Richter Transformation: Clinical Manifestations, Evaluation, and Management

MELANIE DOUGLAS, MS, PA-C

From Memorial Sloan Kettering Cancer Center, New York, New York

Author's disclosure of conflict of interest is found at the end of this article.

Correspondence to: Melanie Douglas, MS, PA-C, 1275 York Avenue, New York, NY 10065
E-mail: douglasm@mskcc.org

https://doi.org/10.6004/jadpro.2022.13.5.6

Abstract

Richter transformation is a devastating and rare but not uncommon development of an aggressive B-cell lymphoma in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma. Prognosis is dismal, with survival generally in the realm of months to a couple of years. Many patients progress quickly after traditional first-line immunochemotherapy. Nonetheless, novel therapies are on the horizon. It is important that the advanced practitioner have awareness and knowledge of this condition in order to furnish a crucial timely diagnosis and to provide appropriate treatment.

CASE STUDY

Presentation

A 70-year-old Caucasian woman who was diagnosed 2 months ago with chronic lymphocytic leukemia (CLL) via complete blood cell count and peripheral flow cytometry on active surveillance presented to the clinic with a 2-week history of night sweats along with low-grade fevers and associated chills. She also complained of early satiety. Her oncologist arranged for her to be admitted to the hospital for expedited workup.

Upon presentation to the ward, the patient was hemodynamically stable, with intermittent fevers up to 100.4°F. She denied any localizing symptoms concerning for infection. On physical exam, she was in no acute distress and nontoxic-appearing with intact pulses. No palpable lymphadenopathy was noted. There were no focal neurologic deficits, and cardiopulmonary exam was benign. Her abdominal exam was remarkable for splenomegaly; there was no tenderness, distention, or peritoneal signs.

Evaluation and Initial Management

Initial bloodwork was significant for elevated lactate dehydrogenase (LDH) of 881 U/L, elevated beta-2 microglobulin level of 2.9 mg/L, elevated phosphorus level of 5.7 mg/dL with remainder of electrolytes

J Adv Pract Oncol 2022;13(5):525–534

within normal limits, serum creatinine of 0.7 mg/dL (within normal), and new thrombocytopenia with platelet count of 120 × 10^9/L. White blood cell count came back elevated at 23.1 × 10^9/L with predominant lymphocytosis (58% lymphocytes), which was unchanged from the patient's white blood cell counts from time of initial CLL diagnosis. Hemoglobin level was stable at 12.6 mg/dL, and hepatic and coagulation panels were unremarkable. Lactic acid and procalcitonin were within normal ranges, and submitted blood cultures did not grow any organisms. The fevers were deemed likely related to the patient's malignancy.

A PET scan was completed, which demonstrated splenomegaly and abdominopelvic lymphadenopathy. Lymph node and bone marrow biopsies were performed. While the team awaited results, pulsed methylprednisolone was initiated for tumor debulking. Due to concern for development of tumor lysis while on steroids, the patient was prophylactically initiated on IV hydration and was given rasburicase 3 mg IV.

The lymph node expressing the highest standardized uptake values (SUV) on PET scan was biopsied, and the pathology was consistent with diffuse large B-cell lymphoma (DLBCL). The bone marrow biopsy showed DLBCL, as well as a small second abnormal population with a CLL-like immunophenotype. Both biopsies revealed non-germinal B-cell-like immunophenotype with *MYC* and *BCL6* translocations noted on fluorescence in situ hybridization (FISH). These results were consistent with Richter transformation (RT). Additionally, FISH carried out on the bone marrow biopsy revealed 4% *TP53* deletion; *TP53* gene anomalies have been tied with a risk of acquiring RT. Finally, given a higher risk of central nervous system relapse with the two characteristic gene rearrangements of "double-hit" lymphoma, a lumbar puncture was carried out to check for leptomeningeal disease, which revealed no evidence of malignant cells.

Richter transformation (RT), also known as Richter syndrome, is the relatively uncommon development of an aggressive large B-cell lymphoma or Hodgkin lymphoma (HL) in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL; Ben-Dali et al., 2018; Tadmor & Levy, 2021). Chronic lymphocytic leukemia and SLL are lymphoproliferative disorders featuring accumulation of "functionally incompetent mature B lymphocytes, usually monoclonal" (Taylor et al., 2018, p. 259). Chronic lymphocytic leukemia is the most common adult leukemia in Western countries (Taylor et al., 2018). About one third of patients ultimately never require treatment; expectant monitoring is carried out to watch for disease progression and observe clinical course (Taylor et al., 2018).

Richter transformation is a serious and devastating complication of CLL/SLL. Diffuse large B-cell lymphoma (DLBCL) makes up approximately 90% of RT cases (Al-Sawaf et al., 2021). This clonal transformation was first described by Maurice Richter in 1928 (Allan & Furman, 2019). Approximately 2% to 10% of patients with CLL develop RT (Ben-Dali et al., 2018). One third of patients diagnosed with RT have newly diagnosed CLL (Al-Sawaf et al., 2021). The median time frame from initial diagnosis of CLL to development of RT is approximately 2 to 4 years (Ben-Dali et al., 2018).

