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Release date: January 10, 2019; Expiration date: January 10, 2020

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

Kerrin M. Rosenthal, MA; Kimberly Callan, MS; Genevieve Emberger Hartzman, MA; Erin Hesler; Kristina M. Gregory, RN, MSN, OCN; Rashmi Kumar, PhD; Karen Kanefield; and Kathy Smith.

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Deborah Stephens, DO, Panel Member, has disclosed that she has no relevant financial relationships.

Mary A. Dwyer, MS, CGC, Senior Manager, Guidelines, NCCN, has disclosed that she has no relevant financial relationships.

Hema Sundar, PhD, Oncology Scientist/Senior Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

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Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma, Version 2.2019

Featured Updates to the NCCN Guidelines

William G. Wierda, MD, PhD[1,*]; John C. Byrd, MD[2,*]; Jeremy S. Abramson, MD[3]; Syed F. Bilgrami, MD[4]; Greg Bociek, MD, MSc[5]; Danielle Brander, MD[6]; Jennifer Brown, MD, PhD[7,*]; Asher A. Chanan-Khan, MD[8]; Julio C. Chavez, MD[9]; Steve E. Coutre, MD[10]; Randall S. Davis, MD[11]; Christopher D. Fletcher, MD[12]; Brian Hill, MD, PhD[13]; Brad S. Kahl, MD[14]; Manali Kamdar, MD[15]; Lawrence D. Kaplan, MD[16]; Nadia Khan, MD[17]; Thomas J. Kipps, MD, PhD[18]; Shuo Ma, MD, PhD[19]; Sami Malek, MD[20,*]; Anthony Mato, MD[21]; Claudio Mosse, MD, PhD[22]; Vishala T. Neppalli, MD[23]; Mazyar Shadman, MD, MPH[24,*]; Tanya Siddiqi, MD[25]; Deborah Stephens, DO[26,*]; Nina Wagner, MD[27]; Mary A. Dwyer, MS, CGC[28,*]; and Hema Sundar, PhD[28,*]

ABSTRACT

Chronic lymphocytic leukemia (CLL) is generally characterized by an indolent disease course. Histologic transformation (also known as Richter's transformation) to more aggressive lymphomas, such as diffuse large B-cell lymphoma or Hodgkin lymphoma, occurs in approximately 2% to 10% of patients and is associated with a poor prognosis. These NCCN Guidelines Insights discuss the recommendations for the diagnosis and management of patients with histologic transformation.

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[1]The University of Texas MD Anderson Cancer Center; [2]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [3]Massachusetts General Hospital Cancer Center; [4]Yale Cancer Center/ Smilow Cancer Hospital; [5]Fred & Pamela Buffett Cancer Center; [6]Duke Cancer Institute; [7]Dana-Farber/Brigham and Women's Cancer Center; [8]Mayo Clinic Cancer Center; [9]Moffitt Cancer Center; [10]Stanford Cancer Institute; [11]University of Alabama at Birmingham Comprehensive Cancer Center; [12]University of Wisconsin Carbone Cancer Center; [13]Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [14]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [15]University of Colorado Cancer Center; [16]UCSF Helen Diller Family Comprehensive Cancer Center; [17]Fox Chase Cancer Center; [18]UC San Diego Moores Cancer Center; [19]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [20]University of Michigan Rogel Cancer Center; [21]Memorial Sloan Kettering Cancer Center; [22]Vanderbilt-Ingram Cancer Center; [23]Roswell Park Comprehensive Cancer Center; [24]Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; [25]City of Hope National Medical Center; [26]Huntsman Cancer Institute at the University of Utah; [27]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; and [28]National Comprehensive Cancer Network.

