Nilotinib Therapy in Patients with Chronic Myeloid Leukemia Who Have Failed Imatinib

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Abstract

Chronic myeloid leukemia (CML) results from a single translocation that produces the BCR–ABL fusion oncogene, which is detectable in virtually all patients. Imatinib mesylate has radically changed the outlook for newly diagnosed patients and represents the current standard of care for this disorder. While most patients do well well with imatinib upfront, a minority of patients do not. In addition, this therapy offers little benefit for patients with advanced-phase disease. Several mechanisms underlie imatinib failure, point mutations within the Abelson tyrosine (ABL) kinase domain being the most significant of these. The development of novel agents designed to overcome imatinib resistance led to the creation of the high-affinity BCR-ABL inhibitor nilotinib. The purpose of this article is to summarize the pre-clinical and clinical data on nilotinib in patients with CML who have failed prior therapy with imatinib or dasatinib.

Keywords

Imatinib, nilotinib, dasatinib, tyrosine kinase inhibition, BCR–ABL, resistance, targeting, rational drug design

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Rationale for Second-generation Tyrosine Kinase Inhibitors

Despite the very impressive data from the pivotal International Randomized Study of Interferon and STI571 (IRIS) that earned imatinib its place as a standard of care in the current management of chronic myeloid leukemia (CML), disease progressed by 7% over five years of therapy in chronic-phase (CP) patients.[1] An emerging challenge facing clinicians now is how best to manage primary or secondary imatinib resistance and/or intolerance.

Imatinib Intolerance

Imatinib therapy is well tolerated in the majority of patients; however, a small group will experience adverse events (AEs). Most reactions to imatinib are of mild to moderate grade, but from available data the treatment is discontinued due to drug-related adverse reactions in 2.4% of newly diagnosed patients, in 4% of patients in CP after failure of interferon-alpha therapy, in 4% of patients with accelerated phase (AP), and in 5% with blastic phase (BP).[2] The most frequently reported drug-related adverse reactions are edema, nausea and vomiting, muscle cramps, musculoskeletal pain, diarrhea, and rash. In general, AEs are more likely to occur in older patients where the potential for drug–drug interaction is higher and in patients with advanced-phase disease. Adverse reactions can usually be managed with either a reduction of the dose or an interruption of treatment along with appropriate supportive measures (concomitant growth factor therapy, diuretics, antiemetics, etc.).[3–5] However, in rare cases permanent cessation of therapy is the only solution to manage the intolerant patient.[6]

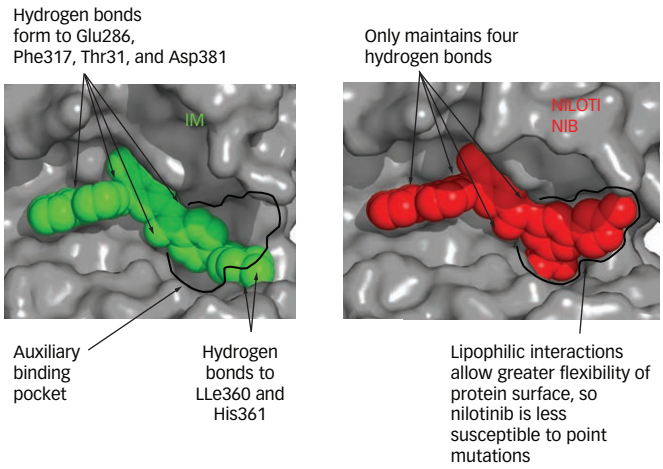
Imatinib Resistance

Several point mutations within the Abl-kinase protein have been reported that can mediate resistance to imatinib.[7] Of these mutations, the gatekeeper T315I mutation is the most clinically relevant.[8–11] Amplification of BCR-ABL may account for resistance to imatinib in a small percentage of cases, and these patients may or may not respond to increased doses of the drug.[7,12] Activation of other signaling pathways such as the Src family of kinases (SFKs),[13] the presence of p-glycoprotein efflux pumps through MDR-1 gene expression,[14] and plasma binding of α-1 acid glycoprotein[15] with imatinib are other less important mediators of resistance. Given the new unmet needs in CML that emerged following the use of imatinib, investigators began to explore the development of new compounds to overcome imatinib resistance. It is against this background that nilotinib was conceived (see *Figure 1*).

