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In this month's Leukemia Insights newsletter, written by Fadi Haddad, M.D., and Elias Jabbour, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we outline clinical trials offered for patients with myeloproliferative neoplasms. Learn more about our Leukemia program.

Update on the management of 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) can 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 phase (AP) and blastic phase (BP) of the disease. With the use of second-generation TKIs as initial therapy, such events occur in only 1-2% of patients per year, and rarely after the first four years of treatment. Patients diagnosed in AP also have excellent outcomes, particularly when treated with second- generation TKIs.[2] The few patients who progress to BP still have poor outcomes; TKI-based combinations with chemotherapy or immunotherapy are the best of limited options, more in the lymphoid than myeloid phenotype.[3,4]

Six TKIs are approved by the FDA for the treatment of CML. Four of them (imatinib, dasatinib, nilotinib, and bosutinib) are approved as initial therapy, while ponatinib and asciminib are approved only for patients with T315I mutation and those who have 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.[5] Omacetaxine has clinical efficacy, albeit modest, against the T315I mutation. 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).

There is increasing recognition of the possibility of treatment discontinuation for certain patients with deep molecular responses. When done properly, approximately 50% of

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patients can maintain major molecular response without therapy.[6] However, this option is available to fewer than 50% of patients. TKIs alone do not eradicate leukemic stem cells. Strategies to eliminate them, 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 other agents. Below, we discuss strategies that are currently ongoing at MD Anderson Cancer Center.

Initial Therapy for CML-CP

1. Phase II study assessing safety and clinical activity of the combination of ASTX727 (oral decitabine) with dasatinib in patients with newly diagnosed CML-CP

Research done at MD Anderson demonstrated that dasatinib 50 mg daily (half of the approved dose) leads to similar rates of response as the 100 mg daily dose and is better tolerated.[7] Therefore, this has become our standard approach. Even though a significant number of patients with CML-CP are functionally cured with long-term TKI therapy, approximately 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 (the oral formulation of decitabine). Decitabine was studied 123 patients with resistant CML (64 in BP, 51 in AP, 8 in CP) and found to be effective, 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 additional information, please contact Dr. Elias Jabbour or any other leukemia doctor.

2. Phase II study of asciminib in patients with newly diagnosed CML-CP

Asciminib is a novel, first-in-class oral TKI specifically targeting the ABL myristoyl pocket that potently inhibits the kinase activity of BCR::ABL1 via allosteric binding. It has potential to be active against most ABL1 kinase domain mutations that confer resistance to approved TKIs, including the T315I mutation. In the Phase III ASCEMBL trial of patients failing at least 2 prior TKIs, treatment with asciminib was associated with improved efficacy and toxicity profile compared with bosutinib.[8] This led to the FDA approval of asciminib for patients who failed ≥2 prior TKIs. Recently, an interim analysis of frontline therapy with asciminib 40 mg twice daily in patients with newly diagnosed CML-CP showed encouraging results with favorable tolerability and efficacy.[9] Frontline therapy with asciminib may significantly improve the depth of response with a favorable safety profile. Additionally, we aim with asciminib to increase the proportion of subjects eligible for TKI discontinuation after 3 to 5 years of therapy and decrease the risk of molecular relapse. This treatment is anticipated to be safe without excessive myelosuppression. The dose of asciminib used in this trial is 80 mg daily.

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

Salvage Therapy for CML-CP

Second-Line Treatment

1. Phase II study of ponatinib as second-line therapy for patients with CML-CP resistant to a prior second-generation TKI

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 mutation. Responses were durable, with major cytogenetic response maintained for at least five years in more than 80% of patients who

achieved this response.[10] Ponatinib is FDA approved for patients previously treated with two or more TKIs, 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 reductions. 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.

2. Phase II study of asciminib as second-line therapy for patients with CML-CP resistant to a prior TKI

Asciminib is approved for the treatment of patients with CML-CP who had received at least 2 prior therapies and those with the T315I mutation. This phase II study aims to evaluate the efficacy and safety of asciminib in patients with CML-CP who failed only 1 previous TKI. This treatment is not anticipated to have excessive myelosuppression. The dose of asciminib used in this trial is 80 mg daily for patients without the T315I mutation and 200 mg twice daily in patients with the T315I mutation.

This study will be open soon. For additional information, please contact Dr. Ghayas Issa or any other leukemia doctor.

3. A Phase II multicenter, open-label, single-arm dose escalation study of asciminib monotherapy in second line CML-CP (ASC2ESCALATE)

Asciminib is approved for the treatment of patients with CML-CP previously treated with 2 or more TKIs and those with the T315I mutation. The purpose of this multicenter study is to investigate the efficacy and safety of asciminib as second-line therapy for patients with CML-CP who had experienced treatment failure or intolerance to 1 prior TKI. The starting dose of asciminib is 80 mg daily. After 6 months of treatment, patients with a level of disease (BCR::ABL1 transcripts) less than 1% will continue the same dose of asciminib, whereas those with higher level of disease will increase the dose of 200 mg daily.

