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Clinical Pharmacokinetic and Pharmacodynamic Overview of Nilotinib, a Selective Tyrosine Kinase Inhibitor

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Abstract

Nilotinib, an oral inhibitor of the tyrosine kinase activity of Abelson protein, is approved for the treatment of patients with newly diagnosed chronic myeloid leukemia (CML) in chronic phase and patients with CML in chronic phase or accelerated phase resistant or intolerant to prior therapies. This review describes the pharmacokinetic and pharmacodynamic data of nilotinib in patients with CML and in healthy volunteers. Nilotinib is rapidly absorbed, with a peak serum concentration approximately 3 hours after dosing. The area under the plasma drug concentration-time curve over 24 hours and the peak serum concentration of nilotinib were dose proportional from 50-400 mg once daily. The metabolism of nilotinib is primarily via hepatic cytochrome P450 (CYP) 3A4 according to in vitro studies. In the clinical setting, exposure to nilotinib was significantly reduced by the induction of CYP3A4 with rifampicin and significantly increased by the inhibition of CYP3A with ketoconazole. Additionally, nilotinib is a competitive inhibitor of CYP3A4/5, CYP2C8, CYP2C9, CYP2D6, and uridine diphosphate glucuronosyltransferase 1A1. The bioavailability of nilotinib is increased by up to 82% when given with a high-fat meal compared with fasted state. There is a positive correlation between the occurrences of all-grade total bilirubin elevations and the steady-state nilotinib trough concentrations. Fredericia method corrected QT interval change from baseline was observed to have a correlation with nilotinib exposure. No significant relationship between nilotinib exposure and major molecular response at 12 months was seen at therapeutic doses of nilotinib 300–400 mg, probably due to the narrow range of the doses investigated.

Keywords

drug-drug interactions, nilotinib, pharmacokinetics, pharmacodynamics, tyrosine kinase inhibitors

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm characterized by the expansion of hematopoietic cells carrying the fusion oncogene *BCR-ABL*, which encodes the BCR-ABL protein tyrosine kinase. The hallmark of CML is the Philadelphia chromosome (Ph), which is the result of a reciprocal translocation in which the *ABL* proto-oncogene on chromosome 9 is fused with the *BCR* gene on chromosome 22, t(9;22)(q34;q11), and can be detected by cytogenetic analysis.[1–3] CML accounts for 15% of adult leukemias.[4] The incidence of CML varies from 0.6–2.0 cases per 100 000 population, increases with age, and is higher in men than in women.[5] Imatinib was the first BCR-ABL tyrosine kinase inhibitor (TKI) approved for the treatment of CML and initiated the new era of targeted therapy using TKIs. Subsequently, a second generation of ABL TKIs, including nilotinib, dasatinib, ponatinib, and bosutinib, have been developed to decrease the resistance or intolerance to imatinib treatment. Together with imatinib, the development of nilotinib and other second-generation ABL TKIs has revolutionized the treatment of CML, with near-normalization of survival for most patients.[6–11]

Nilotinib (Novartis Pharmaceuticals Corporation, East Hanover, New Jersey) is an orally active inhibitor of the tyrosine kinase activity of the Abelson (ABL) protein that has a higher potency and selectivity for ABL kinase than does imatinib.[12–16] Nilotinib has 20 to 50 times the inhibitory activity of imatinib in imatinib-sensitive CML cell lines and 3 to 7 times the activity in imatinib-resistant cell lines. Nilotinib is effective against most imatinib-resistant cell lines (32 of 33) with mutant ABL kinases.[17,18]

Nilotinib is approved for the treatment of patients with newly diagnosed Ph+ CML in chronic phase (CML-CP), with a recommended dose of 300 mg twice daily, and for the treatment of patients with CML-CP or CML accelerated phase (CML-AP) resistant or

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intolerant to prior therapy, including imatinib, with a recommended dose of 400 mg twice daily.[19]

The pharmacokinetics (PK) and pharmacodynamics (PD) of nilotinib have been evaluated in several single- and multiple-dose clinical studies in both healthy volunteers and in patients with CML. The purpose of this review is to summarize the PK and PD properties of nilotinib, drug-drug and food-drug interactions, and exposure-efficacy and exposure-safety relationships.

