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Long-term safety and efficacy of ponatinib in intolerant chronic myeloid leukemia: subanalysis of the observational study of Iclusig® (ponatinib) treatment in patients with chronic myeloid leukemia in Italy

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Data Availability Statement

Incyte Corporation (Wilmington, DE) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymized data sets owned by Incyte for the purpose of conducting legitimate scientific research. Researchers may request anonymized data sets from any interventional study (except phase 1 studies) for which the product and indication have been approved on, or after, January 1, 2020, in at least 1 major market (eg, United States, European Union, and Japan). Data will be available for request after the primary publication, or 2 years after the study has ended. Information on Incyte's clinical trial data sharing policy and instructions for submitting clinical trial data requests are available at: https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132838-960

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The introduction of tyrosine kinase inhibitors (TKIs) into clinical practice for the treatment of patients with chronic myeloid leukemia (CML) has improved long-term outcomes, including overall survival (OS); the life expectancy of patients with CML is now approaching that of the general population.[1] However, within the first 5 years of using TKI treatment, about 30% to 40% of patients need to switch treatment because of resistance and/or intolerance.[2] Patients who develop intolerance to second-generation TKIs (2G-TKIs) have a higher probability of a low adherence rate and consequently an increased rate of resistance compared with patients who do not develop intolerance.[3] Treatment options for patients with intolerance to 2G-TKIs include the third-generation TKIs asciminib and ponatinib. Asciminib binds to a myristoyl pocket in the ABL kinase, unlike other TKIs that target the adenosine triphosphate binding area, and is approved for the treatment of patients with Philadelphia chromosome-positive CML in chronic phase (CP).[4] Ponatinib is specifically designed to potently inhibit the BCR::ABL1 fusion protein with or without the presence of TKI-resistant mutations, including T315I.[3] The ability of ponatinib to counteract TKI resistance regardless of mutation status is demonstrated in efficacy and safety findings over up to 5 years in the CML clinical trial setting.[5-7] Despite >10 years of real-world clinical experience, limited data have been published regarding ponatinib treatment in patients with CML intolerant to 2G-TKIs. Here, we present results from a *post hoc* analysis of patients with CML treated with ponatinib after intolerance to other TKIs and who participated in the Observational study of Iclusig® (ponatinib) Treatment in patients with CML in Italy (OITI). Overall, ponatinib demonstrates a manageable long-term safety profile and represents a promising treatment option for patients with CML with previous TKI intolerance.

OITI is a non-interventional study of patients aged ≥18 years with CP, accelerated phase, or blast phase CML who started ponatinib treatment in routine clinical practice across 26 academic and hospital centers in Italy. Across the study, all patients were resistant to dasatinib or nilotinib or were intolerant to dasatinib or nilotinib and subsequent treatment with imatinib was not deemed clinically appropriate. The study population comprised a prospective cohort (patients starting treatment with ponatinib after site activation during the 12-month enrollment period), a retrospective cohort (patients starting treatment with ponatinib but who died or were lost to follow-up prior to site activation), and a retrospective/prospective cohort (patients starting treatment with ponatinib prior to site activation and who were still on treatment or in follow-up at study end). The primary

endpoint was achievement of a complete cytogenetic response (CCyR) within 6 months of starting ponatinib treatment. In the absence of cytogenetic evaluation, molecular assessment was used; patients with a molecular response 2 (MR2) or better (≤1% *BCR::ABL1* ratio) were considered to have a CCyR. Secondary endpoints included the rate of patients with CCyR, major MR (MR3), and deep MR (DMR), measured every 3 months. This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the coordinating ethics committee (Università La Sapienza, Rome, Italy), as well as all ethics committees at participating trial centers. All patients provided informed consent.

