National PBM Drug Monograph
Imatinib Mesylate (Gleevec™)
VHA Pharmacy Benefits Management Strategic Healthcare Group
and the Medical Advisory Panel

Introduction

Chronic Myelogenous Leukemia (CML) is a myeloproliferative disorder that results from a malignant transformation of progenitor cells leading to clonal proliferation and accumulation of myeloid cells. CML is responsible for 15% of adult leukemias. The median age at diagnosis is between 50 and 60 years old. The Philadelphia chromosome (Ph+) has been implicated as a causative factor in CML. This chromosomal abnormality is present in > 95% of patients with the diagnosis.

The disease progresses through three phases: chronic, accelerated and blast crisis. Clinical characteristics and laboratory findings worsen as patients progress through the three phases. Similarly, treatment within each phase becomes more difficult as the disease progresses. The majority of patients present in the chronic phase and may be asymptomatic. The duration of the chronic phase may last 4-6 years. In the accelerated phase, which may last for up to 12 months, patient symptoms may worsen. Immature leukemic cells, known as blasts, appear in the peripheral blood. The final phase is known as blast crisis. During this time, blast cells occupy > 30% of cells within the bone marrow or peripheral blood. Invasion of the blood with blast cells puts the patient at increased risk for infection, bleeding and anemia. This final phase may last 3-6 months.

The goal of treating CML is to induce a hematologic and cytogenetic response. Briefly, hematologic responses reduce and stabilize peripheral blood cell counts. Cytogenetic responses eliminate or reduce the abnormal Philadelphia chromosome positive cells.

Treatment options to date have included stem cell transplantation (SCT), interferon and chemotherapy. SCT provides the only treatment option to cure CML, but only limited populations are candidates for such therapy. Due to the high rates of morbidity and mortality, SCT is not recommended in patients > 50-55 years of age. Interferon has been shown to induce complete hematologic and cytogenetic responses in patients with chronic phase disease. A survival benefit has been noted with interferon among low-risk patients. Unfortunately, interferon is a drug given by subcutaneous injection that is often times limited by its adverse effect profile. Discontinuation of interferon due to adverse events has been reported in 5-18% of patients. Chemotherapy with oral agents, hydroxyurea and busulfan, have been associated with hematologic responses, but rarely result in cytogenetic responses. These agents do not affect survival.

Imatinib mesylate (Gleevec) provides another therapeutic option in the treatment of CML.

Clinical Pharmacology

The Philadelphia chromosome is a characteristic abnormality of CML present in approximately 95% of patients diagnosed with this disease. This abnormality results from breaks in chromosomes 9 and 22 leading to translocation and ultimately the *bcr-abl* fusion gene that encodes for an unregulated tyrosine kinase protein. The *bcr-abl* protein binds to ATP resulting in the transfer of phosphate from ATP to tyrosine residues on various substrates. This action normally allows signal transduction to progress downstream, resulting in abnormal cell proliferation. Imatinib blocks the ATP-binding site to the *bcr-abl* kinase thereby interrupting the transfer of phosphate and inhibiting kinase activity. It also inhibits the receptor for platelet-derived growth factor and c-Kit tyrosine kinases, the latter having a key role in gastrointestinal stromal tumor proliferation.

Pharmacokinetics

Absorption: Imatinib is well absorbed with an estimated bioavailability of > 97%. Absorption is rapid and maximal concentrations are reached within 1-2 hours.

Distribution: *In vitro* studies indicate that imatinib is 95% bound to plasma proteins, primarily albumin and α1-acid glycoprotein.

Metabolism: Imatinib is metabolized by the cytochrome P450 system, isoenzyme 3A4.

Elimination: The primary route of excretion is through the feces (68%), mostly as metabolites, with a small percent of elimination via the renal route (13%). The half-life of imatinib is estimated between 18-22 hours and its major metabolite, the N-desmethyl derivative, has an estimated half-life of 40 hours. No clinical studies were performed in patients with impaired hepatic function or decreased renal function.

