RETRACTED ARTICLE: Outcomes with frontline nilotinib treatment in Turkish patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase

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ABSTRACT

Objectives: Nilotinib is a BCR-ABL1 tyrosine kinase inhibitor approved for the treatment of patients with chronic myeloid leukemia in chronic phase (CML-CP). This study was the first prospective evaluation of the efficacy and safety of nilotinib in Turkish patients with newly diagnosed CML-CP. The primary endpoint of the study was the rate of major molecular response (MMR; BCR-ABL1 ≤ 0.1% on the International Scale [BCR-ABL1 IS]) by 12 months.

Methods: Patients with newly diagnosed CML-CP were treated with nilotinib 300 mg twice daily. This analysis was based on the first 12 months of follow-up in a 24-month study. This study is registered with ClinicalTrials.gov (NCT01274351).

Results: Of 112 patients enrolled, 66.1% (80% CI, 59.7–72.0%) achieved MMR and 22.3% achieved a deep molecular response of MR4.5 (BCR-ABL1 ≤ 0.0032%) by 12 months. During the first year of treatment, one patient progressed to blast crisis and two patients died. Safety results were consistent with previous studies. Most adverse events (AEs) were grade 1/2. Most frequently reported nonhematologic AEs of any grade were elevations in bilirubin, alanine aminotransferase, and triglycerides.

Conclusion: These results support the use of nilotinib 300 mg twice daily as a standard-of-care treatment option for patients with newly diagnosed CML-CP with low and intermediate risk.

KEYWORDS

BCR-ABL1; chronic myeloid leukemia; molecular response; nilotinib; tyrosine kinase inhibitor

Introduction

Prognosis for patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP) has improved significantly since drugs targeting tyrosine kinase activity of oncogenic BCR-ABL1 protein became the standard of care [1,2]. Imatinib, the first BCR-ABL1 tyrosine kinase inhibitor (TKI) approved for use in CML-CP patients [3,4], was shown to be well tolerated in most patients and to result in higher rates of hematologic, cytogenetic, and molecular responses and prolonged progression-free survival (PFS) and higher survival rates compared with previous standard therapy, interferon–alfa plus cytarabine [5–7]. Although imatinib resulted in favorable outcomes in many patients, some were intolerant of or resistant to imatinib [5,8]. To meet the needs of such patients, newer, second-generation BCR-ABL1 TKIs, such as nilotinib, were developed [9].

Although nilotinib was initially used only in the second-line setting following imatinib resistance or intolerance [10,11], it was approved by the US Food and Drug Administration and the European Commission for use in patients with newly diagnosed CML-CP based on results from the pivotal phase 3 Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENESTnd) study [12,13]. In ENESTnd, nilotinib demonstrated good tolerability and improved efficacy vs. imatinib in newly diagnosed CML-CP patients, including lower
risks of progression to accelerated phase/blast crisis (AP/BC) and death due to CML [14-18].

Herein, we present primary analysis results of multicenter, single-arm, phase 2 study designed to evaluate the efficacy and safety of nilotinib 300 mg twice daily in newly diagnosed Ph+ CML-CP in Turkey. This study is the first prospective trial of nilotinib in CML patients in Turkey. This study is also investigating whether frontline treatment with nilotinib 300 mg twice daily results in a high rate of deep molecular response (evaluated based on MR4.5) during the first 2 years of therapy, which may enable patients to become future candidates for studies investigating treatment-free remission (i.e. TKI discontinuation studies [19]).

Patients and methods

Patients

Patients aged ≥18 years with Ph+ CML-CP, who were newly diagnosed within 6 months before the study, were eligible. The criteria for the diagnosis of CML-CP included <15% blasts and <30% blasts plus promyelocytes in peripheral blood and bone marrow, <20% basophils in peripheral blood, ≥100×10⁹ platelets/L, and no extramedullary involvement except for hepatosplenomegaly. Patients had to have the Eastern Cooperative Oncology Group performance status ≤2, adequate organ function, and normal baseline levels of serum potassium, magnesium, calcium, and phosphorous. Patients receiving previous treatment for CML with compounds other than anagrelide and hydroxyurea were excluded; one exception was for patients requiring treatment before the study, who could be treated with imatinib for ≤31 days. Patients were also excluded for any serious, uncontrolled medical conditions or impaired cardiac function, including left ventricular ejection fraction <45%, indeterminable QT interval on electrocardiogram (ECG), acquired or familial history of long QT syndrome, clinically significant ventricular or atrial tachyarrhythmia or resting bradycardia (<50 beats/min), corrected QT interval >450 ms on baseline ECG, history of myocardial infarction (MI) in 12 months before the study, or other significant cardiac disorders. Treatment with potent inhibitors of cytochrome P450 3A4 and agents that could prolong the QT interval was prohibited.

