CLL in Focus

Richter Transformation of Chronic Lymphocytic Leukemia in the Era of Novel Agents

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Abstract: The increased use of several effective novel targeted therapy agents has revolutionized therapy for patients with chronic lymphocytic leukemia (CLL). Disease progression in patients with CLL continues to occur, however. In particular, 3% to 25% of patients treated with a novel agent develop Richter transformation (RT); that is, histologic transformation of CLL to an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL). RT that develops in the novel agent era is frequently associated with adverse molecular alterations, such as *TP53* disruption and complex karyotype. As a result, patients with RT in the era of novel agents typically have poor responses to the traditional chemotherapy used to treat de novo DLBCL. These patients also tend to have poor survival outcomes, with a median overall survival of less than 1 year. In this article, we review the contemporary literature of RT, particularly in the context of novel agents used for CLL, and discuss the management approach of RT in the novel agent era.

Keywords
Chronic lymphocytic leukemia, ibrutinib, immune checkpoint inhibitor, Richter transformation, venetoclax

Introduction

Richter transformation (RT) refers to histologic transformation of chronic lymphocytic leukemia (CLL) to an aggressive lymphoma. More than 90% of people with RT present with diffuse large B-cell lymphoma (DLBCL). Transformation to classical Hodgkin lymphoma or other types of lymphoma is less common. RT often presents clinically with rapidly progressing lymphadenopathy, prominent B symptoms (fevers, chills, night sweats, and unintentional weight loss), and lactate dehydrogenase (LDH) elevation.[1] Although the outcome of CLL has been improving with novel targeted agents, such as the Bruton tyrosine kinase (BTK) inhibitors ibrutinib (Imbruvica, Pharmacyclics/Janssen) and acalabrutinib (Calquence, AstraZeneca), the phosphoinositide 3-kinase δ (PI3Kδ) inhibitors idelalisib (Zydelig, Gilead) and duvelisib (Copiktra, Verastem), and the B-cell lymphoma/leukemia 2 (BCL2) inhibitor venetoclax (Venclexta, AbbVie/Genentech), the outcome of DLBCL-type RT (DLBCL-RT) remains poor. In fact, new challenges in the management of DLBCL-RT have emerged in the era of novel agents. In this article,

we review the incidence, biology, prognosis, and clinical management of DLBCL-RT in the novel agent era.

Incidence of RT in the Novel Agent Era

Prior to the novel agent era, the reported incidence of RT in CLL patients treated with chemotherapy or chemoimmunotherapy (CIT) ranged from 1% to 10% after a median follow-up of 3 to 13 years.[2,3] For example, follow-up data from several German CLL frontline trials (CLL4, CLL5, CLL8, and CLL2M) showed that 75 (5.1%) of 1458 CLL patients developed RT after a median observation time of 69 months.[4] In a frontline trial of fludarabine, cyclophosphamide, and rituximab (Rituxan, Genentech/Biogen; FCR) from MD Anderson Cancer Center, 24 (8%) of 300 patients developed RT after a median follow-up of 12.8 years.[5] A Mayo Clinic cohort study with a median follow-up of 4 years reported a cumulative incidence of RT of approximately 0.5% per year from diagnosis and 1% per year from initial treatment in 1641 newly diagnosed CLL patients.[1,6]

The reported incidence of RT in CLL patients treated with ibrutinib ranged from 3% to 7% in different clinical trials and retrospective studies. Three-year follow-up of the pivotal PCYC-1102 trial (Safety of PCI-32765 in Chronic Lymphocytic Leukemia) and the PCYC-1103 extension study (Safety and Tolerability Study of PCI-32765 in B Cell Lymphoma and Chronic Lymphocytic Leukemia) showed that 1 (3.2%) of 31 treatment-naive patients and 7 (6.9%) of 101 previously treated patients developed RT on ibrutinib, with the majority of RT occurring within 15 months of ibrutinib initiation.[7,8] Two-year follow-up of the RESONATE trial (A Phase 3 Study of Ibrutinib Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia) showed that 8 (4.1%) of 195 patients treated with ibrutinib in the relapsed/refractory setting developed RT.[9] In a study of 308 CLL patients who received ibrutinib in 4 clinical trials at Ohio State University (OSU; most in the relapsed/refractory setting), 18 (5.8%) developed RT after a median follow-up of 20 months, and the cumulative incidence of RT at 18 months was 6.5%.[10] In a similar study at MD Anderson, among 127 patients receiving ibrutinib in 4 clinical trials, 1 (3.4%) of 29 treatment-naive and 6 (6.1%) of 98 previously treated patients developed RT, with transformation occurring within 13 months in most cases.[11] The incidence of RT with ibrutinib appeared to be lower in the frontline setting.[7,8,11] Follow-up of several frontline phase 3 trials, including A041202 (NCT01886872), E1912 (NCT02048813), FLAIR (ISRCTN01844152), and CLL13 (NCT02950051), will provide additional insight regarding this issue.

