

ADVANCES IN LLM

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The Current Status of Ponatinib in the Treatment of Chronic Myeloid Leukemia



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H&O What is ponatinib, and how does it differ from other treatments for chronic myeloid leukemia (CML)?

MD As is widely known, imatinib (Gleevec, Novartis) was the first of the so-called tyrosine kinase inhibitors (TKIs) developed for the treatment of CML. Imatinib was followed by second-generation TKIs, such as dasatinib (Sprycel, Bristol-Myers Squibb) and nilotinib (Tasigna, Novartis). Clinical experience has shown that a significant proportion of patients exhibit primary or acquired resistance to TKIs. Mutations in the kinase domain of BCR-ABL1 that impair drug binding are a key mechanism of resistance. Imatinib has a number of vulnerabilities, whereas the number of mutations conferring resistance to nilotinib and dasatinib is more limited. We know of one mutation, called T315I, that confers resistance against all first- and second-generation TKIs. The resistance of T315I against all first- and second-generation TKIs defined the need for an agent that could address this mutation.

Ponatinib (Iclusig, Ariad) was specifically designed to afford coverage of the T315I mutation. It binds to the kinase in a way that is similar to imatinib but is active against single mutations, including T315I. The first clinical trial of ponatinib was initiated in 2008.

H&O Did the clinical trials demonstrate efficacy among CML patients with the T315I mutation?

MD Yes. The first seminal paper describing the preclinical characterization of ponatinib was published in 2009 in *Cancer Cell*. The results of the subsequent phase 1

trial, which were published in the *New England Journal of Medicine* in 2012, showed that the drug had significant activity in CML patients whose disease had failed to respond to prior TKI treatment, including those with the T315I mutation. Activity was also demonstrated in patients with acute lymphoblastic leukemia (ALL) harboring the Philadelphia chromosome, the mutation that triggers most cases of CML and a subtype of ALL.

This clinical activity led to a large phase 2 clinical trial known as PACE (Ponatinib Ph+ ALL and CML Evaluation), which confirmed the responses seen in phase 1. The results, which were published in the *New England Journal of Medicine* in 2013, led to regulatory approval.

H&O Has ponatinib become a mainstay of treatment for CML patients with the T315I mutation?

MD Yes. The product label approved by the US Food and Drug Administration (FDA) states that the drug is for patients with the T315I mutation or for whom no other TKI is indicated. This broad indication reflects the finding in clinical trials that ponatinib showed a benefit for patients with this particular mutation, for patients with other mutations, and also for patients in whom no BCR-ABL1 mutations are detectable.

H&O Toward the end of 2013, problems emerged with side effects. Could you discuss what happened?

MD The phase 2 trial of ponatinib continued following regulatory approval of ponatinib, and a variety of vascular

adverse events began to emerge. These adverse events included myocardial infarctions, strokes, peripheral arterial occlusive disease, and some venous thromboembolism. The incidence of these side effects increased with longer observation, which led to temporary withdrawal of ponatinib from the US market. During that time, the drug was available in the United States only through single-patient investigational new drug (IND) applications.

After about 2 months, the FDA reissued regulatory approval, with stipulations requiring the manufacturer to provide additional data on cardiovascular and thromboembolic events and a new product label that is somewhat more restrictive than the earlier version.

H&O What are the implications for physicians recommending ponatinib for the treatment of CML?

MD Physicians using ponatinib for the treatment of CML need to make a thorough risk-benefit assessment. The patient has to belong to a population for whom the potential benefit clearly outweighs the potential risk. Of course, this consideration should always be part of providing care to patients, and is not specific to ponatinib.

H&O For what patient populations is ponatinib an appropriate treatment choice?

MD Ponatinib is not approved for first-line treatment, and it is oriented toward patients whose disease has progressed during treatment with other TKIs, including those with the T315I mutation. For patients who have failed second-generation TKIs, there are not many good therapeutic alternatives. Some patients may try omacetaxine (Synribo, Teva) or a conventional drug such as hydroxyurea, but these are palliative therapies only, leaving allogeneic stem cell transplant as a potentially curative alternative. Given the risks of transplant, ponatinib may be a better choice, particularly for patients in the chronic phase. For patients without the T315I mutation who have developed resistance to imatinib, a second-generation inhibitor would likely be the appropriate salvage treatment. If the second-generation inhibitor proves ineffective, then a strong case can be made for ponatinib.

