A Case Study Approach to Chronic Myelogenous Leukemia

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The author has no conflicts to disclose.

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Abstract

Chronic myelogenous leukemia (CML) is a bone marrow disorder characterized by the translocation of chromosomes 9 and 22. CML typically progresses through three stages: chronic phase, accelerated phase, and blast phase or blast crisis. Treatment options and prognosis for patients with newly diagnosed CML have improved dramatically in the past decade. Today, with first- and second-generation tyrosine kinase inhibitors (TKIs) available, the goal of therapy is 100% survival and a normal quality of life. Currently, there are three TKIs approved by the US Food and Drug Administration for patients with CML: imatinib, dasatinib, and nilotinib. Imatinib is approved for use as first-line therapy in patients with newly diagnosed CML. Nilotinib was recently approved for use as first-line therapy; along with dasatinib, it is also approved for use in patients with imatinib-resistant CML or in those patients who are intolerant of imatinib. Oncology advanced practitioners must understand these agents and their side effects to properly educate patients and their support systems, identify side effects early, intervene promptly, and minimize significant toxicity.

J Adv Pract Oncol 2010;1:171–181

The treatment options and prognosis for patients with newly diagnosed chronic myelogenous leukemia (CML) have improved dramatically in the past decade. From 1990 through 1992, patients in the United States with newly diagnosed CML had a 1 in 4 chance of being alive in 5 years (Jemal, Seigel, Ward, Murray, Xu, & Thun, 2007). Until 2000, in patients under age 60 with newly diagnosed CML, bone marrow transplant was the preferred first-line therapy for those with a human leukocyte antigen (HLA)-identical sibling donor. For those without an available sibling donor, interferon was the preferred initial therapy, although it had significant toxicity and low efficacy (Bittencourt et al., 2008).

In 2001, imatinib received US Food and Drug Administration (FDA) approval for use in newly diagnosed or interferon-refractory CML patients. By 2002 through 2004, 1 in 2 newly diagnosed CML patients could be expected to be alive in 5 years (Brenner, Gondos, & Pulte, 2009). In 1997, 4,300 people in the United States were diagnosed with CML, with 2,400 deaths related to the disease. In 2009, there were 5,050 new CML diagnoses but

only 470 CML-related deaths, further reflecting significant strides in therapeutic efficacy and improvement in overall prognosis (Jemal, S2009; Parker, Tong, Bolden, & Wingo, 1997; The Leukemia and Lymphoma Society, 2010).

CML accounts for 15% to 20% of adult leukemia cases in western countries. Worldwide, CML incidence is 1 case per 100,000 people, with a slightly higher incidence in men. The disease occurs in children and adults, with approximately 3% of total cases occurring in children. Overall, the most common age at diagnosis is 50 to 70 years old. In 2007, there were approximately 2 million people worldwide living with CML (The Leukemia and Lymphoma Society, 2010; Sessions, 2007; Jabbour, Cortes, Ghanem, O'Brien, & Kantarjian, 2008; D'Antonio, 2005).

CML is a bone marrow disorder characterized by the translocation of chromosomes 9 and 22, known as the Philadelphia chromosome (Ph). The chromosome 9 breakpoint is always within the gene encoding the Abelson murine leukemia (Abl). Abl fuses to chromosome 22 within the breakpoint cluster region (Bcr). This results in the formation of the oncoprotein Bcr-Abl (The Leukemia and Lymphoma Society, 2010; Faderl, Kantarjian, & Talpa, 1999). Bcr-Abl activates tyrosine kinase, a protein involved in promoting cell division and inhibiting programmed cell death, or apoptosis. The activation of Bcr-Abl tyrosine kinase results in immature myeloid cells with strong proliferation and survival signals, disrupted differentiation, decreased immune surveillance, and increased tendency for drug resistance

