A 28-year-old woman is referred for advice about the management of recently diagnosed chronic myelogenous leukemia (CML). She was in excellent overall health but was incidentally found to have an elevated white-cell count of 31,000 per cubic millimeter. Bone marrow aspirate and biopsy showed a hypercellular marrow with myeloid hyperplasia with less than 2% myeloid blasts and the presence of the Philadelphia (Ph) chromosome with no additional abnormalities. She was started on 400 mg of imatinib mesylate daily, and 3 weeks later her blood counts are normal. She is interested in discussing her further treatment and, in particular, the advisability of allogeneic stem-cell transplantation. She has no siblings, and a preliminary computer search of the worldwide donor list suggests that there may be only one or two fully histocompatible donors.

**The Clinical Problem**

CML is a myeloproliferative disorder that is a consequence of an acquired mutation affecting hematopoietic stem cells. This mutation results in a balanced translocation between chromosomes 9 and 22, initially identified in 1960, and termed the Ph chromosome [t(9;22)(q34;q11)].

CML occurs at roughly the same frequency in countries around the world and is no more common in one ethnic or racial group than in any other. The annual incidence rate is 1.6 cases per 100,000 adults (approximately 5000 new cases per year in the United States), with a male-to-female ratio of 1.4 to 1. The median age at diagnosis is approximately 55 years, with less than 10% of patients under the age of 20 years.

It is common for the diagnosis to be made after leukocytosis is found on routine blood tests in asymptomatic patients; nearly 90% of patients who receive the diagnosis of CML have chronic-phase disease. Patients with chronic-phase CML have elevated white-cell counts with circulating immature precursors and frequently have thrombocytosis and splenomegaly. After approximately 4 to 5 years, untreated CML inevitably progresses to the more aggressive accelerated and blast phases, characterized by the development of constitutional symptoms and an increasing number of leukemic blasts in the blood and bone marrow. The median survival of patients in the blast phase is less than 6 months, with infection and hemorrhage being the most common causes of death.

**Pathophysiology and Effect of Therapy**

The Ph translocation found in CML results in the juxtaposition of a portion of the human homologue of the Abelson murine leukemia (ABL) gene from chromosome 9...
and the breakpoint cluster region {BCR} gene of chromosome 22, which in virtually all cases results in the formation of a BCR-ABL fusion protein with a molecular mass of 210 kd. The BCR-ABL protein contains the active tyrosine kinase region of ABL, producing a cytokine-independent, constitutive proliferative signal and affects a variety of downstream pathways. This signal results in continuous cell growth and replication.5 Retroviral transfection with BCR-ABL alone is sufficient to initiate a myeloproliferative disorder in murine models,6,7 a finding that encouraged efforts to develop pharmacologic approaches to inhibit this discrete process.

Morphologically, chronic-phase CML resembles a benign expansion of myelopoiesis. However, the chronic phase is a genetically unstable state, and the high proliferative rate allows for the accumulation of additional molecular and chromosomal abnormalities, a process termed “clonal evolution.” Clonal evolution leads to impairment of hematopoietic differentiation, ultimately resulting in acute leukemia (blast-phase CML). Approximately one third of acute leukemias resemble B-lineage acute lymphocytic leukemia (ALL), whereas the rest of such cases are similar to acute myeloid leukemia (AML), often with an undifferentiated phenotype.

Imatinib mesylate {Gleevec, Novartis} is an inhibitor of multiple tyrosine kinases, including ABL, BCR-ABL, platelet-derived growth factor receptor (PDGFR), and c-kit. By preventing the phosphorylation of BCR-ABL, imatinib selectively inhibits downstream signaling and the growth of BCR-ABL–positive cells, inducing apoptosis of these cells. In May 2001, the Food and Drug Administration {FDA} approved the use of imatinib in the treatment of CML.

Single-nucleotide mutations in the BCR-ABL gene producing conformational changes in the BCR-ABL protein, which can affect the binding of imatinib to specific activation or kinase sites, can be detected in approximately half the patients who are resistant to imatinib.8-10 At least 40 such mutations have been characterized, some of which result in only modest changes in sensitivity to imatinib, whereas others produce complete resistance to the drug. Other mechanisms of resistance are not well characterized in patients in whom mutations are not detected.

