Report from the Food and Drug Administration

U.S. Food and Drug Administration Drug Approval Summary: Conversion of Imatinib Mesylate (STI571; Gleevec) Tablets from Accelerated Approval to Full Approval

Martin H. Cohen, John R. Johnson, and Richard Pazdur
Division of Oncology Drug Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Rockville, Maryland

ABSTRACT

Imatinib mesylate (Gleevec, Novartis Pharmaceuticals East Hanover, NJ) received accelerated approval on May 10, 2001 for the treatment of patients with chronic myeloid leukemia (CML) in (a) chronic phase after failure of IFN-α therapy, (b) accelerated phase, and (c) blast crisis. The accelerated approval was accompanied by a postmarketing commitment by Novartis Pharmaceuticals to continue patient follow-up to determine duration of treatment response and survival. The present review, based on a safety and efficacy report submitted on December 20, 2002, summarizes data applicable to the conversion of these three CML indications to full approval status.

Results: Chronic phase CML: Five hundred thirty-two chronic phase CML patients who had not benefited from prior IFN therapy were treated at a starting imatinib mesylate dose of 400 mg p.o. qd; dose escalation to 800 mg p.o. qd was allowed. Patients had received a median of 14 months of IFN therapy at doses ≥25 million IU/wk and were all in late chronic phase, with a median time from diagnosis of 32 months. Median duration of imatinib mesylate treatment was 29 months, with 81% of patients treated for ≥24 months (maximum 31.5 months). Initial favorable treatment responses were sustained. An estimated 87.8% of patients who had a major cytogenetic response maintained their response 2 years after their initial response. After 2 years of treatment, an estimated 85.4% of patients were free of progression to accelerated phase or blast crisis, and the estimated overall survival was 90.8% (95% confidence interval, 88.3-93.2). Accelerated phase CML: Patients enrolled totaled 293: 235 with CML accelerated phase, 48 with relapsed/refractory acute lymphocytic leukemia, 2 with relapsed/refractory acute myelocytic leukemia, and 8 with relapsed/refractory CML in lymphoid blast crisis. Patients received imatinib mesylate 400 or 600 mg p.o. qd. Dose escalation was permitted, to a maximum of 800 mg/d, taken as 400 mg bid. Efficacy results were improved in patients receiving imatinib mesylate 600 mg qd versus patients receiving 400 mg qd. The median duration of hematologic response was 29 versus 17 months and the estimated 24-month maintained hematologic response rate was 61% versus 42%. The median survival of patients treated with imatinib mesylate 600 mg qd was not reached versus 20.9 months for patients receiving 400 mg qd. Estimated 24-month survival rate was 66% versus 46%. The median survival in the advanced leukemia population (acute lymphocytic leukemia, acute myelocytic leukemia, and lymphoid blast crisis) was only 5 months, and only two patients are still on treatment. Blast crisis CML: A total of 260 patients were recruited. The imatinib mesylate dose was initially 400 mg qd (37 patients) but was subsequently increased to 600 mg qd (223 patients). Patients receiving imatinib mesylate 600 mg qd had a higher hematologic response rate than did patients receiving 400 mg (33% versus 16%). Major cytogenetic responses occurred in 15% of the 260 study patients. The overall median survival was 6.9 months: 7.1 months for patients treated with imatinib mesylate 600 mg and 4.7 months for patients receiving imatinib mesylate 400 mg. Estimated 12-month survival rate for all study patients was 32.1% and estimated 24-month survival rate was 18.3%. Safety: Imatinib mesylate was generally well tolerated, but relatively frequent reports of common toxicity criteria grade 3/4 neutropenia and thrombocytopenia were encountered. The most frequently reported adverse events included gastrointestinal disturbances, edema, rash, and musculoskeletal complaints. These rarely led to discontinuation of therapy.

Conclusions: The results confirm those of the interim analysis and suggest that imatinib mesylate represents an effective therapeutic agent for the treatment of patients with CML in chronic phase after failure of IFN-α therapy, in blast crisis, and in accelerated phase.

INTRODUCTION

On December 5, 2003, the U.S. Food and Drug Administration converted the approval of imatinib mesylate tablets (Gleevec, Novartis Pharmaceuticals) for the treatment of adult patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in (a) chronic phase after failure of IFN-α therapy, (b) accelerated phase, and (c) blast...
crisis from accelerated to regular approval. Accelerated approval, allowed on May 10, 2001 (1), permits approval of a drug for a serious or life-threatening disease for which treatment is inadequate based on an effect on a surrogate end point (in this case, cytogenetic and hematologic responses) that is reasonably likely to predict clinical benefit. Patient follow-up was relatively short at the time of accelerated approval (3-7 months after recruitment of the last chronic phase, accelerated phase, or blast crisis patient), too short to establish clinical benefit. Therefore, Novartis Pharmaceuticals was required to continue patient follow-up to determine response duration and to obtain additional safety data.

Imatinib mesylate subsequently received accelerated approval for treatment of newly diagnosed CML on December 20, 2002; this indication has not yet been converted to regular approval.

EXPERIMENTAL DESIGN

Study Populations. Definitions of CML chronic phase, accelerated phase, and blast crisis are summarized in Table 1. Definitions or hematologic and cytogenetic response criteria for each of the three CML phases are summarized in Table 2.

Chronic Phase CML Study. The primary objective of the study was to determine the rate of complete cytogenetic response (CCyR) and major cytogenetic response (MCyR) to imatinib mesylate. Secondary objectives, many of greater interest in assessing clinical benefit, included determination of the rate and duration of complete hematologic response (CHR) and the duration of CCyR and MCyR. Other secondary objectives included evaluation of the safety profile of imatinib mesylate; measurement of time to accelerated phase disease or blast crisis and determination of overall survival. The first patient was recruited on December 6, 1999, whereas the last patient was recruited on May 30, 2000. Data cutoff for this analysis was July 31, 2002.

