



Biology and Treatment of Richter Transformation

Adalgisa Condoluci^{1,2,3} and Davide Rossi^{1,2,3*}

¹ Division of Hematology, Oncology Institute of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland, ² Laboratory of Experimental Hematology, Institute of Oncology Research, Bellinzona, Switzerland, ³ Università della Svizzera Italiana, Lugano, Switzerland

Richter transformation (RT), defined as the development of an aggressive lymphoma on a background of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), represents a clinical unmet need because of its dismal prognosis. An increasing body of knowledge in the field of RT is arising from the recent development of preclinical models depicting the biology underlying this aggressive disease. Consistently, new therapeutic strategies based on a genetic *rationale* are exploring actionable pathogenic pathways to improve the outcome of patients in this setting. In this review, we summarize the current understandings on RT biology and the available treatment options.

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*Correspondence:

Davide Rossi
davide.rossi@eoc.ch

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DEFINITION OF RICHTER TRANSFORMATION

Richter transformation (RT) is defined as the development of a high-grade lymphoma in patients with a previous or concurrent diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (1).

RT was originally depicted as a ‘reticular cell sarcoma’ with presence of ‘leukemic and tumor cells’ on a lymph node biopsy from a male patient with CLL and rapid clinical deterioration by Maurice N. Richter in 1928 (2). The occurrence of secondary aggressive lymphomas on a CLL background took the definition of ‘Richter transformation’ in 1964, when a case series of 14 patients with CLL developing malignant reticulopathy was described by Lortholary and colleagues (3).

The estimated incidence of RT in patients with CLL/SLL previously treated with chemo/chemoimmunotherapy was reported to be 0.5–1% per year (4). Different histopathologic variants of RT have been described in the literature, ranging from the more common diffuse large B-cell lymphoma subtype (DLBCL-RT) which accounts for up to 90–95% of RT cases, to the less represented Hodgkin lymphoma subtype (HL-RT) accounting for up to 5–10% of cases (1). Few cases (<1%) of plasmablastic transformation have been also reported (5).

EPIDEMIOLOGY AND CLINICAL FEATURES

The large variability of the reported prevalence of RT (1–23%) has been related to different factors, mainly depending on the diagnostic assessment of RT (biopsy-proven or just clinically suspected), and on the setting (clinical trials involving fit patients or real-world data) from which data were derived (5–8).

Recently, the German CLL Study Group (GCLLSG) reported a 3% prevalence of RT in a cohort of 2,975 patients with CLL longitudinally monitored after their enrolment in clinical trials (9).

Data coming from the SEER database on 74,116 patients with CLL diagnosed between 2000 and 2016, depicts a 0.7% incidence of transformation, mostly emerging with nodal involvement (74%) (10). The gastrointestinal tract, the skeletal system, and the brain/CNS are the most commonly reported extra-nodal sites, being described in 25, 19, and 12% of cases, respectively. Median time to transformation is 1.8–1.9 years for DLBCL-RT (3, 11) and 4.6–7.5 years for HL-RT (12, 13), even if no significant difference according to different histotypes is reported in other datasets (10).

A higher incidence of RT has been reported for highly pretreated relapsed/refractory (R/R) CLL patients enrolled in the first clinical trials with novel agents (2–15%), while in first-line the incidence of RT is 0–4% in this treatment setting (13–21). However, these data refer to short follow-up periods and longer observation time is needed to properly evaluate the impact of chemo-free treatments on second malignancies/transformation. Similar clonal evolution patterns are described for patients experiencing transformation under novel agents or chemo-immunotherapy (CIT) (22, 23).

DIAGNOSIS

Rapid physical deterioration and/or occurrence of B symptoms (i.e., fever with no infectious background, weight loss), rapid and localized growth of lymph nodes, rise in lactate dehydrogenase (LDH) levels, and hypercalcemia, are all signs that should raise suspicion for aggressive transformation, particularly in a patient with known CLL. However, these clinical findings are specific for RT in only 50–60% of cases, the remaining ones being manifestations of histologically aggressive CLL (aCLL) or solid cancers (24).

The gold standard for RT diagnosis is histologic documentation with an open biopsy. Fine needle biopsy may not illustrate the whole lymph node structure, leading to false positive diagnoses (i.e., expanded proliferation centers may be seen in fine needle biopsies from patients with progressive or aCLL) (25).

Role of ¹⁸FDG PET/CT

Since RT is often limited to one single lesion at the time of evolution, any biopsy aimed at confirming RT should be directed at the ‘index’ lesion (the lesion showing the most active dimensional dynamics). ¹⁸FDG PET/CT may assist in the choice of whether and where to perform a biopsy (24, 26, 27). When a standard uptake value (SUV) cut-off of 5 is chosen, the high negative predictive value (97%) of the ¹⁸FDG PET/CT in this setting supports a non-biopsy approach for lesions with SUV <5. Given the limited positive predictive value (53%) of ¹⁸FDG PET/CT for lesions with an SUV ≥5, the biopsy should be performed at the site of the index lesion (24, 26, 27).

A higher positive predictive value (60.6%) has been described when establishing an SUV cut-off of 10, with a sustained elevated negative predictive value (99.2%) and a good correlation with overall survival (OS). Patients with lesions displaying an SUV ≥10 showed a median OS of 6.9 months, while for patients displaying lesions with an SUV <10 the reported median OS was 56.9 months (28). However, for patients with RT arising after kinase inhibitor therapy, the SUV threshold of 10 showed lower negative predictive values (50%) (29).

Morphology and Immunophenotype

Morphology of RT Subtypes

The presence of confluent sheets of large neoplastic B lymphocytes characterizes the morphology of the DLBCL-RT (4, 30). Notably, an enlargement of proliferation centers in lymph nodes can occur also in the ‘aggressive’ or ‘accelerated’ CLL (aCLL), which needs to be distinguished from the proper transformation, as it is associated with an outcome intermediate between typical CLL and classic RT (4). Morphologic discrimination of RT from aCLL is mainly based on the characteristics of B-cells nuclei and growth pattern (a nuclear size equal or larger than macrophage nuclei or >2× a normal lymphocyte and a diffuse growth pattern are more typical for RT) (31, 32).