To address this problem, newer inhibitors of BCR-ABL have been developed; of these, dasatinib {Sprycel, Bristol-Myers Squibb} and nilotinib {Tasigna, Novartis} are furthest along in clinical evaluation. These agents are much more potent in vitro than imatinib and have activity against most, but not all, of the acquired BCR-ABL mutations.10 Dasatinib was approved by the FDA in June 2006 for use in patients who are resistant to or cannot tolerate imatinib. Nilotinib has not yet been approved for clinical use.

**Clinical Evidence**

Allogeneic stem-cell transplantation is the only proven curative treatment for CML.11,12 Because of the possibility of premature death and symptoms related to chronic graft-versus-host disease, contemplation of transplantation is difficult for otherwise asymptomatic patients in the chronic phase. Before the development of imatinib, the principal alternative to bone marrow transplantation was therapy with a high daily dose of interferon alfa, alone or in combination with a low dose of cytarabine, which was recommended for most patients with newly diagnosed CML.13-16

The benefit of imatinib was definitively shown in the International Randomized Study of Interferon and STI571 {IRIS} trial, a comparison of imatinib with interferon plus cytarabine in 1106 newly diagnosed patients.17 In this trial, the estimated rates of complete cytogenetic response (absence of Ph-positive cells in the bone marrow) at 18 months were 76% for patients in the imatinib group and 14% for those in the interferon–cytarabine group. The rates of freedom from progression to the accelerated phase or blast phase were 97% and 92%, respectively. After 5 years of follow-up, the estimated cumulative rate of complete cytogenetic response was 87%, progression-free survival was 83%, and overall survival was 89% in the imatinib group.18

Imatinib has also been evaluated in phase 2 trials in patients with more advanced disease. Rates of hematologic and cytogenetic responses were much lower than in patients with chronic-phase disease, with an estimated survival at 4 years of approximately 40% in the accelerated phase19,20 and less than 10% in blast crisis20,21; median survival for patients with ALL or lymphoid blast crisis was 4.9 months.22 Thus, imatinib is often used as a “bridge” toward allogeneic transplantation in such patients.

Dasatinib and nilotinib have been evaluated in phase 1 and subsequent large phase 2 trials in
patients with CML or Ph-positive ALL who were resistant to or could not tolerate imatinib.\textsuperscript{23-27} In one dasatinib trial, complete cytogenetic response was achieved in 39\% of 127 imatinib-resistant patients with chronic-phase CML.\textsuperscript{29} In one nilotinib trial, a complete cytogenetic response was achieved in 40\% of 320 patients with chronic-phase CML,\textsuperscript{27} all of whom had received previous treatment with imatinib. Since these drugs have been in use for only 1 to 2 years, further follow-up is needed to assess the durability of response and the development of longer-term side effects.

**CLINICAL USE**

Most physicians recommend an initial trial of imatinib for essentially all patients with CML. The chief alternative is allogeneic hematopoietic stem-cell transplantation, which is typically reserved for patients who do not have a response to imatinib or for the occasional patient with intolerable side effects. Possible exceptions include children or adolescents with matched sibling donors, in whom death associated with transplantation is estimated at 10 to 15\%. HLA typing of patients and their siblings should be performed at the time of diagnosis if patients are considered to be potential candidates for transplantation.

For patients with chronic-phase CML, imatinib is initiated at a daily oral dose of 400 mg, a regimen that begins as soon as the diagnosis is made. Patients in the accelerated phase or blast crisis are treated with 600 mg daily. The cost of imatinib is approximately $32,000 per year in the United States for the standard 400-mg daily dose. Dose adjustment is not required in patients with renal dysfunction or with mild-to-moderate hepatic dysfunction. Imatinib should be taken with a meal and a large glass of water to reduce the incidence of nausea.

Imatinib is a substrate for the CYP3A4 metabolic pathway and can inhibit other cytochrome P-450 pathways. Careful monitoring of the international normalized ratio in patients receiving warfarin is advisable. CYP3A4 inhibitors that can increase imatinib levels include diltiazem, verapamil, itraconazole, ketoconazole, clarithromycin, erythromycin, and grapefruit juice, whereas rifampin, phenobarbital, phenytoin, and St. John’s wort can decrease blood levels of imatinib.\textsuperscript{28} Imatinib may be teratogenic, and both men and women are strongly counseled to avoid conception while they are taking the drug. This recommendation presents young patients with a dilemma, since the limited evidence that is available also suggests that interruption of imatinib therapy during pregnancy may be associated with a loss of treatment response.\textsuperscript{29} Thus, patients who choose to have children after the diagnosis of CML face a potentially significant, and poorly defined, risk whether they continue imatinib or not.

