EFFICACY AND SAFETY OF IMATINIB MESYLATE IN ADVANCED GASTROINTESTINAL STROMAL TUMORS

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ABSTRACT

Background  Constitutive activation of KIT receptor tyrosine kinase is critical in the pathogenesis of gastrointestinal stromal tumors. Imatinib mesylate, a selective tyrosine kinase inhibitor, has been shown in preclinical models and preliminary clinical studies to have activity against such tumors.

Methods  We conducted an open-label, randomized, multicenter trial to evaluate the activity of imatinib in patients with advanced gastrointestinal stromal tumor. We assessed antitumor response and the safety and tolerability of the drug. Pharmacokinetics were assessed in a subgroup of patients.

Results  A total of 147 patients were randomly assigned to receive 400 mg or 600 mg of imatinib daily. Overall, 79 patients (53.7 percent) had a partial response, 41 patients (27.9 percent) had stable disease, and for technical reasons, response could not be evaluated in 7 patients (4.8 percent). No patient had a complete response to the treatment. The median duration of response had not been reached after a median follow-up of 24 weeks after the onset of response. Early resistance to imatinib was noted in 20 patients (13.6 percent). Therapy was well tolerated, although mild-to-moderate edema, diarrhea, and fatigue were common. Gastrointestinal or intraabdominal hemorrhage occurred in approximately 5 percent of patients. There were no significant differences in toxic effects or response between the two doses. Imatinib was well absorbed, with pharmacokinetics similar to those reported in patients with chronic myeloid leukemia.

Conclusions  Imatinib induced a sustained objective response in more than half of patients with an advanced unresectable or metastatic gastrointestinal stromal tumor. Inhibition of the KIT signal-transduction pathway is a promising treatment for advanced gastrointestinal stromal tumors, which resist conventional chemotherapy.

GASTROINTESTINAL stromal tumors are mesenchymal neoplasms that appear to be related to the interstitial cells of Cajal of the myenteric plexus, with which they share certain differentiation markers.1,2 Gastrointestinal stromal tumors express the cell-surface transmembrane receptor KIT that has tyrosine kinase activity and is the protein product of the KIT proto-oncogene. There are frequent gain-of-function mutations of KIT in gastrointestinal stromal tumors.3,4 These mutations result in the constitutive activation of KIT signaling, which leads to uncontrolled cell proliferation and resistance to apoptosis. It has recently been reported that KIT activation occurs in all cases of gastrointestinal stromal tumor, regardless of the mutational status of KIT.1

Unresectable or metastatic gastrointestinal stromal tumor is a fatal disease that resists conventional cytotoxic chemotherapy.5,6 In a recently reported series, the response rate to doxorubicin was less than 5 percent.6 The effectiveness of radiation therapy for this disease has not been proved.5 The median duration of survival for patients with a metastatic gastrointestinal stromal tumor is approximately 20 months, and for patients with local recurrence it is 9 to 12 months.5

Imatinib mesylate (formerly STI571, now referred to as Gleevec in the United States and Glivec in Europe [Novartis]) is a selective inhibitor of certain protein tyrosine kinases: the intracellular ABL kinase, the chimeric BCR-ABL fusion oncprotein of chronic myeloid leukemia, the transmembrane receptor KIT, and the platelet-derived growth factor receptors.7,10 Imatinib is highly active in patients with chronic myeloid leukemia and other Philadelphia chromosome–pos-
ive leukemias, in which it inhibits the dysregulated kinase activity of the BCR-ABL fusion protein.\textsuperscript{11,12} We hypothesized that imatinib might also block the constitutive activity of KIT receptor tyrosine kinase in the cells of gastrointestinal stromal tumors. This hypothesis was supported by experiments in human tumor cell lines that are dependent on the KIT pathway. Exposure of these cells to imatinib blocked the kinase activity of KIT, arrested proliferation, and caused apoptotic cell death.\textsuperscript{9,10,13} Subsequently, a single patient treated with imatinib for a chemotherapy-resistant metastatic gastrointestinal stromal tumor had a rapid, substantial, and durable response.\textsuperscript{14} To build on these results, we conducted a multicenter clinical trial to test the efficacy and safety of imatinib in patients with an unresectable or metastatic gastrointestinal stromal tumor.

