Pharmacotherapy for Chronic Myelogenous Leukemia: A Case-Based Approach

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Key Words
Chronic myelogenous leukemia, CML, tyrosine kinase inhibitors, imatinib, toxicity, pharmacotherapy, dasatinib, nilotinib

Abstract
TKIs have become the standard of care for CML. Imatinib was the first to transform the outcomes of this disease. Dasatinib and nilotinib were recently added to the armamentarium for imatinib-resistant disease and, more recently, for first-line therapy. When choosing a TKI for patients, adverse effects, presence of mutations in the BCR-ABL kinase domain, and cost should be considered. Once chosen, drug interactions should be evaluated for all patients. New drugs are being studied to prevent disease progression and for patients with T315I mutations. This article reviews the pharmacotherapy of CML with the aid of a patient case. (JNCCN 2011;9[Suppl 3]:S25–S35)

Case Report
DD is a 60-year-old man who presents to his primary care physician with abdominal pain and fatigue. His past medical history includes hypothyroidism, hypertension, atrial fibrillation, and a deep venous thrombosis 3 years ago. Splenomegaly is found on physical examination. A CBC count is notable for a WBC count of 95,000/m$^3$, platelets of 150,000/m$^3$, and hemoglobin of 8.9 g/dL. After a referral to a hematologist, a bone marrow evaluation is consistent with a diagnosis of chronic phase chronic myelogenous leukemia (CML).

Current medications include:
• Levothyroxine, 50 mcg daily
• Metoprolol XL, 100 mg daily
• Lisinopril, 10 mg daily
• Warfarin, 5 mg daily
• Pantoprazole, 40 mg daily
• Multivitamin, 1 tablet daily
• Acetaminophen, 650 mg as needed 4 times daily

Treatment Options
CML accounts for 15% of leukemias in the adult population. The median age of disease onset is 67 years, although CML can occur in all age groups. The disease comprises chronic, accelerated, and blastic phases. Breakthroughs in therapy for this disease are ongoing, and 3 targeted therapies are currently available for CML. This article provides a case-based review of the current therapy for CML from a pharmaceutical viewpoint. Key points are used throughout to emphasize important ideas.

The key player in CML is the de novo creation of the BCR-ABL fusion oncogene from the reciprocal translocation between chromosomes 9 and 22 (t[9;22] [q34;q11]), also known as the Philadelphia chromosome. The BCR-ABL gene disrupts the regulation of downstream targets that are essential to the proliferation and survival of normal cells. The mutation results in uncontrolled growth of malignant cells, which leads to the pathogenesis of CML.

Therapy then must enable patients to regain control of this regulation; this is determined according to certain end points (hematologic, cytogenetic, and molecular). The clinical manifestations of CML are seen in the patient’s signs and symptoms. For example, DD has an increased WBC count and splenomegaly. A goal of therapy would be to eliminate these symptoms. When
therapy is able to do this, a hematologic response occurs. On diagnosis, DD's peripheral blood or bone marrow aspirate was most likely sent for fluorescence in situ hybridization analysis to determine recurring numeric and structural abnormalities in the chromosomes at baseline. Ideal therapy should also be able to eliminate chromosomal abnormalities in the malignant cells, in this case the Philadelphia chromosome. This is known as a cytogenetic response (CyR). Finally, reverse-transcriptase polymerase chain reaction can detect reductions or increases in BCR-ABL transcripts, which relates to a molecular response. Patients can experience a complete or partial hematologic response; complete (CCyR), partial, major (MCyR), or minor CyR; or a complete or major molecular response (MMR) to therapy.4

Front-Line Therapy

Historically, CML was treated with chemotherapy agents such as hydroxyurea and busulfan to alter leukocyte proliferation. These agents controlled the clinical manifestations of the disease, but they were not capable of eliminating the malignant clone.5 The introduction of interferon-α (INF-α) significantly changed outcomes by providing a significant survival advantage over busulfan or hydroxyurea.6 This drug was also able to produce a CyR, although at the cost of considerable toxicity.

