Leukemia insights

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THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

In this month's Leukemia Insights newsletter, written by Philip A. Thompson, M.B., B.S. (Hons) and William Wierda, M.D., Ph.D., and sponsored in part by the Charif Souki Cancer Research Fund, we outline clinical trials offered for the treatment of Richter Transformation. Learn more about our Leukemia program.

Treatment for Richter Transformation – finally, a new hope emerges

Richter transformation (RT) is classically a morphologic transformation of chronic lymphocytic leukemia (CLL) into diffuse large B cell lymphoma (DLBCL), with aggressive clinical characteristics and course. Less commonly, transformation can be to Hodgkin lymphoma, which has a better prognosis. Rare cases of transformation to other aggressive histological subtypes have been reported.

The most common scenario is for a patient previously treated for CLL to have a rapidly enlarging lymph node, progressive symptoms of fatigue, rising LDH, and, occasionally, rising serum calcium. Clinical suspicion should prompt evaluation with PET-CT to identify hypermetabolic lymph node(s) amenable to biopsy. Histologic review is critical; therefore, core or excisional biopsy is essential. Additionally, molecular assessment of RT cells from tissue sample is important to determine clonal relationship to the CLL. Patients with previously untreated CLL that transformed have what is referred to as *de novo* disease, which has better prognosis with standard chemoimmunotherapy for DLBCL. Increased risk for RT has been associated with CLL with del(17p), mutated *TP53*, complex karyotype, del(11q), and mutated *NOTCH1*. Risk for RT also has been thought to be related to exposure to genotoxic chemotherapy, however, it is seen even among patients treated only with novel targeted agents, indicating the risk more likely related to factors intrinsic to the CLL cells and genomic instability.

Historically, treatment of the DLBCL sub-type of RT was with chemoimmunotherapy (CIT) containing rituximab, commonly R-CHOP, and outcomes were universally poor, with complete remission (CR) rates of approximately 20% and few long-term survivors.

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It's the easiest way to stay current with information on the latest leukemia news, research, and resources. View archived issues.

CONTACT OUR STAFF

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A small minority of patients are eligible for potentially curative allogeneic stem cell transplant, given both low response rates to CIT and the fact that the majority of patients with RT are >70 years of age and have co-morbidities.

In the past 15 years, attempts to improve outcomes for patient with RT centered on intensification of CIT with regimens such as R-EPOCH, R-hyper-CVAD and OFAR. But these strategies have not improved progression-free survival and overall survival, as marginal increases in remission rates were offset by increased toxicity and rapid relapse.

RT is molecularly distinct from *de novo* DLBCL, with more than half of patients with RT having del(17p) and/or mutated *TP53*. These are strong negative prognostic markers and predict for chemoresistance. As treatment options expand, it is more critical than ever to genetically characterize the disease prior to therapy. In particular, the 20% of patients with clonally unrelated DLBCL and patients without *TP53* mutations have significantly better outcomes and may be best served by CIT-based treatments.

Advances in past 5 years have provided hope for better outcomes. The two main milestones are the discovery that treatment with PD1 monoclonal antibodies (mAbs) +/- ibrutinib induces responses in 40%-60% of patients (up to 35% complete remission rate) and the finding that the addition of the BCL2 inhibitor venetoclax to R-EPOCH improves CR rate to approximately 50%. In addition, cellular therapy is producing promising data based on a report from Israel at the American Society of Hematology (ASH) 2020, where 5 of 8 patients achieved CR after CAR T-cell therapy.

Below, we outline several clinical trials at MD Anderson Cancer Center. Importantly, we now have several chemotherapy-free approaches, which work by *TP53*-independent mechanisms and may be better tolerated by older and unfit patients.

R-CHOP + venetoclax (NCT03054896)

The addition of venetoclax to R-EPOCH increased complete remission rate to 50% from a historical 20% with R-EPOCH alone. However, as noted above, many patients with RT are older and have co-morbidities that limit tolerability of intensive chemotherapy regimens. RT is, in most cases, an intrinsically chemotherapy-resistant disease, but the addition of venetoclax appears to sensitize RT cells to chemotherapy-mediated killing. The combination of venetoclax with theless intensive chemotherapy backbone of R-CHOP may achieve similar results with less toxicity. Venetoclax is provided at no cost.

