Optimizing Outcomes Through Pharmaceutical Advances in the Treatment of Chronic Myeloid Leukemia

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Target Audience

This activity is designed for managed care pharmacists. No prerequisites are required.

Learning Objectives

The University of Tennessee College of Pharmacy takes responsibility for the content, quality, and scientific integrity of this continuing education activity. At the conclusion of this activity, the participant should be able to

- evaluate first-line therapy options for chronic myeloid leukemia (CML) and appreciate how combination therapy may maximize therapeutic outcome;
- define strategies for treating CML following imatinib failure;
- analyze results of new tyrosine kinase inhibitors in CML;
- describe the mechanism of action of targeted treatment approaches for patients with CML; and
- appreciate the role of allogeneic bone marrow transplantation for CML.

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*A total of 0.20 CEUs (2.0 contact hours) will be awarded for successful completion of this continuing education program (ACPE Program No. 064-000-07-203-H01). This educational activity is also accredited for a maximum of 2 AMA PRA Category 1 Credits. For faculty disclosures, please see pages S7, S11, and S17. For accreditation information, please see page S18.

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Introduction: Optimizing Outcomes Through Pharmaceutical Advances in the Treatment of Chronic Myeloid Leukemia

David Frame, PharmD

Chronic myeloid leukemia (CML) is a cancer of hematopoietic stem cells. It represents approximately 20% of adult leukemia diagnoses¹ and affects approximately 1 per 100,000 males and 0.6/0.7 per 100,000 females in the United States.² Although the etiology of CML is poorly understood, it is clear that certain environmental exposures can induce the disease. Benzene exposure has been connected with development of various leukemias, including CML.³ The Environmental Protection Agency has regulated benzene exposure, labeling it as a carcinogen and restricting its use; however, benzene is found in many materials, including plastics, rubber, and cigarette smoke, making it difficult to control. Cigarette smoke, in particular, also is associated with increases in myeloid leukemias, as well as increased disease progression for CML.⁴ Ionizing radiation was implicated when cohorts of Japanese survivors of the atomic bombs developed CML, along with acute myelogenous leukemia and acute lymphoblastic leukemia.⁵ The mechanisms by which these environmental exposures lead to CML are poorly understood.

CML is notable because it represents the first cancer to be associated with a specific chromosomal abnormality. In 1960, Nowell and Hungerford reported that white blood cells derived from patients with CML consistently showed the presence of a small aberrant chromosome, termed the Philadelphia chromosome (Ph).⁶ This aberrant chromosome was traced back to the stem cells of individuals with CML and was instrumental in establishing assays for monitoring disease and, ultimately, the first-line therapies used today. It was realized that the Ph was caused by a translocation of chromosomes 9 and 22.¹ When the breakpoints were mapped, it was discovered that a new protein, BCR-ABL, was formed from the joining of the 2 chromosomes. Expression of BCR-ABL in cell culture was found to be sufficient for transformation, and thus BCR-ABL was identified as the putative cause of CML. Today, we use measures of BCR-ABL protein and mRNA as sensitive assays for disease. Drugs that block BCR-ABL function have been developed, and these have proven so efficacious that within a few years of their introduction, they have

become the front-line therapy for CML.

This supplement covers a symposium held during the Academy of Managed Care Pharmacy's 19th Annual Meeting and Showcase, which was held in San Diego, California, on April 12, 2007. The goal of this symposium was to elucidate how the new BCR-ABL inhibitors have transformed the treatment of CML and how they have affected managed care for this disease state.

The symposium opened with an overview of CML by Jolynn Sessions. She covered the diagnosis criteria for CML and discussed the molecular pathogenesis mediated by BCR-ABL. Details of the translocation of chromosomes 9 and 22 were described, along with the consequences of breakpoint variation for disease. She covered the clinical course of the disease, observing when BCR-ABL inhibitors are most effective. She described tests used to measure disease, including the costs associated with each; these tests included hematologic, cytogenetic, and polymerase chain reaction assays. Sessions also compared the relative sensitivities of each assay and presented the use and appropriate point to employ each assay.

Christopher Fausel continued with a discussion of imatinib, the current front-line CML therapy, which functions by inhibiting BCR-ABL. Taking a historical approach, he opened with a description of early forms of chemotherapy used to treat CML, beginning with busulfan and hydroxyurea, which were replaced by interferon γ with or without cytarabine. He then listed the efficacy and adverse effects of these therapies. He also discussed bone marrow transplant and weighed the possibility of cure against the significant possibility of mortality and adverse effects from the transplant for the survivors. The mechanism of action for imatinib was explained, followed by a review of different clinical trials and the results. Finally, Fausel covered the need to monitor imatinib-treated patients with CML, both for adverse effects and for the rising imatinib-resistant clones.

The symposium ended with a presentation by David Frame, in which he discussed imatinib resistance and outlined mechanisms by which it might arise and strategies for avoiding it. He delineated 5 potential mechanisms by which cancer cells can become resistant to imatinib: (1) increased plasma proteins that bind to imatinib, (2) increased efflux of imatinib through active transporters, (3) the arising of mutations in BCR-ABL that block the ability of imatinib to bind, (4) the arising of mutations in the Src pathway, an alternative means of promoting the transformed phenotype, and (5) the

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amplification of the Ph.

Frame continued with how one might define a sub-therapeutic dose using clinical trial data. The use of dose escalation was presented, along with several clinical trials that compared increased imatinib dosing to other treatment strategies. In general, data demonstrated that despite the increased number of adverse events, increased imatinib dosing appears to be an effective way to stop resistance and determine outcomes earlier. Frame then discussed dasatinib, a new BCR-ABL inhibitor that is currently in clinical trials. Dasatinib was found to inhibit BCR-ABL, most imatinib-resistant mutations of BCR-ABL, and SRC. Clinical trial data were presented to show how dasatinib could be a useful tool in the struggle to combat drug-resistant CML clones. Frame concluded with a detailed economic analysis for a variety of CML treatment strategies, illustrating that imatinib and dasatinib are cost-effective ways to greatly increase quality-of-life years for patients with CML.

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Chronic Myeloid Leukemia in 2007

Jolynn Sessions, PharmD, BCOP

ABSTRACT

BACKGROUND: Chronic myeloid leukemia (CML) is a potentially fatal stem cell cancer that comprises approximately 14% of all leukemias. Although it is estimated that 4,600 people will be diagnosed with CML in the United States in 2007, only 12% of those individuals will die from the disease. That low mortality rate is due to the availability and efficacy of the new kinase inhibitors that target the BCR-ABL oncogene and other targets to hold disease progression in check.

OBJECTIVE: To review the molecular pathogenesis of CML, describe the clinical course of the disease, and explain the current application of cytogenetics and molecular testing for diagnosis and treatment.

SUMMARY: CML is caused by the translocation of chromosomes 9 and 22 to create what is called the Philadelphia chromosome. This translocation removes a critical regulatory domain from the tyrosine kinase, ABL, such that its protein product is constitutively active. This means that the cell escapes the constraints of normal cell growth and proliferates uncontrollably. The modified protein is known as BCR-ABL, and it causes CML by phosphorylating numerous downstream proteins involved in the activation of cell division, among other functions. During the earliest phase of the disease, the chronic phase, kinase inhibitors that target BCR-ABL are effective in stopping disease progression. However, a minority of patients remain unresponsive to this therapy.

Laboratory tests are thus of great importance for this disease. Not only are they required for the diagnosis of CML, but during therapy they can establish the degree of response. That response, in turn, can supply the clinician with a good estimate of the prognosis for the patient. The tests used for CML include complete blood count (CBC) with platelets, cytogenetic analysis, fluorescence in situ hybridization (FISH), and quantitative polymerase chain reaction (PCR). These tests vary in the difficulty of application and in the sensitivity. CBC is commonplace within the average hospital laboratory, whereas cytogenetic analysis, FISH, and PCR require specialized equipment, personnel, and training. Hematologic counts are the least sensitive measures of disease, with a limit of detection of a leukemic burden of 1011 cells. Cytogenetics can detect a burden of 109 cells. Finally, quantitative PCR can detect a burden of as few as 105 leukemic cells. The current costs of these tests range from approximately \$375 to \$1,500 and must be performed every 3 to 6 months to follow the patient's response to therapy.

CONCLUSION: The advent of kinase inhibitor therapy for CML has greatly increased the importance of sensitive analysis of disease burden. Subsequent testing during therapy greatly improves the ability of the clinician to predict the therapeutic outcome. Signs of early treatment failure can give the patient time to switch therapies before the disease progresses to an advanced stage.

