Where Exactly Does Ponatinib Fit in Chronic Myelogenous Leukemia?

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Abstract

Ponatinib holds a unique place in the spectrum of drugs in use for the treatment of chronic myelogenous leukemia. It is perhaps the most active tyrosine kinase inhibitor (TKI) among those currently licensed; 51% of patients resistant to or intolerant of second-generation TKIs experienced a major cytogenetic response and 70% of patients with the highly resistant T315I BCR-ABL1 mutation experienced a major cytogenetic response. However, 1 year after its accelerated approval by the FDA, and midway through its phase III pivotal trial, a high number of vascular occlusive events began to be reported. The FDA put a partial clinical hold on the drug and the phase III trial was halted. Dose-reduction recommendations were made, and the drug is now used in patients for whom no alternative TKI is available and those who have the T315I mutation. Currently, the substantial and durable responses that this drug provides are difficult to balance against the late-in-course vascular occlusive events. The hope is that ongoing research into the mechanism of presumed endothelial damage will provide a better understanding of how to position this drug for optimal use.

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Resistance to Front-Line Therapy: How Big is the Problem?

Ponatinib was fast-tracked by the FDA in December 2012, for use in patients whose disease progressed on or who could not tolerate therapy with first-line agents imatinib, dasatinib, or nilotinib based on results of phase I and II trials that showed greater than 70% major cytogenetic response rates in heavily pretreated patients. Ponatinib was also approved for patients with the T315I BCR-ABL1 mutation, with similar response rates in this highly resistant mutation. However, less than 1 year later, in October 2013, the FDA temporarily suspended the drug from commercial distribution in the United States because of accumulating reports of vascular occlusive events, including stroke, myocardial infarct, and venous and arterial thrombosis occurring at rates higher than previously reported. A national multicenter trial that was comparing ponatinib and imatinib in patients with newly diagnosed chronic phase disease was halted. Patients with the T315I mutation or who had no other tyrosine kinase inhibitor (TKI) option required a single-patient Investigational New Drug (IND) approval from the FDA to receive the drug. Ponatinib was re-released in December 2013, with revised prescribing information, including a boxed warning of vascular risks. In turn, ponatinib’s sponsor, ARIAD Pharmaceuticals, Inc. (Cambridge, MA), is actively attempting to clarify the mechanisms underlying the vascular occlusive events.

To better understand how ponatinib fits into the chronic myelogenous leukemia (CML) treatment paradigm, the degree of resistance to first-line drugs imatinib, dasatinib, and nilotinib must be understood. Despite the extraordinary response rates first reported in the original International Randomized Study of Interferon and STI571 (IRIS) trial that compared imatinib versus interferon plus cytarabine in patients with newly diagnosed chronic phase CML, the 5-year update pub-
lished in 2006 showed that 157 of the original 553 patients (28%) had discontinued imatinib and, of these, most did so because of an unsatisfactory therapeutic effect. A more recent update at a median follow-up at 7 years reported that the discontinuation rate was 35%; 17% of patients had not experienced a complete cytogenetic response (primary resistance), 10% of patients had achieved a response but then experienced disease progression (secondary resistance), and 8% of patients were intolerant. Thus, only approximately 55% of patients in the original imatinib cohort remained on imatinib at 7 years.

Because dasatinib and nilotinib were approved for first-line therapy in 2007, long-term data regarding the incidence of resistance are limited to 5-year analyses. In the most recent update presented by Cortes et al at the 2013 American Society of Hematology meeting, 67% of patients with newly diagnosed CML randomized to dasatinib in the original Dasatinib versus Imatinib Study In Treatment-Naïve CML Patients (DASISION) trial remain on dasatinib. Similarly, only 60% of patients randomized to front-line nilotinib (300 mg/m² dose) on the original Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENESTnd) trial remain on nilotinib. In summary, resistance, either primary or secondary, to the 3 TKIs approved for first-line use ranges between 38% and 45%.

**Mutation Analysis**

More than 100 point mutations within the BCR-ABL1 kinase domain either interfere directly with TKI binding or prevent the BCR-ABL molecule from assuming the inactive conformation that is required for TKI binding. However, point mutations are identified in only approximately 50% of clinically resistant patients, with a higher incidence in patients with accelerated and blastic phase CML. In instances in which the mutation does not affect binding or BCR-ABL1 conformation, its presence may be a marker for genetic instability.

