Phase II Trial of STI571 in Myelofibrosis with Myeloid Metaplasia

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Running head: STI571 in myelofibrosis with myeloid metaplasia

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Abstract

In a phase II study, 23 patients with myelofibrosis with myeloid metaplasia (MMM) were treated with STI571 at a constant dose of 400 mg/day. Treatment was held in 16 patients (70%), after 1-12 weeks, because of side effects (neutropenia, 6 cases; musculoskeletal pain, 5 cases; thrombocytosis, 4 cases; edema, 3 cases; diarrhea and hyperbilirubinemia, 1 case). Including patients where re-treatment at a reduced dose was possible, 11 patients (48%) were able to continue treatment beyond 3 months. None of the patients experienced a response in anemia and only two had partial responses in splenomegaly. A greater than 50% increase in platelet count was documented in 11 patients (48%) but not in those with baseline platelet counts of <100 x 10^9/L. In vitro, STI571 caused variable degrees of growth suppression of both myeloid and erythroid progenitors that unfortunately did not translate into clinical benefit.

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Introduction

Myelofibrosis with myeloid metaplasia (MMM) is a clonal stem cell disorder that is characterized by anemia, marked splenomegaly, bone marrow fibrosis, and extramedullary hematopoiesis. Median survival is estimated at 5 years and causes of death include transformation into acute myeloid leukemia and consequences of progressive cytopenia and cachexia. Conventional treatment provides symptomatic improvement in less than a third of the patients and does not improve survival. Promising investigational treatments include allogeneic hematopoietic stem cell transplantation (HSCT), autologous HSCT, and drug therapy with either thalidomide or etanercept.

Although the clonal nature of MMM is well established, the pathogenesis of the florid bone marrow stromal reaction that includes collagen fibrosis, neo-angiogenesis, and osteosclerosis is poorly understood. Current information suggests a pivotal role for megakaryocyte/monocyte-derived cytokines, such as platelet derived growth factor (PDGF), transforming growth factor-β, and basic fibroblast growth factor, all of which are angiogenic and fibrogenic. This cytokine-mediated bone marrow stromal reaction may contribute to clinical phenotype and disease progression.

STI571 is an orally bioavailable 2-phenylaminopyrimidine derivative that inhibits bcr/abl and related kinases. This drug has resulted in impressive hematological as well as cytogenetic response rates in chronic phase chronic myeloid leukemia. In vitro, STI571 also inhibits the tyrosine kinase activities of c-kit, ARG kinase, and the PDGF-receptor. In addition, STI571 also inhibits c-kit or PDGF receptor-dependent cell proliferation ex vivo and in vivo. Because both PDGF and c-kit have been implicated in the pathogenesis of MMM, we evaluated the efficacy of STI571 in this disorder.
Methods

Previously published criteria were used for diagnosis of MMM.\textsuperscript{1,16} In addition to a pretreatment history and physical examination, all study patients underwent a pretreatment bone marrow examination with cytogenetic and fluorescent in situ hybridization (FISH) studies. Oral STI571 was administered as single agent therapy according to a protocol approved by the Mayo Clinic Institutional Review Board. All patients were started at a dose of 400 mg/day. The National Cancer Institute-designed Common Toxicity Criteria Version 2.0 were used to grade toxicity. STI571 was held in the event of ≥ grade 3 toxicity in neutropenia or thrombocytopenia and ≥ grade 2 toxicity in other parameters. Upon complete resolution of side effects, the drug was restarted at 200 mg/day. Recurrence of side effects at the reduced drug dose level required withdrawal from the study.

The effects of STI571 on peripheral blood myeloid and erythroid colony formation were evaluated in 19 of the 23 study patients. Twenty mL of peripheral blood (in EDTA) was obtained from each patient before starting protocol treatment. Peripheral blood mononuclear cells (PBMC) were obtained through ficoll-hypaque density centrifugation, washed in Dulbecco’s phosphate buffered saline, and re-suspended in Iscove’s Modified Dulbecco’s Medium. Isolated PBMC were then plated in growth-factor-containing methylcellulose medium \textit{Methocult} (StemCell Technologies; Vancouver CA) in diluent (0.1% dimethylsulfoxide) containing 0, 3.125, 6.25, 12.5, or 25 μM STI571. After incubation for 14 days at 37°C in 5% CO\textsubscript{2}, myeloid (CFU-GM) and erythroid (CFU-E, BFU-E) colonies were counted by light microscopy using morphologic criteria established by the manufacturer.

Results and Discussion

Between May and October, 2001, twenty-three patients (median age 63 years; range, 37-78) with MMM were treated with STI571 at an initial dose of 400 mg/day. Table 1 outlines the pre-treatment clinical and laboratory characteristics of the patients. Seven patients were in a high-risk prognostic category,\textsuperscript{17} 9 were...
red blood cell transfusion-dependent, 11 had substantial constitutional symptoms, and 8 were previously treated with chemotherapy. None of the patients were splenectomized and the median palpable spleen size was 10 cm (range, 0-25) below the left costal margin. Fifteen patients (65%) had clonal cytogenetic abnormalities. FISH studies did not reveal an abnormal bcr/abl fusion signal in any patient.

