Chronic Myeloid Leukemia Therapy:  
Focus on Second-Generation Tyrosine Kinase Inhibitors

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**Background:** Chronic myeloid leukemia, the most common adult leukemia, is characterized by the Ph+ chromosome produced by the fusion of the BCR gene from chromosome 22 and the ABL gene from chromosome 9. Inhibition of the deleterious effects of this potent oncogene by the tyrosine kinase inhibitor (TKI) imatinib has revolutionized care of this disease, but intolerance and resistance does occur.

**Methods:** The authors have reviewed both the preclinical and the clinical data concerning second-generation TKIs intended to circumvent or ameliorate issues with imatinib intolerance or resistance.

**Results:** Two second-generation TKIs, dasatinib and nilotinib, are currently approved by the US Food and Drug Administration. Both have shown significant clinical activity in patients with chronic myeloid leukemia (CML) and Ph+ acute lymphoblastic leukemia (ALL) who are resistant or intolerant to imatinib or other therapies.

**Conclusions:** The TKIs are a superb example of an effective targeted approach for a malignant disease. As more clinical data become available and additional novel agents are developed, specific therapy and dosing strategies for individuals with CML will depend on the status of their disease, the anticipated side effects, and concurrent drug therapy.

**Introduction**

Chronic myeloid leukemia (CML), arguably one of the most well-understood neoplasms, accounts for approximately 20% of all leukemias diagnosed in adults. CML is a disease of phases that, if left untreated, progresses from the initial chronic phase (CP-CML) to the accelerated phase (AP-CML) followed by the terminal blastic phase (BP-CML). It is characterized by a chromosomal translocation known as the Philadelphia chromosome (Ph+). This translocation fuses the ABL gene from chromosome 9 to the BCR gene on chromosome 22, resulting in an oncogene that plays a central role in the initial development of CML. The Ph+ is present in greater than 90% of adults with CML and in 20% to 30% of adults with acute lymphoblastic leukemia (ALL).
BCR-ABL is now recognized as a primary molecular target in Ph+ leukemias, and the use of selected BCR-ABL tyrosine kinase inhibitors (TKIs) have changed the prognosis of patients with these malignancies.1,2,3

The management of CML has changed dramatically over the last decade with the introduction of imatinib mesylate (Gleevec® , Novartis Pharmaceuticals Corp, East Hanover, New Jersey). Imatinib is a specific inhibitor for BCR-ABL as well as several other tyrosine kinases, including c-KIT and platelet-derived growth factor receptor (PDGFR), and has been shown to induce complete hematologic and cytogenetic remissions in the majority of patients with CP-CML.4-6 However, approximately 15% of patients with CP-CML do not achieve complete cytogenetic responses (CCyRs) with imatinib, and another 1% to 2% are considered to be imatinib-intolerant.7,8 Imatinib intolerance is defined as the inability to tolerate greater than 400 mg of imatinib per day or discontinuation because of toxicity.

In addition, patients with AP-CML, BP-CML, and Ph+ ALL often fail to achieve high rates of CCyR, frequently the result of development of imatinib resistance.9,10 Resistance to imatinib is defined as a failure to achieve complete hematologic response (CHR) at 3 months, a CCyR at 6 months, or a major cytogenetic response (MCyR) at 12 months.11 Some patients are intrinsically resistant to imatinib, while others may acquire resistance during treatment.12 The 2-year incidence of resistance is estimated to be 80% in BP-CML, 40% to 50% in AP-CML, and 8% to 10% in CP-CML.13 Various mechanisms contribute to imatinib resistance, including increased efflux of the drug from the cancer cell mediated by membrane transporters such as multidrug-resistance gene 1 protein (MDR-1), increased expression of BCR-ABL kinase through gene amplification, increased imatinib binding by plasma proteins, and clonal evolution.14,15 Imatinib resistance in most cases may be attributable to point mutations within the ABL kinase domain, which occur in 22% to 55% of cases.12 These point mutations result in destabilization of the inactive conformation of the enzyme that is required for binding of imatinib.1,6,16,17 In some cases of imatinib-resistant cell lines, Lyn and Hck are overexpressed, which suggests the Src family kinases may be involved in BCR-ABL independence and progression to imatinib resistance.12

In an attempt to override resistance, several second-generation ATP competitive Abl kinase inhibitors have been developed and are currently commercially available in the United States. These include dasatinib (Sprycel®, Bristol-Myers Squibb Co, Princeton, New Jersey) and nilotinib (Tasigna®, Novartis Pharmaceuticals Corp). In addition, there are investigational compounds with activity in imatinib-resistant CML, including bosutinib and INNO-406. The pharmacology, dosing, clinical efficacy, and safety of these second-generation TKIs are reviewed here.

