Minimal cross-intolerance with nilotinib in patients with chronic myeloid leukemia in chronic or accelerated phase who are intolerant to imatinib

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Nilotinib has significant efficacy in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) and in patients with CML-CP or CML in accelerated phase (CML-AP) after imatinib failure. We investigated the occurrence of cross-intolerance to nilotinib in imatinib-intolerant patients with CML. Only 1/75 (1%) patients with nonhematologic imatinib intolerance experienced a similar grade 3/4 adverse event (AE), and 3/75 (4%) experienced a similar persistent grade 2 nonhematologic AE on nilotinib. Only 7/40 (18%) patients with hematologic imatinib intolerance discontinued nilotinib, all because of grade 3/4 thrombocytopenia. Ninety percent of imatinib-intolerant patients with CML-CP who did not have complete hematologic response (CHR) at baseline (n = 52) achieved CHR on nilotinib. Nilotinib induced a major cytogenetic response in 66% and 41% of patients with imatinib-intolerant CML-CP and CML-AP (complete cytogenetic response in 51% and 30%), respectively. Minimal cross-intolerance was confirmed in patients with imatinib-intolerant CML. The favorable tolerability of nilotinib in patients with imatinib intolerance leads to alleviation of AE-related symptoms and significant and durable responses. In addition to its established clinical benefit in patients with newly diagnosed CML and those resistant to imatinib, nilotinib is effective and well-tolerated for long-term use in patients with imatinib intolerance. This study is registered at http://www.clinicaltrials.gov as NCT00471497 (*Blood*. 2011;117(21):5600-5606)

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disease characterized by a cytogenetic abnormality—the Philadelphia (Ph) chromosome. The Ph chromosome is formed by a reciprocal translocation involving chromosomes 9 and 22[1] and results in an oncogenic fusion gene encoding BCR-ABL. This constitutively active tyrosine kinase is implicated in the development of Ph chromosome-positive (Ph^+) CML.[2] Diagnosis of Ph^+ CML typically occurs in the chronic phase (CML-CP), which is characterized by $< 10\%$ blasts in the peripheral blood (PB) and BM, with mild or no symptoms and a high likelihood of treatment response.[3] The accelerated phase (AP) is a transition period during which patients frequently acquire multiple cytogenetic abnormalities.[3] The AP can progress to blast crisis (BC), where 30% or more blasts are present in the PB and/or BM.[3]

Characterization of BCR-ABL and the development of targeted BCR-ABL tyrosine kinase inhibitors (TKIs) have revolutionized Ph^+ CML treatment. Imatinib mesylate (Glivec/Gleevec; Novartis Pharmaceuticals Corporation) is a BCR-ABL inhibitor. In the pivotal phase 3 International Randomized Study of Interferon and STI571 (IRIS) trial, patients with Ph^+ CML-CP were randomly assigned to either imatinib or the previous standard of care, ie, interferon combined with cytarabine.[4] This study was overwhelmingly positive in favor of imatinib and led to the approval of imatinib for the treatment of newly diagnosed Ph^+ CML-CP.

Nilotinib (Tasigna; Novartis Pharmaceuticals Corporation) is a potent and selective second-generation inhibitor of BCR-ABL.[5,6] Nilotinib was rationally designed on the basis of the crystal structure of imatinib in complex with the ABL kinase. Through chemical changes, the binding affinity for ABL was improved compared with imatinib, making it less susceptible to point mutations because of a different topologic fit in the kinase active site. In the phase 2 registration trial, the administration of oral nilotinib (400 mg twice daily) demonstrated significant and durable response rates among patients with Ph^+ CML-CP or CML-AP who were resistant or intolerant to imatinib therapy.[7,8] On the basis of positive efficacy and safety outcomes, nilotinib has been approved for the treatment of patients with Ph^+ CML-CP and CML-AP who have not responded to previous therapy, including imatinib, because of resistance or intolerance. Nilotinib is also now approved in the United States, the European Union, Japan, Switzerland, and other countries for the treatment of patients with newly diagnosed Ph^+ CML-CP on the basis of the results of the Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENESTnd) study, in which investigators showed superior response rates and significantly improved the time to progression to AP/BC for nilotinib over imatinib.[9]

Because nilotinib is structurally similar to imatinib, the possibility of cross-intolerance with imatinib was investigated. The objective of this post-hoc analysis of the pivotal phase 2 study was to

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determine the incidence and characteristics of cross-intolerance between nilotinib and imatinib in patients with Ph^+ CML-CP or CML-AP who previously did not respond to imatinib therapy because of intolerance. The overall safety and efficacy profile of nilotinib in this patient population also was evaluated.

