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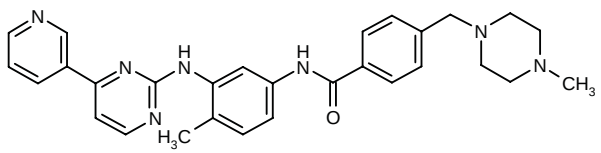
Imatinib Mesilate

Prop INNM

Treatment of Chronic Myeloid Leukemia
Brc-Abl Tyrosine Kinase Inhibitor

GGP-57148B
STI-571
Gleevec™
Glivec™

4-(4-Methylpiperazin-1-ylmethyl)-*N*-[4-methyl-3-[4-(3-pyridyl)pyrimidin-2-ylamino]phenyl]benzamide methanesulfonate



.CH_3SO_3H

$C_{29}H_{31}N_7O.CH_4O_3S$ Mol wt: 589.7175

CAS: 220127-57-1
CAS: 152459-95-5 (as free base)

EN: 229058

Synthesis

The condensation of 1-(3-pyridyl)ethanone (I) with dimethylformamide dimethylacetal (II) gives 3-(dimethylamino)-1-(3-pyridyl)-2-propen-1-one (III) (1), which is cyclized with 1-(2-methyl-5-nitrophenyl)guanidine (IV) – obtained by reaction of 2-methyl-5-nitroaniline (V) with cyanamide (VI) – in refluxing isopropanol to yield the pyrimidine derivative (VII). Reduction of the nitro group of (VII) with H_2 over Pd/C in THF affords the corresponding amino compound (VIII), which is finally condensed with 4-(4-methylpiperazin-1-ylmethyl)benzoyl chloride (IV) in pyridine (1, 2). Scheme 1.

Description

Crystals, m.p 207-12 °C (1); m.p. 211-3 °C (2).

Introduction

Chronic myeloid leukemia (CML) is a hematologic stem cell disorder which mainly affects older adults (median age = 45-55 years), although people of all ages can suffer from the disease. Fifteen to twenty percent of all adult leukemias are of this category and 1-2 individuals per 100,000 are afflicted yearly (3). Over 90% of CML patients and 10-25% of acute lymphoid leukemia (ALL) patients have a characteristic chromosomal abnormality known as the Philadelphia (Ph) chromosome (4). This abnormality is the result of the reciprocal translocation of chromosomal DNA between chromosome 9 and 22. In the Ph chromosome, the main part of the *ABL* gene is translocated onto the *BCR* gene giving rise to a fusion, which possesses constitutive tyrosine kinase activity. This activity leads to the ongoing activation of growth promoting proteins, eventually leading to the generation of a tumor (5). There are three types of fusion proteins found, depending on the break point in *BCR*. The first type, $p210^{bcr\text{-}abl}$, is characteristic of CML and is seen in 95% of CML patients and also in about 50% of Bcr-Abl-positive ALL. The first exon of c-*ABL* is replaced by *BCR* sequences encoding 927 or 902 amino acids. The second type, $p190^{bcr\text{-}abl}$ or $p185^{bcr\text{-}abl}$, occurs in about 50% of Bcr-Abl-positive ALL. The third type, $p230^{bcr\text{-}abl}$, is associated with very rare Ph-positive chronic neutrophilic leukemia. All these fusion proteins are deregulated tyrosine kinases as compared with the native Tyr kinase $P145^{abl}$ (3, 4, 6).

CML develops in three phases: chronic, accelerated and blastic. In the chronic phase, which lasts 4-6 years, the patient displays relatively mild signs and symptoms. Hematologic analysis in this phase reveals leukocytosis with the majority of patients showing > 100,000/mm^3. Anemia often proportionally accompanies the leukocytosis. Increased platelet counts are observed in approximately 50% of patients. Peripheral blood smears show a full spectrum of maturing myeloid cells ranging from blast