Written informed consent was obtained from all patients. The study was conducted according to the ethical principles of the Declaration of Helsinki and the protocol and all amendments were approved by the institutional review board, independent ethics committee, or research ethics board at each center.

Study design and treatment

This was a multicenter, open-label, single-arm phase 2 study of nilotinib as a frontline treatment for Ph+ CML-CP patients. All patients received oral nilotinib 300 mg twice daily for a planned treatment duration of 24 months or until early discontinuation.

Treatment was to be interrupted in patients with grade 2 or 3 nonhematologic toxicities or grade 3 or 4 hematologic toxicities until improvement to grade <2 (nonhematologic) or <3 (hematologic). Following the third or fourth occurrence of a grade 2 or 3 nonhematologic or grade 3 or 4 hematologic toxicity, nilotinib was to be initially resumed at a dose of 400 mg/day. Following any occurrence of grade 4 nonhematologic toxicity or the fifth occurrence of grade 3 or 4 hematologic toxicity, the study steering committee was consulted about treatment resumption or permanent discontinuation.

Study endpoints

The primary efficacy endpoint was the cumulative rate of major molecular response (MMR) by 12 months. MMR was defined as BCR-ABL1IS ≤0.1%, as measured by real-time quantitative polymerase chain reaction (RQ-PCR) in peripheral blood.

Secondary efficacy endpoints included the rate of CCyR at 6 and 12 months; cumulative rate of CCyR by 12 months; time to and duration of CCyR; cumulative rates of MMR by 3, 6, and 9 months; time to and durability of MMR; cumulative rate of complete hematologic response (CHR) by 12 months; event-free survival (EFS); defined as time from first dose of study treatment until any of the following events: loss of CHR, loss of PCyR/CCyR, progression to AP/BC, or death due to any cause; PFS (defined as time from first dose of study treatment until progression to AP/BC or death due to any cause); and safety. The rate of BCR-ABL1IS ≤10% at 3 months and cumulative rate of MR4.5 (defined as BCR-ABL1IS ≤0.0032% by RQ-PCR) in a sample with a minimum of 32,000 ABL1 copies [20]) by 12 months were also evaluated.

Efficacy and safety assessments

Evaluations, including hematologic assessments, were conducted every 15 days during the first 3 months, monthly until month 12, and every 3 months until the end of study (24 months). Peripheral blood samples were collected at months 3, 6, 9, 12, 15, 18, 21, and 24 for molecular response analysis by RQ-PCR. All RQ-PCR assays were performed by the single European Treatment and Outcome Study–standardized central laboratory [20] using primers and probes for BCR-ABL1 and the control gene, ABL1, which were determined through a collaboration of 25 centers as part of the Europe Against Cancer program [21]. RQ-PCR tests were performed in triplicate. Results were reported as the mean ratio of BCR-ABL1 to ABL1, standardized to the International Scale using an established conversion factor. To assess cytogenetic
response, bone marrow aspirations and/or biopsies were performed at months 6 and 12, at the final visit, or until patients achieved CCyR or MMR. Mutational analysis was performed in patients who withdrew from the study due to the failure of nilotinib treatment or progressed to AP/BC while receiving nilotinib.

Safety evaluations occurred at each visit and included physical examinations, adverse event (AE) assessments per Common Terminology Criteria for Adverse Events version 3.0 and evaluation of hematologic and biochemical abnormalities. Additionally, ECGs were performed at baseline, 15 and 30 days after initiation of treatment, every 3 months until month 12, and every 6 months or at the discretion of the physician. Safety findings were based on AE reporting. Adherence to study treatment was evaluated by an investigator through examination of the number of nilotinib capsules and information provided by patients. Patients who withdrew before completion of the study were monitored for survival every 3 months until 2 years after the start of the study.

Statistical analyses

The sample size was calculated in 80% confidence interval (CI) using the exact test for single proportion to attain a 15% improvement in the rate of MMR compared to the pivotal study of frontline imatinib (International Randomized Study of Interferon and STI571 [IRIS] [5–7]).