Initially, patients should undergo clinical evaluation and have a complete blood count and serum chemical analysis performed every 2 weeks. When a complete hematologic response is achieved (defined as normal white-cell and platelet counts and no evidence of splenomegaly), follow-up can be performed monthly with a longer-term monitoring of response every 3 to 4 months.

The goal of treatment with imatinib is to reduce the number of cells containing the Ph chromosome, decreasing the probability of the development of new mutations leading to blast crisis. The level of the Ph chromosome and BCR-ABL can be monitored in a variety of ways, including standard cytogenetics (sensitivity, approximately 5\%), fluorescence in situ hybridization (FISH; sensitivity, approximately 1\%), and reverse-transcriptase polymerase chain reaction (RT-PCR; sensitivity, approximately 1/10\(^6\) to 1/10\(^9\)). FISH and RT-PCR analysis can be performed on peripheral blood, obviating the need for repetitive bone marrow examination.\textsuperscript{30-32} Monitoring should be performed approximately every 3 months. When the results of FISH become negative or there is a major drop in the transcript number on RT-PCR analysis, bone marrow biopsy should be performed to confirm a complete cytogenetic response.

Thereafter, it is recommended that patients be evaluated every 3 to 4 months with clinical examination, assessment for side effects, and RT-PCR analysis. Since RT-PCR reporting is not standardized among laboratories in the United States, it is advisable to send serial samples to the same laboratory when assessing changes over time. Results can fluctuate, and if there is an apparent rise in levels, the values should be repeated before changes in treatment are initiated. Even in patients who become RT-PCR “negative,” it is usually possible to detect residual BCR-ABL-positive cells when their bone marrow is cultured in vitro. Clinically, it has been observed that almost all patients, including some who had negative results on RT-PCR, have had a relapse after discontinuation of imatinib.\textsuperscript{33}
Hence, it is recommended that imatinib be continued indefinitely. Approximately 15 to 20% of patients with newly diagnosed CML do not have a complete cytogenetic response to imatinib. A small number have side effects that prevent further treatment with the drug, and a small number who have a cytogenetic response will relapse with a Ph-chromosome recurrence, often heralded by a rise in the BCR-ABL transcript number. For those who do not have an initial response or who have a relapse, it is important to confirm that the patient is taking imatinib as prescribed. A serum level may be checked if doubt remains after the patient’s compliance has been reviewed. For patients who have a complete cytogenetic response followed by a relapse, one option is to increase the dose of imatinib to 400 mg twice daily, although preliminary results of a randomized trial suggest that changing to dasatinib is superior to increasing the dose of imatinib from 600 to 800 mg daily. Dasatinib or nilotinib should be used for patients who are resistant to or cannot tolerate imatinib. In the absence of comparative trials, the choice between these drugs should be based on an assessment of potential side effects in individual patients.

For any patient in whom treatment with imatinib fails, it is important to reconsider the option of stem-cell transplantation. Patients with mutations such as the T315I mutation, in whom CML is known to be highly resistant to all the available drugs, should be considered for transplantation or for treatment with an experimental agent.

**Adverse Effects**

Imatinib treatment is associated with a variety of adverse effects, most of which are typically mild to moderate in intensity and generally abate after the first few months of treatment (Table 1). Most patients do not require dose reduction or interruption of therapy, and almost all patients can receive long-term treatment with the recommended daily dose of 400 mg taken with food. Transient neutropenia or thrombocytopenia, which can occur during the first 1 to 2 months of treatment, is due to variability in the pace of regeneration of normal hematopoiesis after imatinib suppression of Ph-derived hematopoiesis.

A recent study described 10 patients in whom congestive heart failure developed after long-term imatinib use, with experiments suggesting that very high doses of imatinib could induce mitochondrial damage and apoptosis in cultured myocardial cells and in vivo in mice. However, in a review of approximately 1200 patients treated at the M.D. Anderson Cancer Center, the incidence of congestive heart failure was identical to that of age-matched subjects in the Framingham study. Some patients with heart disease were able to continue treatment with imatinib concurrent with appropriate cardiac management. Other large analyses did not show an increase in the incidence of congestive heart failure in imatinib-treated patients.