This article features a relevant case study and reviews clinical sequelae, epidemiology and prognosis, diagnostic evaluation, and management of RT, focusing on the commonly seen DLBCL-type transformation. It is important to recognize symptomatology and manifestations of RT promptly, as time is of the essence. Data show that this clinical entity progresses rapidly. Additionally, when treating this disease, frequent monitoring is imperative to gauge whether there is a treatment response vs. disease progression; quick disease progression can occur despite therapy. Traditional induction immunochemotherapies are discussed, as well as novel targeted therapies that have the option to be utilized in combination with established immunochemotherapy regimens. Especially if a positive treatment response is obtained to first-line therapy, a stem cell transplant (SCT) can be pursued in qualifying patients in hopes of achieving a durable response. Furthermore, chimeric antigen receptor

(CAR) T-cell therapy as well as novel targeted therapies have demonstrated promising results in patients with relapse. As RT is a challenge to treat, it is critical to consider clinical trials and novel agents besides traditional therapies.

RISK FACTORS

Risk factors for development of RT include *TP53* gene aberrations, *NOTCH1* mutation, *CDKN2A* alterations, subset 8 stereotype, and c-MYC activation (Al-Sawaf et al., 2021, p. 170; Ben-Dali et al., 2018). Subset 8 stereotype is defined by the expression of stereotyped *IGHV4-39/IGKV1(D)-39* B-cell receptors (Gounari et al., 2015). Other risk factors for RT include elevated lactate dehydrogenase (LDH), elevated beta-2 microglobulin, advanced stage disease, poor Eastern Cooperative Oncology Group (ECOG) performance score, and lymphadenopathy (lymph nodes measuring greater than 3 cm; Ben-Dali et al., 2020; Allan & Furman, 2019). Furthermore, patients not responding to first-line therapy for CLL/SLL are at increased risk of developing RT as well as those who have been treated with a higher number of therapies (Maurer et al., 2016).

CLINICAL PRESENTATION

Onset of RT tends to be heralded by accelerated, pronounced increase in lymphadenopathy (often abdominal), splenomegaly, and B symptoms (fevers, night sweats, weight loss; Ben-Dali et al., 2020). Extranodal involvement may be present, especially in the gastrointestinal tract, bone marrow, central nervous system (CNS), or skin (Tadmor & Levy, 2021). In some cases, RT could present merely as an extranodal mass (Condoluci & Rossi, 2019). Signs and symptoms of extranodal involvement may manifest such as early satiety, gastrointestinal bleeding, rash, pathologic fractures, headache, blurred vision, or dyspnea. Physical examination may capture asymmetric and rapid growth of bulky lymph nodes, splenomegaly, and/or hepatomegaly (Tadmor & Levy, 2021; Jain and O'Brien, 2018). Common laboratory findings include elevated LDH, paraproteinemia, hypercalcemia, anemia, and thrombocytopenia (Montolio Breva et al., 2021). These symptoms and findings may also be associated with progression of disease, so it is necessary that a proper diagnostic workup be pursued (Montolio Breva et al., 2021). Chronic lymphocytic leukemia can also transform to prolymphocytic leukemia (PLL; Taylor et al., 2018). Table 1 shows baseline characteristics of 46 patients treated for RT included in a retrospective study at an individual institution from 2006 through 2014 (Rogers et al., 2018).

DIAGNOSIS

The site that exhibits the most fluorodeoxyglucose (FDG) avidity on PET scan should be biopsied, and a standardized uptake value (SUV) greater than 5 has a higher sensitivity for diagnosing RT. A core biopsy is preferred to a fine needle aspiration so that a sufficient amount of tissue can be analyzed. Figure 1 depicts a diagnostic algorithm. Histopathologic features pointing to RT would usually be enlarged CD20-positive B cells with a diffuse growth pattern of large cells, "similar to de novo DLBCL" (Al-Sawaf et al., 2021, p. 170). In approximately 80% of cases of RT, there is PD-1 expression on flow cytometry; this is, however, unusual in de novo DLBCL (Al-Sawaf et al., 2021). Cytogenetics and fluorescence in situ hybridization (FISH) would capture characteristic gene alterations. In a minority of cases, histologic features such as Reed-Sternberg cells with CD30 and CD15 positivity would be consistent with HL (Condoluci & Rossi, 2019).

During workup for RT, it is imperative to be cognizant of whether a lumbar puncture is warranted. It is sensible to proceed when one or more risk factors for CNS disease is present, including "double-hit" or "triple-hit" DLBCL (involving rearrangements of two or three particular genes), high International Prognostic Index (IPI) score, high LDH, and involvement of extranodal sites such as testis, epidural space, breast, bone marrow, kidney, and adrenal gland (Knorr & Moskowitz, 2018; Zahid et al., 2016). It is also important to be on the lookout for clinical signs and symptoms of CNS involvement, including headaches, behavioral disturbances, nerve palsies, balance impairments, and seizures (Krawczyk-Kulis & Kyrcz-Krzemien, 2015). In these cases, imaging such as MRI of the brain and spine in addition to lumbar puncture may be warranted for a more complete workup.

