Practical Management of Patients With Chronic Myeloid Leukemia Receiving Imatinib

By Michael W.N. Deininger, Stephen G. O'Brien, John M. Ford, and Brian J. Druker

Abstract: The introduction of imatinib, a specific inhibitor of the Bcr-Abl tyrosine kinase, has dramatically changed the management of chronic myeloid leukemia (CML). More than 10,000 patients worldwide have been treated with imatinib in clinical trials, and a large body of information has accumulated about the use of this drug. The purpose of this article is to review practical guidelines in regard to optimal dosing, monitoring, managing common side effects such as myelosuppression, and potential drug interactions. The treatment recommendations are intended to optimize therapy with imatinib while taking into account a patient's specific circumstances.


IMATINIB MESYLATE (Gleevec, Glivec [Novartis, Basel, Switzerland], formerly STI571) is a small molecule signal transduction inhibitor that specifically targets a limited set of protein tyrosine kinases—Abl, Arg (Ab1-related gene), KIT, platelet-derived growth factor receptor (PDGF-R)—and their oncogenic forms, most notably Bcr-Abl. Imatinib represents the archetype of a new class of anticancer agents, small molecules with high selectivity toward a specific molecular target that is known to be responsible for the establishment and maintenance of the malignant phenotype.

In chronic myeloid leukemia (CML), the efficacy of imatinib is unprecedented, with rates of complete hematologic response (CHR) approaching 100% in patients in the chronic phase. Although therapy with imatinib is generally well tolerated, it is not devoid of side effects. Particularly common side effects include myelosuppression, nausea, edema, fatigue, headaches, muscle cramps, arthralgias, myalgias, diarrhea, and skin rashes. Patients were rapidly accrued onto a series of clinical trials (closely monitored phase I6,7 and II protocols5,8,9 and "expanded access" protocols with less stringent documentation requirements). Only 3 years passed between the enrollment of the first CML patient in the phase I protocol and approval by the Food and Drug Administration (FDA) of imatinib for the treatment of patients with CML in advanced phase or after failing interferon alfa (IFN-α) therapy. Results recently have become available from a phase III trial that shows imatinib to be vastly superior to IFN-α plus cytarabine in newly diagnosed patients in regard to hematologic response, cytogenetic response, and time to progression to accelerated phase or blast crisis. These data have led to FDA approval of imatinib for treatment of patients with newly diagnosed CML.

The novel mode of action of imatinib implies that optimal dosing, monitoring, and to some extent, the management of side effects will have to follow principles that differ from the paradigms of conventional cytotoxic chemotherapy. Our aim in this article is to provide practical management guidelines for patients on imatinib. It is evident that our recommendations are based on the information that is currently available, and they may have to be modified in the future.

PROPER DOSING OF IMATINIB

Dose-Response Relationships

The standard dose-response relationship for chemotherapeutic agents defines the optimal drug dose that results in maximal tumor cell killing or other therapeutic effect without unacceptable toxicity. For many conventional cytotoxic drugs, toxicity is limiting before the dose-response curve plateaus, and the theoretical maximum therapeutic potential cannot always be exploited. In contrast to such nonselective therapies, molecularly targeted drugs such as imatinib may be less constrained by the usual dose-response considerations, with optimal therapeutic levels considerably lower than toxic levels. Regardless, defining a dose-response curve as best as possible would assist in determining the optimal dose of therapy.

Lower Doses of Imatinib

Some data defining dose-response relationships are available from the phase I study of imatinib in patients with chronic-phase disease who failed interferon therapy (Fig 1). In this study, at a dose of 200 mg per day, three (33%) of nine patients achieved a CHR, but only one of these patients (11%) had his or her bone marrow revert to a normal morphology. This was the only patient in this dose cohort to have a cytogenetic response, and this was a complete cytogenetic response. At 250 mg daily, a CHR has been reported in more than 80% of patients, and at 300 mg daily, over 90% of patients have achieved a CHR.

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occurred in four (57%) of seven patients. In this cohort, two (28%) of seven patients had their marrow morphology revert to normal, but only one patient (14%) had a cytogenetic response. In contrast, at 300 mg per day or greater, 53 (98%) of 54 patients achieved CHRs. The majority of these patients (80%) had bone marrow that appeared normal, and the cytogenetic response rate was 54% (29 of 54), with 31% major cytogenetic responders. Although based on small numbers of patients, these data suggest that daily doses between 200 and 300 mg are on a steep part of the dose-response curve.

Another approach would be to recommend dosages on the basis of the mechanism of action of imatinib. As the mechanism of action of imatinib is to inhibit the Bcr-Abl tyrosine kinase, it would seem likely that to achieve maximum therapeutic benefit, one needs to use a dose that maximally inhibits Bcr-Abl kinase activity or, alternatively, a dose that inhibits sufficient Bcr-Abl kinase activity to induce apoptosis. From preclinical studies, 1 \( \mu \text{mol/L} \) trough levels appear optimal for cell killing in vitro. In the phase I clinical trial, 1 \( \mu \text{mol/L} \) trough levels were achieved in patients using imatinib at a daily dose of 300 mg and correlated with significant therapeutic benefits. These data, combined with the dose-response data above, indicate that 300 mg is a threshold dose for inducing optimal therapeutic responses.

To ensure that the majority of patients were above this threshold, a dose of 400 mg per day was selected for use in the phase II studies of patients in chronic phase who failed interferon therapy. As the half-life of imatinib is 13 to 16 hours, once-daily administration is appropriate. At the time of the last update of this study, imatinib induced a CHR in 95% of patients, a major cytogenetic response (MCR, Philadelphia [Ph] chromosome-positive metaphases of 35% or less) in 60% and a complete cytogenetic remission (CCR) in 41% of patients with a median follow-up of 18 months. Even more impressively, the rates of CHR, MCR, and CCR for newly diagnosed patients treated with 400 mg per day of imatinib were 96%, 83%, and 68%, respectively, at 12 months of follow-up in the recently reported phase III study (Table 1).

