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Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Phase 2 study of nilotinib in pediatric patients with Philadelphia chromosome–positive chronic myeloid leukemia

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KEY POINTS

- **Nilotinib demonstrated efficacy and a manageable safety profile in pediatric patients with newly diagnosed and pretreated Ph$^+$ CML-CP.**

Chronic myeloid leukemia (CML) is rare in children and accounts for ≤15% of all myeloid leukemia cases. When we initiated this study with nilotinib, imatinib was the only tyrosine kinase inhibitor indicated for pediatric patients with Philadelphia chromosome–positive (Ph$^+$) CML in chronic phase (CP); alternative treatment options were needed, particularly for patients who developed resistance or intolerance (R/I) to imatinib. This phase 2 study enrolled pediatric patients with either Ph$^+$ CML-CP R/I to imatinib or dasatinib or newly diagnosed Ph$^+$ CML-CP. Data presented are from analyses with minimum follow-up of up to 24 cycles (1 cycle is 28 days). Fifty-nine patients with Ph$^+$ CML-CP were enrolled, and 58 were treated (R/I, n = 33; newly diagnosed, n = 25). Major molecular response (MMR) rate at cycle 6 in the R/I cohort was 39.4% (primary end point); 57.6% of patients achieved or maintained MMR and 81.8% achieved or maintained complete cytogenetic response (CCyR) by 24 cycles. In patients with newly diagnosed disease, rates of MMR by cycle 12 and CCyR at cycle 12 were 64.0% each (primary end points); by cycle 24, cumulative MMR and CCyR rates were 68.0% and 84.0%, respectively. The safety profile of nilotinib in pediatric patients was generally comparable with the known safety profile in adults, although cardiovascular events were not observed in this study, and hepatic laboratory abnormalities were more frequent; no new safety signals were identified. In summary, nilotinib demonstrated efficacy and a manageable safety profile in pediatric patients with Ph$^+$ CML-CP. This trial was registered at www.clinicaltrials.gov as #NCT01844765. (*Blood*. 2019;134(23):2036-2045)

Introduction

Chronic myeloid leukemia (CML) is rare in children and accounts for ≤15% of all myeloid leukemia cases.[1] Its incidence increases with age, rising to 1.2 cases per million per year in adolescents.[2,3]

Several BCR-ABL1 tyrosine kinase inhibitors (TKIs) are available for treating adults with Philadelphia chromosome–positive (Ph$^+$) CML, including imatinib, nilotinib, dasatinib, bosutinib, and ponatinib. However, before November 2017,[4,5] only imatinib was approved for treating pediatric patients. Because some patients developed resistance or intolerance (R/I) to imatinib, alternative treatments were needed in this population. A phase 3 trial reported that 27% of pediatric patients receiving first-line imatinib experienced an unsatisfactory response or intolerance, and a phase 4 trial of first-line imatinib reported that 30% of patients had discontinued treatment after a median of 13.5 months, most frequently because of unsatisfactory therapeutic effect.[6,7]

Nilotinib demonstrated a positive risk-benefit profile in adults with newly diagnosed Ph$^+$ CML in chronic phase (CP)[8] or with Ph$^+$ CML in CP or accelerated phase (AP) and R/I to previous therapy.[9,10] Thus, it was anticipated that nilotinib could be an additional treatment option in pediatric patients. Previously, a phase 1 study evaluated the pharmacokinetic (PK) profile of nilotinib in pediatric patients with Ph$^+$ CML-CP or Ph$^+$ acute lymphoblastic leukemia who had relapsed or were R/I to previous therapy with imatinib and/or dasatinib.[11] In that study, nilotinib was shown to have clinical activity and a manageable safety profile in pediatric patients, and the recommended nilotinib dose (230 mg/m^2 twice per day) was established for future studies because it delivered exposure comparable to the adult dose of 400 mg twice per day.[11] Although the approved nilotinib dose in adults is lower for patients with newly diagnosed disease (300 mg twice per day) compared with those who are R/I to imatinib (400 mg twice per day), the dose of 230 mg/m^2 twice per day was considered appropriate for pediatric patients with either newly diagnosed or R/I disease because CML tends to present with more aggressive clinical features in pediatric patients compared with adults.[12]

The aim of this ongoing, multicenter, open-label, phase 2 study was to investigate the efficacy and safety of nilotinib at the recommended dose of 230 mg/m^2 twice per day in pediatric patients with Ph$^+$ CML. The results reported are from analyses with a minimum follow-up of up to 24 cycles.

Methods

Study design and patients

Eligible patients (age 1 year to younger than 18 years) were enrolled into 1 of 3 cohorts: patients with Ph$^+$ CML-CP R/I to imatinib or dasatinib, patients with Ph$^+$ CML-AP R/I to imatinib or dasatinib, and patients with newly diagnosed Ph$^+$ CML-CP. Nilotinib was administered orally in capsule form at a dose of 230 mg/m^2 twice per day. Additional information and key eligibility criteria are available in supplemental Methods (available on the *Blood* Web site).

Study end points and assessments

The primary objective was to assess the efficacy of nilotinib. In patients with Ph$^+$ CML-CP R/I to imatinib or dasatinib, the primary efficacy end point was the major molecular response (MMR) rate at 6 cycles (response rates at a given time point were calculated on the basis of the number of patients with a response at this time point, regardless of whether they had previously achieved a response). In patients with newly diagnosed Ph$^+$ CML-CP, the primary efficacy end points were MMR rate by 12 cycles (response rates by a given time point were calculated on the basis of the cumulative rate of patients who achieved a response at any time up to this time point) and complete cytogenetic response (CCyR) rate at 12 cycles. Additional information on assessments and secondary end points is available in supplemental Methods. Safety and efficacy data are reported for all patients on the basis of a data cutoff of May 3, 2017, when all patients had completed 24 cycles or discontinued early.

