Drug Therapy

Imatinib Mesylate — A New Oral Targeted Therapy

David G. Savage, M.D., and Karen H. Antman, M.D.

Imatinib (Gleevec, Novartis, Basel, Switzerland), formerly referred to as STI571, is an inhibitor of specific protein tyrosine kinases that was targeted to the platelet-derived growth factor (PDGF) receptor (Fig. 1). It was found to inhibit the constitutively active fusion product arising from the Philadelphia (Ph) chromosome of chronic myelogenous leukemia (CML) and c-kit (CD117), which is overexpressed in gastrointestinal stromal tumors. Studies of imatinib in other tumors that express c-kit or the PDGF receptor are under way. Imatinib was approved by the Food and Drug Administration in May 2001 for the treatment of CML that is refractory to interferon therapy and in February 2002 for the treatment of gastrointestinal stromal tumors.

Protein Kinases as Therapeutic Targets

Protein kinases are enzymes that transfer phosphate from adenosine triphosphate to specific amino acids on substrate proteins (Fig. 2). The phosphorylation of these proteins leads to the activation of signal-transduction pathways, which have a critical role in a variety of biologic processes, including cell growth, differentiation, and death. Protein kinases are composed of two subfamilies, the protein serine–threonine kinases and the protein tyrosine kinases. Several protein kinases are deregulated and overexpressed in human cancers and are thus attractive targets for selective pharmacologic inhibitors. The most extensively studied is the BCR-ABL tyrosine kinase of CML. Imatinib impairs BCR-ABL–mediated transfer of phosphate to its substrates (Fig. 2). In early trials, imatinib has had extraordinary activity against CML and gastrointestinal stromal tumors.

Chronic Myelogenous Leukemia

Clinical Features

CML arises as the result of a mutation in a pluripotent stem cell and is characterized by progressive granulocytosis, marrow hypercellularity, and splenomegaly. The diagnostic hallmark is the Ph chromosome (Fig. 3), which is present in all dividing cells of hematopoietic lineage, as well as in B and T cells in some patients, but is absent in all other cells. Although hematopoiesis is overwhelmed by the Ph chromosome–positive clone, a normal Ph-chromosome–negative pool of stem cells persists. The goal of treatment is the suppression or elimination of the Ph-chromosome–positive clone and the restoration of Ph-chromosome–negative hematopoiesis.

CML has a biphasic or triphasic course but is usually diagnosed during the initial, or chronic, phase, in which the granulocytic population expands but remains able to differentiate. The chronic phase is relatively stable and responds to therapy, but it eventually evolves into an intermediate, accelerated phase, in which increasing doses of hydroxyurea are needed to control disease, followed by a blast phase. Blast-phase disease resembles acute leukemia. Its phenotype is myeloblastic in 70 to 80 percent of patients and lymphoblastic in 20 to 30 percent.

With conventional treatment the median survival among patients with CML is about five years, but the range is very broad. Some patients with an aggressive form of chronic-phase disease survive only months, whereas others, who have indolent, chemoresponsive CML, live 10 years or longer.

Figure 1. Imatinib Mesylate.

Molecular weight, 589.7
Formula, C30H35N7SO4

From the Herbert Irving Comprehensive Cancer Center, Columbia University College of Physicians and Surgeons, New York.
Pathogenesis

The Ph chromosome is a truncated chromosome 22 that results from a reciprocal exchange of genetic material between the long arms of chromosomes 9 and 22 (Fig. 3). The translocation — t(9;22) — results in the juxtaposition of 3' DNA sequences derived from the Abelson (ABL) proto-oncogene normally located on chromosome 9 with 5' sequences of the breakpoint cluster region (BCR) gene on chromosome 22.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)

The ABL proto-oncogene is homologous with the transforming gene present in the Abelson leukemia virus, which causes leukemia in mice.\(^4\)\(^5\) ABL encodes a tyrosine kinase that is tightly regulated, whereas the activity of BCR-ABL is autonomous and markedly increased relative to that of normal ABL.

