Original Study

Evaluating the Impact of a Switch to Nilotinib on Imatinib-Related Chronic Low-Grade Adverse Events in Patients With CML-CP: The ENRICH Study

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Abstract

Chronic treatment-related adverse events adversely affect quality of life, treatment adherence, and clinical outcomes of many patients taking imatinib. The ENRICH (Exploring Nilotinib to Reduce Imatinib Related Chronic Adverse Events) study evaluated the effect of switching 52 such patients to nilotinib. Within 3 months of switching, improvements in imatinib-related adverse events and quality of life and ongoing achievement and maintenance of molecular and cytogenetic responses were observed.

Background: Many patients with chronic myeloid leukemia in chronic phase experience chronic treatment-related adverse events (AEs) during imatinib therapy. These AEs can impair quality of life and lead to reduced treatment adherence, which is associated with poor clinical outcomes. **Patients and Methods:** In the phase II ENRICH (Exploring Nilotinib to Reduce Imatinib Related Chronic Adverse Events) study (N = 52), the effect of switching patients with imatinib-related chronic low-grade nonhematologic AEs from imatinib to nilotinib was evaluated. **Results:** Three months after switching to nilotinib, 84.6% of the patients had overall improvement in imatinib-related AEs (primary endpoint). Of 210 imatinib-related AEs identified at baseline, 62.9% had resolved within 3 months of switching to nilotinib. Of evaluable patients, most had improvements in overall quality of life after switching to nilotinib. At screening, 65.4% of evaluable patients had a major molecular response (*BCR-ABL1* $\leq$ 0.1% on the International Scale). After switching to nilotinib, the rate of the major molecular response was 76.1% at 3 months and 87.8% at 12 months. Treatment-emergent AEs reported with nilotinib were typically grade 1 or 2; however, some patients developed more serious AEs, and 8 patients discontinued nilotinib because of new or worsening AEs. **Conclusion:** Overall, results from the ENRICH study demonstrated that switching to nilotinib can mitigate imatinib-related chronic low-grade nonhematologic AEs in patients with chronic myeloid leukemia in chronic phase, in conjunction with acceptable safety and achievement of molecular responses. This trial was registered at www.clinicaltrials.gov as NCT00980018.

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Introduction

In patients with newly diagnosed Philadelphia chromosome–positive (Ph^+) chronic myeloid leukemia in chronic phase (CML-CP), chronic mild to moderate imatinib-related adverse events (AEs) can negatively affect patient quality of life (QOL), leading to reduced adherence to therapy,[1-3] which is associated with poor responses

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and poor long-term outcomes.[4-7] Therefore, the proper management of AEs is critical for ensuring optimal outcomes.[1,3,6,8] When treatment interruptions and reduced adherence result from imatinib-related toxicities, switching patients to another tyrosine kinase inhibitor (TKI) can improve tolerability and treatment adherence, thereby optimizing responses.

Nilotinib is more potent and selective than imatinib,[9] has demonstrated superior efficacy compared with imatinib,[10-14] and is associated with a safety profile distinct from that of imatinib.[10-14] Compared with imatinib, the incidence of nausea, vomiting, diarrhea, muscle spasms, and edema is lower with nilotinib, although the incidence of rash, headache, and pruritus is higher with nilotinib.[12] In a subset analysis of 95 patients with CML-CP who discontinued imatinib because of intolerance (>75% for grade 3/4 AEs) and switched to nilotinib, cross-intolerance (defined as the occurrence of the same AE with nilotinib that was associated with intolerance to imatinib) was uncommon.[15] In that study, no patient required nilotinib dose reductions or discontinued nilotinib treatment due to the same AE that had led to imatinib discontinuation.[15] Cardiovascular AEs have been reported to varying degrees with all TKIs approved for treatment of CML[14,16-23] and were reported more frequently with nilotinib than with imatinib in the pivotal trial of frontline nilotinib versus imatinib (ENESTnd).[13,14]

The phase II ENRICH (Exploring Nilotinib to Reduce Imatinib Related Chronic Adverse Events) study was conducted to evaluate whether imatinib-related chronic low-grade nonhematologic AEs could be improved and responses optimized by switching patients from imatinib to nilotinib.

Patients and Methods

ENRICH was a phase II, single-arm, open-label, multicenter, exploratory study to determine the effect of switching to nilotinib on the AE profile of patients with low-grade toxicities associated with imatinib therapy (ClinicalTrials.gov identifier, NCT00980018).

Study Design and Treatments

Adults (aged ≥ 18 years) with CML-CP and an Eastern Cooperative Oncology Group performance status of ≤ 2 were eligible. The patients had been treated with imatinib (any dose) for ≥ 3 months before screening and experienced a Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 nonhematologic AE during imatinib therapy that had persisted for > 2 months or had recurred > 3 times despite best supportive care. The patients were required to have achieved the following efficacy milestones with imatinib therapy: after 3 months, a complete hematologic response (CHR); after 6 months, Ph^+ < 95% (≥ 20 metaphases required for standard bone marrow cytogenetics); after 12 months, Ph^+ < 35%; and after 18 months, Ph^+ 0% or *BCR-ABL1* ≤ 0.1% on the International Scale (*BCR-ABL1*^{IS}; documented within 3 months). Patients meeting any of the following criteria were excluded: any grade ≥ 3 nonhematologic AE within 30 days of screening; previous accelerated or blast phase; loss of a CHR or cytogenetic response (CyR); previously documented T315I mutation; previous treatment with any TKI other than imatinib; impaired cardiac function (including congenital long QT syndrome or a known family history of long QT syndrome, a history or presence of clinically significant ventricular or atrial tachyarrhythmias, clinically significant resting bradycardia, an inability to monitor the QT interval by electrocardiography, Fridericia-corrected QT > 450 ms on the baseline electrocardiogram, myocardial infarction within 1 year of starting the study drug, or other clinically significant heart disease); impaired gastrointestinal function or gastrointestinal disease that could significantly alter absorption of nilotinib; acute or chronic liver, pancreatic, or renal disease; a history of a significant bleeding disorder; pregnancy or nursing; treatment with a cytochrome P450 3A4 inhibitor; or medication with the potential to prolong the QT interval.