FDA Approved Indication(s) and Off-label Uses

Imatinib is FDA-approved for the treatment of patients with Philadelphia chromosome positive chronic myelogenous leukemia (CML) in blast crisis, accelerated phase or chronic phase after failure with interferon alfa (IFN-α) therapy and for treatment of patients with Kit (CD-117) positive unresectable and/or metastatic gastrointestinal stromal tumors. Off-label use includes the first-line treatment of Philadelphia chromosome positive CML and Ph+ ALL.

Current VA National Formulary Status

Imatinib is not on the VA National Formulary.

Dosage and Administration

Imatinib is available in 100mg capsules. The manufacturer-recommended starting dose for patients in chronic phase CML is 400mg daily. The recommended starting dose for patients in accelerated phase or blast crisis is 600mg daily.

Table 1. Starting Dose for Imatinib Mesylate

CML Phase	Imatinib Mesylate 100mg capsules
Chronic Phase	**4 capsules once daily with meal**
Accelerated Phase	**6 capsules once daily with meal**
Blast Crisis	**6 capsules once daily with meal**

Dose increases may be considered for patients that have not experienced severe adverse drug effects, such as neutropenia and thrombocytopenia, when any of the following conditions apply: disease progression; failure to achieve a satisfactory hematologic response after a minimum of 3 months of therapy; loss of hematological response.

Table 2. Dose Titration for Imatinib Mesylate

CML Phase	Imatinib Mesylate 100mg capsules
Chronic Phase	**6 capsules once daily with meal**
Accelerated Phase	**4 capsules twice a day with meals**
Blast Crisis	**4 capsules twice a day with meals**

The daily dose may be increased from 400mg to 600mg for patients with chronic phase CML. Similarly, the daily dose may be increased from 600mg to 800mg for patients with CML in an accelerated phase or blast crisis. Daily doses of 800mg should be administered as 400mg given twice daily.

Duration of treatment with imatinib should be maintained for as long as the patient continues to receive benefit. Daily doses of imatinib should be taken with a glass of water at mealtime.

Dose Adjustments

Hepatotoxicity and other non-hematologic adverse reactions

If severe non-hematologic adverse reactions occur, withhold Imatinib until the reaction resolves and resume treatment at an appropriate dose depending on the severity of the reaction. If bilirubin is >3 x institutional upper limit of normal (IULN) or transaminses > 5 x IULN hold imatinib until bilirubin < 1.5 x IULN and transaminases <2.5 x IULN. Then restart at reduced dose (i.e., 400mg → 300mg or 600mg → 400mg)

Hematologic Adverse Reactions

Table 3. Dose Adjustments for Neutropenia and Thrombocytopenia

CML Phase	Hematologic Toxicity	Adjustments
Chronic (starting at 400mg)	**ANC <1.0 x10^9/L and/or Platelets <50,000/L**	**1. Hold imatinib until ANC >1.5 x10^9 and platelets >75,000 2. Resume treatment at 400mg 3. If recurrence of toxicity repeat step 1 and resume at reduced dose of 300mg**
Accelerated or Blast Crisis (starting at 600mg)	**ANC <0.5 x10^9/L and/or Platelets <10,000/L**	**1. Check if toxicity is related to leukemia (bone marrow aspirate/biopsy) 2. If unrelated to leukemia, reduce to 400mg 3. If toxicity persists for 2 weeks, reduce dose to 300mg 4. If toxicity persists 4 weeks and still unrelated to leukemia, hold imatinib until ANC ≥1x10^9/L and platelets ≥20,000 and resume at 300mg**

Adverse Effects (Safety Data)

Toxicity was graded according to the Common Toxicity Criteria of the National Cancer Institute.

Non-hematologic Toxicity

Overall adverse effects with imatinib were considered to be of mild to moderate grade. The most common adverse effects were nausea, vomiting, fluid retention, muscle cramps and diarrhea. Edema appeared to be dose-related and more common among the elderly population. Fluid retention can be managed with interruption of imatinib treatment and supportive care; however, some of these events may be life threatening and careful monitoring should be observed.

Increases in liver transaminases and total bilirubin occurred in 1.1-3.5% of patients in CML trials. Management of these abnormalities included dose reduction or interruption of therapy. Permanent discontinuation of treatment due to these abnormalities was required in less than 0.5% of patients participating in clinical trials. Of note, one patient chronically taking acetaminophen died from acute hepatic failure.