The HL-RT subtype is characterized by the presence of Reed–Sternberg cells either in a typical background of small T cells, epithelioid histiocytes, eosinophils and plasma cells or scattered in a background of CLL cells (4, 30, 33).

Phenotype

DLBCL-RT cells express CD20, and less typically CD5 (~30% of cases), or CD23 (~15% of cases) (4, 34). PD-1 expression is described in DLBCL-RT neoplastic B-cells, while a weak expression is restricted on the paraimmunoblasts of proliferation centers of CLL samples and rarely found in *de novo* DLBCL specimens (35, 36). The positivity of transformed B-cells for PD-1 showed a 90% correlation with molecularly defined clonal relationship between CLL and DLBCL-RT. Accordingly, PD-1 expression has been proposed as a candidate surrogate for defining the clonal relationship of DLBCL-RT (35).

HL Variant

Hodgkin and Reed–Sternberg cells show a characteristic CD30⁺/CD15⁺/CD20⁻ immunophenotype and are often EBV positive (4, 34).

Clonal Relationship Between RT and the Underlying CLL

The definition of clonal relationship between RT and the underlying CLL relies on the analysis of the rearrangement of IGHV-D-J genes [by PCR or next-generation sequencing (NGS) methods]. Most cases of DLBCL-RT (~80%) are clonally related to the previous CLL phase, representing true transformations (34, 37). Clonally unrelated cases represent *de novo* DLBCL arising in a patient with concomitant CLL, and are usually described on an IGHV-mutated CLL background (4). Clonal

relationship impacts meaningfully on the prognosis of patients with DLBCL-RT, with clonally related cases showing a median OS of less than 1 year. Conversely, for patients with clonally unrelated RT the reported survival is ~65 months, similarly to *de novo* DLBCLs (6, 30).

Clonal relationship between HL-RT and the underlying CLL has been reported in only 30% of cases (30).

BIOLOGY OF RT

Genetic alterations leading to RT are progressively being described for DLBCL-RT, which displays some common characteristics with other transformed lymphomas. Less is reported on HL-RT, whose molecular background and behavior are similar to *de novo* HL.

Biology of DLBCL-RT

Somatic alterations involving genes of tumor suppression, cell cycle and proliferation pathways (i.e., mutations or disruptions of *TP53*, *NOTCH1*, *MYC*, and *CDKN2A*) are the main genetic clues of DLBCL-RT and can explain its aggressive disease kinetics and chemoresistance (30, 37, 38).

TP53 is a master regulator of the DNA-damage-response pathway, and leads to cell apoptosis if activated (i.e., as in response to the antiproliferative effect of chemotherapies). *TP53* mutations/deletions can be acquired at the time of transformation and are the most frequent genetic lesions of DLBCL-RT, being described in 60% cases (38).

MYC is involved in a transcription regulating network and is found altered in ~40% of DLBCL-RT (11, 30, 37–39).

CDKN2A is a negative regulator of cell cycle transition from G1 phase to S phase and can be deleted in 30% of RT cases (30, 38). The rapid kinetics and aggressive behaviour of RT may be explained by cell cycle deregulation linked to *CDKN2A* alterations. It has been recently demonstrated that a concomitant loss of function of *TP53* and *CDKN2A/CDKN2B* enables a B-cell receptor (BCR)-dependent proliferation of large pleomorphic cells with a diffuse RT-like morphology (40).

The biased usage of subset 8 configuration in the BCR has been associated to *NOTCH1* somatic mutations. This molecular setting allows for autonomous BCR signaling and a dynamic responsiveness of neoplastic B cells to auto-antigens and/or immune stimuli from the microenvironment (33, 41). The reported 5-year rate of transformation for patients with CLL and subset 8 usage is ~70% (31).

NOTCH1 mutations represent the only validated risk factor for RT. The reported cumulative risk of developing DLBCL-RT is 45% among patients with CLL and mutated *NOTCH1*, while it is 4% for CLL with wild-type *NOTCH1* (42–44).

Mutational whole-genome sequencing (WGS) data from paired circulating CLL and RT biopsies were reported and independently confirmed by RNA expression profiling for 17 patients diagnosed with DLBCL-RT. RT was characterized by mutations in the DNA damage pathway and in poor-risk CLL drivers (45). *TRAF3* (a signaling regulator), *NF-κB*, and mitogen-activated protein kinase pathways, were reported to commonly

harbor heterozygous deletions (45). *PTPN11*, a positive regulator of the MAPK–RAS–ERK signaling pathway, was overexpressed in RT samples (45). *SETD2* (showing alterations in ~30% of RT samples) and *PTPRD*, a tumor suppressor gene found silenced in many cancers *via* hypermethylation, were recurrently deregulated. Compared with the paired CLL, RT samples were characterized by increased mutational burden mainly related to some genes previously unrecorded in CLL (*BDKRB1*, *WWP1*, *TFCP2*, *SVIL*, *SLC9B1*, *RELN*, *PTK2*, *IRF2BP2*, *IL7*) (45), and whose role in RT pathogenesis needs to be clarified by functional studies. Further mutations were described in non-coding regions of immune-regulatory genes (i.e., *BTG2*, *CXCR4*, *NFATC1*, *PAX5*, *NOTCH1*, *SLC44A5*, *FCRL3*, *SELL*, *TNIP2*, and *TRIM13*), suggesting their potential role in RT pathogenesis (45). Consistently, distinct immune signatures between peripheral blood and lymph nodes from patients with RT have been depicted in another study (46). A low T-cell TCR clonality was found in peripheral blood, with a consequent high diversity of the T cell repertoire and a potentially active host immune response. RT samples were characterized by enhanced PD-L1 expression in histiocytes and PD-1 in neoplastic B cells, and also infiltration of FOXP3-positive T cells and CD163-positive macrophages. These findings depict a peculiar RT-immune microenvironment and may explain the higher response rates to immune checkpoint inhibitors (47).