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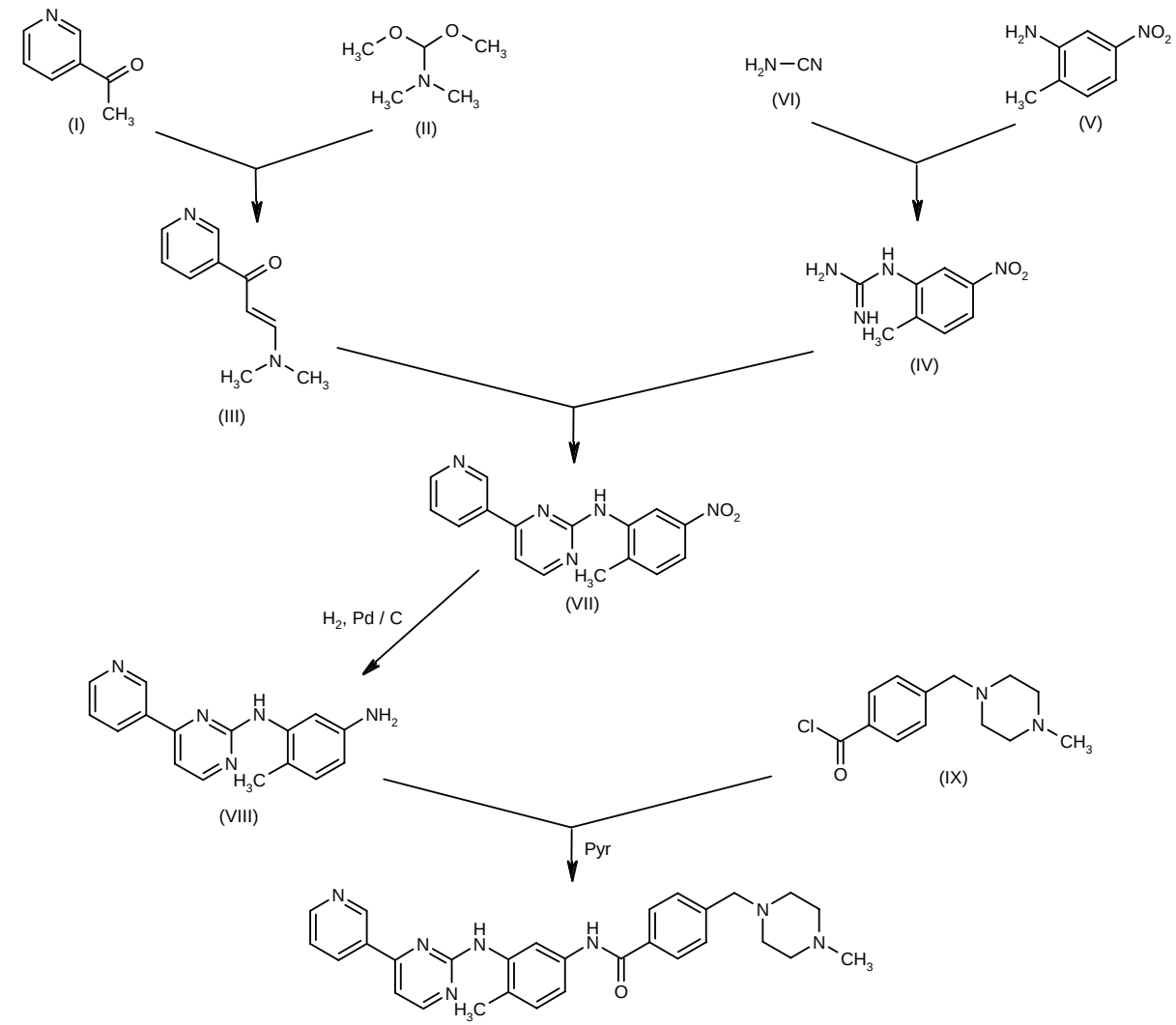
Scheme 1: Synthesis of Imatinib



to neutrophils. Basophilia is a characteristic feature and eosinophilia is common. The bone marrow shows hypercellularity with myeloid hyperplasia. In the accelerated phase, an increase in blast cells in the blood is observed with a more pronounced symptomatology, which may last up to 1 year. The blastic phase may be an acute leukemia with severe symptoms and patient survival of 3-6 months. CML is found and diagnosed by routine blood tests in one-third or more of CML patients. Fortunately, 85-90% of them are only in the chronic phase (7).