The incidence of RT in CLL patients treated with venetoclax appeared to be higher than that in patients treated with ibrutinib, in the 10% to 25% range. In the pivotal trial of venetoclax for relapsed or refractory CLL, 18 (15.5%) of 116 patients developed RT after a median follow-up of 17 months, with 11 diagnosed within 1 year of the study.[12] In patients with deletion 17p (del[17p]) treated with venetoclax, 11 (10.3%) of 107 developed RT after a median follow-up of 1 year.[13] The initial venetoclax/rituximab trial reported RT in 5 (10.2%) of 49 patients after a median follow-up of 28 months, with all cases developing within 9 months of study enrollment.[14] In the MURANO trial (A Study to Evaluate the Benefit of Venetoclax Plus Rituximab Compared With Bendamustine Plus Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia), 6 (3.1%) of 194 patients receiving venetoclax/rituximab developed RT after a median follow-up of 2 years.[15] In an Australian study, 17 (25.4%) of 67 patients receiving venetoclax in 3 clinical trials developed RT after a median follow-up of 23 months.[16] The high incidence of early RT in venetoclax trials raises the possibility of pre-existing transformation prior to trial treatment. In a phase 2 trial of venetoclax for patients whose disease progressed after ibrutinib, pre-existing RT was screened for and these patients were excluded from the trial if confirmed with biopsy, and 5 (5.5%) of 91 patients in the trial developed RT after a median follow-up of 14 months.[17]

Evolving Role of PET and the Importance of Biopsy

Positron emission tomography (PET) played an important role in diagnosing RT in the CIT era. A study by Bruzzi and colleagues at MD Anderson reported that a maximum standardized uptake value (SUVmax) of greater than 5 had a sensitivity of 91% and a specificity of 80% in detecting RT.[18] Two other studies showed a similar sensitivity but lower specificities of an SUVmax greater than 5 in detecting RT: an Italian study by Mauro and colleagues[19] reported a sensitivity of 88% and a specificity of 67%, whereas Falchi and colleagues[20] from MD Anderson reported a sensitivity of 88% and a specificity of 47%. A study by Michallet and colleagues[21] reported a high sensitivity (91%) as well as a high specificity (95%) when using an SUVmax cut-off of greater than 10 to detect RT.

In the novel agent era, progression of CLL during therapy with a BTK or PI3K inhibitor is often associated with aggressive disease.[10,11,22] The changing biology of progressive CLL in the novel agent era may affect the value of PET in differentiating between RT and CLL. Mato and colleagues[23] reported that in CLL patients whose disease progressed on a BTK or PI3K inhibitor and

who were screened for participation in a clinical trial of venetoclax, an SUVmax cutoff of 10 or greater on PET scan had a low sensitivity (71%) and specificity (50%) in detecting 8 cases of RT among the 35 patients who underwent biopsy. In a Mayo Clinic cohort study (n=92), our group reported that an SUVmax of 5 or greater had a high sensitivity (96%) but a very low specificity (20%) in differentiating RT (n=25) from other pathologies in patients who underwent biopsy (n=54), whereas an SUVmax of 10 or greater had a low sensitivity (56%) and a moderate specificity (73%).[24] There is probably no longer an ideal "one-size-fits-all" cutoff of SUVmax in the novel agent era, and the role of PET scan should be revisited. A tissue biopsy should be strongly considered in patients receiving a BTK or PI3K inhibitor who have suspected RT and an SUVmax of 5 or greater on PET. In the Mayo Clinic study, approximately 40% of the patients with an SUVmax of 5 to 10 and two-thirds of the patients with an SUVmax of 10 or greater were diagnosed with RT,[24] emphasizing the importance of tissue biopsy in patients with an SUVmax of 5 or greater.