According to the model proposed by Teng et al. to classify tumor microenvironments based on PD-L1 expression in tumor cells and tumor-infiltrating lymphocytes (TIL), RT may harbor a type I microenvironment (PDL1⁺, TIL⁺), reflecting an adaptive immune resistance environment, which can be the target of checkpoint inhibitors (48, 49). CLL, on the other hand, seems to be characterized by immunological ignorance defined as type II microenvironment (PD-L1[−], TIL[−]) with poor expected response from checkpoint suppressors (47–49).

An increased *LAG3* gene expression has been reported in RT, with respect to *de novo* DLBCL and other transformed lymphomas (50). *LAG3* membrane protein is expressed on both neoplastic B cells and/or TILs and is involved in the delivery of inhibitory stimuli on activated T cells. In RT, *LAG3* shows a strong positive correlation with HLA Class II and immune regulatory genes (namely, *TIGIT* and *PD-1*), with an immune microenvironment characterized by potential adaptive immune resistance when *LAG3* is overexpressed (51, 52).

Constitutive phosphorylation of AKT is higher among patients with CLL at high risk for RT transformation (i.e., CLL with *NOTCH1* mutation, aggressive CLL with *TP53* disruption) (53). In a new experimental TCL1 mouse model of CLL with a constitutively active Akt allele (Akt-C) in B cells, the development of an aggressive lymphoma and a massive splenomegaly was reported by the age of 7 months confirming the driving role of AKT for RT-like transformations. Akt-C mice showed a highly expressed NOTCH signaling, with an expansion of CD4 T cells expressing DLL1 (the NOTCH1 ligand present on T cells) in the microenvironment. This upregulation has been related to the *NOTCH1* activation of tumor cells, accordingly to their commitment for transformation.

Regulating the homing of immune cells, the CXCR4–CXCL12 axis is crucial for the interaction of CLL cells and microenvironment (54–57). In the Eμ-TCL1 mouse model, the introduction of a gain-of-function *Cxcr4* mutation (*Cxcr4*^{C1013G}) that hyperactivates CXCR4 signaling, led to cell cycle dysregulation via *PLK1/FOXM1* (58). These neoplastic cells showed a transcriptional signature similar to that of patients with RT.

The main pathways with a reported involvement in RT pathogenesis are resumed in **Table 1** and **Figures 1, 2**.

PROGNOSIS OF RT

The DLBCL-RT prognosis is overall poor, with a reported median OS of 10 months (10). As already described, the most

impactful prognostic factor is the clonal relationship between the transformed DLBCL and the underlying CLL (see section *Clonal Relationship Between RT and the Underlying CLL*).

Prognostic Scores

The RT prognostic score based on clinical and laboratory variables (Zubrod performance status >1, increased LDH levels, platelets ≤100× 10⁹/L, tumor size ≥5 cm, and >2 prior lines of therapy) allows to differentiate 4 risk groups, with a median survival of 13–45 months for low risk patients (0–1 risk factors); 11–32 months for low-intermediate risk (2 risk factors); 4 months for high-intermediate risk (3 risk factors); 1–4 months for high risk patients (4–5 risk factors) (59).

Complex karyotype (CK) diagnosed on the underlying CLL has a negative impact on RT-related outcome (60). Type-2 CK

TABLE 1 | Summary of the main biomarkers involved in DLBCL-RT pathogenesis.

Biomarker (s)	Frequency	Role	Consequence	Note	Reference
<i>Biased usage of BCR subset 8</i>	8%	BCR signaling	Autonomous signaling and increased response to auto-antigens and immune stimuli	5-years transformation rate of patients with CLL and subset 8 usage: ~70%	(33, 41)
<i>TP53</i>	60%	Regulation of DNA-damage-response pathway	Inactivation	Impaired apoptosis in response to the antiproliferative effect of chemotherapies due to <i>TP53</i> loss may explain the chemorefractoriness of RT	(38)
<i>MYC</i>	40%	Regulation of transcription network	Overexpression	Key transcription factor which regulates up to 15% of human genes, constantly involved in transformation from indolent to aggressive lymphomas	(11, 30, 37–39)
<i>CDKN2A</i>	30%	Regulation of cell cycle	Inactivation	Concomitant loss of function of <i>TP53</i> and <i>CDKN2A/B</i> leads to BCR-dependent proliferation of abnormal B cells	(42–44)
<i>NOTCH1</i>	40%	NFκB activation	Activation	<i>NOTCH1</i> gene have been reported in ~10% of patients with CLL at diagnosis, mainly those with CLL of the IGHV-UM	(53)
<i>AKT signaling</i>	>50%	Driver of protein synthesis, cell survival, proliferation, and glucose metabolism	Activation, constitutive phosphorylation	AKT is activated in high-risk CLL and in >50% of patients with RT. Constitutive AKT may amplify the NOTCH1 signal or add additional signals that accelerate transformation	(45)
<i>SETD2</i>	30%	Histone methyltransferase that catalyses the trimethylation of lysine 36 on histone 3 (H3K36me3), epigenetic regulator of gene transcription	Inactivation	Deletions and mutations in ~7% of CLL patients requiring treatment	(45)
<i>TRAF3</i>	–	Signaling regulator, namely, Toll-like receptor signaling, NF-κB, and mitogen-activated protein kinase pathways	Inactivation	TRAF3 deficiency enhances survival of B cells and increases transformation risk via upregulation of PIM3 and c-MYC expression	(45)
<i>PTPN11</i>	–	Regulator of MAPK-RAS-ERK pathway	Activation	Rare CLL driver	(45)
<i>PTPRD</i>	–	Tumor suppressor colocated with <i>CDK2NA</i>	Inactivation	Receptor protein tyrosine phosphatase regulating cell growth	(45)
<i>LAG3</i>	–	Membrane protein expressed in B cells and/or TILs	Increased gene expression	Immune checkpoint gene. LAG3 protein is expressed on immune cells and in the setting of persistent antigen exposure; co-expressed with other immune checkpoints in dysfunctional T cells.	(50)
<i>CXCR4</i>	–	G-protein-coupled receptor regulating hematopoietic stem cell homeostasis, myelopoiesis, lymphopoiesis, and homing of immune cells toward its ligand C-X-C motif chemokine 12 (CXCL12)	Activation via <i>PLK1/FOXM1</i>	Involved in the migration and trafficking of malignant B cells	(58)

BCR, B-cell receptor; *CLL*, chronic lymphocytic leukemia; *TIL*, tumor infiltrating lymphocytes; *RT*, Richter transformation.