Study eligibility included Ph+ CML, ages ≥18 years, and with IFN failure or intolerance defined as any of the following: (a) failure to achieve a CHR, lasting for at least 1 month despite ≥6 months of IFN or an IFN-containing regimen, in which IFN was administered at a dose of at least 25 million IU (MIU)/wk. During this treatment period, the cumulative duration of hydroxyurea therapy may not have exceeded 50% of the treatment period with the IFN-containing regimen (hematologic resistance); (b) bone marrow cytogenetics showing >65% Ph+ after 1 year of IFN-based therapy (cytogenetic resistance); (c) an increase in the Ph+ chromosome in bone marrow cells by at least 30 percentage points (e.g., from 20% to 50% or from 30%

### Table 1 CML phase definitions

<table>
<thead>
<tr>
<th>Chronic phase (all five criteria must be fulfilled):</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. &lt;15% blasts in peripheral blood and bone marrow</td>
</tr>
<tr>
<td>2. &lt;30% blasts + promyelocytes in peripheral blood or bone marrow</td>
</tr>
<tr>
<td>3. &lt;20% basophils in peripheral blood</td>
</tr>
<tr>
<td>4. ≥100 × 10^9/L platelets</td>
</tr>
<tr>
<td>5. No extramedullary involvement other than spleen or liver</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Accelerated phase (at least one of the four criteria must be fulfilled):</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ≥15% blasts in peripheral blood or bone marrow</td>
</tr>
<tr>
<td>2. ≥30% blasts + promyelocytes in peripheral blood or bone marrow (but &lt;30% blasts in peripheral blood and bone marrow)</td>
</tr>
<tr>
<td>3. ≥20% basophils in peripheral blood</td>
</tr>
<tr>
<td>4. &lt;100 × 10^9/L platelets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blast crisis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ≥30% blasts in peripheral blood or bone marrow</td>
</tr>
<tr>
<td>2. Extramedullary involvement other than spleen or liver</td>
</tr>
</tbody>
</table>

(These two evaluations take preference over chronic and accelerated phase results.)

### Table 2 CML response criteria

<table>
<thead>
<tr>
<th>Hematologic response criteria (all responses to be confirmed after ≥4 wk):</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blast crisis and accelerated phase</strong></td>
</tr>
<tr>
<td>• CHR</td>
</tr>
<tr>
<td>&lt;5% blasts in bone marrow</td>
</tr>
<tr>
<td>No blasts in peripheral blood</td>
</tr>
<tr>
<td>No extramedullary involvement</td>
</tr>
<tr>
<td>• No evidence of leukemia</td>
</tr>
<tr>
<td>As for CHR, but without complete recovery of peripheral blood (i.e., 1.0 ≤ absolute neutrophil count &lt; 1.5 × 10^9/L and 20 ≤ platelets &lt; 100 × 10^9/L)</td>
</tr>
<tr>
<td>• Return to chronic phase</td>
</tr>
<tr>
<td>&lt;15% blasts in peripheral blood and bone marrow</td>
</tr>
<tr>
<td>&lt;30% blasts + promyelocytes in peripheral blood and bone marrow</td>
</tr>
<tr>
<td>&lt;20% basophils in peripheral blood</td>
</tr>
<tr>
<td>No extramedullary involvement other than spleen or liver</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chronic phase CML</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CHR</td>
</tr>
<tr>
<td>WBC &lt; 10 × 10^9/L</td>
</tr>
<tr>
<td>Platelets &lt; 450 × 10^9/L</td>
</tr>
<tr>
<td>No blasts + promyelocytes &lt; 5% in peripheral blood</td>
</tr>
<tr>
<td>&lt;20% basophils in peripheral blood</td>
</tr>
<tr>
<td>No extramedullary involvement</td>
</tr>
<tr>
<td>• Loss of CHR</td>
</tr>
<tr>
<td>WBC &gt; 20 × 10^9/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytogenetic response criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complete: 0% Ph+ cells</td>
</tr>
<tr>
<td>• Partial: &gt; 0-35% Ph+ cells</td>
</tr>
<tr>
<td>• Minor: &gt; 35-65% Ph+ cells</td>
</tr>
<tr>
<td>• Minimal: &gt; 65-95% Ph+ cells</td>
</tr>
<tr>
<td>• None: &gt; 95% Ph+ cells</td>
</tr>
<tr>
<td>• Not done: &lt; 20 metaphases were examined and/or response could not be assigned</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Loss of MCyR</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Loss of CCyR: increase to &gt; 0% Ph+ cells</td>
</tr>
<tr>
<td>• Loss of PCyR: increase by ≥30% Ph+ cells compared with lowest value before current assessment or an increase to ≥65% Ph+ cells</td>
</tr>
</tbody>
</table>

NOTE: Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation; therefore, unconfirmed CCyR or partial cytogenetic responses (PCyR) might have had a lesser cytogenetic response on a subsequent bone marrow evaluation. A confirmed cytogenetic response is based on two bone marrow cytogenetic evaluations, the latter done at least 1 month after the initial bone marrow study.

* A bone marrow sample was to be considered as assessable for cytogenetic response only if it contained ≥20 metaphases. This condition was always maintained for affirmation of complete response. However, an assessment of partial response was retained in a sample with < 20 metaphases when it was immediately preceded or followed by a complete or partial response in another sample.
60%), confirmed by two samples at least 1 month apart, or an absolute increase to >65% (cytogenetic refractoriness); and (d) a rising WBC count (to a level >20 \times 10^9/L confirmed by two samples taken at least 2 weeks apart) for patients achieving a CHR while receiving IFN or an IFN-containing regimen at a dose of at least 25 MIU/wk. During this treatment period, the cumulative duration of hydroxyurea therapy may not have exceeded 50% of the treatment period with the IFN-containing regimen (hematologic refractoriness), or (e) intolerance to IFN therapy defined as a grade >3 nonhematologic toxicity persisting for at least 1 month, for patients receiving IFN alone or in combination when IFN was administered at a dose of at least 25 MIU/wk. Patients who were intolerant of IFN were to have been diagnosed ≥6 months before the time of entry into the study.

Patients received imatinib mesylate 400 mg p.o. qd. Dose escalation was permitted to 600 mg p.o. qd or to a maximum of 800 mg daily taken as 400 mg bid.