KEYWORDS: BCR-ABL, Cytogenetics, Fluorescence in situ hybridization, Polymerase chain reaction, Chronic myeloid leukemia

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The American Cancer Society estimates that in 2007 approximately 4,600 patients are going to be diagnosed with chronic myeloid leukemia (CML) in the United States. CML accounts for approximately 15% to 20% of all adult leukemias, which includes chronic lymphocytic leukemia, acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL), and the incidence is approximately 1 to 1.5 per 100,000 people.¹ Fortunately, only 12% to 15% of these patients are estimated to die from this disease because of the availability of kinase inhibitors and the use of allogeneic hematopoietic stem cell transplants. Kinase inhibitors do not cure the disease; rather, they hold it in check for a while.

Diagnosis of CML

The standard CML work-up will initially involve a history and a physical examination. Blood is drawn to obtain a complete blood count (CBC) with platelets as well as a baseline chemistry to assess their renal function and hepatic function. Other assessments, such as morphological assessments of bone marrow aspirates, cytogenetics, fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR) will be described below. CML can present at any age; however, the median age for diagnosis is 53 years. The disease can be divided into 3 phases, and diagnosis can occur in any of these phases.

Clinical findings associated with CML have been well described.² More than 80% of patients complain of fatigue, regardless of the phase of CML. Interestingly, approximately 40% of these patients go to their primary care physicians for something unrelated, and in the process it is determined that their white blood cell (WBC) count is abnormally high. Otherwise, these patients are asymptomatic regarding their CML. These patients are in what is called the chronic phase (CP) of CML. At least 40% of patients present with splenomegaly. The spleen, and sometimes the liver, become packed with cells. This leads to sensations of early satiety, in addition to weight loss and anorexia. Bone pain is also a feature. CML by definition involves a WBC count >25,000. Erythrocytosis, increased platelet counts, and basophilia are also heralding factors of CML, specifically as the disease moves into the more advanced stages. The bone marrow is hypercellular with evidence of myeloid hyperplasia.

Clinical Phases of CML

CML can be divided into the CP, which is followed by the accelerated phase (AP) and subsequently the blastic phase (BP). AP and BP sometimes are lumped together and considered to be advanced-phase CML. The entire continuum from CP to BP lasts a median of 3 to 5 years. This time period can be broken down into the CP, which, if untreated, lasts for 2 to 5 years; the AP,

which can last up to a year; and finally the fatal BP, which lasts from 3 to 6 months. As stated previously, a patient can present in any of these 3 stages.

The International Randomized Interferon versus STI571 (IRIS) trial was a pivotal study that created some useful definitions.³ CP is defined as having within the peripheral blood and bone marrow less than 15% blasts, less than 20% basophils, and less than 30% blasts plus promyelocytes, with the Philadelphia chromosome (Ph; t9:22 chromosomal translocation) being present in these transformed cells. It is during this phase that kinase inhibitors have had such a marked effect on therapy.

The AP has been defined differently by different medical groups. Sokal et al. originally proposed that AP was achieved when blasts are $\geq 5\%$ of both the periphery and the bone marrow; basophils are $\geq 20\%$ of the periphery; and platelets are $> 1012/L$ or are low; and evidence exists of clonal evolution, progressive splenomegaly, and anemia.⁴ In comparison, the International Bone Marrow Transplant Registry (IBMTR) defines AP as $\geq 10\%$ blasts in the periphery and bone marrow, with $\geq 20\%$ of the periphery being made up of a combination of basophils plus eosinophils; the presence of a persistent thrombocytosis; and again, evidence of clonal evolution, progressive splenomegaly, and anemia.⁵ The M.D. Anderson Cancer Center defines AP as $\geq 15\%$ peripheral blasts with $> 20\%$ peripheral basophils, < 1011 platelets/L, and the presence of clonal evolution.⁶ Finally, the World Health Organization (WHO) defines AP as blasts comprising 10% to 19% in both the periphery and bone marrow, with basophils accounting for $> 20\%$ of the periphery, platelet counts $< 1011/L$ or $> 1012/L$, and evidence of clonal evolution and progressive splenomegaly.⁷ Commonalities between these different scales are an increasing number of peripheral blasts, increased peripheral basophils, and the presence of clonal evolution. Additionally, these patients are beginning to fail in their response to therapy.

Clonal evolution is defined as the appearance of cytogenetic abnormalities in addition to the Ph. Approximately 50% to 80% of patients who progress exhibit these abnormalities. One common finding is the appearance of a second Ph. Trisomy 8, another common cytogenetic abnormality associated with AP CML, consists of 3 copies of chromosome 8. Other abnormalities, such as isochromosome 17q, or deletions of the p53 tumor suppressor gene (chromosome 17p), also are observed.

BP is characterized by a much higher percentage of blasts, both in the periphery and bone marrow. WHO defines BP as $\geq 20\%$ blasts in the periphery or nucleated bone marrow cells, extramedullary blast proliferation, and the presence of large foci or clusters of blasts in bone marrow biopsies.⁸ IBMTR defines the BP as $\geq 30\%$ blasts in the periphery or bone marrow, along with extramedullary infiltrates of leukemic cells.⁸ Perhaps the most important aspect of BP is that it transforms into an acute leukemia and has to be treated as such. Interestingly, 60% to 70% of patients transform into a myeloid leukemia, whereas 20% to 30% of these

patients have the capability of transforming into a lymphoid blast crisis that is treated as an ALL as opposed to an AML.

■ Biology of CML

Examination of the chromosomal structure of cells of lymphoid, eosinophil, or platelet lineage from the patient with CML shows that all these lineages contain the Ph. This indicates that CML is a stem cell disease. To define it more specifically, CML is a myeloproliferative disorder. It is a clonal expansion of the translocation of chromosomes 9 and 22. The consequence of this translocation is the creation of an unregulated tyrosine kinase activity. CML was first described in 1960 and was the first disease state to be associated with a specific cytogenetic abnormality.⁹

Chromosome 9 contains the tyrosine kinase gene, ABL, named for the Abelson murine leukemia virus. Chromosome 22 contains the BCR (for breakpoint cluster region). In CML a translocation occurs to form a different chromosome, and this chromosome encodes for an oncoprotein that has very strong tyrosine kinase activity. As suggested by its name, the BCR has multiple sites at which the breakpoint can occur. These breakpoints have different implications for the aggressiveness of the disease.¹⁰ The p210 form of BCR-ABL is the most common form observed in patients with CML. The p230 form of BCR-ABL actually is associated with a more indolent disease. Finally, the p190 form of BCR-ABL is also diagnostic for the Ph, but this is most commonly seen in ALL as opposed to CML. The ABL gene region has just 1 breakpoint; thus, there are no variants that can affect disease. The ABL protein normally is a regulated kinase with the usual constraints of a kinase. In contrast, the BCR-ABL kinase continues to phosphorylate downstream protein targets associated with cellular proliferation without constraint. These targets include RAS, RAF, and AKT, among others.² In addition to dysregulating proliferation, these phosphorylation events also create changes in the adherence properties of these cells as well as diminished apoptosis (programmed cell death). All these alterations then lead to the development of CML.

■ Monitoring the Patient With CML

At diagnosis it is estimated that a patient has a load of 1012 leukemic cells (Figure). Assuming that the patient responds to therapy, the first assessment is to determine the number of blasts and basophils in a blood sample. If there are no or few blast cells in the blood and the blood count returns to within normal limits, this is referred to as a hematologic response (HR).⁸ If the assessment is that no leukemic cells can be detected, the HR is complete (CHR); otherwise it is partial (PHR). As shown in the Figure, this CHR assessment has a limit of detecting approximately 1011 leukemic cells or more in the body. An additional aspect of the CHR is the loss of any sign of splenomegaly.

The next level of assessment is cytogenetics. Using chromosomal spreads or FISH, the number of cells containing the Ph is determined. The reduction in leukemic cells observed by these

FIGURE Therapeutic Responses as a Function of the Number of Leukemic Cells Within the Body

CCR = complete cytogenetic response; CHR = complete hematologic response; MCR = major cytogenetic response.

tests is referred to as a cytogenetic response (CR). As shown, a reduction to 1% to 34% of evaluated response is considered a major CR. Less of a response is considered a minor CR. No detectable Philadelphia positive (Ph+) cells would be a complete CR (CCR).

Finally, the most sensitive assessment is quantitative PCR. The result of this assessment is referred to as the molecular response. PCR results are often reported as 10-fold (log) reductions, as shown in the Figure. Currently, our final limit of detection is an approximate load of 105 leukemic cells.

All these assessments are measures of residual disease. They are important, as it has clearly been demonstrated that the lower the leukemic cell burden, the longer the therapeutic response and the better the outcome for the patient.