Initial treatment with STI571 at 400 mg/day was held in 16 patients (70%) after 1-12 weeks because of side effects. Severe to moderate neutropenia (ANC < 1 x 10^9/L) occurred in 6 patients at a median of 25 days (range, 15-75) from initiation of treatment. Interestingly, this side effect was observed in 6 of 10 patients with a pre-treatment white blood cell count (WBC) of <5 x 10^9/L but not in any of 13 patients with a baseline WBC of >5 x 10^9/L. Drug-induced neutropenia resolved in all patients after treatment discontinuation. In contrast to CML, where thrombocytopenia is observed with STI571, a greater than 50% increase in platelet count was documented in 11 patients (48%). Of these patients, 4 had thrombocytosis, with platelet count (x 10^9/L) increasing from 436 to 1086 in patient 2, 246 to 610 in patient 4, 848 to 1517 in patient 12, and 343 to 604 in patient 20. Unfortunately, none of the platelet increases occurred in patients with pretreatment platelet counts below 100. In addition to these hematological side effects, non-hematological side effects included limb pain or exacerbation of pre-existing joint and muscle pain (5 cases; patients 7, 15, 16, 18, and 22), peripheral edema (3 cases; patients 3, 12, and 13), diarrhea (1 case; patient 6), and hyperbilirubinemia (1 case; patient 6). Both fluid retention and musculoskeletal pain occurred in only those patients with a previous history of the same.

Protocol treatment was restarted at the reduced dose of 200 mg/day in 12 of the 16 patients whose treatment was held because of side effects. The aforementioned side effects recurred and necessitated permanent cessation of treatment in 9 patients. Overall, 11 patients (48%), including those where a treatment re-challenge at 50% dose reduction was possible, were able to continue treatment beyond 3 months (7 at 400 mg/day and 4 at 200 mg/day). Of these, 5 patients have discontinued treatment after 3 months because of
either side effects or personal decision. The remaining 6 patients have either completed the scheduled 6 months of treatment (3 patients) or are currently on therapy. To date, none of the patients have experienced a response in anemia and only 2 patients have obtained a greater than 50% reduction in spleen size (patients 4 and 10). Post treatment BM specimens were available in 5 patients and showed no change from pretreatment findings.

To determine whether the hematological side effects of STI571 therapy were predicted from in vitro assays, we examined the effects of STI571 on colony formation by circulating myeloid (figure 1a) or erythroid (figure 1b) progenitor cells. As a basis for comparison, the peak and trough STI571 concentrations are estimated to be 4.6 and 1.5 µM, respectively, in patients receiving 400 mg/day. In these assays, the drug demonstrated variable degrees of growth suppression of both myeloid and erythroid progenitors that were more pronounced at higher than therapeutic concentrations. There was no correlation between in vitro drug activity and in vivo clinical effects.

The current study reveals a high incidence of STI571 toxicity in MMM and identifies a patient population that is at risk for developing specific side effects. The prevalence of side effects as well as the strict protocol requirements may have masked potential activity at higher dose levels. The observed effect of the drug on platelet count was inconsistent with the stimulatory effect of PDGF on bone marrow stromal production of thrombopoietin as well as the expansion of megakaryocyte progenitors. Unfortunately, these effects of STI571 were not accompanied by any discernible clinical benefit. However, the current study does not rule out the possibility of a favorable drug effect in the context of either a longer treatment duration or an STI571-based combination therapy.
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*Spleen size denotes palpable spleen below the left costal margin.
*The presence of constitutional (Cx) symptoms required ≥ grade 2 fatigue, weight loss, night sweats, or musculoskeletal pain.
*A hemoglobin (Hgb) of “0” denotes transfusion dependency.
*Dx-Rx denotes interval duration from initial diagnosis; *NN, normal cytogenetics; NA, not available; Structural, structural anomalies of chromosomes 2 and 8.
*WBC, white blood cell count, *ANC, absolute neutrophil count.
*Dupriez score: ‘0’ = Hgb ≥ 10 g/dL and WBC ≥ 4 but ≤ 30 x 10^9/L, ‘1’ = either Hgb < 10 g/dL or WBC < 4 or > 30 x 10^9/L, ‘2’ = Hgb < 10 g/dL and WBC < 4 or > 30 x 10^9/L.
Figure 1. Ex vivo effect of STI 571 on the growth of myeloid (CFU-GM) and erythroid (BFU-E + CFU-E) progenitors from the peripheral blood of 19 of 23 study patients with myelofibrosis with myeloid metaplasia.
References.


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