Leukemia insights

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In this month's Leukemia Insights newsletter, written by Ghayas Issa, M.D., and Elias Jabbour, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we outline the clinical trials offered for the treatment of chronic myeloid leukemia. Learn more about our Leukemia program.

Update of the Management and Clinical Trials for Chronic Myeloid Leukemia

Introduction

With adequate access to tyrosine kinase inhibitors (TKIs) and proper management and monitoring, patients with chronic myeloid leukemia (CML) now have a nearly normal life expectancy.[1] This is in part due to the significant decrease in the rate of transformation from chronic phase (CP) to the more aggressive accelerated (AP) and blast phases (BP) of the disease. With the use of second-generation TKIs as initial therapy, such events occur in only 1% to 2% of patients per year, and rarely after the first four years of treatment. Patients diagnosed in accelerated phase also have excellent outcomes when treated with TKIs, particularly the second- generation options.[2] The few patients who progress to blast phase still have poor outcomes, with a median survival of 7 to 11 months, although TKI-based combination chemotherapy has produced modest improvements, more in those with the lymphoid than myeloid phenotype.[3,4]

Six TKIs are approved for the treatment of CML. Four of them (imatinib, dasatinib, nilotinib and, most recently, bosutinib) are approved as initial therapy, while ponatinib and asciminib are approved only for patients with T315I (the only approved TKIs with activity against this gate-keeper mutation) and for those who failed at least 2 TKIs. Omacetaxine mepesuccinate, a semi-synthetic derivative of homoharringtonine is approved for CML-CP or AP after failure or intolerance to ≥2 TKIs. Omacetaxine has clinical efficacy, albeit modest, against T315I. Although generally safe, TKIs have side effects, some immediate but generally mild (e.g., diarrhea, myelosuppression, edema) and others more serious but frequently occurring later (e.g., pleural effusion, arterio-thrombotic events, pulmonary hypertension).

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There is increased recognition of the possibility of treatment discontinuation for certain patients with deep molecular responses. When done properly, nearly 60% of patients can maintain major molecular response without therapy. However, this option is available to fewer than 50% of patients. TKIs alone do not eradicate leukemic stem cells (LSC). Strategies to eliminate these LSC, thus increasing the pool of patients eligible for discontinuation and/or the success rate after discontinuation, are being explored. This involves trials using TKIs in combination with agents. Below, we discuss strategies that are currently ongoing at MD Anderson Cancer Center for the management of patients with CML.

INITIAL THERAPY

1. Phase II trial of lower-dose dasatinib with the oral hypomethylating agent ASTX727 for early chronic phase CML (Protocol 2021-0271)

Analysis from research done at MD Anderson demonstrated that dastinib 50 mg (half of the approved dose) leads to similar rates of response as the 100 mg dose and is better tolerated.[5] Therefore, this has become the standard approach at MD Anderson. Even though a significant number of patients with CML-CP are functionally cured with long-term TKI therapy, more than 50% of patients relapse after treatment discontinuation. In an effort to improve chances of treatment-free remission, we have designed a study combining lower-dose dasatinib with the oral hypomethylating agent ASTX727 (oral decitabine). Decitabine was found in the past to be effective in 123 patients with resistant CML (64 blastic, 51 accelerated, 8 chronic) with objective response rates of 28%, 51%, and 63%, respectively. Based on these findings, we hypothesized that the combination of ASTX727 with lower-dose dasatinib may significantly improve the depth of response and cure rates. This study is ongoing. For more information, contact Dr. Elias Jabbour or any other leukemia doctor.

2. Phase III randomized trial of the allosteric inhibitor asciminib (ABL001) vs standard of care as initial therapy for chronic phase CML (Protocol 2021-0828)

Asciminib is an allosteric inhibitor of ABL kinase activity, meaning that it binds to a different region of the kinase than other TKIs. In a Phase I study, it showed significant clinical efficacy among patients with resistance to 2 or more TKIs and among patients with T315I. It was recently FDA approved for patients previously treated with two or more TKIs, and for those with the T315I mutation. In this study, patients with newly diagnosed CML will be treated with either asciminib or any standard-of-care TKI approved for newly diagnosed disease. This study is ongoing. For more information, please contact Dr. Ghayas Issa or any other leukemia doctor.

