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Richter Transformation in the Canadian Landscape: Clinical Perspectives and Emerging Trends

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Introduction

Over the past decade, the treatment landscape for chronic lymphocytic leukemia (CLL) and its lymphoma counterpart, small lymphocytic lymphoma (SLL), has evolved significantly. The shift from chemoimmunotherapy (CIT) to the increased use of targeted agents, such as Bruton's tyrosine kinase inhibitors (BTKi) and B-cell lymphoma 2 inhibitors (BCL2i), has led to marked improvements in patient outcomes.¹ Despite these advancements, some patients still experience disease transformation to a more aggressive histology known as Richter Transformation (RT), and the clinical outcomes with this histology remain dismal, with median overall survival (OS) typically shorter than one year.^{2,3} Therefore, RT represents a significant unmet need for patients with CLL/SLL. This review describes recent advances in the understanding and management of RT within the Canadian landscape, focusing on transformation to diffuse large B-cell lymphoma (DLBCL).

Epidemiology and Clinical Presentation

Originally described by Maurice Richter in 1964,⁴ RT is a rare and unpredictable event, occurring in approximately 4% of patients with CLL/SLL, both in clinical trials with CIT² and in landmark trials with targeted agents.^{5,6} However, a recent observational study reported a lower incidence of RT in patients diagnosed with CLL during the targeted therapy era. This reduction is hypothesized to be due to either decreased exposure to CIT, thereby avoiding the selection of early subclones prone to chemotherapy-induced mutational processes, or a protective effect of targeted agents suppressing the culprit subclone susceptible to cause transformation.⁷ RT is suspected in patients with

CLL/SLL who experience rapid disease progression and/or new onset constitutional symptoms, often with elevated lactate dehydrogenase (LDH), hypercalcemia, and/or extranodal involvement.⁸ These worrisome findings should raise concern for disease transformation to a more aggressive histology and prompt investigations, including a positron emission tomography (PET) scan and a biopsy of the most fluorodeoxyglucose (FDG)-active lesion if amenable. In the CIT era, a threshold standard uptake value (SUV) of 10 has been recognized as both sensitive and specific to properly identify patients with RT.⁹ Unfortunately, this threshold may be less reliable in the era of novel agents as it has been shown to have reduced sensitivity and specificity for patients on BTKis.¹⁰

Pathology and Biology

Most patients with histology-confirmed RT undergo transformation to DLBCL, which requires confirmation of sheets of large B cells by immunohistochemistry for accurate diagnosis. However, a subset may develop the Hodgkin variant of RT or exhibit pro-lymphocytic progression of CLL, previously termed B-cell prolymphocytic leukemia, which is no longer recognized as a separate entity by the most recent update of the World Health Organization Classification of Haematolymphoid Tumours.¹¹ As the underlying histology of RT will dictate treatment decisions, it is essential to confirm the transformation subtype at diagnosis. While DLBCL is the most common form of RT, patients with prolymphocytic progression are typically treated with CLL-directed therapies, and those with Hodgkin lymphoma are treated accordingly, often with a more favourable prognosis.¹² It is also important to interpret large B cells identified in pathology reports with caution, as cases of

“pseudo-transformation” have been observed following short interruptions of BTKi therapy, with complete resolution upon reinstating therapy, suggesting it does not represent true transformation.¹³ In cases where a biopsy is not feasible, patients with a clinical diagnosis of transformation have similarly poor outcomes.¹⁴

In recent years, improved insights have been gained into the biology of RT, owing in part to new large-scale multi-omic analyses of paired CLL and RT samples, largely of DLBCL histology.¹⁵ RT is now understood to arise through subclonal evolution, with recent studies demonstrating early seeding of the subclone responsible for RT even decades before clinical transformation.¹⁶ Certain genetic features of the underlying CLL have a higher risk of development of RT, including unmutated immunoglobulin status, *TP53* and *CDKN2A/B* loss, activating *NOTCH1* mutations, *MYC* amplification, and certain B cell receptor (BCR) stereotypes, specifically subset #8.¹⁵ In addition, increased programmed cell death protein 1 (PD-1) expression has been observed in clonally related Richter cells, which is generally not observed in *de novo* DLBCL, leading to interest in PD-1 blockade as a therapeutic target.^{17,18} Overall, this deeper understanding of the biological mechanisms driving RT is shaping the development of new therapeutic approaches and guiding the design of clinical trials utilizing novel treatment strategies.