Reports of cutaneous reactions, characterized as exanthematous pustulosis, have been noted in CML and gastrointestinal stromal tumors (GIST) trials. These reactions appear to be dose-related.

Hematologic Toxicity

Neutropenia and thrombocytopenia was noted in the treatment of CML. These cytopenias appear to be dose-related, especially with doses ≥ 750mg. Grade 3 / 4 effects were noted to be more frequent in blast crisis and accelerated phase than compared to chronic phase CML. Episodes of neutropenia noted in clinical trials lasted approximately 2-3 weeks, whereas the duration of thrombocytopenia ranged from 3-4 weeks.

Table 4. Adverse Events

Effect	All grades (%)	Grades 3 / 4 (%)**
Nausea	55-68	2-5
Fluid retention	51-68	2-10
Muscle cramps	34-46	0.4-0.9
Diarrhea	33-49	0.9-4
Vomiting	28-54	0.9-3
Neutropenia		8-46
Thrombocytopenia		12-31
Anemia		4-40

** See Appendix A for grade definitions.

Precautions/Contraindications

Fluid Retention and Edema:

Fluid retention and edema are potential complications of imatinib therapy. Severe fluid retention, such as pleural effusion, ascites, pulmonary edema, has been reported to occur in 1-2% of patients. The risk of edema has been noted to be greater in patients on higher imatinib doses and age > 65 years. Management involves regular monitoring for signs and symptoms of fluid retention.

Gastrointestinal Irritation:

Stomach upset may be associated with imatinib therapy. To prevent stomach upset, imatinib doses should be taken with food and a glass of water.

Hematologic Toxicity:

Neutropenia and/or thrombocytopenia have been associated with imatinib therapy. Monitoring of complete blood counts should be performed weekly for the first month of therapy; biweekly for the second month and then periodically thereafter (eg. every 2-3 months). Hematologic toxicity has been found to be more frequent among patients in accelerated phase or blast crisis, than in those in chronic phase of CML.

Hepatotoxicity:

Hepatotoxicity has been associated with imatinib therapy. Elevations of liver function tests (LFT's), including transaminases, bilirubin and alkaline phosphatase have been managed with dose reduction or interruption of therapy. It is recommended that baseline liver function tests be performed prior to initiation of imatinib. In addition, LFT's should be monitored monthly or as clinically indicated. Patients with preexisting hepatic impairment should be closely monitored during imatinib therapy as their risk of hepatotoxicity may be increased.

Toxicities from Long-Term Use:

The effects of imatinib therapy on a long-term basis are unknown in humans. Animal research suggests that liver and kidney toxicity and immunosuppression are potential complications of long-term use of imatinib.

Drug Interactions

Imatinib is primarily metabolized by CYP3A4. Other isoenzymes, 1A2, 2D6, 2C9 and 2C19, play a minor role in imatinib metabolism. Due to the metabolic pathway, several drug interactions are possible. The following are examples of drugs that may affect imatinib concentrations:

> Enzymatic inhibitors of CYP3A4, such as ketoconazole, erythromycin, itraconazole and clarithromycin, may increase imatinib plasma concentrations.
>
> Drugs that are enzyme inducers of CYP3A4, such as phenytoin, carbamazepine and phenobarbital, may reduce imatinib plasma concentrations.

Imatinib may affect the metabolic pathway of other drugs. The following are examples of drugs that may have their plasma concentrations altered by imatinib:

> Enzyme inhibition of CYP3A4 by imatinib is thought to be the mechanism responsible for the increase in C_{max} and AUC of simvastatin. Because of this mechanism, caution should be exercised when co-administering medications that are substrates of CYP3A4 and have a narrow therapeutic window, such as cyclosporine.
>
> Warfarin is a substrate of CYP2C9. Therefore, it is recommended that patients who require anticoagulation be managed with a low molecular weight heparin or standard heparin.

Response Criteria

The efficacy of imatinib has been based upon both hematologic and cytogenetic response criteria.