Methods

Study design and patient population

The study described here is a post-hoc analysis of the pivotal phase 2 registration study—a multicenter, international, single-arm, open-label trial that examined the efficacy and safety of nilotinib in patients with Ph^+ CML-CP or CML-AP resistant to or intolerant of previous imatinib therapy.[7,8] Patients with Ph^+ CML-CP or CML-AP who were intolerant to imatinib were evaluated to determine the occurrence, if any, of cross-intolerance between nilotinib and imatinib and to determine the safety of nilotinib use in patients who did not respond to previous imatinib therapy because of intolerance.

All patients either had a minimum of 24 months of follow-up or had discontinued the study. Because the goal of this study was to examine cross-intolerance (ie, patients who were intolerant to imatinib and also became intolerant to nilotinib), only patients who experienced intolerance to imatinib were included in this analysis. However, patients with major cytogenetic response (MCyR) at baseline were excluded from study entry; therefore, patients with intolerance on the nilotinib registration study were selected with an element of resistance. For this study, imatinib intolerance was defined as follows: any adverse event (AE) of grade 3/4 severity or persistent grade 2 AE (regardless of causality) lasting 1 month or longer or recurring > 3 times despite optimal supportive care and dose reductions. The following categories of AEs were considered "nonhematologic": fluid retention, gastrointestinal disturbances, liver toxicity, myalgias/arthralgias, and rash/skin toxicity. All other nonhematologic AEs were classified as "other" in the analysis for cross-intolerance. Patients experiencing multiple reasons for imatinib intolerance were included in each AE category.

Cross-intolerance was defined as occurrence during treatment with nilotinib (regardless of causality) of the same imatinib drug-related AE(s) (grade 3/4 or persistent grade 2) that led to imatinib intolerance. Cytopenias, which are reported as hematologic AEs, are common in patients with CML during the early phase of therapy but can be a consequence of underlying disease (particularly relevant in this case because patients were required per protocol to have active disease at baseline) and are reversible in most cases. Therefore, hematologic cross-intolerance between imatinib and nilotinib was defined as discontinuation of nilotinib because of the same AE that caused imatinib intolerance.

Study treatment

All patients received an oral dose of 400 mg of nilotinib twice daily. In patients with no previous dose reduction because of toxicity and in the absence of serious AEs, dose escalation of nilotinib to 600 mg twice daily was allowed in patients who did not achieve a hematologic, cytogenetic, or major cytogenetic response within 3, 6, or 12 months, respectively, or who demonstrated loss of hematologic or cytogenetic response or disease progression. The decision to escalate the dose of nilotinib was at the discretion of the treating physician.

Patients were allowed 2 dose reductions, if required, for the management of grade 3/4 AEs. The dose was first reduced to 200 mg twice daily, and, if further reduction was necessary, to 400 mg once daily. The once-daily dose is lower because solubility-limited absorption has been observed with greater doses of nilotinib, resulting in greater drug exposure with a twice-daily dose than with a once-daily dose.[10] For grade 3 or greater hematologic AEs, nilotinib could be delayed for up to 42 days from the last dose with blood counts performed twice weekly and bone sampling every 14-21 days until the absolute neutrophil count was $\geq 1 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L. In the event of a dose interruption, and depending on the AE, nilotinib could be resumed at the same dose or at the next lowest dose once the AE resolved. For hematologic AEs, treatment could be resumed at the same dose if absolute neutrophil count and platelets returned to the designated levels within 14 days of the last dose. If blood counts rebounded within 15 to 42 days of the last dose, treatment was resumed at the next lowest dose.

Patients were required to discontinue nilotinib treatment if toxicities recurred with the same or worse severity at the lowest dose. If a patient required a dose delay of > 21 days (or > 42 days for hematologic toxicity), the patient was discontinued from the study.