Table 1. Definitions of accelerated phase and blast crisis

Sokal et al criteria	IBMTR criteria	MDACC criteria	WHO criteria
Acelerated phase			
Peripheral blood or marrow blasts > 5% Basophils > 20% Platelet count > 1,000,000 cells/µL despite adequate therapy Clonal evolution Frequent Pelger-Huet-like neutrophils, nucleated erythrocytes, megakaryocyte nuclear fragments Marrow collagen fibrosis Anemia or thrombocytopenia unrelated to therapy Splenomegaly Leukocyte doubling time < 5 days Fever of unknown origin	Leukocytes poorly controlled with hydroxyurea or busulfan Rapid leukocyte doubling time (< 5 days) Peripheral blood or marrow blasts > 10% Peripheral blood or marrow blasts and promyelocytes > 20% Peripheral blood basophils and eosinophils > 20% Anemia and thrombocytopenia unresponsive to hydroxyurea or busulfan Persistent thrombocytosis Clonal evolution Progressive splenomegaly Development of myelofibrosis	Peripheral blood blasts > 15% Peripheral blood blasts and promyelocytes > 30% Peripheral blood basophils > 20% Platelet count < 100,000 cells/µL unrelated to therapy Clonal evolution	Blasts 10%–19% of WBCs in peripheral blood and/or nucleated bone marrow cells Peripheral blood basophils > 20% Persistent thrombocytopenia (< 100,000 cells/µl) unrelated to therapy of persistent thrombocytosis (> 1,000,000 cells/µL) unresponsive to therapy Increasing spleen size and increasing WBC unresponsive to therapy
Blast Crisis			
	Blasts >30% in bone marrow or peripheral blood Extramedullary infiltrates		Blasts > 20% in bone marrow or peripheral blood Extramedullary blast proliferation Large foci or clusters of blasts in bone marrow biopsy

Note: IBMTR = International Bone Marrow Transplant Registry; MDACC = The University of Texas M. D. Anderson Cancer Center; WBC = white blood cells; WHO = World Health Organization. Information from Sokal, 1988; Savage, 1997; Kantarjian, 1993: Swerdlow, 2008; DeVita, 2001.

(Jabbour et al., 2008). Although ionizing radiation has been linked to some cases of CML, the causes and risk factors associated with developing CML are largely unknown (D'Antonio, 2005).

CML typically progresses through three stages: chronic phase, accelerated phase, and blast phase or blast crisis (Table 1). Each progressive phase is characterized by shortening duration, worsening clinical features, increasing laboratory abnormalities, and less favorable responses to therapy. The majority of patients (approximately 85%) are diagnosed with CML in chronic phase (CP-CML). In the era of CML treatment before imatinib, the median duration of CP-CML was 5 to 6 years. The median duration of accelerated phase was 6 to 9 months; for blast phase, the median survival was 3 to 6 months (Jabbour et al., 2008; Faderl, et al., 1999). Today, with first- and second-generation tyrosine kinase inhibitors (TKIs) available, the goal of therapy is 100% survival and a normal quality of life (Baccarani et al., 2009).

Case Study

Mrs. A is a 53-year-old female who presents to her primary care provider with a 3-month history of night sweats and weight loss. She had previously been in good health, and other than surgical repair of an ankle fracture at age 40, has an unremarkable medical history. A multivitamin and calcium are her only usual medications; she has no allergies, does not smoke, and drinks alcohol socially about once per month.

Mrs. A's physical examination is completely normal except for splenomegaly at 3 cm below the left costal margin. Her initial hematologic parameters confirmed a total white blood cell count of 110,000 cells/µL, with 5% myeloblasts and 3% basophils in peripheral blood; her hemoglobin and platelet counts are within normal ranges. She is referred to a hematologist/oncologist for further workup.

CML Symptoms

Although approximately 30% of patients with CML are diagnosed based on an incidental finding with no symptoms, approximately 70% will present with symptoms. Common complaints include fatigue, abdominal discomfort due to splenomegaly, weight loss, and sweating. Laboratory findings commonly include leukocytosis, with a white blood cell count in the 100,000–400,000 cells/µL range and potentially exceeding 600,000 cells/µL (Beutler, Lichtman, Coller, Kipps, & Seligsohn, 2000).

Mrs. A's hematologist/oncologist performs a bone marrow aspirate and biopsy. Bone marrow cytogenetic studies confirm the presence of the chromosomal translocation of t(9;22) and she is diagnosed with CP-CML. Mrs. A is started on oral imatinib 400 mg daily.