**Accelerated Phase CML Study.** The primary objective was to determine the rate of hematologic response lasting ≥4 weeks. Secondary objectives included determination of the duration of hematologic response, overall survival, cytogenetic response, time to blast crisis, and tolerability and safety of imatinib mesylate treatment. The first patient was recruited on August 9, 1999, whereas the last patient was recruited on May 12, 2000. Data cutoff for this analysis was December 16, 2002.

To be eligible for the study, patients had to be ages ≥18 years, with performance status ≤2, and with a histologically confirmed diagnosis of Ph+ CML in myeloid blast crisis (Table 1). Both newly diagnosed patients and patients who had received prior therapies for CML accelerated phase or blast crisis were eligible. Newly diagnosed patients were not to have received prior accelerated phase or blast crisis therapies, with the exception of IFN or hydroxyurea.

Patients received imatinib mesylate 400 or 600 mg p.o. qd. Dose escalation was permitted, to a maximum of 800 mg daily, taken as 400 mg bid.

**Blast Crisis Phase CML Study.** The primary objective was to determine the rate of hematologic response lasting ≥4 weeks. Secondary objectives included determination of the duration of hematologic response, overall survival, cytogenetic response, and tolerability and safety of imatinib mesylate treatment. The first patient was recruited on June 30, 1999, whereas the last patient was recruited on May 12, 2000. Data cutoff for this analysis was July 31, 2002.

To be eligible for the study, patients had to be ages ≥18 years, with performance status ≤2, and with a histologically confirmed diagnosis of Ph+ CML in myeloid blast crisis (Table 1). Both newly diagnosed patients and patients who had received prior therapies for CML accelerated phase or blast crisis were eligible. Newly diagnosed patients were not to have received prior accelerated phase or blast crisis therapies, with the exception of IFN or hydroxyurea.

Patients received imatinib mesylate 400 or 600 mg p.o. qd. Dose escalation was permitted, to a maximum of 800 mg daily, taken as 400 mg bid.

**RESULTS**

**Chronic Phase CML Study.** Table 3 summarizes patient demographics characteristics and Table 4 summarizes pertinent data concerning disease history at baseline. Patients studied were in late chronic phase CML, with a median time since diagnosis of 32 months. As expected, patients with cytogenetic failure had the longest IFN exposure, and IFN-intolerant patients the shortest. Even for IFN intolerant patients, however, 26% received IFN for 6 to 12 months and 30% received it for ≥1 year.

The median duration of imatinib mesylate exposure at the time of the data cutoff was 29 months. The maximum imatinib mesylate exposure was 31.5 months. Eighty-one percent of patients were on treatment for ≥24 months.

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>All patients (N = 532)</th>
<th>Hematologic failure (n = 152)</th>
<th>Cytogenetic failure (n = 188)</th>
<th>IFN intolerant (n = 192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>57.0</td>
<td>55.5</td>
<td>53.0</td>
<td>59.0</td>
</tr>
<tr>
<td>Minimum-maximum</td>
<td>18-90</td>
<td>18-79</td>
<td>23-77</td>
<td>20-90</td>
</tr>
<tr>
<td>Age category (y), n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>168 (31.6)</td>
<td>57 (37.5)</td>
<td>64 (34.0)</td>
<td>47 (24.5)</td>
</tr>
<tr>
<td>≥50 to &lt;60</td>
<td>153 (28.8)</td>
<td>38 (25.0)</td>
<td>65 (34.6)</td>
<td>50 (26.0)</td>
</tr>
<tr>
<td>≥60 to &lt;70</td>
<td>159 (29.9)</td>
<td>47 (30.9)</td>
<td>44 (23.4)</td>
<td>68 (35.4)</td>
</tr>
<tr>
<td>≥70</td>
<td>52 (9.8)</td>
<td>10 (6.6)</td>
<td>15 (8.0)</td>
<td>27 (14.1)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>311 (58.5)</td>
<td>102 (67.1)</td>
<td>111 (59.0)</td>
<td>98 (51.0)</td>
</tr>
<tr>
<td>Female</td>
<td>221 (41.5)</td>
<td>50 (32.9)</td>
<td>77 (41.0)</td>
<td>94 (49.0)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>463 (87.0)</td>
<td>128 (84.2)</td>
<td>161 (85.6)</td>
<td>174 (90.6)</td>
</tr>
<tr>
<td>Black</td>
<td>32 (6.0)</td>
<td>13 (8.6)</td>
<td>10 (5.3)</td>
<td>9 (4.7)</td>
</tr>
<tr>
<td>Oriental</td>
<td>8 (1.5)</td>
<td>3 (2.0)</td>
<td>3 (1.6)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Other</td>
<td>29 (5.5)</td>
<td>8 (5.3)</td>
<td>14 (7.4)</td>
<td>7 (3.6)</td>
</tr>
<tr>
<td>Eastern Cooperative Oncology Group performance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>26 (4.9)</td>
<td>1 (0.7)</td>
<td>13 (6.9)</td>
<td>12 (6.3)</td>
</tr>
<tr>
<td>Grade 0</td>
<td>316 (59.4)</td>
<td>102 (67.1)</td>
<td>118 (62.8)</td>
<td>96 (50.0)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>172 (32.3)</td>
<td>43 (28.3)</td>
<td>54 (28.7)</td>
<td>75 (39.1)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>18 (3.4)</td>
<td>6 (3.9)</td>
<td>3 (1.6)</td>
<td>9 (4.7)</td>
</tr>
</tbody>
</table>
**Confirmed Cytogenetic Response Rate.** Confirmed cytogenetic responses are shown in Table 5; 38% of study patients attained a CCyR and 59% had a MCyR. More than 50% of the MCyRs were noted at the time of the first on-study bone marrow (3 months). The percentage of patients with a MCyR steadily increased with increasing time on treatment. Approximately 9% of MCyRs occurred after 1 year of treatment and ~7% occurred after 2 years of treatment. The MCyR rate was highest in patients with a recent diagnosis of CML (within 1 year of study enrollment) and was lower in patients with laboratory evidence of more advanced disease (i.e., high WBC count, high platelet count, low hemoglobin, and ≥3% blasts in the peripheral blood).