Among the point mutations identified to date, the T315I mutation is the most common. Structurally, threonine (Thr) at Abl residue 315 is replaced with isoleucine. For imatinib, dasatinib, nilotinib, and bosutinib to bind the ATP-binding pocket, these compounds must form a hydrogen bond with Thr315. The presence of isoleucine prevents this hydrogen bond formation, causing steric hindrance, which prevents their binding. This mutation is associated with more advanced disease and confers a significantly worse prognosis than other mutations.

In one large study of 222 patients with this mutation, Nicolini et al reported that 17% experienced progression to accelerated phase and 25% to blastic phase, with a median overall survival after mutation detection of 22.4 months.

Ponatinib was specifically designed to circumvent resistance to the T315I mutation by having a triple carbon-carbon bond between the purine and methylphenyl groups, which allows the drug to bind to the ATP-binding pocket without steric interference.

**Ponatinib Clinical Development**

The original ponatinib phase I data were derived from 81 patients with resistant hematologic malignancies, including 60 patients with CML and 5 with Ph+ acute lymphoblastic leukemia (ALL). Seven dose levels were tested, ranging from 2 to 60 mg. Pharmacokinetic analysis showed that at a dosage of 30 mg/d, the trough blood concentration was higher than the 40 nM concentration required to suppress the emergence of BCR-ABL1 mutations in preclinical testing. More than 70% of the patients received a dosage of 30 mg/d or higher.

In the chronic phase group, 98% of patients received 2 or more of the approved TKIs (imatinib, dasatinib, nilotinib) and 63% received all 3. Within this group, 98% of the patients had a complete hematologic response, 72% had a major cytogenetic response, and 44% had a major molecular response. Of the 12 patients with chronic phase CML with the T315I mutation, 100% had a complete hematologic response and 92% had a major cytogenetic response, including 75% of patients who experienced a complete cytogenetic response. Eight of the 12 patients (67%) had a major molecular response; of these, 3 (25%) had a 4-log reduction of their BCR-ABL transcript, or a value of 0.01% or less as measured on the International Scale. Notably, no vascular events were noted among the most frequent treatment-related adverse events, and the only cardiac event was noted QT prolongation in 4% of patients.

The phase II clinical trial of ponatinib was published less than a year later in November 2013. In
this large trial, 449 patents with CML or Ph+ ALL, all of whom were resistant to the second-generation TKIs dasatinib or nilotinib (88%) or had unacceptable side effects (12%), were treated with ponatinib, 45 mg/d. Most patients were in chronic phase (270 of the 449 patients; 60%), and more than half had received imatinib, dasatinib, nilotinib, or bosutinib. The T315I mutation was present in 24% of the patients with chronic phase CML, and in 21%, 39%, and 69% of patients with accelerated phase CML, blastic phase CML, and Ph+ ALL, respectively. In the group of patients with chronic phase CML who were either resistant to or intolerant of dasatinib or nilotinib, a major cytogenetic response, complete cytogenetic response, and major molecular remission was seen in 56%, 48%, and 31%, respectively. Importantly, for the first time, significant responses were seen in patients with the T315I mutation: 72% of patients experienced a major cytogenetic response, 70% a complete cytogenetic response, and 58% a major molecular response. Moreover, the median times to major cytogenetic, complete cytogenetic, and major molecular responses were short (2.8, 2.9, and 5.5 months, respectively). In patients with the T315I mutation in accelerated phase, 56% achieved a major cytogenetic response, 33% a complete cytogenetic response, and 22% a major molecular response. The estimated progression-free survival rate of these patients, including those with the T315I mutation, was 67%, with a median of 29 months, and the overall survival rate was 86% at 2 years, with the median not reached.

In summary, within a year, ponatinib was shown to be an extremely active drug in a group of heavily treated patients, and in those with a BCR-ABL mutation resistant to all previous TKIs (Table 1).

### Cumulative Vascular Toxicity: The New Problem

The nonhematologic toxicity reported in the phase I trial seemed to be similar to that seen with imatinib and nilotinib.\(^1\) The most common adverse effects (≥10%), in descending order and of any grade, included rash (32%), arthralgias (17%), increased lipase (15%), fatigue (14%), acneiform dermatitis (14%), dry skin (14%), nausea (14%), pancreatitis (14%), headache (12%), hypertriglyceridemia (12%), myalgia (12%), abdominal pain (10%), and increased alanine aminotransferase level (10%). The remainder of the side effects, including those related to the cardiovascular system, were reported as prolonged QT interval (4%), congestive heart failure (1%), decreased left ventricular ejection fraction (1%), fluid retention (1%), and cardiomyopathy (1%). At a median follow-up of 56 weeks (range, 2–140 weeks), there was no strong signal showing the cardiovascular system was at risk.

