Leukemia insights

SEPTEMBER 2022

MONTHLY EDITION

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 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 histologic 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 a 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 a 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 is 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. Only 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.

ABOUT MyMDAnderson

myMDAnderson is a secure, personalized web site helping community physicians expedite patient referrals, as well as improve continuity of care through information access and streamlined communications.

Physicians who have referred patients to MD Anderson or plan to do so, can utilize the HIPAA-compliant features of myMDAnderson to:

- Refer a patient
- View your patient's appointments Access patient reports
- Send and receive secure messages

JOIN THE COVERSATION

Connect with us.

JOIN OUR MAILING LIST

If you would like to receive an electronic issue of the MD Anderson Leukemia Insights e-Newsletter on a monthly basis, please email us at Leukemia@mdanderson.org.

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

CONTACT OUR STAFF

Mary Alma Welch - Editor
Lisa Palacios - Publishing Editor
Leukemia@mdanderson.org

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 the 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 the 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 the less intensive chemotherapy backbone of R-CHOP may achieve similar results with less toxicity, and preliminary results are very encouraging in this regard. 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, presented at ASH 2021, demonstrated a very high CR rate. This chemotherapy-free approach may be better tolerated by older and unfit patients. Venetoclax, obinutuzumab and atezolizumab are provided at no cost.

Pirtobrutinib (LOXO-305) combined with venetoclax and obinutuzumab (NCT05536349)

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. A larger cohort will be presented at ASH this year, confirming these favorable response rates. The phase I BRUIN study is now closed. However, an investigator-initiated study combining pirtobrutinib, obinutuzumab and venetoclax will open soon at MD

Anderson. The hope is that synergy between pirtobrutinib and venetoclax will be achieved, with limited toxicity.

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 seen in approximately half of treated patients. VLS-101 is provided at no cost.

FT819 off the shelf CAR-T (NCT04629729)

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 5 of 8 complete responses in patients with refractory RT, a result similar to that seen in *de novo* DLBCL. Similar data have been published in a retrospective analysis from patients treated with commercial axicabtagene ciloleucel at the Ohio State University. FT819 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. FT819 is provided at no cost.

Nivolumab, ipilimumab, 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. The study is now enrolling, beginning with a 6-patient safety cohort of ibrutinib + ipilimumab, before enrolling the 3-drug combination cohort. Nivolumab and ipilimumab will be provided at no cost.

Epcoritamab

Epcoritamab is a novel bi-specific antibody (DuoBody®), targeting CD3 and CD20. It achieved an overall response rate of 69%, with 42% CR rate in patients with relapsed/refractory DLBCL (54% ORR and 34% CRR in patients with prior CAR-T cell therapy), which is very high in such a difficult-to-treat population. A Phase I study is ongoing evaluating epcoritamab in relapsed/refractory CLL and Richter's Syndrome. This study will soon open at MD Anderson.

Announcements

MD Anderson Cancer Center Leukemia Fellowship Accepting Applications

The goals of the Leukemia Fellowship Program are to train competent, qualified, caring and empathic physicians who are mindful of the significance of their role in the diagnosis and management of patients with the acute and chronic leukemias as well as myelodysplastic syndromes and myeloproliferative disorders.

The Leukemia Fellowship Program accepts applications for potential positions **August 1 through October 31, 2022**, with the program accepting a limited number of new fellows each year. Initially, a one-year commitment to the Program is required. Fellows in their first year may be considered for an additional year at their request.
The Leukemia Fellowship is non-standard and commences July 1 through June 30 and is recognized by the Texas Medical Board as an approved fellowship program. The program is affiliated with The University of Texas MD Anderson Cancer Center's Hematology/Oncology Fellowship which is accredited by ACGME.

For general inquires, please send an email to leuktrain@mdanderson.org or visit our Leukemia Fellowship page for additional information and requirements.

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.