Table 1. Baseline Characteristics of 46 Patients With Richter Syndrome

Patient characteristics	**Median (range)**	**n available**
Age at RS diagnosis, yr	67 (38–83)	46
Time from CLL to RS diagnosis, mo	52.9 (0.4–198.1)	46
Number of prior CLL treatments	3 (0–13)	46
ECOG PS at diagnosis	1 (0–4)	28
CLL risk factors	**n (%)**	**n available**
Complex CLL karyotype	28 (67)	42
*IGH*V unmutated	27 (84)	32
FISH panel positive		
BCL6 (3q27)	6 (15)	40
MYC (8q24)	17 (40)	42
D12Z3 (12cen)	12 (30)	40
ATM (11q23)	12 (29)	41
D13S319 (13q14.3 90 or 1)	22 (55)	40
TP53 (17p13.1)	20 (49)	41
del 6q	5 (13)	40
Baseline laboratory values	**Median (range)**	**n available**
Absolute neutrophil count, × 10^9/L	2.3 (0–17.5)	44
Platelet count, × 10^9/L	117 (16–290)	44
Serum creatinine, µmol/L	79.6 (44.2–353.6)	44
Albumin, g/L	33 (11–44)	44
Total bilirubin, µmol/L	12.0 (3.4–60.0)	44
Lactate dehydrogenase, IU/L	7.34 (2.14–50.0)	44

Note. Baseline laboratory values are from cycle 1 day 1 of R-EPOCH treatment. CLL = chronic lymphocytic leukemia; ECOG PS = Eastern Cooperative Oncology Group performance status; FISH = fluorescence in situ hybridization; *IGHV* = immunoglobulin gene heavy chain; RS = Richter syndrome. Reprinted from "A single-institution retrospective cohort study of first-line R-EPOCH chemoimmunotherapy for Richter syndrome demonstrating complex chronic lymphocytic leukaemia karyotype as an adverse prognostic factor," by K. A. Rogers et al., 2018, *British Journal of Haematology, 180*(2), 259–266. [Table 1].

RETURN TO CASE STUDY

Treatment and Clinical Course

A mediport was placed for chemotherapy administration. A baseline electrocardiogram demonstrated normal sinus rhythm with no ischemic changes, and an echocardiogram revealed ejection fraction of 59% with normal diastolic and systolic function. Methylprednisolone was then discontinued, and the patient was promptly initiated on 6 cycles of dose-adjusted R-EPOCH (rituximab [Rituxan], etoposide, prednisone, vincristine [Oncovin], cyclophosphamide [Cytoxan], and hydroxydaunorubicin, also known as doxorubicin [Adriamycin]).

Throughout administration of the first cycle of the immunochemotherapy, the patient remained admitted for tumor lysis laboratory monitoring. She was continued on aggressive IV hydration of normal saline at a rate of 200 mL milliliters per hour. A uric acid level was checked, which was found to be elevated at 10.1 mg/dL. She was started on daily allopurinol of 300 mg and was given a second dose of rasburicase 3 mg. Phosphorus level was elevated at 5.7 mg/dL, so the patient was also started on sevelamer 800 mg three times daily. She was placed on telemetry, which revealed no arrhythmias, strict intake and output documentation were carried out, and tumor lysis labs were

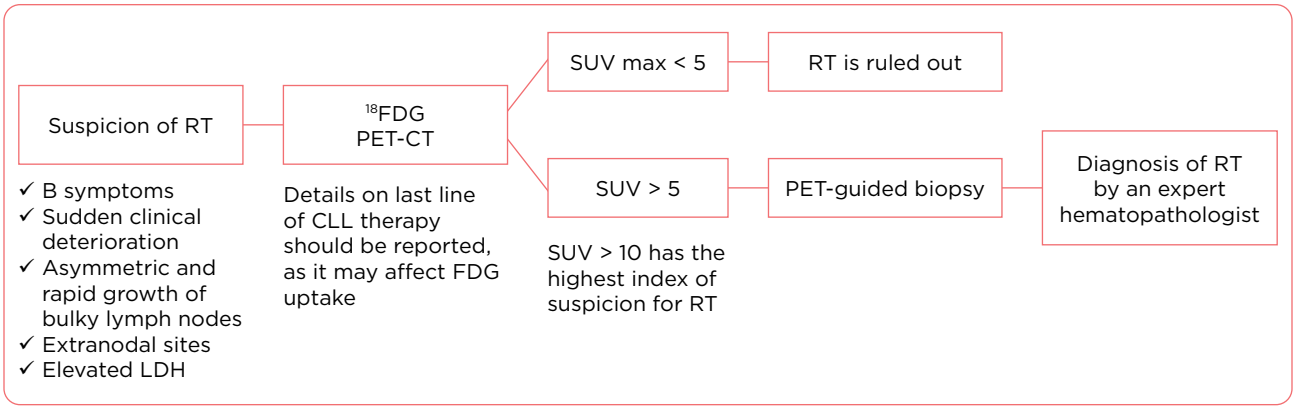

Figure 1. Diagnosis of Richter transformation. ^{18}FDG PET-CT = PET-CT with ^{18}F-fluorodeoxyglucose; CLL = chronic lymphocytic leukemia; LDH = lactate dehydrogenase; RT = Richter transformation; SUV = standardized uptake value. Adapted with permission from Tadmor & Levy (2021).

frequently monitored. Furosemide was given intravenously on an intermittent basis to keep her net fluid balance close to even. Within 48 hours, her tumor lysis labs demonstrated improvement, with normalization of serum uric acid and phosphorus levels. Telemetry monitoring was discontinued and sevelamer was stopped.

