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Leukemia (PH Wiernik, Section Editor)

Treatment of Richter's Syndrome

Adalgisa Condoluci, MD[1,2]
Davide Rossi, MD, PhD[1,2,*]

Address
[*,1]Division of Hematology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland
Email: davide.rossi@eoc.ch
[2]Laboratory of Experimental Hematology, Institute of Oncology Research, Bellinzona, Switzerland

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Opinion statement

Based on the available literature, mostly derived from retrospective or non-randomized phase I or II studies, it is difficult to define an optimized treatment approach for patients developing Richter's syndrome (RS). Early recognition of chronic lymphocytic leukemia (CLL) patients presenting clinical features suspected for a transformation is useful to avoid exposing them to multiple lines of therapy that, being targeted to CLL progression, have poor efficacy against RS. Because of the low specificity (~ 50–60%) of clinical signs of RS (such as rapid and discordant bulky localized lymphadenopathies, elevated LDH levels, emergent physical deterioration, and/or fever in the absence of infection), a ^{18}FDG PET/CT and a biopsy are recommended to confirm RS. A ^{18}FDG PET/CT showing low uptake is helpful to rule out RS and avoid unnecessary risks and costs of performing a biopsy. A ^{18}FDG PET/CT showing a high uptake is not diagnostic of RS but may help in the choice of the site where the biopsy is to be performed. In the setting of the diffuse large B-cell lymphoma (DLBCL) variant of RS, the definition of a clonal relationship between RS and the underlying CLL may guide the choice of treatment. If a clonal relationship is confirmed (the most common situation), rituximab-CHOP-like treatment does not guarantee long-lasting remissions, and should be used as induction therapy followed by consolidation with a stem cell transplant in physically fit patients. If the CLL and RS are clonally unrelated (the less common situation), the management should be that of a de novo DLBCL. In the setting of the rare Hodgkin lymphoma variant of RS, which is usually clonally unrelated to the CLL, ABVD with or without radiotherapy may be curative of the aggressive lymphoma.

Introduction

Richter's syndrome (RS) is defined as the transformation of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) into an aggressive lymphoma. RS may present with a diffuse large B-cell lymphoma (DLBCL)

morphology, or, rarely, with a Hodgkin lymphoma (HL) morphology [1]. To allow early and proper treatment, a prompt diagnosis is of major importance, and involves clinical suspicion as well as an accurate and ^{18}FDG-PET/CT-driven choice of nodal or extra-nodal site of biopsy [2, 3, 4•]. Clinical features suspected for a transformation are the development of new B symptoms, the asymmetric rise of bulky lymph nodes, and/or the sudden rise of lactate dehydrogenase (LDH) levels. RS could also develop in extra-nodal sites, and it might be included in the differential diagnosis of an extra-nodal mass developing in patients with a known CLL. The specificity of these clinical findings for transformation is only 50–60%, with the remaining cases showing either progressive or "accelerated" CLL, or even a solid cancer [2]. Consistently, histological documentation of transformation mandates a biopsy of the suspected lesion. ^{18}FDG PET/CT may support the choice of whether performing a biopsy and may tailor the biopsy to the likely transformed site. Because of the high negative predictive value (97%) of ^{18}FDG PET/CT, CLL patients for whom a RS is suspected, but whose scan shows low uptake, can be spared from the biopsy. Conversely, because of the limited positive predictive value (53%) of ^{18}FDG PET/CT, in CLL patients for whom a RS is suspected and the ^{18}FDG PET/CT shows a high uptake, a biopsy should be directed at the index lesion (i.e., the lesion showing the most avid ^{18}FDG uptake) [2].