Biopharmaceutics Characterization

Nilotinib, a synthetic aminopyridine, has a molecular weight of 529.5 Da and is formulated as a hydrogen chloride monohydrate salt. Nilotinib is a weak base. The pK_a1 is 3.0 and pK_a2 is around 6.2. The solubility of nilotinib decreases with increasing pH. It is slightly soluble (>1 mg/mL) in acidic milieu (at pH 1) and very slightly soluble in water (at pH 2 and 3). It is almost insoluble (<0.1 mg/mL) in a phosphate buffer with pH >4.5.[19] Nilotinib is a moderately permeable compound with a Caco-2 permeability of 2.7×10^{-6} cm/s, and an estimated human permeability of approximately 1.5×10^{-4} cm/s.[20] Therefore, nilotinib is provisionally classified as a Class IV compound (low/moderate aqueous solubility and moderate permeability) according to the Biopharmaceutics Classification System (BCS).[19,20]

Absorption, Distribution, and Elimination

Due to its poor aqueous solubility, no intravenous formulations of nilotinib have been developed for investigation in humans and, thus, the absolute oral bioavailability could not be determined based on clinical data. However, using gut absorption modeling, the absolute oral bioavailability of nilotinib was estimated to be low to moderate in fasted humans.[20]

A study conducted in 4 healthy volunteers demonstrated that the absorption of nilotinib was ≥30% of the dose following a single oral dose of 400-mg nilotinib radiolabeled with ^{14}C to a specific activity of 25 μCi/mg. Peak serum concentrations of total radioactivity and nilotinib were reached approximately 3 hours after dosing.[21] The mean apparent volume of distribution after oral administration was 579 L; serum protein binding was high (99.1%).[22]

The major circulating component was unchanged parent drug, accounting for 87.5% ± 9.2% of the total area under the plasma drug concentration-time curve (AUC). More than 15 minor and trace metabolites were identified; none of them contributed to the in vivo activity of the parent drug.[21,23] The terminal elimination half-life ($t_{1/2}$) of nilotinib was approximately 16 hours. The mean apparent serum clearance after oral administration was 29.1 L/h. A complete recovery (97.9% of the dose) was achieved within 7 days. Excretion was mainly via feces (93.5%; 69.0% unchanged) and partially via renal elimination (4.4%).[21]

Radiolabeled studies in the rat indicated poor brain and central nervous system (CNS) penetration of nilotinib,[24] and clinical data available are very limited. In a clinical study, patients (N = 4) with BCR-ABL+ aggressive leukemia who experienced CNS relapse after allogeneic stem cell transplantation were given nilotinib 400 mg twice daily (3 adult patients) or 150 mg twice daily (1 pediatric patient); median nilotinib/plasma concentration ratio was 0.53% (range 0.23%–1.5%) without apparent impact by dose level. It is worthwhile to note that 3 of the 4 patients achieved long-lasting (>1 year) responses.[25]

Clinical Pharmacokinetics in Patients With CML

In a phase 1 dose-escalation study, 119 patients with CML-CP, CML-AP, or CML-BC or who had Ph+ acute lymphoblastic leukemia resistant or intolerant to imatinib received nilotinib 50–1200 mg daily, nilotinib 400 mg twice daily, or nilotinib 600 mg twice daily. Serum samples for PK analyses were collected on days 1, 8, 15, and 28. In this study, the peak serum concentration (C_{max}) of nilotinib was reached 3 hours after dosing. The steady-state serum concentration was achieved by day 8. The mean serum trough concentration (C_{trough}) at steady state was approximately 530 ng/mL at 400 mg daily, 900 ng/mL at 400 mg twice daily, and 1220 ng/mL at 600 mg twice daily. At steady state, the exposure was found to increase dose proportionally with nilotinib 50–400 mg once daily, but no appreciable difference in nilotinib exposure was found for the 400-mg once-daily or 800-mg once-daily doses. Similarly, no consistent exposure increase was observed for nilotinib 600 mg twice daily compared with nilotinib 400 mg twice daily. Exposure at the steady state was greater with nilotinib 400 mg twice daily (approximately 35%) than with a daily nilotinib dose of 800 mg (Figure 1).[26] The coefficient of variation percentage (CV%) for C_{max} was 34%–72% and for AUC from time 0 to the end of the dosing interval τ ($AUC_{0\text{-}\tau}$) was 32%–64%.This variability was independent of dosing schedule and considered to be moderate.[27]