### Maximal Tolerated Dose

During the phase I study, a maximum daily dose of 1,000 mg was reached and there was no convincing dose-limiting toxicity. However, 11 of the 13 grade 3 toxicities with a suspected causal relationship to imatinib occurred at doses greater than 750 mg per day. In addition, at daily doses greater than 750 mg, there was a higher frequency of nausea, vomiting, muscle cramps, edema, fatigue, and diarrhea. In an EORTC study of patients with gastrointestinal stromal tumor, 1,000 mg per day was the maximally tolerated dose, with nausea, vomiting, fluid retention, and skin rashes being the dose-limiting toxicities.

### Doses Higher Than 400 mg per Day

The recommended dose for patients with CML in chronic phase was 400 mg per day of imatinib. This dose was selected based on responses seen in the phase I study, pharmacokinetic data, and a lack of sufficient safety data for higher doses. An obvious question is whether there is any benefit to using doses above 400 mg per day. As additional safety data from the phase I study emerged, patients with advanced-phase disease were treated with 600 mg per day. Thus, in the phase II study of patients in the accelerated phase, 77 patients were treated with 400 mg and 158 patients with 600 mg per day of imatinib. In the phase II study of patients with myeloid blast crisis, 36 patients were treated with 400 mg and 223 patients with 600 mg per day. Retrospective analysis of prognostic factors in patients with accelerated-phase disease showed that the 400- and 600-mg cohorts were well matched. In both studies, there was a trend toward higher hematologic and major cytogenetic response rates in patients treated with 600 mg per day of imatinib (Table 2). In the accelerated-phase study, patients treated with 600 mg per day had a statistically significant improvement in time to disease progression and survival.

In a subsequent study of patients in accelerated phase, patients were also treated with 600 mg daily of imatinib. As opposed to the accelerated protocol cited above, in this expanded access study, patients who otherwise had chronic phase features but had cytogenetic abnormalities besides a single Ph chromosome, were defined as accelerated. Fifteen such patients with this definition of accelerated phase were enrolled at Oregon Health and Science University and had a median disease duration of 45 months.

### Table 1. Responses to Imatinib in the Chronic Phase of Chronic Myeloid Leukemia

<table>
<thead>
<tr>
<th>Patients failing interferon, %</th>
<th>400 mg</th>
<th>600 mg</th>
<th>400 mg</th>
<th>600 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 454, median follow-up 18 months)</td>
<td>95</td>
<td>60</td>
<td>41</td>
<td>62</td>
</tr>
<tr>
<td>Newly diagnosed patients, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 553, 12-month follow-up data)</td>
<td>96</td>
<td>83</td>
<td>68</td>
<td>79</td>
</tr>
</tbody>
</table>

**Abbreviations:** CHR, complete hematologic response; MCR, major cytogenetic response; CCR, complete cytogenetic response.

### Table 2. Results With 400 mg Versus 600 mg of Imatinib per Day in Patients With Advanced-Phase Disease

<table>
<thead>
<tr>
<th></th>
<th>CHR, %</th>
<th>MCR, %</th>
<th>CCR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg</td>
<td>65</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>600 mg</td>
<td>71</td>
<td>37</td>
<td>28</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, %</td>
<td>0.002</td>
<td>0.014</td>
<td>0.002</td>
</tr>
<tr>
<td>TTP, months</td>
<td>Not reached</td>
<td>8 mos</td>
<td>Not reached</td>
</tr>
<tr>
<td>12-month survival, %</td>
<td>65</td>
<td>78</td>
<td>(P = .014)</td>
</tr>
</tbody>
</table>

**Abbreviations:** HR, hematologic response; CHR, complete hematologic response; MCR, major cytogenetic response; TTP, time to progression.
With a median follow-up of 12 months, the major cytogenetic response rate was 80% (12 of 15 patients), with a complete cytogenetic response of 67% (10 of 15). None of these patients has relapsed.\textsuperscript{14} Although a small study, the results for these relatively poor prognosis patients compare favorably with the 12-month results in newly diagnosed patients with CML treated with 400 mg per day of imatinib.

The experience with doses higher than 600 mg per day is limited. In patients with chronic-phase disease in the phase II study who failed to achieve a cytogenetic response following 1 year of imatinib therapy, dose escalation to 800 mg per day has been allowed. Limited experience suggests that up to one third of patients will achieve a major cytogenetic response with dose escalation (Druker B, unpublished data). Investigators at M.D. Anderson have recently reported results treating newly diagnosed patients with chronic-phase CML with 400 versus 800 mg per day of imatinib.\textsuperscript{15} With 6 months of follow-up, the complete cytogenetic response rate was 65% for patients treated with 800 mg per day of imatinib as opposed to 52% for patients treated daily with 400 mg of imatinib.

These data indicate that doses higher than 400 mg per day may yield improved responses; however, daily doses above 600 mg are associated with greater toxicity. In the accelerated and blast crisis studies, the main effect of higher doses was on time to progression and on survival. As the response rates for newly diagnosed patients with chronic-phase CML are already quite high, this implies that comparative studies of higher-dose imatinib therapy in this patient population will require time to progression or survival as end points. Alternatively, rates of molecular remission, if they correlate with improved survival, may be a useful early end point.