The prognosis for CML is poor. In the chronic phase, the disease can be controlled by anticancer agents like interferon-alpha, hydroxyurea, cytarabine (ara-C), homoharringtonine and busulfan. Chemotherapy can be effective in inducing hematologic responses, but this form of therapy does not affect the progression of the disease. The first-line management option for CML is interferon-α. It can induce both hematologic and cytogenetic responses, decreasing Ph-positive cells and prolonging patient survival to approximately 1-2 years. However, interferon treatment is accompanied with significant side effects. New developments include combination therapies using ara-C in addition to interferon-α to further improve survival rates. To date, the only real cure is allogeneic stem cell transplantation (SCT), but this treatment is not available for everyone. Only 15-20% of CML patients are eligible for SCT due to the lack of suitable donors or age restrictions. This rate can be increased to 30% if unmatched sibling donors are used. Without SCT the average survival is 6 years, although one institution reported a 10-year survival rate of 70% (8-10).

Without any real therapy available for all CML patients, it is clear that the demand for a cure remains a priority. The most ideal treatment approach would be a specific inhibitor of the Bcr-Abl tyrosine kinase. Initially designed as a platelet-derived growth factor receptor (PDGFR) tyrosine kinase inhibitor, a signal transduction inhibitor (STI) lead compound was further developed into CGP-57481, later named STI-571 (imatinib mesilate) (11). This 2-phenylaminopyrimidine derivative binds to the ATP binding site in tyrosine kinase. Interaction of STI-571 keeps Bcr-Abl in a nonactive state in which Tyr^{393} in an activation loop is not phosphorylated (12).

Preclinical testing showed exclusive binding to and inhibition of Abl kinase and the related kinases c-Kit, the receptor for stem cell factor (SCF) and PDGFR kinase. STI-571 specifically inhibits these three tyrosine kinases and has great potential for the treatment of Ph-chromosome-positive diseases.

Pharmacological Actions

STI-571 was found to be specific for all Abl kinases, the PDGFR kinase and c-Kit tyrosine kinase *in vitro*. An IC_{50} of 0.038 μM was obtained for STI-571 on Abl kinase activity and an IC_{50} of 0.05 μM on PDGFR kinase activity (1). Further studies showed IC_{50} values of 0.1 μM for both PDGF-AA-stimulated PDGFR phosphorylation and SCF-stimulated phosphorylation. SCF-induced activation of MAP (mitogen-activated protein) kinases was inhibited by STI-571 with an IC_{50} of 0.1-1 μM. PDGF-BB-mediated MAP kinase activation in rat A10 muscle cells was similarly inhibited and PDGF-BB-mediated inositol phosphate release was inhibited with an IC_{50} of 0.25 μM (13).

The application of STI-571 to a range of cell lines expressing the various forms of Bcr-Abl fusion kinases resulted in a dose-dependent decrease in proliferation. The Bcr-Abl expressing cell lines used were p210-expressing MO7ep210, K562, BV173, KCL22, KYO1, EM3, KU812, MC3, LAMA84, 32Dp210; p185-expressing 32Dp185, TOM1, SD1; and p230-expressing AR230 (14-21). Most of these cell lines were developed from CML patient tumors except for TOM1 and SD1 which were derived from Ph-positive ALL patients (15). The murine myeloid cell line 32Dcl was virally transfected with either the p210- or the p185-encoding cDNA to generate the lines 32Dp210 and 32Dp185 (14).

Invariably, all Bcr-Abl-expressing cell lines, as opposed to Bcr-Abl-negative cell lines (not listed), were sensitive to STI-571 and exhibited dose-dependent growth inhibition at doses below 1 μM and complete inhibition of proliferation with higher concentrations (14, 15, 18-21). Growth inhibition occurred within 48-72 h (15, 17) and within 16-24 h a decrease in cycling cells and induction of apoptosis was observed (18, 21). Results of experiments with cells cultured in the presence of 1 μM STI-571 demonstrated that 20-21 h are sufficient to block cell proliferation, while an exposure time of 6-7 h was not very effective (20).

