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ORIGINAL REPORT

Nilotinib As Front-Line Treatment for Patients With Chronic Myeloid Leukemia in Early Chronic Phase

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A B S T R A C T

Purpose
Although most patients with chronic myeloid leukemia (CML) in chronic phase respond well to front-line therapy with imatinib, some patients do not achieve the desirable end point, and others may eventually lose response or are intolerant.

Patients and Methods
Patients with newly diagnosed CML in chronic phase were treated with nilotinib 400 mg twice daily on an empty stomach as initial therapy.

Results
Among 51 patients in chronic phase observed for at least 3 months, 50 (98%) achieved a complete cytogenetic remission (CCyR), and 39 (76%) achieved a major molecular response (MMR). Responses occurred rapidly, with 96% of patients achieving CCyR by 3 months and 98% achieving CCyR by 6 months. The projected event-free survival at 24 months is 90%, and all patients are alive after a median follow-up time of 17 months. Grade ≥ 3 neutropenia occurred in 12% of patients, and thrombocytopenia in occurred 11%. Nonhematologic toxicity was usually grade 1 to 2 and manageable. The actual median dose at 12 months was 800 mg (range, 200 to 800 mg).

Conclusion
Nilotinib is an effective option for the initial management of CML in early chronic phase, producing high rates of CCyR and MMR, with most patients reaching these responses early during their therapy.

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INTRODUCTION

Imatinib (Gleevec, Glivec; Novartis, Basel, Switzerland) at 400 mg daily is the standard therapy for patients with chronic myeloid leukemia (CML). Results from the International Randomized Study of Interferon Versus STI571 (IRIS) trial show that 82% of patients achieve a complete cytogenetic response (CCyR), and a majority also achieve a major molecular response (MMR).[1] Responses are usually durable, with 4% to 7% of patients per year losing response or transforming in the first 3 years; thereafter, these rates decrease to annual rates of 1% to 2%. After 7 years, the projected overall survival (OS) rate is 90%, with an event-free survival (EFS) rate of 81%.[1] Although a survival advantage could not be demonstrated in IRIS because of its cross-over design, there was an EFS advantage over the interferon arm. Other studies comparing historical responses to interferon-based therapy have confirmed this improvement in outcome of patients with CML treated with imatinib.[2,3] Despite these excellent results, 18% of patients do not achieve a CCyR, approximately 10% of patients who achieve CCyR eventually lose their response, and 4% to 8% of patients are intolerant to imatinib.[1]

Thus, the outcome with imatinib is not optimal in 30% to 35% of patients, making it necessary to investigate new strategies to further improve the outcome of patients with early chronic-phase CML. These strategies include higher doses of imatinib, combination therapy, and the use of second-generation tyrosine kinase inhibitors (dasatinib, nilotinib, and bosutinib).[4] Newer tyrosine kinase inhibitors are generally more potent inhibitors of Bcr-Abl kinase activity, are active against most imatinib-resistant tumors harboring Bcr-Abl kinase domain (KD) mutations, and have demonstrated high efficacy with a favorable toxicity profile in CML after imatinib failure.[5-7]

Nilotinib, a potent inhibitor of the Abl kinase structurally similar to imatinib, was rationally designed to improve binding affinity against Bcr-Abl and improve specificity over that of imatinib.[8]

Nilotinib is approximately 30 times more potent in vitro than imatinib against wild-type Bcr-Abl and retains activity against most of the common imatinib-resistant Bcr-Abl KD mutants, except T315I.[9] Nilotinib has been approved for the treatment of patients with CML in chronic or accelerated phase with resistance or intolerance to imatinib. Among patients treated for chronic phase after imatinib failure, a major cytogenetic response (MCyR; Philadelphia chromosome [Ph] –positive metaphases ≤ 35%) was achieved in 59% of patients, and CCyR was achieved in 44%.[10] Among patients treated in accelerated phase after imatinib failure, a MCyR was achieved in 32% of patients.[11] We initiated a phase II study to determine whether front-line nilotinib therapy could improve the outcome of patients with early chronic-phase CML.