The PK of nilotinib 300 mg twice daily and 400 mg twice daily were evaluated in the context of a phase 3 study in newly diagnosed patients with CML-CP. Pharmacokinetic samples (n = 4936) from 542 nilotinib-treated patients, including 34 patients who participated in a full PK assessment, were obtained. Pharmacokinetic samples were taken every 3 months for up to 12 months. Nilotinib concentrations were

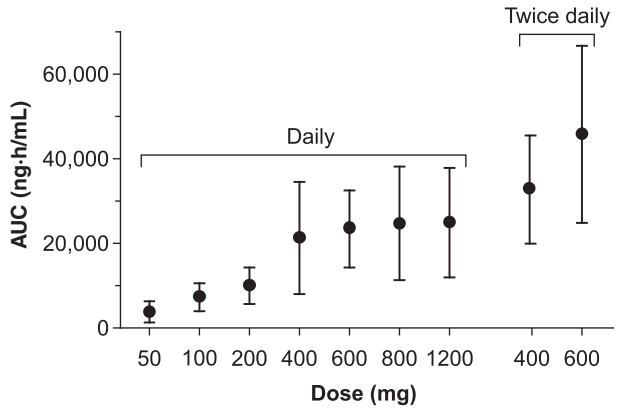

Figure 1. Total steady-state serum levels of nilotinib, according to daily dose. The graph shows the area under the plasma drug concentration-time curve (AUC) during the first 24 hours after the first dose of nilotinib was administered, according to the total amount of drug patients received, either once or twice daily. The points represent the mean levels of the drug and the I bars represent the standard deviations. The total number of patients in whom levels were tested is as follows: 50 mg daily (3 patients), 100 mg daily (4 patients), 200 mg daily (3 patients), 400 mg daily (8 patients), 600 mg daily (4 patients), 800 mg daily (18 patients), and 1200 mg daily (8 patients), as well as 400 mg twice daily (30 patients) and 600 mg twice daily (18 patients). From Kantarjian H, et al. *N Engl J Med*. 2006;354(24):2542–2551. Copyright © 2006 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

stable over 12 months in both arms (C_{trough}: geometric mean 1123 ng/mL [CV%, 64.1] for 300 mg twice daily; geometric mean 1239 ng/mL [CV%, 51.9] for 400 mg twice daily). The geometric mean of steady-state AUC for 400-mg twice-daily dosing was 13.4% higher than for 300-mg twice-daily dosing, indicating dose-proportional increase in exposure (Table 1).[28]

Factors Affecting Nilotinib Pharmacokinetics

Demographic Factors

Nilotinib exposure in female patients was approximately 20% greater than in male patients based on a population PK evaluation in a phase 1/2 study in imatinib-resistant or -intolerant patients.[29] Based on a similar analysis of a phase 3 study in patients with newly diagnosed CML, nilotinib exposure in female patients was approximately 10% higher than in male patients.[28] Those differences in exposure were not clinically meaningful and no dose adjustment was needed.