First-Line Treatment of CML

Currently, there are three TKIs approved by the FDA for patients with CML: imatinib, dasatinib (Sprycel), and nilotinib (Tasigna). Imatinib is approved for use as first-line therapy in patients with newly diagnosed Ph+ CP-CML, accelerated phase CML (AP-CML), or blast phase CML (BP-CML). Nilotinib was recently approved for use as first-line therapy in patients with CP-CML, and along with dasatinib, it is also approved for use in patients with imatinib-resistant CML or in those patients whom are intolerant of imatinib. (National Comprehensive Cancer Network [NCCN], 2010).

Patients with CML are treated after initial diagnosis without a watch and wait period. The goal of initial therapy in patients with newly diagnosed chronic phase CML is to keep the disease in chronic phase as long as possible, thus prolonging the time it takes for a patient's disease to progress to a more advanced phase (NCCN, 2010; Novartis Oncology, http://2010a; Bristol-Myers Squibb, 2010; Novartis Oncology, 2010b). Imatinib efficacy is a result of binding to the Bcr-Abl protein, preventing active configuration into an oncoprotein (Kantarjian et al., 2009). As stated above, imatinib was approved by the FDA in 2001; this approval was based on the IRIS (International Randomized Study of Interferon and STI571) trial, which established that imatinib was superior to interferon alfa plus cytarabine in a randomized trial of patients with newly diagnosed CP-CML (Kantarjian et al., 2009; O'Brien, et al. 2008). At 7 years of follow-up, the estimated freedom from progression rate to accelerated phase or blast crisis was 93%, with an overall survival rate of 86%, and 57% of patients randomized to imatinib remaining on imatinib with a complete cytogenetic response (Kantarjian et al., 2009; O'Brien, et al., 2008).

Mrs. A comes in for a routine visit 4 weeks after initiating imatinib. She states that her night sweats are improving and her weight has stabilized. She also reports mild intermittent nausea and puffy

eyes, which are evident on visual observation. She is instructed to take imatinib with a meal and a large glass of water at least 2 hours before bedtime, in an attempt to improve her nausea. She is prescribed a low-dose diuretic for her periorbital edema.

Side Effects of Imatinib

Superficial edema is the most common imatinib-related side effect. Muscle cramps, diarrhea, nausea, rash, fatigue, and abdominal pain are also common symptoms (Druker et al., 2001). See Table 2 for a list of common side effects. Laboratory abnormalities include neutropenia, thrombocytopenia, anemia, and elevated liver enzymes (Druker et al., 2001). Management of common TKI side effects is described in Table 3 (Deininger, 2008). Gastrointestinal side effects include nausea, vomiting, and diarrhea. Taking imatinib with a meal and a large glass of water and avoiding taking a dose within 2 hours of bedtime can improve nausea and vomiting (Druker et al, 2001). Although Mrs. A is taking imatinib 400 mg once daily, taking 400 mg twice daily may also improve GI side effects for patients on 800 mg daily. If conserva-

Table 2. Common tyrosine kinase inhibitor side effects in chronic phase CML

Side effect	Imatinib	Dasatinib	Nilotinib
Fluid retention	62% 60% superficial edema	34% 18% superficial edema 18% pleural effusion	11% peripheral edema
Nausea	50%	18%	31%
Muscle cramps	49%	NR	11%
Musculoskeletal pain	47%	19%	21%
Diarrhea	45%	23%	22%
Rash	40%	13%	33%
Fatigue	39%	21%	28%
Headache	37%	32%	31%
Adominal pain	37%	12%	11%
Joint pain	31%	13%	18%
Nasopharyngitis	31%	NR	16%
Hemorrhage	29% –1.6%GI –0.2% CNS	11% –2%GI –0% CNS	NR
Myalgia	24%	13%	14%
Vomiting	23%	7%	21%
Upper respiratory tract infection	21%	12% (all infections)	NR
Cough	20%	NR	17%
Neutropenia	17%	36%	28%
Thrombocytopenia	9%	23%	28%
Anemia	4%	13%	8%
Dyspnea	NR	13%	11%
Constipation	11%	NR	21%
Hypophosphatemia	NR	10%	10%
Elevated lipase	NR	NR	15%

Notes: CML = chronic myelogenous leukemia; CNS = central nervous system; GI = gastrointestinal; NR = not reported.
Sources: Novartis Oncology (2010a), Druker, et al. (2001); Bristol-Myers Squibb (2010), and Novartis Oncology (2010b).