Thirty-five of the 343 patients who had achieved MCyR during treatment had a confirmed loss of response. Of these 35 cases, 7 had achieved a confirmed CCyR. Only 10 (2.9%) of the MCyR patients progressed to accelerated phase or blast crisis. The estimated rate of patients still in MCyR after 18 months is 90.0% [95% confidence interval (95% CI), 86.6-93.4] and at 24 months is 87.8% (95% CI, 83.8-91.7).

**Complete Hematologic Response.** A CHR was achieved in 503 of 532 study patients (95% CI, 92.3-96.3) CHR was lost during treatment in 117 (23.2%) patients. Sixty-six (13.1%) of these patients progressed to accelerated phase or blast crisis.

**Time to Accelerated Phase or Blast Crisis.** Of the 532 patients, 85 (16.0%) patients had values indicating progression to accelerated phase or blast crisis. The estimated probabilities (95% CI) of being free of progression to accelerated or blast crisis are 88.4% (85.7-91.2) at 18 months and 85.4% (82.4-88.5) at 24 months.

**Survival.** At time of analysis, 65 (12.2%) of the 532 patients had died. Of the 64 deaths (1 death was reported after bone marrow transplant), 8 occurred on study treatment and 56 occurred during follow-up after discontinuation of treatment (mostly due to progression; n = 45). The estimated probabilities (95% CI) of being alive are 94.2% (92.2-96.2) at 18 months and 90.8% (88.3-93.2) at 24 months.

**Accelerated Phase CML Study.** Demographics and performance status of the study population are summarized in Table 6. As indicated, patients receiving imatinib mesylate 400 or 600 mg/d were comparable.

Disease history is provided in Table 7. The median time from accelerated phase diagnosis to study entry was 1.4 and 0.8 months for the imatinib mesylate 400 and 600 mg treatment groups. Approximately 54% of each treatment group had splenomegaly (spleen palpable below the costal margin) and ~21% of patients had hepatomegaly. The median WBC count of all treated patients was 21.4 × 10^3/L and ~10% of each treatment group had basophils ≥20%.

**Efficacy results are displayed in Table 8.** The primary efficacy variable was confirmed hematologic response. As indicated, the hematologic response rate was higher in patients receiving imatinib mesylate 600 mg/d compared with patients receiving imatinib mesylate 400 mg/d. In addition to imatinib mesylate administration at 600 mg/d, factors

<table>
<thead>
<tr>
<th>Disease history</th>
<th>All patients (N = 532)</th>
<th>Hematologic failure (n = 152)</th>
<th>Cytogenetic failure (n = 188)</th>
<th>IFN intolerant (n = 192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since first diagnosis of CML (mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>32.0</td>
<td>32.3</td>
<td>32.7</td>
<td>29.6</td>
</tr>
<tr>
<td>Minimum-maximum</td>
<td>3-218</td>
<td>3-131</td>
<td>10-184</td>
<td>3-218</td>
</tr>
<tr>
<td>Time since first diagnosis of CML, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 mo</td>
<td>5 (0.9)</td>
<td>1 (0.7)</td>
<td>0</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>≥6 to &lt;12 mo</td>
<td>44 (8.3)</td>
<td>20 (13.2)</td>
<td>2 (1.1)</td>
<td>22 (11.5)</td>
</tr>
<tr>
<td>≥12 to &lt;24 mo</td>
<td>145 (27.3)</td>
<td>37 (24.3)</td>
<td>51 (27.1)</td>
<td>57 (29.7)</td>
</tr>
<tr>
<td>≥2 to &lt;5 y</td>
<td>226 (42.5)</td>
<td>68 (44.7)</td>
<td>89 (47.3)</td>
<td>69 (35.9)</td>
</tr>
<tr>
<td>≥5 y</td>
<td>112 (21.1)</td>
<td>26 (17.1)</td>
<td>46 (24.5)</td>
<td>40 (20.8)</td>
</tr>
<tr>
<td>Duration of IFN at ≥25 MIU/wk (mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14.0</td>
<td>12.1</td>
<td>22.1</td>
<td>7.0</td>
</tr>
<tr>
<td>Minimum-maximum</td>
<td>0-135</td>
<td>1-83</td>
<td>4-135</td>
<td>0-117</td>
</tr>
<tr>
<td>Duration of IFN at ≥25 MIU/wk (mo), n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>102 (19.2)</td>
<td>21 (13.8)</td>
<td>1 (0.5)</td>
<td>80 (41.7)</td>
</tr>
<tr>
<td>≥6 to &lt;12</td>
<td>120 (22.6)</td>
<td>54 (35.5)</td>
<td>16 (8.5)</td>
<td>50 (26.0)</td>
</tr>
<tr>
<td>≥12</td>
<td>305 (57.3)</td>
<td>77 (50.7)</td>
<td>171 (91.0)</td>
<td>57 (29.7)</td>
</tr>
<tr>
<td>Time since IFN stopped (mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.1</td>
<td>0.1</td>
<td>0.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Minimum-maximum</td>
<td>0-4</td>
<td>0-4</td>
<td>0-3</td>
<td>0-3</td>
</tr>
</tbody>
</table>

**Table 5.** Confirmed cytogenetic response rate, chronic phase CML.
associated with improved overall hematologic response rate included gender (females 78%, males 65%), platelets ≥100 × 10^9/L (76% versus 62%), blasts <15% in bone marrow (82% versus 69%), and hemoglobin ≥100 g/L (77% versus 49%).

MCyR, duration of hematologic response, time to progression, and overall survival were also greater in the imatinib mesylate 600 mg/d treatment group. The median survival in the advanced leukemia population (acute lymphocytic leukemia, acute myelocytic leukemia, and lymphoid blast crisis) was only 5 months, and only two patients are still on treatment.

**Blast Crisis CML.** Baseline demographics and performance status of the study population are summarized in Table 9. Table 10 summarizes prior disease history. As indicated, 37 patients received imatinib mesylate 400 mg/d and 223 received imatinib mesylate 600 mg/d. One hundred sixty-five (63.5%) patients were considered previously untreated for blast crisis, as either no accelerated phase or blast crisis treatment was recorded or they had received only IFN, hydroxyurea, or low-dose cytosine arabinoside, which was considered palliative treatment in this setting. The remaining 95 (36.5%) patients had received cytotoxic chemotherapy and/or bone marrow transplantation for advanced disease.