Some studies included analysis of the inhibition of protein phosphorylation by STI-571. In general, IC_{50} values lower than the concentrations needed for complete growth inhibition were found, ranging from 0.15-0.35 μM (14, 16).

Related fusions that displayed similar dysregulated phosphorylation activities were Tel-Abl and Tel-PDGFR. The Tel-Abl fusion was identified in a few single cases of acute myelogenous leukemia, ALL and atypical CML. The TEL-PDGFR fusion was cloned from chronic myelomonocytic leukemia patients with a t(5;12) translocation (22). Separate expression of the Tel-Abl and Tel-PDGFR fusions in 32Dcl3 cells allowed testing of the effects of STI-571 on autophosphorylation and cell proliferation. The IC_{50} values for the inhibition of tyrosine phosphorylation by STI-571 on Tel-Abl and Tel-PDGFR were 0.35 and 0.15 μM, respectively. Cell proliferation was inhibited completely with 1 and 10 μM STI-571, while the parental cell line that was not fusion-transfected was not inhibited by these concentrations (14).

Effective cytotoxicity against patient tumor-derived cells was demonstrated in several studies. Tumor-derived cells were taken from CML patients as well as Ph-positive ALL patients. Again a decrease in colony formation and cytotoxic effect were shown with STI-571 with IC_{50} values typically less than 1 μM (15, 16, 18, 20, 23).

In the first experiment using STI-571 on a growing myeloid 32Dp210 tumor in C3H/HEJ mice, tumor regression was achieved after 5 days of STI-571 administration (50 mg/kg/day i.p. from day 8 for 10 days). Doses of 10 and 25 mg/kg/day were also effective in retarding tumor growth (16).

In another tumor model, using Bcr-Abl-positive KU812 or MC3 tumor cells in nude mice, animals were treated with different STI-571 dosing schedules. In the first experiment, 50 mg/kg was administered once daily i.p. for 25 days without significant effect on tumor growth. In a second experiment, the schedule was changed to twice-daily administrations, which resulted in significant growth retardation on days 17, 21 and 25, although none of the mice survived. In a third experiment, the dose was increased to 50 mg/kg i.p. or 160 mg/kg p.o. every 8 hours for 11 days. All animals in the p.o. group remained tumor free, whereas 1 animal in the i.p. group developed a tumor. No tumor growth was observed in the survivors for up to 240 days. In a fourth experiment, STI-571 was applied to a more advanced tumor (mean tumor weight = 286-289 mg) in mice. Treatment consisted of 3 administrations of 160 mg/kg/day for 11 days. By day 8 all tumors disappeared in all treated animals as compared to the untreated group where the tumor weights increased to more than 600 mg. All treated animals were tumor free after the treatment; however, 33% (4/12) relapsed between days 48 and 60 while the remaining 8 animals remained tumor free (+210 days). A longer treatment schedule of 18 days failed to avoid relapse (20).

Further experiments used nude mice challenged with KU812 cells and STI-571 treatment (160 mg/kg p.o. every 8 h for 11-21 days) starting at different time points after

Table I: Pharmacokinetic parameters of imatinib in patients with chronic myelogenous leukemia after once daily oral administration (Prous Science Integrity database).

Dose (mg)	AUC	C_{max}	T_{max} (h)	$t_{1/2}$ (h)	Ref.
25	–	–	–	11-14	42
25	1.0-5.4[a]	0.1-0.4[c]	0.5-3.0	11-14	43
25 (day 1)[f]	–	71.5/179.3[d]	–	10-23	44
50	–	–	–	11-14	42
50	–	–	–	11-14	43
85	–	–	–	11-14	42
400 (day 28)[f]	–	4.6[c]	–	13-16	26
400 (fasted/fed)[g]	36341/33221[b,e]	2817/2407[d]	2.7/3.7	15.1/17.1	27
140	≤ 23[a]	≤ 1.8[c]	0.5-3.0	11-14	42
600 (day 1)[f]	–/59535[b,e]	3395/3925[d]	–	10-23	44

[a]μM·h/l; [b]μg·h/l; [c]μM; [d]μg/l; [e]AUC_{0-24}; [f]at steady state; [g]administered for 8 days

the challenge (1, 8, 15 days). Although all tumors regressed with treatment, all mice receiving treatment from 15 days after the challenge relapsed (24).

