The Effect of Imatinib Mesylate on Patients with Philadelphia Chromosome-positive Chronic Myeloid Leukemia with Secondary Chromosomal Aberrations

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ABSTRACT

Purpose and Experimental Design: The acquisition of secondary chromosomal aberrations in chronic myeloid leukemia (CML) patients with Philadelphia chromosome-positive (Ph+) karyotype signifies clonal evolution associated with disease progression to accelerated/blastic phase. Therefore, these aberrations are of clinical and biological importance. We identified 58 cases with secondary abnormalities in addition to t(9;22)(q34;q11.2) or its variants in a review of 137 CML patients treated with imatinib mesylate (STI571). Clinically 13 patients were in chronic phase, 24 in accelerated phase, and 21 in blastic phase.

Results: More than 50% of cases showed the major routes of CML clonal evolution [+8, i(17q), +Ph, and/or +19]. The remainder exhibited minor routes of secondary abnormalities with −17/17p−, 11p−/rearr(11p), and −7/7 rearr(7) as the most frequent abnormalities. Of particular interest, one case developed an inv(16)(p13q22) as a secondary anomaly during blastic transformation. The bone marrow was consistent with myelomonocytic morphology with eosinophilia. Cytogenetic responses to imatinib mesylate occurred in 15 of 58 (26%) patients; 12 achieved complete cytogenetic remission, 2 had a major response, and 1 had a minor response, with most responses noted within 3–6 months. Seven patients remain in remission >17–30 months, 2 patients relapsed between 12 and 19 months on therapy, and 1 patient was treated by bone marrow transplantation.

Conclusions: Although some Ph+ CML patients with clonal evolution can have a complete cytogenetic response to imatinib mesylate, responses tend to be brief, and such patients may benefit from subsequent stem cell transplantation. Therefore, CML patients with clonal evolution may require therapy additional to imatinib mesylate for maximal eradication of the Ph+ leukemic cells.

INTRODUCTION

CML is a clonal myeloproliferative disorder of pluripotent hematopoietic progenitor cells characterized by massive proliferation and accumulation of myeloid cells that differentiate normally (1, 2). The cytogenetic hallmark of CML is the Ph chromosome that results from a reciprocal t(9;22)(q34;q11.2) translocation or its variants t(V;9;22) (3). The molecular consequence of this translocation is the formation of the BCR/ABL gene fusion usually located on the Ph chromosome (4, 5). The BCR/ABL encodes a chimeric protein of Mr 210,000, the predominant fusion protein in CML (6). Whereas the native c-abl protein is mainly nuclear and has tightly regulated kinase activity, the chimeric bcr/abl oncoprotein is localized in the cytoplasm and has a constitutively activated tyrosine kinase. Similar to other kinases, the bcr/abl functions by binding to ATP and transfers phosphate from ATP to tyrosine residues, activating multiple signal transduction pathways. The latter causes excessive cellular proliferation, arrests apoptosis, and decreases cellular adhesion. It has been shown that the enhanced tyrosine kinase activity of bcr/abl protein is essential for CML pathogenesis and is likely to represent the initiating event (7).

Clinically, CML progresses through three distinct phases: a chronic phase that is easily controlled followed by an ill-defined unstable accelerated phase, leading to a terminal blastic phase. The latter phase resembles acute leukemia and is highly refractory to chemotherapy with ≤20% response rate and a median survival of 3–6 months (8). The majority of CML patients show the Ph chromosome as the sole change throughout the chronic phase. As CML transforms to advanced phases, the Ph+ cells acquire new karyotypic abnormalities, most often a second copy of the Ph chromosome, i(17q), and trisomy 8 and 19. The increased genetic instability of the Ph+ leukemic clone facilitates the emergence of subclones with highly malignant phenotypes (9, 10).