Because the BCR-ABL gene is significant in the genesis of this disease, research focused on this target. CML treatment was revolutionized with the advent of imatinib mesylate (Gleevec), which was able to inhibit the BCR-ABL tyrosine kinase. Initial trials showed a marked effect with imatinib as a second-line therapy in patients for whom treatment INF-α had failed or those with more advanced disease.7 Imatinib for use in front-line therapy for newly diagnosed patients was established by the results of the IRIS trial. The trial included 1106 patients who were randomized to receive either imatinib, 400 mg daily, or INF-α plus low-dose cytarabine.8 After a median follow-up of 19 months, the rate of MCyR at 18 months was 87.1% in the imatinib group and 34.7% in the group given INF-α plus cytarabine. The estimated rate of freedom from progression to accelerated or blast phase CML was significantly improved in the imatinib arm and in the follow-up period. Imatinib was also better tolerated than combination therapy. This study led to the FDA approval of imatinib for first-line therapy of chronic phase CML. Initial treatment with imatinib also has continued to show efficacy in follow-up data.9,10 These data confirm that imatinib can induce high durable response rates and decrease risk of relapse.

The proven efficacy of imatinib, 400 mg daily, as first-line treatment for chronic phase CML has led researchers to explore escalating the starting dose of imatinib. This was done in the TOPS study and the Italian Group for Adult Hematologic Diseases (GIMEMA 021/ELN) high-dose imatinib trials.11,12 Standard-dose imatinib (400 mg daily) was compared with high-dose imatinib (800 mg daily) in both trials. A recent update of the TOPS study reported no significant difference between the standard-dose and the high-dose treatment arms for either CCyR or MMR rates 24 months out.13 The GIMEMA 021/ELN study confirmed the TOPS findings. Additionally, although no statistical difference in adverse effects was seen between the dosing approaches, compliance was lower in the high-dose arm.

Differing from the previous 2 high-dose trials, the ISTAHIT study found an initial difference in both the cytogenetic and molecular responses. High-dose imatinib led to higher rates of MCyR and CCyR than standard-dose at 3 and 6 months. This result was paralleled by a significantly higher MMR rate at 6 months in the high-dose imatinib arm. At 12 months, however, the rates of MCyR were comparable between the arms (57% vs. 59%).14 The clinical significance of this has not been determined.

In addition to high-dose imatinib, patients now have more options for front-line therapy with the introduction of the second-generation tyrosine kinase inhibitors (TKIs). Originally approved for imatinib failure or intolerance, dasatinib (Sprycel) and nilotinib (Tasigna) can now be used in front-line therapy because of results of 2 different trials.

Dasatinib was compared with imatinib first-line and after a minimum follow-up of 12 months; the rates of confirmed CCyR and MMR were higher with dasatinib than with imatinib. Responses were experienced in a shorter time with dasatinib, and progression to accelerated or blastic phase CML occurred less often in the dasatinib arm.15 Nilotinib was examined as front-line therapy initially in a phase II single-center trial. Responses occurred rapidly and 93% of patients treated with nilotinib, 400 mg twice daily, obtained a CCyR in 24 months of follow-up.16 A phase III trial compared
2 different doses of nilotinib (300 mg twice a day and 400 mg twice a day) with imatinib as first-line treatment. At 12 months, the rates of MMR for both nilotinib doses were nearly twice that for imatinib, and the CCyR rates were significantly higher. Significant improvement in time to progression to the accelerated or blast phase was seen in the nilotinib arms compared with the imatinib arm. Because of these data, the FDA approved nilotinib, 300 mg twice daily, as first-line therapy for CML.

**TKI Monitoring**

When starting imatinib therapy, patients with CML should be monitored to assess therapy response and detect relapse. Guidelines have suggested parameters for assessment time points, and a general interpretation is depicted in Table 1. Criteria for TKI success have also been outlined and are summarized in Table 2. Currently, no data suggest time points to monitor dasatinib and nilotinib response when used first-line; however, guidelines have stated that the same time points used for imatinib can be used for dasatinib and nilotinib.