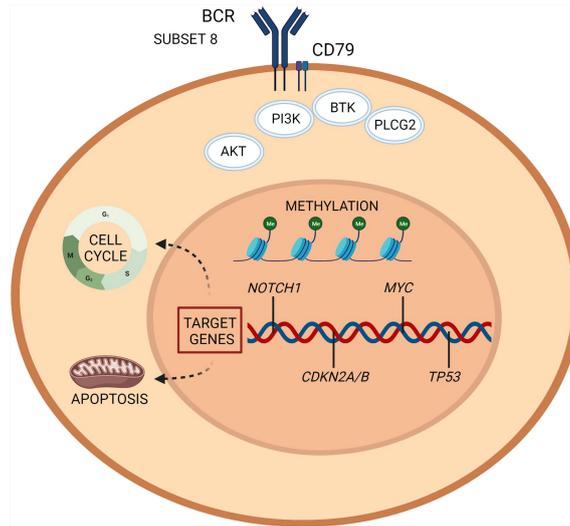


FIGURE 1 | Richter transformation: intrinsic vulnerabilities and targets for treatment. A representation of the molecular pathogenesis of Richter transformation, resulting from a number of epigenetic and genetic lesions occurring in the tumor cell population. Recurrently mutated genes affect DNA repair, B cell receptor, and chromatin modification. Created with BioRender.com.

(CK2, CK with major structural abnormalities) or high-CK (CK with >5 chromosome abnormalities), together with IGHV unmutated status, 11q deletion, *TP53* disruption and Binet stage B/C, have been identified as predictors for RT prognosis. According to the Richter syndrome scoring system, patients with high-CK and/or CK2 show a 10-year risk of developing RT of 31%; patients with unmutated IGHV/11q deletion/*TP53* disruption/>B Binet stage show a 10-year risk of 12%; while

patients with mutated IGHV without CK and with wild type *TP53* display a 10-year risk of developing RT of only 3% (60).

Role of Previous Treatment

Longer survival is reported for patients with treatment-naïve CLL when compared to the relapsed/refractory setting (12 vs 7 months) (10, 61–65). RT after ibrutinib or venetoclax shows an aggressive behavior. The median OS after progression for double

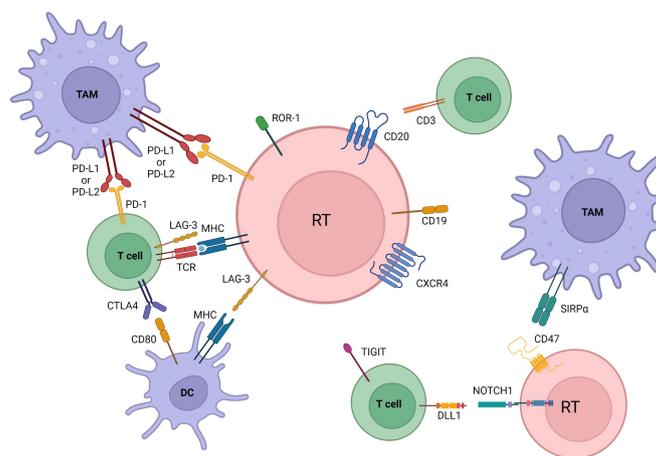


FIGURE 2 | Microenvironmental crosstalks and druggable targets in Richter transformation. Pathway activation and changes in immune checkpoints profile are also involved in transformation. Communication between the tumoral cells, dendritic cells, tumor associated macrophages (TAM), and T cells is established by direct contact, chemokine/cytokine receptors, adhesion molecules and ligand-receptor interactions. Immune inhibitory molecules (PD-L1 among others) facilitate tumor cells to evade immune-response and maintain tolerance. All of the here represented are druggable targets in RT. BCR, B cell receptor; DC, dendritic cells; TAM, tumor associate macrophage. Created with BioRender.com.

class-resistant CLL patients (i.e., CLL resistant to both BTK and BCL2 inhibitors) is 3.6 months, and this class of patients represents a clinical unmet challenge in the era of novel agents (66).

TREATMENT OF DLBCL-RT

History and comorbidities of patients developing RT drive the choice of treatment in this challenging setting. A proposed algorithm for DLBCL-RT is depicted in **Figure 3**.

Chemo-Immunotherapy

Translating treatment experience from the aggressive B-cell non-Hodgkin lymphoma setting, combinations of anti-CD20 monoclonal antibodies and polychemotherapy regimens have been indicated to treat patients with DLBCL-RT.

The historical standard regimen for DLBCL R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) produced response rates of up to 67% (complete response, CR 7%), reaching a median progression free survival (PFS) of 10 months and a median OS of 21 months. Reported adverse events were mainly hematological (65%), while severe infections were described in 28% of patients (67). Another case series reports data on 48 patients with DLBCL-RT treated with R-CHOP with a response rate of 37% and a median OS of 35 months (9).

The combination of CHOP chemotherapy with the anti-CD20 ofatumumab (O) showed an overall response rate (ORR) of 46% (CR 27%), a median PFS of 6 months and a median OS of 11 months. Reported adverse events were infections and

hematologic toxicities (thrombocytopenia, febrile neutropenia, sepsis) (68, 69).