Prognosis

RT is associated with a dismal prognosis, and several factors are recognized as influencing patient outcomes. The Richter Prognostic Score, developed in the CIT era, assigns one point for each of the following features: Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 , LDH >1.5 times the upper limit of normal, thrombocytopenia $<100 \times 10^9/L$, tumour size >5 cm, and ≥ 2 prior lines of CLL-directed therapy. Patients with low (0-1 factor), intermediate-low (2 factors), intermediate-high (3 factors), and high (4-5 factors) scores have a reported median OS of 13, 11, 4, and 1 months, respectively.¹⁹ As more epidemiologic studies emerge, it is recognized that any prior CLL therapy is a poor prognostic factor, both in the CIT and novel agent era, even without prior chemotherapy exposure.²⁰

Another key prognostic factor in RT is the clonal relationship between DLBCL and

the underlying CLL. Clonally unrelated DLBCL accounts for approximately 20% of RT and tends to have more favourable outcomes, resembling those with *de novo* DLBCL.^{21,22} Clonality can be determined by sequencing the immunoglobulin heavy-chain variable region gene in both the aggressive disease and underlying CLL, with identical sequences indicating clonally-related disease. Given that clonality is a strong predictor of outcomes and testing is becoming increasingly available in Canada, we strongly recommend performing this analysis at the time of RT diagnosis to guide management decisions. Lastly, the presence of a *TP53* mutation not only increases the risk of RT but is also a well-recognized predictor of poor outcomes in RT.^{21,23}

Management

The standard treatment for RT remains largely similar to that of *de novo* DLBCL, involving multi-agent CIT with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Response rates range from 60-70%; however, the duration of response is short, with a reported median progression-free survival (PFS) of only 10 months.²⁴ Consolidation strategies with reduced intensity allogeneic hematopoietic stem cell transplant are proposed in eligible patients, particularly when the RT is clonally related to the underlying CLL/SLL. While prospective trials are lacking, retrospective studies have demonstrated long-term remissions, with 30% of patients remaining progression-free 3 years following allogeneic hematopoietic stem cell transplant.²⁵ As a result, transplantation is often considered in first remission.⁸ Despite this recommendation, real-world studies demonstrate that transplant is only pursued in a minority of patients. Canadian data from Puckrin *et al.* found that among 99 patients with RT in Alberta, 20% were treated with the intent to undergo a transplant, and of those, 25% successfully underwent allotransplant, representing only 5% of the total RT population.²⁶ Currently, many alternative treatment strategies are being explored to overcome the poor prognosis of RT, including the incorporation of novel targeted agents into treatment protocols. Selected studies are summarized in **Table 1**.

BTKi and BCL2i have been trialed for RT with demonstrated clinical activity; however, these therapies are not durable as single agents. A phase I/II trial of acalabrutinib monotherapy

Class of Therapy	Design	Previously Treated CLL/SLL	Previously Treated RT	ORR (CR), %	Outcome, Months	Reference
R-CHOP n=15	Phase II	Median prior lines: 2 (range 0-4)	n/a	67 (7)	mPFS, 10 mOS, 24	²⁴
Venetoclax Addition						
VR-EPOCH n=27	Phase II	78% Median prior lines: 1 (range 0-7)	7%	62 (50)	mPFS, 10.1 mOS, 19.6	³²
VR-CHOP n=27	Phase II	100% Median prior lines: 1 (range 1-9)	15%	68 (48)	mPFS, 7.2 mOS, 19.5	³³
VR-CHOP n=13	Retrospective	69% Median prior lines: 1 (range 0-5)	23%	54 (46)	mPFS, 14.9 mOS, NR	³⁴
Bruton Tyrosine Kinase Inhibitors						
Acalabrutinib n=25	Phase I/II	56% Median prior lines: 1 (IQR 0-2)	56%	40 (8)	mPFS, 3.2 mDOR, 6.2	ACE-CL-001 ²⁷
Zanubrutinib n=13	Phase I/II	92% Median prior lines: 1 (range 0-5)	85% Median 1 (range 0-3)	62 (15)	mPFS, 17.3 mOS, 29.3	²⁹
Pirtobrutinib n=82	Phase I/II	Median prior lines: 2 (range 0-13)	100%	50 (13)	mDOR, 7.4 mOS, 12.5	BRUIN ³¹
PD-1 blockade						
Pembrolizumab n=23* *2 with HL variant	Phase II	n/a	100% Median 3 (range 1-6)	4 (0) *excluding HL variant	mPFS, 1.6 mOS, 3.8	KEYNOTE-170 ³⁵
Novel agent combinations						
Tislelizumab- zanubrutinib n=59* *48 analyzed	Phase II	n/a	21%	58 (19)	mDOR, NR at 13.9; follow- up mPFS, 10 12-month OS: 75%	RT1 ³⁶
Atezolizumab, venetoclax, obinutuzumab n=28	Phase II	71% Median prior lines: 1 (range 0-3)	0%	68 (36)	12-month PFS: 43% 12-month OS: 64%	MOLTO ³⁷