The Ph chromosome is present in approximately 95 percent of patients with classic CML. About half of the remaining 5 percent of patients have been found to have the BCR-ABL gene when the polymerase chain reaction (PCR) is used for identification and are classified as being Ph-chromosome–negative, BCR-ABL–positive. Although the precise oncogenic mechanism of BCR-ABL is unknown,\(^4\)\(^7\) its tyrosine kinase activity leads to the chronic phase of CML.\(^25\) Transplantation of hematopoietic stem cells containing a BCR-ABL gene construct into mice results in a disease resembling CML.\(^26\)\(^27\)

The Ph chromosome is also detected in about 25 percent of adults and 5 percent of children with acute lymphoblastic leukemia (ALL) and is associated with an aggressive course and poor survival.\(^28\)\(^29\) Only about one third of patients with Ph-chromosome–positive ALL have the
Figure 3. Translocation Leading to the Philadelphia (Ph) Chromosome and the Role of BCR-ABL in the Pathogenesis of CML (Panel A) and the Effect of Normal (Panel B) and Abnormal (Panel C) c-kit Function on Platelet-Derived Growth Factor and Gastrointestinal Stromal Tumors.

The Ph chromosome is a foreshortened chromosome 22 resulting from an exchange between the long arms of chromosomes 9 and 22 (Panel A). The translocation — t(9;22) — results in the juxtaposition of 3' DNA sequences derived from the ABL proto-oncogene on chromosome 9 with 5' sequences of the breakpoint cluster region (BCR) gene on chromosome 22, forming a fusion gene, BCR-ABL. (The reciprocal formation of the ABL-BCR fusion gene on chromosome 9q+ is not depicted.) BCR-ABL produces a chimeric messenger RNA (not shown) from which a fusion BCR-ABL oncoprotein is translated. The length of the BCR-ABL protein varies and is determined by the breakpoint within the BCR gene. Chronic-phase CML is driven by the constitutively active BCR-ABL tyrosine kinase protein, which activates multiple pathways, leading to the malignant expansion of myeloid cells through the stimulation of mitosis, the disruption of cytoadherence and regulatory control by stromal cells, and the inhibition of apoptosis. Differentiation and maturation of the leukemic clone are relatively intact in chronic-phase CML, but BCR-ABL is also thought to promote genomic instability, leading to secondary mutations and to the blast phase. Imatinib mesylate inhibits the tyrosine kinase activity of the BCR-ABL oncoprotein, thus blocking the leukemogenic effects of the Ph chromosome. Dimerization and activation of the normal c-kit receptor by its ligand stem-cell factor are shown in Panel B. The proto-oncogene c-kit encodes a transmembrane tyrosine kinase receptor located on the long arm of chromosome 4 (4q11–q12). In gastrointestinal stromal tumors, in-frame deletions and point mutations in c-kit produce ligand-independent constitutive activation of c-kit (Panel C). Mutations of c-kit in the juxtamembrane domain in gastrointestinal stromal tumors (exon 11) are found in approximately 60 percent of cases. Mutations also occur in the extracellular domain (exon 9) and in the more distal phosphokinase domain (exon 13). ATP denotes adenosine triphosphate, ADP adenosine diphosphate, and P phosphate.
210-kD BCR-ABL protein characteristic of CML; approximately two thirds have a smaller chimeric BCR-ABL protein of 185 to 190 kD that has more potent tyrosine kinase and oncogenic activity.\textsuperscript{3,25,31}

The continuously (or constitutively) active BCR-ABL oncprotein phosphorylates substrates of remarkable diversity, including RAS, that activate multiple signaling pathways (Fig. 3).\textsuperscript{4,6,32} Because RAS serves as a critical control point for signal transduction from cell membrane to nucleus,\textsuperscript{32-37} the BCR-ABL–mediated overexpression of RAS appears to alter signal transduction in a target stem cell, leading to abnormal mitosis and neoplastic expansion. In addition, BCR-ABL reduces cellular adhesion to stromal matrix,\textsuperscript{38-41} which may disrupt the interaction between hematopoietic cells and stromal cells and membrane signaling mediated by cytoadhesion molecules, allowing myeloid progenitor cells to remain longer in the proliferative phase before undergoing differentiation.\textsuperscript{42} BCR-ABL also diminishes cellular responsiveness to apoptotic stimuli, providing a survival advantage to the leukemic clone.\textsuperscript{43-46} In theory, since chronic-phase CML is dependent on the tyrosine kinase activity of BCR-ABL, a potent BCR-ABL inhibitor might eliminate the leukemic clone and restore normal Ph-chromosome–negative hematopoiesis.