Two morphologic variants of RS can be pathologically recognized. The DLBCL variant of RS shows confluent sheets of large neoplastic B lymphocytes resembling either centroblasts or immunoblasts [5–7]. Importantly, CLL cases presenting with numerous proliferation centers and an increased number of prolymphocytes and paraimmunoblasts, but lacking clear features of DLBCL, should not be diagnosed as RS and criteria for the distinction between RS and "accelerated CLL" have been proposed [8, 9]. These characteristics include the occurrence of (i) tumor of large B-cells with nuclear size equal or larger than macrophage nuclei or more than twice a normal lymphocyte and (ii) diffuse growth pattern of such large cells (not just presence of small foci). By applying these criteria, up to 20% of cases diagnosed as RS will be properly classified as "accelerated" CLL [9]. Phenotypically, tumor cells invariably express CD20, while CD5 expression is maintained only in a fraction (~ 30%) of cases, and CD23 expression is even more rare (~ 15% of cases) [5]. Diagnosis of the HL variant is defined by the presence of classical Reed-Sternberg cells harboring a CD30-positive/CD15-positive/CD20-negative phenotype in a proper polymorphous background of small T-cells, epithelioid histiocytes, eosinophils, and plasma cells [10]. Based on the analysis of the rearrangement of *IGHV-D-J* genes, most (~ 80%) of the DLBCL variants of RS are clonally related to the preceding CLL phase, thus representing true transformations [5, 7]. In contrast, only a fraction (~ 30%) of the HL variants of RS are clonally related to CLL [10]. Thus, a variable number of RS (~ 20% with DLBCL morphology and ~ 70% with HL morphology) harbors distinct *IGHV-D-J* rearrangements compared to the preceding CLL, representing de novo lymphomas developing in a CLL patient [5, 7, 10].

Treatment options of the DLBCL variant of RS

Chemotherapy approaches

Patients presenting RS have often a history of multiple treatments for the preceding CLL, with an older age translating in a number of comorbidities that influence the choice of treatment. Regimens indicated for aggressive B-cell non-Hodgkin lymphomas have been proposed to treat patients developing the DLBCL variant of RS.

R-CHOP

A prospective multicenter phase II trial (NCT00309881) including 15 patients with RS evaluated efficacy and tolerability of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) for up to eight courses. This regimen resulted in a response rate of 67% (CR 7%), median progression-free survival (PFS) of 10 months, and median overall survival (OS) of 21 months (Table 1). The overall response rate (ORR) was

significantly associated with lower levels of LDH, higher levels of hemoglobin, and a longer time period from CLL diagnosis to transformation. The treatment-related mortality was low (3%). Hematotoxicity occurs in 65% of patients, while infections were the most common severe non-hematologic toxicity in 28% of patients [16]. In a retrospective series of 12 RS patients treated with R-CHOP, the response rate was 50% and the median OS was 15 months [23].

CHOP-O

Ofatumumab (O) is an anti-CD20 monoclonal antibody which showed an increased CD20-binding affinity compared to rituximab and minimal toxicities in the treatment of relapsed/refractory CLL as a single agent [24]. CHOP-O has been evaluated in a prospective multicentric non-randomized phase II trial including 37 evaluable DLBCL variants of RS patients. The ORR was 46% (CR 27%, PR 19%) after 6 cycles of CHOP-O followed by 6 cycles of ofatumumab maintenance every 8 weeks, with a median PFS of 6 months and a median OS of 11 months [18] (Table 1). Treatment-naïve patients showed a significantly superior survival than patients who had received one prior line of CLL therapy, with ORR of respectively 53 vs 40%. Adverse events were infections and hematologic toxicities (thrombocytopenia, febrile neutropenia, sepsis) [18] (Table 1).

R-EPOCH

R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) is used in high-grade B-cell lymphoma with rearrangements of *MYC* and *BCL2* and/or *BCL6* (double-hit and triple-hit lymphomas). Since *MYC* is frequently rearranged in the DLBCL variant of RS, R-EPOCH has been investigated in this disease as first-line therapy in a single-institution retrospective cohort including 46 RS patients [17]. Results showed a 20% response rate, a median PFS of 3 months, and a median OS of 6 months (Table 1). Characteristics of underlying CLL influenced outcomes of R-EPOCH, with worse PFS and OS in deletion 17p and complex karyotype patients. Adverse events were recorded up to 87% of all administered therapy and were mainly due to hematologic toxicities (febrile neutropenia and infections) [17].

