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Ponatinib: An oral tyrosine kinase inhibitor for the treatment of chronic myelogenous leukemia and Philadelphia chromosome -- positive acute lymphoblastic leukemia

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Focus on ponatinib

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Ponatinib (Iclusig; Ariad Pharmaceuticals) is an oral tyrosine kinase inhibitor (TKI) that was approved by FDA on December 14, 2012, for the treatment of adult patients with chronic-phase, accelerated-phase, or blast-phase chronic myelogenous leukemia (CML) that is resistant or intolerant to previous TKI therapy, and for Philadelphia chromosome (Ph)–positive acute lymphoblastic leukemia (Ph+ALL).[1]

CML accounts for a little over 10% of adult leukemias. In 2013, an estimated 5,920 cases will be diagnosed in the United States.[2] CML is a hematopoietic stem cell disease that is characterized by the Ph, which is formed from the translocation of chromosomes 9 and 22. A fusion protein product of Ph, BCR-ABL, is believed to give rise to CML and a subset of acute lymphoblastic leukemias that are positive for Ph (Ph+ALL). This BCR-ABL contains an activated tyrosine kinase domain that promotes cell growth. Current treatment for both CML and Ph+ALL includes TKIs such as imatinib (Gleevec), nilotinib (Tasigna), dasatinib (Sprycel), and bosutinib (Bosulif).[3]

Many patients are now showing resistance to standard TKI therapy. A major mechanism of resistance is mutation of the BCR-ABL kinase domain. One of the most common mutations (up to 20% of patients) is the T315I substitution, which leads to resistance to all the current TKIs.[3] Specifically, the isoleucine side chain of the T315I mutation does not form a hydrogen bond with the TKI, which then prevents the binding of the drug to BCR-ABL. Ponatinib has a unique scaffold chemical structure unlike other current TKIs. Due to its structure, ponatinib does not form a hydrogen bond with the T315 mutation, but is still able to link to the isoleucine side chain of the T315 mutation of the BCR-ABL through a novel triple bond linkage.[4]

Cortes et al[3] conducted a phase 1 dose-escalation clinical trial in 81 patients with resistant hematologic cancer including 60 with CML and 5 with Ph+ALL to determine the recommended dosage for ponatinib. Patients were eligible if they had relapsed or were resistant to standard care. In addition, they had to be older than age 18 and to have an Eastern Cooperative Oncology Group performance status of 2 or lower (range 0–5, with 0 being fully active). Ponatinib was administered once daily at a dose ranging from 2 to 60 mg. The median follow-up was 56 weeks.

Ninety-eight percent of patients with chronic-phase CML (CP-CML; n=43) had a complete hematologic response, 72% had a major cytogenic response, and 44% had a major molecular response. In the subset of patients with CP-CML who had the T315I mutation (n=12), all had a complete hematologic response and 92% had a major cytogenic response. All 13 patients with CP-CML without detectable mutations had a complete hematologic response, and 62% had a major cytogenic

response. In addition, in patients with accelerated-phase (AP) or blast-phase (BP) CML or Ph+ALL (N=22), 36% had a major hematologic response and 32% had a major cytogenic response.

This phase 1 trial led to a recommended dosage of 45 mg daily and showed that ponatinib was effective and had activity in patients in whom previous therapy had failed with multiple TKIs, including patients with the T315I mutation.[3]

The phase 1 trial was followed by the phase 2 PACE (Ponatinib Ph+ALL and CML Evaluation) trial, which led to the approval of ponatinib.[1,5] Patients with refractory CML or Ph+ALL resistant or intolerant to dasatinib or nilotinib or with the T315I mutation were enrolled in a single-arm, open-label, international multicenter trial. All patients were administered 45 mg ponatinib daily. The trial enrolled 449 patients—267 patients with CP-CML, 83 patients with AP-CML, 62 patients with BP-CML, and 32 patients with Ph+ALL. The median time from diagnosis to the ponatinib trial was 6 years, and the majority of patients had been treated with multiple TKIs. Prior treatment included imatinib (96%), dasatinib (85%), nilotinib (66%), and bosutinib (7%). It should also be noted that 94% of patients had failed ≥2 TKIs and 59% had failed ≥3 TKIs. Almost one-third of patients (29%) had the T315I mutation. The primary efficacy endpoint in the CP-CML cohort was major cytogenic response within 12 months, which was defined as 65% normal cells, or major hematologic response in the AP-CML, BP-CML, and Ph+ALL cohort within 6 months of treatment, defined as normal white blood cell counts.[5, 6]

A major cytogenic response was achieved in 54% of patients with CP-CML, including 49% who had been resistant or intolerant to previous TKI therapy and 70% with the T315I mutation. A complete cytogenic response defined as no measurable Ph-positive cells was achieved in 44% of patients. Major hematologic responses were seen in 52% of patients with AP-CML, 31% with BP-CML, and 41% with Ph+ALL.[6] There are no current data showing improvement in progression-free or overall survival.

Ponatinib is also currently being evaluated against imatinib for treatment-naïve CP-CML patients in an international, multicenter randomized trial.[7]

The most frequent adverse events during the PACE trial were hypertension (68%), rash (54%), abdominal pain (49%), fatigue (39%), headache (39%), dry skin (39%), constipation (37%), arthralgia (26%), nausea (23%), and pyrexia (23%). Myelosuppression also occurred in 48% of patients, with the incidence being higher in patients with AP-CML, BP-CML, and Ph+ALL. There were also cases of pancreatitis (6%), and it is recommended that serum lipase levels are checked every 2 weeks for the first 2 months of treatment and then monthly.[6]

The labeling for ponatinib also includes a boxed warning for both arterial thrombosis and hepatotoxicity. Serious arterial thrombotic events occurred in 8% of patients, with myocardial infarction or worsening coronary artery disease being the most common. Peripheral arterial events, deep vein thrombosis, pulmonary

embolism, and congestive heart failure were also reported. Aspartate aminotransferase or alanine aminotransferase elevation was seen in 56% of patients, and 3 cases of acute liver failure resulting in death did occur.[6]

Ponatinib is a substrate of CYP3A4 and is expected to interact with both inducers and inhibitors of the enzyme. Coadministration with a strong inducer such as carbamazepine or phenytoin is not recommended, and a dosage adjustment is recommended in patients taking a concurrent CYP 3A4 inhibitor such as clarithromycin or ketoconazole. Medications that elevate the gastric pH, such as antacid H-2 blockers and proton pump inhibitors, should also be avoided due to the reduction in bioavailability of ponatinib.[6]

Ponatinib will be available in both 15- and 45-mg tablets. The usual dose will be 45 mg once daily with or without food. A dosage reduction to 30 mg once daily is recommended in patients being treated with a strong CYP 3A4 inhibitor. Dosage adjustments are also recommended for patients experiencing myelosuppression, elevations in liver enzymes, or elevations in serum lipase and/or a diagnosis of pancreatitis.[6]

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