Enrolled patients received nilotinib 300 mg twice daily for 12 cycles (1 cycle = 28 days) during the study. No washout period was required between imatinib and nilotinib treatment. The patients were followed up for safety evaluations for 28 days after the last dose of study drug.

Endpoints and Assessments

Imatinib-related chronic low-grade (grade 1 or 2) nonhematologic AEs, hereafter referred to as imatinib-related AEs, were assessed on days 1 and 15 of cycle 1 and at the end of cycles (EOC) 1, 2, 3, 6, 9, and 12. The primary endpoint of the study was the percentage of patients with overall improvement in imatinib-related AEs at EOC 3 after the switch to nilotinib. Overall improvement was defined as either a decrease in CTCAE grade or resolution of ≥ 50% of a patient's imatinib-related AEs. The secondary endpoints included the rate of complete CyR (CCyR; defined as negative fluorescence in situ hybridization [FISH] findings or 0% Ph^+ cells) among patients without CCyR at baseline; the rate of major molecular response (MMR) at EOC 1, 2, 3, 6, 9, and 12; *BCR-ABL1*^{IS} log changes following switch to nilotinib; the time to, and duration of, CCyR and MMR during the study; the time to the first documented and optimal improvement in imatinib-related AEs; and safety.

The time to the first documented improvement of imatinib-related AEs was defined as the interval from the first dose of the study drug until the first documented decrease in CTCAE grade. The time to optimal improvement of imatinib-related AEs was defined as the interval from the first dose of the study drug until a maximum decrease in the sum of the CTCAE grades of the events. AEs with an onset date on or after the date of study drug initiation or that had worsened or recurred during study treatment were included in the analysis of AEs occurring during nilotinib treatment. Serious AEs (SAEs) occurring at any point from the initiation of study drug until 28 days after stopping study participation were also analyzed. Nilotinib dose reductions were required for patients with grade 3/4 AEs concerning white blood cells and platelets and grade 2 to 4 nonhematologic AEs. Discontinuation from the study was required if any toxicity had not resolved after 28 days. AEs were assessed using CTCAE, version 4.0.

The times to CCyR and MMR were defined as the interval from the first dose of the study drug to the first documented CCyR or MMR, respectively. The duration of CCyR was defined as the interval from the first documented CCyR to the date of the first documented loss of CCyR or study termination, whichever was earlier. The duration of MMR was defined similarly. Bone marrow cytogenetic assessment was required at screening if no

documentation was available that the patient had achieved the efficacy milestones during imatinib therapy that were required for study eligibility. For patients with < 18 months of previous imatinib therapy and without CCyR at screening, additional bone marrow cytogenetic assessments were required during the study. Once CCyR was documented by cytogenetics, no additional bone marrow assessments were required unless a loss of response was suspected or early discontinuation was required before EOC 12. Peripheral blood FISH was performed at EOC 1, 2, 3, 6, and 9 until achievement of CCyR and at EOC 12 for all patients.

The exploratory endpoints included a change in overall QOL and in the MD Anderson Symptom Inventory Chronic Myeloid Leukemia Module (MDASI-CML) score, both assessed at baseline and at EOC 1, 3, 6, 9, and 12. For evaluation of overall QOL, the patients rated their QOL within the previous 24 hours and the previous 7 days on an 11-point scale by responding to the following: "rate your quality of life within the last 24 hours on a scale of 0 to 10" and "rate your quality of life within the last 7 days on a scale of 0 to 10," with an increasing QOL score indicating improvement. The MDASI-CML module is a patient-reported outcome measure for the evaluation of symptom burden in patients with CML and comprises 20 core and CML-specific symptom items (ie, vomiting, nausea, diarrhea, dry mouth, pain, drowsiness, shortness of breath, sadness, difficulty remembering, disturbed sleep, distress, fatigue, numbness, muscle soreness, swelling, malaise, rash or skin change, bruising easily or bleeding, lack of appetite, and headache)[3] and 6 interference items (ie, general activity, work, walking, enjoyment of life, mood, and relationships with other people). After completion of the present study, the MDASI-CML module was validated, and headache was added as a CML-specific item.[3] The patients scored each symptom or interference item on an 11-point scale, with a decreasing MDASI-CML score indicating improvement. For MDASI-CML symptom items, a rating of 0 indicates "not present" and 10, severity "as bad as you can imagine." For MDASI-CML interference items, a rating of 0 indicates "did not interfere" and 10, "interfered completely."

Statistical Analysis

The efficacy analyses included all patients who had received ≥ 1 dose of study drug. The safety analyses included all patients who had received ≥ 1 dose of the study drug and had had ≥ 1 evaluable postbaseline safety assessment. The primary endpoint was assessed using a 95% confidence interval (CI) using the normal approximation to the binomial. The proportion of imatinib-related AEs with improvement was assessed using a quasi-likelihood method[24,25] that accommodated the unknown covariance associated with measuring the overall effect of AEs for individual patients. Times to CCyR, MMR, first documented improvement in any imatinib-related AE, and optimal improvement in imatinib-related AEs were analyzed using the Kaplan-Meier product limit method. The planned sample size was 50 patients to assess the primary endpoint with a 2-sided 95% CI within 14% of the true percentage. All statistical analyses were performed using SAS software, version 9.1.3.

Ethics Statements

The present study was conducted in accordance with the Declaration of Helsinki and local applicable laws and regulations. The institutional review board or independent ethics committee at each participating study center approved the protocol. Each patient provided written informed consent before study participation.