**Dasatinib**

Dasatinib is an orally available multitargeted kinase inhibitor of BCR-ABL, Src family, c-Kit, EPHA2, and PDGFRβ.18-21 Dasatinib is structurally unrelated to imatinib and is approximately 325-fold more potent against BCR-ABL inhibition.22 Unlike imatinib, dasatinib can bind to both the active and the inactive conformations of the ABL kinase domain. Dasatinib has been shown to inhibit 18 of the 19 BCR-ABL mutations in vitro that are resistant to imatinib.20,23 Dasatinib has activity against many imatinib-resistant kinase domain mutations of BCR-ABL, including those within the phosphate-binding loop (P-loop) as well as those in the activation loop and other sites in the COOH-terminal loop.22,24,25 Dasatinib may overcome resistance mechanisms of imatinib, including alternate signaling pathways involving the Src family kinases and MDR-1 gene overexpression.26,27 Most of the clinically relevant mutations are inhibited by dasatinib with the exception of the T315I mutation, which confers resistance to imatinib, dasatinib, and nilotinib.22,24

Dasatinib is currently approved by the US Food and Drug Administration (FDA) for the treatment of adults with CP-CML, AP-CML, or BP-CML with resistance or intolerance to prior therapy, including imatinib. Dasatinib is also indicated in Ph+ ALL that is resistant or intolerant to prior therapy. The FDA-approved dosing schedule of dasatinib is dependent on disease and phase. The recommended starting dose is 100 mg by mouth once daily for treatment of CP-CML and 70 mg by mouth twice daily for treatment of AP-CML, BP-CML, and Ph+ ALL. Additionally, dosing modifications are warranted based on response, toxicity, and concurrent therapy (Table 1).

Dasatinib is extensively metabolized in the liver, primarily by the cytochrome P450 (CYP450) isoenzyme CYP3A4. As a result, there is potential for various drug interactions, and concomitant administration with CYP3A4 inhibitors or inducers should be avoided (Table 2). If coadministration cannot be avoided, a dose adjustment may be warranted, and strict monitoring for toxicity and efficacy is required. In addition, the solubility of dasatinib is pH-dependent, and long-term suppression of gastric acid secretion reduces dasatinib exposure.

**Clinical Trial Data for Dasatinib**

The approved indications for dasatinib are the result of a series of international phase II studies, known as SRC/ABL Tyrosine Kinase Inhibition Activity Research Trials (START), that demonstrated the clinical efficacy in achieving hematologic, cytogenetic, and molecular responses in patients with CML following imatinib failure.

The START-C trial, a phase II, open-label multicenter study, evaluated dasatinib in patients with CP-CML who were resistant or intolerant to imatinib.28-30 Dasatinib was administered at a dose of 70 mg orally twice
daily, with a permissible dosage increase to 90 mg twice daily for inadequate responses. Dosage reductions to 50 mg or 40 mg twice daily were permitted for toxicity. Dose interruptions were required in 87% of patients and reductions in nearly 75% of patients, with the median dose being 101 mg/day. The primary endpoint was the rate of MCyR. After a median follow-up of 24 months, data are available for 387 patients (288 were imatinib-resistant, 99 were imatinib-intolerant). CHR was attained in 91% of patients, with 62% achieving an MCyR (55% imatinib-resistant and 63% for those with baseline BCR-ABL mutations). Responses were seen across all mutations with the exception of T315I. These cytogenetic responses were complete in 53% of patients. The MCyRs were durable, with only 12% losing response at 24 months. At 24-month follow-up, the progression-free and overall survival rates were 66% and 82%, respectively. Dose interruptions were required in 87% of patients with resistance or intolerance to prior therapy including imatinib. Dasatinib was administered at a dose of 70 mg orally twice daily, with a dosage increase to 100 mg orally twice daily for inadequate responses. Dosage reductions to 40 mg or 50 mg twice daily were permissible for persistent toxicity. The primary endpoint of the study was major hematologic response (MHR). With a median follow-up of 14.1 months, CHRs were attained in 45% of patients, while MCyRs and CCyRs were seen in 39% and 32%, respectively. The 12-month progression-free and overall survival rates were 66% and 82%, respectively. Dose interruptions were required