Nilotinib Therapy in Chronic Myeloid Leukemia

The clinical efficacy of nilotinib has been thoroughly evaluated in CML. The phase I component of this evaluation consisted of a dose-escalation study

Figure 1: Interaction of Imatinib and Nilotinib with BCR-ABL



The reduced requirement for hydrogen bonding with nilotinib compared with imatinib (IM) allows for a tighter steric fit into the adenosine triphosphate (ATP) binding pocket. Source: Swords R et al., Clin Lymphoma Myeloma*, 2007.*[32]

assessing the safety and tolerability of nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). The larger phase II protocol included six arms: three of these arms involved patients with imatinib failure in CP, AP, and BP CML,[16–18] another arm involved patients with imatinib and/or dasatinib failure, a further arm involved patients with imatinib/dasatinib failure in AP and blastic crisis, and the remaining arm included patients with Ph+ ALL and rarer disorders such as systemic mastocytosis. All of the trials included patients who had previously received imatinib therapy but were either resistant to or intolerant of the treatment.

While nilotinib has been initially developed as a second-line therapy, it is also being evaluated for use in the first-line setting. The Italian GIMEMA CML Working Party study includes treatment-naïve adult patients with CML in early CP (CP-CML).[19] Initial data for 73 previously untreated patients with early CP-CML show that the complete hematological response (CHR) rate after three-month treatment with nilotinib 400mg twice-daily (BID) was 100%. Of 48 patients who completed six months of therapy, the CHR was 98%. The complete cytogenic response (CCyR) rate was 78 and 96% at three and six months, respectively. One patient had progressive disease at six months. The ongoing MD Anderson Cancer Center study includes patients with untreated CP-CML or with <1 month of therapy with imatinib,[20] and also involves a small cohort of patients with previously untreated AP-CML.

Safety and Tolerability

The primary objectives of the phase I study were to determine the safety and tolerability of nilotinib and to characterize its biological and pharmacokinetic profiles.[21] Hematological and cytogenetic responses were evaluated as secondary end-points. The trial recruited 119 patients (106 with Ph+ CML and 13 with Ph+ ALL). The most common toxicities observed were mild to moderate skin rashes, transient and clinically insignificant hyperbilirubinemia, and myelosuppression. Grade 3/4 neutropenia occurred in 9% of patients who received the nilotinib 400mg BID dose and in 22% of patients who received the 600mg BID dose.[21]

Table 1: Nilotinib Cross-intolerance in Patients with Imatinib Intolerance—Non-hematological Adverse Events

Reason for Imatinib Intolerance	Imatinib-intolerant* Grade 3/4 AE or Persistent Grade 2 AE, n	Grade 3/4 AE or Persistent Grade 2 AE on Nilotinib**, n	Discontinued Nilotinib Due to an AE, n
CML-CP			
Non-hematological	57	4	0
Skin rash	26	0	0
Fluid retention	17	0	0
GI	17	3	0
Diarrhea	12	3	0
Liver toxicity	9	1	0
ALT	3	1	0
AST	4	0	0
Myalgia/arthralgia	10	0	0
CML-AP			
Non-hematological	15	0	0
Skin rash	5	0	0
Fluid retention	5	0	0
GI	1	0	0
Diarrhea	1	0	0
Liver toxicity	3	0	0
ALT	1	0	0
AST	0	0	0
Myalgia/arthralgia	2	0	0

**Patients with multiple reasons for imatinib intolerance are counted for each reason category. **Number of imatinib-intolerant patients who experienced any grade 3 or 4 adverse event or grade 2 adverse event that persisted for more than 30 days during nilotinib therapy and was the same corresponding reason for imatinib intolerance. AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CML-AP = acute-phase chronic myeloid leukemia; CML-CP = chronic-phase chronic myeloid leukemia; GI = gastrointestinal. Source: Jabbour et al., 2008.*[26]

Table 2: Nilotinib Cross-intolerance in Patients with Imatinib Intolerance—Hematological Adverse Events