Most CML patients express the bcr/abl protein making it an ideal target for therapy. Recently, STI571 was designed specifically to inhibit the tyrosine kinase activity of the bcr/abl protein (11). This agent functions by blocking the binding of ATP to the kinase domain of the bcr/abl protein (12, 13). Preclinical studies have shown that in vitro STI571 inhibited proliferation of cell

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The abbreviations used are: CML, chronic myeloid leukemia; Ph, Philadelphia; imatinib mesylate, signal transduction inhibitor 571 (STI571); KCI, Karmanos Cancer Institute; CCR, complete cytogenetic response; MCR, major cytogenetic response; FISH, fluorescence in situ hybridization; CR, cytogenetic response.
lines expressing bcr/abl and in vivo was also successful in eradicating bcr/abl-containing tumors in nude mice (12–14). Furthermore, initial clinical trials with STI571 demonstrated promising results in all phases of CML (15–17). In this study, we evaluated the effects of STI571 (Novartis, Pharma AG) therapy on CML patients with additional cytogenetic changes superimposed on the Ph chromosome as part of Phase II international clinical trials conducted at the KCI.

MATERIALS AND METHODS

Patients. Patients were enrolled into three Phase II clinical trials of STI571 for the treatment of CML in chronic phase after IFN-α failure, accelerated phase, and blastic phase. Some of these patients were treated on protocols of which the clinical results have been described recently, whereas others were treated on subsequent “expanded access” studies at the KCI. Briefly, male or female patients were eligible for the studies if they were ≥18 years of age and had a diagnosis of CML. The patients were required to be positive for Ph chromosome t(9;22)(q34;q11.2) or its variant t(V;9;22). CML patients who were Ph negative but BCR/ABL gene fusion-positive were also eligible. The chronic phase of CML was defined by the presence of <15% blasts, <20% basophils, and <30% blasts plus promyelocytes in the peripheral blood and marrow, and a platelet count of at least 100,000/mm³. In addition to the above criteria, CML patients were eligible for the chronic phase trial if they were resistant or refractory to a regimen containing IFN therapy. A failure of treatment with IFN was defined as lack of complete hematological response despite >6 months of IFN-α therapy (hematologic resistance), lack of CR (>65% Ph+) after 1 year of therapy (cytogenetic resistance), or hematological or cytogenetic relapse. Patients with severe intolerance to IFN-α were also eligible. Accelerated phase CML was defined by at least 15% to <30% blasts, ≥30% blasts plus promyelocytes in peripheral blood or marrow, at least 20% peripheral basophils, or thrombocytopenia defined as platelet counts of <100,000/mm³, unrelated to therapy. CML in blastic phase was defined by at least 30% blasts in peripheral blood or marrow, or the presence of extramedullary disease other than liver or spleen enlargement. Patients with karyotypic evolution without other criteria of advanced disease were treated on chronic phase trials. All of the patients gave written informed consent to participate in the studies, and the studies were reviewed and approved by our Institutional Clinical Research Review Board. CML patients in institutional trials at the KCI. CML patients in phase II studies at the KCI.

RESULTS

We have identified 58 cases Ph+ CML with secondary abnormalities in a review of 137 CML patients treated with STI571 at KCI as part of multicenter Phase II clinical trials. The characteristics of the patients are summarized in Table 1.
These secondary abnormalities appeared exclusively in the Ph+ clone in all of the patients, a sign of clonal evolution. Most of the cases showed the major pathways of CML karyotypic evolution including an extra copy of the Ph chromosome in 25 cases, trisomy 8 in 21 cases, trisomy 19 in 7 cases, trisomy 21 in 5 cases, rearrangement of chromosome 7 in 5 cases, rearrangement of 17q in 4 cases, deletion of 17p in 4 cases, and trisomy 8 in 2 cases. Other less frequent abnormalities observed in our cases were loss of 17p in 2 cases, rearrangement of 17q in 2 cases, +17p in 1 case, and trisomy 21 in 1 case. Of particular interest, 1 patient had a pericentric inversion of chromosome 11 (mostly 11p) in 6 cases, and 5q− in 6 cases. Of these 7 patients remain Ph−; 0:20 BCR:ABL−; 0:20 CR: A 17 m+; 1 patient (#15) had advanced disease, and 1 was in accelerated phase after relapse from allogeneic bone marrow transplantation (Table 2, case 11). CCRs were achieved as early as 3 months and as late as 15 months after the initiation of therapy. Eleven of the 12 patients who had a CCR tested negative for BCR/ABL gene fusion by FISH (Table 2). Three patients showed partial CRs, 2 major responses, and 1 minor response. Seven of 15 CR patients continue on STI571, in contrast to the usual form associated with acute promyelocytic leukemia. Of the 58 cases, 34 had more than one secondary aberration, and various combinations were seen at variable frequencies.

