplet therapies that combine venetoclax with a BTKi and obinutuzumab are being examined in two single-arm trials. The GIVeRS trial, is a phase II study evaluating the efficacy of obinutuzumab in combination with venetoclax and ibrutinib. A total of 10 patients were enrolled, 6 were treatment naive and 4 had R/R RS. At 3 and 6 months, the ORRs were 70% and 22.2% and CRs were 40% and 11.1% respectively, consistent with a high early response rate but subsequent progression, suggesting its utility as bridging to consolidation with cellular therapy [84]. On the other hand, NCT05536349 is utilizing pirtobrutinib, venetoclax, and obinutuzumab. Notably, the latter trial is assessing this triplet therapy in treatment-naïve patients, and the therapy is time-limited. Another triplet therapy was proposed by the CLL group at the Mayo Clinic, assessing venetoclax with a BTKi and immunotherapy. This combination, comprising venetoclax, acalabrutinib, and durvalumab (NCT05388006), is administered for 12 cycles, followed by maintenance venetoclax and acalabrutinib for one year, in the absence of disease progression or unacceptable toxicity. Furthermore, the combination of CIT with an anti-body drug conjugate is also being explored. A trial is currently underway to evaluate polatuzumab vedotin in combination with a modified infusional dose-adjusted R-EPOCH-like regimen in RS patients (NCT04679012). The results of the aforementioned trials have not yet been reported, however along with efficacy, the safety and toxicity profiles of the triplet therapies, in particular, will need to be established.

ROR1 is an oncofetal protein that is present on the surface of CLL and RS cells. Zilovertamab vedotin (ZV), is an anti ROR-1/monomethyl auristatin E antibody-drug conjugate, which has demonstrated activity in DLBCL-RS in pre-clinical and clinical studies, however such responses were not durable [85]. WaveLINE-001, a phase I study assessed ZV in patients with R/R B-NHL, and 7 patients with RS were included. After 14 months of follow up, the RS cohort demonstrated an ORR of 57%, with 1 patient achieving CR and 3 a PR, along with a mOS of 19.4 months. However, the mDOR was only 4 months [86].

Conclusion

The management of RS continues to pose significant challenges, resulting in generally poor outcomes when treated with the traditional CIT regimens alone. Encouraging data have emerged with CAR-T cellular therapies, CD20/CD3 bispecific antibodies and combining novel agents with CIT. One substantial obstacle in establishing a standardized RS treatment protocol stems from the rarity of the disease and the absence of randomized controlled trials. Collaboration among multiple centers will be needed to address this ongoing and unmet clinical need within the field.

Data Availability Statement:

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Funding Sources:

This research received no external funding.

Conflict of Interest Disclosure:

M.A. and S.R.J. declare no conflict of interest. GP is shareholder of Amgen, Eli Lilly, Crispr Therapeutics and equity owner of Mevox.

Author Contributions:

Conceptualization M.A. and G.P., investigation M.A., S.R.J. and G.P., writing original draft preparation M.A and S.R.J., writing—review and editing M.A., S.R.J. and G.P., Supervision G.P. All authors have read and agreed to the published version of the manuscript.

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