Increased urinary phosphate excretion, decreased blood calcium and phosphorous levels, and increased levels of parathyroid hormone have been noted in a relatively small group of patients. The explanation for these findings is not clear, although inhibition of PDGFR has been postulated, and confirmation is needed. Nonetheless, this observation raises concern about acceleration of osteomalacia over time. Longer follow-up of imatinib-treated patients with monitoring for the occurrence of these side effects and others not yet detected is imperative.

The short-term toxicity profile of dasatinib and nilotinib differ from each other and from that of imatinib. Both dasatinib and nilotinib can produce myelosuppression requiring dose adjustments, whereas dasatinib can produce pleural and occasionally pericardial effusions in 15 to 20% of patients, more commonly in those with more advanced CML. Nilotinib can produce usually asymptomatic elevations in unconjugated bilirubin and lipase. Side effects of imatinib do not usually recur when patients are subsequently treated with dasatinib or nilotinib, a finding that suggests that the mechanisms of the toxic effects may not be related only to the inhibition of tyrosine kinases.

**Areas of Uncertainty**

There has been interest in evaluating higher initial doses of imatinib on the basis of the superiority of higher-dose imatinib in the accelerated phase and a retrospective analysis comparing the conventional dose of 400 mg daily with 400 mg twice daily in patients in the chronic phase. Patients receiving the higher dose had more rapid and higher initial rates of complete cytogenetic response and major molecular response, albeit with more side effects, a much higher financial cost, and a sugges-
tion that patients receiving the standard dose eventually derive a similar overall benefit. A prospective, randomized comparison has been completed, and the results should be available soon.

Trials comparing dasatinib and nilotinib with imatinib for the initial therapy of CML are in early stages. These more potent BCR-ABL inhibitors may have a more profound effect on the CML stem cell, possibly allowing consideration of treatment cessation. This possibility is of particular interest to younger patients interested in having children. Preliminary in vitro data suggest that dasatinib may not eliminate these progenitors, however. Combinations of BCR-ABL inhibitors, used either concurrently or sequentially, are also under consideration.

Approximately 5 to 10% of patients receiving imatinib have clonal cytogenetic changes in Ph-negative cells (Fig. 1). Sometimes these changes are transient, particularly with respect to trisomy 8, which may come and go on repeated sampling without any apparent clinical effect. There has been speculation that inhibition of normal tyrosine kinases by imatinib might allow damage to occur in normal hematopoietic precursors, but this remains a hypothesis.

The implications of these cytogenetic changes are uncertain. Longer follow-up is necessary to determine whether the incidence of new clonal changes will increase further. These clones cannot be detected by FISH or RT-PCR analysis of peripheral blood, and many centers repeat bone marrow examinations every 1.5 to 2 years for cytogenetic studies. To date, the occurrence of frank myelodysplasia and evolution to AML has been low, noted most commonly in patients with monosomy 7; many clinicians consider allogeneic transplantation if this chromosomal deletion is detected.

### Table 1. Adverse Events Associated with Imatinib Therapy.

<table>
<thead>
<tr>
<th>Event</th>
<th>Treatment and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Imatinib should be taken with meals; infrequent need of antiemetic drugs</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Potentially chronic problem generally responds to antispasmodics; other causes (e.g., lactase deficiency, infection) should be considered</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Very uncommon after initial 1–2 mo; dose reduction or temporary cessation of imatinib with return to 400-mg dose on recovery; growth-factor support needed only rarely</td>
</tr>
<tr>
<td>Hepatic dysfunction (usually elevated aminotransferase levels)</td>
<td>Early and usually transient occurrence; rare reports of hepatic failure, with one fatal case associated with the concomitant use of high doses of acetaminophen; acetaminophen and excessive alcohol use should be avoided</td>
</tr>
<tr>
<td>Rash</td>
<td>Usually mild, macular or papular, and transient; if more severe, imatinib should be stopped and restarted at a lower dose; use of corticosteroids can benefit some patients; rarely, severe recurrent rashes preclude continued therapy with imatinib</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>Of variable severity, usually manifested by peripheral edema and responsive to intermittent use of diuretics; generalized swelling with skin tightness in some patients</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>Very common and has poor response to diuretics but generally decreases during the day when the patient is not recumbent</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Generally mild but can be persistent; incidence is not well quantified</td>
</tr>
<tr>
<td>Muscle cramps, myalgias, and arthralgias</td>
<td>Perhaps the most prominent long-term side effect, occasionally with elevated creatine kinase levels; cause is unknown; decreased cramping reported with calcium or magnesium replacement, quinine, and (anecdotally) with yoga; some improvement in myalgias and arthralgias with nonsteroidal analgesics</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>Uncommon; associated with decreased testosterone levels and improves with testosterone replacement</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Uncertain association with imatinib</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Further study required</td>
</tr>
<tr>
<td>Macrocytic anemia</td>
<td>Generally mild occurrence in about 10% of patients; vitamin B₁₂ deficiency should be ruled out; very occasionally, more profound anemia can be treated with erythropoietin; cause is unknown, with speculation about c-kit inhibition</td>
</tr>
</tbody>
</table>