Hyper-CVAD

The hyper-CVAD regimen, a fractioned cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen, resulted in a response rate of 41% (CR 38%) of patients, but the median OS was only 10 months (Table 1). This aggressive regimen was invariably complicated by severe hematotoxicity in all cases, translating into a high severe infection rate of 50% and a treatment-related mortality of 14% [11]. Combination of hyper-CVAD alternating with methotrexate and ara-C regimen with rituximab resulted in a response rate of 43% (CR 38%), but the median OS was 8 months (Table 1). This combination was highly toxic (severe hematotoxicity in all cases, severe infection rate of 39%, and treatment-

related mortality of 22%) despite the prophylaxis with granulocyte-macrophage colony-stimulating factor (GM-CSF) [12].

Platinum-containing regimens

The first results of phase I–II clinical trial of oxaliplatin, fluradabine, ara-C, and rituximab (OFAR 1) were encouraging, with response rates of 50% for RS patients (CR 6–20%) (Table 1). Nevertheless, this regimen was associated with short duration of response (mean PFS of 3 months and mean OS of 6–8 months) and severe myelosuppression [14]. The OFAR 2 trial was designed with the aim of improving clinical outcomes and decreasing toxicities, and introduced modification of oxaliplatin and cytarabine doses. Despite this adjustment, hematologic toxicity was still significant with 80% of patients developing grade 3–4 neutropenia/thrombocytopenia and 20% grade 3–4 infections. The ORR was 39% (CR 6.5%); the median PFS was 3 months; the median OS was 7 months; and at 2 years only 19.7% of patients with RS were alive [15] (Table 1).

In summary, chemoimmunotherapy regimens generally successful in treating highly aggressive lymphomas have shown promising activity in the treatment of the DLBCL variant of RS in terms of complete response rate. However, these results have to be considered from a wider standpoint, involving the high rates of severe toxicities and the short-lasting remission durations. Providing an acceptable balance between activity and toxicity, R-CHOP and OFAR regimens represent the backbone for induction treatment in patients with DLBCL variant of RS.

Radioimmunotherapy

A single-institution trial investigating ^{90}Y ibritumomab tiuxetan involved seven patients with histologically proven RS and < 25% lymphoma and/or CLL in the bone marrow [13, 25]. Patients receive a dose of 111In-labeled ibritumomab tiuxetan of 1.6 mg. One week later, patients received 0.3 or 0.4 mCi/kg of ^{90}Y ibritumomab tiuxetan and 250 mg/m^2 iv rituximab on days 1 and 8 before infusion of ibritumomab tiuxetan. No responses have been documented in RS patients treated with radioimmunotherapy, with 100% of progression at a median time of 40 days [13] (Table 1).

Stem cell transplantation

Stem cell transplantation (SCT) has been explored as post-remission therapy in RS patients because of the short duration of responses with the sole chemotherapy. Nevertheless, only a small fraction of patients with RS (~ 10–15%) can access SCT generally due to limitations imposed by age, performance status, and donor availability [23, 26].

The mechanisms by which SCT could be effective in Richter's syndrome are dose intensity delivered by high-dose cytotoxic therapy and, in the case of allogeneic SCT, graft-versus-leukemia activity. The efficacy of autologous SCT