**Key Points:**

- Imatinib is efficacious and produces durable results in CML.
- Imatinib can be used at higher doses in first-line therapy.
- Imatinib, dasatinib, and nilotinib can be used in first-line therapy.

**Case Update:** DD is started on imatinib, 400 mg daily, and is assessed for a response at 3 months.

**Imatinib**

The pharmacokinetics of imatinib have been well evaluated. After oral absorption, it is approximately 95% bound to albumin and α1-acid glycoprotein. Most imatinib is metabolized by cytochrome P450 (CYP) isoenzyme CYP3A4. Furthermore, imatinib is a potent competitive inhibitor of isoenzymes CYP2C9, CYP2D6, and CYP3A4, and therefore is likely to increase the blood levels of drugs that are substrates of CYP2C9, CYP2D6, or CYP3A4. Because of this, a patient’s medication list should be thoroughly evaluated for potential drug interactions. Theazole antifungals are known inhibitors of CYP3A4. Both ketoconazole and voriconazole have been shown to increase plasma imatinib levels.

Other CYP3A4 inhibitors include verapamil, clarithromycin, and ritonavir. Ritonavir, however, did not result in increased steady-state plasma concentrations in a recent study. Furthermore, these agents along with proton pump inhibitors inhibit P-glycoprotein, which can potentially increase imatinib’s plasma concentration. Ideally, when concomitant therapy cannot be changed, patients should be monitored diligently for increased adverse reactions.

**Possible Drug Interactions**

Clinicians should be aware of any possible drug interactions when considering imatinib therapy. Using DD as an example, a few drug interactions are important to mention. Initiation of imatinib therapy in patients receiving levothyroxine has resulted in elevated levels of thyrotrin and symptoms of hypothyroidism. Researchers postulate that imatinib induces the metabolism of levothyroxine much like rifampin. Therefore, an increase in the levothyroxine dose may be warranted when initiating imatinib treatment for hypothyroid patients on levothyroxine. Serum thyroxine and thyrotrin levels should be routinely evaluated during DD’s clinic visits, and signs and symptoms of hypothyroidism should be monitored. DD is also taking a CYP2D6 substrate, metoprolol, which can be of concern because of imatinib’s inhibitor effects on this metabolic pathway. Monitoring for hypotension and bradycardia caused by increased metoprolol concentrations are pertinent with this combination. Atenolol poses no interaction risk with imatinib and may be an alternative β-antagonist for DD. In addition, acetamino-
phen given concomitantly with imatinib can possibly cause an increased risk of hepatotoxicity because of imatinib’s ability to inhibit the O-glucuronidation of acetaminophen. Frequent monitoring of liver enzymes is advised and a maximum daily dose of 1300 mg of acetaminophen has been recommended. DD should be told to limit his acetaminophen intake. Lastly, because warfarin is metabolized by CYP2C9 and CYP3A4, the manufacturer states that patients who require anticoagulation should receive low-molecular-weight or standard heparin instead of warfarin. However, in a recently published case study of 8 CML patients receiving both imatinib and warfarin, none of the patients showed abnormal international normalized ratio (INR) values and none experienced bleeding or occurrences of thrombotic events during imatinib treatment. Nonetheless, because of the hypothetical interaction, INR should be monitored frequently.

Case Update: At 3 months, DD has experienced a complete hematologic response and is continued on imatinib, 400 mg daily. At his next clinic visit, a CBC count shows an absolute neutrophil count (ANC) of 900/mm³.

### Monitoring Toxicities and Consideration of Medical History

Clinicians should also be aware of how to monitor for and manage toxicities associated with imatinib. A CBC count should be performed weekly for the first month, every 2 weeks for the second month, and periodically thereafter (e.g., every 2–3 months). Hematologic toxicities, including neutropenia, thrombocytopenia, and anemia, are common with imatinib therapy. DD has grade 3 neutropenia, and therefore imatinib therapy should be suspended until the ANC is greater than 1500/mm³ and then reinitiated at the same dose. If neutropenia occurs again, imatinib should be suspended and then reinitiated at a reduced dose of 300 mg. Data support the use of myeloid growth factors for patients with resistant neutropenia. Grade 3 to 4 thrombocytopenia is managed similarly; therapy should be held until the platelet count is greater than 75,000/mm³. If thrombocytopenia were to reoccur, the reduced dose should be initiated. Importantly, many toxicities are self-limiting and the dose can be re-escalated after resolution.