Results

Patients and Treatments

The ENRICH study was conducted across 15 centers in the United States and 4 centers in Canada; 52 patients were enrolled from December 10, 2009 to August 15, 2012 (study completion date, December 27, 2012). The baseline demographics and characteristics of all enrolled patients are listed in Table 1. All evaluable patients had a CHR at baseline, and most patients had a CCyR and an MMR at baseline (86.5% and 65.4%, respectively). Forty patients (76.9%) completed the study per protocol, and 12 discontinued early, 8 because of AEs (15.4%), 3 by withdrawal of consent (5.8%), and 1 because the patient was lost to follow-up (1.9%). The median duration of nilotinib exposure during the study was 336 days (range, 6-617 days).

Impact of Switching to Nilotinib on Imatinib-Related AEs

Among the 52 patients, 210 imatinib-related AEs were identified at baseline, including 154 grade 1 AEs and 56 grade 2 AEs. The most common imatinib-related AE at baseline was fatigue (n = 29; 13.8%), followed by diarrhea and nausea, each occurring in 20 patients (9.5%; Table 2).

Of the 210 imatinib-related AEs at baseline, 132 (62.9%) had resolved, 13 (6.2%) had improved, 55 (26.2%) were unchanged, and 6 (2.9%) had worsened at EOC 3. Information was missing for 4 AEs (1.9%; Figure 1A). Of the imatinib-related fatigue AEs, 16 of 29 (55.2%) had improved or resolved at EOC 3, as had 19 of 20 imatinib-related diarrhea AEs (95.0%) and 16 of 20 imatinib-related nausea AEs (80.0%). Similarly, ≥ 50% of imatinib-related AEs of muscle spasms, peripheral edema, periorbital edema, arthralgia, myalgia, headache, dyspepsia, rash, face edema, weight increase, pruritus, vomiting, bone pain, and amnesia had improved or resolved by EOC 3. Of the 6 imatinib-related AEs that had worsened by EOC 3, 5 had worsened from grade 1 to grade 2 (fatigue [n = 2], pruritus [n = 1], headache [n = 1], and memory impairment [n = 1]) and 1 had worsened from grade 2 to grade 3 (generalized pain). At EOC 12, 151 of 210 imatinib-related AEs (71.9%) had either improved or resolved, and 34 imatinib-related AEs (16.2%) had resolved but then reappeared. The AE type that most frequently resolved and reappeared was muscle spasms (resolved and reappeared in 5 of 14 patients [35.7%]).

An overall improvement (resolution of, or reduction in, CTCAE grade for ≥ 50% of a patient's imatinib-related AEs) was observed in 37 of 52 patients (71.2%) at EOC 1 (Figure 1B). By EOC 3, 7 additional patients had achieved an overall improvement. Thus, the total number of patients with an overall improvement at EOC 3 (primary endpoint) was 44 of 52 (84.6%; 95% CI, 72.5%-92.0%). No additional patients achieved an overall improvement after EOC 3, and all 44 patients with overall improvement at EOC 3 maintained the improvement through EOC 12. Thus, the proportion of patients with overall improvement was 84.6% at all points beyond EOC 3. The estimated median time to the first improvement of any imatinib-related AE was 1 month (95% CI, 0.3-1.0 month), and the estimated median time to optimal (ie, maximum) improvement

Table 1 Patient Demographic and Baseline Characteristics (N = 52; Nilotinib 300 mg BID)

Characteristic	Value
Age (years)	
Mean	51.7
Range	34-82
Male gender (%)	50.0
Caucasian (%)	86.5
ECOG performance status (%)	
0	44.2
1	48.1
2	7.7
Time since diagnosis (mo)	
Median	31.4
Range	3.0-179.3
Previous imatinib dose (mg/d)	
Median	400
Range	300-800
Duration of previous imatinib treatment (mo)	
Median	31.1
Range	2-145[a]
Patients with complete cytogenetic response[b] (%)	86.5
Patients with major molecular response (%)	65.4
Imatinib-related AEs at baseline (n)	
Median	3
Range	1-11
Imatinib-related AEs per patient at baseline (%)	
1	5.8
2	21.2
3	30.8
≥ 4	42.3

Abbreviations: AE = adverse event; BID = twice daily; ECOG = Eastern Cooperative Oncology Group.
[a]One patient with < 3 months of previous imatinib treatment was enrolled and treated (protocol deviation).
[b]Based on prestudy results, fluorescence in situ hybridization assessment at screening, and bone marrow aspirate at screening.

of imatinib-related AEs was 1.9 months (95% CI, 1.0-2.1 months). No patient had an overall worsening (defined as an increase in CTCAE grade for ≥ 50% of imatinib-related AEs) at any time point. In 30 patients (57.7%), all imatinib-related AEs had improved at EOC 12, although 3 patients (5.8%) did not have improvement in any imatinib-related AE at EOC 12 (Figure 1C). As expected, a negative correlation was found at all observation points (at EOC 3, $r = -0.42$) between the number of imatinib-related AEs and the proportion of AEs that improved after switching to nilotinib (ie, patients with a higher number of imatinib-related AEs were less likely to achieve overall improvement).

AEs During Nilotinib Treatment

After switching to nilotinib, 51 patients (98.1%) developed new or worsening AEs, including AEs with a suspected relationship to the study treatment in 44 patients (84.6%). The most common new or worsening nonhematologic AEs (regardless of a relationship to the study drug) of any grade were fatigue (19 of 52 patients; 36.5%), rash (18 of 52 patients; 34.6%), headache (17 of 52 patients; 32.7%), constipation (14 of 52 patients; 26.9%), arthralgia (13 of 52 patients; 25.0%), nausea (12 of 52 patients; 23.1%), and pruritus (12 of 52 patients; 23.1%). The most common AEs suspected to be related to study treatment were headache (14 of 52 patients; 26.9%), rash (13 of 52 patients; 25.0%), fatigue (12 of 52 patients; 23.1%), and pruritus (11 of 52 patients; 21.2%). Although most AEs reported during nilotinib treatment were grade 1 or 2, 20 patients (38.5%) had grade 3 AEs during nilotinib treatment (Table 3), and 1 patient experienced a grade 4 AE of cardiac arrest. This patient had a history of hypertension before study entry and no other known cardiovascular risk factors. Grade 1 QT prolongation (450-480 ms) was observed in 1 patient; QT or Fridericia-corrected QT > 500 ms was not observed in any patient.