Table 1. Summary of the published induction regimens for Richter syndrome

Reference	Study design	Patients	RS type	Regimen	ORR	CR	PFS/FFS
Dabaja et al. 2001 [11]	Clinical trial	26	DLBCL	hyper-CVXD	41%	38%	na
	Clinical trial	16	DLBCL	FACPGM	6%	6%	1 month
Tsimberidou et al. 2003 [12]	Clinical trial	30	DLBCL	R + hyper-CVXD + GM-CSF/R + HDM-ara-C+ GM-CSF	43%	27%	na
Tsimberidou et al. 2004 [13]	Clinical trial	7	DLBCL	^{90}Y ibritumomab tiuxetan	0%	0%	1 month
Tsimberidou et al. 2008 [14]	Clinical trial	35	DLBCL	OFAR1	50%	20%	3 months
Tsimberidou et al. 2013 [15]	Clinical trial	31	DLBCL	OFAR2	38%	6%	3 months
Langerbeins et al. 2014 [16]	Clinical trial	15	DLBCL	R-CHOP	67%	7%	10 months
Rogers et al. 2015 [17]	Clinical trial	46	DLBCL	R-EPOCH	38%	20%	3 months
Eyre et al. 2016 [18]	Clinical trial	37	DLBCL	CHOP-O	46%	27%	6 months
Kuruvilla et al. 2014 [19]	Clinical trial	6	DLBCL	Selinexor	33%	0%	na
Hillmen et al. 2016 [20]	Clinical trial	29	DLBCL	Acalabrutinib	38%	14%	3 months
Tsang et al. 2015 [42]	Retrospective	4	DLBCL	Ibrutinib	75%	25%	na
Ding et al. 2017 [45]	Clinical trial	9	DLBCL	Pembrolizumab	44%	11%	na
Jain et al. 2016 [21]	Clinical trial	3	DLBCL	Nivolumab + Ibrutinib	na	na	na
Davids et al. 2017 [22]	Clinical trial	7	DLBCL	Venetoclax	43%	0%	na
Bockorny et al. 2011 [30]	Retrospective	67	HL	ABVD (31%), MOPP (16%), CHOP (13%), other (40%)	52%	27%	12 months

Reference	OS	Neutropenia (grades 3–4)	Thrombocytopenia (grades 3–4)	Infection (grades 3–4)	TRM
Dabaja et al. 2001 [11]	10 months	100%	79%	39%	14%
	10 months	90%	83%	55%	18%
Tsimberidou et al. 2003 [12]	8 months	100%	40%	39%	22%
Tsimberidou et al. 2004 [13]	na	29%	71%	14%	0%
Tsimberidou et al. 2008 [14]	8 months	85%	95%	8%	3%
Tsimberidou et al. 2013 [15]	6 months	89%	77%	17%	8%

Table 1. (Continued)

Reference	OS	Neutropenia (grades 3–4)	Thrombocytopenia (grades 3–4)	Infection (grades 3–4)	TRM
Langerbeins et al. 2014 [16]	21 months	55%	65%	28%	3%
Rogers et al. 2015 [17]	6 months	na	na	na	na
Eyre et al. 2016 [18]	11 months	33%	25%	51%	0%
Kuruvilla et al. 2014 [19]	na	na	na	na	na
Hillmen et al. 2016 [20]	na	10%	na	na	na
Tsang et al. 2015 [42]	na	na	na	na	na
Ding et al. 2017 [45]	na	na	na	na	na
Jain et al. 2016 [21]	na	na	na	na	na
Davids et al. 2017 [22]	na	na	na	na	na
Bockorny et al. 2011 [30]	20 months	na	na	na	na

RS Richter syndrome, *ORR* overall response rate, *CR* complete response rate, *PFS* progression-free survival, *FFS* failure-free survival, *OS* overall survival, *TRM* treatment-related mortality, *DLBCL* diffuse large B-cell lymphoma, *HL* Hodgkin lymphoma, *hyper-CVXD* fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone, *R+hyper-CVXD+GM-CSF/R+HDM-ara-C+* GM-CSF, rituximab, fractionated cyclophosphamide, vincristine, liposomal daunorubicin, dexamethasone and granulocyte-macrophage colony-stimulating factor alternating with rituximab, methotrexate, ara-C, and granulocyte-macrophage colony-stimulating factor, *FACPGM* fludarabine, ara-C, cyclophosphamide, cisplatin, and granulocyte-macrophage colony-stimulating factor, *OFAR* oxaliplatin, fluradabine, ara-C, and rituximab, *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, *ABVD* adriamycin, bleomycin, vinblastine, and dacarbazine, *MOPP* mechlorethamine, vincristine, procarbazine, and prednisone, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone, *CHOP-O* cyclophosphamide, doxorubicin, vincristine, prednisone plus ofatumumab, *na* not available

sustains the high-dose principle. In fact, although there is no clear plateau in relapse-free survival among patients who undergo autologous SCT, only a fraction of relapses seem related to RS, while the remainder were due to CLL, suggesting that autologous SCT may be efficacious on the eradication of the RS component but not on the underlying CLL component. The existence of a graft-versus-leukemia effect in RS is suggested by the plateaus of the relapse-free survival among RS patients treated with reduced intensity conditioning allogeneic SCT [27].