In summary, 300 mg per day of imatinib appears to be the threshold dose for optimal therapeutic responses, with 400 mg per day being the recommended dose for patients with chronic-phase disease. Patients with advanced-phase disease enrolled in nonrandomized phase II studies had superior outcomes when treated daily with 600 mg per day as compared to 400 mg of imatinib. Whether the same will be true for patients in the chronic phase is unknown. Doses of 800 mg per day are less well tolerated than lower doses, as this approaches the maximally tolerated dose. As the toxicity of 800 mg per day is greater than at lower doses, treatment with this dose is reserved for patients who relapse or are resistant to imatinib or for patients in clinical trials attempting to determine the risk benefit ratio of higher-dose therapy.

Is Flat Dosing With 400 and 600 mg per Day Appropriate, Regardless of Patient Size?

From population-based pharmacokinetic studies, there is no evidence that the size of the patient has an effect on the plasma levels of imatinib.\textsuperscript{16} In our institution, we have treated 17 patients in the chronic phase who weighed over 250 pounds (113 kg). These patients, who had failed prior therapy with IFN, were treated with 400 mg per day of imatinib. Fifteen (88%) of 17 patients achieved a CHR, and 10 (58%) of 17 achieved a major cytogenetic response. Although based on only a small number of patients, these response rates are similar to those seen in phase II studies. Thus, our experience confirms the pharmacokinetic data that flat dosing is appropriate.

Starting Therapy and Hematologic Monitoring

Imatinib therapy may be instituted as soon as the diagnosis of Ph-positive CML has been established, even if the white blood count (WBC) is dramatically elevated. For patients with a WBC over 20,000/mm$^3$, concomitant therapy with allopurinol is recommended until the WBC is consistently less than 20,000/mm$^3$. Tumor lysis syndrome has been rare, even in patients with advanced-phase disease, but maintaining adequate hydration is essential, and patients in advanced phases should be monitored for this complication. After initiating therapy with imatinib, the WBC should begin to fall within the first 2 weeks and usually normalizes within 4 to 6 weeks. The decline in the platelet count is typically delayed by 1 to 2 weeks. In patients receiving therapy with hydroxyurea and who have normal blood counts, the hydroxyurea should be tapered and discontinued within the first week of imatinib therapy. For patients with elevated WBCs who begin imatinib while on hydroxyurea, the hydroxyurea may need to be continued for 1 to 3 weeks while closely monitoring the WBC. Similar guidelines apply for patients with elevated platelet counts on therapy with anagrelide, but with a week or two added to the time course. For patients with a WBC or platelet count below the lower limits of normal because of recent CML therapy (typically, an IFN-treated patient), all therapy should be discontinued and the blood counts allowed to recover to at least an absolute neutrophil count (ANC) of 1,500/mm$^3$ and a platelet count of at least 100,000/mm$^3$ before starting imatinib. If blood counts are below normal because of advanced-phase disease, imatinib may be started immediately, regardless of the blood counts.

Complete blood counts (CBCs) should be monitored weekly in patients with chronic-phase disease during the first month of imatinib therapy. In the absence of significant myelosuppression (ANC $<1,500$ mm$^3$ or platelet count $<100,000$ mm$^3$), hematologic monitoring can be reduced to every 2 weeks until 12 weeks of therapy is reached. Thereafter, the frequency of monitoring can be lengthened to monthly or even longer, depending on the stability of the counts and the cytogenetic status. For patients in accelerated phase or blast crisis, CBCs should initially be performed at least weekly, depending on the patient’s clinical situation.

MANAGING ADVERSE EVENTS DURING IMATINIB THERAPY

Myelosuppression

Incidence and onset of myelosuppression. Myelosuppression is particularly common in patients with CML treated with imatinib and is more common in patients with advanced disease (Table 3). In the phase III randomized trial of newly diagnosed patients in the chronic phase, grade 3 neutropenia (ANC $<1,000$ mm$^3$) was experienced by 11% of patients, grade 4 neutropenia (ANC $<500$ mm$^3$) occurred in 2% of patients, grade 3 thrombocytopenia (platelets $<50,000$ mm$^3$) occurred in 6.9% of patients, and grade 4 thrombocytopenia (platelets $<10,000$ mm$^3$) occurred in less than 1% of patients.\textsuperscript{10} It was
mandated, according to protocol, to interrupt therapy with imatinib for grade 3 or 4 myelosuppression. These same guidelines were used in the phase II trial of patients who failed IFN-α, representing a later stage of chronic phase. In this study, there was a higher incidence of grade 3 and 4 myelosuppression, with grade 3 and 4 neutropenia experienced by 27% and 8% of patients, respectively, and grade 3 and 4 thrombocytopenia developed in 19% and 1% of patients, respectively.5

In patients with accelerated phase and blast crisis, interruption of therapy for grade 3 or 4 myelosuppression was not mandated, because of the life-threatening nature of the disease. Using these guidelines, myelosuppression was more common in patients with blast crisis as compared with patients with accelerated-phase disease (Table 3).6,9 Further, imatinib induced prolonged aplasia in 1% of patients in blast crisis.8

Myelosuppression can occur at any time during imatinib therapy, but it usually begins within the first 2 to 4 weeks of starting therapy for blast crisis, with a slightly later onset in patients in accelerated or chronic phase. Clinical features associated with a greater risk of myelosuppression include an increased percentage of bone marrow blasts and a lower hemoglobin level,17 as well as longer time from diagnosis, a history of cytopenias induced by IFN-α, and previous busulfan therapy. It is wise to monitor patients with these risk factors more closely, particularly during the early phases of treatment. A minority of patients (<5%) experience repeated episodes of severe myelosuppression, and prolonged interruptions of therapy may be required. It has been suggested that these patients have a higher risk of relapse,18 but it is unknown whether this is a consequence of more advanced disease, insufficient treatment intensity, or both.