Safety

Safety assessments consisted of the following: monitoring and recording all AEs and serious AEs; regular monitoring of hematology, blood chemistry, and urine values; regular measurement of vital signs; physical examination, including weight and performance status; and repeat cardiac assessments, including electrocardiograms. Hematology and serum chemistries were performed at baseline; day 1 of each 28-day cycle before the administration of nilotinib or ≤ 72 hours before dosing intended on day 1 of each cycle (if nilotinib was being withheld); on or within 24 hours of days 8, 15, and 22 of cycles 1 and 2; on or within 24 hours of day 15 of cycle 3 and each subsequent cycle; and at the time of study completion. The National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 were used to grade toxicities.[11]

Efficacy evaluation

For patients with CML-CP, complete hematologic response (CHR) was defined as follows: no blasts or promyelocytes in the PB, white blood cell count $< 10 \times 10^9$/L, platelets $< 450 \times 10^9$/L, PB basophils $< 5\%$, PB myelocytes and metamyelocytes $< 5\%$, and no evidence of extramedullary involvement. For patients with CML-AP, CHR was defined as follows: BM blasts $< 5\%$, no PB blasts, absolute neutrophil count of at least 1.5×10^9/L, platelet count of at least 100×10^9/L, PB basophils $< 5\%$, and no evidence of extramedullary involvement. Major cytogenetic response included complete (CCyR; 0% Ph^+ metaphases) and partial ($> 0\%$-35% Ph^+ metaphases) cytogenetic responses. Progression-free survival was defined as the time from the start of nilotinib to the earliest date of progression to AP or BC, discontinuation because of progression (as assessed by investigator), or death from any cause on nilotinib therapy.

Study conduct

The registration study protocol was reviewed and approved by the institutional review board or ethics committee of each participating study center. All study patients provided written informed consent before study participation for the treatment protocol and for the post-hoc analysis described here in accordance with the Declaration of Helsinki.

Results

Patients and demographics

Of the 321 patients in CML-CP and 137 in CML-AP enrolled in the phase 2 nilotinib registration trial, 95 (30%) and 27 (20%), respectively, were intolerant to imatinib and had at least 24 months of nilotinib treatment (or discontinued the study) and were included in this analysis. Baseline characteristics of the subjects are shown in Table 1. The median duration of previous imatinib therapy was 14 months for patients with CML-CP and 9 months for patients with CML-AP. The median duration of CML was 40 months for patients with CML-CP and 57 months for patients with CML-AP. Most patients (63 [66%] with CML-CP and 18 [67%] with CML-AP) previously received a maximum dose of < 600 mg of imatinib per day. Only 15 (16%) and 2 (7%) imatinib-intolerant patients with CML-CP and CML-AP, respectively, were previously treated with at least 800 mg of imatinib per day, for a median

Table 1. Baseline demographics and disease characteristics

	CML-CP (n = 95)	CML-AP (n = 27)
Median age, y (range)	59 (29-82)	58 (31-76)
Male, %	40	44
Previous history of imatinib therapy		
Median duration of previous imatinib, mo (range)	14 (0.3-64)	9 (0.1-68)
Previous greatest dose of imatinib, n (%)		
< 400 mg/d	0	1 (4)
400 to < 600 mg/d	63 (66)	17 (63)
600 to < 800 mg/d	16 (17)	7 (26)
800 mg/d or greater	15 (16)	2 (7)
Missing	1 (1)	0
Duration of CML		
Median time since first diagnosis of CML, mo (range)	40 (5-266)	57 (2-161)
Best response to imatinib, n (%)		
CHR (no CyR)	35 (37)	2 (7)
Any CyR	47 (49)	3 (11)

AP indicates accelerated phase; CHR, complete hematologic response; CML, chronic myeloid leukemia; CP, chronic phase; and CyR, cytogenetic response.

duration of therapy at this dose of 3.1 months (range, 0.1-21.3 months) and of 3.7 months (range, 0.3-7.1 months) for patients with CML-CP and CML-AP, respectively.