Of 110 patients enrolled with CP-CML, 36 were intolerant to the most recent TKI, which was defined as patients who had developed adverse events (AEs) that prevented continuation of their previous TKI treatment. The median age at the start of ponatinib treatment was 61 (range, 29-84) years (Table 1). Most patients presented with at least one cardiovascular risk factor, most commonly hypertension (in 26 patients; 72%). Fourteen (39%) patients received ponatinib as second-line therapy, 16 (44%) as third-line (3L), and six (17%) as fourth-line or later. The median duration of last TKI therapy before ponatinib was 2.8 (range, 1.0-4.8) years (Table 2). The last TKI received before ponatinib was most commonly dasatinib (72% of patients), and the most common AEs leading to discontinuation of prior therapy were pleural effusions (n=16 patients), hematologic AEs (n=3), hepatic toxicity (n=3), gastrointestinal AEs (n=2), and cardiovascular AEs (n=2).

The most common ponatinib starting dose was 15 mg (42% of patients); 39% of patients received ponatinib 30 mg and 19% received ponatinib 45 mg. Median ponatinib treatment duration was 3.1 (range, 2.6-4.7) years. Dose modifications occurred in 20 (56%) patients, most commonly due to medical decision (45%) and achievement of at least a major cytogenetic response (25%).

With respect to efficacy, among patients with known MR level, 60% (21 of 35 patients) were in MR3 or DMR at enrollment; this percentage increased over time with ponatinib, reaching 74% (26 of 35 patients) at 6 months, 80% (20 of 25 patients) at 12 months, 90% (18 of 20 patients) at 24 months, and 94% (17 of 18 patients) at 36 months (Figure 1). Median progression-free survival (PFS) and OS were not reached after a median follow-up of 3.5 (range, 0.1-7.5) years. The estimated PFS and OS rates at 12, 24, and 36 months

were both 97% (95% confidence interval [CI], 92-100), 97% (95% CI, 92-100), and 94% (95% CI, 86-100), respectively.

With respect to safety, 31 ponatinib-related AEs were observed in 15 patients, most commonly hypertension (n=4 [11%] patients), increased lipase, increased alanine aminotransferase, and increased aspartate aminotransferase (each n=2 [6%]). The severity of AEs was reported for only 23 events, of which 10 were mild (43%), 8 were moderate (35%), and 5 were severe (22%). Cardiovascular AEs occurred in 10 (28%) patients overall, including two cases of arterial occlusive events (AOEs), which were classified as moderate and did not lead to treatment discontinuation. Most cardiovascular AEs were classified as mild or moderate (67%), while 33% were severe (n=1 each for hypertension, abnormal cardiovascular examination, and angina pectoris). One patient who switched from bosutinib to ponatinib had cross-intolerance. They experienced a similar degree of hepatic toxicity, which was managed with a ponatinib dose reduction and did not require permanent discontinuation. Fifteen (42%) patients discontinued ponatinib, 7 (19%) due to AEs, 3 (8%) due to progression or death, 2 (6%) due to other reasons, and 1 each (3%) due to medical decision, achievement of good molecular response, and starting other therapies.

In patients with CML intolerant to a TKI, a switch to a different TKI should be considered to improve signs and symptoms, especially when a dose reduction of the ongoing therapy does not limit toxicity. Due to intolerance, patients with CML may have poor adherence to TKIs, which can lead to disease relapse or failure to achieve a complete remission, which can contribute to the emergence of resistant subclones. In this analysis of patients with CML with TKI intolerance, molecular assessments at baseline prior to starting ponatinib showed that 10 (29%) patients did not have an MR, four (11%) patients were in MR2, 12 (34%) patients were in MR3, and nine (26%) patients were in DMR. At last follow-up of 18 evaluable patients at 36 months, the rate of DMR had increased to 67%. For patients who need other treatment options due to intolerance, ponatinib offers a promising and valid strategy that can maintain disease control and manage toxicity concerns.

The decision to use ponatinib should be based on a thorough evaluation of the patient’s medical history, risk factors, and prior treatment experiences. Results from this analysis showed a favorable safety profile with a low dose ponatinib strategy.