H&O What are the criteria for determining whether ponatinib would be appropriate for such patients?

MD There are 2 main factors to consider: the aggressiveness of the disease and the patient's comorbidities. For patients with aggressive disease—for example, a relapse into blast crisis—the priority is to exploit the

strongest inhibitor available in order to provide the maximum chance of controlling the disease with a TKI; an allogeneic stem cell transplant is a possible option following TKI initiation. The choice of TKI at this stage needs to be decided according to which drug offers the highest likelihood of disease control. The advantage of ponatinib is its comprehensive coverage of BCR-ABL1 mutants, including T315I.

With regard to comorbidities, patients with diabetes, hypertension, preexisting coronary artery disease, a history of strokes, or peripheral arterial occlusive disease would all be at a higher risk of experiencing vascular side effects on ponatinib. In these cases, there is no replacement for clinical judgment. If the clinician's assessment is that the risks of the CML override the risk of the comorbidities and their potential aggravation by ponatinib, then there is a sound rationale for using it. However, if there is a concern about potentially serious cardiovascular events resulting from ponatinib that place the patient at greater risk than the CML does, it should not be used. Guidelines are available to help clinicians navigate the available treatments, but nothing can replace clinical judgment.

H&O As a clinician who treats patients with CML, could you discuss your experience when ponatinib was taken off the market?

MD Patients were very concerned about losing access to the drug, especially those patients who had no alternative. However, during that time patients could apply for a single-patient IND. These INDs were typically granted, but the bureaucracy associated with the application was significant. The fact that many clinicians went through the bureaucratic process to obtain ponatinib for their patients helped convince the FDA of the need for this agent. The patient population likely to benefit from this drug may not include tens of thousands of people, but there are a significant number of individuals who have no other option. These were the patients who worried about losing their life-saving medication.

H&O Did a parallel situation occur in Europe with regard to rescinding approval temporarily?

MD The European Medicines Agency (EMA) took a slightly different approach. The drug label in Europe was more restrictive from the start, and did not change when the cardiovascular events became more apparent. The EMA issued a statement urging clinicians to evaluate patients very carefully, but the label was not changed.

The different responses make for an interesting juxtaposition. The FDA had a more lenient approval and then

took the extreme approach of pulling the drug from the market. The EMA was stricter from the beginning and simply remained that way, avoiding the upheaval among patients that occurred after ponatinib's suspension.

H&O Could there have been more measures in place during the clinical trials so that these adverse events would have been observed earlier?

MD Of course it is easy to be wise in hindsight. A more detailed analysis of the PACE trial has shown a correlation between the risk of these adverse events and dosing. A lower dose correlates with a lower risk. Starting with a lower dose may reduce the thromboembolic events by a significant margin, but this assertion needs to be tested in clinical trials.

One practical consideration in light of the trials could be that patients who achieve a good response at the recommended starting dose of 45 mg could then have their dose reduced. Clinicians can monitor these patients carefully to be sure that the response is being maintained at this lower dose.

Another practical consideration raised by the ponatinib story has to do with prevention. Are there any measures that can be taken to prevent the blood clots from occurring in the first place? With lenalidomide (Revlimid, Celgene) for myelodysplastic syndrome or myeloma, patients are advised to take anticoagulation drugs because lenalidomide

carries a high risk of deep vein thrombosis. There may be a similar preventive treatment for ponatinib. This possibility needs to be explored in a clinical trial setting.

H&O Is this change in approval status unusual occurrence for a new drug?

MD None of this is unusual. When a new drug is approved, there is always a period of learning how to use it. There was, and is, a great medical need for ponatinib. Even with imatinib, which was approved 13 years ago, there is still some debate about the optimal dose. Sometimes it just takes a little while to be sure of how best to use a particular agent.

Suggested Reading

Baccarani M, Deininger MW, Rosti G et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. 2013;122(6):872-884.

Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2012;367(22):2075-2088.

Cortes JE, Kim DW, Pinilla-Ibarz J, et al; PACE Investigators. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2013;369(19):1783-1796.

O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. *Cancer Cell*. 2009;16(5):401-412.