Data reported from the Mayo Clinic registry on 13 RS patients able to proceed to SCT (10 autologous SCT, 2 allogeneic SCT, and 1 autologous followed by allogeneic SCT) showed that the median survival of patients who received SCT (5 years) was better than those who did not receive SCT (< 1 year) [27] (Table 2). Consistently, the outcome of 20 RS patients who underwent SCT (17 allogeneic SCT and 3 autologous SCT) at the MD Anderson Cancer Center was better than that of patients who could not beneficiate SCT. The estimated cumulative 3-year survival probability was 75% for those who were transplanted in CR or PR, compared with 21% for patients who underwent SCT as salvage therapy for relapsed/refractory RS. Furthermore, the estimated 3-year survival probability was 27% for those patients who initially responded to chemotherapy for RS, not subsequently undergoing SCT, suggesting that post-remission transplant increases the duration of remission in patients who respond to induction [23].

The role of both autologous and allogeneic SCT as post-remission therapy in RS has been retrospectively investigated by the European Group for Blood and Marrow Transplantation (EBMT) (Table 2). At 3 years, the survival after allogeneic SCT was 36 and 59% after autologous SCT, with a respective relapse-free survival of 27 and of 45%. The non-relapse mortality at 3 years was 26% after allogeneic SCT and 12% after autologous SCT [27].

The main factor influencing the post-transplant outcome is disease activity at SCT. Indeed, patients who undergo SCT with chemotherapy-sensitive RS had a superior survival compared to those who undergo transplantation with active and progressive disease. The major benefit of SCT was obtained in young (< 60 years) patients. Among patients receiving allogeneic SCT, those conditioned with a reduced intensity regimen had the longest survival [27].

Overall, these data suggest that both autologous SCT and reduced intensity conditioning allogeneic SCT can be effective in young patients with a chemosensitive Richter's syndrome. For patients suitable to transplant but lacking a donor, autologous stem cell transplantation may be an alternative option.

HL variant

Doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) is the standard of care for de novo HL, and it is the most frequently used regimen for treating the HL variant of RS, with a response rate ranging from 40 to 60% and a median overall survival of 4 years [28•, 29–31] (Table 1). Although ABVD has generally acceptable adverse-event rates, it is associated with the risk of serious pulmonary toxic effects due to the bleomycin exposure [32]. Translating the available evidences from the advanced-stage disease trials, it is possible to omit

Table 2. Stem cell transplant in Richter's syndrome

Reference	Patients	Age < 60years	Transplant	CR/PR at transplant	RIC	VUD
Tsimberidoue et al. 2006 [23]	17	52%	Allogeneic	41%	Na	52%
Cwynarski et al. 2012 [27]	25	60%	Allogeneic	60%	72%	44%
Cwynarski et al. 2012 [27]	34	65%	Autologous	82%	–	–

Reference	3-Year relapse	3-Year RFS	NRM	3-year OS	Prognostic factors
Tsimberidoue et al. 2006 [23]	na	na	na	75% (if remission at transplant)	Remission at transplant
Cwynarski et al. 2012 [27]	47%	27%	26%	36%	• Remission at transplant • Age < 60 years • RIC
Cwynarski et al. 2012 [27]	43%	45%	12%	59%	None

CR complete response, *PR* partial response, *RIC* reduced intensity conditioning, *VUD* volunteer-unrelated donor, *RFS* relapse-free survival, *NRM* non-relapse mortality, *OS* overall survival

bleomycin if interim PET shows negative Deauville score (score of 1 through 3) after 2 cycles of ABVD. On the contrary, in case of a positive interim PET, it might be considered either to escalate BEACOPP in fit and younger patients or to add radiotherapy in unfit or older patients [33••]. Since the outcome of the HL variant of RS appears to be longer than that observed in the DLBCL variant of RS, stem cell transplantation is less used for consolidation of this condition.