Table 3. Management of common tyrosine kinase inhibitor side effects

Side effect	Management recommendations
Nausea and vomiting	Take with food (except nilotinib); antiemetics; appetite stimulants; change in dosing schedule
Rash	Emollients; topical/systemic steroids
Diarrhea	Antidiarrheals; diet modification
Muscle cramps	Tonic water, quinine, calcium gluconate
Fatigue	Activity with adequate rest; stress management; assess nutritional status; consider other causes (thyroid function, electrolyte abnormalities, bleeding, other psychosocial impacts)
Fluid retention	Diuretics; chest x-ray if dyspnea present
Bone pain	Nonsteroidal anti-inflammatory drugs
Elevated liver function parameters	Temporarily interrupt therapy, modify dose, or discontinue per agent-specific prescribing information
Weight gain	Diuretics, diet, exercise
Myelosuppression	Temporarily interrupt therapy, modify dose, or discontinue per agent-specific prescribing information

Note: Information from Deininger (2008), Galinsky & Buchanan (2009), Bauer & Romvari (2009), and Bryant (2009).

tive measures do not result in adequate relief of side effects, antiemetics with or without proton pump or H2 blockers may be needed to control the nausea and vomiting (Druker et al., 2001).

Musculoskeletal side effects of imatinib may include muscle cramps, bone pain, and arthralgias. Calcium supplements, nonsteroidal anti-inflammatory agents, or mild narcotics may be used to relieve these symptoms. Edema and fluid retention are generally mild; however, they may be severe and lead to pulmonary edema, pleural/pericardial effusion, and ascites. For mild edema or fluid retention, a low-salt diet with or without diuretics is appropriate. For severe fluid retention, diuretics and dose reduction or discontinuation should be considered. In addition, patients experiencing more than mild fluid retention should be instructed to weigh themselves regularly; they should be educated about parameters for intervention or notification of their health-care team.

Skin rash is also common but generally mild. Most frequently, a maculopapular rash is noted on the arms and trunk. This rash responds well to antihistamines and topical or oral steroids. Fortunately, severe desquamation is rare and should prompt interruption of imatinib and the initiation of systemic steroids (Deininger, 2008; Druker et al., 2001).

Lastly, congestive heart failure (CHF) may be associated with imatinib therapy (Atallah & Cortes, 2007). Due to a significant proportion of patients with CML being older in age, there is a high likelihood that a significant number will present with a history of CHF or other medical condition(s) predisposing to CHF. Baseline echocardiograms are a prudent consideration when initiating imatinib in the elderly, those with known CHF, or those at high risk for developing CHF. In addition, teaching patients about the signs and symptoms of fluid retention, including monitoring weight gain, will promote early identification of fluid overload and heart failure (Atallah & Cortes, 2007).

Food and Drug Interactions

Another important factor for patients taking imatinib, dasatinib, or nilotinib is adequate education regarding food and drug interactions. All three TKIs are CYP34A substrates with potential drug-drug and drug-food interactions (Deininger, 2008). Drugs that may increase TKI concentrations include ketaconazole, itraconazole, erythromycin, clarithromycin, ritonavir, and atazanavir. Increased concentrations may lead to heightened side-effect profiles. Drugs that may decrease TKI concentrations include dexamethasone, phenytoin, carbamazepine, rifampin, St. John's wort, grapefruit, and phenobarbitol. Decreased TKI concentrations may lead to reduced efficacy. If

Table 4. Criteria for cytogenetic, hematologic, and cytogenetic response

Cytogenetic response
- Complete: No Ph+ metaphases
- Major: 0%–35% Ph+ metaphases (complete + partial)
- Partial: 1%–34% Ph+ metaphases
- Minor: 35%–90% Ph+ metaphases

Complete hematologic response
- Normal peripheral blood counts with leukocyte count < 1,000,000 cells/μL
- Platelet count < 450,000 cells/μL
- No immature cells (ie, myelocytes, promyelocytes, or blasts) in peripheral blood
- No signs and symptoms of disease, including no palpable spleen