A total of 9 patients (17.3%) had SAEs. These included 3 patients with infection (2 with a suspected study drug relationship [1 patient also had ovarian torsion]; the third patient had acute cholecystitis and hypotension); 2 patients with pancreatitis (both with a suspected study drug relationship); the patient noted in the previous paragraph with cardiac arrest (suspected study drug relationship); 1 patient with injury (scapula fracture/cartilage injury); 1 patient with facial palsy and coronary artery disease; and 1 patient with arthralgia (suspected study drug relationship), pain (suspected study drug relationship), pleural effusion (suspected study drug relationship), arteriosclerosis, malignant mesothelioma, and pleural fibrosis. None of the 3 patients with SAEs of infection had grade 3/4 neutropenia at the time of the infection.

Twenty-three patients (44.2%) had AEs that led to dose interruption or reduction. Of the 8 patients who discontinued because of AEs (15.4%), 2 discontinued because of hyperglycemia (neither had a known history of diabetes). Of the remaining 6 patients, 1 discontinued because of cardiac arrest (SAE), hypercholesterolemia, and hypotension; 1 because of pleural effusion (SAE), malignant mesothelioma (SAE), and pleural fibrosis (SAE); 1 because of headache, sore mouth, and stomach pain; and 1 each for cough, vertigo, and myasthenia gravis. Of the AEs leading to discontinuation of study treatment, all, except for malignant mesothelioma, pleural fibrosis, and myasthenia gravis, were suspected to be related to the study drug.

Response

Forty-two patients underwent bone marrow cytogenetic assessments at screening, and 7 patients did not have CCyR at baseline (13.5% of 52 patients; median previous imatinib treatment duration, 4.8 months). All 7 patients had achieved CCyR by EOC 6 (as assessed by FISH). Of these 7 patients, the estimated median time to achieve CCyR was 1.9 cycles and the median duration of CCyR was 282 days.

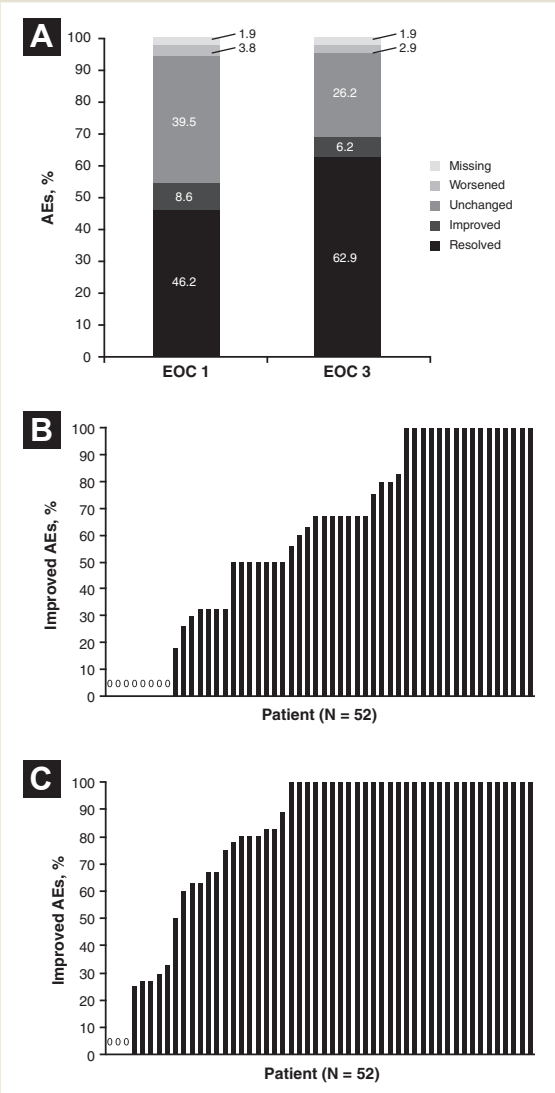
At screening, 34 patients (65.4%) had an MMR. Regarding deeper MR, 19 (36.5%) had MR^4 (*BCR-ABL1*^{IS} ≤ 0.01%) and 10 (19.2%) had $MR^{4.5}$ (*BCR-ABL1*^{IS} ≤ 0.0032%; Figure 2). Of the 18 patients without an MMR at screening (median previous imatinib treatment duration, 9.5 months), 11 (61.1%) achieved an MMR by EOC 3, and 15 (83.3%) achieved MMR at any point during the study. The estimated median time to achieve an MMR

Table 2 Change in Most Frequently Reported (≥ 3 Patients) Imatinib-Related Chronic Low-Grade (Grade 1 or 2) Nonhematologic AEs at Baseline