Statistical analysis

Data from all study centers were pooled. Primary efficacy end points were analyzed descriptively for each cohort among all patients who received ≥1 dose of study treatment, without hypothesis testing. Response rates were provided with 95% confidence intervals (CIs) using the Pearson-Clopper method by cohort.

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki and local laws and regulations. Written informed consent was provided by representatives of the patients (parents or caregivers) before participation in the study; in addition, assent was obtained from patients who were capable of providing a signature. The study protocol and all amendments were reviewed by the independent ethics committee and/or institutional review board for each study center.

Results

Patients

This study is being conducted at 36 centers across 13 countries; enrollment was completed on July 6, 2015. Fifty-nine patients with Ph$^+$ CML-CP were enrolled, and 58 were treated; 1 patient did not receive study drug because of grade 2 hyperbilirubinemia observed after screening and before study treatment began (Table 1). Thirty-three patients were R/I to imatinib or dasatinib, and 25 had newly diagnosed disease. No patients with Ph$^+$ CML-AP were enrolled. In the R/I cohort, the median age was 13.0 years (range, 2-17 years); 31 patients (93.9%) had received imatinib and 2 (6.1%) had received dasatinib; 3 (9.1%) were imatinib intolerant only, 25 (75.8%) were imatinib resistant only, 3 (9.1%) were both intolerant of and resistant to imatinib, and 2 (6.1%) were resistant to dasatinib; and 21.2% (7 of 33) were already in MMR and 42.4% (14 of 33) were already in CCyR at baseline. Of 29 patients in the R/I cohort with evaluable mutational analyses at baseline, 3 had *BCR-ABL1* baseline mutations (2 were resistant to previous TKIs only, and 1 was resistant to and intolerant of previous TKIs): E255K and E255V (less sensitive to nilotinib[13]) in 1 patient, G250E (sensitive to nilotinib[13]) and E255K in 1 patient, and L387M (unknown sensitivity) in 1 patient. In the cohort of 25 patients with newly diagnosed CML-CP, the median age was 13.0 years (range, 10-16 years). Of 25 patients in the newly diagnosed cohort with evaluable mutational analyses at baseline, no *BCR-ABL1* baseline mutations were detected.

Study drug administration

The method of nilotinib administration was recorded in an acceptability and palatability questionnaire: on cycle 1 day 1, 53 patients swallowed whole nilotinib capsules and 4 took the capsule contents mixed with applesauce (information was missing for 1 patient); on cycle 1 day 28, 49 patients took whole capsules and 3 took the contents mixed with applesauce (information was missing for 6 patients); and on cycle 12 day 28, 44 patients took whole capsules and 1 took the contents mixed with applesauce (information was missing for 13 patients).

Median duration of exposure to nilotinib was 22.1 months (range, 0.5-44 months) in the R/I cohort and 22.3 months (range, 0.7-38.7 months) in the newly diagnosed cohort; median (25th-75th percentile) actual dose intensities were 439.0 mg/m^2 per day (range, 366.2-461.8 mg/m^2 per day) and 402.7 mg/m^2 per day (range, 281.4-443.7 mg/m^2 per day), respectively.

Table 1. Patient demographics and baseline characteristics

Characteristic	R/I to imatinib or dasatinib* (n = 33†)	Newly diagnosed (n = 25)
Age, y		
<12	12 (36.4)	6 (24.0)
12 to <18	21 (63.6)	19 (76.0)
Median (range)	13 (2-17)	13 (10-16)
Female	12 (36.4)	12 (48.0)
Prior antineoplastic TKI therapies		
Imatinib	31 (93.9)	NA
Dasatinib	2 (6.1)	NA
Intolerant		
Imatinib	6 (18.2)‡	NA
Dasatinib	0	NA
Resistant		
Imatinib	28 (84.8)‡	NA
Dasatinib	2 (6.1)	NA
***BCR-ABL1*^{IS} at baseline**		
≤0.0032	1 (3.0)	0
>0.0032 to ≤0.01	1 (3.0)	0
>0.01 to ≤0.1	5 (15.2)	0
>0.1 to ≤1	10 (30.3)	0
>1 to ≤10	9 (27.3)	0
>10	5 (15.2)	25 (100)
Atypical transcripts	1 (3.0)	0
Missing	1 (3.0)	0
Known *BCR-ABL1* mutation at baseline, n/m§	3/29	NA

Data are presented as number (%) unless otherwise specified.

IS, International Scale; NA, not applicable.

*Patients were resistant to and/or intolerant of 1 previous TKI, either imatinib or dasatinib.

†One additional patient was enrolled in this cohort but did not receive nilotinib treatment and was excluded from the analyses.

‡Three patients were both imatinib intolerant and imatinib resistant and are counted in both categories.

§Numerator (n) is the number of patients with known baseline mutations. Denominator (m) is the number of patients with an evaluable baseline mutational assessment. Mutations detected at baseline were E255K and E255V in 1 patient, G250E and E255K in 1 patient, and L387M in 1 patient.