Class of Therapy	Design	Previously Treated CLL/SLL	Previously Treated RT	ORR (CR), %	Outcome, Months	Reference
Bispecific antibodies CD20xCD3						
Epcoritamab n=10	Phase Ib/II	n/a	40%	60 (50)	n/a	⁴⁰
Glofitamab n=11	Phase II	n/a	Median 3 (range 1-4)	64 (46)	n/a	⁴¹
Mosunetuzumab n=20	Phase II	n/a	Median 2.5 (range 1-10)	40 (20)	n/a	⁴²
Chimeric antigen receptor (CAR)-T cell therapy						
CAR-T (axi, tisa, liso-cel) n=69	Retrospective	Median 4 prior lines of therapy for CLL and/or RT (range 1-15)		63 (46)	mPFS, 4.7 2-year PFS: 29% mDOR, 27.6 mOS, 8.5	⁴⁶

Table 1. Selected clinical trials for the treatment of Richter transformation; courtesy of Alina S. Gerrie, MD, MPH, FRCPC and Jean-Nicolas Champagne, MD, FRCPC

Abbreviations: **CLL:** chronic lymphocytic leukemia; **pts:** patients; **CR:** complete response rate; **HL:** Hodgkin lymphoma; **IQR:** interquartile range; **mDOR:** median duration of response; **mOS:** median overall survival; **mPFS:** median progression-free survival; **n:** number; **n/a:** not available; **NR:** not reached; **ORR:** overall response rate; **R-CHOP:** rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; **RT:** Richter transformation; **VR-EPOCH:** venetoclax, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin.

demonstrated some degree of B cell receptor dependence in RT, with an overall response rate (ORR) of 40%, but a short duration of response (DOR) of only 6.2 months.²⁷ The addition of acalabrutinib to R-CHOP vs. R-CHOP alone is currently under study in the STELLAR trial, which will be the first reported randomized controlled trial conducted solely in RT.²⁸ Zanubrutinib has been studied as monotherapy for RT, with an ORR of 62% and favourable PFS and OS of 17 and 29 months, respectively, although only 13 patients were included in the monotherapy arm.²⁹ As many patients with CLL have previously been treated with covalent BTKi's, there is growing interest in non-covalent BTKi's for the treatment of RT, given their effectiveness in settings of BTKi resistance. Both nemtabrutinib and pirtobrutinib are active in RT, the latter demonstrating response rates of approximately 50% and more durable responses up to 7.4 months in a dedicated RT cohort in the phase I/II BRUIN trial.^{30,31}

In a multicentre phase II study, venetoclax was added to dose-adjusted rituximab, etoposide,

prednisone, vincristine, cyclophosphamide, and doxorubicin (VR-EPOCH) using an accelerated ramp-up in cycle 2. This combination yielded the highest response rates seen thus far in prospective trials in RT, with an ORR of 62%, and 50% of patients achieving a complete response (CR), resulting in a median PFS and OS of 10.1 and 19.6 months, respectively.³² Eight patients successfully proceeded to consolidative allogeneic hematopoietic stem cell transplant. However, this increase in effectiveness was observed at the expense of significant toxicity, which primarily consisted of cytopenias and infections. This led to a de-escalation of the CIT backbone in an additional cohort with R-CHOP in combination with venetoclax (VR-CHOP), whereby venetoclax was given in an accelerated inpatient ramp-up in cycle 2 over 5 days, followed by 400 mg daily on days 1-10 of each cycle.³³ Among 25 evaluable patients, the ORR was 68% with a CR rate of 48%, and median PFS and OS of 7.2 and 19.5 months, respectively, as well as decreased toxicity, including less neutropenia, compared

to VR-EPOCH (36% vs. 65%).³³ A multicentre retrospective study of venetoclax-based regimens for RT treatment demonstrated more favourable outcomes of VR-CHOP over venetoclax with BTKi or in combination with more intensive CIT regimens, with all venetoclax-based regimens having improved outcomes compared to historical controls.³⁴ In this indication, venetoclax currently remains off-label; however, it may be accessible in the context of underlying CLL.

