

New BCR-ABL tyrosine kinase inhibitors for imatinib-resistant leukemias

Dasatinib and nilotinib provide a novel and effective approach to treating imatinib-resistant CML and Philadelphia chromosome-positive ALL.

What's new, what's important

Successful development of the BCR-ABL tyrosine kinase inhibitor imatinib (Gleevec) for chronic myeloid leukemia (CML) marked the beginning of the era in targeted therapy of cancer. But resistance to imatinib soon became apparent.

Relapse from imatinib stems from the evolution of leukemic subclones with imatinib-resistant *BCR-ABL* mutations. Two novel tyrosine kinase inhibitors, dasatinib (Sprycel) and nilotinib (AMN107), are specific inhibitors of these mutations. The US Food and Drug Administration (FDA) granted accelerated approval for use of dasatinib in the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase CML with resistance or intolerance to prior therapy, including imatinib. Dasatinib was also approved for use in the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

The FDA has granted orphan-drug status to nilotinib and designated it for fast-track review. Nilotinib is currently available only through clinical trials. Novartis, the company developing the drug, has launched a global program, ENACT (Expanding Nilotinib Access in Clinical Trials), to provide expanded access to nilotinib.

The development of these two novel agents is an exciting advancement in the treatment of CML and Ph+ ALL and marks the beginning of the era of next-generation targeted therapies.

—Jame Abraham, MD
Section Editor

The *BCR-ABL* gene created by the formation of the Philadelphia chromosome (Ph) encodes the fusion protein BCR-ABL. Unregulated activity of the ABL tyrosine kinase in this protein causes chronic myelogenous leukemia (CML) and Ph-positive acute lymphoblastic leukemia (ALL). Imatinib (Gleevec), a BCR-ABL tyrosine kinase inhibitor, can induce remission in all stages of CML and is currently first-line therapy for newly diagnosed Ph-positive chronic-phase CML and second-line therapy for interferon alpha-resistant CML and relapsed or recurrent Ph-positive ALL. However, resistance to imatinib has become an increasingly important problem.

Recent phase I studies have assessed two new oral BCR-ABL tyrosine kinase inhibitors, dasatinib (Sprycel) and nilotinib (AMN107), in imatinib-resistant CML and Ph-positive ALL. Dasatinib

differs from imatinib in that it can bind to both active and inactive conformations of the ABL kinase domain. It has been shown to be active against numerous imatinib-resistance mutations in *BCR-ABL*. Nilotinib has a higher binding affinity and selectivity for the ABL kinase than does imatinib, is more potent than imatinib against imatinib-sensitive CML cells, and, like dasatinib, is active against imatinib-resistant cells.

Dasatinib in imatinib-resistant leukemias

In a phase I dose-escalation study,¹ 84 patients with chronic-phase CML (n = 40), accelerated-phase CML (n = 11), CML with myeloid blast crisis (n = 23), or CML with lymphoid blast crisis or Ph-positive ALL (n = 10) received dasatinib, 15–240 mg/d, in once- or twice-daily doses in 4-week treatment cycles. A total of 50 patients had received prior chemotherapy, and

12 had undergone bone marrow or stem-cell transplantation; 72 were resistant to imatinib, and 12 could not tolerate imatinib treatment.

A maximum tolerated dose was not determined, and no patients withdrew from the study due to toxicity. Myelosuppression was common but not dose-limiting. Grade 3 or 4 neutropenia occurred in 45% of patients with chronic-phase CML and in 89% of those with accelerated-phase CML, CML with blast crisis, or Ph-positive ALL (55% of these patients had grade 3 or 4 myelosuppression at the start of the study). Grade 3 or 4 thrombocytopenia occurred in 35% of patients with chronic-phase disease and in 80% of those with accelerated-phase disease, CML with blast crisis, or Ph-positive ALL.

Summary by Matt Stenger, MS; reviewed by William A. Fintel, MD, President, Blue Ridge Cancer Care, Roanoke, VA.

