Targeted Chronic Myeloid Leukemia Therapy: Seeking a Cure

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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 flulike 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/arthralgia. 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

J Manag Care Pharm. 2007;13(8)(Suppl S-a):S8-S12

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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 ∂ (IFN∂) 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∂. IFN∂ 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∂ 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∂ was combined with low-dose cytarabine; however, the course of the disease was no different from that observed in treatment with IFN∂ alone.

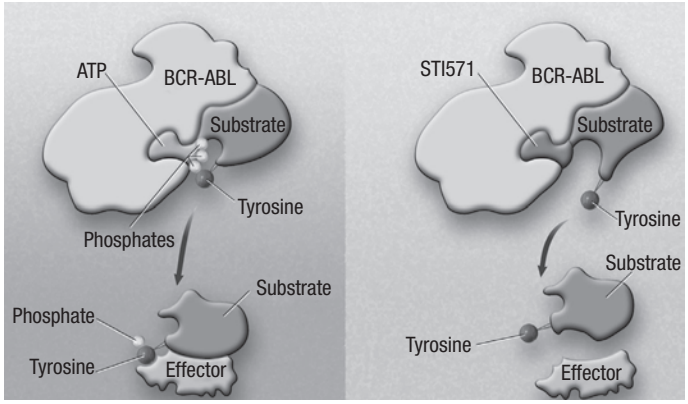
Bone Marrow Transplant

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 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.

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]

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∂ 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∂ 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∂ 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

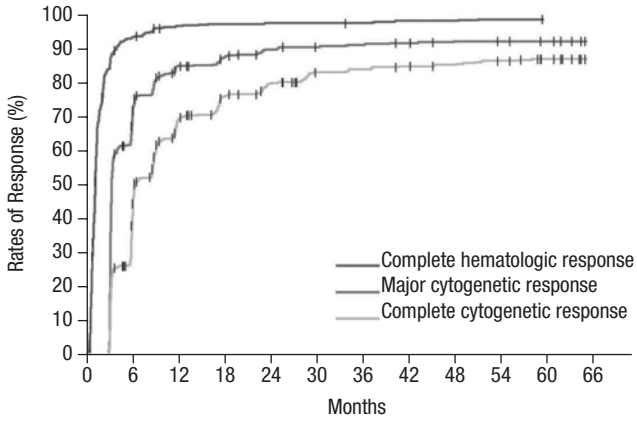
Nausea and vomiting can be largely avoided by taking imatinib with food. Myalgia and arthralgia may be treated with nonsteroidal anti-inflammatory drugs, with the caveat that the platelet count cannot be low. Rash is common. The patient can be rechallenged or the imatinib dose lowered. Novartis will 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 necessitated 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.

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



Adapted with permission from Druker et al.[10]

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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