Of the patients who discontinued imatinib, a grade 3 or 4 AE was the reason for discontinuation in 72 (76%) and 21 (78%) of those with CML-CP and CML-AP, respectively. The remaining 22 (23%) patients with CML-CP (1 patient with unknown information assessed as intolerant by the investigator) and 6 (22%) with CML-AP discontinued using imatinib because of persistent grade 2 AEs lasting at least 1 month. Sixty (63%) patients with CML-CP and 15 (56%) patients with CML-AP were intolerant to imatinib because of nonhematologic AEs. Thirty-one patients in CML-CP and 9 patients in CML-AP (33% for both) were intolerant to imatinib because of hematologic AEs. Two (2%) patients with CML-CP included in this analysis exhibited other symptoms during imatinib therapy besides those that classified them as intolerant—1 had conjunctivitis and the other had interstitial lung disease. Ten (11%) patients with CML-CP and 4 (15%) patients with CML-AP had unspecified reasons for imatinib intolerance, and 8 (8%) patients with CML-CP and 1 (4%) patient with CML-AP were intolerant to imatinib because of both hematologic and nonhematologic AEs.

Nilotinib was generally well-tolerated in imatinib-intolerant patients. The median dose intensity of nilotinib therapy was 724 mg/d (range, 151-800 mg/d) for patients with CML-CP and 769 mg/d (range, 184-1149 mg/d) for patients with CML-AP (Table 2). Imatinib-intolerant patients with CML-CP received nilotinib therapy for a median of 24.7 months (range, 0-36 months), and patients with CML-AP received nilotinib for a median of 5.1 months (range, 0-38 months). None of the 95 imatinib-intolerant patients with CML-CP had their dose increased. One (4%) imatinib-intolerant patient with CML-AP received an increase in dose. Nilotinib dose interruptions occurred because of AEs (per protocol) in 65 (68%) and 13 (48%) patients with CML-CP and CML-AP, respectively. However, the median cumulative duration of dose interruptions was short, lasting 24 days (range, 1-345 days) and 17 days (range, 4-234 days) for patients in CML-CP and CML-AP, respectively. Overall, the median percentage of time lost to dose interruptions (relative to the time on therapy) was only 2% and 1% for patients in CML-CP and CML-AP, respectively.

Cross-intolerance

Cross-intolerance as the result of nonhematologic toxicity was rare. As shown in Table 3, 75 of 122 (61%) patients in this analysis previously experienced grade 3/4 or persistent grade 2 nonhematologic toxicity on imatinib therapy (60 of 95 [63%] CML-CP and 15 of 27 [56%] CML-AP patients). Of these patients, only 1 of 60 (2%) patients with CML-CP experienced the same nonhematologic toxicity with grade 3/4 intensity (diarrhea; successfully managed with antidiarrheal medicines) during nilotinib therapy as on previous imatinib therapy. Three of 60 (5%) patients with CML-CP experienced the same persistent grade 2 nonhematologic toxicity during nilotinib therapy that they had experienced on previous imatinib therapy. Importantly, of the 4 of 60 (7%) patients in CML-CP who had the same grade 3/4 or persistent grade 2 nonhematologic toxicity with nilotinib as they did previously with imatinib, no patients had their nilotinib dose reduced, interrupted, or permanently discontinued because of the nonhematologic AE. No patient in CML-AP experienced a recurrence of either the same nonhematologic grade 3/4 or persistent grade 2 toxicity on nilotinib.

Thirty-one patients with CML-CP and 9 with CML-AP (33% for both) experienced a grade 3/4 or persistent grade 2 hematologic AE during imatinib therapy that led to discontinuation of imatinib. Overall, 17 of 31 (55%) patients in CML-CP and 4 of 9 (44%) patients in CML-AP with hematologic imatinib intolerance experienced a grade 3/4 hematologic AE on nilotinib (Table 4). However, only 7 of 31 (23%) patients in CML-CP with hematologic imatinib intolerance discontinued nilotinib, all because of grade 3/4 thrombocytopenia, and 12 (39%) required dose reduction because of recurrence of the same hematologic AE. Discontinuation of nilotinib because of thrombocytopenia occurred in 4 of these 7 (57%) patients within the first 3 months of therapy and within 3-5 months in the other 3 patients. No patient in CML-AP discontinued nilotinib because of hematologic AEs. Overall, cross-intolerance between nilotinib and imatinib was infrequent, and thrombocytopenia was the only AE that required nilotinib discontinuation in a minority of patients with CML-CP and hematologic imatinib intolerance (7/40 [18%]).