All efficacy analyses were performed in the intent-to-treat population. The primary endpoint was the cumulative rate of MMR by 12 months with 80% CI. Patients who withdrew from the study early or did not have evaluable data for the primary endpoint were considered nonresponders. The safety analysis population was defined as all patients receiving ≥1 dose of nilotinib and having ≥1 postbaseline safety assessment.

Results

Patients

Between 25 January 2011 and 21 March 2013, 112 patients with Ph+ CML-CP were enrolled at 15 study centers in Turkey. The number of patients enrolled at each site was: #1, n = 9; #2, n = 2; #3, n = 1; #4, n = 10; #5, n = 2; #6, n = 3; #7, n = 19; #8, n = 8; #9, n = 8; #10, n = 15; #11, n = 7; #12, n = 9; #13, n = 5; #14, n = 11; #15, n = 3. Baseline characteristics are presented in Table 1. Median age was 47 years and the majority of patients (54.5%) had low Sokal risk scores; 39.3% and 6.3% of patients had intermediate and high Sokal risk scores, respectively. All patients (n = 112) received study treatment.

This analysis (cutoff date, 31 March 2014) includes data through the 12-month visit for all patients. Fifteen patients (13.4%) discontinued study treatment by the 12-month visit, whereas 97 patients (86.6%) remained on treatment at 12 months (Table 2). The most common reason for treatment discontinuation was AEs (7 patients [6.3%]). The median duration of follow-up was 371 days (range, 14–383 days) and the median duration of nilotinib treatment was 358 days (range, 4–372 days).

Efficacy

The cumulative rate of MMR by 12 months (primary endpoint) was 66.1% (74/112; 80% CI, 59.7–72.0%). Among these 74 patients, the median time to MMR was 190 days (range, 90–380 days) and 7 of them had a loss of MMR (based on RQ-PCR results, disease progression, or death) by 12 months, giving a noncumulative MMR rate at 12 months of 59.8% (67/112). In these 7 patients, the median duration of MMR was 91 days (range, 78–102 days). Cumulative rates of MMR by 3, 6, and 9 months were 25.0% (n = 28), 50.9% (n = 57), and 59.8% (n = 67), respectively (Figure 1). Ninety patients (80.4%) achieved BCR-ABL1 ≤10% at 3 months (Table 3). By 12 months, 25 patients (22.3%) achieved a deep molecular response of MR4.5.

The cumulative rate of CCyR by 12 months was 89.3% (100/112) and the median time to CCyR was

### Table 1. Baseline characteristics.

| Age, median (range), years | Nilotinib 300 mg twice daily |
|---------------------------|-----------------------------|
| N = 112                   |                             |
| Male, n (%)               |                             |
| 63 (56.3)                 |                             |
| Sokal risk group, n (%)   |                             |
| Low                       |                             |
| Intermediate              |                             |
| High                      |                             |
| 44 (39.3)                 |                             |
| 7 (6.3)                   |                             |
| Spleen size, n (%)        |                             |
| 61 (54.5)                 |                             |
| Median duration of nilotinib treatment was 358 days (range, 4–372 days). |
90 days (range, 78–362 days). Nearly all patients (97.3% [109/112]) achieved CHR by 12 months; the median time to CHR was 29 days (range, 22–92 days). The non-cumulative rates of CCyR at 6 and 12 months were 80.4% (n = 90) and 75.0% (n = 84), respectively.

By 12 months, 1 patient (0.9%) had disease progression to BC and 2 patients died (1.8%). The estimated PFS rate at 1 year was 96.5%. The patient progressed to BC had a low Sokal risk score at baseline and received treatment for 276 days, including 2 treatment interruptions due to AEs lasting 7 days each. An E255V mutation in BCR-ABL1 was detected at the time of discontinuation. Both of the deaths were due to MI. One was a 75-year-old man who had no known cardiovascular risk factors at baseline and received treatment for 57 days until his death. The other one was a 72-year-old man who was on study for 263 days before his death; he had a previous MI that was not reported at screening and during the study, he discontinued treatment for 15 days due to prolonged QT interval, refused the recommended angiography and bypass, and died 119 days after continuing treatment.

