Leukemia insights

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In this month's Leukemia Insights newsletter, written by William Wierda, M.D., Ph.D., and sponsored in part by the Charif Souki Cancer Research Fund, we provide a summary of the progress made in the last ten years in treatment for patients with Chronic lymphocytic leukemia (CLL). Learn more about our Leukemia program

Relapsed and refractory chronic lymphocytic leukemia (CLL) - next steps

Remarkable progress has been made in the past decade in treatment for patients with CLL. More patients than ever are achieving remission, and treatments are improving overall survival. This is due to the development of oral small molecule inhibitor targeted therapy against key proteins of the B-cell receptor signaling pathway, such as Bruton tyrosine kinase (BTK) and phosphoinositide 3-kinase (PI3K), and against the anti-apoptotic protein BCL-2. These agents are highly effective in both first-line and relapsed CLL, even in patients with high-risk features such as del(17p) and mutated TP53. The BTK inhibitors (BTKi) ibrutinib, acalabrutinib and zanubrutinib, and the BCL2 inhibitor venetoclax have proven most effective. Chemoimmunotherapy is not being used for previously treated CLL and is now infrequently used in the first-line setting.

Highly effective disease reduction and durable disease control are achieved with continuous treatment with B-cell receptor signaling pathway inhibitors, while BCL2i-based treatment produces deep remission with fixed-duration treatment. Complimentary clinical activity, non-overlapping toxicities, and in vitro data demonstrating synergy were the basis for combined targeted therapy, which was well-tolerated and produced deep and durable remissions with fixed-duration treatment. Owing to the chronicity of CLL and the fact that use of these agents is not mutually exclusive, therapeutic sequencing is an important consideration for long-term disease management. Our preferred strategy is to begin with fixed-duration treatment to achieve deep remission. Therefore, efforts at therapeutic development have been to optimize targeted therapy combinations. Decisions about retreatment on relapse/progression are based on remission duration.

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CONTACT OUR STAFF

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

Relapsed CLL is higher risk than untreated disease since it is universally associated with shorter time-to-event endpoints. High-risk features for relapsed patients include greater number of prior treatments, refractory (to any agent) CLL, del(17p), mutated *TP53*, and complex karyotype. General treatment strategies include: 1) combined targeted therapy with new agents against established therapeutic targets, such as BTKi plus BCL2i; 2) new targeted agents against new targets; and 3) immune-based treatment strategies, including cellular therapy. Critical clinical features for patients with relapsed CLL include treatment-refractory disease and Richter transformation (RT); both threaten to shorten patient survival. Therapeutic resistance is seen with progression while on treatment and, additionally for fixed-duration BCL2i-based treatment, "short" time to needing next treatment.

New agents against established targets

BTK and BCL2 are established therapeutic targets for highly effective small molecule inhibitors. Currently available BTKi covalently bind to BTK at the C481 amino acid and irreversibly inhibit function. One major mechanism of resistance to covalent BTKi's is mutation in C481, preventing covalent binding. Work is ongoing to develop BTKi that bind reversibly to BTK, independent of C481, to enable continued treatment with a BTKi for patients who are developing resistance to a covalent inhibitor. Venetoclax binds BCL2, blocking function and favoring a pro-apoptotic balance in BCL2 family proteins, hurling the CLL cells into cell death. Resistance to venetoclax can involve mutation of BCL2 that causes conformational change that does not allow venetoclax binding, but this is not the dominant resistance mechanism. Clinical complimentary activity, *in vitro* synergy, and non-overlapping toxicities between BTKi and BCL2i led to trials studying combined targeted therapy. We developed a randomized phase II trial with acalabrutinib plus venetoclax to determine if the addition of obinutuzumab to this combination produces faster undetectable measurable residual disease (uMRD) status in treatment-naïve and previously treated patients with CLL (NCT04169737). Total treatment is 24 cycles of acalabrutinib plus venetoclax, with half of the patients randomized to receive obinutuzumab for the first 6 cycles. At the end of the first year, all patients are assessed for response. If at that time a patient is MRD-positive, they can receive 6 cycles of obinutuzumab for during the first half of the second year of treatment, regardless of receipt of prior obinutuzumab. This trial will provide some insights about the therapeutic benefit of obinutuzumab in combined targeted therapy. All drugs are provided at no cost to patients. Prior combined targeted therapy is excluded, but not treatment with BTKi or BCL2i administered separately.

Zanubrutinib is a covalent, irreversible BTKi currently approved for treatment of mantle cell lymphoma but is anticipated to receive approval for CLL. Beigene developed zanubrutinib and is also developing an oral BCL2i, BGB-11417. We are currently enrolling previously treated patients in a phase I/II trial of combined zanubrutinib and BGB-11417 (NCT04277637). This trial of all oral therapy is intended to assess tolerability and toxicities of BGB-11417 combined with zanubrutinib and to assess efficacy. Study drugs are provided at no cost to patients.

Pirtobrutinib as an oral non-covalent, reversible BTKi with significant activity in treatment of relapsed CLL, including CLL refractory to a covalent BTKi, and has a very favorable toxicity profile. It is not yet approved for CLL, but this is anticipated.