Excisional biopsy is preferred whenever possible. Partial sampling via fine-needle aspiration or core needle biopsy may miss the foci of transformed lymphoma and lead to a false-negative diagnosis in patients with RT. On the other hand, partial sampling of regions containing discrete large cells in an expanded proliferation center, which are typically present in histologically aggressive CLL (increased number of large cells, large confluent proliferation centers, or high proliferation rate), may lead to a false-positive diagnosis of RT. The pathology diagnosis can be challenging and the slides should be reviewed by an experienced hematopathologist. The diagnostic challenges were illustrated by several studies in which central pathological review confirmed RT in only 80% of cases.[25,26] Differentiating between progressive CLL and RT remains challenging but is critical in the novel agent era, as CLL progression on a BTK or PI3K inhibitor is frequently associated with aggressive disease. Cases with increased discrete large cells, which may represent immunoblasts in enlarging proliferation centers in the background of CLL cells, should not be misdiagnosed as RT. The diagnosis of RT should be restricted to cases with confluent sheaths of centroblast- or immunoblast-like large neoplastic lymphoma cells.

Molecular Mechanisms of RT in the Novel Agent Era

Based on accumulated data in the CIT era,[27-29] the molecular mechanism of DLBCL-RT is distinct from de novo DLBCL. Disruption of *TP53* by del(17p) or a somatic mutation was detected in up to 60% of RT cases vs 10% to 20% of de novo DLBCL cases. Gain-of-function *NOTCH1* mutation was reported in approximately 30% of patients with RT, frequently among those with trisomy 12. *CDKN2A/B* deletion was found in approximately 30% of RT cases and could co-exist with a *TP53* disruption or *NOTCH1* mutation. Although BCL2 overexpression was frequently detected in RT,[29] amplification or translocation involving *BCL2* was not as common as reported in germinal center B-cell–like (GCB) DLBCL. *MYC* aberration, caused by t(8;14) or another structural alteration or deletion of the *MYC*-negative regulator MGA, was present in approximately 50% of DLBCL-RT.[27-31] These molecular abnormalities suggest that defects in cell cycle regulation, DNA damage repair, and apoptosis contribute to the development of RT. The majority of cases of DLBCL-RT have the unmutated immunoglobulin heavy chain variable region gene (*IGHV*), and a subset of cases of RT have biased usage of stereotyped immunoglobulin genes, that is, subset 8 (*IGHV4-39/IGHD6-13/IGHJ5*). Subset 8 is associated with enriched trisomy 12 and the *NOTCH1* mutation,[32-34] suggesting that B-cell receptor (BCR) signaling also contributes to the development of RT.

In the novel agent era, scarce data are available on the molecular mechanisms of RT. A number of studies showed a high prevalence (65%-70%) of *TP53* disruption in RT that developed after ibrutinib; for example, 8 out of 14 in the OSU cohort, 6 out of 6 in a University of Chicago study, 4 out of 9 in the MD Anderson study, 4 out of 5 in the Mayo Clinic study, and 5 out of 6 in a National Institutes of Health study.[10,11,22,35-37] Complex karyotype and the presence of near-tetraploidy are associated with RT development in CLL patients treated with ibrutinib.[38] All DLBCL-RT cases in the OSU cohort had complex karyotypes.[10] Davids and colleagues[39] presented a large cohort of RT patients in the era of novel agents, including 59 cases following a BTK inhibitor, 6 cases following a PI3K inhibitor, and 6 cases following a BCL2 inhibitor. Approximately 50% of the RT cases had del(17p), 25% had trisomy 12, and 75% had complex karyotypes. Approximately 90% of the cases had unmutated *IGHV*, but no particular enrichment of specific *IGHV* usage was noted in this cohort.

Although *BTK* and *PLCG2* mutations are frequently detected in CLL that is resistant to ibrutinib,[40] the role of these mutations in RT development has been understudied. Kadri and colleagues[35] compared the genomic abnormalities in paired CLL blood and RT tumor tissue in 6 CLL patients who developed RT on ibrutinib. The majority of genetic aberrations (60%-95%) were found in both CLL leukemia cells and the RT tumor tissue. An additional 1 to 15 RT-specific mutations were identified in the RT tissue,[35] with 8q gain (*MYC*) being the only recurrent RT-specific aberration. Among 4 RT patients

who had a *BTK* mutation in their CLL cells, 2 patients had the same *BTK* mutations in their RT tissue; in a third patient, a subset of CLL cells had BTK^{C481S} but the RT tissue contained a major clone of BTK^{C481Y}. In addition, all BTK mutations uncovered in this cohort occurred with co-existing *TP53* disruption. These data suggest that *TP53* disruption may provide a permissive environment for the clonal CLL cells carrying a *BTK* mutation to expand and to evolve into RT, providing evidence of BCR activation in RT development.