Although the mechanism for blastic transformation is unknown, possible scenarios have been considered. For example, BCR-ABL promotes genomic instability in the leukemic clone,\textsuperscript{47} which may lead to secondary mutations (e.g., trisomy 8). Blast-phase cells may be more dependent on these secondary oncogenic aberrations than on the tyrosine kinase activity of BCR-ABL. As the leukemic clone becomes unable to differentiate, blast cells accumulate, leading inexorably to a blast crisis.

**RATIONALE FOR THE DEVELOPMENT OF IMATINIB**

Because of their unregulated activity in various human cancers, BCR-ABL, protein kinase C, and the epidermal growth factor receptor were among the first protein kinases targeted for selective inhibition.\textsuperscript{4} In 1988 Yaish and colleagues described a family of compounds called tyrphostins with specificity for epidermal growth factor receptor,\textsuperscript{48} proving that pharmacologic inhibitors could target a specific tyrosine kinase. At about this time chemists at Ciba–Geigy (which later became Novartis) screened their compound libraries for molecules with tyrosine kinase inhibitory activity and identified 2-phenylaminoprymidine compounds as the most promising agents. Because the initial inhibitors were of low specificity and potency, similar compounds were synthesized that had better structure–activity relations with different kinase targets.\textsuperscript{3} Imatinib was developed as a specific inhibitor of the PDGF receptor.\textsuperscript{49} However, it was also a powerful and relatively selective inhibitor of all ABL tyrosine kinases, including the 210-kD BCR-ABL and the BCR-ABL of 185 to 190 kD. The only other tyrosine kinase inhibited by imatinib was c-kit, the receptor for stem-cell factor.\textsuperscript{49,50} Other tyrosine kinase receptors, such as epidermal growth factor receptor, FLT1, and FLT3, were unaffected.\textsuperscript{49,51}

Druker and colleagues\textsuperscript{3,52} recognized that the BCR-ABL protein was an ideal target for imatinib, since the BCR-ABL mutation is present in almost all patients with CML, the BCR-ABL protein is unique to leukemic cells and expressed at high levels, and its tyrosine kinase activity is essential for its ability to induce leukemia. In 1996, Druker et al. reported that imatinib specifically inhibited or killed proliferating myeloid cell lines containing BCR-ABL but was minimally harmful to normal cells.\textsuperscript{52} When cells from patients with CML were grown in colony-forming assays in vitro, imatinib reduced the formation of BCR-ABL–positive colonies by about 95 percent at concentrations of 1 µM. Other laboratories confirmed or extended these observations.\textsuperscript{53-55} Imatinib also suppressed the growth of cells from patients with Ph-chromosome–positive ALL, including those with the BCR-ABL of 185 to 190 kD.\textsuperscript{53,54}

The striking in vitro results led to experiments to determine the effectiveness of imatinib in vivo. Since apoptosis could be averted in cells expressing BCR-ABL if exposure to imatinib was limited to 16 hours or less, Druker and colleagues reasoned that continual suppression of BCR-ABL would require long-term treatment with a well-tolerated oral formulation.\textsuperscript{3,56} When given in a regimen that ensured the continual inhibition of BCR-ABL, oral imatinib therapy suppressed or eradicated the growth of BCR-ABL–positive human tumors in mice, with minimal side effects.\textsuperscript{56,57}

**STANDARD TREATMENT OF CML AND THE NEED FOR BETTER THERAPY**

Patients with chronic-phase CML are treated with hydroxyurea or interferon alfa. Hydroxyurea is an oral agent that typically returns blood counts to normal, shrinks the spleen, and has few toxic effects (Table 1).\textsuperscript{59,60} In contrast, interferon alfa must be administered subcutaneously, is toxic, and controls blood counts in only about two thirds of patients. Nevertheless about 25 percent of these patients have a major cytogenetic response (defined as the disappearance of the Ph chromosome from at least 66 percent of marrow cells in metaphase) and about 10 percent have a complete cytogenetic response (defined as the reversion to Ph-chromosome–negative status). Interferon alfa therapy extends survival by about one to two years as compared with hydroxyurea.\textsuperscript{61-71} The addi-
tion of cytarabine to interferon alfa therapy may provide further benefit. Because interferon alfa reduces the number of Ph-chromosome-positive clones and improves survival, it is the drug of choice for patients who are unable to undergo allogeneic stem-cell transplantation. For patients with refractory disease or those who cannot tolerate interferon alfa, autologous stem-cell transplantation is an alternative, but it may not increase survival, and relapse is inevitable.5,16