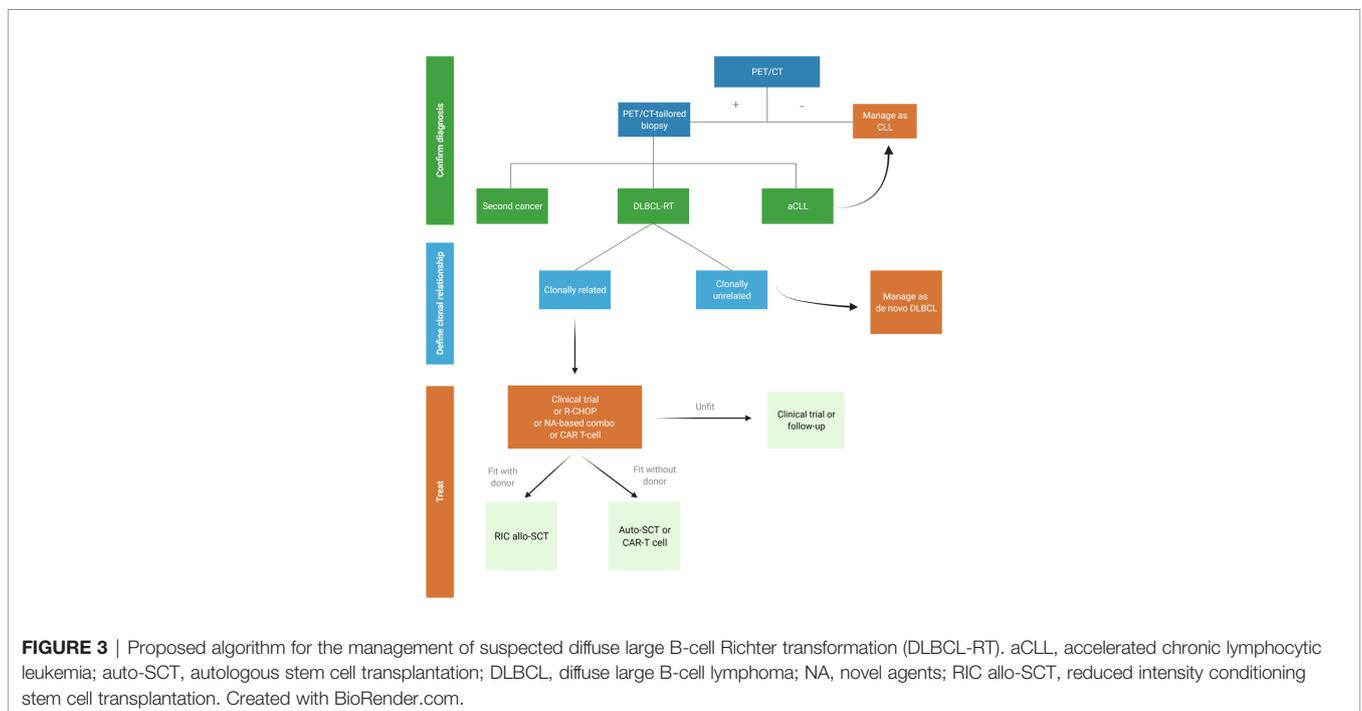
More aggressive CIT regimens were assessed, though not achieving an improved outcome. R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), a regimen indicated in high grade B-cell lymphoma, reached a response rate of only 20%, a median PFS of 3 months and a median OS of 6 months (70). Shorter PFS and OS were observed in patients with disrupted *TP53* and an underlying CLL characterized by complex karyotype.

Poor median OS and response rates of 40% were reported with the hyper-CVAD regimen (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), alone or in alternating combination with methotrexate and ara-C. Severe hematotoxicity, high infection rates (developed by 50% of patients) and a treatment-related mortality of nearly 20% were reported (71), even under the proper prophylaxis with granulocyte-macrophage colony stimulating factor (GM-CSF) (72).

The OFAR 1 and 2 trials explored the combination of oxaliplatin, fluradabine, ara-C and rituximab at different dosages to prevent toxicities. The ORR ranged from 39 to 50%, being characterized by a median PFS of 3 months and a median OS of 6–8 months (73, 74). The main complication was myelotoxicity, with no significant improvement in myelosuppression severity for patients enrolled in the OFAR 2 trial compared to the OFAR 1 trial (74).

Consolidation With Stem Cell Transplantation

Due to the high rate of relapses and poor OS after CIT, stem cell transplantation (SCT) has been proposed as a consolidation



strategy for DLBCL-RT. The benefit of receiving SCT is underlined by a median survival of 5 years vs <1 year for patients not undergoing SCT, and relies on high-dose cytotoxic therapy combined to a graft-versus-leukemia effect in the case of allogeneic SCT. The latter is confirmed by a plateau in relapse-free survival curves after allogeneic SCT (75).

However, most patients (~85%) cannot access SCT, either due to their poor performance status, a refractory disease to induction treatments, and/or the lack of donor availability (75).

The Center for International Blood and Transplant Research (CIBMTR) registry study evaluated outcomes in 53 and 118 patients with DLBCL-RT treated with autologous SCT and allogeneic SCT, respectively. A 37% relapse incidence, 48% PFS, and 57% OS at 3 years was reported in the autologous SCT cohort. For patients treated with allogeneic SCT, relapse incidence, PFS, and OS at 3 years were 30, 43, and 52%, respectively. In the latter cohort, outcomes strongly correlated with the response status at SCT (3-year OS 77% for patients reaching a CR with induction therapy versus 57% for partial responses), while cytogenetic abnormalities and prior novel therapy did not show an impact on survival (76).

A single-center retrospective analysis of 23 RT patients undergoing reduced intensity conditioning (RIC-SCT) reports a 5-year PFS of 40% and OS of 58% (77). Young age (<60 years), deeper response at SCT and having received <3 previous lines of therapy positively correlated with outcomes, while cytogenetic/molecular features and exposure to novel agents did not show an impact on PFS/OS (77, 78). Total body irradiation (TBI) resulted in poorer outcomes (77).

A median OS of 17 months has been recently reported by GCLLSG for 3 patients undergoing allogeneic SCT for RT (9).