Other factors, including patient age, body weight, and ethnic origin, did not significantly alter nilotinib PK.[28,30]

Organ function and/or impairment

Nilotinib exposure is increased in subjects with impaired hepatic function. In an open-label single-dose study, AUC of nilotinib (after a single 200-mg dose), was found to have increased by 35% in subjects with mild (Child-Pugh class A, score 5–6) or moderate (Child-Pugh class B, score 7–9) liver impairment and by 19% in subjects with severe impairment compared with healthy controls. The mean $t_{1/2}$ of nilotinib was similar between subjects with mild hepatic impairment and the healthy control group (approximately 15.1 and 16.0 hours, respectively), but was prolonged in the subjects with moderate and severe hepatic impairment (21.6 hours and 32.4 hours, respectively).[31] These effects are considered modest, hence nilotinib dose adjustment in patients with hepatic impairment is not considered necessary.

No significant differences between the serum nilotinib concentrations before and after hemodialysis were observed in 3 patients with imatinib-resistant/-intolerant CML who were on hemodialysis for chronic renal failure, suggesting that nilotinib is neither cleared nor influenced by hemodialysis.[32]

Table 1. Steady-State PK Parameters of Nilotinib Patients With CML-CP

	C_{trough} (ng/mL)	C_{max} (ng/mL)	$AUC_{0-\tau}$ (ng·h/mL)
Nilotinib 300 mg twice daily (n = 16)[a]			
Geometric mean (CV%)	1,123	1,360	11,865
	(64.1)	(58.6)	(56.8)
Nilotinib 400 mg twice daily (n = 15)[a]			
Geometric mean (CV%)	1,239	1,595	13,656
	(51.9)	(47.0)	(51.3)

$AUC_{0-\tau}$, area under the plasma drug concentration-time curve from time 0 to the end of the dosing interval τ, where τ is 12 hours; C_{max}, peak serum concentration; C_{trough}, trough serum concentration; CV, coefficient of variation.
[a]Full PK samples were collected from 17 patients in each arm, 3 of whom (1 in the 300-mg twice-daily arm and 2 in the 400-mg twice-daily arm) did not have sufficient data points for the calculation of full PK parameters and were excluded from this analysis.

Drug-Drug Interactions

In vitro data have shown that nilotinib is metabolized primarily in the liver via oxidation and hydroxylation pathways mediated by the cytochrome P450 (CYP) 3A4 enzyme. In vitro studies[19,33] have also indicated that nilotinib is a competitive inhibitor of CYP3A4/5, CYP2C8, CYP2C9, CYP2D6, and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Potential drug-drug interactions have been investigated in the following clinical studies, and a summary of observed drug-drug interactions with nilotinib is described in Table 2.

The effect of CYP3A4 induction and inhibition on nilotinib PK was further evaluated in 2 studies conducted in healthy volunteers using rifampicin (a strong CYP3A4 inducer) or ketoconazole (a CYP3A inhibitor). Coadministration of rifampicin

Table 2. Summary of Observed Drug-Drug Interactions

Coadministered Drug	Mechanism of Interaction for the Coadministered Drug	Change in Nilotinib AUC	Change in Nilotinib C_{max}
Rifampicin	CYP3A4 inducer	↓ 80%	↓ 64%
Ketoconazole	CYP3A inhibitor	↑ 3.0-fold	↑ 1.8-fold
Grapefruit juice	CYP3A4 inhibitor	↑ 29%	↑ 60%
Esomeprazole	Proton pump inhibitor	↓ 33%	↓ 27%
Famotidine 2 hours after nilotinib administration	H2 receptor antagonist	↔	↔
Aluminum hydroxide and magnesium hydroxide 2 hours before or 2 hours after nilotinib administration	Antacid	↔	↔

	Coadministered Drug		
Nilotinib Dosing Regimen	Name/Role	Change in AUC[a]	Change in C_{max}[a]
800 mg single dose with a high-fat meal	S-warfarin/CYP2C9 substrate	↔	↔
600 mg single dose	Midazolam/CYP3A substrate	↑ 31%	↑ 20%
400 mg twice daily for 12 days	Midazolam/CYP3A substrate	↑ 2.6-fold	↑ 2.0-fold

