Ponatinib: Targeting the T315I Mutation in Chronic Myelogenous Leukemia

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**H&O** What is chronic myelogenous leukemia (CML), and how is it currently treated?

**NS** CML is a myeloproliferative disorder that is associated with the presence of the BCR-ABL tyrosine kinase. While timely allogeneic stem cell transplantation was previously the preferred treatment modality in eligible patients, the chronic phase of CML can now be well-controlled in the vast majority of patients with orally administered selective inhibitors of BCR-ABL, such as imatinib (Gleevec, Novartis), dasatinib (Sprycel, Bristol-Myers Squibb), and nilotinib (Tasigna, Novartis), which are generally well-tolerated.

**H&O** What is the current outlook for those who harbor T315I mutations?

**NS** The BCR-ABL/T315I mutation, which was first identified by Drs. Mercedes Gorre and Charles Sawyers at the University of California, Los Angeles, is unfortunately highly resistant to imatinib, dasatinib, and nilotinib, the other approved BCR-ABL tyrosine kinase inhibitors (TKIs). Patients whose disease evolves this mutation have no effective medical options, and allogeneic stem cell transplantation has been the only treatment strategy to offer any substantial promise of providing long-term disease control.

**H&O** What is ponatinib, and how is its mechanism of action different from other CML drugs?

**NS** Ponatinib (ARIAD Pharmaceuticals) is a novel, orally active, multi-targeted TKI. The primary target for ponatinib is BCR-ABL, which is considered the hallmark of CML and Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL). Ponatinib is considered to be a pan-BCR-ABL inhibitor. It was designed to bind BCR-ABL with very high potency, and to inhibit the entire spectrum of mutants conferring resistance against other TKIs, including the T315I mutant that is resistant to all current therapies. In preclinical studies, ponatinib exhibited broad-spectrum inhibition of all BCR-ABL mutants.

**H&O** Can you discuss some key findings from the phase I trial of oral ponatinib?

**NS** The trial included 74 patients with refractory disease, 60 of whom had CML. Sixty patients were known to have had prior TKI therapy, and 95% had been resistant to at least 2 TKIs. Of the 9 evaluable CML patients who had the T315I mutation, all achieved a major cytogenetic response, 8 patients had a complete cytogenetic response, and 7 patients had a major molecular response. Encouragingly, responses in chronic phase appeared to be remarkably durable, considering the heavily pretreated and highly resistant nature of disease in most of these patients. Of the 38 chronic phase
CML patients, 95% achieved or maintained a complete hematologic response, 66% had a major cytogenetic response, 53% had a complete cytogenetic response, and 43% had a major molecular response. Of the 17 patients in advanced stages of CML, 35% achieved or maintained a major hematologic response, 24% had a major cytogenetic response, and 12% had a complete cytogenetic response. Ponatinib appeared to be generally well-tolerated. The most common adverse events (≥10%) included thrombocytopenia, headache, nausea, arthralgia, fatigue, anemia, increased lipase, muscle spasms, rash, myalgia, and pancreatitis.

**H&O** Are there any emerging data that suggest additional promise for ponatinib?

**NS** The preliminary analysis of the phase I clinical trial revealed evidence of clinical antitumor activity in patients with resistance to approved, second-generation TKIs, including patients with the T315I mutation of BCR-ABL. This study, in addition to the strong preclinical data that characterize ponatinib, provides the rationale for moving to a pivotal phase II trial in a population of patients with CML and Ph+ ALL who are resistant or intolerant to prior TKI therapy, and in patients with the T315I mutation. Interim clinical data from the fully enrolled, pivotal PACE (Ponatinib Ph+ ALL and CML Evaluation) trial of ponatinib will be presented in December at the 53rd annual meeting of the American Society of Hematology (ASH).

Further, ponatinib has in vitro activity against FLT3, which is pathologically activated in approximately 30% of patients with AML. Seven FLT3 kinase inhibitor-naïve, FLT3-ITD-positive AML patients were treated in our phase I study, and 2 achieved normalization of bone marrow blast percentage, albeit with incomplete hematologic recovery. A phase II study of ponatinib in FLT3-ITD-positive AML is warranted.

**H&O** What are the future avenues of research in this area?

**NS** Given its apparent invulnerability to resistance-conferring BCR-ABL kinase domain mutations—the most common molecular mechanism of loss of response to BCR-ABL kinase inhibitors—it will be interesting to see how ponatinib fares in previously untreated, chronic phase CML patients, particularly with respect to durability of response. As our ability to treat BCR-ABL-dependent mechanisms of resistance to kinase inhibitors improves, it is possible that BCR-ABL-independent mechanisms will become more commonly encountered. A molecular understanding of these BCR-ABL-independent mechanisms of resistance will be important to further improve treatment outcomes. Another prominent area of research in CML involves attempts to eradicate CML stem cells, and achieve true cure of disease. Many such studies are currently in their infancy.

**Suggested Readings**