Blast-phase CML is resistant to both hydroxyurea and interferon alfa. Multiagent chemotherapy induces responses in only about 20 percent of patients with myeloblastic transformation and 50 percent of those with lymphoblastic transformation. However, even patients who have a response typically relapse quickly and die of progressive disease.73-76

Allogeneic stem-cell transplantation is the only curative therapy for CML and is the standard treatment for patients less than 40 years of age who have an HLA-identical sibling.5,16,18,77-82 Many survivors have donor-derived normal hematopoiesis for more than 10 years. The outcome is determined by several factors, including the patient’s age, the interval from diagnosis to allogeneic stem-cell transplantation, the degree of HLA matching, and the phase of CML. The likelihood of leukemia-free survival is about 60 to 70 percent among patients with chronic-phase CML who receive allografts from HLA-identical siblings, but ranges from 0 to 15 percent among similar patients with blast-phase CML.

Advanced age and the lack of a matched donor make allogeneic stem-cell transplantation involving an HLA-identical sibling unfeasible in all but about 15 percent of patients with newly diagnosed CML. Allogeneic stem-cell transplantation involving an unrelated donor is an option for an additional 10 to 15 percent of patients, but morbidity and mortality are generally higher.84,85 However, excellent leukemia-free survival rates have been reported in young patients who receive transplants from unrelated donors who are HLA-matched with the use of high-resolution molecular methods. For older patients and those with coexisting conditions that preclude conventional transplantation, allogeneic stem-cell transplantation after low-intensity, nonablative conditioning seems to be a promising approach.70

**PHASE 1 TRIALS OF IMATINIB FOR CML**

**Chronic Phase**

On the basis of the promising preclinical data, in June 1998 Druker and coworkers initiated a phase 1 trial designed to determine the safety and efficacy of imatinib in patients with chronic-phase CML.10 Patients who had no response to interferon alfa or who were unable to tolerate the drug were eligible. Remarkably, of 54 patients who received oral doses of at least 300 mg per day, 53 (98 percent) had normal leukocyte and platelet counts, usually within four weeks after the initiation of treatment. Cytogenetic responses occurred in 29 patients (54 percent), including 17 (31 percent) who had major responses and 7 (13 percent) who had complete responses. The time from the initiation of treatment to a cytogenetic response was substantially shorter with imatinib than with interferon alfa. Phosphorylation of CRK-oncoprotein–like protein (CRKL), a major substrate of BCR-ABL kinase, was markedly reduced in leukemic cells, demonstrating the effect of the imatinib on its target. Side effects were mild to moderate (Table 2) and were usually reversible when the dose was reduced or treatment was suspended.

A once-daily oral dose of 400 mg of imatinib was

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**TABLE 1. COMPARISON OF HYDROXYUREA, INTERFERON ALFA, AND IMATINIB MESYLATE FOR THE TREATMENT OF CML.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>HYDROXYUREA</th>
<th>INTERFERON ALFA</th>
<th>IMATINIB MESYLATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Ribonucleotide reductase inhibitor</td>
<td>Not known</td>
<td>Selective inhibitor of BCR-ABL</td>
</tr>
<tr>
<td>Oral administration</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>High cost of drug</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Induces rapid hematologic responses</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Induces cytogenetic responses</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Commonly toxic</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Active against blast phase</td>
<td>No</td>
<td>No</td>
<td>Somewhat</td>
</tr>
<tr>
<td>Improves survival</td>
<td>No</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>May worsen results of allogeneic stem-cell transplantation</td>
<td>No</td>
<td>Perhaps*</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Prolonged therapy with interferon alfa appears to worsen the outcome, but not if treatment with the drug is stopped at least three months before transplantation.64
rapidly absorbed, with a maximal mean plasma concentration of 2.3 µg per milliliter (4.6 µM). The terminal half-life ranged from 13 to 16 hours, and the levels of imatinib increased by a factor of 2 or 3 after one month. At doses of 300 mg or higher, plasma levels were equivalent to the effective in vitro concentration of 1 µM. The smallest dose that inhibited the phosphorylation of CRKL was 400 mg, and this dose was thus recommended for use in future studies.