* Unless otherwise stated, most toxic effects are mild to moderate and generally abate after the first few months of treatment.
The clinical practice guideline of the National Comprehensive Cancer Network, which was last updated in February 2007, and guidelines of the National Cancer Institute, last updated March 1, 2007, are very similar and recommend that imatinib be used as the preferred first-line treatment for patients with newly diagnosed CML.\textsuperscript{46,47} For patients who do not have a cytogenetic response to imatinib, recommendations include the use of higher doses of imatinib or alternative tyrosine kinase inhibitors, allogeneic stem-cell transplantation, and enrollment in a clinical trial of an investigational therapy.

Two recent studies offered consensus statements about standardization of the methodology for molecular monitoring of patients with chronic-phase disease and suggested measures of response to be achieved at intervals after the initiation of treatment.\textsuperscript{31,32} Failure to reach these goals would indicate that a modification of therapy should be considered.

**Recommendations**

Although the young patient described in the vignette is a potential candidate for hematopoietic stem-cell transplantation, my recommendation is that she continue to take imatinib at the standard dose of 400 mg daily with the intention of continuing long-term treatment if she has a response. Initially, she should have a physical examination and blood tests monthly, RT-PCR analysis or FISH to check for the BCR-ABL translocation every 3 months, and subsequent bone marrow examination to assess the cytogenetic response. She should be strongly cautioned to use contraception because of the risk to the fetus if she should become pregnant while taking imatinib. Computer searches for unrelated donors and umbilical cord blood units\textsuperscript{48} should be conducted intermittently. If the patient does not have a complete cytogenetic response or if her disease recurs, transplantation should be reconsidered along with other options, including increasing the dose of imatinib and switching to either dasatinib or nilotinib.

Dr. Schiffer reports receiving lecture fees from Novartis and grant support from Novartis and Bristol-Myers Squibb and serving on the companies’ advisory boards. No other potential conflict of interest relevant to this article was reported.

**Figure 1. Clinical Course of CML after the Development of Cytogenetic Abnormalities in Philadelphia-Chromosome–Negative Cells.**

The possible clinical outcomes are shown in a patient with chronic myelogenous leukemia (CML) in whom cytogenetic abnormalities developed in cells that tested negative for the Philadelphia (Ph) chromosome after 2 years of imatinib treatment. Typically, 100\% of the cells in metaphase are Ph-positive at the time of diagnosis. There is little information about whether other clones are present in small numbers at diagnosis among the overwhelming number of Ph-positive cells. In an analysis of bone marrow obtained from two patients in whom trisomy 8 developed, such clones could not be detected by fluorescence in situ hybridization with the use of centromeric probes (unpublished data). After 6 months of treatment, there was a partial cytogenetic response; at 1 year, there was a complete cytogenetic remission. The figure shows three possible scenarios: the disappearance and then recurrence of the new clonal changes in patients continuing to have complete cytogenetic remission; uncommon progression to myelodysplasia or acute myeloid leukemia (AML); and relapse of the CML with the disappearance of the new clone, possibly related to suppression by the now dominant Ph-positive clone. With further treatment and partial suppression of the Ph-positive clone, it is common to have varying mixtures of the clones, sometimes including the development of clones with other cytogenetic abnormalities in Ph-negative cells.

**References**


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