Along with the dose-adjusted R-EPOCH, the patient was placed on venetoclax (Venclexta), which was ultimately escalated to 400 mg daily. During these cycles, the patient received intrathecal methotrexate for CNS prophylaxis as well. After the fourth cycle, a PET scan was performed, which demonstrated partial response. Thereafter, stem cells were harvested from the patient's sister. The plan was that the patient would ultimately undergo an allogeneic transplant for consolidation. The fifth cycle of chemotherapy was complicated by neutropenic fevers from a bacteremia that required hospitalization, and, as a consequence, the sixth cycle was delayed by 3 weeks.

Unfortunately, following the course of induction therapy, a PET scan revealed new FDG-avid soft tissue lesions, new FDG-avid lymphadenopathy, and new high-grade FDG avidity in the right temporal lobe and right cerebellum. A brain MRI was then pursued, which showed multiple new cerebral and posterior fossa lesions. A diagnostic lumbar puncture did not reveal abnormal B cells. For relapse with CNS involvement, the patient was started on pulsed dexamethasone 40 mg daily IV for 4 days along with rituximab and high-dose methotrexate (R-MTX). Two weeks following the high-dose methotrexate infusion, the patient received two cycles of R-IVAC (rituximab, ifosfamide, etoposide, and cytarabine) with intrathecal methotrexate. Mesna was started in conjunction to reduce risk of hemorrhagic cystitis.

A week and a half following completion of the salvage induction therapy regimen, the patient presented to the emergency room with nausea and vomiting, headaches with photophobia, anorexia, dizziness, slurred speech, confusion, and somnolence with inability to ambulate or perform activities of daily living over the past 2 days. On physical exam, she was lethargic, spontaneously opening eyes to the sound of a voice, and only able to respond with short phrases when interviewed. Speech was slowed and slurred, and horizontal nystagmus was noted. She was oriented to name and place, but not to time. She was able to follow some simple commands but displayed difficulty with complex commands such as repeating sentences and touching her left ear with her right thumb. Brain and spine MRIs were completed, which revealed diffuse leptomeningeal enhancement, hyperintensity in the right cerebellum, and cerebral edema. At this time, a diagnostic lumbar puncture revealed an elevated opening pressure, elevated protein concentration, lymphocytosis, and abnormal B cells. In the setting of confirmed leptomeningeal metastases, the patient was initiated on high-dose dexamethasone of 10 mg every 6 hours and on prophylactic levetiracetam 500 mg every 12 hours. Neurosurgery was consulted for eventual placement of an Ommaya reservoir.

Nevertheless, despite 5 days of systemic steroids, this patient's symptomatology and clinical manifestations progressively worsened to the

point of obtundation along with hemodynamic instability. A goals-of-care discussion ensued with the patient's primary oncologist, hospital team, and family. The decision was made for the patient to be discharged home with hospice care. Three weeks later, the patient passed away peacefully with family by her side.

PROGNOSIS

Compared with de novo DLBCL, RT unequivocally carries a poorer prognosis (Kalmuk et al., 2019). Once RT-DLBCL (RT of DLBCL type) is diagnosed, the median survival time is 1 year (Wang & Ding, 2020). A retrospective study of 204 patients diagnosed with RT from a single center analyzed cases diagnosed from 1993 to 2018. It was found that patients treated with a first-line R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) regimen had a median overall survival of 15.3 months (Wang & Ding, 2020). Patients treated with other immunochemotherapy regimens as first line, including R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), R-CEPP (rituximab, cyclophosphamide, etoposide, procarbazine, prednisone), and R-CVP (rituximab, cyclophosphamide, vincristine, prednisone) had a median overall survival of 12.8 months. After achieving at least a partial response, just 11.8% of patients in this study proceeded to an SCT. This sample consisted of 24 patients, and median post-SCT survival was notably 55.4 months.

A nationwide retrospective cohort study in Denmark followed 3,772 patients with CLL from 2008 to 2016, of which 113 had biopsy-proven RT. Patients were identified using the Danish National CLL Registry. Findings of this study demonstrated that those diagnosed with RT who were treatment naive had a superior survival compared with those who were previously treated for CLL (Ben-Dali et al., 2020). Treatment itself or progressive CLL may be related to this phenomenon (Ben-Dali et al., 2020).