**CRs.** CRs were observed in 15 of 58 (26%) CML patients with secondary chromosomal abnormalities who were treated with STI571. These 15 patients included 6 of 13 CP, 6 of 24 AP, and 3 of 21 BP patients. Their cytogenetic data are summarized in Table 2. A single additional abnormality was observed in 11 of 15 (74%) CR cases and 2 additional abnormalities in the other 4 cases. As seen in Table 2, none of the 15 CR cases had chromosome 7 or 5 abnormality. On the other hand, 30 of 43 (70%) non-CR cases had 2 or more additional abnormalities.

Of those 15 CR patients, 12 patients achieved a CCR.

**Discussion**

The role of Ph chromosome in the development and pathogenesis of CML is well documented. Early in the chronic phase of CML, the Ph chromosome is likely the sole genetic event in the majority of patients (9, 10). Because BCR/ABL alone is insufficient to initiate CML, one might assume that STI571 is an ideal therapy to block this genetic defect. Results from clinical trials have revealed that STI571 therapy is able to induce hematological remission in the vast majority of newly diagnosed CML patients and those in CP for whom previous IFN therapy

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Phase</th>
<th>Prior to ST1571</th>
<th>3m Ph:Na</th>
<th>6m Ph:N</th>
<th>9m Ph:N</th>
<th>12m Ph:N</th>
<th>15m Ph:N</th>
<th>CR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CP</td>
<td>t(9;15),+8</td>
<td>4:16</td>
<td>3:17</td>
<td>0:20 BCR:ABL−</td>
<td>0:20 BCR:ABL−</td>
<td>0:20 BCR:ABL−</td>
<td>CCR</td>
<td>A 30m+</td>
<td></td>
</tr>
<tr>
<td>2 CP</td>
<td>t(9;22),+11</td>
<td>0:20 BCR:ABL−</td>
<td>0:20 BCR:ABL−</td>
<td>0:20 BCR:ABL−</td>
<td>CCR</td>
<td>A 24m+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 CP</td>
<td>t(9;22),+21</td>
<td>0:20 BCR:ABL−</td>
<td>0:20 BCR:ABL−</td>
<td>0:20 BCR:ABL−</td>
<td>CCR</td>
<td>A 30m+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 CP</td>
<td>t(9;22),14q+</td>
<td>4:16</td>
<td>4:16</td>
<td>6:14 BCR:ABL−</td>
<td>12.8 BCR:ABL−</td>
<td>CCR</td>
<td>A progressed 12m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 CP</td>
<td>t(9;22),inv(11)</td>
<td>20:0</td>
<td>2:18</td>
<td>6:14 BCR:ABL−</td>
<td>20:0 BCR:ABL−</td>
<td>CCR</td>
<td>A 30m+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 CP</td>
<td>t(9;22),+8, +19</td>
<td>8:12</td>
<td>3:17</td>
<td>0:20 BCR:ABL−</td>
<td>20:0 BCR:ABL−</td>
<td>MCR</td>
<td>D 13m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 AP</td>
<td>t(9;22),+8, +Ph</td>
<td>0:20 BCR:ABL−</td>
<td>0:20 BCR:ABL−</td>
<td>0:20 BCR:ABL−</td>
<td>CCR</td>
<td>A 19 m+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 AP</td>
<td>t(9;22),i(17q)</td>
<td>5:15</td>
<td>0:20</td>
<td>0:20 BCR:ABL−</td>
<td>0:20 BCR:ABL−</td>
<td>2:18 BCR:ABL−</td>
<td>0:20 BCR:ABL−</td>
<td>CCR</td>
<td>A progressed 19m</td>
</tr>
<tr>
<td>9 AP</td>
<td>t(9;22),t(Ph)</td>
<td>20:0</td>
<td>0:20</td>
<td>0:20 BCR:ABL−</td>
<td>0:20 BCR:ABL−</td>
<td>Hypocellular BCR:ABL−</td>
<td>0:20 BCR:ABL−</td>
<td>CCR</td>
<td>A 17 m+</td>
</tr>
<tr>
<td>10 AP</td>
<td>t(9;22), +Ph</td>
<td>9:11</td>
<td>0:20 BCR:ABL−</td>
<td>0:20 BCR:ABL−</td>
<td>CCR</td>
<td>D 18m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 AP</td>
<td>BCR:ABL+, i(17q)</td>
<td>BCR:ABL−</td>
<td>BCR:ABL−</td>
<td>BCR:ABL−</td>
<td>CCR</td>
<td>A 30m+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 AP</td>
<td>t(9;22),t(+8,8p)−</td>
<td>12.8</td>
<td>0:20</td>
<td>0:20</td>
<td>MCR</td>
<td>D 7m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 BP</td>
<td>t(9;22),14q+</td>
<td>6:14</td>
<td>0:20</td>
<td>0:20</td>
<td>7:13</td>
<td>CCR</td>
<td>D 14m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 BP</td>
<td>t(9;22),i(17q)</td>
<td>6:14</td>
<td>0:20</td>
<td>0:20</td>
<td>7:13</td>
<td>CCR</td>
<td>D 14m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 BP</td>
<td>t(9;20),+8</td>
<td>6:14</td>
<td>0:20</td>
<td>0:20</td>
<td>7:13</td>
<td>MCR</td>
<td>A 8m</td>
<td></td>
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</tr>
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</table>

