

Ponatinib: a miracle or a disaster in chronic myeloid leukemia**Ayan Pal, Buddhadev Panja*, Trayambak Dutta, Subhrojyoti Bhowmick, Sarmila Nath, Sipra Bhattacharjee**

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ABSTRACT

Chronic myeloid leukemia (CML), the most common myeloproliferative disorder, occurring due to balanced reciprocal translocation between chromosome 9 and 22 and resulting in a chimeric oncogene called breakpoint cluster region-abelson (*BCR-ABL*) whose protein product has tyrosine kinase activity, causes uncontrolled proliferation of the myeloid cells. Although, imatinib, the first-generation tyrosine kinase inhibitor (TKI) achieved an extremely high response rate, some patients developed resistance to it. Thus, second-generation TKIs such as nilotinib, dasatinib, bosutinib were developed which proved very useful, till the emergence of T315I point mutation which occurs in the *BCR-ABL* gene and renders CML resistant to previous TKIs. Ponatinib, a third generation TKI approved by the United States Food and Drug Administration (FDA), showed great promise as it was effective even against T315I point mutation. However, a recent increase in the incidence of blood clots observed in patients taking ponatinib has resulted in FDA temporarily suspending all trials, marketing and distribution of the drug. Hence, whether ponatinib evolves as a miracle or disaster for the patients of CML is yet to be answered.

Keywords: Chronic myeloid leukemia, Ponatinib, Ponatinib Philadelphia positive acute lymphoblastic leukemia and chronic myeloid leukemia evaluation, Evaluation of ponatinib versus imatinib in CML, T315I mutation

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal hematopoietic disorder caused by an acquired genetic defect in pluripotent stem cells. CML is the most common leukemia in adults in India and the annual incidence ranges from 0.8 to 2.2/100,000 population in males and 0.6-1.6/100,000 population in females in India.¹ The median age of diagnosis is 38-40 years.² This is a decade earlier than the median incidence in the western world. Though CML is predominantly a disease affecting adults, children and young adults may also be affected.

The disease is characterized by an insidious onset of symptoms, progressive splenomegaly, anemia, leukocytosis, marrow hypercellularity and cytogenetically by the presence of Philadelphia (Ph) chromosome t(9;22)(q34;q11). The disease follows a biphasic or triphasic course that starts with an initial chronic phase (CP), which after an average of 5-5.5 years, may progress to an intermediate phase called

accelerated phase (AP) followed by blast phase (BP) or blast crisis. At the time of presentation, 90-95% of patients are in the CP while the remaining may have features of advanced disease.³

The characteristic genetic change in CML is the formation of Ph chromosome, which is formed by balanced reciprocal translocation between long arms of chromosome 9 and 22. This transposes Abelson (ABL) proto-oncogene from chromosome 9 to breakpoint cluster region (BCR) on chromosome 22 creating the *BCR-ABL* fusion gene. The transcribed fusion protein, which resides in the cytoplasm, has tyrosine kinase activity leading to uncontrolled proliferation of clonal cells.

The main goal of CML treatment is a complete cytogenetic response, which means the absence of detectable Ph translocations in the bone marrow. The major modality of treatment of CML is inhibitors of the enzyme tyrosine kinase. They competitively inhibit adenosine triphosphate,

which is required for phosphorylation of tyrosine residues of downstream proteins in the signaling pathways of ABL tyrosine kinase. The most common tyrosine kinase inhibitor (TKI) used is imatinib.

Imatinib is regarded as first-generation drug since it is the first BCR-ABL TKI to be used in the treatment of CML. Although the treatment with imatinib had extremely high response rate and a low relapse rate in CML patients, some patients developed resistance or intolerance to imatinib.⁴ The subset of patients who are resistant to imatinib are then moved to a second-line treatment.

Second-generation drugs have decreased resistance and intolerance than imatinib, of which currently marketed are nilotinib, dasatinib, and bosutinib. The emergence of T315I point mutation that occurs in the BCR-ABL gene rendered CML resistant to most TKIs. Thus, third-generation drugs like ponatinib was developed, which is effective even against T315I point mutation, which is emerging as a common pathway to failure of both first and second-line treatments.

Discovery

Ponatinib is a rationally designed, small-molecule organic compound developed by ARIAD Pharmaceuticals in Cambridge, Massachusetts.