In a meta-analysis evaluating the outcome of patients with RT undergoing allogeneic SCT, the relapse rate was 28% and the non-relapse mortality 24%, showing similar rates previously reported for patients diagnosed with other lymphoproliferative diseases (78).

Overall, young and fit patients with DLBCL-RT attaining deep responses with induction treatment can benefit both from autologous SCT and RIC allogeneic SCT, while TBI-containing RIC should be considered with caution.

Novel Agents

Recent advances in the understanding of deregulated molecular pathways in RT led to investigate the efficacy of targeted agents, with promising results.

XPO1 is a nucleo-cytoplasmic transporter of tumor suppressor proteins, whose activity is often upregulated in cancers. Selinexor, a selective inhibitor of nuclear export, acts with the aim of maintaining tumor suppressors within the nucleus to preserve their activity. In DLBCL-RT selinexor produced a response rate of 33% with an acceptable toxicity profile (79). Unfortunately, the phase 2 study (NCT02138786) was closed prematurely due to enrolment hurdles.

Bruton's tyrosine kinase (BTK), a component of BCR, plays a central role in B-cell malignancies, regulating cell proliferation and survival. Ibrutinib, the first-in-class BTK inhibitor, showed

activity in DLBCL-RT (80–82), with a survival benefit and a 16 months PFS (82). Responses to ibrutinib rechallenge have been reported after incidental RT diagnosis upon ibrutinib discontinuation in three patients with CLL (83). Acalabrutinib is a second generation oral BTK-inhibitor with an ORR of 40% (CR 8%) (84) and a median PFS of 3 months. The phase 1/2 BRUIN study (NCT03740529) evaluated safety and efficacy of pirtobrutinib (loxo-305), a next generation, highly selective, non-covalent BTK inhibitor in previously treated RT (85). Among 15 patients, pirtobrutinib reached a response rate of 67% (CR 13%). The 6-month PFS rate was estimated to be 52%. The median number of prior lines of system therapy was 6, with 82% of DLBCL-RT patients having received a prior BTK inhibitor, 59% a prior BCL-2 inhibitor, and 6% CAR T-cell therapy.

The reversible BTK inhibitor nemtabrutinib (previously known as ARQ531 or MK-1026) showed efficacy in *in vivo* BTK-resistant CLL/RT models (i.e., Eμ-MYC/TCL1 murine model recapitulating the disease phenotype of RT) (86, 87). Inhibitory activity of ARQ531 on the BCR pathway was reported both upstream and downstream of BTK *via* SYK, AKT, and MEK1/ERK. This effect was maintained also in presence of the C481S BTK resistance mutation and autoactivating *PLCγ2* mutations. Safety and activity profile of nemtabrutinib are being explored in ongoing clinical trials enrolling patients with B-cell malignancies, including RT (NCT03162536, NCT04728893) (see **Table 2**).

Patients with *TP53/NOTCH1*-disrupted high-risk CLL and RT display increased constitutive AKT phosphorylation (88). Some activity data has been reported with the PI3K inhibitor idelalisib in patients with RT (89), prompting further investigation of these agents in this condition.

Considering that DLBCL-RT harbors *TP53* alterations, novel treatments and combinations in this setting need to act in a *TP53*-independent way. Venetoclax inhibits BCL2 and is strongly active in high-risk CLL, acting independently from *TP53* (90). In the M12-175 (NCT01328626) phase I study, 7 patients with DLBCL-RT were treated with escalating doses of venetoclax, attaining a response rate of 43% (no CRs reported) (90). In the phase 2 study on the combination venetoclax-R-EPOCH (NCT03054896), the ORR reached 62% (42% CR with unmeasurable residual CLL in bone marrow). Median PFS and median OS were 10.1 and 19.6 months, respectively. Main adverse events were related to grade 3–4 neutropenia (65%), thrombocytopenia (50%) and febrile neutropenia (38%). No tumor lysis syndrome (TLS) occurred with daily venetoclax ramp-up after 1 lead in cycle of R-EPOCH (91).

Immune checkpoint deregulation is common in the setting of DLBCL-RT, which frequently develops upon an exhausted immune system. Immune checkpoint blockade with the monoclonal anti-PD1 antibody pembrolizumab produced 44% response rate (NCT02332980) (47). Importantly, responses were observed only in patients previously exposed to ibrutinib, with a median OS not reached (median OS of 10.7 months for the whole cohort). Preclinical studies reported synergistic antitumor effects between BTK and the PD-1/PD-L1 inhibitors (92). Ibrutinib exerts immune modulating effects through IL-2 inhibition,

TABLE 2 | Ongoing trials with targeted agents in diffuse large B-cell Richter transformation.

Interventions	Targeted pathway and/OR Antigen	Ref.
Acalabrutinib + R-CHOP	BTK	NCT03899337
Ibrutinib + DA-EPOCH-R	BTK	NCT04992377
Venetoclax + DA-EPOCH-R	BCL-2	NCT03054896
Blinatumomab after R-CHOP	CD19	NCT03931642
Polatuzumab vedotin + DA-EPOCH-R	CD79b	NCT04679012
Epcoritamab	CD3/CD20	NCT04623541
Nemtabrutinib (ARQ 531)	BTK	NCT03162536
		NCT04728893
Ibrutinib + Nivolumab	BTK + PD-1	NCT02420912
Zanubrutinib + Tislelizumab	BTK + PD-1	NCT04271956
Duvelisib + Nivolumab	PI3K + PD-1	NCT03892044
Copanlisib + Nivolumab	PI3K + PD-1	NCT03884998
Duvelisib + Venetoclax	PI3K + BCL-2	NCT03534323
Umbralisib + Ublituximab	PI3K, CK1 + CD20	NCT02535286
Obinutuzumab + Ibrutinib + Venetoclax	CD20 + BTK + BCL-2	NCT04939363
Atezolizumab + Obinutuzumab + Venetoclax	PD-L1 + CD20 + BCL-2	NCT02846623
Atezolizumab + Obinutuzumab + Venetoclax	PD-L1 + CD20 + BCL-2	NCT04082897
Ipilimumab + Ibrutinib + Nivolumab	CTLA-4 + BTK + PD-1	NCT04781855
TG-1801 + Ublituximab	CD47/CD19 + CD20	NCT04806035
ALX148 + Rituximab + Lenalidomide	CD47 + CD20	NCT05025800
VIP152	CDK9	NCT04978779
Zilovertamab vedotin (VLS101)	ROR1	NCT03833180
CD19 CAR-T cell	CD19	NCT04892277
CD19 CAR and PD-1 Knockout T Cells	CD19	NCT03298828
CAR70/IL15 NK cells	CD70	NCT05092451