RESISTANCE OR INTOLERANCE TO PRIOR TKI

1. Phase Ib study of olverembatinib (HQP1351) (Protocol 2019-0705)

Olverembatinib is a new TKI with broad-spectrum activity against BCR-ABL mutations, including T315I. In a recent analysis presented at the American Society of Hematology Annual Meeting in 2021, olverembatinib led to a complete hematologic response (CHR) in 97%, a complete cytogenetic response in 62% and major molecular response in 51% of patients who received ≥ 2 TKIs (101 patients at that data cut-off). Among those with a T315I mutation, the CHR rate was 100% and the MMR rate was 71%. The 3-year PFS rate among patients in CP (n=86) was 96.3%. The goal of this study is to evaluate the pharmacokinetics of olverembatinib and determine the recommended Phase 2 dose.
This study is ongoing. For more information, please contact Dr. Elias Jabbour or any other leukemia doctor.

2. Phase II study of ponatinib in patients treated with 1 prior TKI (Protocol 2012-0669)

Ponatinib has demonstrated significant clinical activity in patients with resistance to two or more TKIs. In the registration PACE study, rates of major cytogenetic response of 60% and major molecular response of 40% were reported, including patients with T315I. Responses were durable, with major cytogenetic response maintained for at least five years in more than 80% of patients who achieved this response.[6] Ponatinib is FDA approved for patients previously treated with two or more tyrosine kinase inhibitors, and for those with the T315I mutation. Although ponatinib is associated with a relatively higher risk of arterio-thrombotic events, this risk can be mitigated with appropriate dose adjustments. Given the potency of ponatinib and the chance to maintain long-term remission following treatment with this drug, we are investigating use of ponatinib in patients who received 1 prior TKI.

This study is ongoing. For additional information, please contact Dr. Elias Jabbour or any other leukemia doctor.

3. Phase IIIb study of asciminib (ABL001) for CML patients with resistance or intolerance to prior therapy (Protocol 2020-1135)

This is a study of two dose schedules of asciminib (80 mg daily vs 40 mg twice a day) for patients with resistance or intolerance to prior therapy. For those with the T315I mutation, the dose is 200 mg twice a day per the FDA-approval label.

This study is ongoing. For more information, please contact Dr. Ghayas Issa or any other leukemia doctor.

4. Phase I study of K0706 for treatment of patients with resistance to prior TKIs (all stages) (Protocol 2016-0648)

K0706 is a third-generation TKI that, like most other TKIs, binds to the ATP-binding pocket of the kinase domain. Preclinical studies have demonstrated potent activity against all mutations against which it has been tested, including T315I. A Phase I study to determine the dose-limiting toxicity and maximum tolerated dose of K0706 in patients with CML in all stages with resistance to prior TKI or with the T315I mutation is currently enrolling patients. Two dose levels have been fully enrolled, and dose escalation continues. The drug is orally administered and continues uninterrupted in the absence of unacceptable toxicity or progressive disease.

This study is ongoing. For information, please contact Dr. Yesid Alvarado or any other leukemia doctor.

CML IN ACCELERATED OR BLAST PHASE

Fortunately, fewer patients today face this scenario, which still confers a very poor prognosis despite the use of TKIs. We are exploring treatment options that may improve the prognosis.