*Provided content development and/or authorship assistance.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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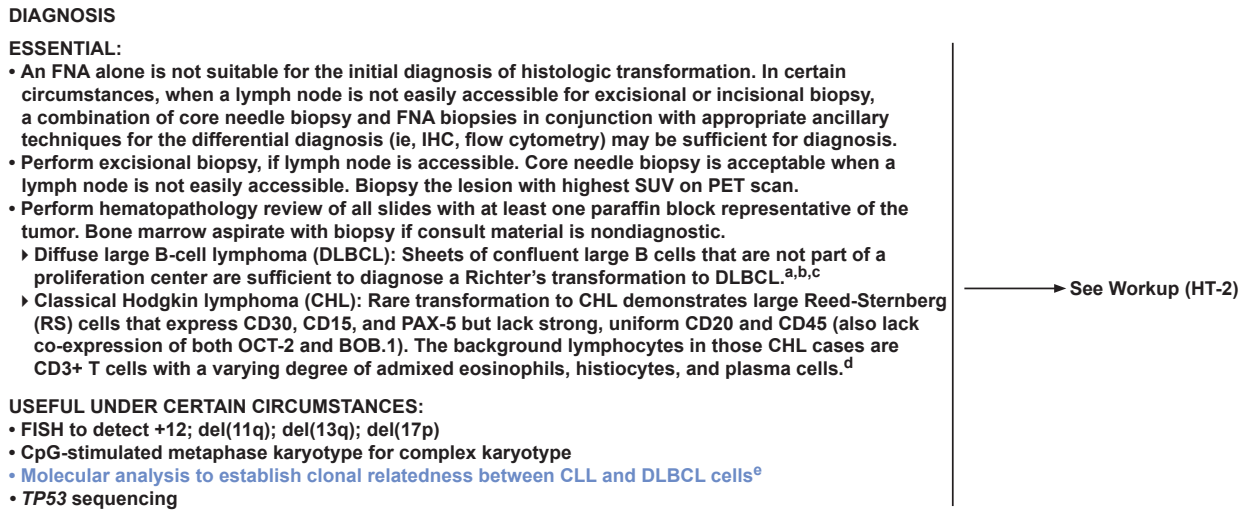


[a]While occasionally an increase in proliferative rate can be shown with Ki-67, this is not considered diagnostic of a transformation.
[b]Proliferation centers in CLL may express c-MYC and/or cyclin D1. This does not change the diagnosis.
[c] First, "CLL with expanded proliferation centers" or "accelerated CLL" may be diagnosed in cases where proliferation centers in CLL are expanded or fuse together (>20x field or 0.95 mm^2) AND show Ki-67 proliferative rate >40% or >2.4 mitoses/proliferation center. Second, progression to "CLL with increased prolymphocytes" or "CLL/PLL" may occur when there are increased prolymphocytes in the blood (>10%–<55%). Neither of these findings should be considered a transformation event, but rather as progression of CLL. B-PLL should be reserved for the diagnosis of de novo leukemias that are not associated with CLL.
[d]If morphologic RS cells are identified but the background cells are still the B cells of CLL, an EBV stain such as EBER should be performed. EBV infection of CLL can produce RS-like proliferations, but the background cells are still CLL and not the reactive mix typically seen in Hodgkin lymphoma. These cases should NOT be considered a Richter's transformation event.
[e]*IGHV* sequencing of CLL and histologically transformed tissue should be done to establish the clonal relationship.

Histologic Transformation (Richter's) and Progression

Overview

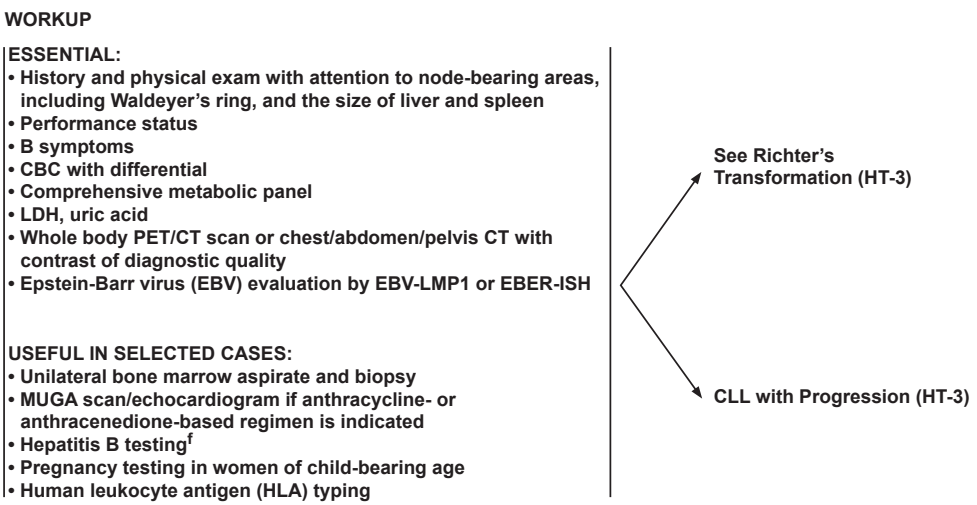
Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) constitutes approximately 7% of newly diagnosed cases of non-Hodgkin's lymphoma.[1] CLL remains the most prevalent adult leukemia in Western countries. In 2018, an estimated 20,940 people were diagnosed with CLL and an estimated 4,510 people died of the disease in the United States.[2] CLL is generally characterized by an indolent disease course. Histologic transformation (also known as Richter's transformation) to more aggressive lymphomas, such as diffuse large B-cell lymphoma (DLBCL) or Hodgkin lymphoma (HL), occurs in approximately 2% to 10% of patients during the course of their disease and treatment.[3–5] Unlike CLL, clinical outcomes in patients with histologic transformation are exceedingly poor, with a pattern of no to minimal response to chemoimmunotherapy regimens and a median survival of 5 to 8 months.[6]