A previous retrospective study assessed 52 consecutive patients with CML treated with ponatinib because of previous TKI intolerance.[8] Intolerance was most frequently (67% of patients) due to dasatinib, mainly pleural effusions.[8] The ponatinib starting dose was primarily 15 or 30 mg, which was decided according to frailty status. Most of these patients received ponatinib as 3L (44%). Forty percent of patients improved the depth of MR after a median follow-up of 19 months, including patients treated with ponatinib 15 mg. Only four patients experienced an AOE.[8]

A retrospective Japanese study found that 62 of 193 (32%) patients with CP-CML received ponatinib due to intolerance to other TKIs.[9] Eleven patients had cross-intolerance, and thrombocytopenia and increased lipase levels were the most common AEs reported. Overall, 12 of 193 (6%) patients had an AOE; univariate analysis revealed age, hypertension, and diabetes as related prognostic factors.[9]

In this observational study over a median follow-up of 3.5 years, ponatinib demonstrated a manageable long-term safety profile in patients with CP-CML with previous intolerance to other TKIs. Only one patient experienced cross-intolerance. At 3 years, the estimated PFS and OS rates were high, and 94% of patients achieved or maintained an MR3 or DMR. The early adoption and dose-optimization strategy of ponatinib could represent a suitable option in the setting of TKI-intolerant patients.

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Table 1. Baseline demographics and patient-related clinical characteristics.

Variable	Total (N=36)
Age at start of ponatinib treatment, median (range), years	61 (29-84)
Male, n (%)	20 (56)
Ethnicity, n/n* (%)	
Hispanic or Latino	15/34 (44)
Other	19/34 (56)
Unknown	2
Sokal score at diagnosis, n/n* (%)	
Low	6/26 (23)
Intermediate	15/26 (58)
High	5/26 (19)
Unknown	10
BCR::ABL1 mutation, n/n* (%)	
No mutation	16/18 (89)
T315I	1/18 (6)
Other	1/18 (6)
Unknown	18
Cardiovascular risk factors, n (%)	
Hypertension	26 (72)
Hypercholesterolemia	8 (22)
Type 2 diabetes mellitus	2 (6)
Molecular response prior to ponatinib treatment, n/n* (%)	
No response	10/35 (29)
MR2	4/35 (11)
MR3	12/35 (34)
DMR (MR4/MR4.5/MR5)	9/35 (26)
Unknown	1
Line of ponatinib treatment, n (%)	
2	14 (39)
3	16 (44)
4+	6 (17)

*Evaluable patients only; excludes patients with unknown results.

DMR: deep molecular response; MR: molecular response.

Table 2. Previous TKI therapy.