In chronic phase CML, a hematologic response was defined as a 50% reduction in WBC counts from baseline sustained for at least 2 weeks. A Complete Hematologic Response (CHR) was defined as WBC < 10,000 per mm^3 and platelet count < 450,000 per mm^3 maintained for at least 4 weeks.

Cytogenetic responses (CR) were defined in terms of percentage of cells in metaphase existing within the bone marrow that were Philadelphia (Ph) chromosome positive. These responses were based upon a sample size of twenty cells in metaphase. A Complete Cytogenetic Response (CCR) was defined as no Ph(+) cells. A partial CR was defined as $\leq$ 35% cells that were Ph(+). A minor CR was defined as 35-65% cells that were Ph(+). A lack of CR was identified when >65% cells were Ph(+). A major cytogenetic response (MCR) is comprised of complete and partial responses.

In blast crisis CML, a hematologic response is defined as a decrease in bone marrow blast count $\leq$ 5%, the disappearance of blasts in the peripheral blood, an absolute neutrophil count > 1000 cells/mm^3 and platelet count > 100,000 cells/mm^3. Patients who did not meet the criteria for a complete hematologic response may be categorized according to marrow response. A marrow response is defined as either a decrease in the blast count $\leq$ 5% or between 5-15% regardless of peripheral blood cell counts.

Disease progression is defined as an increase in marrow blasts > 15%, increase in peripheral blood blasts > 5% or WBC > 20,000 cells/mm^3. A relapse is defined as evidence of disease progression or death.

Clinical Trials

Citation	Efficacy and safety of a specific inhibitor of bcr-abl tyrosine kinase in CML Druker BJ, et al. NEJM 2001; 344(14): 1031-1037.
Study Goals	The primary endpoint was to determine the safety and tolerability of imatinib. A secondary endpoint was to determine antileukemic activity.
Methods	**Design:** Phase I, dose-escalating, open-label trial Patients were assigned successively to one of 14 cohorts. Cohort dosing ranged from 25-1000 mg/day. Doses were given once daily except for 800 and 1000 mg doses. These doses were divided into a twice-daily regimen.
Criteria	**Inclusion:** CML in chronic phase; age ≥ 18 years; Philadelphia chromosome (+), failed interferon-alfa therapy Time between most recent therapy and start of STI571: hydroxyurea – one week, interferon alfa and cytarabine – 2 weeks, busulfan – 6 weeks. **Exclusion:** platelet count < 100,000 cells/mm3; inadequate renal, hepatic, cardiac function and performance status
Results	N = 83 patients June 1998 – May 2000 **Safety profile** Most common adverse effects (A/E): nausea (43%), myalgias (41%), edema (39%), diarrhea (25%) All were considered to be grade 1 or 2 (mild or moderate). 5% grade 3 anemia (all doses ranged from 600-1000mg) 16% grade 3 thrombocytopenia 14% grade 3 neutropenia **Hematologic response** Doses ≥ 140mg/day - all patients had a hematologic response Doses ≥ 300mg/day – 98% (53/54) had complete hematologic responses (CHR) CHR duration – median 265 days (range, 17-468) Response onset – typically within 2 weeks of treatment initiation **Cytogenetic response** Doses ≥ 300mg/day – 54% (29/54) had major or minor response 31% (17/54) had major cytogenetic response 13% (7/17) had complete cytogenetic response Response onset – varied between 2-10 months after treatment initiation Median time to best response was 148 days (range, 48-331)
Conclusions	Rate of CHR increased as daily dose increased from 85-300mg. CHR typically occurred within 4 weeks after treatment initiation. Overall, adverse effects were mild. A dose-response relationship was noted with higher doses (≥ 400mg/day). STI571 has significant activity with patients who have failed interferon therapy.