TREATMENT

Current Treatment Options

Regarding current treatment options for RT, anthracycline-based immunochemotherapy regimens remain the standard-of-care treatment option for RT, along with other aggressive lymphomas (Rogers et al., 2018). The following treatment options are considerations for RT-DLBCL only. This article does not address treatment options for RT-HL (RT of HL type). Regimen considerations have included R-CHOP, CHOP-O (ofatumumab [Kesimpta], cyclophosphamide, doxorubicin, vincristine, prednisone), R-EPOCH, and hyper-CVAD (fractioned cyclophosphamide, vincristine, doxorubicin, dexamethasone), which has often been given in combination with methotrexate and cytarabine as well as rituximab (Condoluci & Rossi, 2017). Ofatumumab is a novel anti-CD20 monoclonal antibody that has displayed more cytotoxicity than rituximab and has not been found to improve outcomes in comparison (Rossi et al., 2018). Hyper-CVAD has demonstrated a response rate of 41% and a median overall survival of 10 months, with severe hematologic toxicity occurring in as much as 50% of patients and treatment-related mortality in 14% (Rossi et al., 2018). R-CHOP has demonstrated a response rate of 67% with a median progression-free survival of 10 months and a median overall survival of 21 months for RT, as well as a low treatment-related mortality of 3%. Infections have been found to occur in 28% of patients (Rossi et al., 2018).

A retrospective cohort study of 46 patients treated with R-EPOCH revealed a high toxicity with death in 30% of patients. Twenty-two percent of patients treated with R-EPOCH had required hospitalization for neutropenic fever or infection (Rossi et al., 2018). However, this study also found that 71% of patients without a complex CLL karyotype had an overall survival of 1 year with R-EPOCH chemoimmunotherapy induction (Rogers et al., 2018). Generally, out of these aforementioned therapies, patients treated with R-CHOP seem to fare best due to lower treatment toxicities, but the survival data reflect a need for novel therapeutics for patients with RT.

Another consideration in front-line therapy for RT-DLBCL is CNS prophylaxis, which in fact remains controversial (National Comprehensive Cancer Network, 2022), as more prospective studies would be helpful to corroborate effectiveness. Most cases of CNS involvement occur after first-line therapy for RT-DLBCL. It has been hypothesized that CNS involvement may be present but

undetectable in some cases during initial diagnosis (Zahid et al., 2016). In high-risk groups, the estimated reported incidence of CNS relapse may be as high as 40%, with the time to relapse within the first 6 to 9 months (Savage, 2017). When a patient has risk factors for CNS disease such as double- or triple-hit gene rearrangements, high IPI score, high LDH, or involvement of extranodal sites (testis, epidural space, breast, bone marrow, kidney, adrenal gland), intrathecal methotrexate is used almost ubiquitously for CNS prophylaxis. Intrathecal methotrexate is usually administered concurrently when the initial diagnostic lumbar puncture is carried out and with cycles of systemic immunochemotherapy. Another option is intrathecal cytarabine (Zahid et al., 2016). Administration of high-dose methotrexate at a dose of 3 to 3.5 g/m^2 for two to four cycles, which penetrates the CNS, may be utilized for CNS prophylaxis or treatment of CNS involvement (National Comprehensive Cancer Network, 2022). High-dose methotrexate has the possibility of causing significant nephrotoxicity, but prompt and effective treatment with IV hydration, high-dose leucovorin, and glucarpidase usually offsets the need for dialysis (Howard et al., 2016).

In patients with RT who achieve a response to induction therapy, SCT is suggested to bring about a durable response for fit patients without disqualifying comorbidities, given short responses observed with chemotherapy (Allan & Furman, 2019). Unfortunately, the majority of patients do not qualify given the high prevalence of elderly age among these patients and decline in performance status in association with rapid disease progression (Allan & Furman, 2019). A retrospective study utilized data from the Center for International Blood and Marrow Transplant Research registry with a cohort of 65 patients receiving their first autologous SCT and a cohort of 61 patients receiving their first allogeneic SCT as therapy for RT from 2007 through 2017 (Herrera et al., 2021). Results confirmed that disease status at the time of allogeneic SCT correlated with survival; patients in complete response at the time of allogeneic transplant had decreased incidence of relapse (Herrera et al., 2021). As patient characteristics in the two cohorts exhibited notable differences such as complete response status, cytogenetics, and use of novel therapies prior, outcomes of autologous vs. allogeneic SCT were not compared directly (Herrera et al., 2021). Nonetheless, it was concluded that both autologous and allogeneic SCT provided a proportion of treated patients with a durable remission (Herrera et al., 2021).

A multicenter retrospective study by the European Group for Blood and Marrow Transplantation included 59 registered patients with the diagnosis of RT, with 34 having received an autologous SCT and 25 having received an allogeneic SCT from 1997 to 2007 (Cwynarski et al., 2012). Study results demonstrated a 3-year overall survival of 59% for autologous SCT and 36% for allogeneic SCT in patients with RT (Wang & Ding, 2020). Younger adults less than 60 years of age in the allogeneic SCT cohort had a 42% relapse-free survival at 3 years, which was comparable to 45% for the autologous SCT cohort (Cwynarski et al., 2012). Also, patients who underwent allogeneic SCT while in complete or partial remission fared better than those who did so with progressive disease. "When [allogeneic SCT] as a postremission therapy was included in the Cox proportional hazards regression model (multivariate analysis), it independently correlated with prolonged survival" (Cynarski et al., 2012, p. 2212). Autologous SCT tends to be more favorable in elderly patients, but allogeneic SCT may provide more sustained disease control.