Other imatinib toxicities include gastrointestinal upset, rash, liver toxicity, cardiac toxicities, and edema. Congestive cardiac failure was reported in 0.1% to 1% of patients during clinical trials of imatinib. Dose-related edema was reported to be one of the most frequent side effects in elderly patients with newly diagnosed CML. Diuretics along with a dose reduction should be considered for these patients. Throughout the course of imatinib therapy, patients should be weighed and monitored for signs and symptoms of fluid retention. Patients with pre-existing cardiac disease are at a higher risk for cardiac failure and should be followed up closely.

### Key Points:
- Imatinib is mainly metabolized by CYP3A4; it inhibits -2C9, -2D6, and -3A4. Clinicians should be mindful of drug interactions.
- Imatinib has many dose-limiting adverse drug reactions.
- Clinicians should be aware of cardiac toxicities for all patients, especially those with a significant past medical history.

### Resistance

Although imatinib has been considered a breakthrough in the treatment of CML, patients can still develop drug resistance. In the IRIS trial, 31% of patients did not experience a CCyR after 12 months of treatment. Primary resistance and poor imatinib outcomes have been correlated with overexpression of the multidrug resistant gene (MDR1), which decreases intracellular concentrations of imatinib, and a low level of human organic cation transporter-1. Other primary reasons include patient nonadherence to the regimen, drug oral bioavailability, and protein plasma binding. A routine assessment of patient adherence is essential for optimal outcomes. The ADA-GIO (Adherence Assessment with Glivec: Indicators and Outcomes) study showed that patients with a suboptimal response were less likely to adhere to imatinib. Although no clinical data support routine measurement of imatinib plasma levels, this may be useful in determining patient adherence. Secondary

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<td><strong>Time</strong></td>
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Patient adherence is essential for positive outcomes to therapy, and nonadherence can confer resistance. Point mutations are a common cause of TKI resistance by causing amino acid substitutions inside the BCR-ABL kinase domain. This disrupts the binding site of imatinib to the tyrosine kinase. At least 90 mutations have been identified and occur in up to 90% of patients who develop secondary resistance to imatinib. The BCR-ABL kinase domain has 4 components: phosphate-binding loop, intervening sequence, activation loop, and catalytic loop. Point mutations can occur within any of these components, and different amino acid substitutions can occur within the same portion. Although preexisting point mutations are of concern when starting a TKI, mutation analysis is not routinely performed on initiation of therapy. The NCCN Guidelines recommend mutation analysis only if an inadequate initial response is seen or disease progression occurs. Because some TKIs are more resistant to certain mutations than others, these data should help determine which TKI should follow imatinib.

The T315I mutation is resistant to all currently available TKIs. Mutations F317 and V299 tend to be resistant to dasatinib, whereas Y253, E255, and F359 are resistant to nilotinib. Furthermore, some mutations are more prevalent in certain disease phases. Mutations M351, M244, F317, and H396 are more frequent in chronic phase disease, whereas Y253, E255, and T351 occur more often in accelerated or blast phase disease. 

Key Points:
- Patient adherence is essential for positive outcomes to therapy, and nonadherence can confer resistance.
- Point mutations are a common cause of TKI resistance and should be looked for after first-line drug resistance or disease progression.
- The T315I mutation is resistant to imatinib, dasatinib, and nilotinib.

Case Update: At 12 months, DD has tolerated imatinib and experienced a complete hematologic response but only a minor CyR. At this clinic visit, a bone marrow evaluation shows his disease is no longer responding to imatinib therapy. An ABL tyrosine kinase domain mutation analysis showed a D276G mutation (imatinib-resistant; dasatinib- and nilotinib-sensitive).