PATIENTS AND METHODS

Study Group

From July 2005 to February 2009, patients with CML in early chronic phase referred to The University of Texas M. D. Anderson Cancer Center were offered front-line nilotinib therapy. Eligibility criteria included the following: diagnosis within 6 months from the start of study treatment; no prior CML therapy other than hydroxyurea or a maximum of 1 month of therapy with standard-dose imatinib; age 18 years or older; performance status of 0 to 2; and adequate organ function. Patients with clonal evolution were eligible provided they met all other criteria for chronic phase (ie, blasts < 15%, blasts plus promyelocytes < 30%, basophils < 20%, and platelets > 100×10^9/L unless related to therapy). Patients with cardiac conditions, including uncontrolled angina, myocardial infarction within 12 months, congenital prolonged QTc syndrome or pretreatment QTc more than 450 milliseconds, uncontrolled hypertension, right bundle branch block plus left anterior hemiblock, complete left bundle branch block, or bifascicular block, and patients with history of clinically significant ventricular arrhythmias were excluded. The study was approved by the institutional review board, and all patients signed an institutional review board–approved informed consent.

Therapy

Patients received treatment with the standard dose of nilotinib of 400 mg twice daily, administered at least 2 hours after and 1 hour before meals. Treatment was continued until disease progression or unacceptable toxicity. Patients with grade 3 to 4 nonhematologic toxicity had their treatment transiently interrupted. Treatment was restarted after resolution to grade ≤ 1 with a reduction of one dose level to daily doses of 200 mg twice daily (200 mg once daily if a subsequent dose reduction was required). For hematologic toxicity, treatment was interrupted for grade 3 neutropenia (neutrophils < 0.5×10^9/L) or thrombocytopenia (platelets < 40×10^9/L). Treatment was restarted at the same dose if recovery to neutrophils more than 1×10^9/L and/or platelets to more than 60×10^9/L occurred within 2 weeks or restarted with a reduction of one dose level if recovery time was longer than 2 weeks. Patients with recurrent grade 3 to 4 neutropenia or thrombocytopenia could have an additional reduction of one dose level, with the lowest acceptable dose being 200 mg once daily. Hematopoietic growth factors were not routinely used.

Patients had a CBC and blood chemistry every 1 to 2 weeks for the first 3 months and then every 6 weeks. In addition, bone marrow aspiration, cytogenetic analysis, and peripheral-blood quantitative reverse transcription polymerase chain reaction (RT-PCR) for the BCR-ABL fusion transcript were performed at baseline, every 3 months for 1 year, and every 6 months thereafter. Response criteria were as previously defined.[12] Briefly, complete hematologic response (CHR) required complete normalization of peripheral-blood counts, normal differential, and no splenomegaly. Cytogenetic response was based on G-banded karyotypes with at least 20 metaphases counted and was categorized as complete (0% Ph-positive metaphases), partial (1% to 35% Ph-positive metaphases), or minor (36% to 95% Ph-positive metaphases). MMR was defined as a BCR-ABL/ABL transcript ratio of less than 0.1% (international scale), and a complete molecular response was defined as undetectable transcripts with an assay sensitivity of at least one in 10^5 cells.[13] Patients who had not achieved CCyR by 6 months after treatment or who developed resistance had mutational analysis of the entire ABL KD (codons 220 to 500) by standard Sanger dideoxy chain termination DNA sequencing after two-step quantitative RT-PCR amplification of the BCR-ABL fusion transcript. Those with detectable KD mutations had sequencing of the baseline sample.

Statistical Analysis

The primary objective was to improve the MMR rate at 12 months from the expected 40% based on historical experience with standard-dose imatinib.[14] Two end points are being monitored, the MMR probability by 12 months and the toxicity rate, with the first interim analysis planned after 50 patients had been accrued (study designed for a maximum of 100 patients). Early stopping rules covered efficacy, based on molecular response rate at 12 months and MCyR rate at 6 months, and toxicity at any time. The distributions of time-to-event end points, namely OS and EFS, were estimated using the Kaplan-Meier method. Survival was measured from the time treatment was started to the date of death from any cause or date of last follow-up. EFS was measured from the start of treatment to the date of any of the following events while on therapy: death from any cause, loss of CHR, loss of CCyR, discontinuation of therapy for toxicity or lack of efficacy, or progression to accelerated or blastic phases. Transformation-free survival (TFS) was measured from the start of therapy to the date of transformation to accelerated or blast phases while on therapy or to the date of last follow-up.

RESULTS

Efficacy

The median age for the 61 patients presenting in chronic phase was 46 years (range, 19 to 86 years); the median time from diagnosis to treatment was 0.8 months (range, 0 to 5.5 months). Most patients had low or intermediate Sokal risk score (Table 1); four patients had clonal evolution at diagnosis. Twelve (20%) of 61 patients had received imatinib before start of nilotinib for a median of 22 days (range, 2 to 28 days). The median follow-up time was 17.3 months (range, 1 to 43 months).