Patient disposition

Overall, 38 of 58 patients were still receiving treatment at the data cutoff for the 24-cycle analysis: 23 (69.7%) of 33 in the R/I cohort and 15 (60%) of 25 in the newly diagnosed cohort. Of the 10 patients in the R/I cohort who discontinued from the study, 5 discontinued because of adverse events (AEs), 1 for an alternative cancer therapy (bone marrow transplant), 1 because of lack of efficacy, 1 because of progression to AP/blast crisis (BC), and 2 because of protocol deviation (noncompliance). Of the 10 patients in the newly diagnosed cohort who discontinued, 6 discontinued because of AEs, 3 discontinued because of lack of efficacy, and 1 withdrew consent (Table 2). The median time on study treatment was 22.6 months (range, 0.7-44 months) in the R/I cohort and 22.6 months (range, 1.4-39.6 months) in the newly diagnosed cohort.

Efficacy

The primary end point (MMR at 6 cycles) in the R/I cohort was achieved by 13 (39.4%) of 33 patients, including 6 of the 7 who were in MMR at baseline (imatinib resistant, 5; imatinib intolerant, 1; Table 3). MMR was achieved or maintained by 19 (57.6%) of 33 patients by cycle 12 and by cycle 24. By the data cutoff, MMR was achieved by 20 (60.6%) of 33 patients (including 7 who were in MMR at baseline). The median time to first MMR among the 20 patients who achieved MMR was 2.8 months (range, 0-38.8 months). Confirmed loss of MMR was not reported in any patient. CCyR was achieved or maintained by 27 (81.8%) of 33 patients by cycle 12 and cycle 24 (14 patients [42.4%] in the R/I cohort were in CCyR at baseline).

The primary end points (MMR by 12 cycles and CCyR at 12 cycles) in the newly diagnosed cohort were each achieved by 16 (64.0%) of 25 patients (Table 3). MMR was achieved by 17 (68.0%) of 25 patients by cycle 24. By the data cutoff, MMR was achieved by 18 (72.0%) of 25 patients; the median time to first MMR among the 18 patients who achieved MMR was 5.6 months (range, 2.7-33.0 months). Two of the 18 patients who achieved MMR on treatment had confirmed loss of MMR by the cutoff date and had discontinued study treatment. CCyR was achieved by 21 (84.0%) of 25 patients with newly diagnosed disease by cycle 24; the median time to CCyR among these 21 patients was 5.6 months (range, 2.8-5.8 months). Of the 21 patients who achieved CCyR on treatment, 1 had confirmed loss of CCyR and discontinued study treatment. MMR and CCyR rates at different time points are reported in Table 3.

One imatinib-resistant patient (age 10 years at baseline) progressed to BC after 10.1 months on treatment; the patient discontinued study treatment, was followed up for survival, and died as a result of progression to lymphoid BC ~8 months after the end of nilotinib treatment. No other deaths were reported on study. The estimated overall survival rate at 24 months was 96.9% (95% CI, 79.8%-99.6%). Estimated rate of event-free survival at 24 months was 96.3% (95% CI, 76.5%-99.5%) in the R/I cohort (Figure 1) and 91.2% (95% CI, 69.0%-97.7%) in the newly diagnosed cohort (Figure 2). No patient had emergent mutations while receiving treatment.

PK

Multiple trough plasma concentration (C_{trough}) measurements were evaluable from 30 patients in the R/I cohort and 25 patients in the newly diagnosed cohort at steady state during the first year of treatment. PK characteristics and exposure-response (*BCR-ABL1* level) were similar between the 2 cohorts.

Patients in the R/I cohort achieved steady-state concentrations of nilotinib on day 8 of cycle 1 with a geometric mean (percent coefficient of variation [CV%]) C_{trough} of 1365.83 ng/mL (72.89%). Average C_{trough} (CV%) value (n = 30) during the first year of treatment was estimated to be 1407.89 ng/mL (41.67%).

Patients in the newly diagnosed cohort also achieved steady-state concentrations of nilotinib on day 8 of cycle 1 with a geometric mean (CV%) C_{trough} of 1034.49 ng/mL (76.86%). Average

Table 2. Patient disposition

	R/I to imatinib or dasatinib (n = 33)	Newly diagnosed (n = 25)
Treatment ongoing	23 (69.7)	15 (60.0)
End of treatment	10 (30.3)	10 (40.0)
Primary reason for end of treatment		
Adverse events	5 (15.2)	6 (24.0)
Lack of efficacy*	1 (3.0)	3 (12.0)
Patient withdrew consent	0	1 (4.0)
Bone marrow transplant	1 (3.0)	0
Disease progression	1 (3.0)	0
Protocol deviation†	2 (6.1)	0

Data are presented as number (%).

*A patient in the R/I cohort who was not in MMR at cycle 15 discontinued after 14.8 months of study drug exposure. Three patients in the newly diagnosed cohort discontinued because of lack of efficacy: 1 with *BCR-ABL1*^{IS} >10% discontinued after 6.3 months of study drug exposure, 1 with disease progression according to the investigator (but not meeting protocol criteria for progression) discontinued after 19.6 months of study drug exposure, and 1 with loss of MMR discontinued after 13.5 months of study drug exposure.

†Protocol deviations were 2 cases of noncompliance.

C_{trough} (CV%) value (n = 25) during the first year of treatment was estimated to be 1274.30 ng/mL (46.21%).

Pooling all data, the geometric mean (CV%) C_{trough} value during the first year of treatment was estimated to be 1345.51 ng/mL (43.66%). The ranges of C_{trough} values were 1540 to 1910 ng/mL for the younger group (age 2 to <12 years) and 1200 to 1640 ng/mL for the older group (age 12 to 18 years). There was no association between the nilotinib C_{trough} and the *BCR-ABL1* level at 12 cycles in either cohort.