The sole patient in the study who had no hematologic response had low plasma imatinib levels that were attributed to concomitant phenoxytin therapy. Imatinib is a competitive inhibitor of the cytochrome P-450 enzymes CYP3A4 and CYP2D6 and is itself metabolized by CYP3A4. Drugs such as phenoxytin, which increase the activity of CYP3A4, may lead to subtherapeutic levels of imatinib. Conversely, drugs that block CYP3A4 may inhibit the metabolism of imatinib, leading to high plasma levels of imatinib and increasing its toxicity. Whether imatinib interacts with warfarin is not known.

**Blast Phase**

In a companion study Druker et al. treated 58 patients with blast-phase CML and relapsed or refractory Ph-chromosome-positive ALL with 300 to 1000 mg of imatinib daily. The overall rates of response among patients with myeloblastic crisis and lymphoblastic crisis were 55 percent and 70 percent, respectively. Almost 80 percent of patients had a reduction of at least 50 percent in peripheral-blood blasts, usually within the first week after the initiation of treatment.

Of the subgroup of 38 patients who were receiving imatinib for myeloblastic crisis, 17 (45 percent) had a partial hematologic response (defined by a reduction in the marrow blast count to 15 percent or less), and 4 (11 percent) had a complete response (defined by a decrease in the blood and marrow blast count to less than 5 percent, a neutrophil count of more than 1000 per cubic millimeter, and a platelet count of more than 100,000 per cubic millimeter). Three patients had a major cytogenetic response. Most responses were brief, but seven patients (18 percent) remained in complete or partial remission for 3 to 12 months during treatment.

The results for 10 patients with CML in lymphoblastic transformation and 10 with Ph-chromosome-positive ALL were similar; thus, their data were combined. Of these 20 patients, 10 had a partial hematologic response and 4 had a complete response. Two patients had a major cytogenetic response. Nevertheless, all patients who had a response relapsed within four months.

Side effects in patients who received imatinib for advanced leukemia were similar to those in patients with chronic-phase CML. Serious adverse events possibly due to imatinib occurred in 13 patients, usually at doses of 800 to 1000 mg per day. Only three patients had febrile neutropenia; no deaths were attributable to the drug.

**Phase 2 Trials of Imatinib for CML**

Reports of three multi-institutional phase 2 studies involving more than 1000 patients with chronic-phase and advanced-phase CML (Table 2) confirm data on the efficacy and safety of imatinib that were reported in phase 1 studies. One of these studies is reported in detail elsewhere in this issue. More than 90 percent of patients with interferon-resistant chronic-phase CML had a complete hematologic response, and almost half had a major cytogenetic response.

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**Table 2. Frequency of Adverse Effects and Hematologic and Cytogenetic Responses Among Patients Who Were Receiving Imatinib Therapy for CML.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CHRONIC-PHASE CML (N=532)</th>
<th>ACCELERATED-PHASE CML (N=235)</th>
<th>BLAST-PHASE CML (N=260)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg/day</td>
<td>100</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>600 mg/day</td>
<td>0</td>
<td>67</td>
<td>86</td>
</tr>
<tr>
<td>Side effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>58</td>
<td>71</td>
<td>69</td>
</tr>
<tr>
<td>Edema†</td>
<td>56</td>
<td>71</td>
<td>69</td>
</tr>
<tr>
<td>Cramps</td>
<td>50</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37</td>
<td>53</td>
<td>41</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30</td>
<td>55</td>
<td>52</td>
</tr>
<tr>
<td>Rash‡</td>
<td>39</td>
<td>43</td>
<td>34</td>
</tr>
<tr>
<td>Headache</td>
<td>30</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>30</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>Neutrophils, &lt;1.0×10^9/mm^3</td>
<td>34</td>
<td>58</td>
<td>63</td>
</tr>
<tr>
<td>Platelets, 50×10^11/mm^3</td>
<td>17</td>
<td>43</td>
<td>60</td>
</tr>
<tr>
<td>Hemoglobin &lt;8 g/dl</td>
<td>5</td>
<td>39</td>
<td>51</td>
</tr>
<tr>
<td>Drug treatment stopped due to serious adverse events</td>
<td>2</td>
<td>2§</td>
<td>5</td>
</tr>
</tbody>
</table>

*Data are from Druker et al. (and unpublished data), Kantarjian et al., Talpaz et al., and Sawyers et al. The adverse events that are listed occurred in at least 30 percent of patients but were not necessarily related to the drug.