### Table 1. — Dasatinib: Dosing, Precautions, and Monitoring

<table>
<thead>
<tr>
<th>Indications</th>
<th>Dosing</th>
<th>Dosing Modifications</th>
<th>Special Instructions/Precautions</th>
<th>Monitoring</th>
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<tbody>
<tr>
<td>Treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase CML with resistance or intolerance to prior therapy including imatinib</td>
<td>Chronic phase CML: 100 mg p.o. daily</td>
<td>• For hematologic toxicities: Chronic phase CML (starting dose 100 mg p.o. daily) If ANC &lt; 500 or platelets &lt; 100K 1. Stop therapy until ANC &gt; 1000 and platelets &gt; 50K 2. Resume at 100 mg p.o. daily if recovery occurs ≤ 7 days 3. If platelets &lt; 25K or recurrence of ANC &lt; 500 for &gt; 7 days, repeat step 1 and resume at a reduced dose of 80 mg p.o. daily (2nd episode) or discontinue (3rd episode)</td>
<td>• May be taken with or without food. Avoid grapefruits or grapefruit juice 1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If unrelated to disease, interrupt therapy until ANC &gt; 1000 and platelets &gt; 20K and resume at original starting dose 3. If recurrence of cytopenia, repeat step 1 and resume at a reduced dose of 50 mg p.o. b.i.d. (2nd episode) or 40 mg p.o. b.i.d. (3rd episode) 4. If cytopenia is related to leukemia, consider dose escalation to 100 mg p.o. b.i.d.</td>
<td>• Baseline and weekly CBC for the first 2 months of treatment and monthly thereafter or as clinically indicated 1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If unrelated to disease, interrupt therapy until ANC &gt; 1000 and platelets &gt; 20K and resume at original starting dose 3. If recurrence of cytopenia, repeat step 1 and resume at a reduced dose of 50 mg p.o. b.i.d. (2nd episode) or 40 mg p.o. b.i.d. (3rd episode) 4. If cytopenia is related to leukemia, consider dose escalation to 100 mg p.o. b.i.d.</td>
</tr>
<tr>
<td>Treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy</td>
<td>Accelerated, blast, or Ph+ ALL (starting dose 70 mg p.o. b.i.d.) If ANC &lt; 500 or platelets &lt; 10K 1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If unrelated to disease, interrupt therapy until ANC &gt; 1000 and platelets &gt; 20K and resume at original starting dose 3. If recurrence of cytopenia, repeat step 1 and resume at a reduced dose of 50 mg p.o. b.i.d. (2nd episode) or 40 mg p.o. b.i.d. (3rd episode) 4. If cytopenia is related to leukemia, consider dose escalation to 100 mg p.o. b.i.d.</td>
<td>Concomitant drugs that are strong CYP3A4 inhibitors/inducers (see drug interactions) 1. Inhibitors: consider dose decrease to 20 mg p.o. daily 2. Inducers: consider dose increase</td>
<td>1. Stop therapy until ANC &gt; 1000 and platelets &gt; 50K 2. Resume at 100 mg p.o. daily if recovery occurs ≤ 7 days 3. If platelets &lt; 25K or recurrence of ANC &lt; 500 for &gt; 7 days, repeat step 1 and resume at a reduced dose of 80 mg p.o. daily (2nd episode) or discontinue (3rd episode)</td>
<td>1. LVEF evaluation, baseline and periodically in patients with cardiac risk factors 2. Concurrent drug therapies for potential drug/drug interactions and/or decreased exposure</td>
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in 85% of patients and dose reductions in 65%, with the average daily dose being 126 mg.

The treatment of patients with myeloid BP-CML (n = 109) and lymphoid BP-CML (n = 48) was evaluated in the START-B and START-L trials, respectively.33,34 Dasatinib was administered at a dose of 70 mg orally twice daily, with a dosage increase to 100 mg orally twice daily for inadequate responses. Dosage reductions to 40 mg or 50 mg twice daily were permissible for persistent toxicity. Dose interruptions and dose reductions were required for 59% and 52% of patients, respectively, while doses were escalated in 44% of patients. After a minimum follow-up of 12 months, MHRs were induced in 34% of patients with myeloid blast-CML (MB-CML) and 35% of lymphoid blast-CML (LB-CML). MCyRs were attained in 33% of patients with MB-CML and in 52% of LB-CML patients, while CCyRs were achieved in 26% and 46% of patients, respectively. The median progression-free survival was 6.7 months (MB-CML) and 3 months (LB-CML), and the median overall survival was 11.8 months and 5.3 months, respectively.