RT that developed after venetoclax appears to bear similar molecular alterations involving *TP53* disruption. In an Australian study, among 14 patients who developed RT after venetoclax, 10 (71%) had *TP53* disruption, and 5 out of 8 (63%) had complex karyotypes.[16] BCL2 expression by immunohistochemistry was evident in most of these RT cases. In a German study on disease progression following venetoclax, 4 out of the 8 progressive cases were DLBCL-RT.[41] All 8 (100%) cases had evidence of *TP53* disruption at baseline, and all of them, including the 4 RT cases, had acquired additional mutations and genomic instability upon progression. Loss of *CDKN2A/B* occurred in 5 of the 8 cases during progression. In addition, *BRAF* mutation and *CD274* (encoding programmed death ligand 1 [PD-L1]) amplification were also detected in a subset of cases.[41]

Despite advances in understanding the genetic aberrations, much remains to be investigated in the immune evolution underlying RT. Preliminary data from our group showed that PD-L1 expression was increased in RT-involved nodal tissue compared with CLL nodal tissue. Clonality of the T-cell receptor repertoire decreased in patients with RT vs CLL, indicating that a diversification of the T-cell receptor repertoire occurs during CLL transformation to DLBCL,[42] possibly secondary to newly formed tumor antigens owing to the acquired mutations in the process of transformation.

In summary, it is reasonable to speculate that a unique tumor biology (*TP53* disruption, genomic instability, and BCR signaling alterations) as well as a permissive tumor microenvironment (increased PD-L1 expression and T-cell exhaustion) both contribute to the development of RT in CLL patients treated with novel targeted therapies.

Prognosis of RT in the Novel Agent Era

In patients with RT, the transformed DLBCL is clonally related to the underlying CLL in more than 80% of cases.[27] Clonally related RT typically has a poor response to traditional immunochemotherapy used for de novo DLBCL (such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) and a poor survival outcome, with a median overall survival (OS) of less than 1 to 2 years. In contrast, clonally unrelated RT usually responds well to an R-CHOP–like regimen and has a much longer median OS (approximately 5 years).[27] Therefore, it is critical to determine the clonal relationship between the transformed DLBCL and the underlying CLL so that appropriate treatment can be chosen. However, determination of a clonal relationship requires paired CLL and RT samples and complicated molecular analysis of immunoglobulin gene rearrangement, which are not readily available in routine clinical practice. Dr Rong He and colleagues at the Mayo Clinic suggested an alternative test to determine the clonal relationship.[43] Their study showed that PD-1 expression in neoplastic B cells was weak and restricted to paraimmunoblasts within proliferation centers in CLL. Increased programmed death 1 (PD-1) expression was found in 12 out of 15 (80%) cases of DLBCL-RT, but only 1 out of 26 de novo DLBCL cases. A total of 10 DLBCL-RT cases were tested for both PD-1 expression and clonal relationship via molecular analysis. Nine cases of DLBCL-RT were clonally related to the underlying CLL, and 8 of 9 showed 2+ or 3+ of PD-1 staining (on a scale of 1+ to 3+). One of the 10 DLBCL-RT cases was clonally unrelated and lacked staining for PD-1.[43] The excellent concordance between PD-1 expression and CLL and DLBCL-RT clonal relatedness suggests that PD-1 expression is a promising surrogate marker for the CLL and DLBCL-RT clonal relationship.

TP53 disruption and prior CLL treatment were important prognostic factors in RT based on data from the CIT era. In a retrospective study by Rossi and colleagues,[27] approximately 65% of RT patients (n=86) were treated with CHOP, R-CHOP, or an R-CHOP–like regimen, and the median OS was 19 months. In multivariate analysis, *TP53* disruption was identified as the only molecular marker that was prognostic,[27] possibly owing to its role in mediating chemoresistance.[44] Eastern Cooperative Oncology Group (ECOG) performance status and complete remission (CR) to induction therapy were the other 2 important prognostic factors in that study.[27] The prognostic role of *TP53* disruption in patients with RT was also demonstrated in patients treated with R-CHOP[45]; rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH)[46]; CHOP plus ofatumumab (CHOP-O)[47]; or oxaliplatin, fludarabine, cytarabine, and rituximab (OFAR).[48,49] In addition, several studies revealed that the number of prior therapies is highly prognostic.[46,47,50,51] In the National Cancer Research Institute (NCRI) phase 2 study of CHOP-O,[47] patients who were therapy-naive had a significantly superior response rate and survival vs patients who had received prior therapies. Our group also confirmed that treatment-naive RT had a significantly better outcome in a large cohort of 204 RT patients.[50] The