A phase III randomized trial of venetoclax plus rituximab with or without pirtobrutinib is open and enrolling patients (NCT04965493). This trial requires patients be venetoclax-naïve, and treatment is fixed-duration for 24 cycles. Pirtobrutinib is provided at no cost to patients. Another oral non-covalent reversible BTKi that will soon be under phase I investigation at MDACC is TT-01488 (NCT05275504). Study drug will be provided at no cost to patients.

BTK has proven an extremely important therapeutic target in CLL. Small molecule inhibitors binding and blocking kinase activity have clearly improved outcomes. Proteolysis-targeting chimera (PROTAC) is a novel molecule with mechanism to selectively degrade intracellular proteins. Small PROTAC molecules consist of three components: a target protein-binding arm (targeting arm, TA), a degradation machinery-recruiting unit (degradation arm, DA) and a linker. TA is engineered to bind target proteins, whereas DA recruits an E3 ubiquitin ligase, promoting creation of ubiquitin polymers. NX-2127 is an oral PROTAC molecule that targets BTK and cereblon, giving it potentially two mechanisms of action: elimination of BTK and immune modulating IMiD activity. A phase I/II clinical trial with NX-2127 is enrolling patients (NCT04830137). This strategy is a novel mechanism to target BTK for degradation with an oral small molecule and is being investigated in previously treated patients. NX-2127 is provided at no cost to patients.

Novel targets

Translational research demonstrated that protein kinase C-beta (PKCb) is potentially an important therapeutic target in CLL. An oral small molecule inhibitor of PKCb, MS-553, is being developed and tested in a phase I/II clinical trial for patients with relapsed/refractory CLL (NCT05272813). This trial is evaluating MS-553 as monotherapy and combined with venetoclax and rituximab or BTKi, depending on prior therapies the patient has received. Study drug is provided at no cost to patients.

MCL1 is an important anti-apoptotic protein and in CLL cells may be upregulated as a mechanism of venetoclax resistance. MCL1 transcripts are short-lived, and inhibition of CDK9 inhibits transcription of MCL1 and is a way to indirectly reduce intracellular levels of MCL1 in CLL cells. Facraciclib is an inhibitor of CDK9 currently under investigation in a phase I trial alone and combined with venetoclax for patients with relapsed/refractory CLL (NCT05168904). Study drug is provided at no cost to patients.

Immune-based strategies

Immune strategies recruit immune-based mechanisms of treatment and include cell-based therapies such as allogeneic stem cell transplantation (allo-SCT), autologous T-cells transduced to express chimeric antigen receptors (CAR T-cells), immune checkpoint inhibitors, and bi-specific monoclonal antibodies (mAb) or engaging molecules. Long-term remissions and potential cure of relapsed/refractory CLL has been reported with allo-SCT, and more recently with CD19-CAR T-cell therapy in limited numbers. CD19-CAR T-cell therapy has demonstrated significant clinical activity against CLL and was relatively well tolerated. Logistics and toxicities have limited application of these strategies in CLL. Checkpoint mAb against PD-1 (nivolumab and pembrolizumab) showed therapeutic activity, particularly in patients with RT. Very encouraging results were reported with CD3xCD20 bi-specific mAb in B-cell lymphomas and are now being evaluated for patients with CLL. Our therapeutic efforts are focused on CAR T-cell therapy and bi-specific engaging molecules.

Two trials are currently available utilizing CAR-T cell therapy for CLL. ROR1 is a protein normally expressed during embryogenesis and it is not found in adult tissues. It is expressed in >95% of cases of CLL, and a CAR was developed against ROR1. A phase I clinical trial of autologous T-cells transduced to express ROR1-specific CAR is about to open here (NCT05244070).

The ROR1-CAR T-cells and lymphodepleting chemotherapy are provided at no cost to patients. An autologous off-the-shelf CD19-CAR T-cell product, FT819, is also currently study in a phase I trial (NCT04629729). FT819 is provided at no cost to patients.

Building on therapeutic activity seen in RT with nivolumab plus ibrutinib, we developed a clinical trial of ipilimumab plus nivolumab and ibrutinib for relapsed/refractory patients with CLL (NCT04781855). Significant therapeutic benefit was not observed against CLL cells

with nivolumab, but preclinical data indicated CTLA-4 is an excellent therapeutic target in CLL, so we therefore developed the current trial including the CTLA-4 mAb ipilimumab plus nivolumab and ibrutinib. Ipilimumab and nivolumab are provided at no cost to patients.

CD20 mAb's have been very important in advancing treatments for patients with CLL and are associated with improved overall survival. Therefore, CD20 is an important therapeutic target. Mosunetuzumab is a CD3xCD20 bi-specific engager that directs T-cells to react against CD20 on B-cells, including CLL cells. This subcutaneously administered drug is being evaluated in a phase I clinical trial for patients with relapsed/refractory CLL (NCT05091424). Study drug is provided at no cost to patients.

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

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Clinical Faculty (continued)

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

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
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