Duration of drug exposure is summarized in Table 11. Duration of exposure as shorter in pretreated patients (median 92 days) than in untreated patients (median 142 days).

**Table 6 Demographics, accelerated phase CML**

<table>
<thead>
<tr>
<th>Demographic or baseline variable</th>
<th>400 mg (n = 77)</th>
<th>600 mg (n = 158)</th>
<th>All doses (N = 235)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>53.4 ± 12.71</td>
<td>57.0 ± 11.92</td>
<td>55.8 ± 12.28</td>
</tr>
<tr>
<td>Median</td>
<td>55.0</td>
<td>57.5</td>
<td>56.0</td>
</tr>
<tr>
<td>Range</td>
<td>22-86</td>
<td>22-81</td>
<td>22-86d</td>
</tr>
<tr>
<td><strong>Age category (y), n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>25 (32.5)</td>
<td>37 (23.4)</td>
<td>62 (26.4)</td>
</tr>
<tr>
<td>≥50 to &lt;60</td>
<td>26 (33.8)</td>
<td>54 (34.2)</td>
<td>80 (34.0)</td>
</tr>
<tr>
<td>≥60 to &lt;70</td>
<td>21 (27.3)</td>
<td>43 (27.2)</td>
<td>64 (27.2)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>5 (6.5)</td>
<td>24 (15.2)</td>
<td>29 (12.3)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (58.4)</td>
<td>73 (46.2)</td>
<td>118 (50.2)</td>
</tr>
<tr>
<td>Female</td>
<td>32 (41.6)</td>
<td>85 (53.8)</td>
<td>117 (49.8)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>69 (89.6)</td>
<td>141 (89.2)</td>
<td>210 (89.4)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (3.9)</td>
<td>7 (4.4)</td>
<td>10 (4.3)</td>
</tr>
<tr>
<td>Oriental</td>
<td>1 (1.3)</td>
<td>1 (0.6)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (5.2)</td>
<td>9 (5.7)</td>
<td>13 (5.5)</td>
</tr>
<tr>
<td><strong>Eastern Cooperative Oncology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3 (3.9)</td>
<td>9 (5.7)</td>
<td>12 (5.1)</td>
</tr>
<tr>
<td>Grade 0</td>
<td>26 (33.8)</td>
<td>60 (38.0)</td>
<td>86 (36.6)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>31 (40.3)</td>
<td>63 (39.9)</td>
<td>94 (40.0)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>17 (23.1)</td>
<td>24 (15.2)</td>
<td>41 (17.4)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>2 (1.3)</td>
<td>2 (0.9)</td>
</tr>
</tbody>
</table>

**Table 7 Disease history, accelerated phase CML**

<table>
<thead>
<tr>
<th>Time since accelerated phase diagnosis to study entry, n (%)</th>
<th>400 mg (n = 77)</th>
<th>600 mg (n = 158)</th>
<th>All doses (N = 235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 mo</td>
<td>57 (74.0)</td>
<td>118 (74.7)</td>
<td>175 (74.5)</td>
</tr>
<tr>
<td>&gt;6 mo to &lt;1 y</td>
<td>5 (6.5)</td>
<td>18 (11.4)</td>
<td>23 (9.8)</td>
</tr>
<tr>
<td>&gt;1 to &lt;2 y</td>
<td>11 (14.3)</td>
<td>13 (8.2)</td>
<td>24 (10.2)</td>
</tr>
<tr>
<td>&gt;2 to &lt;5 y</td>
<td>3 (3.9)</td>
<td>8 (5.1)</td>
<td>11 (4.7)</td>
</tr>
<tr>
<td>≥5 y</td>
<td>1 (1.3)</td>
<td>1 (0.6)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td><strong>Extradematous involvement</strong></td>
<td>49 (65.6)</td>
<td>92 (58.2)</td>
<td>141 (60)</td>
</tr>
<tr>
<td>Blasts (%) in bone marrow ≥15%</td>
<td>39 (50.6)</td>
<td>79 (50.0)</td>
<td>118 (50.2)</td>
</tr>
<tr>
<td><strong>Other chromosomal abnormalities</strong></td>
<td>27 (35.1)</td>
<td>55 (34.8)</td>
<td>82 (34.9)</td>
</tr>
</tbody>
</table>
Safety. Table 13 lists systemic adverse events and Table 14 lists laboratory adverse events. The most frequent systemic adverse events were fluid retention, nausea, and muscle cramps. There was a trend suggesting increased grade 3/4 adverse events with advancing phase of disease.

In older patients (ages ≥65 years), with the exception of edema, there was no evidence of an increase in the incidence or severity of adverse events. In women, there was an increase in the frequency of neutropenia as well as grade 1/2 superficial edema, headache, nausea, rigors, vomiting, rash, and fatigue. No differences were seen related to race, but there were insufficient numbers of non-Caucasians for proper evaluation.

Cytopenias, particularly neutropenia and thrombocytopenia, were a consistent finding and occurred with increasing frequency with advancing disease phase (i.e., blast crisis > accelerated phase < chronic phase CML). The median duration of the neutropenic and thrombocytopenic episodes varied from 2 to 4 weeks. Neutropenia and thrombocytopenia were usually managed with either dose reduction or an interruption of treatment. In rare cases, permanent discontinuation of treatment was required.

Grade 3 elevation of transaminases or bilirubin occurred in 3% to 6% (Table 14) and were usually managed with dose reduction or interruption. The median duration of these episodes was ≤1 week. Treatment was discontinued permanently because of liver laboratory abnormalities in <1% of patients. However, one patient, who was taking acetaminophen regularly for fever, died of acute liver failure.