The START-L trial also included 46 patients with Ph+ ALL who were resistant or intolerant to imatinib.35,36 In this population, the dose of dasatinib was reduced in 30% of patients and therapy was interrupted in 43%. The average daily dose was 143 mg. The MHR rate was 41%, with CHR seen in 33% of patients. MCyRs were achieved in 57% of patients with a median duration of nearly 7 months. The median overall survival was 8 months, and 22% of patients remained alive and progression-free after 1 year of treatment.

The dosing strategy of dasatinib has also been of great interest. Several studies suggested that comparable responses could be obtained with once-daily administration and lower median daily doses than initially assigned.30,37,38 These observations led to two large phase III trials to further investigate the optimal dosing schedule of dasatinib.

In the first open-label trial, 670 patients with imatinib-resistant or intolerant CP-CML were randomly assigned equally to four dosing arms: 100-mg once daily, 50 mg twice daily, 140 mg once daily, or 70 mg twice daily.39 With a minimum follow-up of 6 months, all measured efficacy endpoints were comparable among the four groups, with the 100-mg daily dosing arm prevailing as the most tolerable. When compared to the FDA-approved 70-mg twice-daily dosing regimen, there was significantly less pleural effusions (all grades) and grade 3/4 thrombocytopenia in the 100-mg daily dosing arm. In addition, fewer patients required dosage reduction and interruption or discontinuation of therapy. This trial supports the idea that intermittent target

<table>
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<tr>
<th>Agent</th>
<th>Effect</th>
<th>Proposed Mechanism</th>
<th>Clinical Management</th>
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<tbody>
<tr>
<td>Ketoconazole</td>
<td>Dasatinib C_{max} and AUC were increased 4- and 5-fold, respectively</td>
<td>CYP3A4 inhibition</td>
<td>- Concurrent utilization should be avoided</td>
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<td></td>
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<td>- Although formal drug interactions have not been conducted, other CYP3A4 inhibitors (voriconazole, posaconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, neflunavir, ritonavir, saquinavir, telithromycin, etc) should be avoided</td>
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<td>- If concurrent therapy must be administered, a dose decrease to 20 mg/day should be considered with strict monitoring for potential toxicity and/or lack of efficacy</td>
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<td>- Concurrent utilization should be avoided</td>
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<td></td>
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<td>- Although formal drug interactions have not been conducted, other CYP3A4 inducers (dexamethasone, phenytoin, carbamazepine, rifabutin, phenobarbital, etc) should be avoided if possible</td>
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<tr>
<td>Rifampin</td>
<td>Dasatinib C_{max} and AUC decreased by 81% and 82%, respectively</td>
<td>CYP3A4 induction</td>
<td>- Concurrent utilization should be avoided</td>
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<td></td>
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<td>- Alternative agents with less enzyme induction potential should be used or a dose increase should be considered with strict monitoring for potential toxicity</td>
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<td>St John's Wort</td>
<td>May result in unpredictable decreases in dasatinib concentration</td>
<td>CYP3A4 induction</td>
<td>- Concomitant use of H2 antagonists or proton pump inhibitors is not recommended</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Increases simvastatin C_{max} and AUC by 37% and 20%, respectively</td>
<td>CYP3A4 substrate</td>
<td>- Agents with narrow therapeutic windows that are CYP3A4 substrates (sirolimus, tacrolimus, cyclosporine, etc) should be administered with caution</td>
</tr>
<tr>
<td>Famotidine</td>
<td>Dasatinib C_{max} and AUC decreased by 61% and 63%, respectively</td>
<td>Solubility of dasatinib is pH dependent</td>
<td>- Concomitant use of H2 antagonists or proton pump inhibitors is not recommended</td>
</tr>
<tr>
<td>Aluminum-Magnesium Hydroxide</td>
<td>Simultaneous administration resulted in a 55% and 58% reduction of dasatinib AUC and C_{max}, respectively</td>
<td>Solubility of dasatinib is pH dependent</td>
<td>- Antacids should be considered in place of above but should not be administered simultaneously</td>
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</table>

- If antacids are needed, the dose should be separated by at least 2 hours before or after the dose of dasatinib as there was no change in AUC when given in this manner
inhibition with TKIs may preserve efficacy while reducing adverse events that are thought to be associated with continuous inhibition of unintended targets.