Table 2. Nilotinib exposure and dose intensity (400 mg twice daily)

	CML-CP (n = 95)	CML-AP (n = 27)
Median duration of nilotinib therapy, mo (range)	24.7 (0-36)	5.1 (0-38)
Median dose intensity,* mg/d (range)	724 (151-800)	769 (184-1149)
Patients with dose interruptions attributable to any AE, n (%)	65 (68)	13 (48)
Median duration of cumulative dose interruptions, d (range)	24 (1-345)	17 (4-234)
Median percentage time lost to dose interruptions while on nilotinib therapy, % (range)	2.4 (0-60.1)	1.1 (0-47.2)

AE indicates adverse event; AP, accelerated phase; CML, chronic myeloid leukemia; and CP, chronic phase.
*Actual average dose intensity = cumulative dose given (ie, daily dose in mg/day)/duration of exposure (day).

Table 3. Nilotinib cross-intolerance in patients with imatinib-intolerance: nonhematologic adverse events

	Reason for imatinib intolerance					
	Nonhematologic AE	Rash/skin	Fluid retention	Diarrhea	ALT/AST elevation	Myalgia/arthralgia
CML-CP (n = 95)						
Imatinib-intolerant* grade 3/4 AE or persistent grade 2 AE, n (%)	60 (63)	28 (29)	18 (19)	12 (13)	3 (3)/4 (4)	10 (11)
Grade 3/4 AE or persistent grade 2 AE on nilotinib, n†	4	0	0	3	1/0	0
Grade 3/4 AE on nilotinib, n‡	1	0	0	1	0/0	0
AE that led to dose reduction on nilotinib, n	0	0	0	0	0/0	0
Discontinuation on nilotinib attributable to AE, n	0	0	0	0	0/0	0
CML-AP (n = 27)						
Imatinib-intolerant* grade 3/4 AE or persistent grade 2 AE, n (%)	15 (56)	5 (19)	5 (19)	1 (4)	1 (4)/0 (0)	2 (7)
Grade 3/4 AE or persistent grade 2 AE on nilotinib, n†	0	0	0	0	0/0	0
Grade 3/4 AE on nilotinib, n‡	0	0	0	0	0/0	0
AE that led to dose reduction on nilotinib, n	0	0	0	0	0/0	0
Discontinuation on nilotinib attributable to AE, n	0	0	0	0	0/0	0
All patients (n = 122)						
Imatinib-intolerant* grade 3/4 AE or persistent grade 2 AE, n (%)	75 (61)	33 (27)	23 (19)	13 (11)	4 (3)/4 (3)	12 (10)
Grade 3/4 AE or persistent grade 2 AE on nilotinib, n†	4	0	0	3	1/0	0
Grade 3/4 AE on nilotinib, n‡	1	0	0	1	0/0	0
AE that led to dose reduction on nilotinib, n	0	0	0	0	0/0	0
Discontinuation on nilotinib attributable to AE, n	0	0	0	0	0/0	0

AE indicates adverse event; ALT, alanine aminotransferase; AP, accelerated phase; AST, aspartate aminotransferase; CML, chronic myeloid leukemia; and CP, chronic phase.

*Patients with multiple reasons for imatinib intolerance are counted in each category.

†Number of imatinib-intolerant patients who experienced any grade 3/4 AE or grade 2 AE that persisted for > 30 days during nilotinib therapy and was the same corresponding reason for imatinib intolerance.

‡Number of imatinib-intolerant patients who experienced any grade 3/4 AE during nilotinib therapy that was the same corresponding reason for imatinib intolerance.

Of the 95 imatinib-intolerant patients with CML-CP, 45 had at least one form of previous interferon treatment, and 7 had previous stem cell transplantation (SCT). None of these patients discontinued using nilotinib because of a recurrence of the same nonhematologic AE that led to discontinuation of imatinib. Five (11%) of these patients with CML-CP previously treated with interferon, and 1 (14%) with prior SCT discontinued nilotinib because of recurrent thrombocytopenia. No patients with CML-AP treated previously with IFN or SCT discontinued nilotinib because of recurrence of the same AE which led to discontinuation of imatinib.