Ponatinib was designed using ARIAD's computational and structure-based drug design platform to inhibit the enzymatic activity of BCR-ABL with very high potency and broad specificity. Ponatinib was intended to target not only native BCR-ABL, but also its isoforms that carry mutations that confer resistance to treatment with existing TKIs, including the T315I mutation for which no effective therapy exists.⁵

Mechanism of action

Ponatinib is a TKI. Ponatinib inhibited the *in vitro* tyrosine kinase activity of ABL and T315I mutant ABL with inhibitory concentration 50 (IC₅₀) concentrations of 0.4 and 2.0 nM, respectively. Ponatinib inhibited the *in vitro* activity of additional kinases with IC₅₀ concentrations between 0.1 and 20 nM, including members of the vascular endothelial growth factor, platelet-derived growth factor, fibroblast growth factor receptor, EPH receptors and SRC families of kinases, and KIT, RET, TIE2, and FLT3. Ponatinib inhibited the *in vitro* viability of cells expressing native or mutant BCR-ABL, including T315I. In mice, treatment with ponatinib reduced the size of tumors expressing native or T315I mutant BCR-ABL when compared with controls.

Advantage of ponatinib over imatinib and other TKIs

Imatinib (Gleevec, previously STI571), was introduced as a first-line treatment for CML almost 12 years ago and radically improved the outcome of patients with CML. It

inhibits the tyrosine kinase activity of BCR-ABL. Imatinib has been the standard therapy for CML due to its remarkable activity and mild toxicity. In the IRIS study (International randomized study of interferon vs. STI571) of first-line treatment with imatinib or interferon and cytarabine in patients with newly diagnosed CP-CML, patients in the imatinib arm had an 8-year overall survival rate of 85% and freedom from progression to advanced disease was 92%.⁶ Imatinib was found to be well tolerated during long-term treatment.

Despite the responses observed with imatinib, resistance to imatinib or relapse in patients with CML developed most frequently because of point mutations within the BCR-ABL coding sequence.^{7,8} This led to the development of newer TKIs of BCR-ABL like dasatinib, nilotinib, bosutinib which effectively inhibit the majority of mutated forms of BCR-ABL that have been associated with imatinib resistance.⁹⁻¹¹ However, the T315I point mutation confers resistance to imatinib, dasatinib, nilotinib, and bosutinib.^{12,13}

Ponatinib (iclusig, previously AP24534) was approved by the United States Food and Drug Administration (USFDA) on December 14, 2012, for use in patients with CML and also Ph chromosome-positive (Ph+) acute lymphoblastic leukemia (Ph+ ALL) who has relapsed or is refractory to other therapies. Many of these patients, but not all, had developed a T315I mutation, which makes the disease resistant to the standard treatment with TKIs such as imatinib.

Ponatinib is a very potent TKI that was specifically designed to treat the T315I point mutation while maintaining efficacy against all other known BCR-ABL permutations. Although ponatinib has many similar side-effects as other TKIs, its ability to treat a previously intractable mutation makes it very promising. Since it is very effective against T315I-mutated BCR-ABL and in patients who have not responded to multiple other TKIs, ponatinib was recently approved as a second-line treatment for CML patients with a boxed warning alerting patients and healthcare professionals that the drug can cause blood clots and liver toxicity.

Clinical studies on ponatinib

The Ponatinib Ph+ ALL and CML evaluation (PACE) trial is a pivotal Phase 2 clinical trial of ARIAD's investigational BCR-ABL inhibitor, ponatinib. It was designed to provide definitive clinical data in patients with resistant or intolerant CML and Ph+ ALL.

It is a global, single-arm clinical study of oral ponatinib in 449 patients with CP, AP, or BP CML, as well as Ph+ ALL. Patients resistant or intolerant to dasatinib or nilotinib, or with T315I mutation of BCR-ABL were enrolled in the trial. The trial was conducted between September 2010 and September 2011.

Patients were grouped into one of six separate cohorts based on their phase of CML (i.e. chronic, accelerated or blast) and BCR-ABL mutation status (i.e. with or without the T315I mutation); Ph+ ALL patients were grouped with BP CML. A total of 160 patients with CP CML were included. The primary endpoints were major cytogenetic response (MCyR) rate for CP patients and major hematologic response (MaHR) rate for AP or BP CML patients and Ph+ ALL patients. Patients receive ponatinib in tablet form once daily at a dose of 45 mg. The PACE trial was conducted at approximately 60 centers in North America, Europe, Australia, and Asia.