**METHODS**

**Patients**

Adults with a histologically confirmed, unresectable or metastatic gastrointestinal stromal tumor that expressed CD117 (a marker of KIT-receptor tyrosine kinase) were eligible for the study. Pathology was reviewed centrally by a single pathologist. Criteria for inclusion were at least one measurable tumor that had not previously been treated with radiotherapy or embolization; adequate hepatic, renal, and cardiac function; an adequate platelet count; and an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or lower. Patients were allowed to have received any number of previous chemotherapeutic regimens (with the last administration of the drug within 4 weeks) and any number of previous courses of imatinib therapy. Patients with a history of previous anticancer treatments were eligible provided the last administration of the drug was at least 4 weeks before study entry and the patients were in good clinical condition.

**Study Design**

We conducted a randomized, open-label, multicenter trial designed to evaluate the activity of imatinib in inducing objective responses in gastrointestinal stromal tumors. Randomization was performed centrally without stratification according to site or any other factor. Blocking, with a block size of four, was used. Secondary objectives were the assessment of pharmacokinetics, safety, time to treatment failure, and survival.

**Pharmacokinetics**

Plasma samples were collected from a subgroup of patients before and after treatment and then 1, 2, 3, 8, 24, 48, and 72 hours after the administration of the drug. Sampling at the same intervals was repeated during treatment and then 1, 2, 3, 8, 24, 48, and 72 hours after the administration of the drug. Assessments were performed at the four centers collected and managed all of the data. The data were then collected in a central data base and made fully available to the principal investigators at each study site. The team met regularly and had twice-monthly conference calls to discuss study progress and results. The overall results were analyzed by the principal investigators and employees of Novartis. This article was written by Dr. Demetri with substantive collaboration from the principal investigators and all other authors.

**Efficacy and Safety Evaluation**

The response of the tumor to imatinib was evaluated after one month, three months, and six months, and every six months thereafter or whenever there was a medical need. Assessments were according to the standard Southwest Oncology Group criteria and were based solely on CT or magnetic resonance imaging (MRI).\textsuperscript{15} Responses were classified as complete responses (disappearance of all disease that could be measured and evaluated); partial responses (50 percent decrease in the sum of the products of the perpendicular diameters of all measurable lesions, the absence of progression, and the absence of new lesions); stable disease (a response that did not qualify as a complete response, a partial response, or disease progression); or disease progression (50 percent increase or an increase of 10 cm\textsuperscript{2} [whichever was smaller] in the sum of the products of the perpendicular diameters of all measurable lesions, worsening of a lesion that could be evaluated, the reappearance of any lesion or the presence of a new lesion, or failure of the patient to return for evaluation because of disease progression). All responses had to be confirmed by repeated imaging within 4 to 12 weeks. Time to treatment failure was defined as the time from the first dose of imatinib to the earliest occurrence of progression, death from any cause, or withdrawal from the trial for any reason other than that the condition no longer required therapy. Data for patients who had not had disease progression or died or who were withdrawn from the trial for any reason other than that their condition no longer required therapy were censored at the time of the last assessment of the tumor. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria.\textsuperscript{16}

Immunohistochemical analysis for the detection of CD117 was performed with the use of polyclonal rabbit antiserum (A4502, Dako) and routine methods for immunohistochemical analysis without any antigen retrieval.\textsuperscript{17} Biopsy specimens of the tumor were obtained from selected consenting patients before and after treatment for the histopathological assessment of treatment, mutational analyses of KIT, and immunoblotting for detection of KIT phosphoprotein.\textsuperscript{4}

**Statistical Analysis**

The original sample size was based on a proof-of-concept approach, according to which we required at least 3 patients with a response among 18 treated patients in each group in order to continue enrolling patients in the study. This rule resulted in a 94 percent probability of rejection of the null hypothesis if either dose level had a true response rate of less than 5 percent and a probability of rejection of the null hypothesis of less than 6 percent if either dose level had a true response rate of 30 percent or greater. Because of the promising results observed, the study was enlarged to allow recruiting of up to 200 patients; 147 patients were recruited. With...
an intention-to-treat population of 147 patients, the 95 percent confidence interval for response rate was no wider than ±8.4 percent. Such a confidence interval was judged sufficient to allow a meaningful comparison with historical data.

After the first 100 patients completed the six-month assessment, an interim analysis was performed, and the evidence of efficacy and safety was judged sufficient for submission to health authorities for registration of the drug. This report provides updated results. All reported P values are two-sided.

**RESULTS**

**Patients**

Between July 2000 and April 2001, 147 patients were recruited at four study centers. Characteristics of the patients are summarized in Table 1. The diagnosis of CD117-positive gastrointestinal stromal tumor was confirmed by central review in 135 of 137 cases (98.5 percent); 2 patients were judged to be ineligible because of the absence of CD117 expression in the proper histopathological context,19 and in 10 cases, pathologic material was unavailable for central review. The analyses presented here include data from all 147 patients on an intention-to-treat basis.