Cytogenetics (karyotyping) is performed on a bone marrow biopsy. The cells derived from the biopsy are cultured for 1 to 3 days, allowing some of them to enter the metaphase state of mitosis, where the chromosomes are condensed and where cytogenetics can be assessed. At this point the cells are stained and the chromosomes are then identified on the basis of characteristic bands of light and dark staining. The sizes and patterns of these bands allow the identification not only of normal chromosomes but also of translocations, amplifications, and deletions. The Ph is thus identified by its unique pattern of bands.

The cost of this test at Emory Healthcare is approximately \$1,500. It is a crucial test and is always done at diagnosis. Not only does it enable the identification of the Ph but it also shows the presence of other cytogenetic abnormalities. This test will be essential in determining whether clonal evolution has occurred within the bone marrow stem cell pool and thus whether the patient has progressed beyond the CP. Furthermore, it is an essential test to be performed if disease progression is suspected. The 5-year survival data from the IRIS trial show that patients with CML who have no CR at 24 months have an 82% chance

of survival at 5 years.¹¹ In comparison, patients with CML who achieve a CCR at 24 months have a 99% chance of survival at 5 years. If the patient has not begun to respond to therapy within 12 months and possibly as early as 3 months, guidelines recommend that therapy be switched at this point rather than at a later date.

FISH involves the use of fluorescent probes to visually demonstrate the presence of the t(9:22) translocation. The probe that binds to a specific sequence within the ABL gene is attached to a red fluorescent marker. The probe that binds to the DNA sequence within the BCR is then attached to a green fluorescent marker. If the translocation has occurred, the 2 probes will be so close together that their colors fuse to produce yellow. FISH has a superior sensitivity to cytogenetics. In the former case, only cells in metaphase can be assessed, and a minimum of 20 cells must be done. Thus, the limit in sensitivity can be as low as 1 in 20 cells. In comparison, FISH is not performed on metaphase cells, and several hundred can be scanned within a sample assessment. FISH also can be performed on blood or bone marrow tissue. The cost for FISH is approximately \$1,000.

Quantitative PCR is by far the most sensitive assay available. The RNA sample is prepared from the blood or bone marrow sample and reverse transcribed to make complementary DNA (cDNA). The cDNA is then amplified for BCR-ABL transcripts and transcripts for a "housekeeping" gene, such as G6PD, using primers that are specific for the 2 genes. Because the amount of material doubles in each cycle, it is possible, once the sample has reached some predetermined level of amplification, to quantify the amount of starting material by counting cycles. To account for potential differences in starting cell numbers, the starting material is normalized to the amount of housekeeping gene starting material. At present, PCR can detect even 1 Ph+ cell within a sample of 1 million cells.

The cost of the test at Emory Healthcare runs about \$370; however, the test requires specialized equipment and training. Often the test is sent out to be performed, which may increase the cost and the time but decreases the burden on the technical staff. There has been some controversy over using this test at diagnosis; however, the reasons for doing so are becoming more apparent. Most important, the performance of this test at diagnosis gives the clinician a firm baseline measure of disease against which therapeutic response can be measured.

Again, returning to the 5-year survival data from the IRIS trial, patients on imatinib therapy who achieved a CCR and greater than or equal to a 3-log reduction in BCR-ABL transcripts had a 100% survival at 5 years. Patients on imatinib therapy who did not achieve a CCR had an 88% survival rate at 5 years.

The criteria for the various responses just described are as follows: PHR and CHR are differentiated by the presence of immature blasts and splenomegaly. The CR is generally described in terms of percentages of Ph+ metaphases, with the minor CR ranging from 35% to 90% and the major CR ranging from 1% to 34%. A CCR is the absence of detectable Ph+ metaphases. Finally,

TABLE

Genetic Test Indications in CML

Test Period	Source	Cytogenetics	FISH	RT-PCR
At diagnosis	Bone marrow	Yes	No	No*
	Blood	No	Yes	Yes
During therapy	Bone marrow	Q 3-6 mo. until CCR, then replace with blood FISH or RT-PCR		
	Blood	No	Q 3-6 mo. after attaining BM CCR if use FISH for MRD assessment	Q 3-6 mo. after attaining bone marrow CCR
After HSCT	Bone marrow	At 3-6 mo., then as indicated	No	No
	Blood	No	Q 6 mo. for 2 yr. if FISH for MRD assessment	Q 6 mo. for 2 yr.
Transformed to AP or BP	Bone marrow	Yes	No	No
	Blood	No	No	No

*New data from the IRIS trial and others indicate that RT-PCR is necessary at diagnosis.

AP = accelerated phase; BM = bone marrow; BP = blastic phase; CCR = complete cytogenetic response; CML = chronic myeloid leukemia; FISH = fluorescence in situ hybridization; HSCT = hematopoietic stem cell transplantation; IRIS = International Randomized Interferon versus STI571; MRD = minimal residual disease; Q = every; RT-PCR = reverse transcriptase polymerase chain reaction.

Adapted with permission from Tefferi et al.¹²

a major molecular response is defined as at least a 3-log reduction in BCR-ABL transcripts, and a complete molecular response is defined as the complete absence of detectable transcripts.

The Table shows a list of recommended tests during the course of diagnosis and treatment and during the various stages of the disease, derived from the work of Tefferi et al.¹² In general, the tests begin with the least specific, most readily available. Cytogenetics or FISH tests are performed every 3 to 6 months until a CCR is achieved. At that point, the examination switches to PCR, which is repeated every 3 to 6 months throughout the patient's time of therapy. The one point of controversy in this Table is the use of PCR during diagnosis. For the reasons stated above, this author believes strongly that the PCR test should be included at diagnosis.

Conclusions

CML therapy has improved to the point where only a small percentage of patients are expected to die of the disease. However,

survivors are not cured. Rather, their disease is held in check. This has placed even more importance on laboratory tests as means of diagnosis and an assessment of therapeutic response. Standard assays such as CBC and cytogenetics, although less sensitive, are important tools because of their ubiquity and prognostic power. More specialized tests, such as FISH and PCR, require more training; however, their sensitivity allows the clinician to quantify residual disease. PCR is emerging as a test to perform from diagnosis throughout therapy because of its immense power to establish a baseline at diagnosis and to establish the degree of response even at early time points in therapy. These early data will be essential to help identify nonresponders and allow them to switch therapies at an early stage of disease progression.

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Targeted Chronic Myeloid Leukemia Therapy: Seeking a Cure

Christopher Fausel, PharmD, BCPS, BCOP

ABSTRACT

BACKGROUND: Chronic myeloid leukemia (CML) is a hematopoietic stem cell cancer driven by the BCR-ABL fusion protein that arises from the translocation of chromosomes 9 and 22. The disease begins with an indolent chronic phase (CP) that can last for 3 to 5 years. If untreated, it progresses into accelerated phase (AP) and within a year, blast phase (BP). Survival at this point is less than 1 year. During disease progression, mutations and the Philadelphia chromosome (Ph) appear (a process called clonal evolution). The only known curative therapy for CML is allogeneic bone marrow transplant (BMT). However, toxicity is formidable, with treatment-related mortality reported in the 30% range. Thus, effective therapy that maintains the patient with CML in CP with minimal toxicity is the goal for treatment of modern therapies. Because the preeminent mutation driving CML is BCR-ABL, therapies targeting BCR-ABL are the logical choice for disease-specific therapy. BCR-ABL inhibitors, such as imatinib, are proof that targeting specific genetic mutations associated with cancer yields a high degree of efficacy with minimal toxicity.

OBJECTIVE: This review will outline the evolution of therapy in CML. Pre-imatinib and imatinib-based treatment strategies, clinical efficacy, and the mechanism of imatinib resistance will be discussed.

SUMMARY: The discovery of the Ph and, subsequently, the identification of BCR-ABL revolutionized the treatment of CML. Cytoreductive chemotherapy, such as busulfan and hydroxyurea, was a mainstay of therapy to control white blood cell (WBC) counts; however, it did not modify the progression of the disease to AP and BP. The overall survival with CML ranges from 45 to 58 months in patients treated with cytoreductive therapy only. Treatment was advanced with the introduction of interferon (IFN) immunotherapy in the 1980s. In some studies, IFN produced a complete hematologic response (CHR) in more than 50% of patients; however, its nonspecific immunostimulatory mechanism also produced severe flu-like symptoms that limited tolerability. Despite the significant toxicity, cost, and inconvenience of injecting IFN thrice weekly, median survival ranged from 60 to 89 months. Allogeneic BMT is the only known curative therapy for CML; however, treatment-related mortality from infection, bleeding, and graft versus host disease, age, and the availability of suitable donors limits its widespread use.