In another large, randomized trial, dasatinib dose optimization was investigated in 611 patients with advanced phases of CML or Ph+ ALL. Patients were randomized to receive 140 mg once daily or 70 mg twice daily. The two arms were comparable with respect to hematologic and cytogenetic response, with a trend toward improved tolerability in the 140-mg daily dosing group. Further follow-up is ongoing to assess the long-term effects of these two dosing schemas.

Clinical trials indicated that dasatinib is generally well tolerated, and most drug-related adverse events are resolved after dosage-reduction or interruption. Common nonhematologic toxicities included diarrhea (49%), headache (40%), hemorrhage (40%), musculoskeletal pain (39%), pyrexia (39%), and anemia (39%), and skin rash (35%). Infection, nausea, and dyspnea were also reported in 34%, 34%, and 32% of patients, respectively. Severe fluid retention was a common complication with dasatinib, occurring in 50% of patients. Fluid retention commonly presented as superficial edema (36%), pleural effusions (22%), or pericardial effusions (4%). Grade 3/4 pleural effusion was reported in 5% of patients. Serious adverse events reported in clinical trials included pyrexia (8%), febrile neutropenia (7%), gastrointestinal bleeding (6%), pneumonia (6%), thrombocytopenia (5%), dyspnea (4%), anemia (3%), cardiac failure (3%), and diarrhea (2%). Dasatinib therapy may also result in severe myelosuppression. The most frequently reported grade 3 or 4 hematologic adverse events were neutropenia (49% to 83%), thrombocytopenia (48% to 83%), and anemia (18% to 70%). Grade 3 or 4 neutropenia, thrombocytopenia, and anemia were reported in patients with all phases of

### Table 3. — Nilotinib: Dosing, Precautions, and Monitoring

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<thead>
<tr>
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<th>Dosing</th>
<th>Dosing Modifications</th>
<th>Special Instructions/Precautions</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of chronic and accelerated phase Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib</td>
<td>400 mg p.o. b.i.d.* (approximately 12 hours apart)</td>
<td>• For hematologic toxicities: If ANC &lt; 1000 and/or platelets &lt; 50K: 1. Stop therapy and monitor blood counts 2. Resume within 2 weeks at prior dose if ANC &gt; 1000 and platelets &gt; 50K 3. If blood counts remain low for &gt; 2 weeks, reduce dose to 400 mg p.o. daily</td>
<td>• Should be taken on an empty stomach; no food should be consumed for at least 2 hours before and at least 1 hour after the dose is taken (the systemic exposure [AUC] was increased &gt; 80% when administered with a high-fat meal)</td>
<td>• Baseline and weekly CBC for the first 2 months of treatment and monthly thereafter or as clinically indicated</td>
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<td>* No relevant increase in exposure when the dose was increased to 600 mg p.o. b.i.d. Available capsule strength: 200 mg (should be swallowed whole with water)</td>
<td>• For ECGs with QTc &gt; 480 msec: 1. Hold therapy and correct serum potassium and magnesium if not within normal range 2. Resume within 2 weeks at prior dose if QTcF returns to &lt; 450 msec and to within 20 msec of baseline 3. If QTcF is between 450 msec and 480 msec after 2 weeks, reduce the dose to 400 mg p.o. daily/ 4. If QTcF returns to &gt; 480 msec following dose reduction to once daily, therapy should be discontinued. 5. An ECG should be repeated approximately 7 days after any dose adjustment</td>
<td>• Prolongs QT interval: correct hypokalemia or hypomagnesemia prior to initiation</td>
<td>• LVEF evaluation, baseline and periodically in patients with cardiac risk factors</td>
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<td>• For nonhematologic lab abnormalities: If serum lipase or amylase, bilirubin, or hepatic transaminases ≥ grade 3: 1. Hold therapy and monitor appropriate labs 2. Resume treatment at 400 mg p.o. daily when lab values return to ≤ grade 1</td>
<td>• Use caution in patients with hepatic impairment and in patients with prior history of pancreatitis</td>
<td>• ECG at baseline, 7 days after initiation, and following any dose adjustments</td>
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<td></td>
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<td></td>
<td>• Elimination is primarily via the feces with minimal renal clearance</td>
<td>• Concurrent drug therapies for potential drug/drug interactions</td>
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<td></td>
<td></td>
<td></td>
<td>• Capsules contain lactose so are not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency, or glucose-galactose malabsorption</td>
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</table>
CML but occurred more frequently in patients with AP-CML, MB-CML, LB-CML, or Ph+ ALL. Grade 3 or 4 elevations in liver transaminases and bilirubin occurred in 1% to 11% and 1% to 8% of patients following dasatinib therapy, respectively. These events were less common in patients with CP-CML compared with those with BP-CML or Ph+ ALL, were typically transient, and resolved following dosage reduction or interruption.18