The exact mechanism of Richter's transformation is not well understood; however, it has been associated with molecular characteristics of the patients' CLL and their prior CLL-directed therapies. Molecular characteristics that have been associated with risk of developing Richter's transformation and that may be linked to the pathogenesis of the disease include[7–14]:

- Unmutated immunoglobulin heavy-chain variable (*IGHV)* status
- Stereotyped B-cell receptor subset 8 combined with *VH4-39* use
- Cytogenetic abnormalities detected by fluorescence in situ hybridization, such as del(17p) and complex karyotype (≥3 clonal chromosome abnormalities)
- Genetic abnormalities, such as *NOTCH1* mutation, *C-MYC* activation, and inactivation of *TP53* or *CDKN2A/B*

However, none of these markers is sufficiently predictive to allow for individualized risk prediction.

Incidence of Richter's transformation increases with the number of prior chemoimmunotherapy regimens, and the rate is higher in patients treated with a combination of purine nucleoside analogs and alkylating agents.[9] Richter's transformation has also been reported after treatment with the novel agents ibrutinib and venetoclax.[15–17] Unlike progressive CLL, Richter's transformation developing after treatment with ibrutinib lacked



[f]Hepatitis B testing is indicated because of the risk of reactivation during treatment (eg, immunotherapy, chemoimmunotherapy, chemotherapy, targeted therapy). Tests include HBsAg and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

HT-2

resistance to *BTK* and *PLCG2* mutations.[16] Although the rate of transformation during venetoclax therapy was significantly higher among patients with heavily pretreated del(17p) CLL, it was less common among a broader group of patients with less heavily pretreated relapsed/refractory CLL.[17] Further study is needed to determine the exact risk profile and mechanism of Richter's transformation.

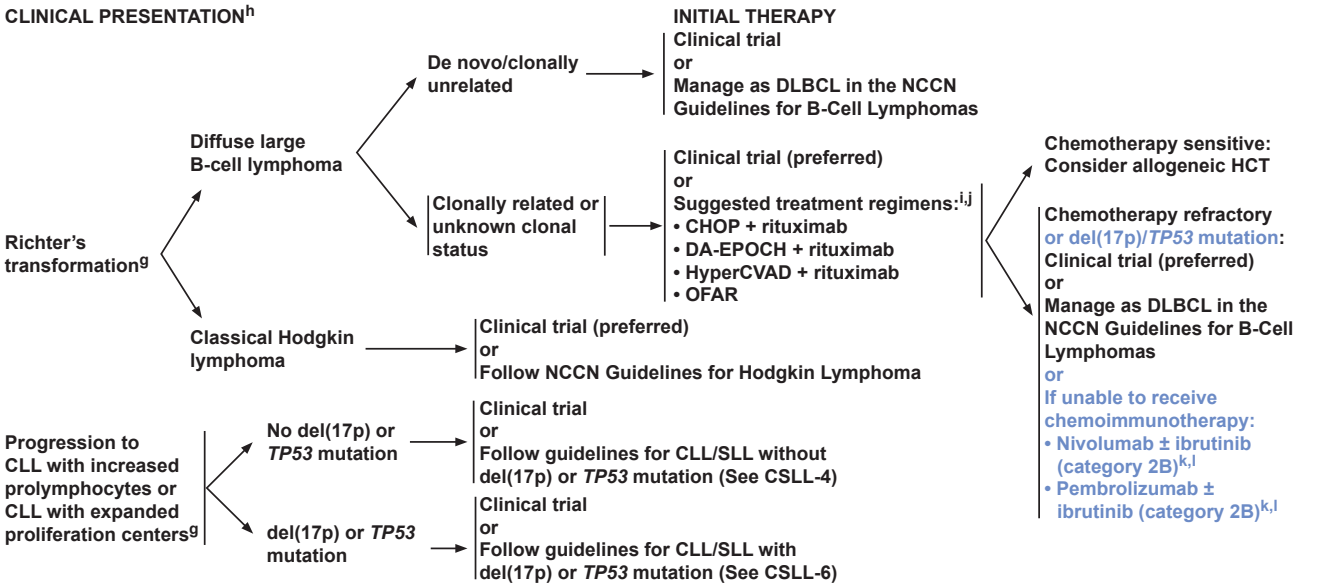
CLL with expanded proliferation centers (accelerated CLL) may be diagnosed when proliferation centers in CLL are expanded or fuse together and show a high Ki-67 proliferative rate (>40%). Progression to CLL with increased prolymphocytes (CLL-PLL) may occur when there are increased prolymphocytes in the blood (>10% to <55%). Neither of these findings are considered to be Richter's transformation, but rather progression of CLL, associated with a more aggressive disease course.[18]