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>400 mg</th>
<th>600 mg</th>
<th>Untreated</th>
<th>Pretreated</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>median</td>
<td>54</td>
<td>56</td>
<td>57</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>minimum</td>
<td>47-58</td>
<td>47-65</td>
<td>50-66</td>
<td>43-61</td>
</tr>
<tr>
<td></td>
<td>maximum</td>
<td>20-69</td>
<td>19-81</td>
<td>19-81</td>
<td>20-73</td>
</tr>
<tr>
<td>Age category, n (%)</td>
<td>&lt;50 y</td>
<td>12 (32.4)</td>
<td>63 (28.3)</td>
<td>38 (23.0)</td>
<td>37 (38.9)</td>
</tr>
<tr>
<td></td>
<td>≥50-60 y</td>
<td>18 (46.2)</td>
<td>68 (30.5)</td>
<td>55 (33.3)</td>
<td>31 (32.6)</td>
</tr>
<tr>
<td></td>
<td>≥60-70 y</td>
<td>7 (18.9)</td>
<td>60 (26.9)</td>
<td>44 (26.7)</td>
<td>23 (24.2)</td>
</tr>
<tr>
<td></td>
<td>&gt;70 y</td>
<td>0</td>
<td>32 (14.3)</td>
<td>28 (17.0)</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male</td>
<td>20 (54.1)</td>
<td>116 (52.0)</td>
<td>85 (51.5)</td>
<td>51 (53.7)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>17 (45.9)</td>
<td>107 (48.0)</td>
<td>80 (48.5)</td>
<td>44 (46.3)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>Caucasian</td>
<td>34 (91.9)</td>
<td>187 (83.9)</td>
<td>138 (83.6)</td>
<td>83 (87.4)</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>1 (2.7)</td>
<td>20 (9.0)</td>
<td>15 (9.1)</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td></td>
<td>Oriental</td>
<td>0</td>
<td>5 (2.2)</td>
<td>4 (2.4)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>2 (5.4)</td>
<td>11 (4.9)</td>
<td>8 (4.8)</td>
<td>5 (5.3)</td>
</tr>
<tr>
<td>Eastern Cooperative Oncology performance status</td>
<td>missing</td>
<td>0</td>
<td>9 (4.0)</td>
<td>6 (3.6)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td></td>
<td>Grade 0</td>
<td>7 (18.9)</td>
<td>35 (15.7)</td>
<td>34 (20.6)</td>
<td>8 (8.4)</td>
</tr>
<tr>
<td></td>
<td>Grade 1</td>
<td>15 (40.5)</td>
<td>93 (41.7)</td>
<td>67 (40.6)</td>
<td>41 (43.2)</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>15 (40.5)</td>
<td>82 (36.8)</td>
<td>55 (33.3)</td>
<td>42 (44.2)</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>0</td>
<td>4 (1.8)</td>
<td>3 (1.8)</td>
<td>1 (1.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease history</th>
<th>400 mg (n = 37)</th>
<th>600 mg (n = 223)</th>
<th>Untreated (n = 165)</th>
<th>Pretreated (n = 95)</th>
<th>All patients (N = 260)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreated for blast crisis, n (%)</td>
<td>26 (70.3)</td>
<td>69 (30.9)</td>
<td>—</td>
<td>95 (100)</td>
<td>95 (36.5)</td>
</tr>
<tr>
<td>Time since CML diagnosis (mo)</td>
<td>Median</td>
<td>42.9</td>
<td>40.6</td>
<td>36.5</td>
<td>42.9</td>
</tr>
<tr>
<td>Minimum-maximum</td>
<td>1-357</td>
<td>0-251</td>
<td>0-251</td>
<td>2-357</td>
<td>0-357</td>
</tr>
<tr>
<td>Time since CML diagnosis (mo), n (%)</td>
<td>&lt;6 mo</td>
<td>2 (5.4)</td>
<td>20 (9.0)</td>
<td>18 (10.9)</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td></td>
<td>≥6 mo to &lt;1 y</td>
<td>2 (5.4)</td>
<td>18 (8.1)</td>
<td>13 (7.9)</td>
<td>7 (7.4)</td>
</tr>
<tr>
<td></td>
<td>≥1 to &lt;2 y</td>
<td>8 (21.6)</td>
<td>40 (17.9)</td>
<td>29 (17.6)</td>
<td>19 (20.0)</td>
</tr>
<tr>
<td></td>
<td>≥2 to &lt;5 y</td>
<td>12 (32.4)</td>
<td>74 (33.2)</td>
<td>54 (32.7)</td>
<td>32 (22.7)</td>
</tr>
<tr>
<td></td>
<td>≥5 y</td>
<td>13 (35.1)</td>
<td>71 (31.8)</td>
<td>51 (30.9)</td>
<td>33 (24.7)</td>
</tr>
<tr>
<td>Time since blast crisis diagnosis</td>
<td>Median</td>
<td>2.3</td>
<td>0.5</td>
<td>0.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Minimum-maximum</td>
<td>0-16</td>
<td>0-148</td>
<td>0-36</td>
<td>0-148</td>
<td>0-148</td>
</tr>
<tr>
<td>Time since blast crisis diagnosis (mo), n (%)</td>
<td>&lt;6 mo</td>
<td>29 (76.4)</td>
<td>204 (91.5)</td>
<td>162 (98.2)</td>
<td>71 (74.7)</td>
</tr>
<tr>
<td></td>
<td>≥6 mo to &lt;1 y</td>
<td>6 (16.2)</td>
<td>9 (4.0)</td>
<td>2 (1.2)</td>
<td>13 (13.7)</td>
</tr>
<tr>
<td></td>
<td>≥1 to &lt;2 y</td>
<td>2 (5.4)</td>
<td>6 (2.7)</td>
<td>0</td>
<td>8 (8.4)</td>
</tr>
<tr>
<td></td>
<td>≥2 y</td>
<td>0</td>
<td>4 (1.8)</td>
<td>1 (0.6)</td>
<td>3 (3.2)</td>
</tr>
</tbody>
</table>
Systemic toxicity did not increase with increased duration of treatment. Cytopenias were not consistently reported as adverse events so that treatment duration effects cannot be precisely determined.

DISCUSSION

Imatinib mesylate has proven to be a very effective drug for the treatment of CML.

The drug initially received accelerated approval for treatment of CML in blast crisis, accelerated phase, and chronic phase after failure of IFN treatment on May 10, 2001. Because the data were consistent and showed a sizable effect, a very rapid review (2.5 months) was possible.