Safety

All patients in both cohorts reported ≥1 AE. The most common (>20% in any cohort) all-grade, all-cause AE terms (using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03) are shown in Table 4 and supplemental Table 1. Grade 3 to 4 all-cause AEs were reported in 18 patients (54.5%) in the R/I cohort and 16 patients (64.0%) in the newly diagnosed cohort. AEs were managed through monitoring and dose modifications. For AEs that required dose reductions, the dose was reduced to 230 mg/m^2 once per day. Upon resolution of toxicities, if appropriate, re-escalation to 230 mg/m^2 twice per day was attempted. In the R/I cohort, 16 patients (48.5%) had dose reductions as a result of AEs, and 20 (60.6%) had dose interruptions as a result of AEs. In the newly diagnosed cohort, 11 patients (44.0%) had dose reductions and 17 patients (68.0%) had dose interruptions as a result of AEs. Dose reductions and interruptions were implemented per the study protocol. AEs led to discontinuation of study drug in 5 patients (15.2%) in the R/I cohort and 6 (24.0%) in the newly diagnosed cohort (supplemental Table 2); AEs leading to discontinuation in >1 patient (across both cohorts) included increases in bilirubin (grade 2 to 3) and rash (grade 2 to 3).

Serious AEs (SAEs) were reported in 9 patients (27.3%) in the R/I cohort and 3 patients (12.0%) in the newly diagnosed cohort and were suspected to be drug related in 3 of these patients (5.2%). SAEs suspected to be drug related were grade 1 growth hormone deficiency in a patient (age 10 years at baseline) in the R/I cohort (slowing of growth was already reported before initiation of nilotinib when the patient was receiving first-line imatinib); diarrhea, abdominal pain, and rash (all grade 1) in a patient (age 16 years at baseline) in the newly diagnosed cohort; and QT prolongation (grade 1) and hyperbilirubinemia (grade 3) in another patient (age 16 years at baseline) in the newly diagnosed cohort. As defined by the study protocol, these SAEs were designated as serious despite their lower grades because the patients were hospitalized. At the data cutoff, the drug-related SAE of growth hormone deficiency and an SAE of leukocytosis

Table 3. Efficacy outcomes in imatinib or dasatinib R/I patients and patients with newly diagnosed disease

Outcome*	R/I to imatinib or dasatinib (n = 33)	Newly diagnosed (n = 25)
MMR		
At baseline	7 (21.2)	0
Rate at 6 cycles (primary end point in R/I patients)	13 (39.4)†	13 (52.0)
Rate at 12 cycles	16 (48.5)†	15 (60.0)
Rate at 24 cycles	17 (51.5)†	14 (56.0)
Cumulative rate by 12 cycles (coprimary end point in newly diagnosed CML)	19 (57.6)†	16 (64.0)
Cumulative rate by 24 cycles	19 (57.6)†	17 (68.0)
Cumulative rate by data cutoff	20 (60.6)†	18 (72.0)
Median time to first MMR, months (range)‡	2.8 (0-38.8)	5.6 (2.7-33.0)
CCyR		
At baseline	14 (42.4)	0
Rate at 6 cycles	24 (72.7)§	21 (84.0)
Rate at 12 cycles (coprimary end point in newly diagnosed CML)	23 (69.7)§	16 (64.0)
Rate at 24 cycles	21 (63.6)§	15 (60.0)
Cumulative rate by 12 cycles	27 (81.8)§	21 (84.0)
Cumulative rate by 24 cycles	27 (81.8)§	21 (84.0)
Estimated EFS at 24 mo, % (95% CI)‖	96.3 (76.5-99.5)	91.2 (69.0-97.7)
Progression to AP/BC on treatment	1 (3.0)	0

Data are presented as number (%) unless otherwise specified.

BC, blast crisis; CHR, complete hematologic response; EFS, event-free survival; MCyR, major cytogenetic response; PCyR, partial cytogenetic response.

*Patients with missing data were counted as nonresponders.

†In the R/I cohort, 6 patients in MMR at 6 and 12 cycles, 7 patients in MMR at 24 cycles, and 7 patients in MMR by 12 cycles, 24 cycles, and the data cutoff were in MMR at baseline.

‡Median time (range) to first MMR among the patients who achieved MMR by the data cutoff.

§In the R/I cohort, 12 patients in CCyR at 6 cycles, 11 patients in CCyR at 12 cycles, 12 patients in CCyR at 24 cycles, and 14 patients in CCyR by 12 and 24 cycles were already in CCyR at baseline.

‖The following were considered events during treatment: loss of CHR, loss of MCyR (MCyR includes both PCyR and CCyR), progression to AP/BC (from CP) or to BC (from AP), or death from any cause.