Nilotinib

Nilotinib (Tasigna™, AMN-107, Novartis Pharmaceuticals Corp) is another orally available second-generation kinase inhibitor of BCR-ABL, KIT, PDGFR, and ephrin receptor kinase. Nilotinib is an analog of imatinib, and it disrupts the ATP-phosphate-binding pocket of the ABL tyrosine kinase and inhibits enzymatic catalytic activity by binding to the inactive conformation of the enzyme, blocking the substrate binding site. In imatinib-sensitive cell lines, nilotinib is 43 to 60 times more potent than imatinib, and in imatinib-resistant cell lines, it is at least 20-fold more potent than imatinib. Similar to dasatinib, nilotinib has no activity against the T315I mutation but was able to overcome resistance in 32 of 33 imatinib-resistant BCR-ABL mutations.41-45

Nilotinib is currently approved by the FDA for the treatment of CP-CML or AP-CML that is resistant or intolerant to imatinib. The approved dosing schedule is 400 mg orally twice daily on an empty stomach at approximately 12-hour intervals. Dosing modifications may be necessary based on toxicity and concurrent drug therapy (Table 3).41

The main metabolic pathways are oxidation and hydroxylation. Nilotinib also undergoes metabolism via the CYP3A4 isoenzyme. As a result, there is potential for multiple drug interactions, and concomitant administration with CYP3A4 strong inhibitors or inducers should be avoided (Table 4). If coadministration cannot be avoided, a dose adjustment may be warranted, and strict monitoring for toxicity and efficacy is required (Table 3). In addition, nilotinib is a competitive inhibitor of CYP3A4, 2C8, 2C9, 2D6, and UGT1A1 in vitro, potentially increasing the concentrations of drugs eliminated by these enzymes. In vitro studies also suggest that nilotinib may induce CYP2B6, 2C8, and 2C9, thereby decreasing the concentration of drugs eliminated via these pathways.41

### Clinical Trial Data for Nilotinib

The appropriate dosing of nilotinib was first examined in a phase I dose escalation study in patients with CML.

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<tbody>
<tr>
<td>Ketoconazole</td>
<td>Nilotinib AUC was increased 3-fold</td>
<td>CYP3A4 inhibition</td>
<td>• Concurrent utilization should be avoided</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Nilotinib systemic exposure (AUC) was decreased by 80%</td>
<td>CYP3A4 induction</td>
<td>• Although formal drug interactions have not been conducted, other potential CYP3A4 inhibitors should be avoided</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Increased midazolam exposure by 30%</td>
<td>CYP3A4 substrate</td>
<td>• If concurrent therapy must be administered, a dose decrease to 400 mg/day may be considered although there is no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors; strict monitoring for potential toxicity and/or lack of efficacy and QTc prolongation is required</td>
</tr>
<tr>
<td>Other Potential Interactions</td>
<td>Increasing the concentrations of concurrent drugs</td>
<td>CYP3A4, CYP2C8, CYP2C9, CYP2D6, and UGT1A1 competitive inhibition</td>
<td>• Agents with narrow therapeutic windows that are CYP3A4 substrates (sirolimus, tacrolimus, cyclosporine, etc) should be administered with caution</td>
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<td>Increased concentrations with drugs that are substrates for P-glycoprotein (Pgp)</td>
<td>Substrate of the efflux transporter Pgp</td>
<td>• No formal drug interaction studies have been conducted but caution should be taken with agents that are metabolized by the noted isoenzymes</td>
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<td>Decreased concentration of concurrent drugs</td>
<td>CYP2B6, CYP2C8, and CYP2C9 induction</td>
<td>• Concurrent administration with warfarin should be avoided</td>
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<td>• No formal drug interaction studies have been conducted but caution should be taken with agents that are substrates</td>
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Table 4. — Nilotinib: Drug Interactions and Management
or Ph+ ALL who were resistant or intolerant to imatinib.46 Patients were assigned to one of nine dose cohorts, ranging from 50 to 1,200 mg once daily and from 400 to 600 mg twice daily. The area under the curve (AUC) of nilotinib plateaus with single doses greater than 400 mg; however, higher AUC levels were achieved with equivalent doses administered on a twice-daily schedule. The maximum tolerated dose was determined to be 600 mg twice daily.