Diagnosis and Workup

The diagnosis of Richter's transformation should be confirmed by excisional lymph node biopsy (if lymph node is accessible). Core needle biopsy is acceptable, when excisional or incisional lymph node biopsy is not feasible (see HT-1, opposite page).

The workup of patients with Richter's transformation or progression is similar to that of patients with CLL/SLL and should include history and physical examination with attention to node-bearing areas, including Waldeyer ring, and the size of liver and spleen; whole-body PET/CT scan; or chest/abdominal/pelvic CT with contrast of diagnostic quality. PET/CT scans are recommended to identify the optimal site for nodal biopsy, and biopsies should be directed to lesions with the highest FDG uptake on PET scans (see HT-2, on this page).[19–22] A maximum standardized uptake value (SUV_{max}) ≥10 on PET scan has been shown to be a valid marker to distinguish Richter's transformation from CLL among patients not treated with kinase inhibitor therapy.[23] However, PET SUV_{max} ≥10 alone lacks both sensitivity and specificity to distinguish Richter's transformation from CLL in patients who develop Richter's transformation while on ibrutinib.[24] Tissue biopsy is required for the definitive diagnosis of Richter's transformation. PET alone is insufficient.

Epstein-Barr virus (EBV) infection has been reported in 16% of patients with Richter's transformation and is associated with a poor outcome.[25] EBV infection can produce Reed-Sternberg (RS)–like proliferations, and presence of morphologic RS cells in a CLL background should not be considered as Richter's transformation. However, RS-like



[g]"Accelerated CLL," "CLL with expanded proliferation centers," and "CLL-PLL or CLL with increased prolymphocytes" (defined on HT-1) are not considered Richter's transformation, but are associated with more aggressive disease and poorer outcome [Gine E, et al, Haematologica 2010 Sept;95(9):1526-1533; Ciccone M, et al, Leukemia 2012;26:499-508; WHO 2016]. Optimal management for these cases has not been established.

[h]For T-cell prolymphocytic leukemia, see NCCN Guidelines for T-Cell Lymphomas.

[i]Richter's transformation to DLBCL (clonally related or unknown clonal status) is generally managed with treatment regimens recommended for DLBCL. However, these regimens typically result in poor responses.

[j]See references for regimens (HT-A).

[k]See Special Considerations for Use of Small-Molecule Inhibitors (CSLL-F).

[l]The panel acknowledged that there is a paucity of data for the use of these regimens in patients with Richter's transformation refractory to chemotherapy or in patients with a del(17p)/*TP53* mutation; however, these regimens may be considered given the limited options available for these patients. Additional data will be forthcoming.

HT-3

cells in a background of CLL may progress to classical HL in some patients.[26] Biopsy specimen should be evaluated for EBV infection using latent membrane protein 1 (LMP1) staining or in situ hybridization of EBV-encoded RNA (EBER-ISH).