EFS was defined as the time between the first dose until any of the following: loss of CHR, loss of PCyR, loss of CCyR, all-cause death during treatment or progression to AP/BC. Fourteen patients experienced an event by 12 months: 1 patient with loss of PCyR, loss of CHR, and progression to BC; 2 patients with loss of CHR; 9 patients with loss of CCyR; and 2 deaths. The estimated rate of EFS at 1 year was 87.2%. BCR-ABL1 mutations were detected in 2 patients; one progressed to BC and one with the Y253H mutation who discontinued treatment due to AEs.

### Safety

The safety of nilotinib 300 mg twice daily was evaluated in all patients (n = 112). The most frequently reported nonhematologic AEs of any grade were increased bilirubin (15.2%), increased alanine aminotransferase (10.7%), and increased triglycerides (10.7%; Table 4). All-grade thrombocytopenia, leukopenia, neutropenia, and anemia were reported in 19.6%, 8.9%, 6.3%, and 3.6% of patients, respectively. Grade 3/4 AEs were reported in 35 patients (31.3%). Grade 3/4 AEs reported in >2% of patients were thrombocytopenia (7.1%), increased lipase (5.4%), decreased phosphate (3.6%), and neutropenia (2.7%).

Few patients (2.7%) developed hyperglycemia and the reported cholesterol elevations and hyperglycemia events were grade 1/2. Grade 1/2 cholesterol elevations were reported in 86 (76.8%) patients. Four patients (3.6%) had QTc prolongation. Ischemic heart

Figure 1. Cumulative rates of major molecular response by 3, 6, 9, and 12 months in nilotinib-treated patients (N = 112). BCR-ABL1 ≤ 0.1% on the International Scale.

Table 3. Molecular, cytogenetic, and hematologic responses.

| Nilotinib 300 mg twice daily | N = 112 |
|-----------------------------|---------|
| **Molecular response** BCR-ABL1 % levels at 3 months, n (%) | |
| ≤10% | 90 (80.4) |
| >10% | 15 (13.4) |
| Unknown | 7 (6.3) |
| Cumulative rate of MR4.5 by 12 months, n (%) | |
| 25 (22.3) |
| **Cytogenetic response** Cumulative rate of CCyR by 12 months, n (%) | 100 (89.3) |
| At 6 months | 90 (80.4) |
| At 12 months | 84 (75.0) |
| **Hematologic response** Cumulative rate of CHR by 12 months, n (%) | 109 (97.3) |
| CCyR: complete cytogenetic response; CHR: complete hematologic response; IS: International Scale; MR4.5: molecular response 4.5 (BCR-ABL1 % ≤0.0032%). |
| *BCR-ABL1 % level at 3 months was unknown for 7 patients who withdrew from the study before 3 months. |

| Table 4. Nonhematologic and hematologic AEs of any causality. |
|---------------------------------------------------------------|
| Nilotinib 300 mg twice daily | Any grade |
| N = 112 | |
| **Nonhematologic** | |
| Increased bilirubin | 17 (15.2) 1 (0.9) |
| Pruritus | 15 (13.4) 2 (1.8) |
| Increased alanine aminotransferase | 12 (10.7) 0 |
| Increased triglycerides | 12 (10.7) 0 |
| Increased lipase | 10 (8.9) 6 (5.4) |
| Influenza | 10 (8.9) 0 |
| Increased alkaline phosphatase | 9 (8.0) 0 |
| Rash | 9 (8.0) 0 |
| Constipation | 7 (6.3) 0 |
| Hair loss | 7 (6.3) 0 |
| Increased amylase | 6 (5.4) 2 (1.8) |
| Increased total cholesterol | 6 (5.4) 0 |
| Upper respiratory infection | 6 (5.4) 0 |
| **Hematologic** | |
| Thrombocytopenia | 22 (19.6) 8 (7.1) |
| Leukopenia | 10 (8.9) 0 |
| Neutropenia | 7 (6.3) 3 (2.7) |
| Anemia | 4 (3.6) 0 |
| **Selected AEs of interest** occurring in >1 patient, n (%) | |
| Decreased phosphate | 5 (4.5) 4 (3.6) |
| Ischemic heart disease | 4 (3.6) 2 (1.8) |
| Hyperglycemia | 3 (2.7) 0 |
| Hypertension | 2 (1.8) 0 |

*Selected AEs reported with nilotinib [12,13].
disease was reported in four patients (3.6%); ischemic cerebrovascular events or peripheral artery disease were not reported. Of four patients with ischemic heart disease, two died due to MI; as discussed earlier, one had previous MI (not reported at screening), and one had no known cardiovascular risk factors at baseline. The remaining two patients having ischemic heart disease completed the study without interruption of nilotinib treatment and one of these patients also received anti-ischemic therapy.

