Leukemia insights

DECEMBER 2020

MONTHLY EDITION

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

In this month's Leukemia Insights newsletter, written by Elias Jabbour, M.D., and Nicholas J. Short, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we describe clinical trials available at MD Anderson Cancer Center for patients with Ph-positive ALL in both the frontline and salvage settings. Learn more about our Leukemia program.

Novel approaches for patients with Philadelphia chromosome-positive ALL

Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL) is an aggressive subtype of ALL characterized by the presence of the BCR-ABL1fusion gene. It accounts for 20% of adult ALL cases. Historically, patient outcome patients have been dismal; however, with the addition of tyrosine kinase inhibitors (TKIs) to intensive chemotherapy, survival rates of 50% were achieved. Later-generation TKIs (e.g. ponatinib) have produced even better results, with 5-year survival rates of 75%.

In this month's newsletter, we describe clinical trials available at MD Anderson Cancer Center for patients with Ph-positive ALL in both the frontline and salvage settings. Many of these approaches focus on decreasing or eliminating intensive chemotherapy and allogeneic stem cell transplantation (ASCT), with the goal of making the treatment effective but more tolerable.

With regard to patient referrals patient, it is important to note that most of these frontline trials allow up to 2 previous cycles of therapy; therefore, patients can be eligible even 1-2 months after diagnosis. Furthermore, the TKIs, monoclonal antibodies (e.g. inotuzumab ozogamicin or blinatumomab), and other investigational agents are provided free of charge as part of the trials.

A. Frontline Trials

In Ph-positive ALL, the 5-year survival rate is 40%-50% in patients treated with the hyper-CVAD chemotherapy regimen plus imatinib or dasatinib, and 75% with ponatinib.

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Lower-intensity chemotherapy with TKIs produces a complete remission (CR) rate of 100%, but a complete molecular response (CMR) rate of only 20%, necessitating ASCT in most patients in first CR to achieve long-term survival.

Additionally, gatekeeper T315I mutations are present at relapse in 75%. This mutation is the dominant mechanism of resistance and relapse for patients treated with first- or second-generation TKIs. For older patients with significant co-morbidities, intensive chemotherapy results in an unacceptable rate of treatment-related mortality. In this population, the 5-year survival rate with lower-intensity chemotherapy plus dasatinib is 35% at best. Innovative strategies using more potent TKIs and other novel agents are needed.

• **Mini-hyper-CVD + ponatinib + blinatumomab –** We have reported a 5-year survival rate of 76% in patients treated with hyper-CVAD plus ponatinib. Our goal now is to reduce the intensity and duration of chemotherapy, which should improve tolerability while maintaining efficacy. We are therefore evaluating the combination of lower-intensity chemotherapy (i.e. mini-hyper-CVD) in combination with ponatinib. We also incorporate into this regimen the CD3-CD19 bispecific T-cell engaging antibody blinatumomab, an agent that has been shown to be highly active in Ph-positive ALL. To date, we have treated 9 newly diagnosed patients, all of whom are in ongoing deep remissions. This regimen is open to patients of all ages with newly diagnosed Ph-positive ALL.

• **Blinatumomab and ponatinib –** Blinatumomab and ponatinib are the 2 most active drugs for the treatment of Ph-positive ALL. We are therefore evaluating them in combination (without chemotherapy) for patients of all ages with newly diagnosed Ph-positive ALL. Among 14 frontline patients treated, this regimen has resulted in high rates of CMR, and all patients are alive without relapse at last follow-up. Importantly, none of these patients has undergone ASCT, suggesting that this chemotherapy-free option may eliminate the need for ASCT in the vast majority of patients with Ph-positive ALL.

B. Relapsed/Refractory Trials

Outcomes after salvage chemotherapy for relapsed/refractory Ph+ ALL using traditional cytotoxic regimens are poor, with less than half of patients achieving a second remission. Remission rates are even lower for patients with multiply refractory disease. Long-term survival rates for patients with R/R ALL are <20%. Novel agents and combinations are needed to induce remission and facilitate the bridge to potentially curative ASCT.

• **Inotuzumab and bosutinib –** A randomized trial comparing inotuzumab with physician's choice of chemotherapy in patients with relapsed/refractory ALL in first or second salvage showed a significant improvement in response rates and survival with inotuzumab. Bosutinib is a second-generation TKI and dual Abl and Src kinase inhibitor that is active in Ph-positive leukemias. A Phase I-II trial assessing the combination of inotuzumab and bosutinib in patients with newly diagnosed and relapsed/refractory ALL is enrolling. Early results are promising. Eighteen patients with relapsed/refractory disease have been treated. The CR/CRi rate is 83%, and CMR rate 53%. The median overall survival is 15.4 months.

• **Blinatumomab and ponatinib –** In addition to being tested in older adults with newly diagnosed Ph-positive ALL (see above), the chemotherapy-free combination of blinatumomab and ponatinib is being evaluated in patients with relapsed/refractory disease. This regimen combines two of the most active agents in Ph-positive ALL, both of which are capable of overcoming the T315I mutation, which is the dominant mechanism of relapse in Ph-positive leukemias.

Initial results are promising, with a CMR rate >75% and a 1-year overall survival of 86%, even in patients with heavily pretreated Ph-positive ALL.

• **Venetoclax and ponatinib –** The Bcl-2 inhibitor venetoclax has shown significant promise across multiple leukemias. There is preclinical rationale for the combination of venetoclax and ponatinib, which shows synergistic activity in preclinical models. Ponatinib may also help to prevent venetoclax resistance by blocking upregulation of Mcl-1, an established resistance mechanism of venetoclax-based regimens. We have completed Phase I of this entirely oral and chemotherapy-free combination of ponatinib, venetoclax and dexamethasone in patients with relapsed/refractory Ph-positive ALL. At the recommended Phase II dose of venetoclax, the CR/CRi rate was 83% with no relapses to date. This trial is now in Phase II expansion and is accruing for patients of all ages with relapsed/refractory Ph-positive ALL.

C. Correlative Studies: A Focus on Improved Risk Assessment

For fit adult patients with Ph-positive ALL and an adequate donor, the current standard of care is ASCT in first remission. However, this approach can be associated with significant morbidity and mortality; therefore, identification of patients who may be cured without ASCT is imperative. We have several initiatives that are integrated into our frontline clinical trials in order to better identify patients at relatively low risk of relapse and in whom ASCT in first remission can be safely deferred. These include:

1. Targeted and whole-genome sequencing of diagnostic Ph-positive ALL samples to identify genomic alterations that influence risk of relapse. For example, *IKZF1* and *CDKN2A/B* deletions are associated with a worse prognosis in patients with Ph+ ALL.

2. Next-generation sequencing for minimal residual disease (MRD) assessment. This method has better sensitivity than standard PCR-based MRD testing and may better identify patients with Ph-positive ALL who do not require ASCT in first remission.

For further information or referrals for patients with ALL, please contact Dr. Elias Jabbour (ejabbour@mdanderson.org).

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.

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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