ADVANCES IN LLM

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

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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 (Ponatinb 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

Cortes J, Talpaz M, Bixby D, et al. A phase I trial of oral ponatinib (AP24534) in patients with refractory chronic myelogenous leukemia (CML) and other hematologic malignancies: emerging safety and clinical response findings. *Blood* (ASH Annual Meeting Abstracts). 2010;116: Abstract 210.

Talpaz M, Shah NP, Deininger MW, et al. Ponatinib in patients with acute myeloid leukemia (AML): Preliminary findings from a phase I study in hematologic malignancies. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29: Abstract 6518.

Cortes J, Dong-Wook K, Pinilla-Ibarz J, et al. Initial findings from the PACE trial: a pivotal phase II study of ponatinib in patients with CML and Ph+ ALL resistant or intolerant to dasatinib or nilotinib, or with the *T315I* mutation. *Blood* (ASH Annual Meeting Abstracts). 2011;118: Abstract 109.