Overall safety

The overall safety profile of nilotinib in imatinib-intolerant patients was generally consistent with the safety profile of nilotinib in imatinib-resistant patients. The most frequently reported drug-related nonhematologic AEs (≥ 10%) among imatinib-intolerant patients in CML-CP were rash (42 [44%] vs 57 [25%] in patients with imatinib-resistant CML-CP), pruritus (28 [29%] vs 56 [25%]), nausea (28 [29%] vs 51 [23%]), vomiting (18 [19%] vs 23 [10%]), headache (17 [18%] vs 40 [18%]), constipation (16 [17%] vs 27 [12%]), diarrhea (16 [17%] vs 23 [10%]), and fatigue (16 [17%] vs 49 [22%]). The most frequently reported drug-related nonhematologic AEs (≥ 10%) among imatinib-intolerant patients in CML-AP were rash (8 [30%] vs 21 [19%] in patients with imatinib-resistant CML-AP), pruritus (4 [15%] vs 20 [18%]), anorexia (4 [15%] vs 4 [4%]), diarrhea (3 [11%] vs 10 [9%]), abdominal pain (3 [11%] vs 7 [6%]), and muscle spasms (3 [11%] vs 10 [9%]). Grade 3/4 nonhematologic AEs were infrequent in patients with intolerance to imatinib.

Pancreatitis (regardless of study drug relationship) was reported in 3 (3%) imatinib-intolerant and 4 (2%) imatinib-resistant patients with CML-CP and 0 and 1 (1%) imatinib-intolerant and -resistant patients, respectively, with CML-AP in the nilotinib registration study. None of these occurred in a patient who previously experienced pancreatitis on imatinib. Similarly, electrocardiogram abnormalities were uncommon on imatinib and no incidences of cross intolerance were reported in nilotinib-treated patients.

Grade 3/4 neutropenia, thrombocytopenia, and anemia (newly occurring or worsening) were experienced by 42 (45%), 31 (33%), and 8 (9%) imatinib-intolerant patients with CML-CP vs 56 (25%), 64 (28%), and 26 (12%) imatinib-resistant patients with CML-CP in the registration study, respectively. Similarly, 11 (42%), 11 (48%), and 5 (19%) imatinib-intolerant patients with CML-AP experienced newly occurring or worsening grade 3/4 neutropenia, thrombocytopenia, and anemia, respectively, vs 44 (42%), 40 (40%), and 32 (30%) patients with imatinib-resistant CML-AP. Dose reductions because of AEs occurred in 29 (31%) of 95 and 5 of 27 (19%) imatinib-intolerant patients in CML-CP and CML-AP, respectively.

Efficacy

Of the patients without CHR at the start of therapy (CML-CP, n = 52; CML-AP, n = 27), 47 (90%) patients in CML-CP and 10 (37%) patients in CML-AP achieved CHR on nilotinib therapy

Table 4. Nilotinib cross-intolerance in patients with imatinib-intolerance: hematologic AEs

	Reason for imatinib intolerance			
	Hematologic AE	Anemia	Neutropenia	Thrombocytopenia
CML-CP (n = 95)				
Imatinib-intolerant* grade 3/4 AE or persistent grade 2 AE, n (%)	31 (33)	3 (3)	9 (9)	25 (26)
Grade 3/4 AE or persistent grade 2 AE on nilotinib, n†	19	1	5	16
Grade 3/4 AE on nilotinib, n‡	17	1	5	14
AE that led to dose reduction on nilotinib, n	12	0	2	10
Discontinuation on nilotinib attributable to AE, n	7	0	0	7
CML-AP (n = 27)				
Imatinib-intolerant* grade 3/4 AE or persistent grade 2 AE, n (%)	9 (33)	1 (4)	3 (11)	6 (22)
Grade 3/4 AE or persistent grade 2 AE on nilotinib, n†	4	1	2	2
Grade 3/4 AE on nilotinib, n‡	4	0	2	2
AE that led to dose reduction on nilotinib, n	3	0	2	1
Discontinuation on nilotinib attributable to AE, n	0	0	0	0
All patients (N = 122)				
Imatinib-intolerant* grade 3/4 AE or persistent grade 2 AE, n (%)	40 (33)	4 (3)	12 (10)	31 (25)
Grade 3/4 AE or persistent grade 2 AE on nilotinib, n†	23	2	7	18
Grade 3/4 AE on nilotinib, n‡	21	1	7	16
AE that led to dose reduction on nilotinib, n	15	0	4	11
Discontinuation on nilotinib attributable to AE, n	7	0	0	7

AE indicates adverse event; AP, accelerated phase; CML, chronic myeloid leukemia; and CP, chronic phase.