†Edema was superficial in most patients. Among patients with accelerated-phase or blast-phase CML, 3 percent and 6 percent, respectively, had more extensive fluid retention, including one patient who died with pleural and pericardial effusions associated with cardiac and renal failure.

‡A case report of a patient with generalized exanthematous pustulosis has been published.

§One patient who was also taking acetaminophen had fatal hepatotoxicity.

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Complete cytogenetic responses occurred in more than 40 percent of patients with chronic-phase CML, a higher rate than that associated with interferon therapy. Hematologic and cytogenetic responses were less common in patients with accelerated- or blast-phase CML than in patients with chronic-phase CML (Table 2), but the results were favorable relative to those achieved with conventional therapy.

Most patients who were receiving imatinib had mild-to-moderate side effects (Table 2), similar to those noted in the phase 1 trials. Adverse events were more common in advanced disease, but it was unclear whether this was due to the phase of the disease or to the higher doses of imatinib that were used. Serious adverse events, including bone marrow necrosis and severe rash, have been reported.

**Resistance of CML to Imatinib**

The relative resistance of blast-phase CML to imatinib is consistent with the hypothesis that secondary mutations (and not BCR-ABL itself) are the primary driving force in the transformed leukemic clone. Nevertheless, Gorre and colleagues demonstrated that point mutations in BCR-ABL may be the primary mechanism of acquired resistance to imatinib, suggesting that the tyrosine kinase activity of BCR-ABL remains crucial in advanced disease. Other potential mechanisms of resistance include amplification of the BCR-ABL gene, overexpression of the BCR-ABL protein, enhanced expression of the multidrug-resistance gene, and excessive binding of imatinib by protein. Whatever the mechanism, the high incidence of resistance suggests that imatinib should be combined with other chemotherapeutic agents in future trials involving patients with Ph-chromosome-positive blast-phase disease. Whether higher doses of imatinib (more than 1000 mg per day) might overcome resistance could also be evaluated.

**Unanswered Questions**

How should imatinib be used relative to other treatments for chronic-phase CML? Since patients with CML have a median survival of about five years and a variable course, follow-up data on patients who have been treated with imatinib are limited. Although the rates of response among patients with chronic-phase CML have been dramatic, the durability of response and the possible long-term effects are unknown.

In patients with newly diagnosed CML, hydroxyurea is the standard short-term therapy to control blood counts before the initiation of interferon alfa therapy or allogeneic stem-cell transplantation. Should imatinib replace hydroxyurea for short-term control? Both hydroxyurea and imatinib are oral agents that can be taken once daily with few toxic effects (Table 1). Imatinib, which induces cytogenetic responses, appears to be the superior agent. Nevertheless, thus far, all the patients who have received imatinib for chronic-phase disease had previously received interferon alfa. It is not known whether imatinib will be as effective against new-onset CML or will jeopardize any subsequent treatment with interferon alfa.

Which patients with CML should proceed directly to allogeneic stem-cell transplantation, a potentially curative treatment, without first undergoing a trial of imatinib? Among patients who are younger than 40 years of age, who have chronic-phase CML, and who have an HLA-identical sibling donor, the leukemia-free survival rate approaches 70 percent after transplantation but is associated with a substantial cost in terms of toxicity. Whether imatinib alone or in combination can cure chronic-phase CML is unknown, but only a fraction of patients have become BCR-ABL-negative on the basis of PCR results. Until more is known about the long-term effects of imatinib, allogeneic stem-cell transplantation remains the primary treatment for young patients with CML who have an HLA-matched related donor.