[a]Mean ratio (with/without coadministered drug, where 1.0-fold represents no change) or percentage change (with/without coadministered drug, where 0% represents no change); symbols ↑, ↓, and ↔ indicate the exposure increase, decrease, and lack of interaction, respectively.

resulted in significant reduction in nilotinib exposure (64% reduction in C_{max} and 80% reduction in AUC) when compared with nilotinib dosing alone. Concomitant administration of ketoconazole resulted in a 3-fold increase in the AUC of nilotinib.[34] Additionally, the exposure of nilotinib when coadministered with grapefruit juice, a CYP3A4 inhibitor,[35] increased C_{max} by 60% and AUC by 29%, without affecting its $t_{1/2}$.[36]

Nilotinib is a weak base, and solubility of nilotinib is reduced with increase in pH. Therefore absorption of nilotinib is dependent on dissolution of nilotinib in an acidic environment in the stomach. The use of esomeprazole, a proton-pump inhibitor, results in increased gastric pH. Coadministration of single oral dose of nilotinib 400 mg once daily with esomeprazole 40 mg once daily in healthy volunteers was found to reduce the C_{max} of nilotinib by 27% and the AUC by 34%. The median time to nilotinib C_{max} increased from 4.0 to 6.0 hours, possibly due to slower dissolution at higher pH and delayed gastric emptying. The $t_{1/2}$, however, did not change. These changes were modest and unlikely to be clinically meaningful.[36,37] The PK of nilotinib are not significantly affected when famotidine is administered 10 hours before or 2 hours after a single 400-mg nilotinib dose or an antacid is administered 2 hours before or 2 hours after the nilotinib dose.[38]

Warfarin is a sensitive CYP2C9 substrate. A 2-period, crossover, randomized study was conducted in which healthy volunteers were given a single oral dose of 25-mg warfarin with either 80- mg nilotinib or matching placebo (all administered 30 minutes after consumption of a high-fat meal). The results suggested that nilotinib at clinically relevant concentrations does not alter the PK or PD of warfarin, as represented by serum warfarin exposure and international normalized ratio/prothrombin time, respectively.[39]

The effect of coadministration of a single oral dose of nilotinib 600 mg and a single 4-mg dose of midazolam (a CYP3A substrate) was evaluated in a healthy volunteer study. The geometric means of the systemic exposure and C_{max} of midazolam increased by approximately 30% and 20%, respectively.[40,41] In another study conducted in patients with CML-CP resistant or intolerant to prior therapy, repeat doses of nilotinib 400 mg twice daily for 12 days increased the systemic exposure and C_{max} of oral midazolam 2 mg by 2.6-fold and 2-fold, respectively.[40]

Effect of food

A study was conducted in 48 healthy volunteers to evaluate the effect of food on nilotinib PK. Following a single dose of nilotinib 400 mg, the systemic exposure of nilotinib increased when given with food. The highest effect was observed when a high-fat meal was taken 30 minutes prior to the nilotinib dose, with the AUC and C_{max} increasing 82% and 112%, respectively, compared with levels under the fasted condition. For a light meal taken 30 minutes prior to the nilotinib dose, the increases in AUC and C_{max} were 33% and 55%, respectively. The impact was lower when a light meal was taken 2 hours prior to the dosing (15% and 29%, respectively). In all cases, the elimination of nilotinib was not affected by the kind of food ingested. Based on this study, food consumption was not allowed within the time window from 2 hours before to 1 hour after nilotinib dosing.[27]

Pharmacogenetics

Nilotinib can increase bilirubin levels by inhibiting UGT1A1. Patients with UGT1A1 genotype (TA)7/(TA)7 were more sensitive to nilotinib-induced hyperbilirubinemia than were patients with the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes. High nilotinib C_{trough} in homozygous carriers of the TA(7) allele was associated

with a higher potential of developing hyperbilirubinemia on nilotinib therapy.[29]