Imatinib functions by competing with adenosine triphosphate (ATP) for binding to the BCR-ABL tyrosine kinase. In the absence of ATP, BCR-ABL is not able to activate downstream effector tyrosine kinase molecules that drive WBC proliferation. The International Randomized Interferon versus STI571 clinical trial was the first to document the efficacy of imatinib as a first-line therapy for patients in CP. More than 90% of these patients had a CHR. Toxicities associated with this therapy are low. Response in patients with advanced CML is less pronounced than in CP and is shorter lived, with less than 30% of patients achieving a CHR. For patients with CML in BP, the only viable therapy is to attempt a temporary reduction in disease burden with a salvage chemotherapy regimen, such as VAC (etoposide, cytarabine, and carboplatin). The goal of this induction chemotherapy is to induce a second remission; then the patient may be considered for allogeneic BMT.

The main toxicities seen with imatinib therapy are myelosuppression, edema, and myalgia/arthritis. In many cases, imatinib dosage can be briefly halted or lowered while the toxicity is managed. Imatinib resistance may develop at any time and inevitably leads to disease progression.

Resistance is usually caused by mutations within BCR-ABL, decreasing the affinity of imatinib binding. Next-generation kinase inhibitors are focused on the ability to inhibit these mutated forms of BCR-ABL.

CONCLUSION: For the majority of patients with CML in CP, the standard of care is to maintain the patient in CP with imatinib therapy. Clinical trials have been extraordinarily successful, with 5-year survival rates greater than 90%. Allogeneic BMT continues to be an option for those who cannot tolerate imatinib or when CML progresses on imatinib therapy.

KEYWORDS: BCR-ABL, Imatinib, Interferon, Leukemia, Myelosuppression

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The history of research into chronic myeloid leukemia (CML) serves as a blueprint for how a cure for cancer might be achieved. In 1960 the Philadelphia chromosome (Ph) was first described.¹ In 1973, CML was further characterized as a translocation of chromosomes 9 and 22.² Subsequently, it was determined that the 9:22 translocation coded for the BCR-ABL tyrosine kinase. General cytotoxic chemotherapy drugs were used at first until interferon γ (IFN γ) was proven superior to cytoreductive therapy in randomized trials in 1994.³ The next phase in drug development targeted the BCR-ABL protein with the inhibitor imatinib. The drug was initially approved by the U.S. Food and Drug Administration in 2001 and then approved as front-line therapy for chronic phase (CP) CML in 2003. With widespread clinical use, imatinib resistance was reported and the mutations leading to resistance were subsequently identified. The second-generation kinase inhibitors, which had efficacy against most of these mutations, entered clinical trials by 2005. This work has continued and new drugs that target the 1 remaining resistant BCR-ABL mutation, T315I, are now the subject of ongoing clinical trials.

The current treatment goals for the patient with CML are to maintain remission and prevent progression of the disease to accelerated phase (AP) or blast phase (BP) while minimizing any therapy-related toxicity. At present, the only proven curative therapy for CML is allogeneic bone marrow transplant (BMT). The data with newer targeted therapies do not have adequate follow-up to determine curative potential. This review will discuss pre-imatinib and imatinib-based therapies used to treat CML, with their respective efficacy and toxicities.

Pre-imatinib Therapies

Cytoreductive Therapy

Busulfan was one of the initial agents to treat CML. It has efficacy in controlling elevated white blood cell (WBC) counts over a period of several years. However, busulfan therapy is not without toxicity. Perhaps the most well-known toxicity is pulmonary fibrosis, commonly termed “busulfan lung.” This toxicity appears to be related to the duration of exposure to the drug. Patients progressed to AP and BP, with a median survival of 45 months.

Hydroxyurea, an S-phase specific agent, was developed as a safer alternative for CML therapy. It provides short-term control of WBC counts and spleen size. Toxicities associated with this therapy include nausea/vomiting, stomatitis, and rash. Patients progressed to AP and BP, with a median survival of 58 months. Busulfan and hydroxyurea did not eliminate the Philadelphia chromosome positive (Ph+) cells from the bone marrow or significantly slow the progression of the disease to AP or BP.

The first drug that was capable of increasing the period of time during which the patient could remain in CP was IFN γ . IFN γ is a nonspecific stimulant of the immune system that upregulates T-cell activity. It produced a complete hematologic response (CHR) in 40% to 80% of patients and a complete cytogenetic response (CCR) in 6% to 10% of patients. This response translated into a median survival of upwards of 89 months. However, because IFN γ is a nonspecific immunostimulant, it also produces flulike symptoms, causes excessive fatigue, and, in some patients, causes depression. In addition to these toxicities, therapy required 3 injections per week and was expensive. Many patients discontinued therapy for toxicity, cost, or compliance reasons. A moderate increase in efficacy was observed when IFN γ was combined with low-dose cytarabine; however, the course of the disease was no different from that observed in treatment with IFN γ alone.

Bone Marrow Transplant

Allogeneic BMT is a potentially curative treatment for CML. Patient eligibility for the procedure is predicated on identification of a suitable donor, patient age, and disease control. The patient must be younger than 60 years. Because the median age of diagnosis for CML is 53 years, many patients are simply too old at diagnosis for BMT to be a viable treatment option. If the transplant is performed using a matched sibling as a donor, the chance for long-term disease-free survival ranges from 50% to 75%.⁴ If the donor is unrelated, the chance of long-term disease-free survival is 40% to 50%, with an increased risk of early mortality and graft versus host disease (GVHD).⁵

The toxicities associated with this technique are formidable. Patients are at risk for bleeding complications and infectious complications during the 2- to 3-week peritransplant period when their blood counts are very low before bone marrow recovery (engraftment). After engraftment, patients are at risk

FIGURE 1 Mechanism of Imatinib-Mediated Inhibition of BCR-ABL

ATP = adenosine triphosphate; STI571 = imatinib mesylate.

Left panel, ATP is bound to BCR-ABL, resulting in the phosphorylation of a tyrosine on the substrate. The substrate is then able to interact with an effector protein. Right panel, STI571 is bound to BCR-ABL in place of ATP. The tyrosine of the substrate is not phosphorylated, and the substrate can no longer interact with the effector protein. Reprinted with permission from Goldman and Melo.⁷

for GVHD, in which the donor bone marrow produces alloreactive T-cells from the donor, which attack the recipient's tissues. Common organs affected by GVHD include the skin, gastrointestinal (GI) tract, and liver. Grade 3 or grade 4 GVHD associated with the liver or the GI tract is associated with mortality approaching 100%.

Autologous BMT is done using Ph negative cells that are recovered after chemotherapy or after ex vivo purging.⁶ Unfortunately, these populations contain quiescent CML progenitors that will ultimately produce an inevitable relapse. Thus, autologous BMT is not a feasible strategy.

Imatinib-based Therapy

Imatinib Mechanism of Action

Imatinib mesylate, originally called STI571, has been commercially available since May 2001. It works by binding to BCR-ABL and blocking its function. BCR-ABL normally places phosphate groups on other proteins, which serve to activate them. These proteins, in turn, activate downstream proteins, creating an expanding cascade of protein activation that ultimately results in uncontrolled growth. To activate these downstream proteins, BCR-ABL requires adenosine triphosphate (ATP), which donates the phosphate group. ATP has a special binding site on BCR-ABL close to where the substrate proteins bind (Figure 1, left panel).⁷ If the ATP binding site is occupied, then ATP cannot donate the phosphate and BCR-ABL can no longer activate downstream signaling proteins that promote cell division (Figure 1, right panel). Disease progression is essentially stopped by blocking this 1 ATP binding site that happens to sit at the initiating node of a

TABLE

Imatinib Clinical Trial Results

Treatment	Outcomes	Notes
Imatinib 400 mg PO daily (IFN failures)	CHR, 95%; MCR, 60% (CCR, 41%; PCR, 19%)	Responses in hematologic IFN failures, cytogenetic IFN failures, and IFN-intolerant patients. Time to MCR: 2.4-19 mo.; 16% relapse; estimated PFS at 18 mo.: 89%. ⁸
Imatinib 400 mg PO daily (front-line)	CHR, 95%; MCR, 85%; overall survival, no difference reached at early follow-up	IRIS trial: imatinib (n = 553) vs. IFN+ Ara-C (n = 553). Median follow-up: 19 mo. Imatinib grade 3/4 toxicities: myelosuppression or elevation in LFTs. Crossing over to imatinib from IFN: CHR was 82.4% and MCR was 56%. ⁹

Ara-C = cytarabine; CCR = complete cytogenetic response; CHR = complete hematologic response; IFN = interferon; IRIS = International Randomized Interferon versus STI571; LFT = liver function test; MCR = major cytogenetic response; PCR = polymerase chain reaction; PFS = progression-free survival; PO = orally. Data from Kantarjian et al.⁸ and O'Brien et al.⁹

large and complex signal transduction cascade. Several different points along this cascade can serve as targets for future therapies; however, this review will focus solely on BCR-ABL.

