Leukemia insights

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In this month's Leukemia Insights newsletter, written by Guillermo Montalban Bravo, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we summarize our approach to the treatment of patients with chronic myelomonocytic leukemia (CMML) and a list of some of our current clinical trials. Learn more about our Leukemia Program.

Treatment Strategies for Chronic Myelomonocytic Leukemia (CMML)

Chronic myelomonocytic leukemia (CMML) is a hematologic disorder characterized by peripheral blood (PB) monocytosis and both myelodysplastic and myeloproliferative features (1, 2). It has a heterogenous clinical presentation and prognosis (3-5), and a variable risk of progression to acute myeloid leukemia (4, 6). Although recently we have witnessed significant advances in our understanding of the biology and genomic characteristics of CMML, this has not translated to new therapies since the approval of azacitidine and decitabine, the only FDA-approved therapies. Despite responses rates of up to 40% with these agents, only 7%-17% achieve complete responses, and loss of response is frequent and associated with short survival (7). This underscores the need to develop novel therapies. As part of the Myelodysplastic Syndrome (MDS) Section at the MD Anderson Cancer Center, composed of a multidisciplinary team of basic researchers, hematopathologists, leukemia physicians, research nurses, advanced practice providers and pharmacists, the CMML Program of the Leukemia Department, with over 80 new patients referred annually, focuses on research to develop novel therapies for the treatment of CMML, and to provide a personalized and integrated therapy based on the disease features of each patient. Below we summarize our approach to the treatment of patients with CMML and a list of some of our current clinical trials.

1. Clinical Trials for Frontline Treatment of Patients with CMML

Given the heterogeneity of CMML, adequate risk stratification is essential to select the optimal treatment for each patient. After an extensive diagnostic workup including peripheral blood and bone marrow morphologic evaluation, conventional karyotyping, flow cytometry assessment and next-generation sequencing (to evaluates a panel of more than 81 genes), CMML can be classified into distinct risk groups. Patients with lower-risk disease tend to have an indolent course but might ultimately require treatment. Those with higher-risk disease (more likely to progress to acute leukemia) may benefit from early intervention with disease-modifying therapy and allogeneic stem-cell transplant. In addition, treatment selection can also vary based on disease subtype and genomic features (Figure 1). For instance, patients with myeloproliferative CMML (MP-CMML, defined as WBC $^{3}13x10^{9}$/L) have more aggressive disease and accompanying mutations, while patients with myelodysplastic CMML (MD-CMML) can have a clinical course more similar to MDS.

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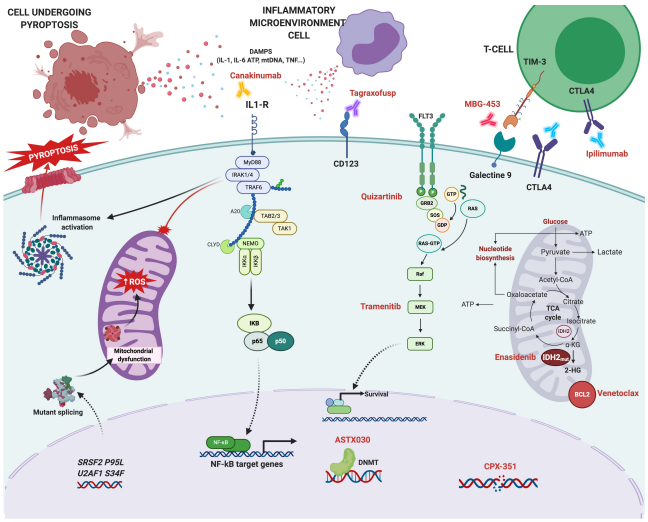

a) Novel Formulations of Azacitidine: ASXT030

Our group has shown that the use of low-dose hypomethylating agents (HMA) in patients with lower-risk CMML can be safe and effective (8, 9) and may be associated with improved outcomes. The recent approval of ASTX727 (Inqovi), a combination of oral decitabine with cedazuridine (a cytidine deaminase inhibitor), for the treatment of CMML, has increased interest in the development of other oral formulations of HMAs. This multiphase clinical trial of oral azacitidine in combination with cedazuridine (ASXT030) is intended to investigate a pharmacokinetically identical oral version of parenteral azacitidine. Patients with previously untreated CMML of all risk categories and subtypes are eligible.