Imatinib-Related AE	Patients With AEs at Baseline (n)[a]	Change in Imatinib-Related AEs After Switching to Nilotinib									
		EOC 1	EOC 3				EOC 12				
		Resolved	Resolved	Improved	Unchanged	Worsened	Resolved	Improved	Unchanged	Worsened	Resolved, Reappeared
Fatigue	29	5 (17.2)	10 (34.5)	6 (20.7)	10 (34.5)	2 (6.9)	11 (37.9)	6 (20.7)	10 (34.5)	1 (3.4)	3 (10.3)
Diarrhea	20	14 (70.0)	19 (95.0)	0	1 (5.0)	0	19 (95.0)	0	1 (5.0)	0	4 (20.0)
Nausea	20	14 (70.0)	16 (80.0)	0	3 (15.0)	0	16 (80.0)	0	3 (15.0)	0	4 (20.0)
Muscle spasms	14	8 (57.1)	12 (85.7)	0	2 (14.3)	0	12 (85.7)	0	2 (14.3)	0	5 (35.7)
Peripheral edema	13	6 (46.2)	8 (61.5)	2 (15.4)	3 (23.1)	0	8 (61.5)	2 (15.4)	3 (23.1)	0	0
Periorbital edema	13	5 (38.5)	9 (69.2)	0	3 (23.1)	0	9 (69.2)	0	3 (23.1)	0	0
Arthralgia	10	4 (40.0)	6 (60.0)	1 (10.0)	3 (30.0)	0	6 (60.0)	1 (10.0)	3 (30.0)	0	2 (20.0)
Myalgia	9	5 (55.6)	6 (66.7)	0	3 (33.3)	0	6 (66.7)	0	3 (33.3)	0	2 (22.2)
Headache	8	1 (12.5)	4 (50.0)	0	3 (37.5)	1 (12.5)	4 (50.0)	0	2 (25.0)	2 (25.0)	2 (25.0)
Dyspepsia	4	2 (50.0)	2 (50.0)	0	2 (50.0)	0	3 (75.0)	0	1 (25.0)	0	1 (25.0)
Rash	4	1 (25.0)	2 (50.0)	0	2 (50.0)	0	3 (75.0)	0	1 (25.0)	0	2 (50.0)
Face edema	4	3 (75.0)	3 (75.0)	0	1 (25.0)	0	3 (75.0)	0	1 (25.0)	0	1 (25.0)
Weight increase	4	1 (25.0)	3 (75.0)	0	1 (25.0)	0	4 (100.0)	0	0	0	0
Insomnia	4	1 (25.0)	1 (25.0)	0	3 (75.0)	0	1 (25.0)	0	3 (75.0)	0	0
Pruritus	3	2 (66.7)	2 (66.7)	0	0	1 (33.3)	2 (66.7)	0	0	1 (33.3)	2 (66.7)
Vomiting	3	3 (100.0)	3 (100.0)	0	0	0	3 (100.0)	0	0	0	0
Abdominal pain	3	1 (33.3)	1 (33.3)	0	1 (33.3)	0	1 (33.3)	0	1 (33.3)	0	0
Bone pain	3	2 (66.7)	3 (100.0)	0	0	0	3 (100.0)	0	0	0	1 (33.3)
Amnesia	3	3 (100.0)	3 (100.0)	0	0	0	3 (100.0)	0	0	0	0

Data presented as n (%).
Abbreviations: AE = adverse event; EOC = end of cycle.
[a]For each AE type, each AE occurred in a distinct patient (ie, the number of events was equal to the number of patients with that AE type).

Figure 1 Effects on Imatinib-Related Chronic Low-Grade Nonhematologic Adverse Events (AEs). (A) Change in Status of Imatinib-Related AEs at End of Cycle (EOC) 1 and 3 Relative to Baseline (Percentages Were Derived From the 210 Total Imatinib-Related AEs Reported at Baseline). Proportion of Imatinib-Related AEs With Improvement at (B) EOC 1 and (C) EOC 12 for Each Patient



was 2.8 cycles. The median MMR duration among the patients who had achieved an MMR during the study was 253 days. Four patients who achieved an MMR during the study later lost the MMR; no patient with an MMR at screening lost it during the study. Of the 41 patients evaluable for MR at EOC 12, 36 (87.8%) had an MMR, 30 (73.2%) had MR^4, and 17 (41.5%) had $MR^{4.5}$.

At screening, the median *BCR-ABL1*^{IS} level reduction was 3.375 (range, 5.13 to 0.64 reduction). Among 46 evaluable patients at EOC 3, the median *BCR-ABL1*^{IS} level reduction was 4.010 (range, 5.04 to 1.45 reduction), representing a median log reduction from study baseline of 0.413 (range, 2.21 reduction to 0.39 increase). Among 41 evaluable patients at EOC 12, the median *BCR-ABL1*^{IS} level reduction was 4.379 (range, 5.32 to 2.36 reduction), representing a median log reduction from study baseline of 0.527 (range, 3.08 reduction to 0.45 increase).

Changes in QOL and MDASI-CML Scores

Throughout the study, QOL improvements relative to baseline were observed in most evaluable patients, although a few patients had worsening QOL relative to baseline (Figure 3). Among 43 patients evaluable for a change in QOL at EOC 1 relative to baseline, the mean QOL scores for the previous 24 hours and the previous 7 days were 7.0 (SD, 2.37) and 6.8 (SD, 2.06), respectively, at EOC 1, compared with 6.3 (SD, 2.11) and 6.1 (SD, 2.19), respectively, at baseline. Considering all patients, 50.0% and 44.2% had improved QOL scores for the previous 24 hours and the previous 7 days at EOC 1 relative to baseline, 13.5% and 15.4% had unchanged QOL scores, and 19.2% and 23.1% had worse QOL scores, respectively (17.3% of patients were not evaluable for the change in QOL from baseline to EOC 1). Among 36 patients evaluable for changes in QOL at EOC 12, the mean overall QOL score for the previous 24 hours was 8.0 (SD, 2.00) and for the previous 7 days was 7.8 (SD, 2.04). Considering all the patients, 57.7% and 50.0% had improved QOL scores for the previous 24 hours and previous 7 days at EOC 12 relative to baseline, 3.8% and 5.8% had unchanged QOL scores, and 7.7% and 13.5% had worse QOL scores, respectively (30.8% of the patients were not evaluable for a change in QOL from baseline to EOC 12).

At baseline, the mean MDASI-CML–specific symptom score and mean MDASI-CML interference item score were 3.07 (SD, 2.03) and 3.92 (SD, 2.78), respectively. Improvements in both MDASI-CML scores relative to baseline were observed throughout the study (Figure 4). Among 38 patients evaluable for a change in MDASI-CML scores at EOC 1, the specific symptom scores decreased by a mean of 1.62 (SD, 2.22) relative to baseline, and the interference item scores decreased by a mean of 1.66 (SD, 3.05) relative to baseline. Among 35 patients evaluable for a change in MDASI-CML scores at EOC 12, specific symptom and interference item scores decreased by a mean of 1.59 (SD, 1.95) and 1.35 (SD, 2.86), respectively, relative to baseline.