Clinical Trials: CP CML

Because many previous cancer therapies have been disappointing, the efficacy data for imatinib are stunning. The initial large trial involved patients who had failed IFN γ treatment.⁸ As a second-line therapy, imatinib was able to produce a CHR in 95% of the patients, resulting in normalization of blood counts. Furthermore, 66% of the patients showed a loss of Ph+ cells or at least a reduction of Ph+ cells in bone marrow biopsies. Cytogenetic and molecular responses are shown in the Table. First-line treatment of newly diagnosed patients with CML with imatinib produced even better results.⁹ This trial, known as the International Randomized Interferon versus STI571 (IRIS) trial, generated a similar number of CHR events; however, a greater number of patients showed a complete loss of Ph+ cells (Table). At the time of publication, there was no survival difference between the groups; however, the trial was only 2 years old at that point. Imatinib did show some toxicity in this 2-year study—specifically, myelosuppression—and some elevation in liver function tests. Patients who failed therapy were able to cross over to the other arm of the study.

At the time of publication of the 5-year follow-up data, 65% of the IFN γ group had switched to imatinib because of failure or intolerable toxicities.¹⁰ More than 80% of these patients achieved a CHR and more than 50% achieved a cytogenetic response

(CR). In comparison, 69% of patients receiving first-line imatinib remained on this therapy after 5 years. Only 3% of patients who discontinued imatinib crossed over to IFN γ therapy. The Kaplan-Meier analysis of imatinib responses are shown in Figure 2.

The percentage of patients who achieved a CHR began to plateau after 12 months. Meanwhile, the percentage of patients who achieved a CCR (complete loss of Ph+ cells) continued to increase for 30 to 36 months. At the 5-year point, virtually 100% of patients had achieved a CHR, 90% had achieved a major CR, and approximately 85% had achieved a CCR. The percentage of patients who remained free of disease progression over this 5-year period was 93%, and the number of patients who died from CML was 5%. These efficacy data are unprecedented for a single agent in the treatment of cancer.

The 5-year toxicity data were equally compelling. The most common toxicities reported were hematologic with the elevated transaminases. Remarkably, these toxicities presented primarily within the first 2 years and then resolved. In most chemotherapeutic programs, toxicities continue to worsen throughout the treatment.

Clinical Trials: Advanced CML

The prognosis for patients with CML in AP and BP is inferior to that seen in CP. It is possible to offer BMT to patients who have progressed to AP; however, the overall survival and treatment-related mortality are demonstrably worse relative to patients in CP who undergo this procedure. Patients with CML in AP do respond to imatinib; however, as the disease burden increases, the efficacy of imatinib decreases. CHR was achieved in 29% of AP patients taking 400 mg imatinib daily (with 26% returning to CP) and in 41% of AP patients taking 600 mg imatinib daily (with 17% returning to CP).¹¹ A major CR was achieved in 18% of AP patients on the 400 mg imatinib dose and in 30% of AP patients on the 600 mg imatinib dose.

BP CML has a clinical course analogous to acute leukemia. Similarly, therapy for this patient population reverts to treating an acute leukemia. One example is the induction chemotherapy regimen VAC (etoposide, cytarabine, and carboplatin). The VAC regimen had an overall CR rate of 58% in 31 patients with median survival of 7 months.¹² These chemotherapy regimens can induce a second temporary CP. The goal with this reinduction chemotherapy is that patients can revert to a second CP long enough to be brought to BMT. Imatinib also has been tested in patients with BP CML.¹³ As in the previous study, 400 mg and 600 mg doses of imatinib were compared. A CHR was achieved overall in 4% of the 2 treatment arms, with a return to CP in 19% overall (22% previously untreated, 15% treated). If tolerated, 600 mg imatinib is the preferred dose.

Monitoring of Patients on Imatinib Therapy

Myelosuppression

Increased risk of myelosuppression is typically seen in patients who have a higher degree of disease burden in the bone marrow, low hemoglobin, a longer period of time from the initial diag-

nosis, and cytopenias with prior therapy. Sometimes supportive therapy using growth factors, such as granulocyte-colony-stimulating factor or erythropoietin, are used; however, there are no randomized trials demonstrating superiority over observation alone.¹⁴

Myelosuppression can be minimized by stopping the drug for approximately 1 month until patients' absolute neutrophil count recovers to >1,500 or their platelets recover to >100,000.¹⁴ If recovery is slow, the imatinib dose is resumed at 300 mg and slowly escalated to 400 mg over time. For patients with advanced CML taking 600 mg imatinib, the strategy is similar. Therapy is held until the counts recover. However, the amount of disease in the bone marrow must be considered. If the level of disease is high, it is paramount to minimize the amount of disease so normal hematopoiesis can be restored. Patients can be transfused or given myeloid growth factors to ameliorate the condition.

Edema

Imatinib induces some degree of edema in patients, often periorbital.¹⁴ The risk of edema is increased in females, in patients older than 65 years, and in patients with cardiac or renal disease. Options include decreasing the dose to 300 mg and instituting diuretics to decrease the fluid burden. For severe cases of edema, it may be appropriate to institute a drug holiday and restart at a lower dose when the patient improves.

Other Toxicities

Nausea and vomiting can be largely avoided by taking imatinib with food. Myalgia and arthralgia may be treated with nonsteroidal anti-inflammatory drugs, with the caveat that the platelet count cannot be low. Rash is common. The patient can be rechallenged or the imatinib dose lowered. Novartis will supply, on request, a very specific algorithm for restarting therapy at a lower dose to try to minimize recurrence of the rash. Finally, imatinib inhibits cytochrome P450 3A4 and thus has numerous drug interactions with other drugs using this liver metabolic pathway.

Imatinib Resistance

Acquired resistance refers to the ability of CML to develop resistance to imatinib over time. Disease progression despite imatinib is inevitable in patients who acquire these mutations. The most common cause is the mutation of BCR-ABL to a form that is no longer sensitive to imatinib. This is the most common form of resistance, and numerous mutations causing resistance have been identified and characterized. Another mechanism leading to resistance is gene amplification. Here the number of BCR-ABL proteins produced exceeds the ability of imatinib to inhibit.

Primary resistance refers to patients who do not respond to imatinib. Again, mutations within BCR-ABL can be the cause. Additionally, other targets, such as SRC, mitogen-activated protein kinase, and the NUP98/DDX10 fusion gene product, have been implicated; however, these targets are much less common. Imatinib resistance leads to disease progression and has neces-

FIGURE 2 Kaplan-Meier Estimates of the Cumulative Best Response to Imatinib Therapy

Adapted with permission from Druker et al.¹⁰

sitated the development of newer drugs capable of inhibiting mutated forms of BCR-ABL. These newer inhibitors will be covered in the next article in this supplement.

Conclusions

CML therapy has progressed from nonspecific cytoreductive chemotherapies with limited efficacy to a highly targeted inhibitor with extraordinary efficacy. More than 90% of imatinib-treated patients in the IRIS trial remain alive and progression free 5 years out. Toxicities are low and occur primarily within the first 2 years of treatment. Resistance is a major problem because it can develop at any time and lead to disease progression. Data from the IRIS trial suggest that acquired resistance is not common, at least within the 5-year span of the trial. Nevertheless, new inhibitors are required to deal with this problem. Inhibitors of this type are currently in clinical trials and show great promise.

DISCLOSURES

This article is based on a presentation given by the author at a symposium held during the Academy of Managed Care Pharmacy's 19th Annual Meeting and Showcase on April 12, 2007, in San Diego, CA.

The author has served as a consultant for Abraxis Oncology and for Amgen Inc.

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New Strategies in Controlling Drug Resistance

David Frame, PharmD

ABSTRACT

BACKGROUND: Chronic myeloid leukemia (CML) is most often caused by the translocation of chromosomes 9 and 22 to create the fusion protein, BCR-ABL. This constitutively active tyrosine kinase promotes cell division and blocks apoptosis, leading to unregulated growth of hematopoietic stem cells. Imatinib is a small molecule that binds to BCR-ABL at the site in which adenosine triphosphate (ATP) binds and blocks BCR-ABL function by blocking its ability to use ATP. As a front-line therapy, imatinib has been tremendously successful, with 80% to 90% of patients with chronic phase (CP) CML remaining progression free for more than 5 years. Increasingly, however, imatinib-resistant clones are appearing that allow the disease to progress. Dealing with the rise of these resistant clones has presented an important challenge to health care providers.

OBJECTIVE: To review the mechanisms by which CML becomes resistant to imatinib and to discuss the new therapeutic alternatives to imatinib and when they should be considered.