Promising Treatment Options

Novel targeted agents including Bruton tyrosine kinase (BTK) inhibitors such as acalabrutinib (Calquence) and ibrutinib (Imbruvica) and the B-cell lymphoma 2 protein (BCL-2) inhibitor venetoclax may demonstrate better outcomes when used synergistically with chemoimmunotherapy as opposed to chemoimmunotherapy alone in a small number of patients (Ben-Dali et al., 2020). Table 2 showcases studies and their outcomes for various therapies utilized for RT. A phase I trial of venetoclax in conjunction with DA (dose adjusted)-EPOCH-R showed seemingly promising results with an overall response rate of 96.7% in a sample size of 30 patients, but with serious toxicities (Chamuleau, 2021). Preliminary data from a phase II trial showed an objective response of 75% with a median overall survival of 16.3 months (Wang &

Table 2. Novel Agents Evaluated for the Treatment of Richter Transformation

Regimen	Author, year	Institution	No. of pts	Median age (y)	CR (%)	ORR (%)	Median PFS (mo)	Median OS (mo)
Ibrutinib	Tsang, 2015	Mayo	4	67	50	75	NA	NA
Ibrutinib	Visentin, 2019	Italy	4	69	0	25	NA	NA
Ibrutinib and O	Jaglowski, 2015	Ohio	3	64	0	33	NA	NA
Acalabrutinib	Hillmen, 2016	San Diego	25	NA	9.5	38	2.1	NA
Veneto	Davids, 2017	Dana-Farber	7	73	0	43	1.0	6.0
Veneto	Bouclet, 2021	France	7	67	0	29	NA	1.1
Veneto and R-EPOCH	Davids, 2020	Dana-Farber	27	63	48	59	16.3	16.3
PDCD1	Rogers, 2019	Ohio	10	69	10	10	NA	2.0
Pembro	Ding, 2017	Mayo	9	69	11	44	5.4	10.7
Pembro	Armand, 2020	Dana-Farber	23	NA	4.3	13	1.6	3.8
Nivo and Ibru	Jain, 2016	MDACC	23	65	35	43	NA	13.8
Bispecific	Alderuccio, 2019	Italy	1	NA	0	100	NA	NA
CAR-T	Turtle, 2017	Hutchinson	5	65	NA	71	NA	NA
CAR-T and Ibru	Gauthier, 2020	Hutchinson	4	65	NA	83	NA	NA
CAR-T	Benjamini, 2020	Israel	8	64	71	71	NA	NA
CAR-T	Kittai, 2020	Ohio	8	64	62	100	NA	NA
DTRM-55	Mato, 2020	MSK	13	71	NA	45	NA	NA

Note. CR = complete remission; Ibru = ibrutinib; Nivo = nivolumab; O = ofatumumab; ORR = overall response rate; OS = overall survival; Pembro = pembrolizumab; PFS = progression-free survival. Adapted with permission from Tadmor & Levy (2021).

Ding, 2020). This regimen was highlighted in the case study with the patient having subsequently developed a neutropenic infection. There was significant hematologic toxicity, with grade 3 to 4 neutropenia in 25 patients, grade 3 to 4 thrombocytopenia in 21 patients, and grade 3 to 4 anemia in 18 patients. Febrile neutropenia of at least grade 3 occurred in 19 patients. Furthermore, eight patients suffered significant gastrointestinal adverse events, including ileus and perforation as well as septic enteritis leading to a patient death (Chamuleau, 2021). Also of note, it is crucial to implement preventative strategies and to closely monitor for tumor lysis syndrome (TLS) in patients receiving venetoclax. Early clinical trials of this drug in relapsed CLL reported some fatal cases associated with TLS (Fischer et al., 2020).

Pirtobrutinib (LOXO-305), a novel selective BTK inhibitor, has shown promise in patients with RT. In the BRUIN study, a multicenter and open-label trial, there was an overall response in two thirds out of a cohort of 15 patients with RT (Mato et al, 2021; Rosa, 2021). This study cohort included patients who had progressed on RT-directed therapy (Rosa, 2021). No dose-limiting toxicities were reported in any of the cohorts, and this agent was discontinued due to adverse effects in only five out of a total study population of 323 patients (Rosa, 2021).

Additionally, novel CAR T-cell therapy has been evaluated in small samples of patients with RT, demonstrating encouraging results. An Israeli study conducted from 2019 through 2020 included eight patients with relapsed, refractory CLL after chemoimmunotherapy and therapy with BTK and/or BCL2 inhibitors, six of whom had RT (Benjamini et al., 2020). There were no fatalities due to CAR T-cell toxicity, and all patients achieved a complete response by day 28 (Benjamini et al., 2020). A phase I clinical trial evaluating escalating doses of CAR T cells in 27 patients with relapsed, refractory non-Hodgkin lymphoma (NHL) and CLL included three patients with RT, two of whom achieved a complete response with the therapy (Vitale & Strati, 2020; Batlevi et al., 2019).

No dose-limiting toxicities were observed in this trial, and cytokine release syndrome occurred in 39% of patients, up to grade 3 in one patient (Vitale & Strati, 2020).