A phase II, open-label study was conducted to evaluate the rate of MCyR with nilotinib in CP-CML resistant or intolerant to imatinib.57,48 Nilotinib was administered at a dose of 400 mg twice daily with dose escalation to 600 mg twice daily for inadequate response. Of the 321 patients enrolled (71% imatinib-resistant and 29% imatinib-intolerant), 206 (64%) had not achieved a CHR with initial therapy. Of these 206 patients, 158 (77%) achieved a CHR with nilotinib therapy, and MCyRs were observed in 57% of patients (55% imatinib-resistant, and 63% imatinib-intolerant). The median time to CHR and MCyR was 1 and 2.8 months, respectively. At 18 months, an MCyR was maintained in the majority of patients (84%), and the overall survival rate was estimated to be 91%.47,48

An additional phase II, open-label study was conducted to evaluate the efficacy and tolerability of nilotinib in 136 patients with AP-CML resistant or intolerant to imatinib.49 Nilotinib was given at 400 mg orally twice daily with escalation permitted to 600 mg twice daily for inadequate responses in the absence of safety concerns. The median dose was 781 mg/day, and treatment duration was 210 days. After a follow-up of 12 months of therapy, 69 of 129 patients (54%) achieved HRs, of which 26% were complete. An MCyR was observed in 40 of 129 patients (31%), with 19% achieving a CCyR. The median time to HR and first MCyR was 1 and 2.8 months, respectively. After 12 months of follow-up, estimated progression-free and overall survival rates were 57% and 81%, respectively.49

A third phase II, open-label study evaluated the efficacy and tolerability of nilotinib in 120 patients with imatinib-resistant or intolerant CML in blast crisis (27 lymphoid, 87 myeloid, and 6 unknown) or relapsed/refractory Ph+ ALL (38 relapsed, 3 refractory).50 Best HR was evaluated for the BP-CML patients, while Ph+ ALL patients were evaluated for complete responses. Nilotinib was administered at 400 mg twice daily, with escalation to 600 mg twice daily for inadequate responses. After a minimum of 6 months of follow-up, CHR was observed in 25 patients (21%) with BP-CML, marrow responses occurred in 7 patients (6%), and 10 patients (8%) returned to CP-CML. Of the 41 patients with Ph+ ALL, 10 patients (24%) achieved a complete response.50

Twelve-month follow-up data are available evaluating efficacy of nilotinib in patients with BP-CML who are either resistant or intolerant to imatinib.51 This phase II, open-label study evaluated 136 patients in BP-CML (105 myeloid blast crisis, 31 lymphoid blast crisis). The initial dose of nilotinib was 400 mg orally twice daily, with permissible escalation to 600 mg twice daily for failure to return to CP, loss of HR or CCyR, or progressive disease. An HR occurred in 29 patients (21%), 15 (11%) of which were complete. An MCyR was observed in 40% of patients and a CCyR in 29%. The estimated overall survival rate at 12 months was 42%. Over 50% of patients have discontinued therapy due to progressive disease, while nilotinib therapy is ongoing in 13 patients (10%).51

Lastly, a phase II, open-label study evaluated nilotinib in CP-, AP-, or BP-CML resistant or intolerant to imatinib and dasatinib.52 Data were reported on 78 patients (34 patients in CP, 18 in AP and 26 in BP). The median duration of dasatinib therapy was 188 days, with progressive disease and adverse events accounting for the primary reasons for discontinuation. Nilotinib at 600 mg twice daily was initiated in patients who experienced disease progression or inadequate hematologic and/or cytogenetic responses at 28 days. The median duration of nilotinib exposure was 112 days. CHR was observed in 18 of 23 CP-CML patients (78%) who were not in CHR at baseline. MCyRs and CCyRs were achieved in 8 of 29 patients (28%) and 3 of 29 patients (10%), respectively. Of the 16 evaluable patients with AP-CML, 6 (38%) demonstrated leukemia-confirmed HRs and 2 (13%) achieved MCyRs while on nilotinib therapy. Of 25 evaluable patients with BP-CML, HRs were achieved in 2 (8%) and MCyRs in 3 (12%).52

