Imatinib Mesylate Therapy in Newly Diagnosed Patients with Philadelphia Chromosome Positive Chronic Myelogenous Leukemia: High Incidence of Early Complete and Major Cytogenetic Responses

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ABSTRACT

Fifty patients with Philadelphia chromosome (Ph)-positive chronic myelogenous leukemia (CML) in early chronic phase received imatinib mesylate 400 mg orally daily. After a median follow-up of 9 months, 49 patients (98%) achieved a complete hematologic response and 45 patients (90%) achieved a major cytogenetic response, complete in 36 patients (72%). Compared with similar patients who received interferon alpha regimens, those receiving imatinib mesylate had higher incidences of complete and major (Ph <35%) cytogenetic responses at 3 months (34% and 74% versus 1-4% and 9-24%, respectively), 6 months (52% and 80% versus 3-7% and 11-28%, respectively), and 9 months (60% and 77% versus 5-11% and 14-30%, respectively) (p values <0.001). Competitive quantitative polymerase chain reaction (QPCR) studies at 9 months showed a median QPCR value (ratio of BCR-ABL/ABL transcripts x 100) of 0.59% overall, and of 0.24% (range 0.001% to 29.5%) for complete cytogenetic response.

Word Count: 144
INTRODUCTION

The causal association between the Philadelphia chromosome (Ph) and BCR-ABL molecular events and the pathophysiology of chronic myelogenous leukemia (CML) has focused research on strategies that suppress the Ph-positive cells or the expression of BCR-ABL. (1-4) These have included allogeneic stem cell transplantation (SCT), interferon alpha (IFN-α), cytosine arabinoside, and others (5-13). Achieving minimal residual disease (major or complete cytogenetic response) has been independently associated with survival prolongation, and has become the therapeutic research goal. Imatinib mesylate (Gleevec, STI571), a selective Bcr-Abl tyrosine kinase inhibitor, has shown activity in all CML phases (blastic, accelerated, chronic after failure of IFN-α). (14-20) Herein, we summarize our results, previously reported in abstract form (21), in patients with newly diagnosed CML treated with imatinib mesylate 400 mg orally daily, demonstrating high early rates of major and complete cytogenetic responses.
STUDY GROUPS AND METHODS

Study Group

Patients with Ph-positive CML in early chronic phase (diagnosis to therapy less than 12 months) were treated; informed consent was obtained according to institutional guidelines. Eligibility criteria were: age 15 years or older; ECOG performance status of 0-2; adequate renal (creatinine less than twice upper limit of normal), hepatic (bilirubin less than twice upper limit of normal), and cardiac functions (NYHA cardiac disease grade 3-4 excluded); no prior imatinib mesylate therapy and no more than one month of IFN-α therapy. Females of childbearing potential were required to have a negative pregnancy test before starting imatinib mesylate; all patients at risk were required to use barrier contraception on therapy. Chronic phase CML was defined as <15% blasts, <20% basophils, and <30% blasts plus promyelocytes in the peripheral blood and bone marrow, and platelet counts ≥ 100 x 10⁹/L.

Therapy and Monitoring

Patients received imatinib mesylate 400 mg orally daily. Patient monitoring and dose reductions of imatinib mesylate for non-hematologic or hematologic toxicities were detailed in previous studies. Patients were kept when possible at a minimal daily dose of 300 mg daily. If therapy at this dose resulted in severe myelosuppression (not manageable with growth factors e.g. procrit, G-CSF), the treatment was interrupted and resumed, rather than the dose
reduced to less than 300mg daily. Severe extramedullary toxicities with doses of 300mg daily resulted in discontinuation of therapy.

Marrow studies including morphology and cytogenetics or interphase fluorescent in situ hybridization (iFISH) were performed every three months; iFISH used the Vysis BCR-ABL ES probe which, in normal controls has a positive mean value of 0.4% ± 1.2% (2SD); the upper normal limit is 1.5%. The iFISH analysis is conducted on 200 interphases. Competitive quantitative polymerase chain reaction (QPCR) studies were conducted on marrow samples as previously described (22-25) (and Guo et al submitted 2002). The QPCR values were expressed as a ratio-percentage (BCR-ABL/ABL transcripts x 100).

Side effects were graded according to National Cancer Institute (NCI) Common Toxicity Criteria, version 2.0.

Response Criteria and Statistical Considerations

Response criteria were as described (6,8). A complete hematologic response (CHR) was defined as WBC less than 10 x 10⁹/L, platelets less than 450 x 10⁹/L, no immature peripheral cells (blasts, promyelocytes, myelocytes), and disappearance of all signs and symptoms related to leukemia, including palpable splenomegaly, lasting for at least 4 weeks. This was further categorized by the best cytogenetic response: complete - Ph-positive 0%, partial- Ph-positive 1% to 34%, and minor - Ph-positive 35% to ≤ 90%. A major cytogenetic response included complete plus partial cytogenetic responses (Ph-positive less than 35%). At least 20 metaphases were analyzed for a cytogenetic response to
be evaluable. If cytogenetic analysis was not successful, the ratio of iFISH on therapy to pretreatment iFISH was considered for cytogenetic response evaluation.