State of art and future directions

Transformed lymphomas show similar molecular signatures presenting deregulation of tumor suppression, cell cycle, and proliferation pathways [7, 34, 35]. Poor outcomes of RS, mainly due to its chemoresistance and its aggressive clinical behavior, are thus explained by the genetic lesions affecting such cellular programs, targeting in particular *TP53*, *NOTCH1*, *MYC*, and *CDKN2A* genes [7, 34, 35]. *TP53*, which is a regulator of the DNA-damage-response pathway and leads to cell apoptosis if activated, plays a central role in mediating the antiproliferative effect of chemotherapies, and its mutations or deletions are described in ~ 60% of DLBCL variant of RS [7]. *TP53* abnormalities are generally acquired at the time of transformation, suggesting that they have been selected at the histologic shift. *CDKN2A*, also known as p16, is a negative regulator of cell cycle transition from G1 phase to S phase. Its deletion is reported in ~ 30% of cases and might support the aggressive kinetics of the DLBCL variant of RS [34, 35]. The *MYC* network, which sustains gene transcription, may be altered by either somatic structural alterations of *MYC* gene (~ 30%) [7, 34–36], by truncating mutations or deletions of its antagonist *MGA* (~ 10%) [37], or by mutations affecting *MYC* trans-regulatory factors as *NOTCH1* (~ 30%) [38, 39]. The DLBCL variant of RS presents a biased usage of the subset 8 configuration in the B-cell receptor (BCR), supporting a role of BCR signaling in transformation [6].

Understanding of cellular programs that are molecularly deregulated in RS has contributed to the development of novel targeted agents for the treatment of this highly aggressive disease. This concern has been supported by the unsatisfactory response rates obtained with conventional chemoimmunotherapy associated to a short response duration without a SCT for consolidation, which cannot be proposed to the majority of RS patients because of the constrains imposed by a combination of age, poor performance status, lack of donor availability, and refractoriness to induction treatments.

Selective inhibitor of nuclear export (SINE)

Selinexor is an oral small-molecule selective inhibitor of nuclear export. The nucleo-cytoplasmic transport of proteins is often misregulated in cancer and depends on the activity of export proteins, including XPO1. XPO1 is the nuclear exporter of several tumor suppressor proteins, including TP53. The enhancement of nuclear exportation is typical in tumor cells, translating into an inhibition of the normal inner tumor-suppressor activity. Selinexor acts by blocking the nuclear exporter XPO1 with the aim to retain

tumor suppressor proteins in the nucleus, activating them in tumor cells. In a phase I study, selinexor showed signal of activity in 33% of the patients with the DLBCL variant of RS that were refractory to the previous chemotherapy regimen [19]. The main adverse events (G1–2) were nausea, anorexia, fatigue, and vomiting. Grade 3–4 adverse events (5%) included thrombocytopenia and neutropenia (31 and 22%) [19] (Table 1). Despite this signal, the SIRRT phase 2 study (NCT02138786), which was tailored at establishing the activity of selinexor in relapsed and/or refractory RS patients, has been prematurely terminated due to enrollment challenges and moderate activity in this rare disease.

BTK inhibitors

A proportion of RS shows biased usage of immunoglobulin gene rearrangements suggesting that BCR played a role at a certain timepoint of the transformed disease. Evidences of a pivotal phase Ib/II study of ibrutinib in 85 pretreated CLL patients showed an ORR of 71%. Despite that, patients developed RS at the time of progression [40]. A phase 3 study comparing ibrutinib to ofatumumab in relapsed/refractory CLL did not record any difference in the rate of transformation to RS between treatment arms [41]. This data has been interpreted as a null activity of ibrutinib in the RS setting. Nevertheless, transient activity of ibrutinib has been reported in the DLBCL variant of RS, including response in three out of four patients (one CR, two PRs) [42] (Table 1). The median time to transformation from CLL was 4 years. In these patients, the median duration of response was 6 months [42]. Acalabrutinib is a highly selective BTK inhibitor showing minimal off-target activity in preclinical studies. In the ACE-CL-001 phase I/II trial (NCT02029443), 29 patients with RS diagnosis, were enrolled [20]. The ORR to acalabrutinib among the DLBCL variant of RS (including relapsed and refractory cases) was 38%, with 14% of CR and 24% of PR (Table 1). The median progression-free survival was 3 months and the median duration of response 5 months. Serious adverse events occurred in 52% of patients (hypercalcemia 10%, fatigue and acute kidney injury 7%) [20].