Clinical Pharmacodynamics in Patients With CML

Exposure-efficacy Relationship

In a PK subanalysis of data from the phase 3 ENESTnd study of nilotinib 300 mg twice daily (n = 282) or nilotinib 400 mg twice daily (n = 281) in newly diagnosed patients with CML-CP, there was no significant association between nilotinib exposure and achievement of major molecular response (MMR; BCR-ABL level on the International Scale ≤0.1%) at 12 months.[28]

A phase 2 study of nilotinib 400 mg twice daily in 493 patients intolerant or resistant to imatinib who had CML-CP, CML-AP, or CML in blast phase reported that patients in the lowest nilotinib C_{trough} quartile had significantly longer time to MMR ($P = .012$) and shorter time to progression (defined as time from study entry to discontinuation due to disease progression or death; $P = .009$) compared with patients in the high C_{trough} quartile groups.[29]

Exposure-safety Relationship

There was no apparent correlation between steady-state nilotinib C_{trough} and all-grade abnormalities (ie, newly occurring or worsening abnormalities from baseline) of hemoglobin, absolute neutrophil count, platelet count, alanine transaminase, aspartate aminotransferase, lipase, or amylase levels in the ENESTnd study. However, a positive correlation was observed between steady-state nilotinib C_{trough} and total bilirubin levels. Patients with a lower nilotinib C_{trough} had lower incidences of all-grade bilirubin abnormalities ($P < .001$).[28,29]

QT prolongation was found to be positively correlated with serum nilotinib concentration in the ENESTnd study. In patients with time-matched serum nilotinib concentrations (both C_{trough} and C_{max}) and Fredericia method corrected QT interval (QTcF) changes on day 8 and day 84 after nilotinib treatment, an increase of 1000 ng/mL in the C_{max} correlated with an increase of 4.2 milliseconds in the QTcF; similarly, an increase of 1000 ng/mL in the C_{trough} correlated with an increase of 6.9 milliseconds in the QTcF.[28,29] In a study in healthy volunteers, nilotinib administration caused a concentration-dependent QT prolongation. The maximum mean placebo-adjusted QTcF changes were 10.4 milliseconds (90%CI, 2.85–18.0) after nilotinib 400 mg twice daily dose administration (without food), and 18.0 milliseconds (90%CI, 9.65–25.8) after nilotinib 800 mg single dose administration (with high-fat meal).[19]

Discussion

Nilotinib is an orally bioavailable second-generation TKI with improved specificity against the unmutated and most mutated forms of the product of the *BCR-ABL* oncogene relative to imatinib.[12–16]

Nilotinib demonstrated improved efficacy over imatinib in newly diagnosed patients with CML-CP as well as in imatinib-resistant/-intolerant patients with CML. Pharmacokinetic-efficacy analyses suggest that nilotinib blood concentrations may be associated with a decline in BCR-ABL transcript levels; however, no association was observed between C_{trough} levels and achievement of MMR at 12 months in patients with newly diagnosed CML, probably due to the narrow range of investigated doses (300–400 mg twice daily) in those patients.[28] In a study with imatinib-resistant or -intolerant patients with CML treated with nilotinib 50–1200 mg daily or 400-600 mg twice daily, population PK/PD analysis indicated that patients with a lower C_{trough} had a significantly longer time to complete cytogenetic response and MMR and shorter time to progression.[27] Overall, nilotinib clinical benefit and risk data supported the use of 300 mg twice daily for newly diagnosed patients and 400 mg twice daily for resistant or intolerant patients.

Following oral administration, absorption of nilotinib was rapid, with C_{max} occurring approximately 3 hours after dosing. Nilotinib exposure (C_{max} and AUC) was dose proportional over the dose range of 50–400 mg once daily. At doses >400 mg once daily, there was no relevant increase in absorption with increasing doses of nilotinib. However, for twice-daily dosing, the increase in maximal exposure values from 300 mg twice daily to 400 mg twice daily was subproportional, suggesting the early reach of plateau.[26] Food, especially a high-fat meal, increased the bioavailability (C_{max} and AUC) of nilotinib. However, it is not recommended for patients to consume high-fat meals in order to take a lower dose of nilotinib, as this approach has not been validated. Food may interact with drug absorption via mechanisms such as delay in gastric emptying and/or changes in gastrointestinal pH and bile excretion.[27] The effect of food on nilotinib absorption was investigated using physiologically based PK modeling; the observed low bioavailability was primarily due to a significant precipitation under fasted conditions, leading to incomplete absorption. The positive food effect of nilotinib resulted from a prolonged precipitation time and increased in vivo solubility under fed conditions. The solubility of nilotinib decreased with increase in pH, hence, nilotinib absorption may be compromised if administered along with gastric acid neutralizing agents. These effects can be minimized by using an appropriate dosing time window. In order