**Historical control groups**

These included patients with Ph-positive early chronic phase CML (diagnosis to therapy less than 12 months) treated with IFN-α alone or with hydrea or gamma interferon (N=274), IFN-α and low-dose cytarabine (N=257), or IFN-α with low-dose cytarabine and homoharringtonine (N=90). These patients had similar follow-up studies as the patients on the current study.

**RESULTS AND DISCUSSION**

**Study groups**

The characteristics of the 50 patients on study are detailed in Table 1. Their median age was 48 years (range 15 to 79 years). The median time from diagnosis to therapy was 1.5 months (range 0 to 11 months). Fifteen patients had no prior therapy; 35 patients had received short courses of hydroxyurea (33 patients) or interferon alpha (less than 2 weeks; 2 patients).

**Response**

The median follow-up time is 9 months. One patient discontinued imatinib mesylate after 4 weeks because of recurrent severe hepatotoxicity; 49 patients (98%) achieved CHR (median time to CHR 2 weeks), and all 49 patients (98%) had a cytogenetic response: complete in 36 (72%) partial in 9 (18%), and minor
in 4 (8%). The major cytogenetic response rate was thus 90% (45 of 50 patients). When only cytogenetic studies (without complementary iFISH studies) were considered, the cytogenetic response rates were complete in 34 (68%), partial in 9 (18%), and minor in 4 (8%). The complete cytogenetic response rate was 35% after 3 months and 53% after 6 months of therapy (Table 2). For interest, we also included the results of patients treated at our institution with imatinib mesylate for chronic phase CML post IFN-α failure (26). Response rates were higher (all p values <0.001) than those achieved with IFN-α regimens (Table 2). Currently, 44 patients continue on imatinib mesylate therapy: 6 patients are off study because of development of myeloid blastic phase (N=2; at 6 and 6 months, respectively), hematologic relapse (N=1; after 6 months of therapy), severe transient liver toxicities (N=2; after 1 month and 9 months, respectively); and non-compliance (N=1). The 2 patients who developed blastic phase had low risk by the Sokal model. The patient with hematologic relapse had high risk. All patients are alive.

Quantitative PCR studies

The QPCR values among patients treated with imatinib mesylate at 9 months on therapy are shown in Figure 1. The median overall QPCR value was 0.59%. Among 27 patients tested in complete cytogenetic response the median QPCR value was 0.24% (range 0.001-29.6%); 7 of them (26%) had QPCR value less than 0.04%, and 21 (78%; 54% of 39 patients tested) had QPCR values less than 1%. Two patients in complete cytogenetic response had high QPCR values.
above 10%; the iFISH studies showed 1% and 3.5% positivity, respectively. The significance of this finding is unknown; it may be related to high BCR-ABL/ABL expression in resting non-dividing cells, and may be potentially predictive of relapse.

Side effects

Side effects of imatinib mesylate were similar to previous trials \(^{(18)}\). Grade 3-4 toxicities were: skin rashes 6%; muscle cramps or aches 2%; fatigue 2%; liver function abnormalities 4%. Myelosuppression associated complications were: granulocytopenia <0.5 x 10\(^9\)/L in 20%; thrombocytopenia < 50 x 10\(^9\)/L in 8%; anemia <9 g/dl in 8%. These required dose interruptions (N=1) or reductions to 300 mg daily (N=2), but no patient had to discontinue therapy permanently because of myelosuppression.

This study demonstrates the superior efficacy of imatinib mesylate compared with IFN-\(\alpha\) regimens in relation to previously defined early surrogate endpoints for long-term prognosis with IFN-\(\alpha\) therapy \(^{(3-11)}\) but not yet convincingly with imatinib mesylate therapy \(^{(18,19)}\) (Table 2). The incidence of complete cytogenetic response with imatinib mesylate was 72% overall and 60% at 9 months of therapy (versus 4% to 11% with IFN-\(\alpha\)). A randomized study of imatinib mesylate versus IFN-\(\alpha\) plus ara-C in early chronic phase showed better cytogenetic response rates (major 63% versus 10%, complete 40% versus 2%,
respectively, at 6 months; p < 0.001), lower failure rates, and less side effects with imatinib mesylate therapy (27).

Achievement of a complete cytogenetic response has been associated with 5-10 year survival rates of 70% to 90%, (5,6,9-11), and has been a consistent reliable early surrogate marker of survival prolongation in CML with IFN-\(\alpha\) therapy. (3-6, 9-11) The observation of a high incidence of complete cytogenetic response early with imatinib mesylate therapy suggests its potential benefit in improving long-term prognosis in CML.