Discussion

In the ENRICH study, switching from imatinib to nilotinib led to improvements in imatinib-related AEs in most patients. Within 1 month after switching to nilotinib, most imatinib-related AEs had either resolved or improved, and by 3 months, the frequency of the AEs that had improved increased further. New AEs were reported during nilotinib therapy, including SAEs; however, the overall QOL and MDASI-CML scores generally improved throughout the study. Nilotinib therapy also resulted in effective disease control, as evidenced by the maintenance and/or achievement of CyR and MR in most patients.

The observed improvements in QOL and MDASI-CML scores in the present study were consistent with those from previous reports, demonstrating the impact of AEs on QOL. Low-grade AEs, including gastrointestinal disorders (eg, nausea and diarrhea), blood and lymphatic system disorders (eg, thrombocytopenia and neutropenia), musculoskeletal disorders (eg, muscle spasms and arthralgia),

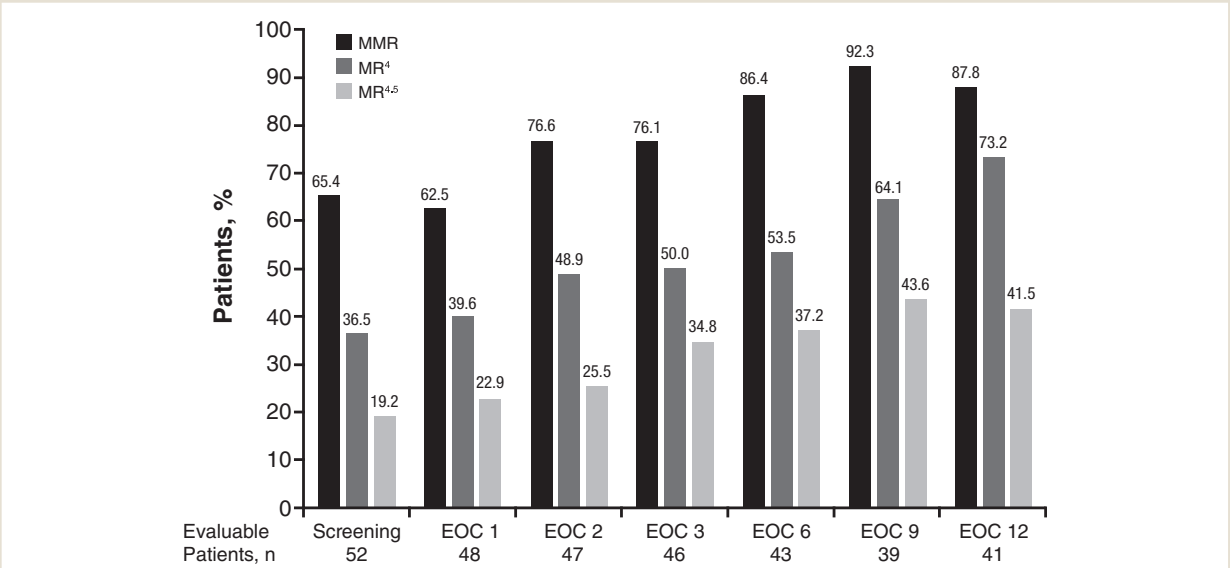
Table 3 Patients With Grade 3 AEs Reported During Treatment With Nilotinib (N = 52)[a]

AE	Grade 3		Total Frequency (Any Grade)	
	Any Cause	Suspected Relationship to Study Drug	Any Cause	Suspected Relationship to Study Drug
Any AE	20 (38.5)	16 (30.8)	51 (98.1)	44 (84.6)
Nonhematologic AE				
Rash	3 (5.8)	2 (3.8)	18 (34.6)	13 (25.0)
Arthralgia	2 (3.8)	2 (3.8)	13 (25.0)	6 (11.5)
Hypotension	2 (3.8)	1 (1.9)	3 (5.8)	1 (1.9)
Pruritus	1 (1.9)	1 (1.9)	12 (23.1)	11 (21.2)
Myalgia	1 (1.9)	0	4 (7.7)	2 (3.8)
Bronchitis	1 (1.9)	1 (1.9)	2 (3.8)	1 (1.9)
Gastroenteritis	1 (1.9)	1 (1.9)	2 (3.8)	1 (1.9)
Pain	1 (1.9)	0	2 (3.8)	1 (1.9)
Pneumonia	1 (1.9)	0	2 (3.8)	1 (1.9)
Rash erythematous	1 (1.9)	1 (1.9)	2 (3.8)	2 (3.8)
Rash exfoliative	1 (1.9)	1 (1.9)	2 (3.8)	2 (3.8)
Rash papular	1 (1.9)	1 (1.9)	2 (3.8)	2 (3.8)
Arteriosclerosis	1 (1.9)	0	1 (1.9)	0
Cartilage injury	1 (1.9)	0	1 (1.9)	0
Cholecystitis acute	1 (1.9)	0	1 (1.9)	0
Dehydration	1 (1.9)	1 (1.9)	1 (1.9)	1 (1.9)
Intervertebral disc protrusion	1 (1.9)	0	1 (1.9)	0
Malignant mesothelioma	1 (1.9)	0	1 (1.9)	0
Menorrhagia	1 (1.9)	0	1 (1.9)	0
Pancreatitis	1 (1.9)	1 (1.9)	1 (1.9)	1 (1.9)
Pancreatitis acute	1 (1.9)	1 (1.9)	1 (1.9)	1 (1.9)
Pleural effusion	1 (1.9)	1 (1.9)	1 (1.9)	1 (1.9)
Pleural fibrosis	1 (1.9)	0	1 (1.9)	0
Rheumatoid arthritis	1 (1.9)	0	1 (1.9)	0
Scapula fracture	1 (1.9)	0	1 (1.9)	0
Tendon rupture	1 (1.9)	0	1 (1.9)	0
Wound infection, bacterial	1 (1.9)	0	1 (1.9)	0
Wound infection, staphylococcal	1 (1.9)	0	1 (1.9)	0
Laboratory abnormalities				
Hyperglycemia	2 (3.8)	2 (3.8)	4 (7.7)	4 (7.7)
Hypokalemia	1 (1.9)	1 (1.9)	3 (5.8)	3 (5.8)
Hypophosphatemia	1 (1.9)	1 (1.9)	3 (5.8)	2 (3.8)
Lipase increase	1 (1.9)	1 (1.9)	3 (5.8)	3 (5.8)
Blood bilirubin increase	1 (1.9)	1 (1.9)	2 (3.8)	2 (3.8)
Hyperuricemia	1 (1.9)	0	2 (3.8)	0