The phase II trial had a similar median follow-up of 60 weeks and showed similar nonhematologic side effects.\(^2\) Notably, a 9% incidence of hypertension was noted for the first time. The incidence of congestive heart failure was 1%.

During the ensuing months, vascular events began to be reported, with an increase in blood pressure among the first. The most recent update on ponatinib toxicity noted that although 47% of patients had a baseline blood pressure of 140/90 mm Hg, 67% of the group experienced at least one episode of elevated blood pressure while on the study; 24% of patients had this listed as an adverse event, and 2% as a serious adverse event (SAE).\(^17\)

With more time on study, the incidence of arterial and venous vascular events began to increase across all categories: cardiovascular, cerebrovascular, and peripheral vascular. These events included fatal myocardial infarcts, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and need for immediate revascularization procedures.\(^18\) The incidence of cardiovascular events increased from 6% at a median time of 12 months (340 patient years) to 9% at 24 months (578 patient years), whereas SAEs increased from 5% to 6% during the same interval (Table 2).\(^17\) Cerebrovascular events increased from 3% to 6% and SAEs from 2% to 4%, whereas peripheral vascular

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**Table 1 Ponatinib Response: Phase II Study**

<table>
<thead>
<tr>
<th>R/I to DA or NIL</th>
<th>Major CyR</th>
<th>Complete CyR</th>
<th>MMR</th>
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<tbody>
<tr>
<td>T315I</td>
<td>72%</td>
<td>70%</td>
<td>58%</td>
</tr>
<tr>
<td>Median time to response (mo)</td>
<td>2.8</td>
<td>2.9</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Abbreviations: CyR, cytogenetic response; DA, dasatinib; MMR, major molecular response; NIL, nilotinib; R/I, resistant/intolerant.

Adapted from Cortes JE, Kim DW, Pinalla-Ibarz J, et al. Ponatinib in patients with CML and Ph+ ALL resistant or intolerant to dasatinib or nilotinib, or with the T315I BCR-ABL mutation: 2-year follow-up of the PACE trial [abstract]. Blood 2013;122:Abstract 650; with permission.
events increased from 4% to 6% and SAEs from 8% to 12%. In aggregate, the total number of arterial events increased from 11% to 17%, and SAEs increased from 2% to 3%. Venous thromboembolic events likewise increased from 3% to 5%, and SAEs increased from 2% to 3% (Table 2). Five of the study patients died from a vascular event, and 5 patients had a vascular event that was believed to have possibly contributed to their death.

ARIAD Pharmaceuticals immediately undertook an in-depth study of all patients in the phase I and II trials in an attempt to identify risk factors for these events. Not surprisingly, the incidence of hypertension, diabetes, hypercholesterolemia, myocardial infarct, coronary artery disease, history of coronary revascularization, and history of stroke was consistently higher in the group of patients who experienced any arterial thrombotic event (n=77), although many of the patients in the no-event group (n=372) had risk factors. For example, 34% of patients were older than 65 years compared with 32% in the no-event group; 78% had a history of hypertension compared with 48% in the no-event group, 45% had a history of any ischemic (cardiac or central nervous system) compared with 17% in the no event group, and 87% had more than 1 risk factor compared with 59% in the no-event group.

Importantly, the dose of ponatinib was found to be an important risk factor. As shown in Figure 1, each 15-mg reduction in dose from the phase II recommended dose of 45 mg/d was calculated to result in a predicted reduction of approximately 40% in the risk of an arterial thrombotic event.

A multivariate analysis of the phase II study found the following factors to be risk factors for arterial thrombotic events: older age (P<.0001), history of diabetes (P=.0003), higher dose intensity to time of first event (P=.0009), history of ischemia (P=.0087), longer time since diagnosis (P=.0228), higher baseline neutrophil level (P=.0276), and higher baseline platelet level (P=.0466). The outcome of the ARIAD and FDA review in October 2013 resulted in several interventions: the ARIAD-sponsored phase III EPIC trial (Evaluation of Ponatinib versus Imatinib in Chronic Myeloid Leukemia) that randomized newly diagnosed patients with chronic phase CML to either ponatinib or imatinib was discontinued; a partial clinical hold was put in place for patients who were already taking the drug and individual INDs were required to continue treatment; black box warnings regarding arterial and vascular thrombotic events were placed in the ponatinib package insert; and dose-reduction recommendations were made for patients already taking ponatinib:

- For patients in chronic phase who had already achieved a major cytogenetic response, the recommended dose of ponatinib is now 15 mg/d.
- For patients who have not yet achieved a major cytogenetic response, the recommended dose is now 30 mg/d.
- For patients with advanced phase CML, the recommended dose is 30 mg/d.

