

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Asciminib for the Treatment of Patients With Chronic Myeloid Leukemia



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H&O What is the current treatment approach for patients with chronic myeloid leukemia (CML)?

JC Patients with CML begin treatment with a tyrosine kinase inhibitor (TKI) upon diagnosis. Four TKIs are approved by the US Food and Drug Administration (FDA) for the frontline treatment of CML. Imatinib was the first TKI. The second-generation TKIs are dasatinib (Sprycel, Bristol Myers Squibb), nilotinib (Tasigna, Novartis), and bosutinib (Bosulif, Pfizer). These drugs are all very effective.

The life expectancy for patients with CML has almost reached that of the general population. To determine the best drug for a particular patient, physicians evaluate characteristics such as comorbidities and treatment objectives; disease characteristics; and drug characteristics and schedule of administration. The efficacy of these treatments allows physicians to consider all of these factors when selecting which drug might be the best match for each patient.

As good as these treatments are, however, studies show that by 5 years, 40% of patients have discontinued or changed therapy. Some patients develop toxicities. Therefore, other options are needed after treatment with first- and second-generation TKIs. There is one third-generation TKI currently approved by the FDA in this setting: ponatinib (Iclusig, Takeda). This drug is effective, with high response rates among patients who have received multiple prior therapies and/or who have the T315I mutation. Ponatinib has been associated, however, with some safety concerns. Although largely manageable,

the risk of arterio-occlusive events may limit its use in some patients. Additional third-generation TKIs would be welcome.

H&O What type of drug is asciminib?

JC Asciminib is a third-generation TKI. It has unique characteristics, and could be considered a first-in-class agent based on its binding site. The other TKIs bind in the location where ATP binds in the BCR-ABL protein. Asciminib is the first TKI to target the ABL1 myristoyl pocket, and it is therefore known as a STAMP inhibitor (which stands for Specifically Targeting the ABL1 Myristoyl Pocket). The myristoyl pocket can self-regulate, meaning that it can inhibit itself to regulate activity. When ABL binds to BCR, it loses the ability to regulate itself, and acts in overdrive. Asciminib binds into that pocket, to inhibit the activity of BCR-ABL. The ABL myristoyl pocket is important because most of the mutations seen in the clinic today tend to affect the ATP-binding pocket. Therefore, many of these mutations are targeted by the approved TKI inhibitors. Most TKI inhibitors lose activity in the presence of some of these mutations, particularly T315I. Only ponatinib has demonstrated activity against T315I in the laboratory and in the clinic. Asciminib works very well against all these other mutations because it binds in this different domain. Asciminib inhibits all of the mutations seen in the clinic among patients who are exposed to the standard TKIs. Importantly, asciminib inhibits T315I. We need more treatments that target this mutation.

H&O What have early data shown?

JC Asciminib has shown remarkable clinical activity in patients who have received treatment with other TKIs. Early studies showed that asciminib can work well in patients who have received 2, 3, or more prior TKIs. It was fairly safe, with few major adverse events. There was not much cardiac toxicity, which is seen with the other TKIs.

H&O What were the findings of your recent study of asciminib in CML?

JC I presented results of a phase 1/2 trial of asciminib in patients with CML and the T315I mutation at the 62nd American Society of Hematology meeting. The only drug currently available for patients with this mutation is ponatinib. In the study, we treated 49 patients with asciminib. The response rate was outstanding. Nearly half of the patients achieved a major molecular response. Importantly, many of these patients had already received ponatinib and required additional therapy. For those patients, a different treatment is not just preferred, but required. In our trial, the response rate was somewhat lower, although still robust, among patients already treated with ponatinib. The response rates were 28.6% for those previously treated with ponatinib and 57.8% for those never treated with ponatinib. These are excellent response rates in such a difficult-to-treat patient population with no other treatment options.

Asciminib was generally well tolerated. The most significant side effects were a mild elevation in one of the pancreatic enzymes and a small reduction in platelets. These events were manageable with dose adjustments and good monitoring.

Earlier studies showed that asciminib has activity in patients without mutations or with other types of mutations. Our study showed that asciminib could be a valuable treatment for patients with CML and the T315I mutation. More data are needed, but asciminib appears to be a promising therapy for patients who require additional treatment after other TKIs.

H&O Are there better candidates for treatment with asciminib?

JC We were not able to identify any particular subgroups with a particular benefit. Asciminib works similarly well across the different mutations and patient characteristics. It is also fairly safe. There is not a high incidence of arterio-occlusive events (although patients should still be monitored for these events). Asciminib appears to be a well-rounded drug.

H&O What is next for asciminib in CML?

JC The randomized phase 3 ASCEMBL trial compared asciminib with bosutinib among patients with CML who had received 2 or more TKIs. The study was performed to generate data for approval of asciminib by the US Food and Drug Administration (FDA). Asciminib significantly improved the major molecular response rate vs bosutinib, and showed better tolerability. Hopefully, the FDA will approve asciminib for the treatment of patients with CML who received other therapies that failed.

Further research will evaluate whether asciminib can be used earlier in the treatment course. Currently, it has been evaluated in patients already treated with several TKIs. However, the efficacy and safety of asciminib raises the possibility that it could be used earlier, perhaps in patients previously treated with 1 or 2 TKIs. When a patient's initial therapy is a second-generation TKI, there are not many treatment options afterward. Asciminib might be useful in this setting. It might even be useful as first-line therapy.

Disclosure

Dr Cortes is a consultant for Novartis, Pfizer, Takeda, and Sun Pharma. He has received research support (directed to his institution) from BMS, Novartis, Pfizer, Takeda, and Sun Pharma.

Suggested Readings

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