Venetoclax + obinutuzumab + atezolizumab (NCT02846623)

Previously at MD Anderson, we evaluated the combination of ibrutinib and nivolumab in patients with RT, and achieved an overall response rate of 43% and CR rate of 35% in RT. Expression of PD1 on T cells (and, intriguingly, on tumor cells) correlated with response. Atezolizumab is a PD-L1 inhibitor, and preliminary data from the first 8 patients on this study, which will be submitted to ASH this year, suggest a high CR rate. This is a chemotherapy-free approach, which may be better tolerated by older and unfit patients. Venetoclax, obinutuzumab and atezolizumab are provided at no cost.

Pirtobrutinib (LOXO-305) (NCT03740529)

Pirtobrutinib is a novel, highly selective and reversible inhibitor of Bruton's tyrosine kinase (BTK), which is potent and has favorable tolerability and pharmacokinetics. Encouraging initial single-agent data in RT were reported in the Phase I BRUIN study, with 6 of 9 patients responding to treatment. These patients had a median of 6 prior treatments, and all had previously received an irreversible BTK inhibitor.

Notably, the drug has so far demonstrated a very favorable adverse event profile, with an only 1% incidence of atrial fibrillation and a <1% incidence of major hemorrhage. The BRUIN study is open to patients with RT. Pirtobrutinib is provided at no cost.

VLS-101 (NCT03833180)

VLS-101 is an ROR1-targeted mAb-drug conjugate with a monomethyl auristatin E payload that demonstrated high response rates in relapsed/refractory mantle cell lymphoma and DLBCL. Dose-dependent peripheral neuropathy and neutropenia were observed, but the drug is generally well-tolerated. The study continues to enroll patients with RT, with encouraging preliminary responses. VLS-101 is provided at no cost.

PBCAR0191 (Off the shelf CD19-CAR-T) (NCT03666000)

Most studies of CAR T-cells in DLBCL have excluded patients with RT. However, recent data from Israel in a small number of patients demonstrated complete responses, similar to that seen in *de novo* DLBCL. PBCAR0191 is an off-the-shelf, allogeneic CAR –T-cell directed against CD19. The major advantage of an allogeneic product is quick availability for patients who often have rapidly progressive disease. Additionally, CAR T-cells produced from patients with heavily pretreated CLL are often exhausted and dysfunctional. The CD19-CAR-T product was created from healthy donors may well overcome productions limitation of the autologous CD19 CAR T-cell strategies. PBCAR0191 is provided at no cost.

Nivolumab, ipilumumab, ibrutinib (NCT04781855)

Immune checkpoint blockade has been successfully utilized in treatment for a variety of solid tumors. Phase II data from a previous study of ibrutinib + nivolumab in RT showed an overall response rate of 43% in 23 patients; furthermore, most responses were complete remissions. This study has been amended to add ipilimumab, a CTLA4 mAb. The hope is that this will enhance efficacy, akin to the improved results with ipilimumab and nivolumab relative to nivolumab monotherapy in melanoma. This study will be open to enrollment in the near future. Nivolumab and ipilimumab will be provided at no cost.

Announcements

2021 Texas Myeloproliferative Neoplasms (MPN) Virtual Workshop

Join Mays Cancer Center, home to UT Health San Antonio MD Anderson, for the Second Annual 2021 Texas Myeloproliferative Neoplasms (MPN) Virtual Workshop on August 19-20, 2021. The focus of this workshop is to bring together medical experts in the field of MPNs to discuss the many new research and therapy options in development for MPN patients. Register for free.

9th Annual Society of Hematologic Oncology (SOHO) Meeting

The ninth annual meeting of the Society of Hematologic Oncology (SOHO 2021) is scheduled for September 8-11, 2021 at the Hilton Americas in Houston, Texas. Hematology/oncology specialists from around the world will gather at the event. Note that SOHO 2021 is designed as a hybrid event, so all content will be available on the SOHO virtual platform for those unable to travel. In addition, there are virtual options for abstract and poster presenters.

Note that SOHO members receive a significant discount on registration fees. SOHO membership is **FREE** for a limited time. Sign up now to receive a SOHO member discount code to apply towards your annual meeting registration fee. Click the following link to begin the secure registration process: https://www.soho2021.com/soho2021/registration

Cure of Leukemias in the Next Decade – A Realistic View

You are cordially invited to join our MD Anderson Cancer Center's Physician Advisory Council CME lecture session presented by Hagop M. Kantarjian, M.D. on September 9, 2021. This live activity has been approved for AMA PRA Category 1 Credits™. View the event flyer or register now.

Leukemia Faculty Contacts

Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress. View our faculty roster.

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