TABLE 1

Hematologic and major cytogenetic responses to dasatinib, 15–240 mg/d

	Number (%) with response				
	Chronic-phase CML (n = 40)	Accelerated-phase CML (n = 11)	CML with myeloid blast crisis (n = 23)	CML with lymphoid blast crisis or Ph-positive ALL (n = 10)	Total (n = 84)
Hematologic response					
Major	37 (92)	9 (82)	14 (61)	8 (80)	68 (81)
Complete	37 (92)	5 (45)	8 (35)	7 (70)	57 (68)
No evidence of leukemia	NA	4 (36)	6 (26)	1 (10)	11 (25)
Minor	NA	0	4 (17)	0	4 (9)
Cytogenetic response					
Overall	25 (62)	4 (36)	12 (52)	9 (90)	50 (60)
Major	18 (45)	3 (27)	8 (35)	8 (80)	37 (44)
Complete	14 (35)	2 (18)	6 (26)	3 (30)	25 (30)
Partial	4 (10)	1 (9)	2 (9)	5 (50)	12 (14)
Minor	0	0	2 (9)	1 (10)	3 (4)
Minimal	7 (18)	1 (9)	2 (9)	0	10 (12)

CML = ch

Adapted from Talpaz et al¹

Myelosuppression required interruption of treatment in approximately 60% of patients; it generally resolved within 3 months, often in association with cytogenetic response. Dasatinib dose reduction was required in 25% of patients. Other adverse events of note included pleural effusion considered related to dasatinib in 15 patients (3 with grade 3 or 4 toxicity); these events were managed with diuretics, thoracentesis, or pleurodesis. Grade 3 or 4 liver function abnormalities occurred in seven patients but resolved within 2–3 weeks without modification of treatment. Grade 1 or 2 hypocalcemia occurred in 60% of patients but was asymptomatic and did not worsen with continued treatment. Other grade 3 or 4 toxicities consisted of gastrointestinal hemorrhage in three patients, pericardial effusion in two, dyspnea or pulmonary edema in two, tumor lysis syndrome in two, and diarrhea in one. Other adverse events included grade 1 or 2 diarrhea (23%), peripheral edema (19%), and headache (10%).

Of patients with chronic-phase CML, 92% experienced complete hematologic responses, and 45% experienced major cytogenetic responses (Table

1). Most of the hematologic responses occurred at doses of 50 mg/d or more, with cytogenetic responses requiring higher doses. Cytogenetic responses were more common in patients who had previously responded to imatinib; however, a major cytogenetic response also occurred in 5 of 18 patients with no response to imatinib, and 9 patients who had minor/partial responses to imatinib had a complete response to dasatinib. A major hematologic response occurred in 70% of patients with CML in accelerated or blast phase or those with Ph-positive ALL, and a major cytogenetic response was observed in all categories of accelerated- or blast-phase disease.

Responses were maintained in 95% of patients with chronic-phase CML who were followed for a median of 12 months and in 82% of those with accelerated-phase disease who were followed for a median of 5 months. Nearly all patients with lymphoid blast crisis or Ph-positive ALL had a relapse within 6 months; a minority of patients with myeloid blast crisis remained on study, but three had maintained complete cytogenetic remission for 10–12 months.

Mutations in the *BCR-ABL* kinase

domain were detected at baseline in 60 patients. Responses were observed across all *BCR-ABL* genotypes examined except for T315I, the only mutation predicted to confer cross-resistance between imatinib and dasatinib. This mutant was the predominant genotype in two patients with no response to dasatinib and was one of four genotypes present in another patient who had no response; over 60 days of treatment, the three susceptible clones in this patient diminished, with T315I being the only clone detected at the time of clinical relapse.