Among the 48 patients who started therapy without CHR, 47 (98%) achieved CHR; the median time to CHR was 3 weeks (range, 0.6 to 12 weeks). The one patient who did not achieve CHR received nilotinib for only 15 days and decided to discontinue therapy despite the absence of drug-related toxicity. Fifty-one patients have been observed for at least 3 months and are thus evaluable for cytogenetic and molecular response. Among the 51 patients, 50 (98%) have achieved, at any time, a CCyR. The one patient who had not achieved a CCyR had a partial cytogenetic response at the time of this report (15 weeks from start of therapy) with no ABL KD mutation detected at last follow-up. An MMR has been achieved in 39 (76%) of 51 evaluable patients; 12 patients (24%) achieved a complete molecular response. The median time to CCyR was 3 months (range, 3 to 6 months), and the median time to MMR was 3 months (range, 3 to 18 months).

Table 2 lists the rates of cytogenetic response over time, with all evaluable patients kept in the denominator up to the time of their last follow-up. Patients who discontinued therapy were considered in the denominator up to the follow-up time that would correspond to the time of this report had they stayed on the study. Cytogenetic responses occurred early, with 90% of patients achieving a CCyR by 3 months and 96% achieving a CCyR by 6 months. Similarly, there was a rapid reduction in transcript levels, with a median BCR-ABL/ABL transcript ratio of 0.02% by 6 months and a steady but slower decline after that, meaning that 81% of patients achieved an MMR by 12 months and 79% achieved an MMR by 18 months.

Table 1. Patient Demographics and Clinical Characteristics at Start of Nilotinib for Patients With Chronic Myeloid Leukemia in Chronic Phase (N = 61)

Characteristic	Median	Range
Age, years	46	19-86
Splenomegaly present		
No. of patients	17	
%	28	
Hemoglobin, g/dL	12.4	8-15.8
WBC, × 10^9/L	47.4	1.4-342.5
Platelets, × 10^9/L	282	73-1,411
Peripheral blood		
Blasts, %	0	0-12
Basophils, %	2	0-13
Bone marrow		
Blasts, %	1	0-5
Basophils, %	2	0-10
Sokal risk		
Low		
No. of patients	43	
%	70	
Intermediate		
No. of patients	14	
%	23	
High		
No. of patients	4	
%	7	
Ph-positive metaphases at start of therapy, %	100	35-100
Clonal evolution present		
No. of patients	4	
%	7	

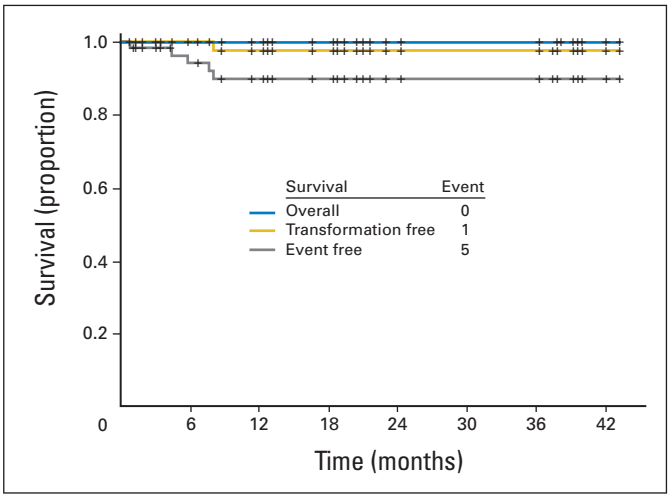

Fig 1. Overall, event-free, and transformation-free survival for all patients treated with nilotinib as initial therapy for chronic myeloid leukemia in chronic phase.

Responses have been durable, with 98% of all patients who achieved a CCyR maintaining this response. The estimated EFS rate at 24 months is 90% (Fig 1), and the estimated TFS rate is 98%. All patients are alive, and of the 34 patients who achieved MMR and who have had subsequent quantitative RT-PCR assessments, none have lost MMR. One patient, who never achieved MMR, developed a sudden, biphenotypic blast phase with a new E255K ABL mutation after 8 months of therapy despite not having any treatment interruptions, and two patients experienced progression to blast phase after being taken off nilotinib therapy as a result of intolerance, with a new F359C ABL mutation in one patient and no KD mutation in the other. One of these patients had achieved a CCyR on nilotinib and was taken off therapy as a result of pericarditis with pericardial effusion; he then underwent an allogeneic stem-cell transplantation and experienced relapse in myeloid blastic phase 8 months after transplantation. The other patient had achieved CCyR after 3 months on nilotinib and experienced relapse in lymphoid blast phase after discontinuing therapy for 1 month because of liver dysfunction; the patient was then treated with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone plus imatinib followed by a matched unrelated donor stem-cell transplantation and continues in remission more than 36 months after diagnosis.