Although grade 3 and 4 neutropenia is frequent, particularly in advanced phases, infectious complications are relatively rare. This low rate of infectious complications as compared to that expected in patients with a similar level of myelosuppression induced by conventional chemotherapy may be related to the lack of mucous membrane damage in patients on imatinib. CNS and gastrointestinal hemorrhages have occurred, most frequently in patients in blast crisis with platelet counts less than 20,000 and with uncontrolled leukemia. Overall, 22 deaths have been associated with imatinib-induced myelosuppression. Although most of these deaths occurred in patients with advanced-phase disease with uncontrolled leukemia, some were in patients in the chronic phase. This indicates that continued monitoring of peripheral blood counts is essential.

Does Imatinib Suppress Normal Hematopoiesis?

In patients with CML, the majority of hematopoiesis is derived from Ph-positive stem cells. With disease progression from early chronic phase to advanced disease, the progenitor cell compartment gradually becomes dominated by Ph-positive cells.19 Because imatinib effectively targets Bcr-Abl, a degree of myelosuppression is expected, and it would be predicted that myelosuppression should be more common in patients with advanced-phase disease. However, it is also possible that myelosuppression is a result of inhibiting KIT on Ph-positive as well as normal primitive progenitor cells. This is an important consideration, as contrasting therapeutic consequences would have to be drawn: if myelosuppression was thought to result from inadequate suppression of the Ph-positive clone such that normal hematopoiesis was unable to recover, this would argue for dose escalation; if myelosuppression was thought to be caused by undesired suppression of normal progenitors, a dose reduction would be the appropriate action.

Both in vitro and in vivo data indicate that imatinib does not severely affect normal hematopoiesis. Therapeutic doses of imatinib inhibit colony formation by normal progenitor cells by only 10% to 20%.2,12 In patients with gastrointestinal stromal tumors treated with imatinib, 13% developed grade 3 neutropenia. Two patients (5%) treated with 800 and 1,000 mg per day of imatinib had grade 4 neutropenia. In contrast, the incidence of grade 3/4 thrombocytopenia was less than 1%.13,20 Thus, imatinib toxicity to normal hematopoiesis is largely restricted to high doses and manifests primarily as neutropenia. Another indication that imatinib does not significantly suppress normal hematopoiesis can be inferred from the recovery of normal blood counts in patients with advanced-phase CML during continuous therapy with imatinib. All these observations indicate that myelosuppression induced by imatinib is a therapeutic effect on the Ph-positive leukemic clone and that inhibition of normal hematopoiesis is minimal.

Managing Myelosuppression

A guiding principle in the management of imatinib-induced side effects is to match the aggressiveness of therapy with the

Table 3. Incidence of Myelosuppression

<table>
<thead>
<tr>
<th>Grade</th>
<th>CP, Newly Diagnosed10</th>
<th>CP, IFN-α Failure5</th>
<th>Accelerated Phase5</th>
<th>Myeloid Blast Crisis8</th>
<th>Patients With GIST11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade 3</td>
<td>11</td>
<td>27</td>
<td>23</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>grade 4</td>
<td>2</td>
<td>8</td>
<td>35</td>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td>Thrombocytopenia, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade 3</td>
<td>7</td>
<td>19</td>
<td>31</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>grade 4</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>12</td>
<td>33</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. Different rules for stopping imatinib for myelosuppression were applied in chronic phase as opposed to advanced phases.

Abbreviations: CP, chronic phase; GIST, gastrointestinal stromal tumor; IFN-α, interferon alfa.
phase of disease (Fig 2). On the basis of dose-response considerations, daily doses less than 300 mg should rarely, if ever, be used. Data indicating that there is minimal suppression of normal hematopoiesis by imatinib further support this statement. Thus, dose reductions below 300 mg per day are unlikely to assist in the recovery of normal hematopoiesis but may allow emergence of imatinib-resistant leukemic clones.

**Chronic Phase**

The primary goal in treating otherwise healthy patients in chronic phase is to avoid the risk of potentially dangerous neutropenia and platelet transfusion dependence. Among possible approaches to managing myelosuppression, interruption of treatment, not dose reduction, is the preferred course of action (Fig 2). For myelosuppression of grade 3 or higher severity (ANC < 1,000/mm³ or platelets < 50,000/mm³), imatinib should be withheld until blood counts recover (ANC > 1,500/mm³ or platelets > 100,000/mm³). This generally occurs within 2 to 4 weeks, and imatinib may be resumed at full dose. If the WBC or platelet recovery is slow, taking more than 4 weeks, it might be reasonable to decrease the dose to 300 mg per day. This dose is raised to 400 mg per day as long as myelosuppression does not recur for at least 4 weeks. This recommendation may be modified slightly for patients with features associated with advanced disease (eg, higher percentage of blast or basophils, or clonal evolution).

**Patients in Accelerated and Blast Phase**

In patients with advanced-phase disease, it is currently unclear whether the best option is to continue therapy with imatinib in the face of severe myelosuppression and to manage complications aggressively (as is standard practice in the management of acute leukemia) or, alternatively, to proceed as with patients in the chronic phase, with dose interruptions for myelosuppression. A major unanswered question is whether continuing imatinib, despite myelosuppression, improves the response rate or merely results in greater morbidity because of infectious and bleeding complications. Because accelerated phase covers a wide spectrum from just beyond chronic phase to just short of blast crisis, it is obviously difficult to give stringent guidelines that would equally apply to all clinical situations. Again, our view has been to match the aggressiveness of therapy to the aggressiveness of the disease (Fig 3).