DLBCL arising from CLL can either be clonally unrelated (21%) or clonally related (79%) to CLL.[8] Richter's transformation to clonally unrelated DLBCL is characterized by a significantly lower prevalence of *TP53* mutations/deletions and a significantly longer median survival than clonally related DLBCL (62 vs 14 months).[8] Most patients with Richter's transformation to clonally related DLBCL carry unmutated *IGHV*.[27] Molecular analysis is useful to establish the clonal relationship between baseline CLL tumor cells and histologically transformed tumor cells (see HT-1, page 14). *IGHV* gene sequencing or clonal *IGHV* rearrangements can be used to establish the clonal relationship between CLL and histologically transformed tumor cells.[8,27]

Treatment

Richter's Transformation to DLBCL

Richter's transformation to clonally unrelated DLBCL should be managed similar to de novo DLBCL, as outlined in the NCCN Guidelines for B-Cell Lymphomas (available at NCCN.org).

For Richter's transformation to clonally related (or unknown clonal status) DLBCL, enrollment in a clinical trial is the preferred initial treatment option (see HT-3, above). In the absence of a suitable clinical trial, chemoimmunotherapy regimens recommended for DLBCL can be used; however, these regimens typically result in poor responses.[6] Elevated platelet counts, higher hemoglobin levels, lower beta-2-microglobulin levels and lower lactate dehydrogenase levels have been identified as independent predictors of higher response rates to chemoimmunotherapy.[6] However, the use of these prognostic variables for selection of therapy for Richter's transformation has not yet been established. Evidence (mostly from single-arm phase I/II studies) to support the use of chemoimmunotherapy regimens for DLBCL arising from CLL are discussed further and are also summarized in Table 1.

In a phase II trial conducted by the German CLL Study Group that included 15 patients with Richter's transformation, R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone), resulted in an overall response rate (ORR) of 67% (7% complete re-

SUGGESTED TREATMENT REGIMENS
REFERENCES

DA-EPOCH-R

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HyperCVAD + rituximab

Tsimberidou AM, Kantarjian HM, Cortes J, et al. Fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone plus rituximab and granulocyte-macrophage-colony stimulating factor (GM-CSF) alternating with methotrexate and cytarabine plus rituximab and GM-CSF in patients with Richter syndrome or fludarabine-refractory chronic lymphocytic leukemia. Cancer 2003;97:1711-1720.

Tsimberidou AM, O'Brien S, Khouri I, et al. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. J Clin Oncol 2006;24:2343-2351.

OFAR

Tsimberidou AM, Wierda WG, Plunkett W, et al. Phase I-II study of oxaliplatin, fludarabine, cytarabine, and rituximab combination therapy in patients with Richter's syndrome or fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2008;26:196-203.

Tsimberidou AM, Wierda WG, Wen S, et al. Phase I-II clinical trial of oxaliplatin, fludarabine, cytarabine, and rituximab therapy in aggressive relapsed/refractory chronic lymphocytic leukemia or Richter syndrome. Clin Lymphoma Myeloma Leuk 2013;13:568-574.

RCHOP

Tsimberidou AM, O'Brien S, Khouri I, et al. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. J Clin Oncol 2006;24:2343-2351.

HCT

Cwynarski K, van Biezen A, de Wreede L, et al. 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. J Clin Oncol 2012;30:2211-2217.

Nivolumab

Jain N, Basu S, Thompson PA, et al. Nivolumab combined with Ibrutinib for CLL and Richter transformation {abstract]: A Phase II Trial. Blood 2016;128:Abstract 59.

Younes A, Brody J, Carpio C, et al. Safety and efficacy of the combination of ibrutinib and nivolumab in patients with relapsed non-Hodgkin lymphoma or chronic lymphocytic leukemia [abstract]. Blood 2017;130:Abstract 833.

Pembrolizumab

Ding W, LaPlant BR, Call TG, et al. Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. Blood 2017;129:3419-3427.

HT-A

sponse [CR]).[28] After a median follow-up of 69 months, the median progression-free survival (PFS) and overall survival (OS) were 10 and 21 months, respectively. Hematologic toxicities and infections were the most common adverse events.

In a single-institution retrospective cohort study of 46 patients with Richter's transformation treated with R-EPOCH (rituximab/etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin), the ORR was 39% (17 of the 44 patients evaluable for treatment response).[29] After a median follow-up of 39 months, median PFS and OS were 4 and 6 months, respectively. Complex karyotype was associated with significantly shorter PFS and OS. The estimated 1-year OS rate was 71% for patients without a complex karyotype.