Reason for Imatinib Intolerance	Imatinib-intolerant Grade 3/4 AE or Persistent Grade 2 AE, n (%)	Grade 3/4 AE or Persistent Grade 2 AE on Nilotinib, n (%)	Discontinued Nilotinib Due to an AE, n (%)
CML-CP			
Hematological AEs	30 (32)	19 (20)	7 (7)
Anemia	3 (3)	1 (1)	0
Neutropenia	8 (8)	5 (5)	0
Thrombocytopenia	25 (26)	16 (17)	7 (7)
CML-AP			
Hematological AEs	9 (33)	4 (15)	0
Anemia	1 (4)	1 (4)	0
Neutropenia	3 (11)	2 (7)	0
Thrombocytopenia	6 (22)	2 (7)	0

Approximately one-third of patients were imatinib-intolerant due to hematological events. Fewer hematological adverse events were observed during nilotinib therapy. Cross-intolerance between nilotinib and imatinib with regard to hematological adverse events was infrequent. No patients with CML-AP discontinued nilotinib due to hematological adverse events. AE = adverse event; CML-AP = acute-phase chronic myeloid leukemia; CML-CP = chronic-phase chronic myeloid leukemia. Source: Jabbour et al., 2008.[26]

In the larger phase II trial, nilotinib-treated patients with CP-CML and who were resistant to or intolerant of imatinib were evaluable for safety and tolerability.[16,22] The study showed a similar toxicity profile to that observed compared in the phase I study. The most frequent grade 3 or 4 hematological toxicities reported were neutropenia (30%) and

Table 3: Summary of Phase I/II Data Supporting Nilotinib for Treatment of Chronic Myeloid Leukemia in Patients Who Have Failed to Respond to Imatinib

Study Phase, Design and Reference	No. Patients, Diseases Treated	Treatments and Dose	Efficacy Outcomes	Other Efficacy Outcomes
Phase I[21] Dose-escalation study	CML-CP: 17 CML-AP: 56	Successively assigned to 1 of 9 dose cohorts, 50–1,200mg OD and 400–600mg BID NTB	11 (65%) CHR 26 (46%) CHR 15 (27%) MCyR	38 (74%) hematological remissions. 31 (55%) cytogenetic remissions. 33 CML-BP (2 (6%) CHR 6 (18%) MCyR after nilotinib. 13 patients (39%) achieved some HR, 9 patients (27%) showed a cytogenetic response.
Phase II[27] Open-label, single-arm study	CML-CP: 321 imatinib-refractory (71%) or -intolerant (29%)	400mg BID NTB	184 (57%) MCyR 132 (41%) CCyR	206 patients had no CHR at baseline. 158 (77%) of these achieved CHR with nilotinib. Median time to CHR and MCyR: 1.0 and 2.8 months. 84% maintained MCyR ≥18 months, estimated overall survival rate: 91%.
Phase II[17,28] Open-label, single-arm study	CML-AP: 129 imatinib-resistant (81%) or -intolerant (19%)	400mg BID NTB	69/129 patients (54%), HR 34 (26%) CHR Median times to first HR and MCyR 1 and 2.8 months	31% MCyR. 19% had CCyR. In imatinib-resistant and imatinib-tolerant patients, 29 and 40% had a MCyR. Median times to first HR and MCyR were 1 and 2.8 months. An estimated 57% of patients showed no disease progression after 12 months. Estimated overall survival rate: 81% of 129 patients.
Phase II[18] Open-label, single-arm study	CML-BP: 120 imatinib-resistant/ -intolerant CML-BP and 41 with relapsed/refractory Ph+ ALL	400mg BID NTB (could be escalated to 600mg BID if response was inadequate	42 (35%) confirmed HR 25 (21%) CHR Complete remission: 10 (24%) (Ph+ ALL patients)	Chromosomal abnormalities other than Ph+ found in 64 (53%) BC and 12 (29%) Ph+ ALL patients. Investigations of nilotinib + systemic chemotherapy in Ph+ CML-BC or ALL treatment is warranted.
Phase II[29,30] Open-label, single-arm study	CML-CP: 16 CML-AP: 9 CML-BP: 17	400mg BID NTB	CML-CP: 13 no baseline CHR: 4 (31%) MCyR; (2 complete [15%] and 2 partial [15%]), 5 (38%) CHR	CML-AP: 2 (22%) returned to CP, 6 (67%) were not evaluable, and there was 1 death (11%). CML-BP: 3 (18%) CHR, 1 (6%) returned to CP, 5 (29%) stable disease, 4 (24%) were not evaluable, and 4 (24%) progressive disease.