Partial hematologic response
Same as complete hematologic response except for:
- Presence of immature cells
- Platelet count < 50% of the pretreatment count but > 450,000 cells/μL
- Persistent splenomegaly, but 50% of the pretreatment extent

Molecular response
- Complete molecular response: Bcr-Abl mRNA undetectable by RQ-PCR
- Major molecular response: > 3-log reduction of Bcr-Abl mRNA

Note: Ph+ = Philadelphia chromosome positive; RQ-PCR = real-time quantitative polymerase chain reaction. Adapted from NCCN (2010).

agents known to impact TKI concentrations must be used, careful monitoring is recommended, and dose adjustment of TKI therapy may be appropriate (Novartis Oncology, 2010a; Deininger & Druker, 2003). In addition, there is an additive risk of bleeding in the setting of concomitant use of TKIs with anticoagulants, nonsteroidal anti-inflammatory agents, and platelet inhibitors including aspirin and thrombolytic agents (Deininger, 2007).

Given this extensive list of potentially interactive drugs, patients should be instructed to consult their oncology health-care team before taking any new prescription or over-the-counter medication (Deininger, 2007; Novartis Oncology, 2010a).

By 3 months, Mrs. A achieves a complete hematologic response, as evidenced by normalization of hematologic parameters, including differential and resolution of splenomegaly. She continues on imatinib 400 mg daily without significant side effects. By 6 months, Mrs. A achieves a complete cytogenetic response (CCyR) and has a 3-log reduction in Bcr-Abl transcripts on real-time quantitative polymerase chain reaction (RQ-PCR) compared to baseline, consistent with a major molecular response (see Table 4). She continues on imatinib 400 mg daily. At 12 months, RQ-PCR is unchanged and she continues on imatinib without dose modification. At 18 months, Mrs. A's RQ-PCR 165 reveals a 2-log increase in tumor load on three occasions. Bone marrow reveals 9% Ph+ cells by conventional cytogenetics, consistent with cytogenetic relapse. Mrs. A is prescribed imatinib 800 mg daily. See Table 5 for the recommended schedule for monitoring patients during different stages of TKI therapy.

Compliance Concerns

Mrs. A's CML is being inadequately controlled on imatinib 400 mg daily. Poor adherence should always be considered and assessed when a patient is not responding to TKI therapy. A patient's ability and willingness to procure and take medications as prescribed must be assessed (Marin et al., 2010). Some potential barriers to adherence include cost, access, and cognitive function/memory (Ruddy, Mayer, & Partridge, 2009). Compliance may be indirectly assessed by questioning the patient, performing pill counts, ascertaining the rate of prescription refills, and questioning caregivers. Direct assessment is accomplished by measuring drug or drug metabolite concentrations and measuring biologic markers. Improving communication between patients and health-care providers can lead to early recognition of inadequate adherence. Supportive approaches can then be instituted to maximize outcomes: emotional support, positive reinforcement, education on local and national sources of assistance with transportation, and information regarding agent-specific programs available through drug manufacturers (Milojkovic et al., 2008; Ruddy, et al., 2009; Marin, 2010).

The IRIS study continues to provide ongoing long-term data on its original subjects. It is generally considered the most reliable source of estimates of imatinib's rate of response, durability, and survival. According to recent IRIS data, 106 of 553 patients (19%) had imatinib doses escalated due to imatinib failure or suboptimal response. The median time from imatinib initiation to initial dose increase is approximately 19 months, which is where Mrs. A is in her imatinib therapy. In general, within 12 months after imatinib dose escalation, 42% of patients can be expected to achieve or regain a cytogenetic remission (Hochhaus et al., 2009).

Table 5. Monitoring for patients receiving tyrosine kinase inhibitor therapy

At diagnosis
- CBC with differential
- Bone marrow morphology, including % blasts and basophils
- Bone marrow cytogenetics
- Bone marrow Bcr-Abl PCR
- Peripheral blood FISH is acceptable to confirm CML diagnosis if bone marrow examination is not feasible

After TKI initiation
- CBC with differential every 2 weeks until normal; then every 4 weeks until stable, then every 3–4 months

While a patient appears to be responding to treatment
- Bcr-Abl transcripts every 3 months
- Bone marrow cytogenetics at 6 and 12 months; 12 month not necessary if in CCyR
- Bone marrow cytogenetics at 18 months if not in CCyR at 12 months