For patients with blast crisis or high-risk accelerated-phase disease (> 15% blasts), our approach has been to adopt an intermediate position attempting to balance these risks and benefits. In these patients, we do not interrupt therapy or reduce doses on the basis of thrombocytopenia. Rather, we support patients with a platelet count under 10,000/mm³ or under 50,000/mm³ with clinically evident bleeding with platelet transfusions. Obviously, if clinically significant bleeding occurs, imatinib should be held immediately, until the bleeding is controlled. For an ANC less than 500/mm³, we continue therapy with imatinib and examine the marrow for cellularity and residual leukemia. In patients whose marrows remain hypocellular or with blasts greater than 30%, imatinib is continued. If the marrow is hypocellular and the ANC is less than 500/mm³ for 2 to 4 weeks, we reduce the dose of imatinib, hold therapy, or consider the use of myeloid growth factors depending on the clinical situation. More recently, we have tended to use myeloid growth factors for approximately 2 weeks. If no recovery occurs, then we hold therapy until neutrophil recovery or leukemia recurs, at which time we reinstitute therapy at full dose. If repeated, prolonged episodes of neutropenia occur, only then would we reduce the dose.

**Use of Myeloid Growth Factors**

The fact that imatinib inhibits only the Ph-positive leukemic clone that comprises the bulk of hematopoiesis in advanced CML raises the issue of myeloid growth factors for treating prolonged therapy-induced myelosuppression. A specific concern is whether these agents would increase the risk of relapse. In a study at Oregon Health and Science University, 18 patients enrolled in the phase II, accelerated-phase CML trial received G-CSF or GM-CSF to treat grade 4 neutropenia (ANC < 500/mm³) that occurred during imatinib therapy. Subcutaneous G-CSF or GM-CSF was administered at daily doses of 300 to 480 µg and 500 µg, respectively. Neutropenia resolved to grade
severity (ANC > 1,500/mm³) in 62% of these patients. Whether this recovery would have occurred without the administration of growth factor would require a randomized clinical trial. However, concurrent administration of growth factors and imatinib was well tolerated. Of note, these patients did not experience a greater rate of relapse, indicating that myeloid growth factors do not adversely affect the antileukemic activity of imatinib (Fig 4).21 As infectious complications during imatinib-induced neutropenia are relatively uncommon, it is not clear whether administration of growth factors reduces the incidence of complications or simply allows the physician and patient to feel more comfortable continuing therapy.

Nonhematologic Toxicity

A large body of information regarding nonhematologic toxicities emerged from the phase II and III studies. The most common nonhematologic adverse events with a suspected relationship to imatinib were nausea, muscle cramps, fluid retention, diarrhea, musculoskeletal pain, fatigue, and skin rashes. Only a minority of patients experienced grade 3/4 toxicity. This is reflected in the low rate of discontinuance of therapy because of toxicity, which was 5%, 3%, and 2% in the phase II studies for blast crisis, accelerated phase, and chronic phase, respectively. The higher rate of severe toxicity in patients with advanced-phase disease may relate to the higher doses administered, though no clear dose-response relationship for toxicity was found at doses between 300 and 600 mg daily. A more likely explanation is the poorer underlying health of patients with advanced-phase disease. The incidence of some specific adverse events was also different according to the stage of disease. For example, vomiting and fluid retention were more common in patients with advanced-phase disease, whereas musculoskeletal symptoms and weight gain were more prevalent in patients in the chronic phase. Again, this may either reflect higher doses of imatinib, the poorer health of patients with advanced-phase disease, or the generally longer duration of therapy in patients in chronic phase. Regardless, the low discontinuation rate indicates that most side effects can be managed successfully with supportive measures. Finally, some toxicities (eg, mild skin rashes, mild elevations of transaminases, bone pain, and arthralgias) may improve spontaneously despite continued therapy at the same dosage. The following sections will review practical aspects of managing some of the common side effects.

Nausea, Vomiting, and Diarrhea

One of the most common toxicities seen with imatinib is nausea, with vomiting being somewhat less common (Table 4). Nausea and vomiting are usually grade 1, are dose-related, and are likely caused by the local irritant properties of the compound. Upper gastrointestinal (GI) bleeding and ulceration has been reported in a small fraction of patients and may represent an extreme form of the local irritant effects. Nausea and vomiting are much more common when imatinib is taken on an empty stomach and can be avoided in most patients if imatinib is taken with food. As the pharmacokinetics of imatinib are not altered whether imatinib is taken with food or fasting,22 it is recommended that imatinib be taken with food, and preferably with the largest meal of the day. Patients with a history of esophagitis or hiatal hernia should take the drug at least 2 hours before bedtime. Because nausea is dose-related, 800-mg doses should be taken as 400 mg bid with two separate meals. Total doses below 800 mg can also be split in half as needed. If symptoms persist despite these recommendations, antinausea medications such as prochlorperazine or ondansetron can effectively control this side effect.

Diarrhea is also a relatively common side effect of imatinib and is dose-related. It is possible that this side effect is caused by inhibition of KIT, which is highly expressed by the interstitial cells of Cajal. These cells are the pacemaker cells of the intestine that mediate intestinal motility. Diarrhea may also be the result of the local irritant effects of the compound, as a sizable fraction of unchanged drug is excreted in the feces following biliary elimination. This side effect is easily managed with antidiarrheal medications in symptomatic patients.
Edema and Fluid Retention

Edema is another common toxicity of imatinib, occurring in more than 50% of patients (Table 4). Edema is dose-related and there is a correlation with its occurrence and plasma levels of imatinib (Ford J, unpublished data). The most common manifestation of this side effect is periorbital edema that is typically worse in the morning. Lower-extremity edema is also seen but is much less common. No specific therapy is required for most cases of periorbital edema. Some patients have found that limiting salt intake may help to control periorbital edema, and in some patients, there have been reports that topical phenylephrine 0.25% may be beneficial. In severe cases, diuretics may be indicated, and in extreme forms that are refractory to these measures, surgery may be an option.23

If edema is more widespread, other fluid retention events should be considered along with the NSAID. Alternatively, COX-2 inhibitors may be tried. If the platelet count is under 100,000/mm³ or the patient has other contraindications to the use of NSAIDs, acetaminophen may be tried cautiously (see below), or mild narcotic analgesics should be used.