MD Anderson group reported a prognostic score based on 5 adverse risk factors (ECOG performance status >1, increased LDH, platelet count ≤100, tumor size >5 cm, and ≥2 prior therapies) that could stratify RT patients into low-risk (0-1), intermediate-risk (2), and high-risk (3-5) categories with distinct survivals in the CIT era.[51]

Data in the novel agent era suggest that RT that develops in patients who received novel agent therapy for CLL has a poor prognosis,[10,16,22,39] likely owing to frequent adverse molecular features. Limited available data have shown that in the novel agent era, more than 90% of RT cases are clonally related to the underlying CLL, more than 70% of the cases have *TP53* disruption, and the majority of cases also have complex karyotypes. A number of studies reported universally poor outcomes with RT that develops after use of ibrutinib, with a median survival of only 2 to 4 months.[10,22,39] In an Australian study of disease progression (including RT) on venetoclax, complex karyotype and fludarabine refractoriness were identified as the key risk factors. Thirteen of 14 patients with DLBCL-RT were treated with chemotherapy, with a response rate of approximately 40% and a median OS of approximately 12 months.[16] Importantly, these RT patients did not have prior exposure to a BTK inhibitor. RT that developed after ibrutinib or venetoclax frequently presents with bulky nodal or extranodal disease, similarly to highly aggressive B-cell lymphoma. Concurrent resistant CLL in bone marrow or blood is common. These clinical features highlight the difficulty in managing these RT cases.

Therapeutic Options for RT in the Novel Agent Era

No randomized clinical trials have been conducted to investigate therapeutic approaches for RT. All available evidence regarding the treatment of RT comes from single-arm clinical trials with small patient numbers, or retrospective studies. Historically, most DLBCL-RT cases were treated with immunochemotherapy regimens used for de novo DLBCL, such as R-CHOP or R-CHOP–like regimens, including R-EPOCH. These data were thoroughly reviewed in a number of prior articles.[3,52-54]

In summary, R-CHOP as first-line therapy for RT has a response rate of 50% to 60% and a median OS of 15 to 21 months.[45] Substitution of rituximab with ofatumumab did not result in a higher response rate (46%) or a longer OS (11 months).[47] Frontline treatment with R-EPOCH was associated with a response rate of 39%, a median progression-free survival (PFS) of 3.5 months, and a median OS of 5.9 months.[46] Incorporating CLL-directed chemotherapy agents, such as with the OFAR regimen, led to a response rate of 38% to 50% and a median OS of 6 to 8 months.[48,49] Platinum-containing regimens, such as dexamethasone, cytarabine, and cisplatin (DHAP) or etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP),[55] and dose-intensified regimens, such as rituximab with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine (R-hyper-CVAD),[56] had higher CR rates. These regimens were associated with severe hematologic toxicity, increased infection, and relatively high treatment mortality, however, resulting in a similar or even shorter survival.[50]

Given the short duration of response achieved with chemotherapy, autologous and allogeneic stem cell transplant have been explored with a goal to maintain durable remission. A retrospective study by EBMT showed that a subset of patients benefited from transplant.[57] The estimated 3-year survival rate was 36% after allogeneic stem cell transplant (alloSCT) and 59% after autologous stem cell transplant (autoSCT). Importantly, retrospective analyses of transplant are subject to selection biases because they enroll patients who achieved at least a partial remission (PR) with chemotherapy and are in good clinical condition, with a good performance status. Unfortunately, the majority of RT patients (80%-90%) are not able to proceed to transplant owing to a lack of good response to chemotherapy, age, or comorbidities. This was illustrated in a study from MD Anderson in which only 20 out of 148 (14%) patients with biopsy-proven RT underwent transplant. Patients who underwent alloSCT in CR or PR did well, with a 3-year survival of 75%.[51] In the Mayo Clinic cohort, only 24 (12%) of 204 RT patients underwent transplant, with a median survival after transplant of 55.4 months.[50]

Because treatment outcomes with chemotherapy have been disappointing and novel agents are emerging, new strategies to manage RT are being actively studied.