CONCLUSION

It is imperative that the advanced practitioner have a high index of suspicion for RT when a patient with established CLL or SLL develops B symptoms, enlarging lymphadenopathy, extranodal manifestations, organomegaly, or incidental laboratory abnormalities such as rising LDH or cytopenias. However, some patients present with RT at the time of initial CLL or SLL diagnosis. Performing a PET scan and taking a biopsy of a suspected area with the most FDG avidity and a high SUV is essential to capture greatest diagnostic sensitivity and to rule out the common differential of disease progression. Prompt diagnosis of this serious condition is essential to maximize treatment effectiveness and to communicate change in prognosis with the patient. These patients should also be referred for clinical trial participation due to a lack of standard therapies with proven benefit, especially beyond first-line treatment. As RT will only become more prevalent with our rapidly growing aging population, it is crucial to remain apprised of the latest treatment strategies and of new therapies in development.

Disclosure

The author has no conflicts of interest to disclose.

References

Al-Sawaf, O., Robrecht, S., Bahlo, J., Fink, A. M., Cramer, P., v Tresckow, J.,...Eichhorst, B. (2021). Richter transformation in chronic lymphocytic leukemia (CLL)—a pooled analysis of German CLL Study Group (GCLLSG) front line treatment trials. *Leukemia*, *35*(1), 169–176. https://doi.org/10.1038/s41375-020-0797-x

Allan, J. N., & Furman, R. R. (2019). Current trends in the management of Richter's syndrome. *International Journal of Hematologic Oncology, 7*(4). https://www.future-medicine.com/doi/full/10.2217/ijh-2018-0010

Batlevi, C., Palomba, M., Park, J., Mead, E., Santomasso, B., Riviere, I.,...Brentjens, R. (2019). Phase I clinical trial of CD19-targeted 19-28Z/4-1BBL "armored" CAR T cells in patients with relapsed or refractory NHL and CLL including Richter transformation. *Hematological Oncology, 37*(S2), 166–167. https://doi.org/10.1002/hon.124_2629

Ben-Dali, Y., Hleuhel, M. H., Andersen, M. A., Brieghel, C., Clasen-Linde, E., Da Cunha-Bang, C., & Niemann, C. U. (2018). Risk factors associated with richter's transformation in patients with chronic lymphocytic leukemia. *Blood, 132*(Supplement 1), 1697–1697. https://doi.org/10.1182/blood-2018-99-112442

Ben-Dali, Y., Hleuhel, M. H., da Cunha-Bang, C., Brieghel, C., Poulsen, C. B., Clasen-Linde, E.,...Andersen, M. A. (2020). Richter's transformation in patients with chronic lymphocytic leukaemia: a Nationwide Epidemiological Study. *Leukemia & Lymphoma*, *61*(6), 1435–1444. https://doi.org/10.1080/10428194.2020.1719092

Benjamini, O., Shimoni, A., Besser, M., Shem-Tov, N., Danylesko, I., Yerushalmi, R.,...Avigdor, A. (2020). Safety and efficacy of CD19-CAR T cells in Richter's transformation after targeted therapy for chronic lymphocytic leukemia. *Blood*, *136*(Supplement 1), 40. https://doi.org/10.1182/blood-2020-138904

Chamuleau, M. E. D. (2021). Dose-adjusted EPOCH-R plus venetoclax: A toxic bend in the road to improving R-CHOP? *Lancet Haematology*, *8*(11), e781–e783. https://doi.org/10.1016/s2352-3026(21)00282-9

Condoluci, A., & Rossi, D. (2017). Treatment of Richter's syndrome. *Current Treatment Options in Oncology*, *18*(12), 75. https://doi.org/10.1007/s11864-017-0512-y

Condoluci, A. & Rossi, D. (2019). *Richter Syndrome*. In: Hallek, M., Eichhorst, B., Catovsky, D. (eds) Chronic Lymphocytic Leukemia. Springer.

Cwynarski, K., van Biezen, A., de Wreede, L., Stilgenbauer, S., Bunjes, D., Metzner, B.,...Dreger, P. (2012). Autologous and allogeneic stem-cell transplantation for transformed chronic lymphocytic leukemia (Richter's syndrome): A retrospective analysis from the chronic lymphocytic leukemia subcommittee of the chronic leukemia working party and lymphoma working party of the European Group for Blood and Marrow Transplantation. *Journal of Clinical Oncology, 30*(18), 2211–2217. https://doi.org/10.1200/JCO.2011.37.4108

Fischer, K., Al-Sawaf, O., & Hallek, M. (2020). Preventing and monitoring for tumor lysis syndrome and other toxicities of venetoclax during treatment of chronic lymphocytic leukemia. *Hematology, 2020*(1), 357–362. https://doi.org/10.1182/hematology.2020000120

Gounari, M., Ntoufa, S., Apollonio, B., Papakonstantinou, N., Ponzoni, M., Chu, C. C.,...Ghia, P. (2015). Excessive antigen reactivity may underlie the clinical aggressiveness of chronic lymphocytic leukemia stereotyped subset #8. *Blood*, *125*(23), 3580–3587. https://doi.org/10.1182/blood-2014-09-603217

Herrera, A. F., Ahn, K. W., Litovich, C., Chen, Y., Assal, A., Bashir, Q.,...Bayer, R. (2021). Autologous and allogeneic hematopoietic stem cell transplantation for diffuse large B-cell lymphoma-type Richter syndrome. *Blood Advances, 5*(18), 3528–3539. https://doi.org/10.1182/bloodadvances.2021004865