Data presented as n (%).
Abbreviation: AE = adverse event.
[a]One grade 4 event (cardiac arrest, with suspected relationship to study drug) was reported during treatment with nilotinib.

psychiatric disorders (eg, insomnia and anxiety), and general disorders and administration-site conditions (eg, fatigue and peripheral edema), have been shown to negatively affect health-related QOL in patients with CML-CP receiving long-term TKI therapy.[26] Specifically, a survey identified fatigue, muscle cramps, and swelling among the factors that most affected QOL.[8] In the present study, fatigue and muscle cramps were among the most frequently reported imatinib-related AEs, and fatigue was also the most frequently observed AE during nilotinib therapy. Because of the potential impact of AEs on QOL and treatment adherence,[1-3,8,26] adequate management of chronic low-grade AEs is crucial for optimizing the outcomes of patients with CML-CP. In the present study, most imatinib-related AEs

Figure 2 Molecular Response (MR) After Switch to Nilotinib (N = 52). Rates of Major MR (MMR), MR^4, and $MR^{4.5}$ Were Calculated Among Evaluable Patients at Each End of Cycle (EOC) Point. Of the 52 Patients, 15 Did Not Have Results for ≥1 Time Point Shown. MMR = *BCR-ABL1*^{IS} ≤ 0.1%; MR^4 = *BCR-ABL1*^{IS} ≤ 0.01%; $MR^{4.5}$ = *BCR-ABL1*^{IS} ≤ 0.0032%



resolved after the switch to nilotinib, although a few imatinib-related AEs worsened or recurred with nilotinib therapy. These results are consistent with previous data[15] showing minimal cross-intolerance between imatinib and nilotinib and suggesting that switching to nilotinib could be an effective option for managing such events for most patients.

Most patients developed new AEs after switching to nilotinib. Most treatment-emergent AEs were grade 1/2; however, some patients developed grade 3/4 AEs, SAEs, or AEs leading to discontinuation of study treatment. Because the patients in the present study had only low-grade AEs before switching to nilotinib, the benefits of nilotinib must be considered together with the potential risk of developing new AEs. The treatment-emergent AEs observed in the present study were consistent with the known safety profile of nilotinib.[10-12,14] Similar to the pattern of AEs observed in the present study, the most frequently reported AEs in a previous trial of second-line nilotinib for patients with imatinib resistance or intolerance were grade 1/2 rash, pruritus, nausea, fatigue, headache, and constipation.[11] Although in the present study, the general trend was favorable, additional evaluation is needed to determine the impact of new AEs on QOL for patients switching from imatinib to nilotinib, in particular, because almost one-third of the patients were not evaluable for a change in QOL at 12 months. In addition to these more common AE types,[10-12,14,17] a higher incidence of cardiovascular AEs has been shown to result from long-term nilotinib compared with long-term imatinib.[13,14,17] In the present study, cardiovascular SAEs of cardiac arrest, arteriosclerosis, and coronary artery disease were observed in 1 patient each. Because the present study was completed after a median of ≈ 12 months of nilotinib therapy, the long-term incidence of cardiovascular AEs and SAEs in this patient population remains unknown. Some biochemical abnormalities that have been reported to occur with nilotinib therapy (ie, lipid and glucose elevations)[27] are modifiable cardiovascular risk factors.[28] Thus, it is important that patients with CML receive proper monitoring and management of cardiovascular risk factors and comorbidities during treatment with any TKI.[16] Although the present trial was not designed to monitor lipid levels, glucose levels were recorded during the course of the study.

Switching to nilotinib also resulted in CyR and MR in this patient population. Importantly, the ENRICH study eligibility criteria excluded patients with treatment failure, as defined by the CML management recommendations in place at the time (European LeukemiaNet 2009 recommendations[29]); thus, all enrolled patients were responding (optimally or suboptimally[29]) to frontline imatinib therapy at the switch to nilotinib. Although it was not possible to evaluate whether switching to nilotinib led to improvements in patients' response levels compared with the response they would have achieved with continued imatinib therapy, the high rates of MR and CyR observed after switch indicate that nilotinib therapy was effective in this patient population. Most patients without MMR at baseline achieved MMR during the study, and no patient who entered the study with MMR lost it with nilotinib treatment. Among evaluable patients at EOC 12, most had MR,[4] and the median *BCR-ABL1*^{IS} level decreased by more than one-half log from study baseline. Additionally, all 7 patients without CCyR at baseline achieved CCyR after switching to nilotinib (although considering the short duration of previous imatinib therapy for these 7 patients, some of them might have eventually achieved CCyR with continued imatinib treatment). These findings are consistent with several studies in which patients with a suboptimal MR, resistance, or intolerance to imatinib achieved improved responses after switching to nilotinib. Furthermore, in previous studies, the higher response

Figure 3 Change in Overall Quality of Life (QOL). For Each End of Cycle (EOC) Point, the Proportion of Patients Reporting Better, Unchanged, or Worse QOL Relative to Baseline Was Calculated Based on the Total Patient Population (N = 52). QOL Was Evaluated at Each EOC Point for the (A) Previous 24 Hours and (B) Previous 7 Days