Imatinib Augmentation
Increasing the dose of imatinib could have been an option for DD if his mutation was imatinib-sensitive. Imatinib dose escalation can induce responses in some patients whose disease does not respond to standard-dose imatinib. This strategy was examined in 84 patients with chronic phase CML. Patients received imatinib dose escalations from 400 to 800 mg daily or from 300 to 600 mg daily. At a median follow-up of 61 months from dose escalation, 40% of patients experienced a CCyR. The responses were durable, with 88% of patients with a MCyR sustaining this response beyond 2 years.

Case Update: DD’s therapy was changed to dasatinib, 100 mg daily.

Dasatinib
Second-generation TKIs are an option for DD. Dasatinib differs from imatinib in that it inhibits the active and inactive BCR-ABL confirmations, and SRC, c-KIT kinases, and platelet-derived growth factor receptor (PDGFR). Dasatinib is also the most potent TKI; it has 325 times more affinity for the BCR-ABL kinase domain than imatinib, and therefore overcomes most imatinib mechanisms of resistance.

Dasatinib was originally studied in a phase I trial in which patients who were refractory to or could not tolerate imatinib therapy were given 15 to 240 mg/d of dasatinib once or twice daily. Based on this trial and pharmacokinetic and pharmacodynamic data, dasatinib was further studied in several phase II trials, known as the SRC-ABL Tyrosine Kinase Inhibition Activity Research Trials (START), at a dose of 70 mg twice daily. These trials sought to establish the efficacy and safety profiles of dasatinib for all phases of CML (chronic, accelerated, and blastic) after imatinib failure or intolerance.

Dose reductions were needed in the chronic phase START trials (START-C, START-R), which led to a phase III study to evaluate an optimal dose for chronic phase CML. Patients were randomly assigned 1:1:1:1 among 4 dasatinib treatment groups: 100 mg once daily, 50 mg twice daily, 140 mg once daily, or 70 mg twice daily. Results showed that 100 mg once daily was able to maintain efficacy while reducing toxicity compared with 70 mg twice daily. Another phase III trial evaluating once-daily dosing
of dasatinib in accelerated phase CML showed an improved toxicity profile with 140 mg daily compared with 70 mg twice daily. Because of the positive findings of the START trials, dasatinib was FDA-approved for second-line therapy in all phases of CML, at doses of 100 mg once daily in chronic phase and 140 mg once daily in accelerated or blastic phase. Dasatinib's role in CML was recently expanded to include a first-line therapy indication at an initial dose of 100 mg once daily.

**Key Points:**
- Increased doses of imatinib are an option for patients refractory to the standard dose in chronic phase disease.
- Dasatinib can be used for patients refractory to or intolerant of imatinib in all phases of CML at a dose of 100 mg daily for chronic phase and 140 mg daily for accelerated or blast phase.
- Daily dosing of dasatinib limits adverse effects.

**Possible Drug Interactions**
Like imatinib, drug interactions are also important with dasatinib. Dasatinib is metabolized by CYP3A4 to its active and inactive metabolites, and is also a weak inhibitor of this enzyme. Additionally, flavin-containing monooxygenase 3 (FMO-3) and uridine diphosphate-glucuronosyltransferase (UGT) are involved in its metabolism. Concomitant drugs that are strong inhibitors or inducers of CYP3A4 should be avoided when initiating dasatinib. The manufacturer recommends that if strong inhibitors are necessary, dasatinib should be reduced to 20 mg/d for patients receiving 100 mg daily and 40 mg/d for those receiving 140 mg daily. However, no clinical data are available for these adjusted doses; they are predicted to adjust the area under the curve (AUC) to the range of what is observed without strong CYP3A4 inhibitors.