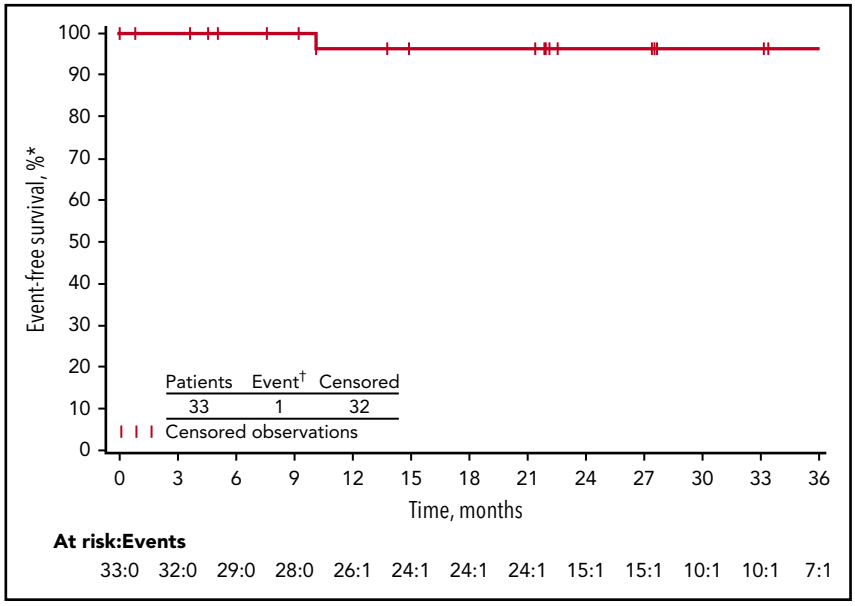

Figure 1. Kaplan-Meier plot of event-free survival in R/I patients. *The following were considered events during treatment: loss of complete hematologic response (CHR), loss of major cytogenetic response (MCyR; MCyR includes both partial cytogenetic response [PCyR] and CCyR), progression to AP/BC (from CP) or to BC (from AP), or death from any cause. †One patient had an event of progression to AP/BC.

that was not suspected to be drug related (R/I cohort) remained ongoing; all other SAEs had resolved.

AEs of special interest are shown in Table 5. No cardiovascular AEs were reported in any patient. Three patients (9.1%) in the R/I cohort and 2 (8.0%) in the newly diagnosed cohort experienced AEs related to increased blood cholesterol (all were grade 1 to 2 except for a single grade 3 AE in the newly diagnosed cohort). Two patients (6.1%) in the R/I cohort and none in the newly diagnosed cohort experienced AEs related to an increase in blood glucose (all grade 1 to 2). AEs related to QT prolongation (specifically, syncope [n = 1] or prolonged QT [n = 7]) were reported in 5 patients (15.2%) in the R/I cohort and 3 (12.0%) in the newly diagnosed cohort (all grade 1 to 2). AEs related to increased hepatic transaminase or bilirubin were reported in 19 patients (57.6%) in the R/I cohort (grade 3 to 4 in 7 patients [21.2%]) and 16 (64.0%) in the newly diagnosed cohort (grade 3 to 4 in 6 patients [24.0%]). No cases of pancreatitis were reported.

The most frequent newly occurring or worsening grade 3 to 4 biochemistry abnormalities (≥2 patients) in the R/I cohort were increased alanine aminotransferase (ALT) (n = 4 [12.1%]), total bilirubin, and blood lipase (n = 3 [9.1%] each). Similarly, the most frequent newly occurring or worsening grade 3 to 4 biochemistry abnormalities (≥2 patients) in the newly diagnosed cohort were increased total bilirubin (n = 4 [16.0%]) and ALT (n = 3 [12.0%]). No cases of grade 3 to 4 increases in glucose were reported in either cohort. By the time of the data cutoff, no relevant abnormalities were detected in the growth and development parameters analyzed (see supplemental Methods), and no cases of delayed puberty were observed.

Discussion

This phase 2 study confirmed the clinical activity of nilotinib 230 mg/m^2 twice per day in pediatric patients with newly diagnosed Ph$^+$ CML-CP or R/I to imatinib or dasatinib. MMR at

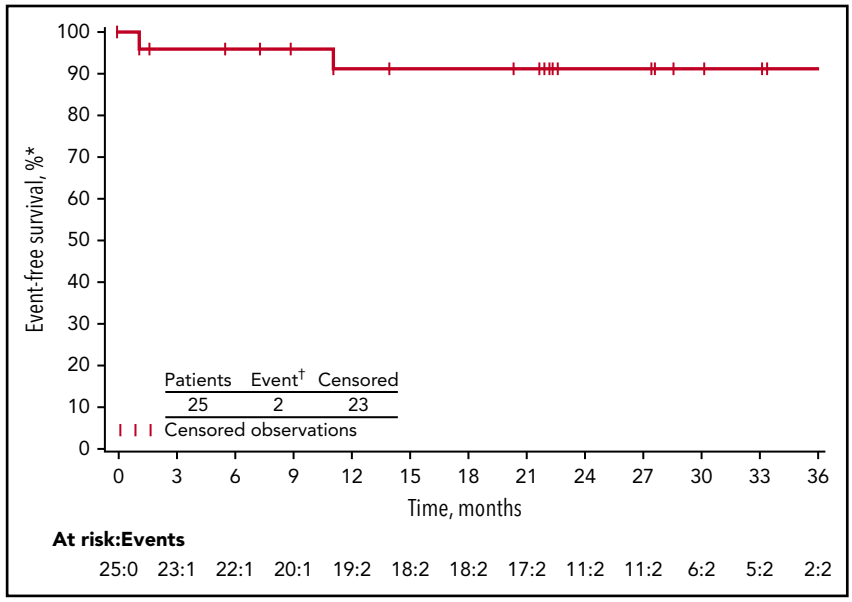

Figure 2. Kaplan-Meier plot of event-free survival in patients with newly diagnosed disease. *The following were considered events during treatment: loss of CHR, loss of MCyR (MCyR includes both PCyR and CCyR), progression to AP/BC (from CP) or to BC (from AP), or death from any cause. †One month after the start of nilotinib treatment, 1 patient temporarily met the technical definition of progression to AP/BC because of increased basophil count. Treatment with nilotinib was temporarily interrupted for 13 days during the first 28-day cycle because of prolonged QT. The patient remained in the study, returned to CP 1 month after progression, and was in CHR after 5.8 months of treatment and in CCyR after 5.3 months of treatment. The patient discontinued from the study because of hyperbilirubinemia after 13.8 months on treatment without losing CHR and CCyR. Progression in this patient was not considered to be clinically notable based on clinical review; however, it was considered as progression to AP/BC in formal statistical analyses. The other patient with an event experienced confirmed loss of MCyR.