ALL = acute lymphoblastic leukemia; BID = twice-daily dosing; CHR = complete hematological response; CML-AP = accelerated-phase chronic myeloid leukemia; CML-BP = blast-phase chronic myeloid leukemia; CML-CP = chronic-phase chronic myeloid leukemia; HR = hematological response; MCyR = major cytogenetic response; OD = once-daily dosing; NTB = nilotinib; Ph+ = Philadelphia chromosome-positive.

thrombocytopenia (28%). Of the non-hematological toxicities observed, the most common were rash, nausea, pruritus, headache, and fatigue. Among the biochemical anomalies noted, almost all were not associated with any clinical sequelae. Prolongation of the QT interval (by over 500msec) from baseline was seen in ≤1% of cases. Most of these toxicities occurred within the first three to six months of therapy.[22] Notable AEs related to fluid retention that have been associated with other BCR-ABL inhibitors, such as pleural effusions (17%) and edema (29–72%), were not commonly seen in patients participating in this study.[16] Safety and tolerability data from the other phase II studies were broadly similar to the CP data.

Data from the Expanding Nilotinib Access in Clinical Trials (ENACT) study were presented at the European Hematology Association (EHA) in June 2009,[23] and provided additional safety information in a large population of patients in all-phase CML with prior imatinib resistance/intolerance. Results were available for 1,793 patients who were enrolled in the study between January 2006 and October 2008 (CP, n=1,422; AP, n=181; BP, n=190). The main toxicities reported for nilotinib therapy were similar to those in the phase I/II studies discussed above. Most grade 3/4 toxicities were hematological (thrombocytopenia 24%, neutropenia 17%); non-hematological toxicities were mainly grade 1/2, but grade 3/4 toxicities were headache, rash, and nausea. In a subgroup analysis of this population, nilotinib was shown to be highly active in patients who had failed on imatinib and dasatinib therapy.

Cross-intolerance between imatinib and nilotinib was shown to be negligible, with only 1% recurrence of non-hematological grade 3/4 AEs associated with imatinib intolerance and 18% discontinuation of nilotinib therapy due to similar grade 3/4 hematological AEs seen with imatinib.[25,26] All of these AEs were thrombocytopenia and were only reported in CP patients. It should be noted that cross-intolerance means that an AE seen with imatinib is not seen in the same patient taking nilotinib. Nilotinib also showed marked efficacy in 59 (63%) imatinib-intolerant CML-CP patients and 10 (40%) imatinib-intolerant CML-AP patients with MCyR during nilotinib therapy. These results reflect the more effective targeting of BCR-ABL by nilotinib (see *Figure 1*).[25,26] A summary of intolerance to nilotinib observed in imatinib-intolerant patients in a study including 321 patients with CML-CP and 136 with CML-AP[26] for non-hematological AEs is given in *Table 1*, and for hematological AEs in the same study in *Table 2*.

Efficacy Data

Efficacy data are available from the phase I trial[21] and the three phase II studies[16–18] conducted in patients with CP, AP, and BP CML, as well as a nilotinib third-line phase II trial in patients with both imatinib and dasatinib

failure. A summary of phase I/II efficacy data supporting the use of nilotinib in CML patients who have failed on imatinib is given in *Table 3*.

Phase I Trial

In this study, 11 of 17 patients (65%) with CML-CP produced a CHR in response to treatment with nilotinib.[21] The treatment provided major cytogenetic remission in six patients (35%), and partial cytogenetic remission (classified as minimal, major, or minor) occurred in nine patients (53%). A further group in the study had CML-AP (n=56), of whom 26 (46%) showed a CHR and 15 (27%) showed a major cytogenetic response (MCyR). Among the total population, 38 (74%) had hematological remissions (classified as complete response, marrow response, or return to CP disease) and 31 (55%) demonstrated cytogenetic remissions. Of the study patients, 33 had CML-BP, of whom two (6%) had a CHR and siz (18%) had a MCyR in response to nilotinib. A group of 13 patients (39%) achieved some degree of hematological response and nine patients (27%) showed a cytogenetic response (classified as minimal, major, or minor).