Since STI-571 is also effective at inhibiting PDGFR phosphorylation, an experiment to explore the usefulness of STI-571 in the treatment of prostate cancer was performed. Human PC-3MM2 prostate cancer cells, which are highly metastatic, were implanted in the tibia and prostate of nude mice and treated with STI-571 (50 mg/kg/day p.o.) with or without paclitaxel (200 μg/week i.p.). STI-571 was effective in inhibiting tumor growth of PC-3MM2 prostate cancer cells in the bone and maintaining bone structure as opposed to control or paclitaxel-treated animals, which experienced significant bone destruction. These effects were enhanced when STI-571 was coadministered with paclitaxel. Similarly, STI-571 alone and in combination with paclitaxel inhibited tumor growth in the prostate, with the combination being most effective (25).

Pharmacokinetics

In vivo pharmacokinetic data on STI-571 were obtained in nude mice challenged with tumor cells and treated with STI-571. After a single i.p. (50 mg/kg) or p.o. (160 mg/kg) dose of STI-571, a 64.7% and 66.4% inhibition, respectively, of Bcr-Abl phosphorylation in the tumor was observed 2 h after administration. At 5 h, inhibition was 53.4% (i.p.) and 46.7% (oral), but by 8 h more than 70% of the activity was restored in both groups. A dose of 50 mg/kg/day i.p. achieved a C_{max} value greater than 3 μM (20).

Pharmacokinetic data for STI-571 in humans were obtained in a phase I, dose-escalating study in 83 CML patients who were in chronic phase (<15% blasts/basophils in blood or bone marrow), were positive for the Ph chromosome and had failed interferon treatment. STI-571 had a plasma half-life of 13-16 h. A once-daily p.o. administration of 400 mg STI-571 was rapidly absorbed. At steady state the C_{max} was 4.6 μM (2.3 μg/ml). Mean plasma trough concentration was 1.46 μM (0.72 μg/ml) 24 h after administration at steady state. The levels increased 2-3 times at steady state with the daily dosing (26). Food intake prior to administration of STI-571 had no significant effects on the bioavailability or other pharmacokinetic parameters (27).

Pharmacokinetic data for STI-571 in patients with CML are shown in Table I.

Toxicity

A reduced growth rate of animals was reported during STI-571 treatment of KU812 or MC3 tumors in mice. The difference in weight gain never exceeded 8% and disappeared after treatment. No abnormalities were found in white blood cell and platelet counts, hemoglobin levels, histopathological analysis, postmortem appearance and myeloid/erythroid ratios in bone marrow specimens. The only abnormality reported was a modest periportal lymphocyte infiltrate in some but not all animals with no sign of hepatocellular necrosis (20).

Clinical Studies

In a phase I, dose-escalating study, 83 CML patients who did not respond to interferon-α treatment, were positive for the Ph chromosome and were in chronic phase of the disease (<15% blasts or basophils in the peripheral blood or bone marrow) were administered once-daily doses of STI-571 ranging from 25-1000 mg/day. A hematologic response (defined as a 50% reduction in the white cell count from baseline, maintained for at least 2 weeks) occurred in all patients administered 140 mg/day or more, and almost all patients who were treated with 300-1000 mg STI-571 responded (53/54). The hematologic response was generated over 2 weeks and the response was complete, with a steady level of white-cell count being achieved after 4 weeks of treatment. The complete hematologic response was maintained in 51 of the 53 patients with a median follow-up of 265 days (range of 17-468 days). Cytogenetic responses were determined as the percentage of cells in metaphase that were positive for the Ph chromosome in bone marrow. Categorization

Box 1: Efficacy and safety of imatinib in chronic myeloid leukemia (26) [Prous Science Integrity database].