Qualitative and quantitative PCR studies have been relevant in assessing minimal residual disease and prognosis. In the setting of allogeneic SCT, persistent reverse transcriptase (RT) PCR positivity after 12 months from transplant was associated with CML relapse in 30% to 40% of patients versus less than 5% for RT-PCR negative patients. (28) The QPCR values for patients “cured” after allogeneic SCT range from 0% to less than 0.03%. (25) With IFN-\(\alpha\) therapy, QPCR values of less than 0.05% have been associated with long-term event-free-survival and low relapse rates. (25) This study demonstrates rapid achievement of very low QPCR values (median 0.59% in the total population; 54% with QPCR values less than 1%) after a short period of 9 months of imatinib mesylate therapy. This compares favorably with the QPCR levels achieved at 9 months with imatinib mesylate therapy post IFN-\(\alpha\) failure in chronic phase (median QPCR values 0.24% versus 0.89% [19 patients tested; p=0.04]). Among 190 samples in complete cytogenetic response after IFN-\(\alpha\) therapy tested by QPCR, the median QPCR value was 0.087% (M.D. Anderson unpublished
data). However, these complete cytogenetic responses had all persisted for more than 12 months, were tested after long-term IFN-\(\alpha\) therapy (not at 9 months into therapy) and occurred in a minority of patients (20% to 25% in our studies). In the study of Hochhaus et al, the median QPCR values for cytogenetic complete response after 6 and 12 months in complete cytogenetic response with IFN-\(\alpha\) were 0.46% and 0.135%, respectively. Again, the complete cytogenetic responses were achieved in a minority of patients (5% to 10%).(25) Since imatinib mesylate resulted in a median overall QPCR value of 0.59% in the total study group, it appears to induce significantly lower levels of molecularly-detectable residual disease in CML compared with IFN-\(\alpha\) therapy. However, the median follow-up time is short in this study, and longer follow-up is needed before definite conclusions can be drawn.
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induces responses in patients with chronic myelogeneous leukemia in late

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Table 1. Characteristics of the Study Groups

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<tr>
<td>Age &gt; 60 years</td>
<td>13 (26)</td>
<td>34 (12)</td>
<td>28 (11)</td>
<td>4 (4)</td>
<td>0.002 (0.004)</td>
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<td>Male gender</td>
<td>26 (52)</td>
<td>166 (61)</td>
<td>146 (57)</td>
<td>46 (51)</td>
<td>NS (NS)</td>
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<td>Splenomegaly</td>
<td>11 (22)</td>
<td>116 (42)</td>
<td>72 (28)</td>
<td>26 (29)</td>
<td>0.001 (NS)</td>
</tr>
<tr>
<td>Hemoglobin &lt; 12 g/dl</td>
<td>19 (38)</td>
<td>107 (39)</td>
<td>95 (37)</td>
<td>28 (31)</td>
<td>NS (NS)</td>
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<td>WBC &gt; 50x10⁹/L</td>
<td>11 (22)</td>
<td>143 (52)</td>
<td>86 (33)</td>
<td>20 (22)</td>
<td>&lt;0.001 (0.02)</td>
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<td>Platelets &gt; 450x10⁹/L</td>
<td>17 (34)</td>
<td>122 (44)</td>
<td>81 (32)</td>
<td>29 (32)</td>
<td>0.01 (NS)</td>
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<td>Peripheral blasts (any)</td>
<td>14 (28)</td>
<td>94 (34)</td>
<td>66 (26)</td>
<td>17 (19)</td>
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<td>Marrow blasts &gt; 5%</td>
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<td>11 (4)</td>
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<td>Peripheral basophils ≥ 7%</td>
<td>10 (20)</td>
<td>46 (17)</td>
<td>42 (16)</td>
<td>16 (18)</td>
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<td>Marrow basophils ≥ 4%</td>
<td>12 (24)</td>
<td>63 (23)</td>
<td>28 (11)</td>
<td>19 (21)</td>
<td>0.02 (NS)</td>
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<td>Cytogenetic clonal evolution</td>
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<td>-</td>
<td>20 (8)</td>
<td>4 (4)</td>
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<td>Good</td>
<td>25 (51)</td>
<td>124 (52)</td>
<td>111 (56)</td>
<td>34 (53)</td>
<td>NS (NS)</td>
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<td>Intermediate</td>
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<td>58 (24)</td>
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<td>Poor</td>
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<td>9</td>
<td>38</td>
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Table 2. Major and complete cytogenetic responses at 3, 6 and 9 months on different regimens

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<th>Regimen</th>
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<th>% cytogenetic response, complete/major</th>
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<td>Imatinib mesylate – early chronic phase CML</td>
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<td>IFN-α</td>
<td>274</td>
<td>4/2</td>
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<tr>
<td>IFN-α + cytarabine</td>
<td>257</td>
<td>1/9</td>
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<td>IFN-α + cytarabine + homoharringtonine</td>
<td>90</td>
<td>4/24</td>
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<td>Imatinib mesylate-chronic phase post IFN-α failure (M.D. Anderson study group)</td>
<td>261</td>
<td>26/44</td>
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Figure 1. Competitive quantitative PCR values at 9 months on imatinib mesylate therapy by cytogenetic response
Imatinib mesylate therapy in newly-diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia: high incidence of early complete and major cytogenetic responses

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