Phase II Trial in Chronic-phase Chronic Myeloid Leukemia

In this study, 321 CML-CP patients were evaluated and were either imatinib-refractory (71%) or -intolerant (29%).[27] Responses were comparable in both the imatinib-resistant and -intolerant groups. Major cytogenetic responses were observed in 57% of patients and CCyR was seen in 41% of cases. Only five patients (4%) who showed a MCyR stopped therapy due to death or disease progression. In total, 206 patients did not have CHR at baseline; of these, 158 of 206 (77%) achieved CHR during nilotinib therapy. The median time to CHR and MCyR was 1.0 and 2.8 months, respectively. The majority of patients (84%) maintained MCyR for at least 18 months and at that point the estimated overall survival rate was 91%. Cross-resistance between nilotinib and imatinib in patients resistant to prior imatinib treatment was minimal.

Phase II Trial in Accelerated-phase Chronic Myeloid Leukemia

In this open-label, single-arm study,[17,28] 129 patients with imatinib-resistant (81%) or -intolerant (19%) AP-CML were enrolled. In this study, nilotinib was started at 400mg BID, and in the case of inadequate response it was increased to 600mg BID. The overall hematological response (HR) rate was 54%, and median times to first HR and MCyR were one and 2.8 months, respectively. Twenty-six percent of patients showed a CHR. MCyR occurred in 31% of patients, and 19% had CCyR. Among the imatinib-resistant and -intolerant patients, 29 and 40% had an MCyR, respectively. After 12 months of treatment, an estimated 57% of patients showed no disease progression, and the overall survival rate was estimated to be 81% of the 129 patients evaluated.

Phase II Trial in Blastic-phase Chronic Myeloid Leukemia

A phase II study obtained efficacy data for 120 patients with imatinib-resistant or -intolerant CML-BP and 41 patients with relapsed/refractory Ph+ ALL.[18] Nilotinib monotherapy showed significant clinical activity and was well tolerated in patients with imatinib-resistant or -intolerant BC and patients with relapsed/refractory Ph+ ALL. A confirmed hematological response was seen in 42 patients (35%), and 25 patients (21%) showed a CHR. Complete remission was reported in 10 Ph+ ALL patients (24%). Chromosomal abnormalities other than Ph+ were found in 64 (53%) of BC patients and 12 (29%) of Ph+ ALL patients. The results indicated that investigation of combinations of nilotinib with systemic chemotherapy in the treatment of Ph+ CML-BC or ALL is warranted.

Phase II Trials of Nilotinib as Third-line Therapy

Data are available for 42 patients with all-phase CML who failed both imatinib and dasatinib.[29,30] Of these, 16 had CP disease, nine had AP disease, and 17 were in blast crisis. Of the CP-CML patients, 13 had no baseline CHR. Four of these 13 patients (31%) had a MCyR (two complete [15%] and two partial [15%]). Five of 13 patients (38%) had a CHR. Of the nine AP patients, two (22%) returned to CP, six (67%) were not evaluable, and there was one death (11%). Of the 17 BP CML patients, three (18%) had a CHR, one returned to CP (6%), five had stable disease (29%), four (24%) were not evaluable, and four (24%) had progressive disease.

Conclusions and Future Directions

Nilotinib is currently being evaluated as a first-line option and has proved to be optimal second-line therapy in CML based on:

- its clinical efficacy;
- its minimal cross-intolerance with imatinib;
- its activity against some relevant mutations (except for T315I);
- its low incidence of grade 3/4 extramedullary AEs, which tend to occur early in therapy; and
- its relatively low incidence of severe myelosuppressive AEs.

Phase III studies are under way in patients with newly diagnosed CML, in which the goal of treatment will be to obtain improved responses over the current standard of care, imatinib. The rapid progression of nilotinib through the regulatory process represents a true triumph of rational anticancer agent design and builds on the expectations raised by the enormous success of imatinib in the clinic. ■

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