Design	Open, multicenter clinical study
Population	Patients with Philadelphia chromosome positive chronic myeloid leukemia in the chronic phase in whom interferon therapy had previously failed (n = 83)
Treatments+	Imatinib, 25-50 mg p.o. o.d. (n = 6) Imatinib, 85 mg p.o. o.d. (n = 4) Imatinib, 140 mg p.o. o.d. (n = 3) Imatinib, 200-250 mg p.o. o.d. (n = 16) Imatinib, 300-1000 mg p.o. o.d./b.i.d. [the 800 and 1000 mg/d doses were administered 400 and 500 b.i.d.] (n = 54)
Adverse Events	I25-140: Grade 3-4 toxicities 0/14 I200-300: Grade 3-4 neutropenia 1/23 (4.3%) I350-500: Grade 3-4 thrombocytopenia 1/18 (5.5%), grade 3-4 neutropenia 1/18 (5.6%), grade 3-4 myalgia 1/18 (5.6%) I600-1000: Grade 3-4 thrombocytopenia 7/28 (25.0%), grade 3-4 neutropenia 7/28 (25.0%), grade 3-4 myalgia 4/28 (14.3%)
Results	Overall hematologic response rate: I300-1000 (54/54 [100.0%]) ≥ I200-250 (16/16 [100.0%]) ≥ I140 (3/3 [100.0%]) > I85 (2/4 [50.0%]) ≥ I25-50 (2/6 [33.3%]) Complete hematologic response rate: I300-1000 (53/54 [98.1%]) > I200-250 (9/16 [56.3%]) > I140 (1/3 [33.3%]) ≥ I85 (1/4 [25.0%]) > I25-50 (0/6) Complete/major cytogenetic response rate: I600 (4/8 [50.0%]) ≥ I400 (3/6 [50.0%]) > I300-350 (5/13 [38.5%]) ≥ I750 (2/6 [33.3%]) ≥ I500 (1/6 [16.7%]) ≥ I1000 (1/7 [14.3%]) ≥ I800 (1/8 [12.5%])
Conclusions	Imatinib was well tolerated and showed significant antileukemic activity in patients with Philadelphia chromosome positive chronic myeloid leukemia in whom interferon therapy had previously failed

+All treatments were administered until unacceptable adverse events and/or disease progression

was based on the percentage: 0% = complete response; 1-35% = partial response; 36-65% = minor response and >65% = no response. In the 200-250 mg dose group, 2 of the 16 patients were responders, while 29 of the 54 patients in the 300-1000 mg dose group responded. Of these 29, 17 had major responses and 7 were complete responses. Cytogenetic responses occurred as early as 2 months and as late as 10 months. The median time to the best cytogenetic response was 148 days (range = 48-331). When tested for the presence of *BCR-ABL* mRNA by *in situ* hybridization and RT-PCR, 2 and 1, respectively, of the 7 patients tested negative for *BCR-ABL*. To further analyze the efficacy of STI-571, the inhibition of protein phosphorylation was measured. CRKL, a tyrosine phosphorylated protein in neutrophils, was chosen as a substrate since it is the most heavily phosphorylated protein in neutrophils in CML patients. Dose-dependent inhibition of CRKL phosphorylation was observed with doses of 85 mg/day and higher (26) (Box 1).

A second phase I clinical study was conducted in 38 CML patients in myeloid blast crisis (MBC) (> 30% blasts in the peripheral blood or bone marrow) and 20 Ph-positive ALL patients in lymphoid blast crisis (LBC) who had not responded to standard induction or consolidation chemotherapy or had relapsed after such therapy. STI-571 doses ranged from 300-1000 mg once daily. A hematologic response (a reduction of 50% or more in peripheral blood blasts) was observed in 79% of the patients (46/58). Of the 38 MBC patients and the 20 LBC patients, 4 patients from each group had a complete hematologic response and 17 MBC patients and 10 LBC patients had a decrease in blasts of 15% or more in the bone marrow. Thus, the number of responding patients was 21 for the MBC patients and 14 for the LBC patients. The median duration of therapy was 74 days (1-349). Relapse occurred in 9 of the 21 responders with MBC between 42 and 194 days and in 12 of the 14 responders with LBC between 42 and 123 days (28) (Box 2).