Nilotinib in imatinib-resistant leukemias

In a separate phase I dose-escalation study,² 119 patients with chronic-phase (n = 17), accelerated-phase (n = 56, including 10 with clonal evolution only), or blastic-phase (n = 33, including 24 with myeloid disease) CML or Ph-positive ALL (n = 13) resistant to imatinib received once-daily oral doses of nilotinib ranging from 50 to 1,200 mg or twice-daily doses of 400 or 600 mg. Patients had previously received median imatinib doses of 600–800 mg/d.

TABLE 2Adverse events in $\geq 4\%$ of patients receiving nilotinib, 50–1,200 mg once daily or 400 or 600 mg twice daily

	Grade 1 or 2/grade 3 or 4 (%)					
	50–200 mg once daily (n = 24)	400 mg once daily (n = 10)	600–1,200 mg once daily (n = 35)	400 mg twice daily (n = 32)	600 mg twice daily (n = 18)	Any dose (n = 119)
Nonhematologic						
Rash/all types	17/0	10/0	20/3	22/0	28/6	20/2
Pruritus	21/0	10/0	17/0	6/3	22/6	15/2
Dry skin	13/0	10/0	17/0	6/0	11/0	12/0
Constipation	17/0	10/0	3/0	0/0	22/0	8/0
Nausea or vomiting	8/0	0/0	6/0	13/0	6/0	8/0
Increased total and conjugated bilirubin	4/0	0/0	0/3	6/3	17/11	5/3
Fatigue	0/0	0/0	0/3	16/0	6/0	5/1
Increased unconjugated bilirubin	0/0	0/0	0/6	6/3	0/11	2/4
Alopecia	13/0	10/0	6/0	0/0	6/0	6/0
Increased lipase	0/0	0/0	0/3	0/9	0/11	0/5
Increased ALT or AST	0/0	0/0	0/9	3/3	0/0	1/3
Hematologic						
Thrombocytopenia	0/13	0/20	0/17	3/25	0/28	1/20
Neutropenia	0/8	0/10	3/14	0/9	0/22	1/13
Anemia	0/4	0/10	9/6	0/6	0/6	3/6

ALT = alanine aminotransferase; AST = aspartate aminotransferase

Adapted from Kantarjian et al²**TABLE 3**

Hematologic and cytogenetic responses to nilotinib, 50–1,200 mg/d

	Number of patients						
	Transformed CML						Chronic-phase CML
	Accelerated phase			Blastic phase			
	Hematologic disease	Clonal evolution only	Total	Myeloid	Lymphoid	Total	
Number of patients, total	46	10	56	24	9	33	17
Hematologic response							
Active disease	46	5	51	24	9	33	12
Complete response	21	5	26	2	0	2	11
Marrow response	3	NA	3	2	1	3	NA
Return to chronic phase	9	NA	9	6	2	8	NA
Total	33/46 (72%)	5/5 (100%)	38/51 (74%)	10/24 (42%)	3/9 (33%)	13/33 (39%)	11/12 (92%)
Cytogenetic response							
Complete response	6	2	8	1	1	2	6
Partial response	3	4	7	4	0	4	0
Minor response	4	1	5	2	0	2	0
Minimal response	9	2	11	0	1	1	3
Major response	9 (20%)	6 (60%)	15 (27%)	5 (21%)	1 (11%)	6 (18%)	6 (35%)
Total	22 (48%)	9 (90%)	31 (55%)	7 (29%)	2 (22%)	9 (27%)	9 (53%)

CML = chronic myelogenous leukemia; NA = not applicable

Adapted from Kantarjian et al²

Dose-limiting toxicity occurred in 18 patients at doses exceeding 600 mg/d, including a predominantly grade 3 elevation in bilirubin level (mostly indirect bilirubin) in 9 patients, grade 3 elevation in aminotransferase level in 3 patients, grade 4 elevation in lipase level in 1 patient, grade 3 or 4 elevation in amylase and lipase levels in 2 patients (including grade 2 pancreatitis in 1 patient with a history of pancreatitis), grade 4 hematologic toxicity in 2 patients, and grade 3 subdural hematoma in 1 patient. The maximum tolerated dose was determined to be 600 mg twice daily. Table 2 shows adverse events that occurred in at least 4% of patients. Thrombocytopenia, neutropenia, and rash (all types combined) appeared to increase in frequency with increasing nilotinib dose. Grade 3 transaminase elevations infrequently occurred at daily doses of 600 mg or more. Elevations of total, conjugated, or (mainly) unconjugated bilirubin levels accounted for 14% of adverse events; these elevations increased in frequency and grade with increasing dose, were not accompanied

