Leukemia insights

OCTOBER 2024

MONTHLY EDITION

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

In this edition of the Leukemia Insights newsletter, written by written by Jayastu Senapati, M.B.B.S., M.D., D.M., and Farhad Ravandi, M.D., we provide a summary of our approach to CHIP/CCUS and an overview of the clonal hematopoiesis and Leukemia Prevention Clinic. Learn more about our Leukemia program.

Treatment Options in T-cell Acute Lymphoblastic Leukemia/Lymphoma

Treatment options in T-cell acute lymphoblastic leukemia and lymphoma (T-cell ALL/LBL) have lagged behind those of B-cell ALL, particularly in the absence of an approved T-cell targeted therapy. However, combination strategies in the frontline setting can lead to high rates of remission, including negative measurable residual disease (MRD), and improved overall survival. Outcomes of patients with relapsed or refractory (R/R) T-cell ALL/LBL are dismal, making it critical to optimize frontline therapy.

The HyperCVAD (hyperfractionated cyclophosphamide/ vincristine/adriamycin/dexamethasone alternating with methotrexate/cytarabine) regimen has been studied in adult ALLs, including T-cell variants, with promising outcomes. Nelarabine is a purine nucleoside analog with potential activity against T-lymphoblasts. In a phase 3 randomized trial in frontline pediatric patients, it was shown to improve disease-free survival (DFS) and reduce central nervous system (CNS) relapses. Asparaginase and its pegylated form (PegAsp) are also known to be active against T-lymphoblasts. The BCL2 agonist venetoclax has been shown in preclinical models to have activity against T-lymphoblasts, particularly the early T-cell precursor (ETP) phenotype. The use of rational combination strategies adding newer agents to HyperCVAD, nelarabine and PegAsp is a prudent approach for frontline T-cell ALL/LBL therapy.

Finally, recent developments in chimeric antigen receptor T-cell therapy (CAR T) against antigens expressed on T-cells is exciting and could open new avenues of therapy in the salvage setting, where treatment options are extremely limited and prognosis dismal. In this issue of Leukemia Insights, we discuss the ongoing and imminent clinical trials for adult patients with T-cell ALL/LBL at MD Anderson Cancer Center.

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

Ongoing Clinical Trial: Frontline

• Venetoclax added to HyperCVAD-Nelarabine and PegAsp (NCT00501826)

This phase 2 clinical trial, ongoing since 2007, has had several amendments to the treatment schedule. Initially, nelarabine and PegAsp were delivered only after 8 cycles of induction-consolidation, but now they are intercalated with consolidation. Venetoclax was added to the induction-consolidation cycles, and in the most recent amendment, venetoclax is continued beyond cycle 1 of induction-consolidation only in patients with the ETP phenotype or persistent MRD after cycle 1. This trial is open to patients ≥ 18 years of age and allows for patients in remission with ≤2 cycles of therapy or failure after one induction cycle. Patients must have adequate performance status and organ function.

For patients with bulky lymphadenopathy or a large mediastinal mass at diagnosis, consolidative irradiation (XRT; 30-39 Gy over 4-5 weeks) is allowed after completion of 8 cycles of HyperCVAD induction-consolidation and before maintenance. Patients also receive 8 doses of prophylactic intrathecal chemotherapy, consisting of methotrexate alternating cytarabine.

In a recent update, among 145 patients and with a median follow up of more than 5 years, the median progression free survival (PFS) was not reached (5-year PFS=64%), nor was median duration of response (DOR) (5-year DOR=72%) or median overall survival (OS) (5-year OS=66%). Among those who received venetoclax (n=46), at a median follow up of more than 2-years, the 2-year PFS, DOR and OS rates were 88%, 94% and 88%, respectively, and appear superior to the 96 patients in the older cohorts who did not receive venetoclax (64%, 69% and 74%, respectively). The regimen is well tolerated overall, and with ETP- and MRD-directed venetoclax administration schedules, excessive risks of cytopenias have been averted. This clinical trial continues to actively accrue patients.

Coming soon: Salvage

• CD-7 directed CRISPR-modified allogenic CAR T-cell therapy

Treatment options for T-ALL/LBL in the salvage setting for T-ALL/LBL primarily have consisted of repurposing chemotherapy used in the frontline setting. Nelarabine is the only drug specifically approved for salvage. Development of targeted agents against T-cell epitopes are important for improving outcomes. In B-cell ALL, CD19-targeted CAR T-cell constructs are approved in the salvage setting, but T-cell leukemias present unique biologic challenges for the development of CAR T-cell therapy, including fratricide (self-destruction of CAR T-cells given expression of similar epitopes on the leukemia and the CAR T-cell product) and contamination of the product with malignant cells during leukapheresis. Additionally, allogeneic products could be associated with a risk of graft versus host disease (GVHD) or inadequate CAR T-cell expansion.

The WU-CART 007 product is designed to address these challenges. It is an allogeneic, CRISPR-modified construct with the CD7 antigen and T-cell receptor (TCR) deleted on the CAR T-cells to reduce fratricide and risks of GVHD respectively. In a phase 1/2 dose escalation and expansion clinical trial (data in preprint; Ghobadi et al, Res Sq . Aug 5 2024;doi:10.21203/rs.3.rs-4676375/v1), among 13 of 26 patients who received the recommended phase 2 dose, 11 were evaluable for response, and the composite complete response rate was 82%. Cytokine release syndrome (CRS) was the most common treatment-related adverse event, occurring in 23 patients (86%; grade 3-4, 19%). Hemophagocytic lymphohistiocytosis (HLH) occurred in 4 patients (15%), 3 of whom had ≥ grade 3, and immune effector cell-associated neurotoxicity was seen in 2 patients (8%). Only one patient had GVHD.

This trial will start soon at our center for adult patients with R/R T-cell ALL/LBL.