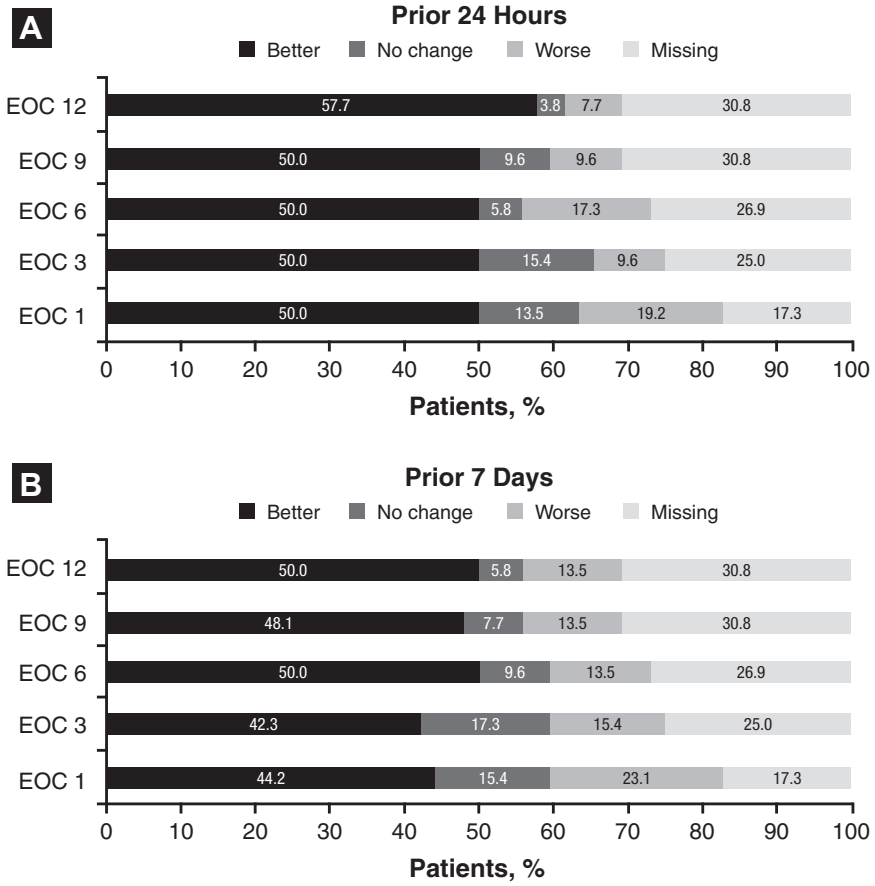
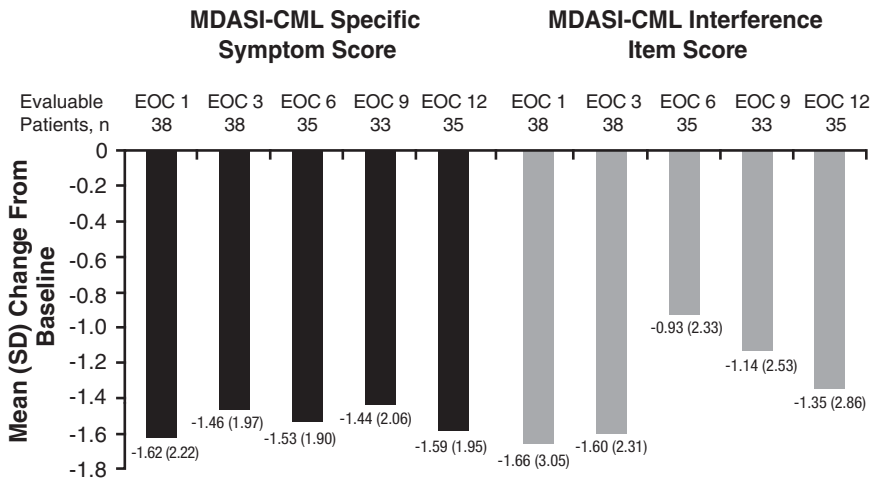


Figure 4 Mean Change in MD Anderson Symptom Inventory Chronic Myeloid Leukemia Module (MDASI-CML) Scores. For Each End of Cycle (EOC) Point, the Mean Change in MDASI-CML Specific Symptom and MDASI-CML Interference Item Scores Relative to Baseline Were Calculated Among Evaluable Patients. A Decrease in MDASI-CML Score Indicates Improvement



rates on nilotinib were associated with improved long-term clinical outcomes.[11,30-32] Overall, the results from the ENRICH study have demonstrated the positive effect of switching to nilotinib in a patient population not previously studied.

Conclusion

Overall, the results from the ENRICH study supported a positive effect of switching to nilotinib for some patients with chronic low-grade nonhematologic AEs during imatinib therapy. The optimal course of therapy for each patient with CML-CP must be determined through consideration of several factors, including imatinib-related AEs, potential nilotinib-related AEs, the relative efficacy of nilotinib versus imatinib, and the relative effect of each drug on overall QOL and treatment adherence.

Clinical Practice Points

- It is well known that many patients with CML-CP treated with imatinib experience chronic low-grade AEs.
- Before the approval of second-generation TKIs, patients experiencing such AEs with imatinib therapy had no treatment options.
- In the registration study for nilotinib (ClinicalTrials.gov identifier, NCT00109707) in patients with resistance and/or intolerance to imatinib, only patients with recurring grade 3/4 AEs or intolerance to imatinib doses of 600 to 800 mg/day were included.
- That study was conducted before second-generation TKIs had been approved, and imatinib dose escalation was the only option for patients with resistance, outside of a clinical trial. Thus, although several approved TKI options are now available for patients with resistance or intolerance to imatinib, no clinical trial has ever evaluated a switch to nilotinib for patients with chronic low-grade AEs from imatinib. The ENRICH study was conducted specifically to address this question.
- For patients with these chronic low-grade treatment-related AEs from imatinib therapy, switching to nilotinib provided improvement of many of these AEs, improved patient QOL, and led to the achievement of CyR and MR.
- With many TKI options now available to physicians who treat patients with CML, these results indicate that nilotinib could be a tolerable and effective treatment option for those patients experiencing chronic, low-grade AEs during imatinib therapy.

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