by aminotransferase elevations or evidence of hemolysis, often occurred in the first week of therapy, and frequently resolved with continued treatment. Bilirubin level increases were observed in 7 of 14 patients with Gilbert's syndrome, compared with 10 of 97 patients in the rest of the population. In addition to the patient with a grade 3 elevation in amylase level, six patients had a grade 3 or 4 elevation in lipase level; three of these six patients also had abdominal pain, including the patient with grade 2 pancreatitis. Among patients with laboratory data, grade 3 or 4 elevations in lipase levels occurred in 9 (16%) of 55 patients and grade 3 amylase level elevations occurred in 3 (5%) of 57 patients, with all elevations occurring at doses of 600 mg/d or higher. The corrected QT interval increased by 5–15 ms in the study group. One patient had pericardial effusion and atrial fibrillation without cardiac enzyme level elevation.

Responses to nilotinib are shown in Table 3. Overall, hematologic responses and cytogenetic responses were observed in 74% and 55%, re-

spectively, of patients with accelerated-phase CML, 39% and 27%, respectively, of those with blastic-phase disease, and 92% (11/12 patients with active disease) and 53%, respectively, of those with chronic-phase disease. Among patients with Ph-positive ALL, 1 of 10 of those with hematologic relapse had a partial hematologic response and 1 of 3 with persistent molecular signs of ALL had a complete molecular remission.

A total of 51 *ABL* mutations were identified in 37 of 91 patients evaluated; nilotinib was active in patients with and without *ABL* mutations, with no differences in response rates observed according to mutation status. No response was observed in two patients with the T315I mutation.

References

1. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med* 2006;354:2531–2541.
2. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* 2006;354:2542–2551.

From the Community Oncologist's Perspective

More and more about less and less?

William A. Fintel, MD | Blue Ridge Cancer Care, Roanoke, VA

Does anyone else remember where they were when they first heard of STI-571, now known as imatinib (Gleevec)? In 1999, a colleague told me that she heard of a drug being used in a Texas clinic where 98% of all new CML (chronic myelogenous leukemia) patients, and most in relapse, were going straight into remission. And it was a pill. What's more, it was a designer drug based on the Philadelphia chromosome translocation! I remember. I think that was the day my white doctor's lab coat

took on a slightly brighter gleam.

In the accompanying article to this commentary, the clinical activity of two new tyrosine kinase inhibitors, dasatinib (Sprycel) and nilotinib (AMN107), to this same translocation is described, but this time the drugs overcome the mutations of the mutation (except for one of the 30-odd resistance mutations, T315I). You can log on to the *New England Journal of Medicine* Web site, www.nejm.org, read the article about dasatinib, and watch a video of the three-

dimensional structure of the *ABL* kinase as it mutates and tries to bind with imatinib and dasatinib. The two *NEJM* articles^{1,2} and an editorial by Brian Druker³ in the same issue provide details of the two agents and perspective on what these new findings mean to us in practice.

Considering how many patients would *actually* be affected by these brilliantly conceived molecules, it does seem to be piling on, to use a football metaphor. According to the American Cancer Society,⁴ the estimated number

of new cases of leukemia in the US in 2006 was around 35,000. Of them, approximately 4,000–5,000 were CML or acute leukemia in BCR-ABL-positive blast crisis.⁴ With a less than 4% annual failure rate with imatinib,⁵ only 600 Americans lost their lives to this rare form of leukemia in 2006.