1. A Phase II study of the combination of decitabine, venetoclax, and ponatinib in patients with Ph+ AML or myeloid blast phase CML (Protocol 2019-0610)

The combination of the hypomethylating agent decitabine and the BCL2 inhibitor venetoclax is the standard approach for older or unfit patients with acute myeloid leukemia (AML). This combination results in high rates of response and eradication of measurable residual disease in most AML subsets and is associated with fewer side effects compared with standard high-intensity chemotherapy. Ponatinib is a potent inhibitor of BCR-ABL kinase activity with a broad effect on all resistance mutations, including T315I. This study is investigating the combination of decitabine, venetoclax, and ponatinib in patients with Ph+ AML or myeloid blast phase CML.

This study is ongoing. For information, please contact Dr. Nicholas Short or any other leukemia doctor.

MANAGEMENT OF MINIMAL RESIDUAL DISEASE

1. A Phase II study of asciminib in combination with other TKIs for management of minimal residual disease (Protocol 2019-0618)

Preclinical data have demonstrated that the combination of asciminib with other TKIs can eradicate the earliest leukemia progenitors. In animal models, no regrowth of leukemia is observed after combined therapy, even after treatment discontinuation. This suggests that such combinations might be effective in eradicating the leukemic stem cell in patients with CML. This could potentially translate into more patients achieving undetectable transcripts and fewer relapses after treatment discontinuation. The Phase I study of asciminib has already established the safety of such combinations. In this study, we will enroll patients receiving dasatinib or nilotinib who have achieved a complete cytogenetic response but have residual detectable transcripts. Patients will continue to receive their prescribed TKI, and asciminib will be added. Close monitoring of transcript levels will be done, and patients who achieve sustained deep molecular responses will be eligible for treatment discontinuation.

This study is ongoing. For further information, please contact Dr. Ghayas Issa or any other leukemia doctor.

OTHER SPECIAL APPROACHES AND CLINICS IN CML

1. Survivorship clinic

Most patients with CML respond well to TKIs and continue therapy for long periods of time, frequently indefinitely. Their life expectancy has reached that of the general population. However, other health conditions may emerge, either as a consequence of the TKI therapy, or coincidentally. These co-morbidities need proper monitoring and management to ensure the optimal holistic outcome for patients with CML. We have established a survivorship clinic for patients with CML receiving long-term therapy with TKI where they are regularly being monitored for those conditions most frequently associated with TKI therapy, with special attention to risk factors for arterio-thrombotic events and second malignancies. They continue regular monitoring of their disease and assessment of long-term adverse events. The quality of life is also regularly assessed. For further information on the CML survivorship clinic, please contact any leukemia doctor.

2. Immune milieu of patients with CML

The answers to several important questions about the disease biology of CML are not known: Why some patients with CML achieve deep molecular responses while on TKIs and others do not, and, more importantly, why some relapse after treatment discontinuation and others do not, sometimes despite the presence of low levels of detectable transcripts. CML is a disease susceptible to immune interventions, perhaps the best example of which is the graft-versus-leukemia effect after stem cell transplant that is best documented in CML. We are currently conducting a comprehensive analysis of the immune milieu of patients with CML with different levels of response to different TKIs. The assessment includes individual cell cytokine analysis and analysis of different T-cell subpopulations and expression of checkpoints. In addition, patients who undergo treatment discontinuation are prospectively monitored before and during discontinuation (and after relapse if this occurs) to better understand the role the immune system may play in maintaining a response in the absence of TKIs. For further information, please contact Dr. Ghayas Issa.

3. Pregnancy

CML is being diagnosed in younger patients. With the improved outcome of patients receiving TKIs, considerations of pregnancy for patients are of greater relevance and

frequency. We have developed extensive experience in the management of patients with CML through pregnancy.[9,10] We have recently reported our experience with 43 female patients with CML and pregnancy in different settings: CML diagnosed while pregnant, unplanned pregnancy while on therapy for CML, and planning to become pregnant while on therapy with TKIs. We have established the possibility of managing patients through their pregnancy with minimal intervention, preserving the safety and wellbeing of both the mother and the baby. For additional information regarding the CML pregnancy clinic, please contact any leukemia doctor.

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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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