The modified R-hyperCVAD regimen (rituximab/cyclophosphamide/vincristine/liposomal daunorubicin/dexamethasone alternating with methotrexate + cytarabine) with growth factor support was also active in patients with Richter's transformation (n=30), resulting in an ORR of 43% (27% CR), and the 1-year OS rate was 28%.[30] However, it was associated with significant toxicity (grade 3 neutropenia was the most common hematologic toxicity) and was not more effective than an alternate hyperCVAD regimen (did not include methotrexate, cytarabine, rituximab, or growth factor support) that was evaluated in an earlier study.[31]

The OFAR regimen (oxaliplatin/fludarabine/cytarabine/rituximab) at different dosing schedules has also been evaluated in patients with Richter's transformation. In a phase I/II trial that included 20 patients with Richter's transformation, OFAR (with increasing doses) resulted in an ORR of 50%.[32] The median response duration was 10 months. After a median follow-up of 9 months, the 6-month OS rate was 53% and the survival rate was higher for patients achieving CR or partial response (PR). A modified OFAR regimen with reduced-dose cytarabine resulted in an ORR of 39% (7% CR), in a phase I/II study that included 35 patients with Richter's transformation. With a median follow-up of 26 months, median survival was 7 months and the 2-year OS rate was 20%.[33] Grade 3/4 neutropenia and thrombocytopenia were the most common hematologic toxicities, occurring in 80% of patients, with both schedules of the OFAR regimen.

R-CHOP, R-EPOCH, R-hyperCVAD, and OFAR are included as options for chemoimmunotherapy, based on available data from clinical trials discussed earlier (see HT-3, opposite page).

Table 1. Chemoimmunotherapy for Richter's Transformation

Regimen	N	Median Follow-Up	ORR	Median PFS	Median OS
R-CHOP[28]	15	69 mo	67% (7% CR)	10 mo	21 mo
R-EPOCH[29]	46	39 mo	39%	4 mo	6 mo
R-hyperCVAD[30]	30	8 mo	43% (27% CR)		1-y OS rate: 28%
OFAR[32]	20	9 mo	50%		6-mo OS rate: 53%
Modified OFAR[33]	35	26 mo	39% (7% CR)		7 mo 2-y OS rate: 20%

Abbreviations: CR, complete response; OFAR, oxaliplatin/fludarabine/cytarabine/rituximab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; R-EPOCH, rituximab/etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin; R-hyperCVAD, rituximab/cyclophosphamide/vincristine/liposomal daunorubicin/dexamethasone alternating with methotrexate and cytarabine.

Allogeneic hematopoietic cell transplant (alloHCT) can be considered for patients with disease responding to initial chemoimmunotherapy.[6,34,35] In a nonrandomized comparative analysis, the estimated cumulative 3-year survival rate was significantly higher (75%) for patients who underwent alloHCT after achieving a CR or PR to initial therapy compared with those who responded to initial therapy but did not undergo alloHCT, or who underwent alloHCT for relapsed or refractory Richter's transformation (75% vs 27% and 21%, respectively; *P*=.019).[6] In a retrospective analysis that evaluated the outcome after autologous HCT or alloHCT in 59 patients with Richter's transformation, the 3-year estimated OS, relapse-free survival, and cumulative incidences of relapse and nonrelapse mortality rates were 36%, 27%, 47%, and 26%, respectively, for alloHCT, and 59%, 45%, 43%, and 12%, respectively, for autologous HCT.[34] In a multivariate analysis, chemotherapy-sensitive disease and reduced-intensity conditioning were found to be associated with superior relapse-free survival after alloHCT. Autologous HCT may also be appropriate for patients with disease responding to initial therapy but are not candidates for alloHCT due to age, comorbidities, or lack of a suitable donor.[34]