Table 4. AEs (all grades, all causes; >20% in any cohort)

AEs	R/I to imatinib or dasatinib (n = 33)*		Newly diagnosed (n = 25)†		All patients (N = 58)	
	All grades	Grade 3 to 4	All grades	Grade 3 to 4	All grades	Grade 3 to 4
AEs related to bilirubin increases‡	17 (51.5)	3 (9.1)	15 (60.0)	4 (16.0)	32 (55.2)	7 (12.1)
Headache	13 (39.4)	1 (3.0)	14 (56.0)	0	27 (46.6)	1 (1.7)
Pyrexia	13 (39.4)	0	8 (32.0)	1 (4.0)	21 (36.2)	1 (1.7)
Increased ALT	10 (30.3)	4 (12.1)	10 (40.0)	3 (12.0)	20 (34.5)	7 (12.1)
Rash	6 (18.2)	2 (6.1)	11 (44.0)	1 (4.0)	17 (29.3)	3 (5.2)
Upper respiratory tract infection	11 (33.3)	1 (3.0)	7 (28.0)	0	18 (31.0)	1 (1.7)
Increased AST	8 (24.2)	1 (3.0)	8 (32.0)	1 (4.0)	16 (27.6)	2 (3.4)
Nausea	8 (24.2)	0	7 (28.0)	0	15 (25.9)	0
Vomiting	5 (15.2)	0	7 (28.0)	1 (4.0)	12 (20.7)	1 (1.7)
Abdominal pain§	3 (9.1)	0	8 (32.0)	0	11 (19.0)	0
Nasopharyngitis	5 (15.2)	0	6 (24.0)	0	11 (19.0)	0
Fatigue	0	0	6 (24.0)	0	6 (10.3)	0

Data are presented as number (%).

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

*The most frequently reported drug-related AEs (>20%) in the R/I cohort included AEs related to bilirubin increases (n = 17 [51.5%] [including increased blood bilirubin: n = 12 (36.4%); hyperbilirubinemia: n = 4 (12.1%); increased conjugated bilirubin: n = 2 (6.1%); and increased unconjugated blood bilirubin: n = 1 (3.0%)]), increased ALT (n = 10 [30.3%]), headache (n = 8 [24.2%]), and increased AST (n = 8 [24.2%]).

†The most frequently reported drug-related AEs (>20%) in the newly diagnosed cohort included AEs related to bilirubin increases (n = 15 [60.0%] [including increased blood bilirubin: n = 8 (32.0%); hyperbilirubinemia: n = 8 (32.0%); increased conjugated bilirubin: n = 2 (8.0%); and increased unconjugated blood bilirubin: n = 2 (8.0%)]), increased ALT (n = 10 [40.0%]), increased AST (n = 8 [32.0%]), headache (n = 8 [32.0%]), and rash (n = 6 [24.0%]).

‡Pooled frequency of events reported under the following terms: increased blood bilirubin, hyperbilirubinemia, increased conjugated bilirubin, and increased unconjugated blood bilirubin. Rates of AEs reported under each of these terms are detailed in supplemental Table 1.

§Two patients with abdominal pain (1 in each cohort) also had amylase and lipase increases, which resolved after interruption of study drug. No events of pancreatitis were reported.

6 cycles was achieved by 39.4% of R/I patients, including 7 patients who did not have MMR at baseline plus 6 of the 7 patients who were in MMR at baseline. Furthermore, by cycle 12, the cumulative MMR rate in this cohort was 57.6%. Among patients with newly diagnosed disease, the cumulative MMR rate was 64.0% by cycle 12 and 68.0% by cycle 24.

Overall, nilotinib was associated with a manageable safety profile, and no new safety signals were identified. The most frequently reported drug-related AEs included increases in bilirubin, ALT, and aspartate aminotransferase (AST), as well as headache in both cohorts. Of 20 patients who discontinued across both cohorts, 11 discontinued because of AEs. Although ischemic cardiovascular events have been reported in adult patients with CML treated with TKIs, including nilotinib,[14] no such cardiovascular AEs were reported in this study. In adults with CML-CP treated with nilotinib, QT prolongation and increases in cholesterol, glucose, and bilirubin have also been reported.[15] In a phase 2 study in adults with Ph$^+$ CML-CP R/I to imatinib and treated with nilotinib 400 mg twice per day, grade 3 to 4 bilirubin increases occurred in 7% of patients, and grade 3 to 4 increases in AST and ALT occurred in 3% and 4%, respectively, at 24 months of follow-up.[16] Similarly, in the ENESTnd trial, adults with newly diagnosed Ph$^+$ CML-CP treated with nilotinib 300 or 400 mg twice per day showed increased ALT and bilirubin levels among the most frequently reported grade 3 to 4 biochemistry abnormalities (300 mg: increased ALT and bilirubin [4.3% each]; 400 mg: increased ALT [9.4%] and bilirubin [9.0%]) at 5 years of follow-up.[15] In this study, the most frequent newly occurring or worsening grade 3 to 4 biochemistry abnormalities in both cohorts were hepatic and occurred more frequently than in adult patients. However, the majority of AEs related to hepatic transaminase or bilirubin increases in this study were grade 1 to 2, and the safety of nilotinib was effectively managed by routine monitoring and dose modifications. Glucose increases were less frequent in this pediatric population than in adults. In the 24-month ENESTnd analysis, grade 3 to 4 laboratory abnormalities of increased glucose were reported in 6% of adult patients with CML-CP who received first-line nilotinib 300 mg twice per day,[17] but there were no grade 3 to 4 AEs or biochemical abnormalities of increased glucose in this population.