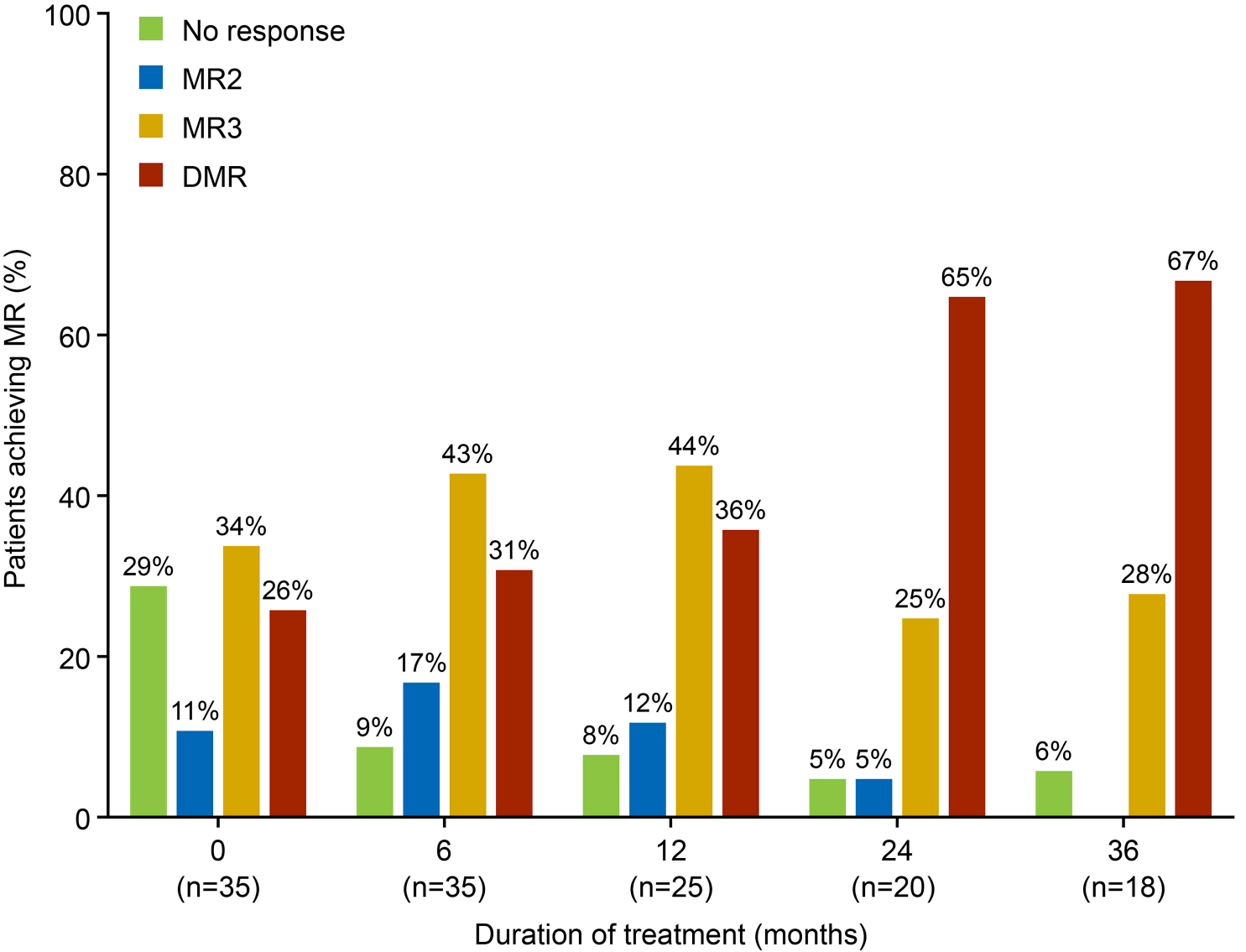
Parameter	Total (N=36)
Last therapy prior to ponatinib, n (%)	
Dasatinib	26 (72)
Bosutinib	5 (14)
Nilotinib	4 (11)
Imatinib	1 (3)
AE leading to discontinuation of prior therapy, n (%)	
Pleural effusion	16 (44)
Hematologic AEs	3 (8)
Hepatic toxicity	3 (8)
Gastrointestinal AEs	2 (6)
Cardiovascular	2 (6)
Other*	10 (28)
Duration of prior TKI therapy, median (range), years	2.8 (1.0-4.8)
Time from last therapy, median (range), months	0.4 (0.0-2.1)

*Other reasons include proteinuria (n=1), pulmonary hypertension (n=1), worsening of pulmonary thoracic symptoms (n=1), progressive worsening of bronchial asthma (n=1), concomitant rheumatoid arthritis (n=1), reactive lymphoid hyperplasia (n=1), unknown (n=2) with dasatinib, cutaneous toxicity with nilotinib (n=1), and unknown (n=1) with imatinib.

AE: adverse event; TKI: tyrosine kinase inhibitor.

FIGURE LEGENDS

Figure 1. MR outcomes. Percentages are derived from the number of evaluable patients at each respective timepoint. DMR: deep molecular response; MR: molecular response.


No response
MR2
MR3
DMR
Patients achieving MR (%)
100
80
60
40
20
0
29%
11%
34%
26%
9%
17%
43%
31%
8%
12%
44%
36%
5%
5%
25%
65%
6%
28%
67%
0
(n=35)
6
(n=35)
12
(n=25)
24
(n=20)
36
(n=18)
Duration of treatment (months)