BCL2 inhibitors

The notion that most of the DLBCL variants of RS present *TP53* disruption is supporting the assumption that novel drugs for this condition need to act independently of *TP53*. Venetoclax is a specific inhibitor of BCL2 that acts in a *TP53*-independent way and is effective in high-risk CLL. In the M12-175 (NCT01328626) phase I study, a limited number ($n = 7$) of the DLBCL variants of RS were treated with escalating doses of venetoclax, achieving a response rate of 43% (no CRs) [22] (Table 1).

PNT2258 is a BCL2-targeted deoxyribonucleic acid inhibitor which induces cell cycle arrest and apoptosis inhibiting BCL2 promoter activity [43]. PNT2258 has shown promising results in terms of tolerability

and durable responses in patients with relapsed or refractory non-Hodgkin's lymphoma [44]. A phase 2 study (NCT02378038) testing single-agent PNT2258 for RS patients has been closed early because of poor enrollment and limited efficacy of this drug.

Immune checkpoint inhibitors

The DLBCL variant of RS often occurs upon an exhausted immune system. T-cell exhaustion is in part sustained by immune checkpoint deregulation, including expression of high levels of checkpoint inhibitory molecules, such as PD-1, on T-cells, and expression of ligands for these molecules, including PD-L1 and PD-L2, on CLL cells.
Pembrolizumab is an IgG monoclonal antibody which activates innate T-cell anti-tumor immunity and targets the PD-1 receptor. Pembrolizumab has shown promising results in the DLBCL variant of RS (MC1485 phase 2 trial; NCT02332980). This phase II clinical trial enrolled nine RS patients and reported responses in four of them (one CR, two PR, one PMR). The median PFS was 5 months and the median OS was 11 months [45] (Table 1). The most frequent G3–4 adverse events were hematologic (20%), and dyspnea and hypoxia (8%). Patients developing RS after receiving prior ibrutinib showed a most favorable OS when treated with pembrolizumab (median not reached after 11 months' follow-up) comparing to RS patients treated with standard chemotherapy before transformation (4 months) [45].
Nivolumab is a human immunoglobulin G4 PD-1 immune checkpoint inhibitor antibody which blocks PD-1 and promotes anti-tumor immunity. A phase 2 clinical trial (NCT02420912) combining ibrutinib and nivolumab was designed upon the evidence that ibrutinib has shown a synergistic activity with checkpoint blockade in preclinical models. Ibrutinib dose was 420 mg once daily, and nivolumab was given 3 mg/kg iv every 2 weeks. The preliminary results described encouraging activity of this doublet in treating RS, with three out of five patients responding to the combination (3 PR) [21] (Table 1).

Chimeric antigen receptor-modified T cells (CAR-T cells)

Lymphodepleting chemotherapy followed by the administration of autologous modified T cells which express a chimeric antigen receptor (CAR) specific for CD19 have shown complete responses in B-ALL (66–90% CR) [46–49] and in CLL/SLL (~ 60%) [50–53, 54•]. CARs are engineered structures combining a single-chain variable fragment (scFv) domain of a targeted antibody with intracellular signaling and costimulatory domains. CTL019 are modified T cells expressing a CAR combining the antiCD19 scFv with CD3ζ signaling domain and a costimulatory signal provided by the 4-1BB (CD137) domain [54•]. The expansion of CD19 CAR-T cells has shown a correlation with cytokine release syndrome (CRS), developing with hyperpyrexia, hypotension, capillary leak, neurotoxicity, and death in severe cases [49, 54•]. Preliminary data on the administration of CAR-T cells in the setting of RS report discouraging responses (one disease progression,

one evolution to PBL), but further studies are warranted [55, 56].

Compliance with Ethical Standards

Conflict of Interest

Adalgisa Condoluci declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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