Novel therapies for CML expand

That number will likely be even smaller in 2007 and the years ahead. Nilotinib binds to the ABL domain 20–50 times more tightly than imatinib does, accounting for its effectiveness. In their phase I study, Kantarjian et al¹ described the use of nilotinib in 119 imatinib-resistant patients. Only 17 patients were in chronic phase, and they experienced the highest response rates; hematologic and cytogenetic responses in this group were 92% and 53%, respectively. Patients in accelerated and blast phases also experienced responses, including some major cytogenetic responses, to the drug, but, predictably, these responses were shorter and less frequent than those observed among patients entering the study in chronic phase. Grade 3 or 4 adverse events, described as elevated levels of bilirubin or hepatic/pancreatic enzymes, occurred in about 5% of treated patients. Myelosuppression and rash increased in frequency as the dose of nilotinib increased. There was also a rare prolongation of the QT interval. Interestingly, myelosuppression, rash, and fluid retention were neither common nor severe for most patients.

Talpaz and colleagues² described their experience with the other tyrosine kinase inhibitor, dasatinib. This medication was approved by the US Food and Drug Administration in June 2006 for adults with chronic-accelerated- or myeloid/lymphoid blast-crisis CML who are resistant to or intolerant of prior therapy with imatinib. Dasatinib binds to active and inactive conformations of the ABL kinase

domain and differs molecularly from imatinib or nilotinib in that dasatinib was built from an Src-family tyrosine kinase inhibitor that can also bind the ABL site. In this phase I study, which included 12 patients who relapsed after bone marrow transplantation, 72 patients were resistant to imatinib and 12 others were imatinib intolerant. Once again, responses among the 37 patients in chronic-phase CML were high; 92% had a complete hematologic response, and 45% had a major cytogenetic response. Major hematologic responses were seen in 5 of 18 patients who previously exhibited no response to imatinib. Major hematologic responses were also seen in 70% of CML patients in the more advanced phases of imatinib-resistant CML, including some in blast crisis. Durable responses lasting more than a year were common in chronic-phase CML patients, but very short benefits were experienced by those who were in any type of blast crisis. Interestingly, the 12 patients who were intolerant of imatinib initially were not intolerant of dasatinib.

Toxicities with dasatinib were significant. Myelosuppression was common. Grade 3 or 4 myelosuppression was seen in 35%–45% of imatinib-resistant patients with chronic-phase CML and 80%–90% of those with higher phase CML. Interruption of dasatinib therapy was necessary in more than half of the patients, but treatment generally could be restarted within 3 months.

Fluid retention was seen in 50% of dasatinib-treated patients, including pleural effusion in 22% and effusion grade 3 or 4 in 5%.⁶ Dasatinib is a CYP3A4 substrate, and the package insert contains several warnings on its use with other medications.⁶

There is no doubt that this is very good news for very few people. By weight of clinical importance, we now seem to know more and more about less and less. It is reminiscent of the near-simultaneous discoveries of three effective agents for hairy cell leukemia in the 1980s.

Are we under-treating CML in the community?

Are community oncologists currently undertreating CML? I am told that most community-based doctors use the 400-mg dose of imatinib, whereas their counterparts in academia tend to use the 800-mg dose. At the same time, more cytogenetic testing is done at universities than in the community (though there are no published data to support this contention). *If* that is true, then we may be allowing an unacceptable mutation rate to occur in our chronic-phase CML patients by simply following their hematologic response. The National Comprehensive Cancer Network (NCCN) guidelines for treating CML do call for regular PCR (polymerase chain reaction) testing and annual bone marrow biopsies. When there was just one drug available and intolerance of that drug in this largely older population was a substantial issue, it was easy to use the lower dose, reminding ourselves that pushing toxicity may lead to more harm than good. Now, with dasatinib on the market, we all may need to pull out the NCCN guidelines a bit more often and consider the alternative drug when resistance or intolerance is seen.

What about major cancers?