When a patient reaches CCyR
- Bcr-Abl transcripts every 3–6 months
- Bone marrow cytogenetics as clinically indicated

When a patient appears to have rising level (1 log increase) of Bcr-Abl transcripts
- Evaluate patient compliance
- If rising levels (1-log increase) with MMR, repeat in 13 months
- If rising levels (1-log increase) without MMR, obtain bone marrow cytogenetics
- Consider mutation testing

Note: CBC = complete blood count; CCyR = complete cytogenetic response; CML = chronic myelogenous leukemia; FISH = fluorescence in situ hybridization; MMR = major molecular response; PCR = polymerase chain reaction; TKI = tyrosine kinase inhibitor. Adapted from NCCN (2010).

After 1 month on imatinib 800 mg daily, Mrs. A presents with complaints of worsening periorbital edema and new mild dyspnea on exertion. Chest x-ray reveals a new small right pleural effusion. Routine hematology studies also reveal an absolute neutrophil count of 950 cells/μL and a platelet count of 67,000 cells/μL. She is instructed to reduce the imatinib to 600 mg daily due to hematologic toxicity. Mrs. A's diuretic regimen is increased, and she very quickly notes resolution of fluid overload. Repeat chest x-ray is normal. Within 1 week of the dose reduction, her hematologic parameters are improving and no further dose reduction for hematologic toxicity is required. After 2 months on imatinib 600 mg daily, RQ-PCR shows a 1-log increase in Bcr-Abl transcripts. Bone marrow cytogenetics reveal 10% Ph+ chromosomes, consistent with imatinib failure. Molecular studies also reveal Bcr-Abl with a Y253H mutation.

Imatinib Resistance

Mechanisms of imatinib resistance include mutations in the Bcr-Abl tyrosine kinase domain and Bcr-Abl gene amplification, overexpression of Bcr-Abl protein, drug influx and efflux mechanisms, Bcr-Abl–independent mechanisms, and quiescent stem cells (Milojkovic et al., 2008; Hughes & Branford, 2003; Shah, 2005; Shah, 2007).

Imatinib resistance can be primary and/or secondary. Primary resistance may be the result of insufficient inhibition of Bcr-Abl due to low plasma levels, activity of drug pumps, etc., or the result of individual variations in normal bone marrow reserve. Primary resistance results in a failure to achieve the desired therapeutic milestones. Imatinib therapeutic milestones indicative of primary resistance are failure to achieve complete hematologic response after 3 months of therapy or any cytogenetic response at 6 months, major cytogenetic response at 12 months, complete cytogenetic response at 18 months, or any loss of response (NCCN, 2010; Novartis Oncology, 2010a; Milojkovic, 2008; Hughes & Branford, 2003; Shah, 2005; Shah, 2007).

The Y253H mutation has been shown to be associated with imatinib resistance in vitro by blocking imatinib binding to Bcr-Abl, thus interfering with its efficacy (Kantarjian, Rousselot, & Pasquini, 2007; Miething, et al., 2006). At this point in Mrs. A's disease course, both dasatinib and nilotinib are appropriate therapy choices. Both are FDA approved for use in patients with imatinib-resistant or -intolerant CML in chronic phase and could be used interchangeably in this scenario. In this setting, no clinical trial has directly compared the two agents.

Second-Line Treatment: Dasatinib and Nilotinib

Dasatinib received its initial FDA approval in 2006. Dasatinib can be dosed at 70 mg twice daily or 100 mg daily. Dasatinib 70 mg twice daily is recommended in accelerated or blast phase, while 100 mg daily is recommended in chronic phase, with the option to escalate to 140 mg daily based on response (Baccarani et al., 2008; Bristol-Myers Squibb, 2010). Nilotinib received its initial FDA approval in 2007 at a dose of 400 mg twice daily for chronic or accelerated phase CML in pa-

tients with imatinib-resistant or -intolerant disease (DeRemer, Ustun, & Natarajan, 2008; Ault; 2007). Both agents have similar efficacy. Most series report complete CCyR rates of around 40% and 18 to 24 month overall survival rates of > 90%.