Howard, S. C., McCormick, J., Pui, C., Buddington, R. K., & Harvey, R. D. (2016). Preventing and managing toxicities of high-dose methotrexate. *Oncologist, 21*(12), 1471–1482. https://doi.org/10.1634/theoncologist.2015-0164

Jain, N., & O'Brien, S. (2018). Clinical evaluation and management of chronic lymphocytic leukemia. *Concise Guide to Hematology,* 401–409. https://doi.org/10.1007/978-3-319-97873-4_33

Kalmuk, J., Wolff, D., Schandl, C., Mazzoni, S., Znoyko, I., Chiad, Z.,...Hess, B. T. (2019). Clinical utility of chromosomal

microarray in establishing clonality and high risk features in patients with Richter transformation. *Blood, 134*(suppl 1), 1736. https://doi.org/10.1182/blood-2019-124514

Knorr, D. A., Moskowitz, C. (2018). Diffuse Large B-cell Lymphoma. In: Drilon, A.E., Postow, M.A., Vasan, N., Carlo, M.I. *Pocket Oncology, 2nd ed*. Wolters Kluwer, Philadelphia.

Krawczyk-Kulis, M., & Kyrcz-Krzemien, S. (2015). Clinical aspects of prophylaxis and treatment of CNS disease in lymphoma patients. *Acta Haematologica Polonica*, *46*(1), 20–27. https://doi.org/10.1016/j.achaem.2014.11.003

Mato, A. R., Shah, N. N., Jurczak, W., Cheah, C. Y., Pagel, J. M., Woyach, J. A.,...Cohen, J. B. (2021). Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): A phase 1/2 study. *The Lancet*, *397*(10277), 892–901. https://doi.org/10.1016/s0140-6736(21)00224-5

Maurer, C., Langerbeins, P., Bahlo, J., Cramer, P., Fink, A. M., Pflug, N.,...Eichhorst, B. (2016). Effect of first-line treatment on second primary malignancies and Richter's transformation in patients with CLL. *Leukemia, 30*(10), 2019–2025. https://doi.org/10.1038/leu.2016.113

Montolio Breva, S., Sánchez Parrilla, R., Giménez Pérez, T., & Araguás Arasanz, C. (2021). Prolymphocytic or Richter's transformation of chronic lymphocytic leukemia? *Clinical Chemistry and Laboratory Medicine (CCLM)*, *59*(8), e338–e340. https://doi.org/10.1515/cclm-2020-1799

National Comprehensive Cancer Network. (2022). NCCN Clinical Practice Guidelines in Oncology: B-cell lymphomas. V2.2022). https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

Rogers, K. A., Huang, Y., Ruppert, A. S., Salem, G., Stephens, D. M., Heerema, N. A.,...Jones, J. A. (2018). A single-institution retrospective cohort study of first-line R-EPOCH chemoimmunotherapy for Richter syndrome demonstrating complex chronic lymphocytic leukaemia karyotype as an adverse prognostic factor. *British Journal of Haematology*, *180*(2), 259–266. https://doi.org/10.1111/bjh.15035

Rosa, K. (2021). Pirtobrutinib elicits encouraging efficacy in CLL, SLL, MCL, & other non-Hodgkin lymphomas. https://www.onclive.com/view/pirtobrutinib-elicits-encouraging-efficacy-in-cll-sll-mcl-other-non-hodgkin-lymphomas

Rossi, D., Spina, V., & Gaidano, G. (2018). Biology and treatment of Richter syndrome. *Blood, 131*(25), 2761–2772. https://doi.org/10.1182/blood-2018-01-791376

Savage, K. J. (2017). Secondary CNS relapse in diffuse large B-cell lymphoma: defining high-risk patients and optimization of prophylaxis strategies. *Hematology*, *2017*(1), 578–586. https://doi.org/10.1182/asheducation-2017.1.578

Tadmor, T., & Levy, I. (2021). Richter transformation in chronic lymphocytic leukemia: Update in the era of novel agents. *Cancers*, *13*(20), 5141. https://doi.org/10.3390/cancers13205141

Taylor, J., Abdel-Wahab, O., & Park, J. H. (2018). Chronic Lymphocytic Leukemia (CLL). In: Drilon, A.E., Postow, M.A., Vasan, N., Carlo, M.I. Pocket Oncology, 2nd ed. Wolters Kluwer, Philadelphia.

Vitale, C., & Strati, P. (2020). CAR T-cell therapy for B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia: Clinical trials and real-world experiences. *Frontiers in Oncology*, *10*(849). https://doi.org/10.3389/fonc.2020.00849

Wang, Y., & Ding, W. (2020). Richter transformation of chronic lymphocytic leukemia in the era of novel agents. *Clinical Advances in Hematology & Oncology, 18*(6), 348–357.

Zahid, M. F., Khan, N., Hashmi, S. K., Kizilbash, S. H., & Barta, S. K. (2016). Central nervous system prophylaxis in diffuse large B-cell lymphoma. *European Journal of Haematology*, *97*(2), 108–120. https://doi.org/10.1111/ejh.12763