Previous therapy included surgery in 144 patients (98.0 percent), chemotherapy for metastatic or unresectable disease in 75 patients (51.0 percent), and radiotherapy in 22 patients (15.0 percent). Patients who had previously undergone chemotherapy had received between one and seven regimens (median, two). None of them had exhibited an objective response to any previous regimen. Patients generally had far-advanced, bulky disease, and the mean total area of tumors was 178 cm² (range, 1 to 1130).

**Pharmacokinetics**

Imatinib was detectable in plasma soon after oral administration of either a 400-mg dose or a 600-mg dose, with a mean half-life in the circulation of approximately 20 hours. The mean plasma concentration increased with increases in the dose, with variability between patients similar to that described in patients with chronic myeloid leukemia.20 The mean (±SE) area under the curve after four weeks of treatment was 61±25 µg-hr per milliliter for the 400-mg dose and 75±31 µg-hr per milliliter for the 600-mg dose.

**Antitumor Response**

With follow-up of more than 9 months for all patients (the median follow-up was 288 days as of October 15, 2001, the last date of data collection for this report), 120 patients (81.6 percent) remained in the study. Data on antitumor response are shown in Table 2. No patient had a complete response. Overall, 53.7 percent of the patients had a partial response. All these partial responses were confirmed by repeated imaging at least 28 days later. The reduction in the bulk of the tumor among patients who had a partial response ranged from 50 percent to 96 percent. An additional 27.9 percent of patients had stable disease, and disease progression was noted in 13.6 percent of patients between one and three months after study entry. The median time to an objective response was 13 weeks. Responses have been durable for more than 46 weeks and the median duration of response has not been reached as of this writing (median follow-up, 24 weeks after the onset of response). There were no significant differences in the rate or duration of response between the dose levels of imatinib mesylate we tested.

The time to treatment failure and overall survival arc shown in Figure 1. Of nine patients who were assigned to receive the lower dose and who were later given the higher dose because of disease progression, one subsequently had a partial response, and two had stable disease after the crossover to 600 mg per day. Nine patients treated with 400 mg per day and five

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**Table 1. Characteristics of the Patients.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>54</td>
</tr>
<tr>
<td>Median Range</td>
<td>18–83</td>
</tr>
<tr>
<td>Sex — no. (%)</td>
<td>Male: 83 (56.5)</td>
</tr>
<tr>
<td></td>
<td>Female: 64 (43.5)</td>
</tr>
<tr>
<td>ECOG status — no. (%)†</td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>62 (42.2)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>57 (38.8)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>27 (18.4)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Site of tumor at diagnosis — no. (%)‡</td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>72 (49.0)</td>
</tr>
<tr>
<td>Stomach</td>
<td>50 (34.0)</td>
</tr>
<tr>
<td>Liver</td>
<td>25 (17.0)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>19 (12.9)</td>
</tr>
<tr>
<td>Omentum</td>
<td>17 (11.6)</td>
</tr>
<tr>
<td>Site of tumor at recurrence — no. (%)¶</td>
<td></td>
</tr>
<tr>
<td>Any recurrent disease‡</td>
<td>132 (89.8)</td>
</tr>
<tr>
<td>Liver</td>
<td>115 (78.2)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>56 (38.1)</td>
</tr>
<tr>
<td>Retroperitoneum</td>
<td>21 (14.5)</td>
</tr>
<tr>
<td>Previous treatment — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>144 (98.0)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>75 (51.0)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>22 (15.0)</td>
</tr>
</tbody>
</table>

*Eastern Cooperative Oncology Group (ECOG) status is graded on a scale from 0 to 5, with 0 denoting fully active and 5 death. A score of 3 indicates that the patient is capable of no self-care but is confined to a bed or chair more than 50 percent of his or her waking hours.

†Some patients had tumors at more than one site; patients with tumors in the liver had metastatic disease at initial presentation.

¶Some patients had recurrent disease at more than one site.
patients treated with 600 mg per day died. Five pa-
tients in the 400-mg group and eight patients in the
600-mg group were withdrawn from the study. Dis-
case progression during treatment occurred in 11 pa-
tients receiving 600 mg per day and 8 patients receiv-
ing 400 mg per day. The estimated one-year survival
rate for all patients was 88 percent. Median survival has
not been reached as of this writing.