Regarding DD's drug therapy, the addition of dasatinib to pantoprazole is of concern. The solubility of dasatinib is pH-dependent. Drugs that increase the pH of the gut have the potential to decrease dasatinib exposure. In a study of 24 healthy volunteers, administration of a single 50-mg dose of dasatinib 10 hours after famotidine resulted in a 61% reduction in dasatinib AUC. Avoidance of both proton pump inhibitors and H₂ antagonists is recommended. DD's pantoprazole should be discontinued. If antacids are necessary for symptom control, DD should be counseled to take any antacid at least 2 hours before or 2 hours after dasatinib.

**Monitoring Toxicities**
Nausea, vomiting, diarrhea, lower-extremity edema, headache, fatigue, dyspnea, skin rash, myelosuppression, prolonged QTc (predisposing to arrhythmias), and gastrointestinal and intracranial bleed are all adverse drug reactions from dasatinib. Fluid retention, commonly pleural effusion and, to a lesser extent, pericardial effusion, has been observed during dasatinib treatment. DD is at increased risk to develop this complication because of his cardiac history and hypertension. A twice-daily dosing regimen and accelerated or blast phase CML are also associated with increased risk of pleural effusion.

Patients treated with dasatinib are at risk of infection. Infections commonly manifest as pneumonia and can lead to complications such as parapneumonic effusion. In addition, development of small pleural effusions from fluid overload is not uncommon in some patients with CML who may require exogenous fluids. If DD were to require fluids or show signs and symptoms of infection, the pleural effusion risk associated with dasatinib must be included in the differential. A chest radiograph is suggested for evaluation. Management may include dasatinib therapy interruption, diuretics, pulse steroids, or, in some cases, thoracentesis.

Dose adjustments are needed for hematologic toxicities. For chronic phase therapy, an ANC of less than 500/mᶜ or a platelet count less than 50,000/mᶜ warrants the suspension of therapy until the counts have recovered. If recovery occurs within 7 days, then the original dose can be reinitiated. If recovery takes longer than 7 days, dasatinib should be reinitiated at 80 mg daily and discontinued if the counts decrease again. The cause of neutropenia and thrombocytopenia in the setting of accelerated and blast phase should be determined before the dasatinib dose is adjusted. If the cytopenia is unrelated to leukemia, dose reductions are recommended.

**Key Points:**
- Dasatinib is metabolized by CYP3A4 and dose reductions may be necessary with concomitant strong inhibitors.
- Pleural effusions are of concern with dasatinib and must be managed.
- Dose adjustment guidelines exist for hematologic toxicities.
Case Update: Within 3 months of dasatinib therapy, DD presents to his oncologist with complaints of shortness of breath and persistent cough. A chest radiograph shows congestion and likely pleural effusions. Levofloxacin is started for possible pneumonia and dasatinib is discontinued. DD is changed to nilotinib, 400 mg twice daily, to continue his CML treatment.

Nilotinib

Nilotinib is the most recent TKI to be added to the CML arsenal. Nilotinib inhibits BCR-ABL, PDGFR, and c-KIT, and is 30 times more potent than imatinib because of its increased ABL kinase selectivity and binding site affinity. Unlike dasatinib, it binds to only the inactive ABL kinase domain.

Nilotinib was first studied in a phase I dose escalation study in patients with imatinib-resistant CML and was found to be active. Based on these results, nilotinib was further evaluated in the imatinib-resistant or -intolerant setting in 2 phase II, open-label clinical trials; one in chronic phase CML and the other in accelerated phase CML. In the chronic phase trial, nilotinib was given at 400 mg twice daily. At 6 months, the MCyR rate was 48% and the CCyR rate was 31%. In a 24-month follow up, 77% of patients experiencing response to treatment were able to maintain an MCyR, and overall survival was 87% for the entire patient population, showing nilotinib’s sustained efficacy. Nilotinib was also given as 400 mg twice daily in the accelerated phase trial. A total of 119 patients were enrolled and an MCyR was observed in 29%. Overall survival at 12 months was 79%. Because of these findings, in 2007 the FDA approved nilotinib use in imatinib-refractory or -intolerant CML in chronic or accelerated phase. Nilotinib has also shown promise in blastic phase disease, although this indication is not yet FDA-approved. Nilotinib recently received approval as first-line therapy for chronic phase disease at a dose of 300 mg twice daily.