Citation	Hematologic, Cytogenetic and Molecular Response to Glivec® in Chronic Phase Ph+ Chronic Myeloid Leukemia (CML) Patients Who Failed IFNα or Did Not Tolerate IFNα: A Prospective Study of the Italian Cooperative Study Group on CML. Rosti G, Alberti D, DeVivo A, et al. Blood 2001; 98(11): 138a. Abstract 581.
Study Goals	To evaluate the efficacy of Glivec for the treatment of chronic phase CML in patients who did not respond or tolerate interferon.
Methods	**Design**: multicenter trial Patients who were hematologically or cytogenetically resistant, or intolerable of interferon were initially started on Glivec 400mg daily. Doses were escalated to 600mg daily if patients did not achieve either a hematologic or cytogenetic response.
Criteria	**Inclusion**: Patients with chronic phase Ph+ CML who were either intolerant or did not respond to interferon therapy.
Results	N = 194 Follow-up > 6 months **Prior interferon therapy** Median 41; range 3-100 months 17%(34 pts) – hematologic resistance 52% (102 pts) – cytogenetic resistance 31% (58 pts) - intolerant **Hematologic response** 93% CHR (89% at 2 months) **Cytogenetic response** 36% at 3 months (major cytogenetic response: Ph+ < 33%) 14% complete cytogenetic response (CCR) 44% at 6 months (major cytogenetic response: Ph+ < 33%) 28% complete cytogenetic response (CCR) **Safety profile** 15 severe adverse events reported: 6 hematologic toxicities 4 hemorrhagic complications 2 fever 3 other
Conclusions	Data collection ongoing. Thus far, results are consistent with Druker et al, NEJM 2001; 344: 1031-1037.

Citation	Activity of a Specific Inhibitor of the BCR-ABL Tyrosine Kinase in the Blast Crisis of Chronic Myeloid Leukemia (CML) and Acute Lymphoblastic Leukemia (ALL) with the Philadelphia Chromosome. Druker BJ, Sawyers CL, Kantarjian H, et al. NEJM 2001; 344(14): 1038-1042.
Study Goals	To evaluate the antileukemic effects and safety profile of STI571 in CML blast crisis and Philadelphia chromosome positive ALL.
Methods	**Design:** Pilot, dose-escalation trial Patients were assigned successively to cohorts of varying doses ranging from 300-1000mg. Doses were given once daily except for the 800 and 1000mg doses. These doses were divided evenly into twice daily dosing.
Criteria	**Inclusion:** CML diagnosis; Ph (+); age ≥ 18 years; blast crisis defined as ≥ 30% blasts in periphery or bone marrow, irrespective of prior therapy Or ALL diagnosis; Ph (+); failed or relapsed on standard induction or consolidation; Adequate renal, liver, cardiac function and performance status required. STI571 treatment was not started until at least 24 hours after treatment with hydroxyurea and ≥ 4 weeks after treatment with standard induction or consolidation therapy ended.
Results	N = 58 patients April 1999 – March 2000 **Safety profile** Most frequent A/E: nausea (55%), vomiting (41%), edema (41%) All were considered to be grade 1 or 2 (mild or moderate) and were dose-related. 40% grade 4 neutropenia 33% grade 3 thrombocytopenia 14% grade 3 or 4 increase in liver transaminases (LFT's) Elevations in LFT's noted a median of 16 days after treatment initiation (range, 7-194) **Myeloid blast crisis** 55% overall response rate (ORR) 10% (4/38) complete hematologic remission (CHR) 45% (17/38) major response (MR) 43% (9/21) relapsed a median of 84 days (range, 42-194) **Lymphoid blast crisis** 70% ORR 20% (4/20) CHR 50% (10/20) MR 86% (12/14) relapsed a median of 58 days (range, 42-123) **Major cytogenetic response** 12% (7/58) ORR 71% (5/7) complete response (CR) 29% (2/7) partial response (PR) defined as < 35% Ph+ cells Reduction in peripheral blasts occurred within one week after treatment initiation.
Conclusions	Therapy with STI571 was well tolerated. Bone marrow suppression was greater among patients in blast crises than compared to patients in chronic phase. Adverse effects were dose-related. Rapid response to therapy noted.