Standard \(^{18}\text{F}\)fluoro-2-deoxy-D-glucose PET
proved to be a sensitive, rapid, and reliable indicator
of response or resistance to imatinib. In all patients with
a response, the \(^{18}\text{F}\)fluoro-2-deoxy-D-glucose up-
take in the tumor had decreased markedly from base
line as early as 24 hours after a single dose of imatinib.
Increases in tumor-related glycolytic activity, activity
at new sites, or both were seen in all patients with dis-
case progression. PET results correlated with subse-
quent evidence of a response or progression on CT
or MRI. PET and CT scans from a representative
patient with a response are shown in Figure 2.

Performance status improved with imatinib treat-
ment. By month 4 of the study, with 144 patients still
receiving treatment, the number of patients with nor-
mal functional status (an ECOG performance status

<table>
<thead>
<tr>
<th>BEST RESPONSE</th>
<th>400 mg (N=73)</th>
<th>600 mg (N=74)</th>
<th>EITHER DOSE (N=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Partial response</td>
<td>36 (49.3 [37.4–61.3])</td>
<td>43 (58.1 [46.1–69.5])</td>
<td>79 (53.7 [45.3–62.0])</td>
</tr>
<tr>
<td>Stable disease</td>
<td>23 (31.5 [21.1–43.4])</td>
<td>18 (24.3 [15.1–35.7])</td>
<td>41 (27.9 [20.8–35.9])</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12 (16.4)</td>
<td>8 (10.8)</td>
<td>20 (13.6)</td>
</tr>
<tr>
<td>Could not be evaluated</td>
<td>2 (2.7)</td>
<td>5 (6.8)</td>
<td>7 (4.8)</td>
</tr>
</tbody>
</table>

*CI denotes confidence interval.

Figure 1. Kaplan–Meier Estimates of Overall Survival and Time to Treatment Failure for All Patients.
Each arrowhead represents the point at which a patient’s data were censored.
The number of patients with substantially impaired functional status (a performance status of 2 to 3) had decreased to 5 percent from 19 percent at entry.

Safety

Treatment with imatinib was generally well tolerated, although virtually every patient had at least some mild or moderate adverse events (grade 1 or 2) that might have been related to therapy. The most common adverse events included edema (in 74.1 percent of patients) that was most frequently periorbital, nausea (in 52.4 percent), diarrhea (in 44.9 percent), myalgia or musculoskeletal pain (in 39.5 percent), fatigue (in 34.7 percent), dermatitis or rash (in 30.6 percent), headache (in 25.9 percent), and abdominal pain (in 25.9 percent) (Table 3). Most of these adverse events were mild or moderate. There was no hyperuricemia or evidence of tumor lysis syndrome, even in patients

Figure 2. Sequential PET Scans Obtained in the Same Patient at Base Line (before Treatment, Panel A), 1 Month after Imatinib Treatment Began (Panel B), and after 16 Months of Continuous Treatment (Panel C).

The images at each point include a two-dimensional PET scan of the body (top), an axial PET scan of a slice through the site of the pelvic tumor (middle), and a correlating CT scan at the corresponding level. The standardized uptake values for the tumor at the three time points were 4.5 (Panel A), 1.24 (Panel B), and 0.75 (Panel C). The uptake in the cardiac blood pool, the myocardium, the liver, the bowel, the bilateral renal collecting system, and the bladder is within physiologic limits in this patient. Images were obtained with the use of similar doses of [18F]fluoro-2-deoxy-D-glucose, acquisition times, and protocols at the three time points. The patient also had similar blood glucose concentrations at each of these three time points.
with very rapid decreases in tumor volume. Serious adverse events (grade 3 or 4) occurred in 21.1 percent of patients. The most serious adverse events were gastrointestinal or intraabdominal hemorrhages in patients with large, bulky tumors, which occurred in approximately 5 percent of patients.

**Histopathological Changes**

A subgroup of biopsies performed after treatment showed reduced numbers of tumor cells and a hypocellular myxohyaline stroma with small numbers of scattered atypical nuclei and, frequently, prominent stromal hemorrhage. Frank necrosis of the tumor was rarely seen (Fig. 3). Other biopsies showed large numbers of residual CD117-positive tumor cells, even in patients whose tumors showed a substantial reduction in size on PET and CT scanning. These residual gastrointestinal stromal tumor cells often showed pyknotic nuclei and reduced cytoplasmic volume, similar in appearance to “crush artifact.”