Under the accelerated procedure, the U.S. Food and Drug Administration may approve a new drug or biologic if the drug has an effect on a surrogate end point that is reasonably likely to predict clinical benefit. Approvals for imatinib mesylate were based on the results of three nonrandomized, single-arm trials including a total of 1,027 CML patients. The surrogate end points supporting imatinib mesylate efficacy were high hematologic and cytogenetic response rates and systemic toxicity did not increase with increased duration of treatment. Cytopenias were not consistently reported as adverse events so that treatment duration effects cannot be precisely determined.

Table 11 Duration of imatinib mesylate exposure, CML blast crisis

<table>
<thead>
<tr>
<th>Duration of exposure</th>
<th>400 mg ( (n = 37) )</th>
<th>600 mg ( (n = 223) )</th>
<th>All patients ( (N = 260) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>114.0</td>
<td>123.0</td>
<td>121.0</td>
</tr>
<tr>
<td>Minimum-maximum</td>
<td>14-1071</td>
<td>3-902</td>
<td>3-1071</td>
</tr>
<tr>
<td>Duration of exposure ( n (%) )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 mo</td>
<td>16 (43.2)</td>
<td>92 (41.3)</td>
<td>108 (41.5)</td>
</tr>
<tr>
<td>3 to &lt;6 mo</td>
<td>11 (29.7)</td>
<td>51 (22.9)</td>
<td>62 (23.8)</td>
</tr>
<tr>
<td>≥6 mo to &lt;1 y</td>
<td>1 (2.7)</td>
<td>35 (15.7)</td>
<td>36 (13.8)</td>
</tr>
<tr>
<td>≥1 y to &lt;2 y</td>
<td>3 (8.1)</td>
<td>14 (10.8)</td>
<td>27 (10.4)</td>
</tr>
<tr>
<td>≥2 y</td>
<td>6 (16.2)</td>
<td>21 (9.4)</td>
<td>27 (10.4)</td>
</tr>
</tbody>
</table>

Table 13 Imatinib mesylate adverse experiences (≥10% of all patients in any trial)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Myeloid blast crisis ( (n = 260) ), ( n (%) )</th>
<th>Accelerated phase ( (n = 235) ), ( n (%) )</th>
<th>Chronic phase, IFN failure ( (n = 532) ), ( n (%) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid retention</td>
<td>72 (11)</td>
<td>76 (6)</td>
<td>69 (4)</td>
</tr>
<tr>
<td>Superficial edema</td>
<td>66 (6)</td>
<td>74 (3)</td>
<td>67 (2)</td>
</tr>
<tr>
<td>Other fluid retention events*</td>
<td>22 (6)</td>
<td>15 (4)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>71 (5)</td>
<td>73 (5)</td>
<td>63 (3)</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>28 (1)</td>
<td>47 (0.4)</td>
<td>62 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>54 (4)</td>
<td>58 (3)</td>
<td>36 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>43 (4)</td>
<td>57 (5)</td>
<td>48 (3)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>53 (19)</td>
<td>49 (11)</td>
<td>30 (2)</td>
</tr>
<tr>
<td>Central nervous system hemorrhage</td>
<td>9 (7)</td>
<td>3 (3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>8 (4)</td>
<td>6 (5)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>42 (9)</td>
<td>49 (9)</td>
<td>38 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30 (4)</td>
<td>46 (4)</td>
<td>48 (1)</td>
</tr>
<tr>
<td>Rash</td>
<td>36 (5)</td>
<td>47 (5)</td>
<td>47 (3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>41 (7)</td>
<td>41 (8)</td>
<td>21 (2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>25 (5)</td>
<td>34 (6)</td>
<td>40 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>27 (5)</td>
<td>32 (2)</td>
<td>36 (0.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>30 (6)</td>
<td>33 (4)</td>
<td>32 (1)</td>
</tr>
<tr>
<td>Weight increase</td>
<td>5 (1)</td>
<td>17 (2)</td>
<td>32 (7)</td>
</tr>
<tr>
<td>Cough</td>
<td>14 (0.8)</td>
<td>27 (0.9)</td>
<td>20 (0)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12 (0)</td>
<td>22 (0)</td>
<td>27 (0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9 (0)</td>
<td>24 (2)</td>
<td>27 (0.2)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10 (0)</td>
<td>17 (0)</td>
<td>22 (0.2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>18 (5)</td>
<td>21 (5)</td>
<td>15 (0.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15 (4)</td>
<td>21 (7)</td>
<td>12 (0.9)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3 (0)</td>
<td>12 (0.4)</td>
<td>19 (0)</td>
</tr>
</tbody>
</table>

*Other fluid retention events include pleural effusion, ascites, pulmonary edema, pericardial effusion, anasarca, edema aggravated, and fluid retention not otherwise specified.

Table 12 Efficacy results, blast crisis CML

<table>
<thead>
<tr>
<th></th>
<th>400 mg ( (n = 37) ), ( % )</th>
<th>600 mg ( (n = 223) ), ( % )</th>
<th>Untreated ( (n = 165) ), ( % )</th>
<th>Pretreated ( (n = 95) ), ( % )</th>
<th>All patients ( (N = 260) ), ( % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic response</td>
<td>16.2</td>
<td>33.2</td>
<td>35.8</td>
<td>22.1</td>
<td>30.8</td>
</tr>
<tr>
<td>CHR</td>
<td>0</td>
<td>9.4</td>
<td>9.7</td>
<td>5.3</td>
<td>8.1</td>
</tr>
<tr>
<td>No evidence of leukemia</td>
<td>10.8</td>
<td>3.6</td>
<td>4.8</td>
<td>4.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Return to chronic phase</td>
<td>5.4</td>
<td>20.2</td>
<td>21.2</td>
<td>12.6</td>
<td>18.1</td>
</tr>
<tr>
<td>MCyR confirmed</td>
<td>5.4</td>
<td>7.6</td>
<td>7.9</td>
<td>6.3</td>
<td>7.3</td>
</tr>
<tr>
<td>CCyR</td>
<td>0</td>
<td>2.2</td>
<td>1.8</td>
<td>2.1</td>
<td>1.9</td>
</tr>
<tr>
<td>PCyR</td>
<td>5.4</td>
<td>5.4</td>
<td>6.1</td>
<td>4.25</td>
<td>5.4</td>
</tr>
<tr>
<td>Overall survival</td>
<td>4.7</td>
<td>7.1</td>
<td>7.7</td>
<td>4.7</td>
<td>6.9</td>
</tr>
<tr>
<td>Estimated 12-mo rate</td>
<td>31.7</td>
<td>32.1</td>
<td>35.2</td>
<td>26.6</td>
<td>32.1</td>
</tr>
<tr>
<td>Estimated 24-mo rate</td>
<td>23.0</td>
<td>17.4</td>
<td>20.5</td>
<td>14.5</td>
<td>18.3</td>
</tr>
</tbody>
</table>
Table 14  Laboratory abnormalities in other CML clinical trials