Will treatment with imatinib enhance or jeopardize the results of subsequent transplantation? Patients with CML who undergo allogeneic stem-cell transplantation in the first one to two years after diagnosis fare better than those who undergo transplantation later. Delaying transplantation for a trial of imatinib may render the leukemia more resistant to the curative effects of this approach. In studies of allogeneic bone marrow transplantation, subgroups of patients who had previously received busulfan or interferon alfa had worse outcomes than those who had received hydroxyurea.

Since imatinib has several advantages over interferon alfa (Table 1), should a trial of imatinib precede a trial of interferon alfa in older patients or those who lack a suitable donor? Interferon alfa prolongs survival, but we do not know whether imatinib does so. Thus, imatinib is currently being compared with combined interferon alfa and cytarabine in a randomized trial. For patients who have had no response to interferon alfa therapy, however, imatinib is clearly the drug of choice.

Imatinib will be combined with other agents to increase the rate of cytogenetic response and improve survival rates among patients with Ph-chromosome-positive leukemias. The use of a combination of imatinib and interferon alfa is especially intriguing for the treatment of chronic-phase CML. Combining imatinib with inhibitors of other key cellular enzymes, such as the farnesyltransferases, is another rational strategy. Imatinib might also be used in vitro to purge stem cells harvested for autologous transplantation.
Imatinib appears to have potent activity in patients with CML who relapse after allogeneic transplantation.103

**IMATINIB FOR GASTROINTESTINAL STROMAL TUMORS**

Until about 1990, most gastrointestinal sarcomas were considered to be leiomyosarcomas because they resembled smooth muscle histologically. However, clinical oncologists observed a distinctly lower rate of response to standard doxorubicin-based regimens among leiomyosarcomas that arose in the gut than among those that arose in the uterus, trunk, or arms and legs. As early as 1983 careful immunocytochemical studies of gastrointestinal sarcomas documented their frequent absence of muscle markers that were typical of leiomyosarcomas located elsewhere in the body. Tumors in the subgroup without muscle or Schwann-cell (i.e., S-100 antigen) markers were eventually termed gastrointestinal stromal tumors. Almost all these tumors expressed c-kit and often CD34, which are also expressed on hematopoietic progenitor cells.

The proto-oncogene c-kit encodes a transmembrane tyrosine kinase receptor located on the long arm of chromosome 4 (4q11–q12). Its ligand is stem-cell factor. This proto-oncogene has a role in the development of normal hematopoiesis as well as in the migration of germ cells and is also expressed in normal human mast cells, immature myeloid cells, melanocytes, epithelial breast cells, and the interstitial cells of Cajal (the gastrointestinal “pacemaker” cells). The immunohistochemical profile of the interstitial cells of Cajal is similar to that of gastrointestinal stromal tumors (they are positive for c-kit and CD34 and negative for desmin and S-100 antigen), and gastrointestinal stromal tumors are thought to originate from these cells. However, because omental and mesenteric primary stromal tumors have an immunohistochemical profile typical of that of gastrointestinal stromal tumors and interstitial cells of Cajal are absent in these locations, gastrointestinal stromal tumors may arise from multipotent mesenchymal stem cells.104

In approximately 60 percent of cases of gastrointestinal stromal tumors, there are mutations in c-kit105 in the juxtamembrane domain, such as in-frame deletions (3 to 18 bp) and point mutations in exon 11. The reported rate of mutation ranges from 21 to 88 percent.106 Mutations in exon 13 and exon 9 have been found in most of the remaining cases. The mutations cause the receptor to be activated constitutively without its ligand. Gastrointestinal stromal tumors with mutant c-kit are more likely to be high-grade tumors, characterized by more frequent recurrences and a higher mortality rate than gastrointestinal stromal tumors with normal c-kit. Stable transfection of the mutant gene leads to malignant transformation of murine lymphoid cells (Ba/F3).105

Approximately 70 percent of gastrointestinal stromal tumors develop in the stomach, 20 percent in the small intestine, and less than 10 percent in the esophagus, colon, and rectum. Gastrointestinal stromal tumors are typically more cellular than other gastrointestinal sarcomas. They occur predominantly in patients who are 40 to 70 years old but in rare cases may occur in younger persons.104,106 Survival rates are correlated with the location of the tumor: the rates are highest for esophageal and stomach tumors and lowest for small-bowel tumors. Age, the mitotic index, and size of the tumor (less than 5 cm vs. 5 cm or more) are also independent prognostic factors.104,106,107