In older patients or patients with a history of cardiac or renal impairment, it is advisable to initiate therapy with 300 mg per day of imatinib, increasing the daily dose to 400 or 600 mg as tolerated. All patients should be monitored closely for evidence of peripheral edema or rapid weight gain, and diuretic therapy should be initiated or their dose of diuretics increased as soon as possible. In patients with severe fluid retention, imatinib should be discontinued, the edema controlled with diuretics. Imatinib can then be restarted, possibly at a reduced dose, while maintaining or increasing diuretic therapy.

Muscle Cramps, Bone Pain, and Arthralgias

Musculoskeletal complaints are another common side effect of imatinib and are manifested as muscle cramps and bone pain. The muscle cramps occur mainly in the hands, feet, calves, and thighs. The pattern, frequency, and severity of cramps are usually constant over time, and they may resemble tetanic contractions. Some patients relate cramps to exertion or describe nighttime occurrence. Despite the fact that ionized calcium and magnesium levels are normal in patients treated with imatinib, calcium and magnesium supplements, as well as quinine, can offer symptomatic relief.

Bone pain and arthralgias have been reported by 20% to 40% of patients. Their onset tends to be in the first month of therapy, and they frequently abate after a few months. The symptoms most frequently affect the femurs, tibias, hips, and knees. Bone or joint pain can be severe and disabling and may be strikingly asymmetric. In some cases, imaging studies were done but failed to detect abnormalities. The etiology of this symptom is unclear, but in some patients it has correlated with clearance of leukemic cells from the marrow. Mild bone pain may be controlled with nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with platelet counts more than 100,000/mm³ and no history of GI bleeding. For those patients with a history of GI bleeding, use of a proton pump inhibitor or H₂ histamine receptor blocker should be considered along with the NSAID. Alternatively, COX-2 inhibitors may be tried. If the platelet count is under 100,000/mm³ or the patient has other contraindications to the use of NSAIDs, acetaminophen may be tried cautiously (see below), or mild narcotic analgesics should be used.

Skin Rashes

Drug-induced skin rashes are experienced by up to 30% of patients treated with imatinib. Rashes are frequently pruritic and most commonly appear as erythematous, maculopapular lesions...
on the forearms or trunk, and less frequently, on the face. Skin biopsies revealed the typical appearance of a toxic drug reaction with a mixed cellular infiltrate. In most cases, the rash is mild, self-limiting, and easily manageable with antihistamines or topical steroids, whereas a short course of oral steroids can be used to treat more severe cases.

In some patients, severe rashes develop with desquamative components, including a report of Stevens-Johnson syndrome. In such cases, immediate discontinuation of therapy and systemic steroids (eg, 1 mg/kg/d) are indicated. Severe skin reactions that were resistant to supportive measures were the most frequent cause for permanent discontinuation of imatinib therapy. However, the incidence of this event is small (≤ 1% of all patients). Depending on the clinical situation, it has been possible to restart imatinib after the rash has resolved. In these cases, prednisone has typically been given at 1 mg/kg/d, tapering to 20 mg per day over several weeks. Imatinib has been restarted at 100 mg per day and the dose increased by 100 mg per week while tapering the steroids, assuming that the rash has not recurred. This approach should only be considered in patients for whom no other treatment option exists other than imatinib.

Rare patients with high basophil counts (> 20%) have developed urticarial eruptions after taking imatinib, presumably because of histamine release from basophils. This rash can be managed by premedication with an antihistamine and will usually resolve once the basophil count normalizes. Apart from the presumed histamine release in patients with high basophil counts, the cause of the skin rashes is unclear. However, inhibition of KIT, which is expressed on skin basal cells, melanocytes, and mast cells, may have a role. Further, as KIT is presumed to have a role in pigmentation, it is not surprising that there have been reports of depigmentation in patients treated with imatinib, but this has not been universal. Paradoxically, there have also been reports of hyperpigmentation and darkening of hair color in a small number of patients.

**Hepatotoxicity**

Hepatotoxicity has been much less problematic than predicted from animal studies. Nonetheless, liver function test abnormalities have been observed, with the most typical pattern being a mild transaminisits, although increases in bilirubin have also been seen. Grade 1 elevations in transaminases have been observed in up to 10% of patients and often normalize despite continued therapy. Grade 3 or 4 elevations in liver function tests have occurred in a much lower proportion of patients, with a predominance in patients with advanced-phase disease, in whom leukemic infiltration of the liver is a possible confounding factor. It is important that the results of the phase III trials indicated that grade 2 to 4 liver toxicity is actually more common in interferon-treated patients than in imatinib-treated patients. Despite this, recurrent liver toxicity was the second most common reason for permanent discontinuation of imatinib therapy, though this applies to less than 1% of patients.

Liver toxicity usually occurs during the first few months of therapy with imatinib but can also appear much later. The etiology of the hepatotoxicity is unclear, though it appears to be a typical drug-induced hypersensitivity on liver biopsy. Because of concerns regarding hepatotoxicity, monitoring LFTs should be performed routinely during imatinib therapy. We recommend obtaining LFTs before treatment is started, every other week during the first month of therapy, and at least monthly thereafter.