b) Immune Checkpoint Inhibitors for the Treatment of CMML

Work from our group and others has shown upregulation of immune checkpoint molecules such as CTLA4, LILRB4 and TIM-3 both in the hematopoietic cells and immune cells of patients with CMML (10, 11), and has suggested that this might be a mechanism of resistance to HMA. Data from prior studies at MD Anderson have shown the safety and efficacy of PD-1 and CTLA-4 inhibitors not only in MDS but also in CMML (12, 13). We are continuing to explore this approach in this Phase 2 study of azacitidine in combination with ipilimumab (NCT02530463) as well as in a Phase 1/2 study of MGB-453 (a TIM-3 inhibitor) in combination with decitabine (NCT03066648) for patients with either myelodysplastic or myeloproliferative CMML with previously untreated intermediate-1 or higher-risk disease.

c) Glutaminase Inhibition in Combination with Azacitidine: Telaglenastat (CB-839)

Glutaminase is an enzyme that converts glutamine to glutamate, an essential metabolite that is highly expressed in leukemia cells. This study of CB-839 in combination with azacitidine (NCT03047993), which has shown preliminary activity not only in MDS but also CMML(14), is exploring the efficacy of this combination in patients with higher-risk CMML either by clinical parameters or genomic features.

d) BCL2 Inhibition in CMML

Work from our group has shown that BCL2 upregulation represents a mechanism of resistance and progression in MDS (15). Prior studies have shown the efficacy of BCL2 inhibitors in higher-risk MDS and AML. To evaluate the efficacy of BCL2 inhibitors in CMML, we are conducting a Phase I-II clinical trial of venetoclax in combination with azacitidine (NCT04160052). This study will try different dose levels and schedules of venetoclax and will help elucidate the activity of this combination as well as potential mechanisms of resistance to the combination.

2. Clinical Trial Options for Patients with CMML Previously Treated with HMA

Given the poor prognosis of patients with CMML after primary or secondary failure to HMA, and the absence of FDA-approved therapies, this is an area of active research. Below are some of the clinical trial options at MD Anderson Cancer Center.

a) BCL2 inhibition in Combination with Hypomethylating Agents

As mentioned above, BCL2 upregulation can be a mechanism of resistance to HMA. In this Phase I-II study of venetoclax in combination with azacitidine (NCT04160052), we are exploring the safety and efficacy of different dose levels of venetoclax in the treatment of higher-risk CMML. This study is supported by the MD Anderson MDS/AML Moon Shot.

b) Inhibition of the IL-1-Inflammatory Axis in Lower-Risk CMML

Inflammatory and innate immune signaling have been shown by our group and others to be key mediators of CMML pathogenesis (16-18). Interleukin-1 (IL-1) is one of the cytokines that mediate pro-inflammatory responses, which in turn promote ineffective hematopoiesis and participate in the biology of MDS. Canakinumab is an anti-IL1 humanized monoclonal antibody approved for the treatment of several autoimmune disorders. It has been shown to be safe and effective in reducing the risk of malignancies and cardiovascular complications, particularly in individuals with clonal hematopoiesis. This study of canakinumab (NCT04239157) will explore different doses to determine its activity in dampening the inflammatory response characteristic of CMML and improving cytopenias and symptoms. The study is intended for patients with lower-risk CMML and anemia who have been previously treated with HMA.

c) Targeting CD123 with Tagraxofusp (SL-401) in Higher-Risk CMML

The interleukin-3 receptor (CD123) is highly expressed in hematopoietic cells and other cellular components, such as plasmacytoid dendritic cells, of patients with CMML. Tagraxofusp (SL-401) is an immunotoxin shown to be highly effective and approved by the FDA for the treatment of blastic plasmacytoid dendritic cell neoplasm. This study (NCT02268253)evaluates the efficacy of different dose levels of tagraxofusp in the treatment of patients with higher-risk CMML defined by presence of excess blasts (CMML-1 or CMML-2) and is being performed in collaboration with the Mayo Clinic of Rochester, MN.

d) Cytotoxic therapy with Low-doses of CPX-351 for Higher-risk CMML

We have previously shown that lower dose schedules of purine analogs and cytotoxic therapy can be safe and effective in the treatment of patients with CMML who have excess blasts and high-risk disease after exposure to HMA. CPX-351 is approved by the FDA for the treatment of AML with MDS-related changes, including blastic transformation of CMML. This study (NCT03896269) examines several lower-dose levels of CPX-351 for the treatment of patients with higher-risk CMML or with >10% blasts (CMML-2) who have prior exposure to HMA.