After imatinib failure, both nilotinib or dasatinib have shown efficacy when given after the other has failed. This is ideal for DD’s scenario, as DD experienced disease progression through imatinib and was unable to tolerate dasatinib. Nilotinib remains a viable option for DD because in this setting durable responses are most likely to occur in patients with chronic phase disease. Another assessment of DD’s drug therapy is necessary when switching TKIs; many interactions and adverse effects overlap with imatinib and dasatinib and others are unique to nilotinib.

Key Points:
- Nilotinib can be used in patients with imatinib-refractory or -intolerant CML in chronic or accelerated phase.
- Either dasatinib or nilotinib can be used when patients experience failure or intolerance to 2 TKIs.

Possible Drug Interactions

Nilotinib is a substrate of the efflux transporters BCRP and P-glycoprotein. Caution should be taken with the coadministration of drugs that inhibit these transporters. Clinicians also should be aware of strong inhibitors and inducers of CYP3A4. Ketoconazole has been shown to increase nilotinib exposure 3-fold, and systemic exposure was decreased approximately 80% with rifampin (an inducer). Concomitant administration with these drugs should be avoided. Voriconazole is used frequently in clinical practice for many patients with leukemia. Although no specific study exists, voriconazole is also a strong CYP3A4 inhibitor, and concern exists regarding the same interaction seen with ketoconazole. No clinical data have determined a degree of dose adjustment if coadministration is necessary. However, consideration should be given to reducing the nilotinib dose to 200 mg orally once daily in patients with newly diagnosed chronic phase CML or to 300 mg orally once daily in patients with resistant or intolerant chronic or accelerated phase disease.

Voriconazole is also of special concern because it has the potential to increase the QTc interval. Nilotinib contains a black box warning for QTc prolongation and sudden death, and therefore drugs that can prolong the QTc should be discontinued and replaced by alternate therapy with an appropriate washout period if needed before nilotinib therapy is initiated. Since DD’s addition of levofloxacin for empiric pneumonia treatment poses this risk, it should be changed. DD should also be evaluated for hypokalemia and hypomagnesemia and have these corrected if found. Furthermore, DD should be counseled to avoid food at least 2 hours before and 1 hour after taking this medication. Food increases nilotinib exposure and subsequent risk of QT interval prolongation.
An EKG should be obtained to monitor the QTc at baseline and 7 days after initiation, and then periodically thereafter. If a QTc greater than 480 ms is found, nilotinib should be held with possible dose adjustments. In March 2010, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for nilotinib because of the QT prolongation risk. The REMS includes an updated medication guide and a communication plan to help reduce medication errors involving food and drug interactions and incorrect dosing intervals.

**Monitoring Toxicities**

Further monitoring is necessary for hepatic toxicity and should be performed at least monthly. Nilotinib is a potent inhibitor of UGT1A1. A pharmacogenetic analysis of 97 patients receiving nilotinib showed a statistically significant increase in the risk of hyperbilirubinemia in those with (TA)7/(TA)7 genotype (UGT1A1*28) relative to the homozygous wild-type and heterozygous genotypes.

Lastly, nilotinib can also cause neutropenia and thrombocytopenia. If myelosuppression persists for more than 2 weeks after holding nilotinib, the dose should be reduced to 400 mg once daily regardless of disease phase.

**Key Points:**
- Nilotinib is a substrate of CYP3A4, and drug interactions should be evaluated accordingly.
- Patients should be monitored for QTc prolongation and hepatic toxicity.
- Dose adjustments for hematologic toxicities are recommended.

**Case Update:** After 18 months from initiation of TKI therapy, DD is found to have an increasing WBC count with blasts. A bone marrow evaluation found 30% blasts, indicating that DD’s disease has progressed to blast phase.