In total, 49 patients (43.8%) had a temporary dose interruption or permanently discontinued treatment due to AEs of any grade; AEs leading to treatment interruption/discontinuation in >2% of patients were thrombocytopenia (n = 10 [8.9%]), increased lipase (n = 9 [8.0%]), increased total bilirubin (n = 8 [7.1%]), and neutropenia (n = 5 [4.5%]).

Discussion

In this first prospective national clinical trial in Turkey, frontline nilotinib treatment demonstrated good efficacy and tolerability in newly diagnosed CML-CP patients. High response rates were achieved during the first 12 months of treatment, including 66.1% of patients with MMR by 12 months; additionally, very few patients progressed or died. The safety profile of nilotinib was similar to those reported in other studies [14–16,18,22].

The results here confirm the high rate of MR4.5 achieved with frontline nilotinib: the rate of patients achieving MR4.5 by 12 months was 22.3% in this study and 11% in the nilotinib 300 mg twice daily arm of the ENESTnd trial [15].

Although efficacy findings from this study cannot be directly compared with those from ENESTnd [14–18], the efficacy of nilotinib was generally consistent between these two studies. The rates of MMR by 12 months and CCyR at 6 and 12 months were 66%, 88%, and 92%, respectively, in this study, and 55%, 67%, and 80%, respectively, in the nilotinib 300 mg twice daily arm of ENESTnd [14,15]. The observed differences in response rates between this study and ENESTnd could be due to different patient populations; for example, 54% of patients in this study had low Sokal risk scores at baseline compared with 37% of patients in ENESTnd [14]. This higher rate of patients with low Sokal risk scores is consistent with rates seen in clinical practice in Turkey.

Among evaluable patients in this study, most achieved BCR-ABL1 ≤10% at 3 months with nilotinib. Nilotinib is known to result in a higher rate of BCR-ABL1 ≤10% at 3 months than imatinib; among evaluable patients in ENESTnd, 91% of those in the nilotinib 300 mg twice daily arm vs. 67% in the imatinib 400 mg once daily arm achieved BCR-ABL1 ≤10% at 3 months [17]. Results from this study confirm those of ENESTnd and other studies demonstrating high rates of early molecular response with nilotinib [17,22,23].

The primary goal of TKI therapy for CML-CP patients is survival [2]. In this study, one progression and no CML-related deaths were reported, confirming the low risk of progression for patients treated with frontline nilotinib.

Safety results were consistent with those from other frontline studies [14–16,18,22]. The most frequently reported AEs of any grade were hematologic or biochemical abnormalities (i.e. thrombocytopenia, increased bilirubin, increased alanine aminotransferase, and increased triglycerides) and most events were grade 1/2. AEs led to study discontinuation in 6.3% of patients, which was generally similar to the rate of 5% observed with nilotinib 300 mg twice daily through the first-year follow-up in ENESTnd [14].

Cardiovascular toxicities occur more frequently in patients with cardiovascular risk factors at baseline [18,24]. In this study, peripheral artery disease or ischemic cerebrovascular events were not reported. However, ischemic heart disease events were observed in four patients; two died due to MI. Notably, one of the deaths occurred in a patient having a previous history of MI, which is known to increase the risk of a subsequent cardiovascular event [25]. Hyperglycemia and elevation of total cholesterol levels were relatively infrequent in this study, perhaps indicating effective monitoring and management of these risk factors during nilotinib treatment.

Conclusions

With the availability of several TKIs for treatment of patients with newly diagnosed CML-CP [2], frontline therapy decisions should be individualized and should consider benefit–risk profile of each agent; patient-specific factors, including comorbidities and disease biology [26]. In randomized studies, nilotinib has demonstrated improved efficacy over imatinib, including higher rates of early and deep molecular response and decreased risk of disease progression, with a manageable safety profile [14–16,18,22]. This study confirms the efficacy and safety of nilotinib 300 mg twice daily in Turkish CML-CP patients and supports the continued use of nilotinib as a standard-of-care first-line treatment option for CML-CP patients with low and intermediate risk. To postulate this statement for high-risk patients, it is required to have more studies enrolling many numbers of patients with high-risk patients with CML-CP.

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