Our current approach to managing patients with hepatotoxicity is to interrupt therapy for grade 3 elevations in transaminases (> five times the upper limit of normal). When the LFTs fall to grade 1 or less (< 2.5 times the upper limit of normal for transaminases or < 1.5 times for bilirubin), imatinib is reintroduced at a reduced dose. If the liver toxicity does not recur within 6 to 12 weeks, re-escalation to the initial dose can be performed while closely monitoring the LFTs. If grade 3 toxicity recurs, a more thorough hepatic evaluation is indicated, as described below. With recurrent grade 3 toxicity, imatinib should normally be permanently discontinued.

Grade 2 LFT abnormalities (2.5 to five times the upper limit of normal) do not require automatic drug discontinuation but must be addressed. Patients should be counseled to avoid alcohol and other hepatotoxins, especially acetaminophen. Less toxic alternative medications should be substituted for nonessential hepatotoxins whenever possible. Persistent grade 2 abnormalities require thorough hepatic evaluation, including screening for viral hepatitis, ferritin levels, alpha1-antitrypsin levels, and ultrasound or liver biopsy if indicated. The decision to continue imatinib with ongoing grade 2 transaminisits needs to be made in light of the clinical situation, and at a minimum, a dose reduction of imatinib may be warranted.

There has been some controversy regarding the safety of acetaminophen in patients treated with imatinib. A patient in accelerated phase taking imatinib together with high-doses of acetaminophen to treat fever died of hepatic failure. Whether this death was causally related to the combination of imatinib and acetaminophen is not known. However, many other patients have taken these two drugs in combination safely. Nevertheless, caution is recommended, and patients should be advised to use acetaminophen in moderation.

**Other Adverse Events**

Other relatively common adverse events reported in clinical trials of imatinib include weight gain and fatigue. The weight gain may be in part related to fluid retention. However, it is clear that fluid retention cannot account for the progressive increases in weight seen in some patients. Some patients have reported an increased appetite while taking imatinib that abates during treatment breaks. A possible contributor to weight gain has been the return of a normal appetite following the discontinuation of interferon, particularly as weight gain is much less common in newly diagnosed patients treated with imatinib than in patients who failed interferon. Regardless, patients prone to weight problems need to be cautioned about the association between imatinib and weight gain. Measures such as decreased caloric intake and increased exercise are recommended to prevent or treat this problem. Fatigue during imatinib therapy has been attributed in part to mild anemia (hemoglobin decrease < 2 g/dL) that can occur early in the course of treatment. Although the hemoglobin frequently returns to baseline levels, many patients have continued to note mild to moderate fatigue of unclear etiology. Numerous less common adverse events have
been observed (Table 4), but their causal relationship to imatinib is less clear.

**Drug Interactions**

Imatinib is predominantly metabolized in the liver by the CYP3A4/5 cytochrome P<sub>450</sub> enzyme system. Plasma levels of imatinib remain stable over time once steady-state levels are achieved, and imatinib is not known to induce its own metabolism. However, drugs known to induce CY3A4/5 levels may decrease therapeutic levels of imatinib. Major inducers of CYP3A4/5 include carbamazepine, dexamethasone, phenytoin, phenobarbital, progesterone, rifampin, and St. John's Wort, along with other inducers, as listed in Table 5. As an example, a patient in the chronic phase receiving concomitant therapy with phenytoin and 350 mg per day of imatinib had an approximately 75% lower plasma imatinib concentration than other patients receiving the same dose, and this patient failed to enter hematologic remission. This individual responded promptly when phenytoin was discontinued, although dose-escalation to 500 mg per day was also performed. In general, all CY3A4/5-inducing medications such as anticonvulsants and steroids should be used with caution, and appropriate alternatives should be substituted whenever possible.

Conversely, drugs that inhibit CYP3A4 enzyme activity might result in increased plasma levels of imatinib. This large class of compounds includes cimetidine, erythromycin, fluoxetine, ketoconazole, ritonavir, itraconazole, and verapamil. Grapefruit juice is also an inhibitor of CY3A4/5, and patients should be cautioned against excessive intake. Although the therapeutic index of imatinib confers a relatively wide margin of error, caution still needs to be exercised, particularly in patients on higher doses of imatinib or in patients already experiencing toxicity.

Many other drugs are metabolized by the CY3A4/5 enzyme system and may compete with imatinib, leading to increased plasma levels of one or both drugs. Of relevance to CML, increased plasma levels of cyclosporine A have been documented in posttransplant patients treated with imatinib. Another example is the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor simvastatin, where two- to three-fold increases in simvastatin levels were observed in patients taking imatinib, with no change in imatinib levels.

Imatinib is also a weak inhibitor of the CYP2D6 and CYP2C9 isoenzymes; therefore, drugs metabolized by these enzymes should be used with caution. Particularly noteworthy on this list is warfarin, a substrate of both CYP2D6 and CYP2C9. One patient receiving warfarin and imatinib suffered a major CNS hemorrhage. Because the warfarin dose was increased before the event, the causality remains uncertain. In other patients, a reduction, rather than prolongation, of prothrombin time was observed. The best approach is to substitute low-molecular weight or standard heparin for warfarin. Alternatively, patients treated with imatinib and warfarin need close monitoring of the INR with adjustment of the warfarin dose, as necessary. Because of the moderate risk of hemorrhage associated with imatinib therapy, anticoagulant therapy should be administered with caution, if at all, in patients with platelet counts less than 100,000/mm³.

**Treatment Approaches for Patients With Ph-Positive Leukemias**

Advanced phases of CML and Ph-positive ALL. For patients with blast crisis of CML and Ph-positive ALL, the response rate to imatinib is high and toxicity is much lower than with standard chemotherapy. However, the durability of responses tends to be quite short, particularly for patients with lymphoid phenotype disease. For these reasons, we consider imatinib as part of a treatment strategy that incorporates conventional chemotherapy or stem cell transplantation. As the outcome of allogeneic stem cell transplantation is improved if patients are returned to a second chronic phase, imatinib may be useful as a relatively nontoxic bridge to stem cell transplantation for patients in blast crisis. For patients not eligible for allogeneic stem cell trans-
plantation, we would consider a clinical trial using a combination of imatinib with chemotherapy.