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

Third-Line Treatment and Beyond

1. A global multicenter, open label, randomized, phase III registrational study of olverembatinib (HQP1351) in patients with CML-CP (POLARIS-2)

Olverembatinib (HQP1351) is a novel third-generation BCR::ABL1 inhibitor that was approved in China for patients with CML-CP resistant and/or intolerant of first- and second-generation TKIs and for those with the T315I mutation. We aim to evaluate olverembatinib in 2 different parts. In part A, we will compare the efficacy and safety of olverembatinib given orally every other day to that of bosutinib (second-generation TKI) given orally daily in patients previously treated with at least 2 TKIs. Part B is a single-arm cohort to evaluate the efficacy and safety of olverembatinib in patients with CML-CP with the T315I mutation previously treated with at least 1 TKI and without other available effective treatment options.

This study will be open soon. For additional information, please contact Dr. Elias Jabbour or any other leukemia doctor.

2. Phase Ib study to determine the safety, tolerability, pharmacokinetics and preliminary efficacy of TGRX-678 in patients with refractory or relapsed CML

TGRX-678 is a potent BCR::ABL1 allosteric inhibitor with a novel structure. It selectively binds to the myristoyl pocket of BCR::ABL1 protein, and, by doing so, restores negative regulation of its kinase activity. This drug has

been evaluated in a Chinese study of 99 patients with CML-CP or CML-AP failing prior TKIs, with or without the T315I mutation. The current study aims to evaluate TGRX-678, given orally daily at different dose levels, among patients intolerant or resistant to ≥2 prior TKIs for patients without T315I mutation, or intolerant or resistant to at least 1 prior TKI for patients with T315I mutation. The dose escalation phase of the study will determine the safety of TGRX-678 and the recommended dose for expansion. The second part of the study is the expansion cohort to determine the recommended Phase 2 dose of TGRX-678.

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

3. A phase I clinical trial to evaluate the safety, tolerability, pharmacokinetics, and efficacy of TERN-701 in patients with chronic myeloid leukemia

TERN-701 is an orally available allosteric inhibitor of BCR::ABL1 that selectively binds to the myristoyl pocket of BCR::ABL1 to restore the negative regulatory function of BCR::ABL1 kinase activity. Nonclinical studies have shown that TERN-701 significantly inhibits the proliferation of tumor cells harboring native (nonmutated) BCR::ABL1 and BCR::ABL1 with mutations in the ATP binding site. TERN-701 also showed equivalent or superior suppression of BCR::ABL1 kinase activity and antitumor activity when compared with asciminib. The purpose of the trial is to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of TERN-701 in patients with previously treated CML-CP and select the optimal dose and schedule of TERN-701 in patients with or without the T315I mutation.

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

4. A Phase Ia/Ib Study of ELVN-001 for the Treatment of Chronic Myeloid Leukemia

ELVN-001 is a potent, oral ABL1 kinase inhibitor with preclinical data supporting the potential to target the T315I mutation. Preclinical studies showed that ELVN-001 has a favorable safety profile, with the potential for less drug-drug interactions, particularly in relationship to CYP3A. This is a first-in-human multicenter clinical trial designed to characterize the safety, tolerability, pharmacokinetic properties, and preliminary efficacy of this drug in patients with CML-CP, with or without T315I mutations, whose disease has failed or who has become intolerant to previous therapies.

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

CML in Lymphoid Blastic Phase

Phase I study of HQP1351 (olverembatinib) with blinatumomab in refractory CML in lymphoid blastic phase and Philadelphia chromosome-positive acute lymphoblastic leukemia

HQP1351 (olverembatinib) is a novel and potent third-generation BCR::ABL1 TKI with robust activity in patients with CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) refractory to previous therapies or with the T315I mutation. Blinatumomab is a bispecific T-cell engager that has demonstrated significant anti-leukemic activity in patients with ALL. More recently, the combination of blinatumomab and ponatinib has resulted in an overall response rate of 83% and a complete molecular response rate of 33% in patients with CML in lymphoid BP.[4] In this multicenter, open-label, randomized phase Ib study, we aim to evaluate the efficacy and safety of HQP1351 given orally every other day in combination with blinatumomab in patients with CML in lymphoid BP or Philadelphia

chromosome-positive ALL who have experienced resistance or intolerance to at least one second- or later-generation TKI.

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

CML in Myeloid Blastic Phase

A phase I study of decitabine, lisaftoclax, and olverembatinib in patients with advanced CML and Philadelphia chromosome-positive acute myeloid leukemia

In a prospective study of 15 patients with advanced CML, the combination of decitabine, venetoclax and ponatinib resulted in an overall response rate of 73%, which translated to a median overall survival of 11.0 months.[11] However, for patients who progress despite ponatinib therapy, there are no effective, commercially available BCR::ABL1 TKIs. Furthermore, ponatinib is associated with the potential for significant cardiovascular toxicity. Olverembatinib is a novel BCR::ABL1 TKI that is active in CML, including in patients with advanced-phase CML and in those with T315I mutations. Lisaftoclax is an oral, selective BCL-2 inhibitor that has shown preclinical and clinical activity in hematologic malignancies with important pharmacologic properties differential from venetoclax, which might lead to lower rates of myelosuppression. The combination of decitabine, lisaftoclax, and olverembatinib has the potential to be active in patients with highly resistant advanced-phase CML, including those with prior ponatinib exposure and/or T315I mutations. The use of olverembatinib may be safer than the use of ponatinib, and thus could offer a superior risk/benefit profile to alternative ponatinib-based strategies in this disease.

This study will be open soon. For additional information, please contact Dr. Nicholas Short or any other leukemia doctor.

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