Immune Checkpoint Inhibitors

Preclinical studies suggest that exhausted T cells contribute to the immunodeficiency status in CLL. Our group reported the first trial of a PD-1 blocking antibody, pembrolizumab (Keytruda, Merck), in CLL (n=16) and RT (n=9) patients.[36] The overall response rate in patients with RT was approximately 40%, whereas no response was seen in patients with CLL. Five of the 9 RT patients had relapsed or refractory disease following prior RT-directed therapies before starting pembrolizumab. All 4 responses to pembrolizumab were observed in patients who developed RT after ibrutinib. The median OS for the RT cohort was approximately 11 months. Increased PD-L1 expression in nodal tissue of RT was detected in responders. PD-1 blockade appeared to be capable of inducing nodal response in RT patients, but did not induce bone

marrow CLL response. Therefore, a combination of PD-1 blockade and CLL targeted therapy is needed to effectively control both diseases. In the MD Anderson trial of the PD-1 antibody nivolumab (Opdivo, Bristol-Myers Squibb) plus ibrutinib, 10 out of 23 (43%) RT patients responded, with a median duration of response of 9.3 months and a median OS of 13.8 months.[58] In another trial of nivolumab and ibrutinib, the overall response rate was 65% in 20 patients with RT, although the PFS was short (~5 months).[59] In contrast to the data from Ding and colleagues,[36] the majority of responses were seen in BTK inhibitor–naive patients in these 2 studies. Although BTK inhibitor–naive patients were likely to respond to ibrutinib in these 2 combination trials, BTK inhibitor–exposed patients may have developed an immune-rich tumor microenvironment[42] that made them more susceptible to immune checkpoint inhibitors. Of note, the OSU group examined off-label use of nivolumab or pembrolizumab in 10 DLBCL-RT patients, all of whom had received prior BTK inhibitor therapy.[60] Nivolumab or pembrolizumab was administered concurrently with ibrutinib in 3 patients and venetoclax in 1 patient. This off-label use of nivolumab or pembrolizumab resulted in poor efficacy, with a median time to treatment failure of 1.2 months. Additional studies are needed to understand immunotherapy in DLBCL-RT. Other studies are ongoing to investigate the combination of immune checkpoint inhibitors with other CLL-targeted therapies, such as acalabrutinib (NCT02362035), venetoclax (NCT02846623, NCT04082897), duvelisib (NCT03892044), and umbralisib (NCT02535286).[61]

Novel Targeted Therapy

Given the poor outcome with chemotherapy in the majority of RT patients, novel targeted therapies are being investigated for use in this setting. Initial case reports from the Mayo Clinic CLL group showed that 3 out of 4 RT patients (3 refractory to chemotherapy) responded to ibrutinib; 1 had an ongoing CR at 2.8 months, 1 had RT progression at 8.5 months, and 1 had CLL progression at 10.8 months.[62] A phase 1/2 trial of acalabrutinib in RT (n=29) showed a response rate of 38%, a median duration of response of 5 months, and a median PFS of 3 months.[63] The first-ever randomized trial in the setting of RT is currently evaluating R-CHOP with or without acalabrutinib (NCT03899337). Patients with RT are allowed to enroll in the ongoing trials of reversible BTK inhibitors, such as ARQ 531 (NCT03162536)[64] and LOXO-305 (NCT03740529).[65] The results of these trials remain to be seen. The PI3K inhibitors umbralisib (NCT02535286, in combination with ublituximab) and duvelisib (NCT03534323, in combination with venetoclax) are also being tested in clinical trials of CLL and RT. Seven patients with DLBCL-RT were included in the first venetoclax trial in humans; the response rate was 43%, with unknown durability.[66] Preliminary data from a phase 2 trial of venetoclax plus DA-EPOCH-R for DLBCL-RT (20% of patients were CLL treatment–naive) showed an objective response of 75%, a median PFS of 10 months, and a median OS of 16.3 months.[67] The immunomodulatory drug lenalidomide (Revlimid, Celgene) is currently being tested for RT in different trials, in combination with obinutuzumab (Gazyva, Genentech; NCT03113695) or the monoclonal CD19 antibody MOR208 (NCT02005289). A novel combination compound containing a new BTK inhibitor in combination with everolimus (Afinitor, Novartis) and pomalidomide (Pomalyst, Celgene) is currently in a phase 1 trial for CLL, RT, and other lymphomas, and early results seem promising.[68]