In the above two studies in CML/ALL patients, STI-571 was generally well tolerated and a maximum tolerated dose (MTD) was never identified The most common side effects of STI-571 were nausea 43 (55%), edema 39 (41%), myalgias 21 (41%), vomiting 18 (41%) and diarrhea 17 (25%). Patients on higher doses (600-1000 mg/day) were more likely to have these side effects. Most adverse events, including those experienced by patients on the highest doses (600-1000 mg/day), were categorized as mild to moderate. Patients with more severe stages of leukemia (MBC and LBC) showed grade 4 neutropenia (40%) and thrombocytopenia (33%) whereas the chronic phase CML patients displayed grade 3 neutropenia (14%) and thrombocytopenia (16%). Liver enzyme levels were also more elevated in the CML patients (grade 3/4 in 14%), but without evidence of a dose relationship. In the MBC and LBC group, 7 patients had grade 2 or higher elevations in liver enzymes. These elevations, however, were not always related to STI-571 treatment. Three patients, each treated with different doses, had grade 3 anemia in the trial with CML patients in chronic

Box 2: Activity of imatinib in chronic myeloid leukemia and acute lymphoblastic leukemia (28) [Prous Science Integrity database].

Design	Open, multicenter clinical study
Population	Patients with Philadelphia chromosome positive acute lymphocytic leukemia or chronic myeloid leukemia in lymphoid blast crisis (n = 58)
Treatments[+]	Imatinib, 300 mg p.o. o.d. (n = 8) Imatinib, 400 mg p.o. o.d. (n = 8) Imatinib, 500 mg p.o. o.d. (n = 9) Imatinib, 600 mg p.o. o.d. (n = 10) Imatinib, 750 mg p.o. o.d. (n = 9) Imatinib, 400 mg p.o. b.i.d. (n = 8) Imatinib, 500 mg p.o. b.i.d. (n = 6)
Adverse Events	I300: grade 3-4 neutropenia 6/8 (76%), grade 3-4 thrombocytopenia 6/8 (63%), grade 3-4 nausea 1/8 (12%), grade 3-4 edema 1/8 (12%) I400-500: grade 3-4 neutropenia 13/17 (76%), grade 3-4 thrombocytopenia 11/17 (64%), grade 3-4 nausea 1/17 (6%), grade 3-4 vomiting 1/17 (6%), grade 3-4 edema 1/17 (6%) I600-1000: grade 3-4 thrombocytopenia 24/33 (72%), grade 3-4 neutropenia 19/33 (57%), grade 3-4 nausea 4/33 (12%), grade 3-4 vomiting 3/33 (9%), grade 3-4 edema 2/33 (6%)
Results	Complete hematologic response rate in patients with myeloid phenotype: I750 (2/7 [28.6%]) ≥ I400 (1/4 [25.0%]) ≥ I500 (1/5 [20.0%]) > I600 (0/8) ≥ I800 (0/7) ≥ I300 (0/6) ≥ I1000 (0/1) Bone marrow response < 15% rate in patients with myeloid phenotype: I1000 (1/1 [100.0%]) > I500 (3/5 [60.0%]) ≥ I800 (4/7 [57.1%]) ≥ I300 (2/6 [33.3%]) ≥ I750 (3/7 [42.9%]) ≥ I600 (3/8 [37.5%]) ≥ I400 (1/4 [25.0%]) Complete hematologic response rate in patients with lymphoid phenotype: I600 (1/2 [50.0%]) ≥ I1000 (2/5 [40.0%]) ≥ I500 (1/4 [25.0%]) > I800 (0/1) ≥ I300 (0/2) ≥ I750 (0/2) ≥ I400 (0/4) Bone marrow response < 15% rate in patients with lymphoid phenotype: I800 (1/1 [100.0%]) ≥ I750 (1/2 [50.0%]) = I400 (3/4 [75.0%]) > I600 (1/2 [50.0%]) ≥ I300 (1/2 [50.0%]) ≥ I1000 (2/5 [40.0%]) ≥ I500 (1/4 [25.0%])
Conclusions	Imatinib was well tolerated and showed substantial activity in the treatment of Philadelphia chromosome positive acute lymphocytic leukemia and blast crises of chronic myeloid leukemia