*Patients with multiple reasons for imatinib intolerance are counted in each category.

†Number of imatinib-intolerant patients who experienced any grade 3/4 AE or grade 2 AE that persisted for > 30 days during nilotinib therapy and was the same corresponding reason for imatinib intolerance.

‡Number of imatinib-intolerant patients who experienced any grade 3/4 AE during nilotinib therapy that was the same corresponding reason for imatinib intolerance.

(Figure 1). MCyR and CCyR were achieved by 63 (66%) and 48 (51%) patients in CML-CP, respectively, and in 11 (41%) and 8 (30%) patients in CML-AP, respectively. Responses were durable, with CCyR maintained at 24 months in 92% of responding patients with CML-CP and confirmed hematologic response maintained at 24 months in 57% of responding patients with CML-AP, corresponding to the primary end points for these populations. At 24 months, estimated progression-free survival was 77% and 47%, and estimated overall survival was 91% and 76% for imatinib-intolerant CML-CP and CML-AP patients, respectively. These rates were greater than those observed in the overall population of the registration study, which includes resistant patients.[12,13] CHR was achieved by 158 of 207 (76%) patients with CML-CP without baseline CHR, and MCyR and CCyR by 190 (59%) and 141 (44%) of 321 patients.[12] In patients with CML-AP, 43 (31%), 44 (32%), and 29 (21%) of 137 patients with CML-AP achieved CHR, MCyR, and CCyR, respectively, in the registration study.[13]

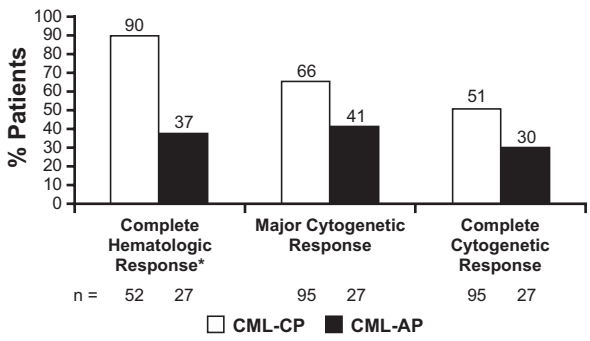

Figure 1. Nilotinib response rates in patients entering the study with imatinib intolerance. *Patients who did not have complete hematologic response at baseline.

Discussion

Nilotinib was rationally designed to interact, like imatinib, with the inactive conformation of BCR-ABL but to be a more potent and selective inhibitor. Given the common target and shared chemical structure of imatinib and nilotinib, this analysis was conducted to determine whether AEs causing imatinib intolerance would recur after therapy with nilotinib. The results suggest that cross-intolerance is infrequent, particularly for patients with nonhematologic AEs, which are the most common reason for imatinib intolerance. The low rates of cross-intolerance associated with imatinib and nilotinib therapy observed in this study are important, as this lack of overlapping AEs allows achievement and maintenance of the planned nilotinib dose intensity, providing patients with an opportunity to achieve the desired outcome with nilotinib.

Drugs with similar chemical structures frequently lead to cross-intolerance. For example, cephalosporin and penicillin can cause significant cross-reactivity.[14] In the case of nilotinib and imatinib, however, nonhematologic cross-intolerance leading to discontinuation did not occur. None of the 75 patients with grade 3/4 or persistent grade 2 nonhematologic toxicity during imatinib therapy required a dose reduction or discontinuation of nilotinib because of the same AE, and only 1 patient experienced grade 3/4 toxicity of the same nature (diarrhea). Importantly, skin reactions seen with imatinib did not recur in any of these patients while on nilotinib. Although grade 3/4 skin reactions are relatively uncommon with imatinib, reported in 2% of patients,[15] it is one of the most common reasons for imatinib treatment discontinuation. Thus, nilotinib represents an effective therapy for patients who develop intractable or severe skin reactions with imatinib and

suggests that the cutaneous AEs on nilotinib may occur via a different mechanism.