**DISCUSSION**

There is compelling evidence from preclinical models that the constitutively activated KIT-receptor ty-
rosine kinase stimulates the proliferation and enhances the survival of neoplastic gastrointestinal stromal tumor cells. In both preclinical experiments and a previous case study, inhibition by imatinib had considerable antiproliferative and proapoptotic effects on gastrointestinal stromal tumor cells. Our study demonstrates, in a large series of patients with advanced gastrointestinal stromal tumors, that imatinib is effective in most patients.

Advanced gastrointestinal stromal tumors are unresponsive to conventional chemotherapy. The high rate of response to imatinib in these patients with bulky disease who had no response to cytotoxic chemotherapy is not only remarkable, but also supports the hypothesis that dysregulated KIT kinase activity is important in human gastrointestinal stromal tumors. Responses, although partial, have lasted for many months, as patients continue to receive daily treatment in our ongoing clinical trial. Our results corroborate the result obtained with imatinib in a single patient with a gastrointestinal stromal tumor, who is still receiving therapy more than 22 months after its initiation (unpublished data), and the confirmed partial responses in 19 patients in a phase 1 study of imatinib in gastrointestinal stromal tumors. Historical data show a median survival of 19 months for all patients with metastatic disease and 9 months for patients with metastatic disease and local recurrence. Despite the extensive metastatic disease in the majority of our patients, 88 percent were alive one year after the initiation of treatment with imatinib, with the median duration of survival not yet reached.

This phase 2 trial was not adequately powered to distinguish between the efficacy of the 400-mg and 600-mg doses. Although there was no statistically significant difference between the dose levels, three of the nine patients who received the higher dose after evidence of disease progression was uncovered had a sustained partial response or stable disease after the crossover. The optimally effective dose of imatinib in...
IMATINIB MESYLATE IN GASTROINTESTINAL STROMAL TUMORS

patients with a gastrointestinal stromal tumor is the subject of large, appropriately powered, randomized studies that are now under way.

The high bioavailability of orally administered imatinib in our study was generally similar to that reported in patients with chronic myeloid leukemia.11 Therapeutic plasma concentrations were attained despite the presence of altered gastrointestinal anatomy from previous, and often extensive, resections.

Overall, imatinib was well tolerated, with adverse effects similar to those reported in a large population of patients with chronic myeloid leukemia. Myelo-toxicity was less frequent in patients with gastrointestinal stromal tumors, suggesting that the myelo-suppression associated with imatinib in hematologic cancers may be related to the pathophysiology of the leukemic bone marrow. An important finding was serious gastrointestinal and tumor hemorrhage in about 5 percent of our patients. These hemorrhages could be related to the underlying disease, but they were probably related to tumor degeneration induced by imatinib.

The close relationship between clinical outcome and the findings on 18F-fluoro-2-deoxy-D-glucose PET scanning indicates that such scanning is a useful complement to standard anatomical imaging with CT or MRI for monitoring the therapeutic effect of imatinib in patients with gastrointestinal stromal tumors. The cellular mechanisms responsible for the rapid decreases in glycolytic activity associated with imatinib treatment remain unknown, particularly given that some biopsies demonstrated the continued presence of substantial numbers of viable CD117-bearing cells.

Although our results indicate that imatinib is effective for many patients with advanced gastrointestinal stromal tumors, resistance of tumors to single-agent therapy is common. In 5 percent of our patients, the tumor exhibited primary resistance to imatinib within the first two months. In other patients with disease progression, resistance became evident only after several months of treatment. Nonetheless, patients with an objective response and the majority of patients with stable disease had durable evidence of a treatment benefit lasting more than six months. These findings contrast somewhat with the experience in patients with advanced chronic myeloid leukemia. In patients treated for blast crisis, most cases of secondary resistance appeared within four months after the initial response. Resistance in patients with chronic myeloid leukemia is caused by more than one molecular mechanism, including amplification of the gene encoding the aberrant kinase and mutation of the drug-binding site in the kinase domain.22 Molecular mechanisms responsible for resistance in patients with gastrointestinal stromal tumors may be quite different. Constitutive activation of KIT receptor tyrosine kinase in gastrointestinal stromal tumors can be caused by mutations in any of several exons, and in a subgroup of patients there is no detectable KIT mutation.4 Even at the most common site of mutations (exon 11), a wide variety of in-frame deletions and substitutions has been reported.24 Careful study of molecular mechanisms will be needed in order to develop rational strategies for preventing or overcoming the emergence of resistance to imatinib in patients with gastrointestinal stromal tumors.

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