Safety

Overall, treatment has been well tolerated. The most common nonhematologic adverse events, regardless of causality, were increased liver enzyme transaminases or bilirubin, skin rash, fatigue, and hyperglycemia (Table 3). Most adverse events were grade 1 to 2 and manageable. Grade 3 or 4 nonhematologic adverse events were uncommon and included elevation of bilirubin (8%), lipase (6%), or amylase (3%). There were no instances of clinical pancreatitis. Cardiovascular events were uncommon, with two instances each of hypertension and QTc prolongation, none of them grade 3 or 4. One patient with a history of pericarditis and pericardial effusion during a previous short exposure to imatinib developed recurrence of these symptoms on nilotinib. Non-neutropenic fever occurred in 6% of patients. Hematologic adverse events were more common but were usually transient and manageable with temporary treatment interruptions and

Table 2. Cytogenetic and Molecular Response to Nilotinib Over Time

Time on Therapy (months)	Cytogenetic			Molecular		
	No. of Patients at Risk	Major Response (%)	Complete Response (%)	No. of Patients at Risk	Major Response (%)	Complete Response (%)
3	50	98	90	50	40	2
6	45	98	96	46	71	4
12	37	97	97	38	81	11
18	28	96	93	29	79	21
24	14	93	93	15	79	20
30	12	92	92	13	75	15

Table 3. Adverse Events on Nilotinib, Regardless of Causality, Present in at Least 5% of Patients or With at Least One Grade ≥ 3 Event (N = 61 patients)

Adverse Event	Any Grade		Grade 3-4	
	No.	%	No.	%
Nonhematologic				
Fatigue	41	67	2	3
Rash	30	49	1	2
ALT elevation	29	48		
AST elevation	28	46		
Hyperglycemia*	27	44	3	5
Bilirubin	24	39	4	7
Headache	24	39		
Nausea	23	38		
Abdominal pain	18	30		
Dyspnea	17	28	1	2
Non-neutropenic fever	16	26	3	5
Diarrhea	13	21		
Hypophosphatemia	9	15		
Anorexia	9	15	1	2
Weight loss	8	13		
Vomiting	7	11		
Lipase elevation	6	10	3	5
Neuropathy	6	10	1	2
Muscle cramps	6	10		
Joint pain	6	10	2	3
Hyperkalemia	4	7	1	2
Increased creatinine	3	5		
Amylase	2	3	1	2
Hematologic				
Neutropenia	34	52	8	12
Anemia	32	49	3	5
Thrombocytopenia	28	43	7	11

*Test was not performed fasting.

occasional dose reductions. Myelosuppression occurred early in most patients; the median time to first episode of grade 3 to 4 myelosuppression was 24 days (range, 19 to 360 days). Grade 3 or greater neutropenia, thrombocytopenia, and anemia occurred in eight patients (12%), seven patients (11%), and three patients (5%), respectively. There have been no episodes of neutropenic fever or major bleeding.

Throughout the study period, 24 patients (37%) have required 45 transient treatment interruptions, with 12 patients requiring more than one interruption (median, three interruptions; range, two to six interruptions). The most common causes for treatment interruption were increased liver enzyme (n = 13), myelosuppression (n = 8), and unrelated procedures or surgeries (n = 8). Dose reductions were required in 11 patients (17%). The actual median dose of nilotinib at 12 months was 800 mg (range, 200 to 800 mg). Ten patients have discontinued therapy, including four for adverse events, two for blastic phase (one started in chronic phase and one started in accelerated phase), two for financial issues, one for patient choice, and one for noncompliance.

DISCUSSION

Despite the significant improvement in the outcome of patients with CML that resulted from the introduction of imatinib therapy, there is need for improvement. The estimated EFS rate at 7 years in the IRIS study was 81%, with a considerable number of patients not accounted for after they were removed from study for various reasons.[1] In an intent-to-treat analysis from a single institution accounting for all patients, EFS was reported to be 81% at 5 years, but it is 63% if patients who do not achieve MCyR or patients who discontinue therapy because of toxicity are also considered as experiencing treatment failure.[15] To improve these results, we investigated nilotinib as initial therapy for patients with early chronic-phase CML. Nilotinib is more potent in vitro than imatinib,[8] has induced CCyR in more than 40% of patients after treatment failure with imatinib,[10] and induces fewer ABL KD mutations than imatinib.[16]