deregulating T-cell proliferation and differentiation signaling. The combination of ibrutinib with nivolumab (an anti-PD1 antibody) was assessed in patients with relapsed or refractory hematological malignancies, namely, high-risk CLL/SLL, follicular lymphoma, DLBCL, and RT (93). The ORR was 65% in the DLBCL-RT cohort (10% CR), with a median duration of response of 6.9 months. A phase 2 trial is exploring the combination of the anti-PD-L1 antibody atezolizumab with venetoclax and the anti-CD20 antibody obinutuzumab in patients with untreated or R/R RT (NCT02846623). Venetoclax treatment is introduced at cycle 2, after obinutuzumab + atezolizumab lead-in. Data from this ongoing trial report an ORR of 100% (71% CR) for the first 7 patients with untreated RT enrolled, with responses achieved early after the introduction of venetoclax (94). After a median follow-up of 11.2 months, three of the complete responders underwent consolidation with allogeneic-SCT and no fatalities were reported.

Glofitamab is a T-cell-engaging bispecific antibody with a 2:1 anti-CD20/CD3 structure, that has been investigated in a phase I study enrolling patients with R/R non-Hodgkin lymphoma (*de novo* DLBCL, transformed follicular lymphoma, primary mediastinal B-cell lymphoma, mantle cell lymphoma, and RT). In this study, the reported ORR and CR rates were 48 and 33%, including 41 and 28% in patients with DLBCL (95). Cytokine release syndrome (CRS) was the most common adverse event (25% grade 3, 2% grade 4), and its incidence increased with higher doses but declined after the first administration (13% events at cycle 2, 6% at cycle 3 or later).

CD19 is a transmembrane protein found invariably on B cells (except for plasma cells) with a pivotal role in BCR signaling (96). Its sustained expression even upon tumoral transformation of B

cells led to the development of CAR T-cell targeting its surface antigenic domain (97, 98). It should be noted that a proportion of patients relapsing after treatment with CD19 CAR-T cells may develop a CD19⁺/CD19^{dim} disease as a mechanism of escape (99–101). In the setting of DLBCL-RT, CD19 CAR-T cells showed response rates at 4 weeks after infusion ranging from 71 to 83% (101–103) and a 1-year OS and PFS of 86 and 59%, respectively (102). In one of these studies 8 patients with RT after chemoimmunotherapy and therapy with BTK and/or BCL2 inhibitors were enrolled (103). Patients received locally produced 1 × 10⁶ autologous CD19 CART-cells/kg, modified with retroviral vector encoding a CAR comprising FMC63 anti-CD19 ScFv linked to a CD28 costimulatory domain, and CD3-zeta intracellular signaling domain. RT patients receiving CD19-CAR T-cells had a median age of 64 years (median age at CLL diagnosis 56 years), being previously treated with a median of 3 lines of therapy for CLL. On day 28 a complete response was reported in all the responders (71%, 5/8 patients). After median follow up of 6 months, two patients proceeded to allogeneic-SCT. CRS grade ≥3 requiring tocilizumab was described in 3/8 patients, while grade 3 central nervous system (CNS) toxicity was experienced by two patients.

Higher response rates (8/9 DLBCL-RT patients) are reported using axicabtagene ciloleucel CAR-T cell therapy (104). Of these patients, 8 were previously treated with kinase inhibitors and one patient died due to an infection. A CR was reported for 5/8 patients, while a partial response was described in 3 patients.

In another phase 1 study, four patients with RT were treated with escalating doses of autologous 19-28z/4-1BBL+ CAR T cells (NCT03085173) (105). Of the responders, 2/3 achieved CR and no severe CRS was reported.

ARI-0001 are autologous T-cells transduced with a CD137-based CAR construct targeting CD19 and developed at the Hospital Clinic of Barcelona (106). The CAR-T product ARI-0001 was administered to six patients with RT (five patients with DLBCL-RT and one patient diagnosed with plasmablastic transformation), achieving CRs in three patients sustained at 1.4, 12.5, and 26.7 months after treatment, respectively. With a median follow-up of 5.6 months, one patient had a stable disease, and two patients experienced a CD19-negative relapse despite no prior anti-CD19 therapy. The safety profile was considered acceptable, with only one fatality reported due to the COVID pandemic in a patient not being treated.

Natural killer (NK) cells belong to the innate immune system and play a central role in immune surveillance. Their manageability relies upon the possibility to administer them without the need for full HLA matching, even when obtained from an allogeneic source (i.e., cord blood) (107). In the setting of CAR-engineering, this translates into an easier manufacture since there is no need to generate a patient-specific product. CAR-NK cells derived from cord blood and transduced with anti-CD19 CAR, interleukin-15, and inducible caspase 9 were explored in patients with CD19⁺ lymphoid tumors including CLL/RT, with promising results (108). Interestingly, one patient with RT experienced CR from his transformed component but persistence of the CLL counterpart. No major toxic effect and/or graft-versus-host disease was reported. Despite the HLA mismatch, CAR-NK cells were found to persist at low levels after 12 months from infusion.

TREATMENT OF HL-RT

The standard of care for *de novo* HL is the regimen indicated for patients with the HL-RT (109–112), with a reported response rate of 40–60% under ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine). The median OS is 4 years in this setting. Bleomycin exposure can cause a severe pulmonary toxicity, leading to investigate the omission of this agent from the standard ABVD regimen (112). Following the results coming from the setting of advanced HLs, bleomycin can be safely omitted after two cycles of ABVD if interim PET shows remission (Deauville score 1–3). Escalation to BEACOPP in fit and younger patients should be considered in case of a positive interim PET, while radiotherapy could be an option for older and unfit patients (113). Stem cell transplantation is less used for consolidation in this setting, because of the longer survival observed compared to the DLBCL variants.