CAR T-Cell or Bispecific Antibody Therapy

Chimeric antigen receptor (CAR) T cells targeting CD19 have been shown to be efficacious in treating relapsed or refractory CLL in multiple trials.[69] The response rate in several trials of tisagenlecleucel (Kymriah, Novartis), JCAR014, CTL119, and lisocabtagene maraleucel, each of which enrolled 14 to 24 patients with CLL, has been in the 60% to 90% range.[70-74] Three patients with DLBCL-RT were included in 2 early CAR T-cell trials, and 2 had a PR.[75,76] The trial of JCAR014 included 5 patients with RT, of whom 2 had a CR and 1 had a PR.[70] CAR T-cell therapy represents a significant therapeutic advance in highly refractory CLL or RT patients. However, it is unclear how durable the response will be. In the first trial of CAR natural killer cells targeting CD19, 1 RT patient was included and achieved remission of the RT component, although the CLL component persisted.[77] The data for cellular therapy in RT appear promising, and further studies are awaited. Blinatumomab (Blincyto, Amgen), a bispecific antibody targeting CD19 and CD3 that acts as a T-cell engager, has been approved for the treatment of acute lymphoblastic leukemia and is also efficacious in treating relapsed or refractory DLBCL, with a response rate of 55%.[78] In one case report, a patient with refractory DLBCL-RT had a rapid complete response to blinatumomab as a bridging therapy to alloSCT.[79] Two clinical trials are testing blinatumomab in patients with RT, either alone (NCT03121534) or after R-CHOP debulking (NCT03931642). Another bispecific antibody targeting CD20 and CD3, XmAb13676, is currently being evaluated for hematologic malignancies, including RT (NCT02924402).