Given the high expression of PD-1 on RT cells, PD-1 blockade has been evaluated in RT, primarily in the relapsed/refractory setting.¹⁷ Unfortunately, this yielded poor response rates when used as monotherapy,³⁵ but prompted trials using combination regimens, including tislelizumab-zanubrutinib in both first-line and relapsed RT³⁶ and, more recently, the MOLTO trial assessed atezolizumab, venetoclax, and obinutuzumab in first-line RT.³⁷ Both trials led to excellent ORRs, with CR rates approaching 20-35%, and durable responses of approximately 1 year. Tislelizumab-zanubrutinib led to a median PFS of 10 months and 12-month OS of 75%, while the MOLTO regimen led to 12-month PFS and OS of 43% and 64%, respectively. Both regimens show promise as first-line treatment options for RT and could potentially replace standard R-CHOP therapy depending on the outcomes with longer-term follow-up. Other emerging treatment options for RT include receptor tyrosine kinase-like orphan receptor 1 (ROR1)-targeting therapy and BTK degraders, which have shown encouraging results in relapsed or refractory B-cell malignancies including CLL/SLL and RT.^{38,39}

Finally, T cell-directed therapies such as bispecific T cell engager antibodies⁴⁰⁻⁴² and anti-CD19 chimeric antigen receptor (CAR)-T cell therapies^{43,44} demonstrate promising activity in the relapsed/refractory setting for RT. The data for bispecific antibodies, primarily CD20/CD3-targeting agents, is sparse, with only a small number of patients enrolled and limited follow-up. Nonetheless, response rates appear similar to those reported in large B-cell lymphoma trials, with CR rates of 40% and ongoing responses for those achieving CR. CAR-T response rates and long-term outcomes in CLL have been generally poor compared to large B-cell lymphoma, hypothetically due to T cell dysfunction or a potentially “cold” tumour microenvironment reported in CLL,⁴⁵ leading to less enthusiasm for this therapy in this setting than in DLBCL. Moreover, patients with RT were excluded from landmark prospective CAR-T trials

for DLBCL. Fortunately, there is emerging real-world data for both axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel) demonstrating encouraging results in patients with RT.^{43,46,47} For patients who received prior CLL/SLL and/or RT-directed therapy, the ORR ranged from 60 to 75%, with 2-year PFS of approximately 30%. For patients who achieved a CR (~50%), the median duration of response was just over 2 years. High non-relapse mortality remains a concern in this patient population, reported in up to 13% of patients at 12 months, and is mainly due to infections.⁴⁶ Given that clonally-unrelated RT shares biological characteristics and prognosis with *de novo* DLBCL, the possibility of offering CAR-T cell therapy as the standard of care for clonally-unrelated DLBCL in the relapsed/refractory setting remains open for consideration.

Based on the encouraging trials listed above and in **Table 1**, a personalized treatment approach is recommended, considering disease characteristics, patient comorbidities, fitness, preferences, as well as cost, healthcare resource utilization, and drug access to guide treatment decisions. Given the relative rarity of RT, most studies are non-randomized, have diverse inclusion criteria, and evaluate different lines of therapy, making cross-trial comparisons challenging. Although randomized controlled trials are underway to compare different first-line treatment strategies, their results will take years to emerge. Taking into account these caveats and focusing on the treatment landscape in Canada, we propose a risk-stratified treatment algorithm illustrated in **Figure 1**. This approach incorporates available and emerging data, including select off-label or unfunded regimens, to address limitations in the current treatment options.

Future Perspectives

The significant unmet need for RT has driven extensive efforts to improve therapy over the past decade. Advances in the understanding of RT biology have provided a strong rationale for integrating novel agents into the therapeutic landscape. However, integrating these agents into high-intensity regimens has also led to increased toxicity. It is important to recognize that patients with RT in the era of novel CLL/SLL therapies are often older and have poorer functional status, limiting their ability to tolerate more intensive therapy.¹⁴ Therefore, clinical trials must refine patient inclusion criteria and therapeutic escalation