Several studies have reported that imatinib has a negative impact on growth and development in children with CML; growth retardation,[18] dysregulation of bone remodeling,[19] and alterations in bone metabolism[20] have been associated with imatinib treatment. A retrospective study reported significant growth deceleration after 12 months of first-line imatinib therapy in pediatric patients.[21] In the 2 cohorts in our study, monitoring of growth and development parameters did not reveal any relevant

Table 5. AEs of special interest

AEs	R/I to imatinib or dasatinib (n = 33)		Newly diagnosed (n = 25)		All patients (N = 58)	
	All grades	Grade 3 to 4	All grades	Grade 3 to 4	All grades	Grade 3 to 4
Cardiovascular events* or cardiac failure	0	0	0	0	0	0
Increased blood cholesterol†	3 (9.1)	0	2 (8.0)	1 (4.0)	5 (8.6)	1 (1.7)
Increased blood glucose‡	2 (6.1)	0	0	0	2 (3.4)	0
Fluid retention	1 (3.0)	0	3 (12.0)	1 (4.0)	4 (6.9)	1 (1.7)
Edema and other fluid retention	1 (3.0)	0	3 (12.0)	1 (4.0)	4 (6.9)	1 (1.7)
Medically severe fluid retention	0	0	0	0	0	0
Hepatotoxicity	20 (60.6)	8 (24.2)	16 (64.0)	6 (24.0)	36 (62.1)	14 (24.1)
Increased hepatic transaminase and bilirubin§	19 (57.6)	7 (21.2)	16 (64.0)	6 (24.0)	35 (60.3)	13 (22.4)
Drug-induced liver injury‖	1 (3.0)	1 (3.0)	0	0	1 (1.7)	1 (1.7)
Myelosuppression (thrombocytopenia)	1 (3.0)	0	8 (32.0)	3 (12.0)	9 (15.5)	3 (5.2)
Pancreatitis	0	0	0	0	0	0
QT prolongation¶	5 (15.2)	0	3 (12.0)	0	8 (13.8)	0
Rash	15 (45.5)	5 (12.2)	15 (60.0)	2 (8.0)	30 (51.7)	7 (12.1)
Renal events	0	0	0	0	0	0
Significant bleeding	0	0	0	0	0	0

Data are presented as number (%).

*No events were reported in any of the cardiovascular event subgroups (ischemic cerebrovascular events, ischemic heart disease, peripheral arterial occlusive disease, or others).

†One 10-year-old girl in the newly diagnosed cohort experienced a grade 3 increase in blood cholesterol requiring dose interruption for 26 days. Nilotinib was restarted while the patient had a mild increase in cholesterol (grade 1), and cholesterol improved to normal limits. None of the other events required dose adjustment or discontinuation.

‡None of these events required dose adjustment or discontinuation.

§These events led to dose adjustments or interruptions in 11 patients in each cohort and discontinuation in 3 patients in each cohort.

‖Several episodes of grade 2 to 3 drug-induced liver injury were reported in 1 patient. Clinically, the episodes reflected increases in transaminase and bilirubin, and there were no signs of severe or progressive liver dysfunction.

¶Preferred terms for AEs in this group included electrocardiogram QT prolonged (n = 7) and syncope (n = 1; newly diagnosed cohort). In 6 of the 8 patients, these events were considered related to nilotinib. Three patients had newly occurring QTcF >450 ms on study, and 4 patients had newly occurring QTcF >480 ms in electrocardiograms performed per protocol; in the patient with syncope, QTcF was normal on the same date, and the physician considered the event to be unrelated to nilotinib. No episode of QTcF >500 ms or >60-ms increase from baseline occurred. In the R/I cohort, 3 of 5 patients with AEs of QT prolongation required dose adjustments or interruptions; none discontinued nilotinib. In the newly diagnosed cohort, 3 of 3 patients with AEs of QT prolongation required dose reductions or interruptions but not discontinuation. All AEs related to QT prolongation had resolved by the data cutoff.

changes with respect to the effect of nilotinib on growth or sexual maturity by the data cutoff. A grade 1 SAE of hormone deficiency suspected to be related to nilotinib treatment was reported in the R/I cohort, although slowing of growth had already been observed when the patient was receiving first-line treatment with imatinib. However, because of the limited number of patients and short follow-up period for this analysis, few conclusions can be drawn regarding the effect of nilotinib on these parameters.

Measurements of C_{trough} in this study showed an average value comparable to the steady-state C_{trough} after 400 mg twice per day in adults.[22] In adults, the approved nilotinib dose is lower for patients with newly diagnosed vs R/I disease, although the PK parameters of both adult doses overlap.[22] The dose of 230 mg/m^2 twice per day was deemed appropriate for pediatric patients with newly diagnosed disease because CML tends to present with more aggressive features in pediatric patients compared with adults.[12] Because a lower nilotinib dose has not been tested in pediatric patients, it cannot be excluded that a lower dose would provide similar efficacy; however, the dose selection was supported by the fact that the safety profile of nilotinib 230 mg/m^2 twice per day in children was comparable with the safety profiles of both the 300-mg and 400-mg twice-per-day doses in adults.[11] In addition, we observed a flat exposure-response relationship for efficacy (*BCR-ABL1* level); this would suggest that the PK fluctuations at the dose of 230 mg/m^2 twice per day would be too small to affect response, and therefore the dose and dosage regimen are appropriate.