A Finnish patient with metastatic gastrointestinal stromal tumor had a rapid and sustained complete response to treatment with 400 mg of imatinib daily for more than 12 months.12 In a European trial of 36 patients with gastrointestinal stromal tumors, oral doses of imatinib that ranged from 300 to 1000 mg daily inhibited tumor growth in 32 patients, 19 of whom had more than a 50 percent decrease in tumor volume.14 Of 36 U.S. patients with unresectable or metastatic gastrointestinal stromal tumors who were randomly assigned to receive 400 mg or 600 mg of imatinib daily, 19 (55 percent) had a partial response (defined by a decrease of at least 50 percent in the size of the lesion); the results were similar with either dose. The disease progressed in four patients (11 percent), but in none of those who had had an initial response.13 In both studies, the severity and frequency of adverse effects were similar to those reported in studies of patients with CML. At twice-daily doses of 500 mg in the European dose-escalation study, nausea and vomiting, edema, and dyspnea were dose-limiting effects. The most common side effects (which generally resolved after the first eight weeks) were nausea and vomiting, rash, edema (particularly periorbital), and conjunctivitis (which in rare cases occurred with bleeding sclerae). Myelosuppression was infrequent, although anemia did occur. Intratumoral and gastrointestinal bleeding developed in fewer than 5 percent of patients.14

**IMATINIB FOR OTHER LEUKEMIAS AND SOLID TUMORS**

In addition to gastrointestinal stromal tumors, c-kit is expressed in a variety of other human cancers, including mast-cell tumors, neuroblastoma, germ-cell tumors, melanoma, small-cell lung cancer, breast and ovarian cancers, and acute myelogenous leukemia.49,50,108-111 Up to 70 percent of the cells of small-cell lung cancer express both c-kit and stem-cell factor.108,112 Although gain-of-function mutations of c-kit occur in both mast-cell neoplasms and gastrointestinal
stromal tumors, the mutations are different, and mast-
cell neoplasms have not proved responsive to imatinib.
In contrast to the ligand-independent activation of

\[
\text{c-kit in gastrointestinal stromal tumors, mastocytosis,}
\text{and germ-cell tumors, in small-cell lung cancer and}
\text{neuroblastoma c-kit may be activated by stem-cell fac-
\text{tor through autocrine growth regulation.}^{49,50,109}
\text{Expression of c-kit (or PDGF)} \text{ does not imply that a}
\text{given tumor will respond to imatinib. The tumor must}
\text{be dependent on the activity of c-kit for imatinib to}
\text{produce an antitumor effect.}
\]

Aberrant PDGF receptors appear to deregulate the
growth of a variety of cancers, such as myelopro-
liferative disorders, gliomas, carcinomas, melanoma,
and sarcomas, including dermatofibrosarcoma protu-
berans.\(^ {49,51,113,114} \) In preclinical studies, imatinib
inhibited the proliferation of both glioblastoma cell
lines expressing PDGF receptors in vitro and in nude
mice\(^ {51,115} \) and human prostate-cancer cells expressing
high levels of PDGF and its receptors that had been
implanted in the bones of nude mice, particularly
when imatinib was combined with paclitaxel.\(^ {116} \) Inhib-
ition of PDGF receptors by imatinib may decrease
interstitial pressure and thus increase the delivery of
chemotherapeutic agents within tumors.\(^ {117} \) Imatinib
is active against chronic myeloproliferative disorders
associated with a translocation between chromo-
somes 5 and 12,\(^ {118} \) in which there is a rearrangement
and overexpression of the gene for PDGF receptor \(\beta\).

CONCLUSIONS
Imatinib is highly active and has an acceptable level
of toxicity when given alone for the treatment of
chronic-phase CML and gastrointestinal stromal
tumors. Imatinib also has limited activity against blast-
phase CML and relapsed Ph-positive ALL, conditions resistant to standard chemotherapy and even to allogeneic stem-cell transplantation. Trials of imatinib are planned or ongoing in patients with acute myelogenous leukemia and in those with solid tumors that express the PDGF receptor or c-kit. The effect of imatinib in combination with other agents is also being evaluated in laboratory models and in the clinic. Our increasing capacity to target anticanicar agents at better-defined neoplastic pathways may change the paradigm for anticancer treatment.

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