Citation	A Phase II Study of STI 571 in Adult Patients with Philadelphia Chromosome Positive Chronic Myeloid Leukemia in Accelerated Phase. Talpaz M, Silver RT, Druker B, et al. Blood 2000; 96(11, pt1): 469a. Abstract 2021.
Study Goals	To determine the rate of hematologic response in patients with accelerated phase CML. Secondary endpoints include: safety, tolerability of STI571, duration of hematologic response, overall survival, cytogenetic response
Methods	**Design:** Phase II, multicenter trial Patients were given STI571 on an outpatient basis. Initially, the dose was 400mg/day (30% of patients). Subsequently, the initial dose was increased to 600mg/day (70%).
Criteria	**Inclusion:** Patients with accelerated phase CML defined as at least one of the following: ≥ 15% but < 30% blasts in peripheral blood or bone marrow; or ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow; or basophils ≥ 20% in peripheral blood; or thrombocytopenia < 100,000 cells not related to therapy
Results	N = 234 August 1999 – March 2000 **Hematologic response** Data is based on 154 patients who completed 4 wks of therapy 78% (120/154) at 4 weeks 18% (22/120) complete response (CR) defined as <5% blasts in bone marrow without circulating blasts in periphery **Safety profile** Most common A/E: Nausea, vomiting, muscle cramps, edema, diarrhea, headache 40% grade 3 and 4 neutropenia 18% grade 3 and 4 thrombocytopenia One death due to liver failure from a possible drug interaction between STI 571 and chronic acetaminophen therapy.
Conclusions	Data collection ongoing. Results will be presented after 15-month follow-up.

Citation	Hematologic, Cytogenetic and Molecular Response to Glivec in Ph+ Chronic Myeloid Leukemia in Accelerated and Blastic Phase: A Prospective Study of the Italian Cooperative Study Group on CML. Rose G, Alberti D, DeVivo A, et al. Blood 2001; 98(11): 138a. Abstract 582.
Study Goals	To evaluate the efficacy of Glivec in patients with Ph+ CML who are in either accelerated or blast phases.
Methods	**Design**: multicenter trial Patients initially received Glivec 600mg daily, then escalated to 800mg (400mg bid) if no response to the lower dose.
Criteria	**Inclusion:** CML diagnosis; Ph (+); age ≥ 18 years Patients with accelerated phase CML defined as at least one of the following: ≥ 15% but < 30% blasts in peripheral blood or bone marrow; or ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow; or basophils ≥ 20% in peripheral blood; or thrombocytopenia < 100,000 cells not related to therapy Blast crisis defined as ≥ 30% blasts in periphery or bone marrow, irrespective of prior therapy
Results	N = 140 75 accelerated phase (disease duration 2-207 mos, median 66 mos) 65 blastic phase (disease duration 2-209 mos, median 42 mos) Follow up of 3-6 months **Hematologic response** Accelerated phase 93% at 1 month (complete 21%) 86% at 3 months (complete 30%) Blastic phase 56% at 1 month (complete 10%) 46% at 3 months (complete 7%) **Cytogenetic response** Accelerated phase – major cytogenetic response (Ph+ <33%) 10% at 3 and 6 months (complete 7%) Blastic phase - major cytogenetic response (Ph+ <33%) 5% at 3 and 6 months 20/65 (31%) died 10/65 (15%) stopped treatment **Safety profile** Accelerated phase 14/75 cases categorized as severe Blastic phase 29/65 cases categorized as severe
Conclusions	Glivec is effective in both accelerated and blastic phases. Treatment was well tolerated. The majority of adverse events are being attributed to the primary disease.

Gastrointestinal Stromal Tumors

Gastrointestinal Stromal Tumors (GIST) are rare tumors arising from mesenchymal cells of the gastrointestinal tract. If discovered early, resection of disease can be curative. Since most patients are asymptomatic with early-stage disease, the diagnosis is often made during advanced stages of disease. At this time, the disease is typically unresponsive to chemotherapy leaving no effective treatment for advanced or metastatic disease.

GIST cells express c-KIT, which is a growth factor receptor that has tyrosine kinase activity. Mutations of c-kit (resulting in continual tyrosine kinase activity) cause ligand-independent tyrosine kinase activity, autophosphorylation, cell proliferation, and activation of downstream signaling pathways. It is thought that imatinib may affect the growth of tumor cells in metastatic GIST via tyrosine kinase inhibition. Please note that the following data is from case report and abstract format.