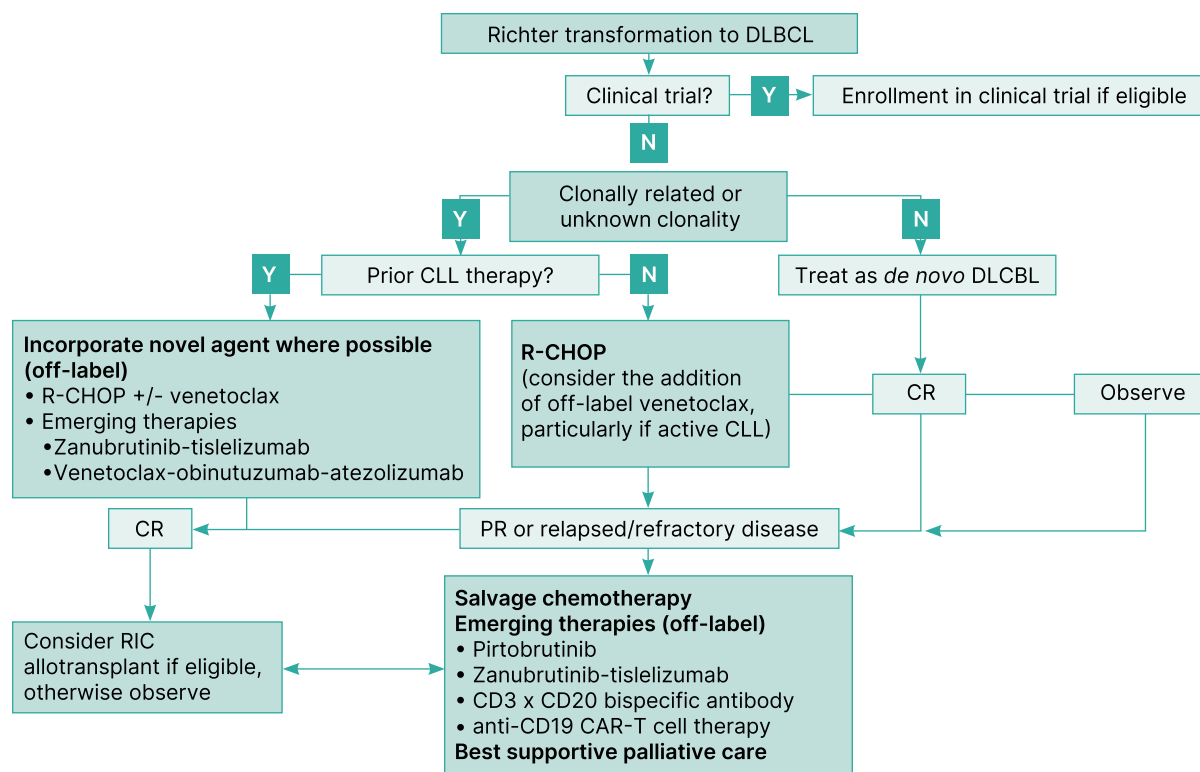


Figure 1. Proposed treatment algorithm for treatment of Richter Transformation (DLBCL) in 2025; courtesy of Alina S. Gerrie, MD, MPH, FRCPC and Jean-Nicolas Champagne, MD, FRCPC

Abbreviations: CAR: chimeric antigen receptor; CLL: chronic lymphocytic leukemia; CR: complete response; DLBCL: diffuse large B-cell lymphoma; PR: partial response; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RIC: reduced intensity conditioning.

should be carefully evaluated to balance efficacy with tolerability.

Beyond therapeutics, several key areas warrant further exploration, including early identification of patients at risk of RT and potential preventative strategies to suppress the culprit clone before clinical transformation occurs. As discussed, a subclonal population from which RT arises may be identified decades before true transformation. Identifying high-risk patients could enable closer monitoring for early signs of RT and open the door for CLL-directed interventions aimed at reducing the likelihood of transformation.

Lastly, drug access remains a challenge in the Canadian healthcare system. While new therapies show encouraging results, most are based on single-arm studies, with a lack of robust randomized data. In addition, patients with RT are often - perhaps justifiably - excluded from large clinical trials of aggressive B-cell lymphomas, making access to novel therapies challenging. Given RT's devastating impact on

the lifetime of a patient with CLL, clinicians in Canada must advocate for improved access to these therapies. It is essential to highlight to regulatory authorities that rare diseases like RT are frequently overlooked in conventional trial designs, yet strong clinical rationale may justify using certain treatments in the absence of large-scale randomized evidence. In addition, we must collaborate to design rational clinical trials for RT treatment within Canada for improved access to novel therapies for our patients.

Conclusion

Despite the challenges that RT presents, advancements in the understanding of its biology and the development of novel therapeutic strategies are driving significant progress in the field. Emerging targeted therapies, improved risk stratification, and ongoing clinical trials are refining treatment paradigms and expanding options for patients. With sustained research

efforts, collaborative clinical trial initiatives, and innovative therapeutic strategies, the future of RT management is evolving toward more personalized and effective treatments, offering greater promise for improved patient outcomes.

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