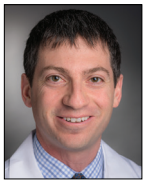
CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Management of Richter Transformation



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H&O How often does chronic lymphocytic leukemia (CLL) transform into aggressive lymphoma?

MD Transformation of CLL into aggressive lymphoma, known as Richter transformation (RT), is relatively uncommon. During the chemotherapy era of CLL treatment, the rate of RT in patients on active treatment was approximately 3% to 4%. The rate of RT remains similar in the current era of targeted therapy.

H&O What forms can this transformation take?

MD The most common form of transformation by far is into diffuse large B-cell lymphoma (DLBCL). Less common forms of transformation are Hodgkin lymphoma and plasmablastic lymphoma; there is also the possibility of a transformation-like event in which CLL morphs into B-cell prolymphocytic leukemia.

H&O How does the management of DLBCL after CLL differ from that of de novo DLBCL?

MD The standard treatment for patients with de novo DLBCL is an anthracycline-based combination chemoimmunotherapy regimen, most often rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). A similar but slightly more-intensive regimen called dose-adjusted R-EPOCH, which contains etoposide, is sometimes used. However, R-CHOP is the most common treatment. We use the same regimens in patients with RT (Figure),[1] but these treatments are less effective in patients with RT. In de novo DLBCL, approximately 60% to 65% of patients experience a cure with R-CHOP or R-EPOCH. In RT, only about 20% to 30% of patients will experience a complete response (CR) with R-CHOP or R-EPOCH, and most of them will eventually experience a relapse.

The recent US Food and Drug Administration approval of polatuzumab vedotin (Polivy, Genentech) in the frontline setting has led to a modified regimen of R-CHOP called pola-R-CHP, in which polatuzumab vedotin replaces vincristine. Pola-R-CHP has become a new standard of care for many patients with de novo DLBCL, but this regimen has not yet made its way to RT outside of clinical trials.

Several ongoing studies are looking at new combination regimens to treat patients with RT.

H&O What new approaches are being investigated for the management of RT?

MD Several ongoing studies are looking at new combination regimens to treat patients with RT. One approach is chemosensitization, in which an agent is added to chemotherapy to try to make the Richter cells more sensitive to treatment. In a phase 2 trial published last year in *Blood*, we combined the BCL2 inhibitor venetoclax (Venclexta, AbbVie/Genentech) with R-EPOCH (VR-EPOCH) in

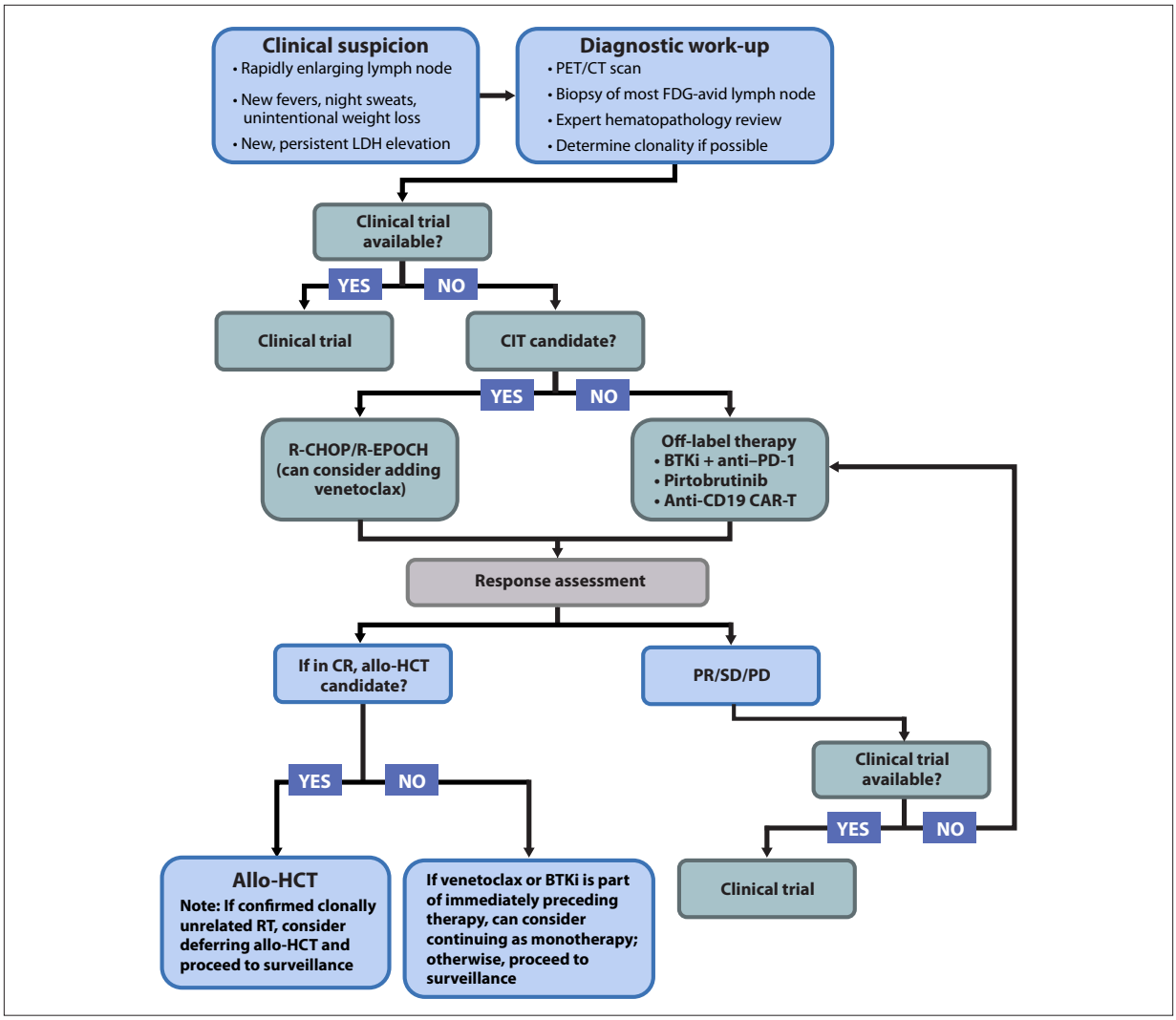

Figure. Summary of the practical management of Richter transformation in 2023.