3. Clinical Trial Options for Specific Genomic Subsets of CMML

a) Targeting *FLT3* and *CBL* Mutations: Quizartinib

Up to 15% of patients with CMML have CBL mutations, and a smaller subset have FLT3-ITD mutations. Mutations in CBL lead to the loss of function of this gene, which normally acts as a negative regulator of JAK-STAT and FLT3 kinase signaling. CBL mutant leukemias have been shown to be dependent on FLT3 signaling. In this study (NCT04493138), we are exploring the activity of quizartinib, a potent FLT3 inhibitor, in combination with azacitidine for the treatment of patients with CMML who have CBL or FLT3 mutations.

b) Targeting *IDH2* Mutations: Enasidenib

Approximately 5%-7% of patients with CMML have IDH2 mutations either at the time of diagnosis, or upon relapse or progression. Given the high efficacy of enasidenib, a mutant-IDH2 small molecule inhibitor, which lead to its approval in AML, this Phase II study (NCT03383575) explores the use of enasidenib in combination with azacitidine in previously untreated patients with intermediate- or high-risk CMML, as well as single agent in those who have prior exposure to HMA.

c) Targeting RAS Mutations: Azacitidine, Venetoclax and Trametinib

Up to 30% of patients with CMML harbor mutations in genes involved in RAS pathway kinase signaling such as NRAS, KRAS, SETBP1, PTPN11, CBL or NF1. These mutations are particularly frequent among patients with myeloproliferative CMML. This study (NCT04487106) explores trametinib, a MEK inhibitor, in combination with azacitidine and venetoclax for the treatment of patients with higher-risk CMML who have RAS pathway mutations.

Figure 1. Current novel drugs under development for the treatment of CMML at MD Anderson Cancer Center.

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Announcements

Leukemia Insights Newsletter

Our Leukemia Insights e-newsletter is now available online. Started in 2007 by Hagop Kantarjian, M.D., Leukemia Insights focuses on our various therapy options at MD Anderson Cancer Center. Click here to visit our new website.

Emil J Freireich Hematology Grand Rounds

The MD Anderson Cancer Center Emil J Freireich Hematology Grand Rounds now has a virtual format. This series highlights the incredible research taking place at MD Anderson Cancer Center while showcasing leaders from our research community, in an effort to remain engaged and inspired during the COVID-19 pandemic. Hosted by the Department of Leukemia in collaboration with the Department of Lymphoma/Myeloma, and Department of Stem Cell Transplantation and Cellular Therapy, we aim to strengthen the connections between the scientific and medical community at MD Anderson Cancer Center, our colleagues, patients and friends from around the world. Click here to visit our new website.

8th Annual Society of Hematologic Oncology (SOHO) Meeting

SOHO 2020 Virtual Registration is now available for delegates that are unable to attend the SOHO annual meeting in person due to COVID-19 travel restrictions or other reasons. The registration fee for virtual attendance includes LIVE stream multi-track session broadcast in real time; opportunities to submit questions to presenters; ability to engage with other virtual participants via chat and other tools; access to the virtual exhibit hall for collaborations, information and FREE giveaways; access to the poster hall for viewing, discussions and collaborations; an online copy of the final program and abstract proceedings published in the official CLML journal supplement, CME credits for physicians and CNE credits for nurses. In addition, on-demand recordings will be available to all delegates for 4-months following the meeting. Go to https://soho.click/2020 to begin the secure registration process.
Note that SOHO members receive a significant discount on registration fees. Sign up now to receive a SOHO member discount code to apply towards your annual meeting registration fee. Go to https://soho.click/join to claim your FREE membership.

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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