SUMMARY: Managed care weighs advances and associated costs to determine the introduction of imatinib has indefinitely lengthened the survival time of patients with CML, transforming this into a chronic disease condition. However, care must be taken to avoid the appearance of imatinib-resistant clones. Resistance can manifest through 1 of several mechanisms, including increased plasma protein binding, increased drug efflux, the appearance of BCR-ABL mutants that have low affinity for imatinib, the appearance of BCR-ABL independent proliferation signals, and the amplification of the BCR-ABL gene. Subtherapeutic dosing is highly likely to result in the selection of a resistant clone; thus, it is of paramount importance to ensure the imatinib dose is sufficient. Measurements of plasma levels of imatinib are proving to be predictive of outcomes, suggesting that the monitoring of imatinib levels will be an important and necessary aspect of monitoring disease. Several clinical trials have shown that high-dose imatinib provides greater and faster response rates. This also may lead to better long-term blockade of disease progression. Waiting until disease progression begins appears to lead to greater resistance to high-dose imatinib and should be avoided. Dasatinib is a next-generation kinase inhibitor that binds to both SRC and to multiple conformations of BCR-ABL. It is capable of blocking several BCR-ABL mutants that are resistant to imatinib. Clinical trials have shown dasatinib is effective in maintaining patients in CP and can return a percentage of patients with advanced CML to CP. Economic analysis indicates that the cost-efficacy ratio for imatinib is approximately \$40,000 per year and compares favorably with the costs of accepted procedures, such as dialysis. Data have shown that tyrosine kinases also have better mortality rates than allogeneic bone marrow transplant for the first 8 years and appear to also be more cost-effective than transplantation for this time frame.

CONCLUSION: New clinical data are beginning to supply us with effective dosing and monitoring parameters for imatinib and dasatinib treatment of CML. Economic analysis indicates that these therapies are acceptable in cost and effective in providing good quality of life to patients.

KEYWORDS: Dasatinib, Drug cost, Drug resistance, Imatinib, Leukemia

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Chronic myeloid leukemia (CML) has now truly become a chronic disease. Before the availability of imatinib, the average survival of the newly diagnosed patient was 3 to 6 years. Now, 80% to 90% of patients are remaining in chronic phase (CP) after 5 years. This creates important issues for the managed care pharmacist, including how these patients will be monitored, how a decision will be made to change therapy, and what costs will be associated with this new population of patients with chronic disease. A change in therapy could be motivated by toxicity to the front-line drug, but most often a change is made because of the appearance of resistant clones. This review will focus first on the emergence of imatinib resistance and newer therapies in clinical trials that can, to some extent, block the activity of these mutated BCR-ABL proteins. Second, the economics of these newer therapies will be compared.

Mechanisms of Imatinib Resistance

There are 5 main mechanisms currently known that may result in imatinib resistance. The first is plasma protein binding. Imatinib binds very strongly to the δ -1-acid glycoprotein.¹ Changes in δ -1-acid glycoprotein may change the amount of binding of this drug, thus changing drug availability. The second mechanism is drug efflux.² Imatinib is a substrate for the P-glycoprotein pump, which can result in decreased intracellular concentrations of imatinib. The third mechanism is the mutation of the BCR-ABL kinase.³ Mutations are common in dividing cancer cells. In the presence of imatinib, cells that generate mutations in BCR-ABL can overcome the ability of this drug to inhibit cell division. Mutations that alter the imatinib binding site without affecting the adenosine triphosphate binding site or the active site of the kinase are very effective at inducing drug resistance. The fourth mechanism is independent of BCR-ABL. Although the 9:22 translocation is necessary to initiate CML, BCR-ABL is only one of several kinases capable of maintaining the proliferation rate of the cell while inhibiting apoptosis. Activity of other kinases and second messengers, including the SRC family of tyrosine kinases, have been implicated in this form of resistance.⁴ The fifth mechanism is gene amplification.³ As the number of Philadelphia chromosomes increases, the number of BCR-ABL proteins expressed in the cell increases and the efficacy of imatinib decreases.

Should Imatinib Levels Be Monitored?

Subtherapeutic imatinib dosing is troubling because, similar to bacterial resistance to an antibiotic, resistant CML mutations may be selected and proliferate. Monitoring imatinib levels will be useful; however, because only a few laboratories in the United States are capable of performing these measurements, the process of monitoring will be expensive. Nevertheless, data are just now being generated, indicating that imatinib levels are quite predictive of response.

In 1 study, 68 patients with CML were examined.⁵ Of these,

TABLE

Response Rates in Patients With Newly Diagnosed CP CML

Response	IM + Low-Dose Ara-C	IM + High-Dose Ara-C	IM + Pegylated IFN	High-Dose Imatinib	Standard-Dose Imatinib
Patients (n)	30	127	76	114	114
Follow-up (mo)	12	18	12	12	18
CHR (%)	100	NR	97	98	96
MCR (%)	83	83	83	96	87
CCR (%)	70	67	70	95	76
MMR (%)	NR	51	47	60	39
CMR (%)	2/15	28	14	26	4
Grade 3/4 neutropenia (%)	27	NR	63	36	14
Grade 3/4 thrombocytopenia (%)	37	NR	28	25	8

Ara-C = cytarabine; CCR = complete cytogenetic remission; CHR = complete hematologic response; CMR = complete molecular response; IFN = interferon; IM = imatinib; MCR = major cytogenetic response; MMR = major molecular response; NR = not recorded. Reprinted with permission from Deininger.⁷

56 were in complete cytogenetic remission (CCR) and of these, 34 had a major molecular response (MMR). Trough levels of imatinib were established for each patient, and the correlation between imatinib trough and degree of response was found to be highly significant. More recently, data from the International Randomized Interferon versus STI571 (IRIS) study demonstrated that the trough concentration (C_{min}) of imatinib was significantly higher in patients who had achieved a CCR (1,009 ng/mL vs. 812 ng/mL, $P = 0.0116$).⁶ Blood samples had been obtained from 551 patients with CML on day 1 (trough sample taken 24 hours after the first dose) and at steady state on day 29 of treatment. Molecular response rates after 1 year showed that only 25% of patients with levels <647 ng/mL went into a molecular response, whereas 40% of patients with levels >647 ng/mL went into a molecular response. After 4 years, 53% of patients with a low C_{min} achieved an MMR versus 80% of patients with a high C_{min}. Each of these patients was given an imatinib dose of 400 mg, but their plasma levels, as well as their responses, varied considerably.

Utility of High-Dose Imatinib Therapy

One strategy that might address the issue of resistance is to increase the imatinib dose. Data supporting this hypothesis consisted of a comparison of 5 independent studies.⁷ The study compared the standard 400 mg dose of imatinib with imatinib plus either cytarabine or interferon β (IFN β) or with high-dose imatinib (600-800 mg). The response rates are shown in the Table. Adding cytotoxic chemotherapy did not improve the overall response to therapy compared with imatinib alone and greatly increased the incidence of grade 3 and 4 neutropenia and throm-

bocytopenia. High-dose imatinib produced the best results of all. An MMR was achieved by 60% of patients at the higher imatinib dose compared with 39% at the standard dose.

In a second trial (the RIGHT trial), 115 patients with CP CML received initial dosing of 800 mg imatinib.⁸ At 16-month median follow-up, it was found that these patients had a rapid MMR. By 6 months, 44% had achieved an MMR compared with patients in the IRIS trial, in which only 21% of patients had achieved an MMR at 6 months on the standard imatinib dose. It should be noted that 10 patients had to discontinue therapy as a result of adverse events. Is the rapidity of the MMR worth the increased toxicity? One would predict that the answer would be yes. Each surviving leukemia cell has the capability to become resistant. With the rapid reduction in the number of cells, the probability of a resistant clone arising may be decreased. Whether or not the initial high-dose therapy will decrease time to resistance will be determined over the course of the long-term monitoring of these patients.

Patients with CML in CP can be ranked as low or high risk as measured by their Sokal score, which is calculated using age, spleen size, platelet count, and peripheral blood blast count.⁹ There are 3 categories of Sokal scores: (1) low risk (<0.8); (2) intermediate risk (0.8-1.2); and (3) high risk (>1.2).¹⁰ Patients with a high score are most likely to progress to advanced disease. The next trial focused on this patient group.¹¹ Again, patients (N = 87) were started on 800 mg imatinib and disease was assessed after 6 and 12 months. For the Sokal trial patients, 90% of the high-dose group achieved a CCR at 12 months, whereas 67% of high-risk patients in IRIS achieved a CCR. However, compliance was an issue. Although compliance was classified as good in the

study, it was close to 50%. In other words, approximately 50% of patients had to drop their imatinib dose to less than 600 mg as a result of toxicities. Thus, a high initial dose of imatinib will bring about a quicker response; however, it appears difficult to keep patients at this dose level because of the likelihood of toxicities.