### Results After Re-release of Ponatinib

The FDA released the partial hold on ponatinib on December 22, 2013. Analysis as of April 2014 showed that most patients on the PACE (Ponatinib Ph+ ALL and CML Evaluation) trial maintained their original response to ponatinib despite dose reduction. Of the 23 patients who had cytogenetic analysis performed after October 2013, none lost their response after dose reduction. Of the 126 patients who had molecular as-

| Table 2 Incidence of Vascular Occlusive Events Over Time |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | AEs as of 7/23/12 | AEs as of 9/3/13 | SAEs as of 7/23/12 | SAEs as of 9/3/13 |
|                                | 12 mo (340 patient years) | 24 mo (578 patient years) | 12 mo (340 patient years) | 24 mo (578 patient years) |
| Cardiovascular                  | 29 (6%)          | 41 (9%)          | 21 (5%)          | 28 (6%)          |
| Cerebrovascular                 | 13 (3%)          | 25 (6%)          | 8 (2%)           | 18 (4%)          |
| Peripheral vascular             | 17 (4%)          | 28 (6%)          | 7 (2%)           | 16 (4%)          |
| Total arterial thrombosis       | 51 (11%)         | 77 (17%)         | 34 (8%)          | 53 (12%)         |
| Venous thromboembolism          | 15 (3%)          | 23 (5%)          | 10 (2%)          | 13 (3%)          |

Abbreviations: AE, adverse event; SAE, serious adverse event.
Adapted from Cortes JE, Kim DW, Pinalla-Ibarz J, et al. Ponatinib in patients with CML and Ph+ ALL resistant or intolerant to dasatinib or nilotinib, or with the T315I BCR-ABL mutation: 2-year follow-up of the PACE trial [abstract]. Blood 2013;122:Abstract 650; with permission.
The safety update from October 10, 2013, to April 7, 2014, showed that most but not all new vascular occlusive events occurred in patients who did not have dose reductions as per the newly issued guidelines. Three patients had a new vascular occlusive event during this interval: 2 who had maintained the original dose (angina, cerebral vascular disorder) and 1 whose event occurred after dose reduction (cerebral artery stenosis). Eight additional patients who had a prior vascular occlusive event had a second event. Two patients who had a non-SAE had an SAE after dose reduction, 1 while maintaining the original dose (acute coronary syndrome) and 1 after dose reduction (coronary artery occlusion). Six patients who had experienced an SAE while on the prehold trial had a second SAE: 4 while maintaining their original dose (angina, cerebrovascular accident, deep vein thrombosis, lacunar infarct), and 2 after dose reduction (peripheral arterial occlusive disease, angina). Despite these results, the overall survival rate at 2 years in the patients who had an arterial thrombotic event (n=61) was 86%, as was the overall survival rate in patients who did not have an event (n=209).17

Ponatinib: The Conundrum

Ponatinib is an extremely active drug in patients who experienced disease progression on at least 1 previous second-generation TKI,1,2 and preliminary data suggest that disease that has progressed on 1 second-generation TKI has a higher chance of responding to ponatinib than the remaining TKIs (dasatinib, nilotinib, bosutinib).20 In addition, ponatinib has marked efficacy in patients who have the highly resistant T315I mutation, with a sustained major cytogenetic response rate of 91% at 12 months.1,2 On the other hand, it is associated with at least a 27% incidence of vascular occlusive events, affecting even young patients without risk factors.3 It is not surprising then, that recommendations regarding its place in the treatment strategy for this disease remain unclear.

Currently, the drug is back in preclinical trials in an attempt to identify the mechanisms underlying the vascular toxicity (Frank Haluska, MD, PhD, personal communication, 2014). Given the wide spectrum of targets that ponatinib affects, including KIT, platelet-derived growth factor receptor (PDGFR) A, and PDGFRB (Figure 2), all of which are present on cardiovascular endothelial cells,21–23 it is possible that inhibition of 1 or more of these targets contributes to this process. Until this is clarified, treatment should, as the package insert states, be reserved for patients with the T315I mutation or those for whom no other TKI therapy is indicated.

References