The efficacy results demonstrated a 54% MCyR rate in patients with CP-CML. 70% of patients with CP-CML with T315I mutation achieved MCyR. The median duration of MCyR had not yet been reached at the time of analysis. For patients with AP-CML, BP-CML and Ph+ ALL, the MaHR rates were 52%, 31%, and 41%, respectively. The median duration of MaHR in patients with AP-CML, BP-CML and Ph+ ALL was 9.5 months, 4.7 months and 3.2 months, respectively.¹⁴

The USFDA approved ponatinib 3 months before its official deadline for acting on the drug's marketing application based on a single Phase 2 trial, results of which were reported at the American Society of Hematology's annual meeting held in Atlanta in 2012.

The evaluation of ponatinib versus imatinib in CML (EPIC) phase-III trial which began in June 2012 with an estimated study completion date of June 2021, is designed to provide definitive clinical data to support regulatory approval of ponatinib in treatment-naïve CML patients.

It is a randomized, open-label, two-arm, multicenter trial that compares the efficacy of ponatinib with that of imatinib in adult patients with newly diagnosed CML in the CP. The trial was being conducted at approximately 150 investigational sites in more than 20 countries. Patients above 18 years of age and diagnosed with CML within 6 months prior to enrollment were selected. Approximately, 500 patients were randomized 1:1 to the standard dose of ponatinib (45 mg given orally once daily) or imatinib (400 mg given orally once daily).

The USFDA issued a partial clinical hold on new trial enrollment for iclusion on 9 October, 2013 due to an increased number of blood clots observed in patients taking the drug.¹⁵ The EPIC trial was later canceled on 18 October.¹⁶

Adverse reactions

The main adverse reactions are:

- Thrombosis and thromboembolism
- Hepatotoxicity
- Congestive heart failure
- Hypertension
- Pancreatitis
- Hemorrhage

- Fluid retention
- Cardiac arrhythmias
- Myelosuppression.

Recent safety issues regarding ponatinib use

Marketing and commercial distribution of ponatinib (Iclusig) has been temporarily suspended, following an ongoing FDA investigation that revealed an increased frequency of severe arterial thrombosis and stenosis. The drug was initially approved with a boxed warning noting that the arterial thrombosis occurred in 8% of patients. Following its investigation, the FDA revealed that approximately 24% of patients in the Phase 2 trial had experienced serious vascular adverse events (AEs), after median treatment duration of 1.3 years. After a follow-up of 2.7 years in the Phase 1 development, the rate of serious vascular AEs was even higher at 48%, have experienced serious adverse vascular events, including fatal and life-threatening heart attack, stroke, loss of blood flow to the extremities resulting in tissue death, and severe narrowing of blood vessels in the extremities, heart, and brain requiring urgent surgical interventions to restore blood flow. In some patients, fatal and serious AEs have occurred as early as 2 weeks after starting ponatinib hydrochloride therapy.¹⁷

The clinical development of ponatinib was placed on hold in early October 2013 while the FDA investigated the AEs associated with the drug. This was shortly followed by the early termination of the phase III EPIC trial on 18 October, which was examining ponatinib in the frontline setting for untreated patients with CML. The drug manufacturer, ARIAD Pharmaceuticals, have agreed to FDA's request to suspend marketing and sales of iclusion while they continue to evaluate the safety of the drug.

The FDA will continue to evaluate whether the benefits of treatment outweigh the risks. Patients currently receiving ponatinib should discuss with their healthcare professionals the risks and benefits of continuing treatment with the drug. At this time, patients and health care professionals are following FDA's new recommendations for the drug:

- Patients currently taking ponatinib hydrochloride who are not responding to the drug should immediately discontinue treatment and discuss alternative treatment options with their healthcare professionals¹⁷
- Patients who are currently taking ponatinib hydrochloride and responding to the drug and whose health care professionals determine that the potential benefits outweigh the risks should be treated under a single-patient Investigational New Drug (IND) application or expanded access registry program while FDA's safety investigation continues. FDA will work with the manufacturer on a plan to quickly transition these patients to a program that will allow access under an IND or expanded access registry program¹⁷
- Health care professionals should not start treating new patients with ponatinib hydrochloride unless no other

treatment options are available and all other available therapies have failed. Upon the determination of their health care professional, these patients can be considered for treatment under an IND or expanded access registry program.¹⁷

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