Will the “big four” (lung, breast, colorectal, and prostate cancers) ever be controlled with a single, genetically targeted agent, as we apparently can accomplish in CML? Dr. Druker, in his editorial,³ appropriately points out that progress in CML is molecularly driven, advancing rapidly, and offering hope right now—and that imatinib grossed \$2.1 billion in 2004! Genomic medicine may be years from controlling the more common diseases, where multiple mutations are at work. This fact is a persistent stain on my white lab coat, wherein genomic medicine has offered palliation to some in advanced stages of these cancers and complete remission to very few. Almost 300,000 Americans died of these four cancers in 2006.⁴

When will the prescription-to-visit cost ratio reach 100:1?

Who remembers the day when targeted therapy in a bottle (tamoxifen) cost about \$100 per month and a physician office visit around \$50—a 2:1 ratio? As the genomic medicines hit their full stride and multiple prescriptions head out the door at a single visit, the ratio of prescription cost to the cost of an office visit can easily top 50:1. As the costs of these new medications escalate, and insurers deflate our physician fees, I can easily see a day when a patient heads out the door paying me less than a \$100 while dropping \$10,000 dollars at the phar-

macy. Dasatinib, I am told, is priced somewhere between the 400-mg and 800-mg dose of imatinib. There is already speculation that these agents should be tested together. Recall that these drugs treat a rare disease. Heaven help our collective pocketbooks if multiple agents one day work for metastatic lung cancer.

No oncologist hopes for the end of barbaric therapy more than I do. I long for the day when targeted agents to the common diseases come into their own, when newly introduced drugs offer complete responses as the norm, and when prescription drug price inflation is in line with the rest of healthcare costs—and my infusion room seems too large.

References

1. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* 2006;354:2542–2551.
2. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med* 2006;354:2531–2541.
3. Druker BJ. Circumventing resistance to kinase-inhibitor therapy [editorial]. *N Engl J Med* 2006;354:2594–2596.
4. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. *CA Cancer J Clin* 2006;56:106–130.
5. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 2006;355:2408–2417.
6. Sprycel [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2006.

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From the Nurses' Station

Oral agents are great...right?

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During the past decade, a number of oral agents have been developed to treat various malignancies. These medications are convenient for patients, allowing them to take their anticancer therapy at home rather than spending time at their oncologist's office to receive chemotherapy infusions. However, since these drugs are not administered in the presence of a healthcare professional, safety issues are a concern.

For example, patients need to be educated about the potential side effects of these medications, and their toxicities must be appropriately managed. Patients also need to clearly understand the importance of taking their medications in the proper amounts and on the correct days. We suggest the following tips:

■ **Provide patients with written instructions** to help ensure that they

take these oral agents properly.

■ **Suggest to your patients that they keep a pill diary and bring it with them to each office visit.** During the visit, we ask patients about the dates they took the agent and the number of pills they took each day. When we can review the diary with them, it is a more accurate assessment than relying on their memories.

■ **Continue to assess and educate patients** about the drugs so that they continue to adhere to their regimen.

Dealing with drug costs

Many of the new oral agents are quite expensive, and cost is frequently a deterrent to taking the medication as prescribed. Agents such as dasatinib (Sprycel) can be obtained from the patient's local pharmacy as well as from his or her outpatient pharmacy. Either way, patients need adequate medication coverage by their third-party payer.

This is especially true for patients who have Medicare Part D as their sole support for obtaining medication coverage. Patients using oral agents must also be educated as to what their plan covers and what they are responsible for. If their coverage is inadequate, they may need to be referred to **Medicare (www.medicare.gov or 1-800-633-4227) for information on supplemental insurance.**

Although pharmaceutical companies continue to offer support programs for patients with no insurance coverage for oral medications, the criteria for eligibility have become more stringent since the Medicare Part D program began. Patients can contact the **Partnership for Prescription Assistance, which provides access to scores of assistance programs, at 1-888-477-2669.**

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