Our approach to patients in accelerated phase is similar to that discussed in the section on myelosuppression, as accelerated-phase disease covers a wide spectrum from late chronic phase to blast crisis. In the accelerated-phase study using single agent imatinib, the major prognostic factors for longer survival were blasts percentage less than 15, absence of cytogenetic abnormalities in addition to a single Ph chromosome, hemoglobin more than 10 gm/dL, and treatment with a daily dose of imatinib of 600 mg as compared with 400 mg.9 For patients with high-risk features, we would treat them as recommended above for blast crisis. However, for patients with none of these features, we would tend to treat with imatinib at 600 mg per day as a single agent, whereas the management of patients with only one or two high-risk features is less clear.

Chronic-Phase CML

The simplistic aim of all leukemia treatment is to cure the patient without undue toxicity. Whether imatinib can achieve this or even improve survival remains uncertain. How to counsel patients regarding transplant versus imatinib is a matter of significant controversy and has been discussed elsewhere.32 However, it is clear that of all nontransplant therapies, imatinib induces the highest rates of complete hematologic and major cytogenetic responses. In patients treated with interferon, major cytogenetic responses have been shown to improve survival, and there are already hints that the same may be true for imatinib-induced major cytogenetic responses. For example, achievement of a major cytogenetic response after 3 months of therapy with imatinib was associated with prolonged survival in the phase II study of patients in chronic phase who had failed interferon.5 Similarly, in examining relapses in later-stage patients in chronic phase who failed therapy with interferon, one group has suggested that failure to achieve a major cytogenetic response at 6 months is a poor prognostic factor.18 A second group has demonstrated that patients with a major cytogenetic response are less likely to relapse and that most patients who will achieve a major cytogenetic response will do so within the first 6 months of therapy.33 Specifically, if patients were greater than 65% Ph positive at 6 months, they had a 10% chance of obtaining a major cytogenetic response at 1 year (95% confidence interval 0% to 30%). However, some patients did respond at later times, presumably because of dose escalation of imatinib. In both studies, there were large numbers of patients with ongoing CHR, but no cytogenetic response. As noted, these patients have a higher risk of relapse, but they are still the minority.

Other end points, most importantly molecular response, may become useful surrogate markers for predicting outcome. In patients undergoing allogeneic stem cell transplantation, the majority of patients attain this landmark. In contrast, with imatinib, only 3% of newly diagnosed patients have obtained a molecular remission.34 It must be stressed that, in the setting of CML, the term molecular response or RT-PCR-negativity implies the use of methodology that is able to detect 1 BCR-ABL-positive cell in a background of 105 to 106 BCR-ABL-negative cells, the threshold used for monitoring patients after allografting. As with cytogenetic response, the correlation of RT-PCR-negativity with durability of remission, although likely, remains to be proven.

Incorporating this information into a useful algorithm is problematic, as goals of therapy may differ depending on the individual patient. For example, the goals of therapy for a young patient with an HLA-matched donor would differ significantly from those of an older patient with numerous concurrent medical problems. We have tried to adopt a practical approach recognizing the enormous variability of patient presentations and preferences. For the majority of patients, the goal of therapy is to achieve a major cytogenetic response, and we monitor bone marrow cytogenetics every 6 months. If a patient is greater than 65% Ph positive at 6 months, given the low likelihood of achieving a major cytogenetic response, we discuss treatment alternatives. This includes increasing the dose of imatinib, clinical trials of combinations of imatinib with other agents, or stem-cell transplant, if this is an option. As the side effects of therapy will likely be increased with any of these options, the risks and benefits must be carefully weighed for each individual patient. If the patient is less than 65% Ph positive at 6 months, we continue therapy as long as the cytogenetics are stable or improving. For patients who become 100% Ph negative, we monitor for minimal residual disease with quantitative RT-PCR for Bcr-Abl transcripts. As we have shown that peripheral blood and marrow results correlate well on this test, we are comfortable monitoring patients with peripheral blood samples using this test; however, we continue to recommend marrows on a yearly basis. If at any point there is a significant increase in the Bcr-Abl levels or a cytogenetic relapse, we offer the same options as outlined above with the same caveats.

DISCUSSION

As with most anticancer drugs, a dose-response relationship can be defined with imatinib. However, clinically significant responses occurred well below the maximally tolerated dose. In defining dose-response relationships, it appears that doses below 300 mg per day are less effective and should rarely, if ever, be used. Whether daily doses higher than 400 mg for patients in the chronic phase or 600 mg for patients with advanced-phase disease will yield improved results is unknown and will likely require large-scale clinical trials for this question to be answered.

The overall clinical experience with imatinib has shown that it is generally well tolerated. Most side effects are mild to moderate in severity, are easily manageable, and are often transient or self-limiting. Careful monitoring for myelosuppression is required, especially in advanced disease. Given the minimal effect of imatinib on normal hematopoiesis, the management of myelosuppression differs from recommendations typically used for chemotherapy.

The goals of therapy with imatinib are difficult to define given the newness of this agent and the lack of data correlating responses with survival. Preliminary data from patients with late chronic-phase disease indicate that patients with cytogenetic responses are less likely to relapse than patients without cytogenetic responses; however, even in patients without cytogenetic responses, relapse rates at 18 months are less than 25%. Obviously, many of these questions will be answered as the data for imatinib mature.
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