[+]All treatments were administered until unacceptable adverse events and/or disease progression

phase. Serious adverse events possibly related to STI-571 that were reported in the trial with the 58 MBC and LBC patients included nausea and vomiting (4 patients), febrile neutropenia (3 patients), elevated liver-enzyme levels, exfoliative dermatitis, gastric hemorrhage, renal failure, pancytopenia and congestive heart failure. These serious events were more frequently observed in the group treated with 800-1000 mg STI-571 (26, 28) (see Boxes 1 and 2).

A small-scale clinical study was undertaken with 3 patients with MBC-CML and 1 patient with Ph-positive ALL who had received SCT but relapsed. Two patients failed to respond to donor lymphocyte infusions and 1 failed to respond to chemotherapy. All 4 patients were treated with STI-571 (600 mg p.o. once daily) without any further treatment. All patients achieved remission, 3 of whom were complete and 1 partial after 1 month of treatment. One patient became 100% Ph-negative with 100% donor hemopoiesis; however, the patient also developed grade 3 skin and liver GVHD. The remaining 3 patients were mixed chimeras and remained *BCR-ABL* positive according to RT-PCR analysis. All were treated with donor lymphocyte infusions (29).

An ongoing multicenter, open-label, phase II clinical study involving hundreds of CML/ALL patients was undertaken to determine the rate of hematologic response and to further explore the safety and tolerability of STI-571, the cytogenetic response, overall survival, duration of hematologic response and symptomatic improvement. Patients were initially treated with 400 mg p.o. once daily (30% of patients) and later with 600 mg p.o. once daily (70%). Preliminary data indicate that overall hematologic responses were observed after 4 weeks of treatment in 38, 48, 59 and 78% of the patients. One study found major cytogenetic responses in 56% of the patients (161/290) after 6 months. In another study, bone marrow cellularity was reduced to normal or less in 35/49 patients (71%) and 6 patients developed marked marrow hypoplasia or aplasia with a median time of 13 weeks. Patients in chronic phase were more likely than patients in MBC to normalize. The phosphorylation of Bcr-Abl protein was inhibited by approximately 50% in 3 patients (30-35).

A phase I trial has recently started on the efficacy of STI-571 in patients under the age of 21 years (36). In addition, a phase III trial is planned that will compare the efficacy of STI-571 with combination therapy including interferon-α and ara-C in newly diagnosed CML patients.

Although the clinical use of STI-571 has focused on leukemias such as CML and ALL, it is also a promising drug for any tumor caused or dependent on the tyrosine kinases that STI-571 specifically inhibits, namely, Abl kinases, c-Kit and PDGFR. In a case report study, a

patient presented with metastatic gastrointestinal stromal tumor (GIST). These tumors are caused by a mutation in c-Kit. STI-571 was administered in 400 mg/day doses and after 4-8 months of treatment, without any major side effects, the liver metastases virtually disappeared as assessed by MRI, PET ([^{18}F]fluorodeoxyglucose) and histology. The major effects observed on PET and histology were evident after 4 weeks of treatment (37).

Several studies are under way to further analyze the efficacy of STI-571 in the treatment of GIST. Results are preliminary but suggest a similar efficacy against GIST as that observed against CML in the above studies. Marked clinical improvement in 89% of initially symptomatic patients has been reported (38-40).

Imatinib mesilate (Gleevec™ received FDA approval on May 10, 2001 for the treatment of patients with CML in blast crisis, accelerated phase or in chronic phase after failure of interferon alfa therapy. Gleevec™ is supplied as a hard gelatin capsule containing imatinib mesilate equivalent to 100 mg of the free base. The recommended dose is 400 mg/day for patients in chronic phase and 600 mg/day for patients in accelerated phase or blast crisis. Novartis has filed regulatory applications seeking approval for the drug, known as Glivec® (imatinib) outside the U.S., in the E.U., Switzer-land, Canada, Australia and Japan (41).

Manufacturer

Novartis AG (CH).

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