<table>
<thead>
<tr>
<th>Common toxicity criteria grades</th>
<th>Myeloid blast crisis (n = 260), 600 mg n = 223, 400 mg n = 37, %</th>
<th>Accelerated phase (n = 235), 600 mg n = 158, 400 mg n = 77, %</th>
<th>Chronic phase, IFN failure (n = 532), 400 mg, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology variables</td>
<td>Grade 3 Grade 4</td>
<td>Grade 3 Grade 4</td>
<td>Grade 3 Grade 4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>16 48</td>
<td>23 36</td>
<td>27 9</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>30 33</td>
<td>31 13</td>
<td>21 &lt;1</td>
</tr>
<tr>
<td>Anemia</td>
<td>42 11</td>
<td>34 7</td>
<td>6 1</td>
</tr>
<tr>
<td>Biochemistry variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>1.5 0</td>
<td>1.3 0</td>
<td>0.2 0</td>
</tr>
<tr>
<td>Elevated bilirubin</td>
<td>3.8 0</td>
<td>2.1 0</td>
<td>0.6 0</td>
</tr>
<tr>
<td>Elevated alkaline phosphatase</td>
<td>4.6 0</td>
<td>5.5 0.4</td>
<td>0.2 0</td>
</tr>
<tr>
<td>Elevated aspartate aminotransferase</td>
<td>1.9 0</td>
<td>3.0 0</td>
<td>2.3 0</td>
</tr>
<tr>
<td>Elevated alanine aminotransferase</td>
<td>2.3 0.4</td>
<td>4.3 0</td>
<td>2.1 0</td>
</tr>
</tbody>
</table>

NOTE: Common toxicity criteria grades: neutropenia (grade 3 >0.5-1.0 x 10^9/L, grade 4 <0.5 x 10^9/L), thrombocytopenia (grade 3 >10-50 x 10^9/L, grade 4 <10 x 10^9/L), anemia (hemoglobin ≥65-80 g/L, grade 4 ≤65 g/L), elevated creatinine (grade 3 >3-6 x upper limit reference range, grade 4 >6 x upper limit reference range), elevated bilirubin (grade 3 >3-10 x upper limit reference range, grade 4 >10 x upper limit reference range), elevated alkaline phosphatase (grade 3 >5-20 x upper limit reference range, grade 4 >20 x upper limit reference range), elevated aspartate aminotransferase or alanine aminotransferase (grade 3 >5-20 x upper limit reference range, grade 4 >20 x upper limit reference range).

~29 months. The maximum duration of study treatment is 32 (chronic phase) to 35 (blast crisis and accelerated phase) months, with 21% of patients treated >1 year and 10% treated >2 years (blast crisis), 61% patients treated >1 year and 45% treated >2 years (accelerated phase), and 91% patients treated >1 year and 81% treated >2 years (chronic phase).

The U.S. Food and Drug Administration converted accelerated approval to regular approval because favorable treatment responses were sustained and clearly represented clinical benefit. In the chronic phase CML study, an estimated 87.8% of patients who achieved MCyR maintained their response 2 years after achieving their initial response. After 2 years of treatment, an estimated 85.4% of patients were free of progression to accelerated phase or blast crisis, and estimated overall survival was 90.8% (95% CI, 83.9-93.2). These results are superior to historical IFN-α or chemotherapy treatment results (2-4). Median survival from randomized trials comparing IFN-α with hydroxyurea or busulfan treatment reports median survival of 61 to 72 months for IFN treatment and 41 to 56 months for hydroxyurea or busulfan.

In accelerated phase CML treatment, results were also favorable. Hematologic response occurred in 72% and MCyR occurred in 27% of treated patients (either imatinib mesylate 400 or 600 mg/d, nonrandomized). These results are superior to historical IFN-α or chemotherapy treatment results (5-7). Overall median survival for patients receiving imatinib mesylate 600 mg/d has not yet been reached and the estimated 24-month survival is 65.8%.

In blast crisis CML, the terminal phase of CML, imatinib mesylate treatment produced a hematologic response rate of 31% and a MCyR rate of 15%. These responses are considerably higher than those described in other blast crisis studies (8). Whereas blast crisis CML is usually fatal in 3 to 6 months (9), imatinib mesylate treatment produced a median survival of 6.9 months, with estimated 12- and 24-month survival rates of 32% and 18%, respectively.

In conclusion, imatinib mesylate produced sustained responses in all three phases of CML. Toxicity is acceptable. Imatinib mesylate represents an important addition to the armamentarium of drugs active in the treatment of chronic myelocytic leukemia.

REFERENCES


Clinical Cancer Research

U.S. Food and Drug Administration Drug Approval Summary: Conversion of Imatinib Mesylate (STI571; Gleevec) Tablets from Accelerated Approval to Full Approval

Martin H. Cohen, John R. Johnson and Richard Pazdur


Updated version  Access the most recent version of this article at: http://clincancerres.aacrjournals.org/content/11/1/12

Cited articles  This article cites 9 articles, 5 of which you can access for free at: http://clincancerres.aacrjournals.org/content/11/1/12.full#ref-list-1

Citing articles  This article has been cited by 11 HighWire-hosted articles. Access the articles at: http://clincancerres.aacrjournals.org/content/11/1/12.full#related-urls

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.