Because high-dose imatinib has greater toxicity, the physician might consider reserving the high-dose regimen for patients who fail therapy at 400 mg. However, this may not be as effective. In a small trial involving 20 patients with hematologic resistance or relapse at 400 mg imatinib, patients were increased to 800 mg. Although 65% went on to achieve a complete or partial hematologic response, only 1 patient achieved a cytogenetic response (CR).¹² Additionally, the response appeared to be of short duration. These data would suggest that by allowing the patient to progress to a more advanced phase of CML, the consequence would be promotion of clonal expansion of resistant cells.

■ Dasatinib

Dasatinib is structurally different from imatinib, and it has some very different properties from imatinib. It not only inhibits the BCR-ABL kinase, but also inhibits SRC kinase.¹³ It binds the BCR-ABL kinase domain in the active and inactive conformation. Imatinib only binds if the kinase is in an inactive form. This becomes important when one considers how resistant mutations block imatinib function. Many of the mutations are located in sites around the kinase that shift the formation of the kinase to an active formation. Thus, these mutations not only make the kinase more active, they block the ability of imatinib to bind. Dasatinib binds to BCR-ABL with a 300-fold increase in affinity, and because it binds BCR-ABL in the active conformation, it is capable of inhibiting cells that develop many of the imatinib-resistant mutations.

The phase I trial was performed on 84 patients with CML, of whom 72 (86%) were resistant to imatinib therapy.¹³ The primary objective of the trial was to define the safety and tolerability of dasatinib with antileukemic activity and correlation to BCR-ABL mutations as a secondary objective. Dasatinib (15-240 mg) was administered orally in 4-week treatment cycles once or twice daily. Interestingly, although complete hematologic response (CHR) was achieved in 92% of patients in CP, CHR also was achieved in 45% of patients in accelerated phase (AP) and 35% of patients in blast phase (BP) CML. This achievement of CHR stands in contrast to imatinib trials that were much less effective in advanced CML.^{14,15} Indeed, whereas virtually no patients with advanced CML achieved a CCR in imatinib trials, 18% and 26% of patients in AP and BP, respectively, achieved a CCR in this phase I dasatinib trial.

An update for this trial was recently reported.¹⁶ After a median follow-up of 13 months, progression-free survival of all patients was 90%. Ninety-one percent of patients achieved a CHR, whereas 58% achieved a major CR. Of these, 41% had never achieved a CR at all on imatinib. Dose interruptions occurred in

331 patients (86%), and dose reductions occurred in 269 (70%), with an average daily dose of 103 mg per day. The major adverse event was pleural effusion, which affected 6% of patients. It is likely that these extraordinary results reflect the greater affinity of dasatinib, as well as its ability to bind to SRC, which is another major kinase signaling pathway that mediates cancer cell growth.

To answer the question of how to treat patients who were imatinib resistant at 400 to 600 mg, a study was done comparing high-dose imatinib to dasatinib in this setting. One hundred fifty patients who were resistant to low-dose imatinib were randomized and treated with dasatinib (70 mg twice daily) or imatinib (800 mg daily).¹⁷ With a minimum follow-up of 10 months, CHR rate was 92% with dasatinib versus 82% with imatinib. Major CR rate was 48% with dasatinib versus 33% with imatinib, and CCR rate was 35% with dasatinib versus 16% with imatinib. In patients with no prior CR, 44% achieved major CR with dasatinib versus 7% with high-dose imatinib. Thus, the results clearly demonstrated that dasatinib is superior to high-dose imatinib for patients with CML who have become resistant to the lower imatinib dose. Another study has demonstrated 100% 2-year survival in 125 imatinib-resistant patients when treated with subsequent dasatinib or nilotinib versus 72% survival with allogeneic transplant or 67% with other therapies.¹⁸

The optimal dasatinib dose is still a matter of debate. Currently, the approved dose is 70 mg twice a day; however, almost 50% of patients experience hematologic toxicities, such as neutropenia and thrombocytopenia and drop to 50 mg per day. This has propelled a trial in which 4 dasatinib dosing regimens (50 mg or 70 mg twice daily vs. 100 mg or 140 mg once daily) are being compared.¹⁹ The trial is ongoing and at present the interim results cannot distinguish between the various doses. The results of this trial are important as they will affect dasatinib dosing in the future.

■ New Thoughts in CML

Bone Marrow Transplant Versus Best Drug

Imatinib and dasatinib are tremendously effective at blocking disease progression; however, they are generally not thought to be curative. Patients live with the possibility of disease recurrence for the remainder of their lives. Currently, the only known curative therapy is allogeneic bone marrow transplant (BMT). However, this is only a potential option for younger patients in good performance status. Even in these patients, the early chance of mortality appears to be greater in those who undergo BMT. To establish relative risks for these 2 strategies, 621 newly diagnosed patients were followed.²⁰ Thirty-eight percent had a matched related donor and chose BMT, whereas the remainder received best drug therapy. At the beginning of this trial, the best drug therapy was IFN α . However, with the availability of imatinib, most of the patients switched to imatinib. Within the first year, BMT mortality was 20% to 30%. Subsequently,

patients succumbed to adverse effects, such as graft versus host disease. Indeed, the drug treatment group showed superior survival results for the first 8 years of the trial, at which point the curves began to superimpose. However, there was a higher rate of molecular remission with transplantation.

Stopping Imatinib After Cytogenetic Remission

If BCR-ABL transcripts are detectable by polymerase chain reaction (PCR), one would argue that the patient still has CML. However, in patients who achieve a complete molecular response (CMR) and no longer have detectable BCR-ABL transcripts, one could legitimately ask whether these patients still have disease. Recently, data were reported on 15 patients who had achieved a CMR for more than 2 years.²¹ The median duration of PCR negativity and imatinib therapy was 32 months (24-46 months) and 45 months (32-56 months), respectively. Eight patients displayed a molecular relapse with a detectable BCR-ABL transcript appearance within the first 6 months. Surprisingly, 7 other patients had an undetectable level of BCR-ABL transcripts after a median follow-up of 20 months (9-24 months). More studies are required to determine if a subset of patients may actually receive a potential cure from the tyrosine kinase inhibitors.

Economics of Treating CML

In general, the new chemotherapy drugs are extremely expensive. Imatinib costs range from \$28,000 to \$60,000 per year, depending on dosing. Dasatinib at 140 mg per day is approximately \$52,000 per year. If one looks at the breakdown of oral chemotherapy from costs reported from 1 health care system, imatinib accounted for 29% of claims in 2006 (Figure).²² This was actually enough for this health care system to actually triple its per-member-per month payment plan. Thus, these drugs can be extremely overwhelming in the overall insurance scheme, especially for small insurers or self-insurers.

If one examines cost utility, current published data are obsolete because they do not take into account the tremendous efficacy of the kinase inhibitors. Nevertheless, if one makes the assumption that a patient with CP CML fails IFN α and is put on a secondary therapy and then compares hydroxyurea to imatinib as that secondary therapy, cost utility analysis shows that imatinib is found to offer considerable health benefits to patients with an incremental cost-effectiveness ratio of \$75,427.²³

Dialysis is a useful marker for assessing the cost of quality-adjusted life-years. Dialysis incurs a cost of \$50,000 to \$60,000 per year, and this has been the benchmark for most cost analysis. If one looks at imatinib versus IFN α , the incremental cost-effectiveness ratio was \$44,270 per quality-of-life year gained.²⁴ This cost is significantly less compared with some of the other biologic anticancer agents. Cetuximab, used for colon cancer, costs \$30,000 to \$40,000 for an additional 2 months of survival.

Another study estimated imatinib-mediated survival at 15.3

FIGURE Distribution of Costs for Oral Chemotherapy Drugs for an Insured Health Plan

Pharmacy claims with dates of service from January 1, 2006, through May 31, 2006. Reprinted with permission from Curtiss FR. Pharmacy benefit spending on oral chemotherapy drug. *J Manag Care Pharm.* 2006;12(7):570-77.²²

years and compared it to the survival data for IFN α of 9.1 years.²⁵ The estimated increase in lifetime cost was calculated as approximately \$241,800. After discounting costs and survival benefits, the incremental lifetime costs were \$168,100 higher with imatinib with incremental cost-effectiveness ratios of \$43,100 per life-year saved and \$43,300 per quality-adjusted life-year saved. Finally, for BMT compared with imatinib therapy, using 2 years of data, the cost-efficiency ratio is \$86,000 for imatinib compared with \$261,000 for BMT.²⁶

Conclusions

Imatinib has turned CML from a relatively rapidly fatal condition into a manageable chronic disease. As with all chronic conditions, disease management must be optimized. Costs must be contained by establishing appropriate dosages and identifying the important disease parameters to monitor. Recent data strongly support the monitoring of imatinib levels to establish the effective dose, as well as high-dose imatinib therapy to achieve more rapid responses and to potentially avoid the more rapid development of resistant disease. Dasatinib is a newer kinase inhibitor that binds to BCR-ABL in the active and inactive conformations, as well as to the SRC kinase, and thus can overcome the resistance caused by several common CML mutations.