allo-HCT, allogeneic hematopoietic stem cell transplant; BTKi, Bruton tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell therapy; CIT, chemoimmunotherapy; CR, complete response; FDG, fluorodeoxyglucose; LDH, lactate dehydrogenase; PD, progressive disease; PD-1, programmed death 1; PET/CT, positron emission tomography/computed tomography; PR, partial response; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; RT, Richter transformation; SD, stable disease.

Republished with permission from Ryan CE, Davids MS. Practical management of Richter transformation in 2023 and beyond. *Am Soc Clin Oncol Educ Book*. 2023;43:e390804.[1]

26 patients with RT.[2] The trial demonstrated good efficacy compared with historical results with R-EPOCH alone. At a median follow-up of 17 months, 13 patients (50%) achieved a CR and 11 patients achieved undetectable measurable residual disease for CLL in bone marrow. Unfortunately, this aggressive chemotherapy regimen also had a fair amount of toxicity, with grade 3 or higher neutropenia in 65% of patients, grade 3 or higher thrombocytopenia in 50%, and febrile neutropenia in 38%. A second arm of this trial consists of venetoclax plus R-CHOP (VR-CHOP) for patients with RT. In results that I presented in June at the International Conference on Malignant Lymphoma (ICML) in Lugano, Switzerland, we found that the CR rate with VR-CHOP was similar to that with VR-EPOCH, at 48%, but the toxicities of the regimen were milder. For example, grade 3 or higher neutropenia was seen in only 36% of patients.[3] The VR-CHOP study arm is ongoing, but so far, the efficacy appears to be similar to that seen in our prior experience with VR-EPOCH, with a bit less toxicity.

Another trial that is looking at an addition to chemoimmunotherapy is the ongoing phase 2 STELLAR trial in the United Kingdom, which is comparing R-CHOP alone vs R-CHOP plus the Bruton tyrosine kinase (BTK) inhibitor acalabrutinib (Calquence, AstraZeneca) in patients with RT (NCT03899337). I believe this is the first randomized phase 2 trial to be conducted in RT, so this is a very important study, and we eagerly await the results.

Another approach to the management of RT is checkpoint inhibition. An industry-sponsored trial that was published by Younes and colleagues in *Lancet Hematology* in 2019 produced some promising initial data on nivolumab (Opdivo, Bristol Myers Squibb) plus ibrutinib (Imbruvica, Pharmacyclics/Janssen) in patients with relapsed non-Hodgkin lymphoma or CLL.[4] Earlier this year, Dr Nitin Jain published data in *Blood Advances* on an investigator-initiated, phase 2 trial with nivolumab plus ibrutinib in 24 patients with RT.[5] This trial also produced promising results, with 10 RT patients (42%) responding to treatment and a median duration of response of 15 months. The response rate was even higher among the 14 patients who had not received prior therapy for RT; 7 (50%) of these patients responded, compared with 3 of the 10 (30%) patients who had received prior therapy for RT.

Other immune-based approaches to RT include chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies. As we await prospective data on CAR T-cell therapy in RT, a 2020 retrospective study by Kittai and colleagues found that 5 of 9 patients with RT who received CAR T-cell therapy with axicabtagene ciloleucel (Yescarta, Kite) experienced a CR.[6] Additionally, the phase 2 ZUMA-25 study, which is looking at the use of brexucabtagene autoleucel (Tecartus, Kite) in adults with rare B-cell malignancies, includes patients with RT (NCT05537766). We look forward to seeing results from this trial.

Regarding bispecific antibodies, data from the phase 1b/2 EPCORE CLL-1 trial presented at the 2022 American Society of Hematology (ASH) annual meeting demonstrated that the anti-CD20/anti-CD3 bispecific antibody epcoritamab was active in 10 patients, of whom 5 had a CR.[7] In addition, we saw similar data from Carlo-Stella and colleagues at the 2023 ICML meeting with the bivalent anti-CD20/anti-CD3 bispecific antibody glofitamab, in which 5 of 11 patients treated achieved a CR.[8]

Another interesting approach is the use of noncovalent BTK inhibitors, such as pirtobrutinib (Jaypirca, Lilly), which is approved for use in relapsed or refractory mantle cell lymphoma. The global phase 1/2 BRUIN trial of pirtobrutinib included a RT cohort. In a presentation by Dr William Wierda at the 2022 ASH annual meeting, the overall response rate (ORR) was 52% for the 75 response-evaluable patients and 50% for the 68 patients previously treated for RT.[9] These data suggest that pirtobrutinib shows some activity in RT and may be a good agent to partner with other treatments.

Also of note, at the most recent American Society of Clinical Oncology annual meeting, we saw some updated data from the phase 2 MOLTO study that is looking at triplet therapy with the programmed death ligand 1 antibody atezolizumab (Tecentriq, Genentech) plus venetoclax and the anti-CD20 monoclonal antibody obinutuzumab (Gazyva, Genentech) in previously untreated RT.[10] Dr Anna Maria Frustaci presented data on 28 patients that showed an ORR at cycle 6 of 67.9%, including a CR rate of 28.6%.

Disclosures

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