Clinical trials indicated that nilotinib is generally well tolerated, and most drug-related adverse events resolved after dosage-reduction or interruption. The most commonly reported adverse reactions (≥10% of CP-CML patients) were rash (33%), pruritus (29%), nausea (31%), fatigue (28%), headache (31%), constipation (21%), diarrhea (22%), and vomiting (21%). The most frequently reported hematologic events (grade 3/4) included neutropenia (31% to 67%), anemia (9% to 42%), and thrombocytopenia (33% to 62%), which occurred more frequently in patients with more advanced disease. The most commonly reported grade 3/4 nonhematologic laboratory abnormalities included elevated bilirubin (9% to 15%), hypophosphatemia (10% to 22%), elevated lipase (9% to 18%), and hyperglycemia (5% to 12%).41,46 No occurrences of pleural/pericardial effusions have been reported with the use of nilotinib.41 Nilotinib labeling contains a black box warning regarding the risk of QT prolongation and sudden cardiac death.51 Five sudden deaths were reported in patients receiving nilotinib therapy; ventricular repolarization abnormalities may have caused the occurrence of these deaths as it is known to prolong QT interval. The
manitotinib should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Electrolyte abnormalities should be corrected prior to initiation of nilotinib. Concomitant use of drugs that prolong the QT interval and CYP3A4 inhibitors should be avoided if possible.

Other Dual Kinase Inhibitors

Two other agents, bosutinib (SKI-606) and INNO-406, are currently under investigation for the management of patients who are resistant or intolerant to imatinib or other TKIs.

Bosutinib is an orally available potent dual Src/Abl kinase inhibitor. It has been shown to be up to 200-fold more potent than imatinib as an inhibitor of Bcr-Abl phosphorylation, but it has minimal inhibitory activity against PDGFR or c-KIT. In addition, bosutinib has demonstrated activity against most imatinib-resistant mutants of Bcr-Abl, with the exception being T315I. In phase II trials, bosutinib has demonstrated clinical activity in imatinib-resistant patients with CML and Ph+ ALL across a wide range of mutations and after failure of other TKIs. Treatment is generally well tolerated, with the most common adverse events being gastrointestinal. The lack of significant inhibition for c-KIT and PDGFR may be responsible for its favorable safety profile, with a lower reported incidence of hematologic toxicity and pleural effusion/edema.53,54

INNO-406 is an orally available, dual Abl/Lyn kinase inhibitor that is up to 55 times more potent than imatinib in Bcr-Abl-expressing cell lines. It inhibits a wide-range of Bcr-Abl kinase domain mutants, excluding T315I. Unlike other second-generation TKIs, it has specific Lyn kinase activity with negligible activity against other Src family member kinases. In a dose-finding phase I trial, INNO-406 was well tolerated and demonstrated clinical activity in a heavily pretreated population across a wide range of dosing.55 Clinical responses were encouraging, and phase II trials are ongoing.

Conclusions

Since the introduction of imatinib nearly a decade ago, the management of CML and Ph+ ALL has been revolutionized by targeted molecular therapy. The currently approved second-generation TKIs, dasatinib and nilotinib, have proven significant clinical activity in patients with CML or Ph+ ALL whose disease has become resistant or intolerant to imatinib or other therapies. In addition, these agents are being studied in the front-line setting to determine if clinical benefits exist over the current standard of care. As more clinical data become available and as additional novel agents enter the market, specific therapy and dosing strategies will presumably be individualized, given the status of disease, potential toxicity of the given TKI, and concurrent drug therapies.

Disclosures

No significant relationship exists between the authors and the companies/organizations whose products or services may be referred to in this article.

The authors have disclosed that they briefly mention agents not yet approved by the US Food and Drug Administration: bosutinib [SKI-606] and INNO-406, which are currently under investigation for patients with CML and nilotinib for patients with Ph+ ALL.

References


April 2009, Vol. 16, No. 2 Cancer Control 139