As both dasatinib and nilotinib are relatively new agents when compared to imatinib, long-term follow up is short and, thus far, quite similar (Stone, Kantarjian, & Baccarani, 2007; Kantarjian, et al., 2007). Both dasatinib and nilotinib are associated with Q–T interval prolongation and arrhythmias. Close monitoring of electrolytes and Q–T interval by electrocardiogram (ECG) are critical in patients receiving dasatinib or nilotinib (Bristol-Myers Squibb, 2010; Novartis Oncology, 2010b; DeRemer, et al., 2008; Ault, 2007). Currently, both are approved for second-line use in CML, however, both are being studied in first-line settings for all phases of CML (Bristol-Myers Squibb, 2010; Novartis Oncology, 2010b; Cortes, et al., 2010; Saglio & Bacarani, 2010; Rosti, et al., 2008; Saglio, et al., 2009).

After a baseline ECG shows no abnormality and laboratory values are found to be within normal limits, Mrs. A is started on dasatinib 100 mg daily. She is also referred to a local transplant center, where she is found to have an HLA-identical sibling. One month after initiating dasatinib, Mrs. A again presents with periorbital edema. She is reinitiated on her most recent diuretic regimen, which was the dose used after she developed a pleural effusion on high-dose imatinib. Two weeks following diuretic therapy, her edema has resolved, and routine laboratory testing reveals a serum potassium level of 2.9. She receives appropriate electrolyte replacement and a repeat ECG. The ECG shows a prolonged Q–T interval. Dasatinib therapy is briefly interrupted, potassium is rapidly corrected, and the ECG normalizes. Dasatinib is reinitiated, and her electrolytes are aggressively monitored.

Dasatinib's side effects most commonly include headache, diarrhea, fatigue, nausea, dyspnea, rash, neutropenia, thrombocytopenia, and anemia (Bristol-Myers Squibb, 2010; Hochhaus et al., 2009; Shah, 2007). Management of patients receiving dasatinib is largely symptom-focused, similar to imatinib. Dasatinib may be taken with or without food. Timing and fed or fasting state can be adjusted to manage nausea, with or without antiemetics. Diarrhea may be managed with diet and antidiarrheal agents. Emollients generally offer symptomatic control of rash, although topical or systemic steroids may be appropriate. Cough or any respiratory symptoms should prompt a chest x-ray, as 10% to 20% of patients receiving dasatinib develop pleural effusion. Dasatinib should be held for an absolute neutrophil count of less than 1,000 cells/μL or a platelet count of less than 50,000/μL. If resolution is noted in 7 days, treatment should be restarted at the previous dose. If not, treatment should be restarted at a reduced dose. If cytopenias occur on two occasions on a reduced dose, dasatinib should be permanently discontinued (Bristol-Myers Squibb, 2010; Hochhaus et al., 2009; Shah, 2007).

Mrs. A achieves complete cytogenetic and molecular response on dasatinib and tolerates therapy without any further significant side effects or dose reductions or interruptions. Twelve months later, rising BCR-ABL transcripts are noted, and mutational analysis confirms the presence of a T315I mutation.

T315I mutations are not overcome by any of the currently approved Bcr-Abl tyrosine kinase inhibitors (imatinib, dasatinib, and nilotinib), and, thus, none have achieved any major activity against this mutation (Shah, 2005; O'Hare & Deininger, 2008; Weisberg, Manley, Cowan-Jacob, Hochhaus, & Griffin, 2007).

Mrs. A is referred back to the transplant center and undergoes myeloablative allogeneic stem cell transplant from an HLA-identical sibling donor. She tolerates transplant well and develops acute grade II graft-vs-host disease (GVHD) involving the skin only. Her GVHD responds well to systemic steroids, and taper is tolerated without further evidence of GVHD. Several months after transplant, Mrs. A returns to the clinic for follow-up.

Nilotinib is the final FDA-approved Bcr-Abl tyrosine kinase inhibitor not yet covered in this case study (Novartis-Oncology, 2010b; DeRemer, et al., 2008; Hazarika et al., 2008). In this case study, nilotinib as a treatment option arises from its use in CP-CML and AP-CML in adults with imatinib-resistant or -intolerant disease. If this patient did not develop a T315I mutation, nilotinib therapy or allogeneic transplant would have been appropriate options.