Clinical trials have been quite successful, not only for patients in CP but to a lesser extent, for patients in advanced stages of the disease. This is most likely because of the ability of dasatinib to block SRC and BCR-ABL kinases. Economic analysis shows that imatinib and dasatinib therapies have a cost-efficacy ratio close to that of dialysis, a marker for accepted costs of quality-of-life years. The cost-efficacy ratio is far superior to the older chemotherapies, such as hydroxyurea and IFN α , and also appears to be superior to BMT. Finally, it appears possible that some patients who have achieved a CMR with imatinib can stop therapy without relapse. More time is needed before it can be determined whether these drugs indeed have a curative effect.

DISCLOSURES

This article is based on a presentation given by the author at a symposium held during the Academy of Managed Care Pharmacy's 19th Annual Meeting and Showcase on April 12, 2007, in San Diego, CA.

The author has served as a consultant for and received honoraria from Bristol-Myers Squibb and Novartis.

UNLABELED/UNAPPROVED USES OF DRUGS

The author has cited applications and dosing of imatinib that are not approved by the U.S. Food and Drug Administration (i.e., 600-800 mg dosing for first-line therapy and 800 mg for refractory patients).

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Optimizing Outcomes Through Pharmaceutical Advances in the Treatment of Chronic Myeloid Leukemia

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Continuing Education for this program is processed solely through the AMCP.org Online Learning Center site at www.amcp.org (Learning Center/Online CE). No mailed forms will be accepted.

The posttest worksheet (below) is provided to assist you in marking your answers prior to entering the online CE center for submission; these pages cannot be submitted for CE credits.

In order to receive CE credit for this program, you must complete the following forms online:

1. Posttest form for this program, "Optimizing Outcomes Through Pharmaceutical Advances in the Treatment of Chronic Myeloid Leukemia," on the AMCP.org Online Learning Center site—to receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the posttest.
2. Program Evaluation form.

Upon successful completion of this program, you will automatically receive your CE statement. Your CE credits will be automatically archived and tracked for you on the AMCP.org Online Learning Center site. All information is kept confidential.

Note: There will be a \$10 processing fee for nonmembers. (See payment instructions on site.)

Posttest Worksheet: Optimizing Outcomes Through Pharmaceutical Advances in the Treatment of Chronic Myeloid Leukemia

1. Chronic myeloid leukemia (CML) accounts for what percent of adult leukemias?
 - a. 0.1%
 - b. 2%
 - c. 20%
 - d. 70%
2. What is the most common symptom shared by patients with CML?
 - a. Fatigue
 - b. Hyperglycemia
 - c. Headaches
 - d. Insomnia
3. According to the definitions set forth in the International Randomized Interferon versus ST1571 trial, a patient with CML with <15% blasts, <20% basophils, and <30% blasts plus promyelocytes, could be in
 - a. chronic phase
 - b. accelerated phase
 - c. blast crisis
 - d. all of the above
4. Which of the following is the correct definition of clonal evolution?
 - a. The propagation of the BCR-ABL translocation from stem cell populations to differentiated lymphoid and myeloid populations
 - b. The expansion of a particular clone of a transformed stem cell
 - c. The accumulation of additional mutations of BCR-ABL
 - d. The accumulation of translocations in addition to the Philadelphia chromosome (Ph)

5. Which response(s) are always assessed first when treating patients with CML?
 - a. The cytogenetic response
 - b. The hematologic response
 - c. The molecular response
 - d. All of the above
6. Which of the following laboratory tests are capable of identifying the presence of the translocation that produces BCR-ABL?
 - a. Quantitative polymerase chain reaction
 - b. Fluorescence in situ hybridization (FISH)
 - c. Cytogenetics
 - d. All of the above
7. What is the approximate cost for performing a cytogenetics assay?
 - a. \$50
 - b. \$300
 - c. \$1,500
 - d. \$5,000
8. What is the current limit of detection of numbers of Ph+ cells in a patient with CML?
 - a. 1 cell
 - b. 100 cells
 - c. 100,000 (10⁵) cells
 - d. 10,000,000 (10⁷) cells
9. Current treatment goals for patients with CML include
 - a. keeping them in remission
 - b. preventing disease progression to advanced stages
 - c. minimizing toxicity
 - d. all of the above
10. Which of the following therapies, historically, was the first drug developed that could extend the time to disease progression for patients with CML?
 - a. Busulfan
 - b. Hydroxyurea
 - c. Interferon α (IFN α)
 - d. Dasatinib
11. Which of the following is a common adverse effect associated with bone marrow transplant therapies?
 - a. Graft versus host disease
 - b. Myelosuppression
 - c. Cardiac toxicity
 - d. All of the above
12. What is the mechanism of action of the tyrosine kinase inhibitors?
 - a. They bind to BCR-ABL substrates and block BCR-ABL access.
 - b. They bind to the active site of the ABL kinase domain and block substrate access.
 - c. They bind to the adenosine triphosphate (ATP) binding site of the ABL kinase domain and block ATP access.
 - d. They bind outside of the kinase domain and change the conformation of BCR-ABL to block ATP access.
13. Which of the following is a common adverse effect associated with imatinib therapy?
 - a. Hypoglycemia
 - b. Myelosuppression
 - c. Liver toxicity
 - d. Recurrent infections
14. Patients with CML who progress to advanced disease are sometimes treated with the VAC (etoposide, cytarabine, and carboplatin) chemotherapy regimen. What is the realistic treatment goal?
 - a. The treatment goal is to cure the disease.
 - b. The treatment goal is to bring the patient back to long-term remission.
 - c. The treatment goal is to bring the patient back to remission to allow bone marrow transplant to be performed.
 - d. The treatment goal is to bring the patient back to remission to allow a switch to dasatinib therapy.
15. Which of the following is a reasonable approach to treating edema associated with imatinib therapy?
 - a. Decrease the imatinib dose
 - b. Administer a diuretic
 - c. Both a and b
 - d. None of the above
16. Which of the following is NOT a mechanism by which resistance to tyrosine kinase inhibitor therapy has been observed to occur?
 - a. Increased efflux through the P-glycoprotein pump
 - b. Secretion of imatinib-metabolizing enzymes
 - c. Appearance of BCR-ABL mutations that block imatinib binding
 - d. Amplification of the Ph
17. Why should imatinib levels be monitored?
 - a. Patients with plasma levels >647 mg/dL showed greater likelihood of edema
 - b. Patients with plasma levels >647 mg/dL showed greater likelihood of achieving a molecular response
 - c. Imatinib plasma levels correlated well with the likelihood of a resistant clone arising
 - d. All of the above
18. Which of the following is the current standard imatinib dose and high imatinib dose?
 - a. 100 mg once daily (standard), 200 mg once daily (high)
 - b. 200 mg once daily (standard), 400 mg once daily (high)

- c. 400 mg once daily (standard), 600 mg once daily (high)
 - d. 600 mg once daily (standard), 1,200 mg once daily (high)
19. How effective is dasatinib in blocking imatinib-resistant BCR-ABL mutations?
- a. Dasatinib cannot block resistant mutants.
 - b. Dasatinib blocks only 1 or 2 resistant mutants.
 - c. Dasatinib blocks most resistant mutants.
 - d. Dasatinib blocks all resistant mutants.
20. Which of the following drugs can block SRC kinase?
- a. IFN γ
 - b. Dasatinib
 - c. Imatinib
 - d. None of the above
21. When is bone marrow transplant an appropriate option?
- a. In older patients with CML who cannot respond to imatinib
 - b. In patients with CML who have progressed to advanced phase disease
 - c. In young patients with CML, as the likelihood of developing resistance to imatinib over time is great
 - d. All of the above
22. What is the cost range of dasatinib therapy for a year?
- a. \$5,000 to \$10,000
 - b. \$10,000 to \$20,000
 - c. \$30,000 to \$60,000
 - d. \$60,000 to \$120,000
23. The cost of dialysis is considered an acceptable cost for assessing the cost of quality-of-life years. What is the yearly cost for this treatment?
- a. \$5,000
 - b. \$10,000
 - c. \$60,000
 - d. \$100,000
24. What is the efficacy of dasatinib in treating patients with CML who failed imatinib?
- a. A complete hematologic response (CHR) was achieved in approximately 12% of patients.
 - b. A CHR was achieved in approximately 32% of patients.
 - c. A CHR was achieved in approximately 72% of patients.
 - d. A CHR was achieved in approximately 92% of patients.

To complete this activity, go to www.amcp.org (Learning Center/Online CE), where you will access the posttest and evaluation form.

NOTES

[illegible]

Supplement