There are no effective treatment options for patients with Richter's transformation refractory to chemoimmunotherapy. Enrollment in a clinical trial is the preferred treatment option, if available. Preliminary data from ongoing clinical trials suggest that anti–PD-1 monoclonal antibodies (nivolumab and pembrolizumab) have promising activity in patients with Richter's transformation.[36–38] In a phase I/II study that included 20 patients with Richter's transformation, nivolumab + ibrutinib resulted in an ORR of 60% (CR, 5% and PR, 55%)[37]; median PFS was 4 months. Diarrhea (31%), pyrexia (23%), and fatigue (23%) were the most common treatment-related grade 1/2 adverse events. Incidence of grade 3/4 febrile neutropenia and anemia were reported in 5% and 20% of patients, respectively. In a phase II study of 25 patients (16 with relapsed CLL and 9 with Richter's transformation to DLBCL), use of pembrolizumab as a single agent resulted in an objective response rate of 44% in patients with Richter's transformation. Median PFS and OS were 5 and 11 months, respectively.[38] Treatment-related grade ≥3 adverse events were reported in 60% of patients. Thrombocytopenia (20%), anemia (20%), neutropenia (20%), and dyspnea and hypoxia (8% each) were the most common grade 3/4 adverse events.

The panel acknowledged that there are limited published data supporting the use of nivolumab and pembrolizumab in patients with Richter's transformation refractory to chemoimmunotherapy or in those with a del(17p)/*TP53* mutation, and that additional data will be forthcoming. However, some panel members felt that given the unmet clinical need and the lack of effective treatment options, inclusion of PD-1 monoclonal antibodies (nivolumab and pembrolizumab) as a treatment option is reasonable (based on the data discussed earlier) for patients with Richter's transformation refractory to chemoimmunotherapy (especially if considering alloHCT). Some panel members also pointed out that these agents would also be appropriate as an initial treatment option for patients with del(17p) or *TP53* mutation and those who are unable to receive chemoimmunotherapy regimens. Few panel members felt that monotherapy with PD-1 monoclonal antibodies (nivolumab or pembrolizumab) is not an effective treatment option for patients with relapsed or refractory Richter's transformation outside of a clinical trial, citing a recent report in which the use of PD-1 monoclonal antibodies for the treatment of relapsed or refractory Richter's transformation in a nontrial population (10 patients with biopsy-proven Richter's transformation to DLBCL, all of whom had received prior therapy with Bruton's tyrosine kinase inhibitors) was associated with poor efficacy and a short time to treatment failure.[39]

Nivolumab and pembrolizumab with or without ibrutinib is included as an option with a category 2B recommendation for patients unable to receive chemoimmunotherapy, with del(17p) or *TP53* mutation, or with chemoimmunotherapy-refractory disease (see HT-3, page 16).

Richter's Transformation to HL

Histologic transformation to HL is clinically less aggressive than Richter's transformation to DLBCL, but is as-

sociated with a poorer prognosis than de novo HL.[4,5,40] Richter's transformation to HL should be managed as outlined in the NCCN Guidelines for HL (available at NCCN.org). ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine) was the most commonly used regimen, resulting in an ORR of 68%, and achievement of CR to the ABVD regimen was the most important factor predicting survival among patients with Richter's transformation to HL.[41,42]

CLL-PLL or Accelerated CLL

Enrollment in a clinical trial is the recommended treatment option, because the optimal management is not established. In the absence of a suitable clinical trial, CLL-PLL should be managed with treatment options outlined for CLL/SLL based on the presence or absence of del(17p) or *TP53* mutation.

Summary

Histologic transformation of CLL to more aggressive lymphomas is associated with a poor prognosis. Histologic transformation to HL is managed with chemotherapy regimens used for the treatment of de novo HL. DLBCL arising from CLL can either be clonally unrelated or clonally related to CLL. Chemoimmunotherapy followed by alloHCT (in patients achieving response to initial therapy) is the standard treatment approach for the management of histologic transformation to DLBCL. However, chemoimmunotherapy regimens typically result in poor responses. Nivolumab and pembrolizumab with or without ibrutinib are reasonable treatment options for patients with del(17p) or *TP53* mutation or those with chemotherapy-refractory disease. Precise diagnosis of histologic transformation and enrollment in clinical trials evaluating novel agents targeting the specific genetic abnormalities implicated in the pathogenesis of histologic transformation will improve the clinical outcomes of patients with histologic transformation.

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Erratum

In the NCCN Guidelines Insights for Small Cell Lung Cancer, Version 2.2018, published in the October 2018 issue of JNCCN (2108;16:1171–1182), the author list was missing the name Jacob Sand, MD. Dr. Sand's affiliation is Dana Farber/Brigham and Women's Cancer Center.

The editorial office apologizes for this error. A corrected copy of the article is available online at JNCCN.org.

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