**Options For Progressive Disease**

DD’s CML obviously failed to respond to TKI therapy. Options for patients experiencing progression to blast phase include chemotherapy using either acute myeloid leukemia or acute lymphocytic leukemia induction-type regimens, depending on myeloid or lymphoid blast phase respectively, plus a TKI. Allogeneic transplantation should follow if the patient is a candidate.

Transplantation could have been considered for DD at a few points during his treatment course, first at 12 months when a CCyR did not occur. The NCCN Guidelines recommend that patients be evaluated for allogeneic transplant during an inadequate response to standard-dose imatinib (summarized in Table 3).

Throughout DD’s treatment course, a clinical trial could have been suggested at the same time transplantation could have been considered. A clinical trial should always be considered for patients with any disease progression. Drugs are currently in the pipeline for patients in chronic phase or who have a T315I mutation for whom treatment with a TKI fails.

**Future Directions**

Bosutinib is a TKI that may be able to be used in the future after imatinib failure or as first-line treatment for chronic phase disease. It is 30 times more potent than imatinib and is a dual ABL/SRC inhibitor. It is being evaluated in phase III trials and is not currently FDA-approved. However, phase II trial results are promising. An MCyR occurred in 40% and 59% of imatinib-resistant and -intolerant patients, respectively. Bosutinib is currently being studied in imatinib-resistant disease and in a phase III trial in the first-line setting of chronic phase CML. Unfortunately, bosutinib is not active for the T315I mutation.

However, omacetaxine, a protein synthesis inhibitor given subcutaneously, shows promise in patients with T315I mutations. This drug’s novel mechanism of action works independently of the tyrosine kinase pathway. A study showed that a reduction of baseline T315I-mutated clone occurred in 57% of patients in chronic phase. Results also seem promising in patients with T315I mutations.

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<th>Table 3 Indications for Evaluation of Allogeneic Transplant</th>
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<tr>
<td>Progression to accelerated or blast phase</td>
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<td>Patients with T315I mutation</td>
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<tr>
<td>Less than complete hematologic response at 3 mo</td>
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<td>No cytogenetic response at 6 mo</td>
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<td>Minor or no cytogenetic response at 12 mo</td>
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<td>Partial cytogenetic response at 18 mo</td>
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to be durable with omacetaxine. A recent case series of 8 patients reported that at a median of 24 months from omacetaxine initiation, 50% continued to have an undetectable T315I/ABL ratio. Omacetaxine also has activity in patients for whom 2 or more TKIs failed. A phase II/III study showed that among patients in chronic phase, 80% obtained a complete hematologic response and 20% a CyR.

Many additional drugs with novel mechanisms are currently being studied for CML, including aurora kinase inhibitors, histone deacetylase inhibitors, and other agents that inhibit a range of kinases.

Key Points:
- Allogeneic transplant or a clinical trial can be considered for TKI-refractory disease or disease progression.
- Bosutinib and omacetaxine are emerging agents for CML.
- Omacetaxine appears active against the T315I mutation.

Follow-Up
If DD were to experience a CCyR on TKI therapy, he should continue to have a peripheral blood evaluation every 3 to 4 months in the clinic to detect any progression or lack of response. The frequency of bone marrow evaluation is controversial, with some centers performing the procedure based on suspicious peripheral blood findings, and others performing it routinely every 18 to 24 months.

Follow-up should also take into consideration cost of therapy when TKI treatment is selected and monitored. The annual treatment costs for TKIs are relatively high. This can be concerning because CML is a chronic condition that requires continuous treatment. Again, the patient’s adherence to therapy and ability to pay for the medication must be assessed.

Conclusions
TKIs have become the standard of care for CML. Imatinib was the first to transform the outcomes of this disease. Dasatinib and nilotinib were recently added to the armamentarium for imatinib-resistant disease and, more recently, for first-line therapy. When choosing a TKI for patients, adverse effects, presence of mutations in the BCR-ABL kinase domain, and cost should be considered. Once chosen, drug interactions should be evaluated for all patients. New drugs are being studied to prevent disease progression and for patients with T315I mutations.

References