Nilotinib is typically started at 400 mg twice daily without food; specifically, food should be avoided 2 hours prior to and 1 hour after each dose. Complete hematologic response rates of

Table 6. Overview of imatinib, dasatinib, and nilotinib

	Imatinib	Dasatinib	Nilotinib
FDA approval	2001	2006	2007
Trade name	Gleevec	Sprycel	Tasigna
CML indication	Initial therapy for all phases of Ph+ CML	Second line for all phases of Ph+ CML, after imatinib	Initial therapy for CP and second line for CP or AP Ph+ CML after imatinib
Initial dose	400 mg daily	CP: 100 mg daily AP/BC: 70 mg bid	400 mg bid
Maximum dose	800 mg daily	CP: 140 mg daily AP/BC: 200 mg daily	400 mg bid
Missed dose instructions	Take dose as soon as remembered	Take next dose as scheduled	Take next dose as scheduled
Food effect	None	None	Do not eat 2 hours before or 1 hour after dose is taken
Black box warnings	None	None	Q–T prolongation and sudden deaths
Use in patients with renal/ hepatic insufficiency	No data	Use with caution in patients with hepatic impairment	Use with caution in patients with hepatic impairment
Contraindication	None	Use with caution in patients with existing lung pathology (eg, pleural effusion)	Do not use in the setting of hypokalemia, hypomagnesemia, or long Q–T syndrome
Use in children	Safety not established	Safety not established	Safety not established

Note: AP = accelerated phase; BC = blast crisis; CP = chronic phase; CML = chronic FDA = US Food and Drug Administration. Information from Novartis Oncology (2010a), Novartis Oncology (2010b), Bristol-Myers Squibb (2010), Deininger (2008), Galinsky & Buchanan (2009), Bauer & Romvani (2009), and Bryant (2009).

65% and major cytogenetic response rates of 40% in chronic phase CML previously treated with imatinib can be expected. Nilotinb's most significant side effect is that of causing a prolonged Q–T interval that rarely but potentially results in sudden death. Nilotinib should not be used in patients with hypokalemia, hypomagnesemia, or long Q–T syndrome. Monitoring with electrocardiogram is recommended at baseline, 7 days after therapy initiation, following dose changes, and periodically thereafter. Laboratory monitoring should also be done per provider discretion (Novartis Oncology, 2010b; DeRemer, et al., 2008; Hazarika et al., 2008).

Conclusion

In conclusion, currently approved TKIs for use in newly diagnosed CML and imatinib resistant or -intolerant CML have improved the outlook for patients with CML in all phases of the disease. For oncology advanced practice providers over the past decade, CML patients have become much more numerous in clinics and offices, not due to an increase in incidence but due to dramatic improvement in survival (Brenner, et al., 2009). Imatinib, dasatinib, and nilotinib are generally well tolerated agents for the treatment of CML (Table 6). All carry the risk of significant toxicity, but with proper monitoring and side-effect management, the majority of patients can be expected to tolerate therapy.

Due to favorable overall tolerance, it is not likely that these patients will require regular care or contact with oncology outpatient nurses. This reality separates patients and their support systems from a significant source of education and psychosocial support within the health-care team (Hartigan, 2003). It is therefore even more critical for oncology advanced practice professionals to understand these agents and their side effects in order to properly educate patients and their support systems, identify side effects early, intervene promptly, and minimize significant toxicity. Dose interruptions, modification, or discontinuation may be appropriate for hematologic as well as other toxicities.

It is also important for oncology advanced practice nurses to be aware of barriers to adherence with oral therapy regimens, which has become a significant issue in the effective treatment of many malignancies (Ruddy, et al., 2009; Partridge, Avron, Wang, & Winer, 2002; Marin, et al., 2010). Imatinib continues to be associated with excellent long-term disease control in patients treated on the IRIS trial at 7 years of follow-up. Dasatinib and nilotinib continue to be studied, both in various phases of CML and in combination with other agents.

Despite current successes, many investigational TKIs are also being developed and studied in CML. Allogeneic stem cell transplant continues to play a role in the treatment of CML, although its placement in treatment planning has largely shifted away from being an initial therapy option to playing a significant role after TKI therapy. Throughout the entire disease process, oncology advanced practice professionals are in a unique position to improve outcomes for patients with CML.

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