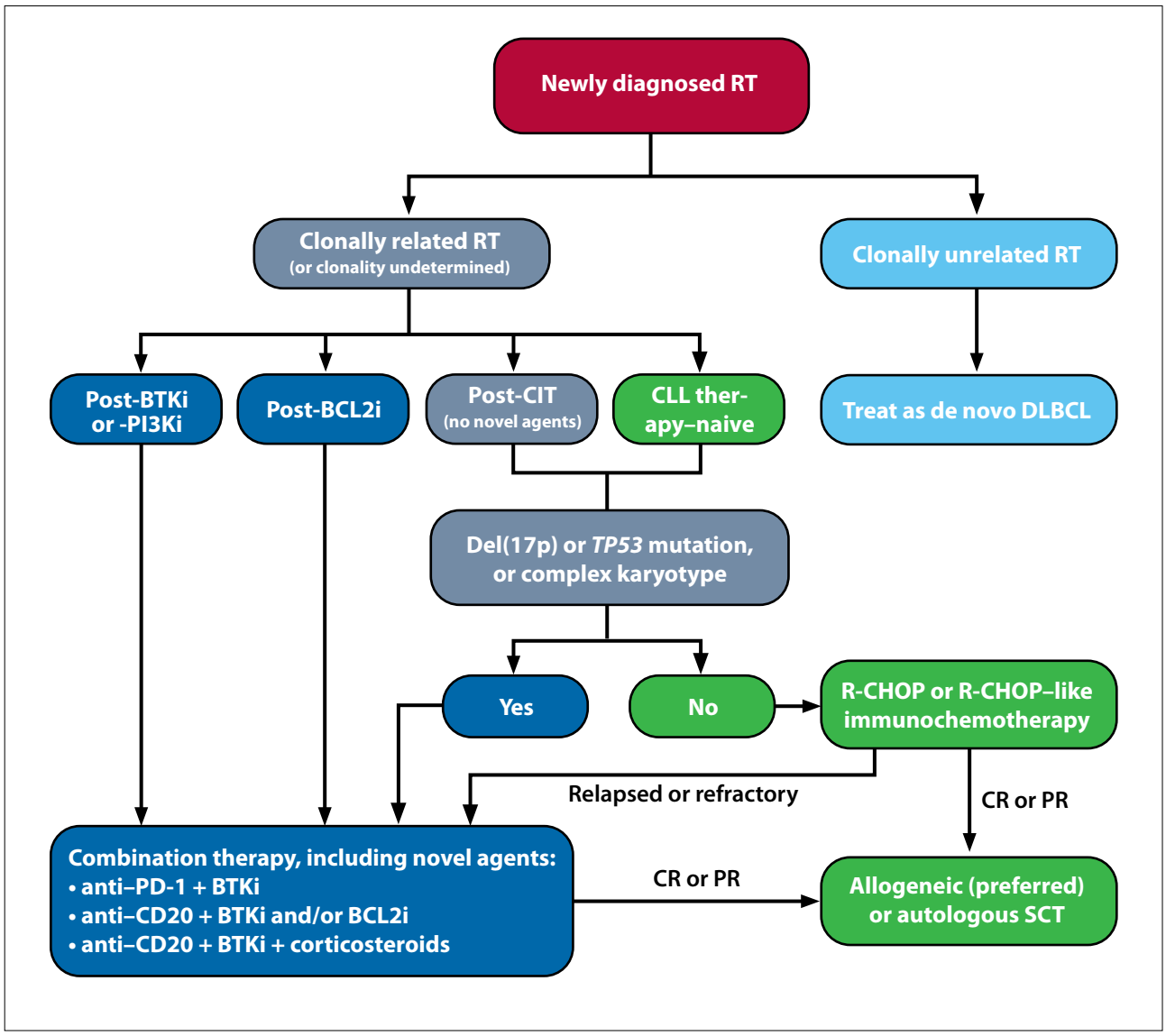

Figure. Proposed algorithm for the management of DLBCL-RT in the era of novel agents.

BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton tyrosine kinase inhibitor; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; CR, complete remission; del(17p), deletion 17p; DLBCL, diffuse large B-cell lymphoma; PD-1, programmed death 1; PI3Ki, phosphoinositide 3-kinase inhibitor; PR, partial remission; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; RT, Richter transformation; SCT, stem cell transplant.

Suggested Approach to Managing RT in the Novel Agent Era

Given the lack of sufficient data, it is challenging to establish standard approaches to the management of DLBCL-RT in the era of novel agents. Further studies are needed to gain a deeper understanding of the tumor biology and immune microenvironment in order to design more effective therapies. However, based on important knowledge from the CIT era and the limited but valuable data in the novel agent era, several factors are critical in choosing treatments for DLBCL-RT in current practice. These include DLBCL-RT clonal relatedness, prior CLL treatment, and molecular features, especially *TP53* disruption and complex karyotype.

A clinical trial is strongly preferred when managing DLBCL-RT. Outside of a clinical trial, a proposed algorithm of management is shown in the Figure, with the caveat that limited supportive data exist. DLBCL-RT that is clonally unrelated to the underlying CLL should

be treated using the same approach as de novo DLBCL, meaning R-CHOP at frontline, and salvage chemotherapy followed by autoSCT in relapsed or refractory cases. If RT is clonally related to CLL, or when the clonal relationship cannot be determined, treatment choice depends on prior CLL therapy. For patients who are CLL treatment–naive, it is acceptable to administer R-CHOP or an R-CHOP–like regimen, given the relatively favorable outcome shown by our group and others.[47,50] However, we do recommend determining *TP53* status and cytogenetics at the time of RT diagnosis for CLL treatment–naive patients and patients who were treated with CIT only for their CLL. Typical CIT regimens include FCR, fludarabine/rituximab (FR), pentostatin/cyclophosphamide/rituximab (PCR), bendamustine/rituximab (BR), and rituximab/chlorambucil (R-chlorambucil). In the absence of *TP53* disruption and complex karyotype, it is reasonable to treat these RT patients with R-CHOP or R-CHOP–like immunochemotherapy, and to consider stem cell transplant in responding patients. In the case of *TP53* disruption and/or complex karyotype, or RT refractory to immunochemotherapy, novel agent–based combination therapy is recommended. Reasonable combinations include an anti–PD-1 antibody plus a BTK inhibitor, an anti-CD20 monoclonal antibody plus a BTK inhibitor and/or a BCL2 inhibitor, and an anti-CD20 monoclonal antibody plus a BTK inhibitor and a high-dose corticosteroid such as methylprednisolone. In patients who develop RT after a BTK inhibitor, a PI3K inhibitor, or a BCL2 inhibitor, durable responses to immunochemotherapy are unlikely and treatment with novel agent combinations as described above is strongly recommended. Consolidation with allogeneic (preferred) or autologous stem cell transplant needs to be considered in RT patients responding to novel combination therapies.

Conclusion and Perspectives

Despite advances in developing novel agents for CLL treatment, RT continues to be a clinical area with unmet needs. Because DLBCL-RT that develops in the era of novel agents typically displays *TP53* disruption and/or complex karyotype, patients should be strongly encouraged to participate in clinical trials to receive treatment that incorporates novel agents. Critical biological questions that remain to be addressed in the era of novel agents include: (1) CLL molecular evolution and risk factors for RT development; (2) molecular heterogeneity of RT after different prior CLL therapies; (3) immune evolution during Richter transformation of CLL; and (4) biomarkers that can help select effective novel therapies for different RT patients. Given the relative rarity of RT, collaborative efforts from multiple academic centers are necessary to address these important questions in the current era of novel agents.

Disclosures

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