Similarly, no recurrence of fluid retention was observed. Peripheral edema is the most frequently reported AE with imatinib, although it is rarely severe. None of the patients who switched to nilotinib because of severe or recurrent peripheral edema experienced a recurrence of these AEs on nilotinib. Of the available TKIs for CML, nilotinib is the TKI that is least prone to cause fluid retention. This may be related to nilotinib's increased specificity toward BCR-ABL and relatively weaker inhibition of PDGFRβ,[16] a receptor that is known to affect fluid retention and serosal inflammation.[17-19]

Cross-intolerance to nilotinib was more likely to be associated with myelosuppression than with other reasons. Myelosuppression is a common AE associated with the use of TKIs in CML. With nilotinib, myelosuppression typically occurs in the first 2-3 months of therapy and can be managed with transient treatment interruptions and, occasionally, dose reductions. In instances in which these measures do not alleviate myelosuppression, response may be affected. Indeed, the presence of grade 3/4 myelosuppression is associated with an inferior outcome to frontline imatinib therapy.[20] It is likely that myelosuppression is a feature of the underlying CML that is less likely to respond to therapy, although frequent treatment interruptions and dose reductions may contribute to lower response rates. In general, the overlapping hematologic toxicities seen between imatinib and nilotinib might be attributable, at least in some patients, to underlying disease and unrelated to a specific TKI. Importantly, only 7 of 31 patients (23%) discontinued nilotinib because of recurrence of the same grade 3/4 or persistent grade 2 hematologic AE that led to their discontinuation of imatinib. Thus, nilotinib should be considered for patients with intolerance because of imatinib-induced myelosuppression because most of these patients will be able to tolerate and respond to nilotinib.

Limitations of the present study include the fact that dose reduction of imatinib was generally not an option for patients before study entry because the achievement of MCyR on imatinib was an exclusion criterion for the nilotinib registration trial. This post-hoc analysis was also restricted to patients who entered the nilotinib registration trial because of imatinib intolerance. This excluded a large number of patients who were enrolled in the study for resistance. However, the incidence of adverse events on nilotinib in patients with resistance to imatinib is generally similar to that reported in this analysis. In addition, grade 1 or transient grade 2 toxicities were not analyzed. Many of these toxicities, however, may be clinically significant because patients remain on TKI therapy for many years, and could be more likely to be recurrent with a different TKI.

In summary, these results confirm that there is minimal cross-intolerance with nilotinib in patients with imatinib-intolerant CML-CP or CML-AP. The minimal cross-intolerance resulted in more patients achieving the planned nilotinib doses and translated into significant clinical responses. Thrombocytopenia was the only imatinib-related AE leading to intolerance that recurred and led to discontinuation of nilotinib therapy in a minority of patients. Overall, as previously reported, imatinib-intolerant patients experienced greater hematologic and cytogenetic responses with nilotinib therapy compared with imatinib-resistant patients.[7,8] These results corroborate that nilotinib is an effective and well-tolerated therapeutic option for the treatment of patients with CML-CP and CML-AP with previous imatinib intolerance.

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Authorship

Contribution: J.E.C., A.H., and F.J.G. designed and performed research, collected, analyzed, and interpreted data, and drafted and approved the manuscript; P.D.l.C. performed research, collected, analyzed, and interpreted data, and drafted and approved the manuscript; G.R. performed research and drafted and approved the manuscript; J.P.-I. and M.B. performed research, collected data, and drafted and approved the manuscript; E.J. drafted and approved the manuscript; K.G. and R.C.W. analyzed and interpreted data and drafted and approved the manuscript; R.E.B. analyzed and interpreted data and drafted and approved the manuscript; and H.M.K. collected, analyzed, and interpreted data and drafted and approved the manuscript.

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Minimal cross-intolerance with nilotinib in patients with chronic myeloid leukemia in chronic or accelerated phase who are intolerant to imatinib

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