Clinical Faculty

Kantarjian, Hagop	*Department Chair*	(713) 792-7026
Garcia-Manero, Guillermo	*Deputy Chair, Chief, Section of Translational Research, Chief, Section of Myelodysplastic Syndromes (MDS), and Director, Leukemia Clinical Fellowship Program*	(713) 745-3428
Wierda, William	*Deputy Chair, Chief, Section of Chronic Lymphocytic Leukemia (CLL), and Leukemia Center Medical Director*	(713) 745-0428
Andreeff, Michael	*Chief, Section of Molecular Hematology and Therapy, Center Medical Director, Bone Marrow Aspiration Clinic*	(713) 792-7261
Borthakur, Gautam	*Chief, Section of Developmental Therapeutics*	(713) 563-1586
Daver, Naval	*Director, Leukemia Research Alliance Program*	(713) 794-4392
DiNardo, Courtney D.	*Co-Leader, Section of Acute Myeloid Leukemia (AML), Co-Leader, Section of Developmental Therapeutics Leader, Hereditary Hematologic Malignancy Clinic*	(734) 358-1053
Ferrajoli, Alessandra	*Leukemia Center Associate Medical Director*	(713) 792-2063
Issa, Ghayas “Gus"	*Co-Leader, Section of Chronic Myeloid Leukemia (CML)*	(713) 745-8432
Jabbour, Elias	*Chief, Section of Acute Lymphoblastic Leukemia (ALL)*	(713) 792-4764
Jain, Nitin	*Director, Cellular Therapy Program*	(713) 745-6080
Kadia, Tapan	*Co-Leader, Section of Acute Myeloid Leukemia (AML), Co-Leader, Section of Developmental Therapeutics, Co-Leader, Leukemia Clinical Fellowship Program*	(713) 563-3534
Montalban Bravo, Guillermo	*Director, Chronic Myelomonocytic Leukemia (CMML) Program*	*(713) 792-4956*
Pemmaraju, Naveen	*Director, Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) Program*	*(713) 794-3604*
Ravandi, Farhad	*Chief, Section of Acute Myeloid Leukemia (AML)*	(281) 216-7806
Sasaki, Koji	*Co-Leader, Section of Chronic Myeloid Leukemia (CML)*	(713) 745-2882
Verstovsek, Srdan	*Chief, Section of Myeloproliferative Neoplasms (MPNs), Director, Clinical Research Center for MPNs*	(713) 745-3429

Leukemia Faculty Contacts *(continued)*

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.

Clinical Faculty

Abbas, Hussein	(713) 745-8433
Alvarado, Yesid	(713) 794-4364
Bose, Prithviraj	(713) 792-7747
Burger, Jan	(713) 563-1487
Chien, Kelly	(713) 745-7584
Kornblau, Steven	(713) 794-1568
Maiti, Abhishek	(346) 725-0901
Masarova, Lucia	(832) 750-4211
Montalban Bravo, Guillermo	(713) 794-3604
Ohanian, Maro	(713) 792-0091
Pemmaraju, Naveen	(713) 792-4956
Short, Nicholas	(713) 563-4485
Swaminathan, Mahesh	(832) 728-8778
Takahashi, Koichi	(713) 745-4613
Thompson, Philip	(713) 792-7430
Yilmaz, Musa	(713) 745-9945

Research Faculty

Battula, Venkata	(713) 563-2227
Bhalla, Kapil N.	(713) 563-8619
Burks, Jared K.	(713) 792-7640
Carter, Bing Z.	(713) 794-4014
Chang, Kyung Hee	(713) 792-4694
Colla, Simona	(713) 794-5223
Estrov, Zeev	(713) 794-1675
Fiskus, Warren	(713) 563-5901
Ganan Gomez, Irene	(713)-792-7828
Han, Lina	(713) 792-7640
Ishizawa, Jo	(713) 792-7640
Keating, Michael	(713) 745-2376
Piya, Sujan	(713) 792-7305
Post, Sean	(713) 794-1458
Pourebrahimabadi, Rasoul	(713) 792-7305
Rytting, Michael E.	(713) 792-4855
Wei, Yue	(713) 792-9854
Zeng, Zhinhong	(713) 792-7640
Zhang, Weiguo	(713) 794-4085