a Ph:N, ratio ph+:normal based on analysis of 20 metaphases. BCR:ABL+, BCR:ABL fusion positive; BCR:ABL−, BCR:ABL fusion negative; AP, accelerated phase; BP, blastic phase; CP, chronic phase; CR, cytogenetic response; CCR, complete CR; MCR, major CR; mCR, minor CR; D, dead; A, alive; m, month.
was either not successful or limited by toxicity (16, 19). The rate of MCR in patients with chronic-phase CML in whom treatment with IFN-α had failed was ~60%. Among those patients, the IFN-intolerant subgroup responded most favorably to STI571, possibly because some of these patients had previously had CRs from the IFN therapy (19, 20). The CCR rate is even higher, ~70%, in newly diagnosed CML patients (21). However, in later-stage CML, the Ph+ clone of most cases acquires additional molecular and/or cytogenetic aberrations, driving the disease to more aggressive phenotypes (9, 10). Thus, MCR was observed in only 24% of patients in accelerated phase and 16% in blastic phase (17, 22, 23). Moreover, the remissions, particularly in blastic phase, were not durable, because most patients relapsed within a few months.

Is imatinib mesylate effective as a single agent in CML with additional cytogenetics changes? Our results suggest that there is a small subset of patients whose Ph+ leukemic cells remain sensitive to imatinib therapy despite the presence of additional abnormalities. Fifteen of the 58 (26%) patients in this study demonstrated CRs, of whom 7 maintained a complete remission with a follow-up ranging from 17 to 30 months. Other studies have reported similar CRs in accelerated and blastic phases defined by hematological criteria, a patient population with a high frequency of secondary cytogenetic abnormalities (17, 22, 23). Of considerable interest is the subgroup of patients with a high frequency of secondary cytogenetic abnormalities (17). The issue of resistance to STI571 has become a subject of intense interest and study (25–27). In a recent study by Gorre et al. (27), it was found that resistance to STI571 therapy was associated with reactivation of BCR/ABL signal transduction in all of the cases examined, caused either by gene amplification of BCR/ABL or point mutations in the BCR/ABL kinase domain. Later the same investigators found that mutations of BCR/ABL gene were common in both acquired and de novo-resistant CML (28). Other mechanisms of STI571 drug resistance have been suggested to include plasma sequestration of drug via α1 acid glycoprotein, multidrug resistance pathways, involvement of other protein kinases, and reentry of the bcr/abl protein in the cellular cytoplasm (29–31).

In conclusion, the impact of additional genetic abnormalities on clinical response to STI571 therapy in CML has important clinical and biological implications. Our study suggests that in CML patients with secondary chromosomal abnormalities, STI571 therapy was capable to eradicate the Ph+ clone in a small subset of patients. Those patients may benefit from subsequent stem cell transplantation (33). However, in many patients, STI571 failed to induce cytogenetic remission suggesting that the Ph+ clone genetically evolved and escaped the dependency on bcr/abl kinase for proliferation. The limited activity of STI571 on CML patients with advanced genetic changes raises the need for combining STI571 with other therapeutic agents to enhance treatment outcome. Recently, in vitro studies have demonstrated either additive or synergistic effect for a number of agents used in combination with STI571, and several Phase I combined therapy clinical trials have been proposed (34, 35).

REFERENCES

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