to achieve predictable drug serum concentrations, it is recommended that nilotinib be administered 2 hours before or 1 hour after food.[27] The PK of nilotinib do not vary significantly with age, ethnic origin, or any other demographic baseline parameter. However, exposure in male patients was lower than in female patients by approximately 10% in newly diagnosed and 16% in refractory/resistant patients.[28,30] However, because the extent of the difference was relatively small, it is unlikely to be clinically meaningful for nilotinib therapy considering the overall interpatient variability.

The interpatient variability was moderate to high (coefficient of variation [CV] at 50–1200 mg/day doses was C_{max}: 34%-72%; $AUC_{0-\tau}$: 32%–64%) and comparable to other TKIs such as imatinib[42] (49% CV in AUC with doses of 25–1000 mg daily) and dasatinib[43] (56% CV in C_{max} with the 100-mg once-daily dose).[29] Factors that may contribute to this interpatient variability include variability in drug absorption or genetic polymorphisms that affect CYP3A4 activity. Nilotinib is primarily metabolized by CYP3A4. It is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6, and UGT1A1, as well as an inducer of CYP2C8, CYP2C9, and CYP2B6. Thus, for all patients, potential drug-drug interactions must be carefully reviewed, especially for elderly patients with substantial comorbidities.

Even though nilotinib has low CNS penetration, it had demonstrated long-lasting (>1 year) treatment response in CNS relapse of BCR-ABL+ leukemias in a small clinical trial.[25] The concentrations of nilotinib in CSF were within the range seen with imatinib,[44] but appeared to show better activity than imatinib. This could be due to superior affinity of nilotinib to BCR-ABL kinase domain and also because nilotinib has potential to show activity even at sub-nanomolar concentrations.[15] It is also suggested by the investigators that the penetration of free nilotinib may be not as low as observed if corrected with the high plasma protein binding of nilotinib. Another clinical study in patients with advanced Parkinson disease (n = 12) also suggested that nilotinib may have low but measurable CNS penetration. The nilotinib cerebral spinal fluid–to–plasma concentration ratio in those patients was estimated to be 5% and 12% for the 150- and 300-mg daily doses, respectively. As both studies were small and with very different patient populations, caution is needed in interpreting these data.[45]

Nilotinib is associated with a concentration-dependent QT prolongation. In patients who have or who are at a risk of developing prolonged QT, it is recommended that nilotinib dosage be reduced or temporarily withheld. Serum potassium and magnesium levels must be monitored in all patients. Additionally, drugs that prolong the QT interval must be avoided.[19] A positive correlation was seen between nilotinib exposure and bilirubin abnormalities. Such an effect is thought to be due to a possible inhibition of UGT1A1-mediated bilirubin glucuronidation by nilotinib. The observed hyperbilirubinemia was reversible and clinically manageable.[29]

Conclusion

Nilotinib, a second generation BCR-ABL inhibitor, is approved for the treatment of patients with newly diagnosed Ph+ CML in chronic phase (CML-CP) and for the treatment of patients with CML-CP or CML-AP resistant or intolerant to prior therapy, including imatinib. Nilotinib has a well-established efficacy and safety profile. An understanding of the PK and PD profiles of nilotinib allows clinicians to tailor treatment to each patient.

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Conflicting of Interest/Disclosures

All authors are employees of Novartis Pharmaceuticals Corporation.

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