The results of this study were encouraging, with a high rate of CCyR (98%) with these responses occurring early after therapy initiation such that 96% of patients had already achieved CCyR by 6 months. To put these results in perspective, we analyzed them in the context of historical data in similar patients treated at our institution with imatinib, either at a standard or high dose. The CCyR occurred at a higher overall rate and considerably faster with nilotinib than with standard-dose imatinib (6-month CCyR: 96% with nilotinib *v* 45% with imatinib[17]) and high-dose imatinib (12-months CCyR: 97% with nilotinib *v* 70% with high-dose imatinib[17]). The higher rate of CCyR is by itself a positive finding, but even if confirmed in randomized trials, it would represent a modest improvement considering that the overall rate of CCyR with standard-dose imatinib is already approximately 80%. The main advantage achieved with nilotinib seems to be the earlier occurrence of responses. The significance of early responses is controversial. It has been suggested that the outcome of patients who achieve CCyR is equivalent regardless of the time required to achieve this response.[18] However, this analysis only considers patients who achieve a CCyR, thus selecting patients with already a favorable outcome. Even in this analysis, there was a trend for more durable remissions in patients who achieved their response within 6 months. However, a patient who has not achieved a CCyR at any given time faces the dual and somewhat competing possibilities of continuing to improve until achieving a CCyR at a later time, or of not improving or even experiencing progression. As more time evolves without achieving a CCyR, the probability of eventually achieving CCyR decreases, and the risk of progression increases.[19] In a similar analysis for molecular response with imatinib,[17] the rates of molecular response were higher than those reported with imatinib, with MMR rates at 12 months of 46% with standard-dose imatinib, 54% with high-dose imatinib, and 81% with nilotinib.

Regardless of the possible significance of the earlier responses, this analysis should be considered with caution because, although the inclusion criteria for all studies are similar without obvious imbalances in patient characteristics, comparisons are made with imatinib-treated historical cohorts. Prospective randomized trials are needed to clarify whether nilotinib therapy improves response rates, time to response, and, more importantly, the long-term outcome (EFS and TFS) compared with imatinib therapy. Also, the results reported here are comparable to those achieved with dasatinib in a parallel study reported separately conducted in parallel to this study, with patients allocated to each study in alternating sequence.

Of note, three patients experienced transformation to blast phase. One of these patients had high-risk disease with 12% blasts at the time treatment was started. Despite achieving a CCyR after 3 months of therapy (never MMR) and no treatment interruptions, the

patient experienced a sudden blastic transformation. Two other patients experienced transformation after treatment discontinuation; one patient experienced transformation to lymphoid blast phase shortly after discontinuing therapy because of liver toxicity, and the other patient experienced transformation 8 months after receiving a stem-cell transplantation in CCyR (achieved on nilotinib). Despite the possible attenuating circumstances that could have contributed to these transformations (ie, high blast count at start, prolonged treatment interruptions), further follow-up and larger series will be required to determine whether there might be an increased risk of such events with nilotinib.

Treatment with nilotinib is well tolerated. The most common adverse events were elevation of liver and pancreatic function tests, particularly bilirubin (indirect), with no clinical consequences. Myelosuppression was also frequent but was mild in most patients, was always transient, usually occurred early during the course of therapy, and responded to transient treatment interruptions and dose reductions. The overall rate of adverse events seems lower in the front-line setting than what is reported with nilotinib after imatinib failure.[5] This is not an unexpected finding and similar to what was reported with imatinib front-line therapy or after interferon failure.[20,21] The toxicity profile compares favorably with what has been reported with imatinib. In this report, the rates of grade 3 or 4 anemia (5%), neutropenia (12%), and thrombocytopenia (11%) seen with nilotinib are similar to the rates reported with imatinib 400 mg daily (4%, 25%, and 17%, respectively)[22] or 800 mg daily (5% to 10%, 14% to 36%, and 18% to 25%, respectively).[23,24] Among nonhematologic adverse events, elevations of lipase and bilirubin (grade 3 or 4 in 6% and 8% of patients, respectively, in this report) have not been reported in detail in studies using imatinib. However, these are usually biochemical abnormalities with no clinical impact, and no cases of pancreatitis were observed.

We conclude that nilotinib is an effective initial therapy for patients with CML in early chronic phase, with a high rate of response and rapid achievement of CCyR in nearly all patients within 6 months from the start of therapy. These results were achieved with a favorable toxicity profile, and accrual to the study continues. The possible superiority of this approach compared with the current standard of imatinib 400 mg daily needs to be evaluated in randomized studies to assess whether such intervention will result in improved EFS and OS. Such studies are ongoing.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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