Before November 2017, imatinib was the only TKI approved for the treatment of pediatric patients with Ph$^+$ CML. It has been investigated in both the newly diagnosed setting[7,23,24] and in patients who are refractory to or intolerant of interferon alfa (IFN-α).[24] In the French national phase 4 trial conducted in 44 pediatric patients with newly diagnosed CML-CP, 31% of patients

treated with imatinib 260 mg/m^2 once per day achieved MMR and 61% achieved CCyR at 12 months.[7] MMR and CCyR rates have also been reported in an Italian multicenter study that enrolled 47 pediatric patients who were either treatment naive or R/I to IFN, although the study was limited by incomplete data (many patients were not included in the response rate calculations). Patients were treated with high-dose imatinib (340 mg/m^2 once per day); at 12 months, 66.6% of evaluable patients (14 of 21) achieved MMR, whereas 91.5% of evaluable patients (33 of 36) achieved CCyR at a median of 6 months.[24] Overall, 15.5% of patients in the Italian study discontinued imatinib because of lack of response or treatment failure.[24] From a clinical perspective, it is important to highlight that patients resistant to IFN-α and patients resistant to imatinib or dasatinib are different, given the limited activity of IFN-α compared with imatinib or dasatinib; as demonstrated by the IRIS trial, first-line imatinib is superior to IFN-based therapy in terms of hematologic and cytogenetic responses in patients with newly diagnosed CML-CP.[25] Comparable depth of response, progression-free survival, and overall survival of patients with CML treated with IFN-based therapies relative to TKI therapy have not been demonstrated. Furthermore, resistance to IFN-α has a different clinical implication compared with resistance to imatinib or dasatinib; although a long-term survival benefit and improved CCyR rates have been observed in patients with CML-CP who received imatinib after failure of IFN-α,[26] only approximately half the patients who switch to a second-generation TKI because of imatinib resistance achieved CCyR.[27]

Hematopoietic stem cell transplantation is an alternative to treatment with TKIs for pediatric patients and, despite its complications, is still considered the only curative treatment for CML.[12] Currently, nilotinib and dasatinib are the only TKIs approved for patients who are R/I to previous therapy, including imatinib, as well as those with newly diagnosed CML-CP.[28,29] Similar to nilotinib, dasatinib has been investigated in phase 1/2 studies in pediatric patients with relapsed or refractory CML[30,31] or newly diagnosed CML.[31] In a recent study, early and durable responses were observed in pediatric patients who were imatinib R/I and newly diagnosed patients with CML-CP who were treated with dasatinib.[31] In patients with R/I CML-CP, the cumulative MMR rate with dasatinib was approximately 30% by 6 months and 55% by 24 months. In newly diagnosed patients, MMR rates by 12 and 24 months were 52% and 70%, respectively.[31] In our study, nilotinib resulted in MMR rates of 39.4% at 6 cycles and 57.6% by 24 cycles in the R/I cohort and 64.0% by 12 cycles and 68.0% by 24 cycles in the newly diagnosed cohort. Drug-related SAEs were more frequently reported in the dasatinib study (R/I, 17% [n = 5]; newly diagnosed, 10% [n = 8])[31] than in our study (R/I, 3% [n = 1]; newly diagnosed, 8% [n = 2]) and were more severe (grade 3 to 4 drug-related SAEs: dasatinib, 17% [n = 5] in R/I and 7% [n = 6] in newly diagnosed patients[31]; nilotinib, 0% in R/I and 4% [n = 1] in newly diagnosed patients), and 4% of patients had dasatinib-related AEs related to pediatric bone growth and development.[31] Although nilotinib and dasatinib induce faster responses compared with imatinib in adults,[15,32] there is a concern about toxicities, including vascular events.[33] However, vascular events were not reported with nilotinib or dasatinib in the pediatric studies.[31]

The goals of CML treatment in both adult and pediatric patients include achieving remission, decreasing the risk of disease progression, and maximizing survival.[12,34] The high rates of MMR in our study suggest that nilotinib may help pediatric patients achieve these treatment goals because achieving MMR is associated with durable long-term remission and decreased risk of disease progression in adults. Because pediatric patients have a longer life expectancy, they are expected to have a longer total duration of TKI therapy than adults. As a result, pediatric patients may be at increased risk of long-term morbidities. Long-term follow-up studies will therefore be critical for evaluating the effects of prolonged TKI therapy and the potential for pediatric patients to achieve deep molecular responses and treatment-free remission.

In conclusion, although the size of this study was limited by the rarity of CML in children, these results demonstrate the efficacy of nilotinib in pediatric patients at the recommended 230-mg/m^2 twice-per-day dose, as well as a manageable safety profile comparable with the known safety profile of nilotinib in adults with Ph$^+$ CML-CP.[15,35] On the basis of the results of this study and the previous phase 1 study, nilotinib 230 mg/m^2 twice per day has been approved in Europe,[4] Japan,[36] and the United States[37] for the treatment of pediatric patients with R/I or newly diagnosed CML-CP. Nilotinib can be seen as a valuable additional therapeutic option for treating pediatric CML.

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Footnotes

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Novartis is committed to sharing, with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel based on scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

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