FUTURE PERSPECTIVES

Diagnosis

Artificial intelligence tools can assist the diagnostic process for patients with a suspected RT. Four biomarkers have been recently identified to have consistent value for an RT-diagnosis model, according to cytologic (nuclear size and nuclear intensity)

and architectural (cellular density and cell to nearest-neighbor distance) characteristics (114). This model was used to distinguish CLL from aCLL and RT cases with a good performance, and could be of support for further studies. Given the importance of distinguishing between aCLL and RT to select the correct therapeutic approach, more efforts to define a biological picture underlying the proliferation of RT cells are of utmost value in the era of targeted therapies.

PET/CT parameters SUV-related (i.e., SUV lean body mass, SUV body surface area, lesion-to-liver SUV ratio, and lesion-to-blood-pool SUV ratio) showed a correlation with DLBCL-RT diagnosis and/or OS and represent possible candidates for diagnostic biomarkers to further explore (115, 116). Moreover, novel PET radiotracers and PET–MRI are being explored in the setting of RT (117).

Biology and Treatment

CDK4/6 inhibitors (i.e., palbociclib) have been recently identified as potential agents to overcome *CDKN2A/B* dysregulation (40). Palbociclib demonstrated activity in inhibiting RT-cell proliferation and showed an *in vitro* synergistic activity when combined with the BCR-signaling directed compounds ibrutinib, idelalisib, and fostamatinib.

LAG3 is an emerging target for immune checkpoint blockade (50). Clinical trials are investigating *LAG3* inhibitors in hematological and solid cancers (NCT02061761; NCT01968109). Further assessment of *LAG3* inhibition, either alone or in combination with anti-PD-1 to enhance anti-tumor T-cell responses in RT is warranted.

Genomic data from the WGS confirm the pathogenic role of DNA damage response (DDR) pathway deregulation in RT (45). The role of DDR inhibitors such as PARP or ATR inhibitors has still to be assessed in RT.

The antibody-conjugate VLS-101 includes a humanized immunoglobulin G1 monoclonal antibody that binds ROR1, which is expressed by CLL lymphocytes to regulate chemotaxis and proliferation signaling (118, 119). VLS-101 attained complete and sustained remissions in RT patient-derived xenografts (RT-PDXs) expressing high levels of ROR1 (120). A phase 1 clinical trial of VLS-101 (NCT03833180) is enrolling patients with RT and other hematological neoplasms. Concomitantly, a phase 1 clinical trial (NCT02706392) is exploring the efficacy of anti-ROR1 CAR-T cells in patients with refractory CLL.

U-RT1, is a cell line derived from a highly proliferating RT clonally related to the underlying CLL (121). It is characterized by a complex karyotype with driver aberrations characteristic for RT such as genetic alterations of *TP53*, *CDKN2A*, and *NOTCH1*. This model represents a valuable tool for RT investigations and drug development.

Data on three newly established PDX models of RT-DLBCLs were recently published, namely, clonally-related and clonally-unrelated RT (122). These PDX models display protein expression of *IRF4*, *TCF4*, and *BCL2*. CRISPR knockout of *IRF4* led to reduced c-Myc levels and increased sensitivity to BET inhibitors. Co-treatment with a BET inhibitor or BET-PROTAC and ibrutinib or venetoclax showed synergistic *in vitro*

lethality in the RT-DLBCL cells. When compared to single agent, combination of BET-PROTAC and venetoclax significantly reduced tumor burden and improved survival in immune-depleted mice engrafted with clonally related RT-DLBCL.

A potential synergistic effect of PI3K and BCL2 inhibitors has been proposed, based on the crosstalk between PI3K and apoptotic pathways (123). It has been shown that the inhibition of PI3K signaling by duvelisib leads to GSK3 β activation and subsequent degradation of both c-Myc and Mcl-1. This crosstalk sensitizes RT cells to BCL-2 inhibition. Drug combination trials are ongoing, also in the setting of RT-DLBCL (NCT03892044).

In the field of CARs, targeting the transmembrane protein CD37 is another potential application for patients with B-cell malignancies. CD37 is expressed in mature B cells and at lower levels also on plasma cells and dendritic cells. Indeed, CD37 CAR-T cells were found to play a cytotoxic activity *in vivo* in B-cell tumor models (124). Dual targeting has already been suggested as a method to overcome treatment resistance due to the development of specific antigen loss consequent to CAR infusion. A bispecific CD37/CD19 CAR-T product is being developed to assess safety and efficacy in preclinical B-cell tumor models. Bispecific CD19/22 CAR-T cells have been already explored in non-Hodgkin lymphomas (NCT03196830), showing promising results (ORR 79.3%, CR 34.5% with 12-month PFS and OS of 40 and 63%, respectively) (125). The employment of CD19 CAR-NK cells in B-cell malignancies is also being explored in

different ongoing phase 1 trials (i.e., NCT04887012, NCT04639739, NCT04796675, and NCT05020678), and novel targets for CAR-NK cells are object of study (i.e., CAR70/IL15-transduced NK cells in NCT05092451). Efficacy of these agents needs to be assessed in the setting of RT.

A list of ongoing trials with targeted agents in RT is reported in **Table 2** (updated from clinicaltrials.gov on Feb 20, 2022).

CONCLUSIONS

Patients with CLL progressing on novel agents represent a new high-risk prognostic group with adverse outcome in case of transformation. The promising combination of CIT with the novel agent venetoclax for DLBCL-RT confirms the synergistic effect of the approaches. The availability of new preclinical models is progressively expanding our understanding of RT biology, laying the foundations for targeted treatments which might be better tolerated.

AUTHOR CONTRIBUTIONS

AC and DR wrote the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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