Citation	STI571, an Active Drug in Metastatic Gastrointestinal Stromal Tumors (GIST), an EORTC Phase I Study. Van Oosterom AT, Judson I, Verweij J, et al. *Proc Annu Meet Am Soc Clin Oncol* 2001; 20. Abstract 2.
Study Goals	To determine the activity of STI571 in metastatic GIST.
Methods	**Design**: Phase I Patients received either STI571 400mg PO daily (n=8) or 300mg PO bid (n=8) or 400mg PO bid (n=4).
Criteria	**Inclusion:** Patients with metastatic GIST and other soft tissue sarcoma subtypes (STS); prior chemotherapy permitted
Results	N = 20 (17 GIST; 3 STS) 80% (16) received prior chemotherapy August 2000 – November 2000 **Safety profile** Toxicity infrequent; considered mild to moderate Included nausea, upper abdominal discomfort, diarrhea, LFT abnormalities, rash, per-orbital edema. Grade 3 reversible rash noted at 300mg bid Grade 4 neutropenic fever noted at 400mg bid Tumor bleeding noted in 3 cases. **Efficacy profile** 4 patients PD (3 with other soft tissue sarcomas – not GIST) 4 patients PR (defined by Response Evaluation Criteria in Solid Tumors) 8 patients SD (tumor size decreased; symptomatic improvement) 3 patients too soon to evaluate at time of publication 1 patient discontinued drug for non-drug-related reason

PD – Progressive Disease; PR – Partial Response; SD – Stable Disease

Citation	Evaluation of the Safety and Efficacy of an Oral Molecularly-Targeted Therapy, STI571, in Patients with Unresectable or Metastatic Gastrointestinal Stromal Tumors (GISTS) Expressing C-KIT (CD117). Blanke CD, von Mehren M, Joensuu H, et al. *Proc Annu Meet Am Soc Clin Oncol.* 2001; 20. Abstract 1.
Study Goals	Evaluate safety and efficacy of STI571 in GIST.
Methods	**Design**: Phase II Patients were randomized to 400mg or 600mg daily oral dose. Those progressing on 400mg were escalated to 600mg.
Criteria	**Inclusion**: Unresectable, metastatic GIST, immunohistochemical documentation of C-kit expression, measurable disease, performance status 0-2, absence of severe liver disease
Results	N = 36 patients (35 evaluable) July 2000 – September 2000 **Safety profile** 26% (9) grade 3 / 4 toxicites included hemorrhage, abdominal pain, abnormal electrolytes **Efficacy profile** (assessment at 1-3 months) 54% (19) PR 34% (12) SD 11% (4) PD 89% of symptomatic patients noted marked clinical improvement Of note, no patient has progressed once achieving an objective response.

PD – Progressive Disease; PR – Partial Response; SD – Stable Disease

Citation	Effect of the Tyrosine Kinase Inhibitor, STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor. Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. New England Journal of Medicine 2001; 344(14): 1052-1056.
Study Goals	To determine the effect of STI571 in a patient with metastatic GIST who has failed numerous treatments.
Methods	**Design**: case report of one patient (50 year old female) Patient was treated with STI571 400mg daily.
Criteria	GIST confirmed as CD117 positive. Prior therapy included surgery, chemotherapy (mesna, doxorubicin, ifosfamide, dacarbazine), thalidomide and interferon alfa.
Results	**Efficacy profile** MRI: Tumor size reduced from 112.5cm^2 to 28cm^2 (52% reduction) over an 8-month period. PET: Scan obtained one month after therapy initiation revealed no abnormal uptake in either liver or kidney. Histology: Decreased density of tumor cells; no indication of inflammation. Endothelial cells were normal. Response has continued $\geq$ 11 months. **Safety profile** Well tolerated; mild, transient nausea noted Grade 1 toxicities included increased frequency of bowel movements, muscle cramps, and ankle edema.

Acquisition Costs and Comparisons

Drug	Dose	Cost/Day/Patient ($)	Cost/Year/Patient ($)
imatinib (Gleevec)	400mg PO qd	$47.60/day	$17,136.00/year
imatinib (Gleevec)	600mg PO qd	$71.40/day	$25,704.00/year
imatinib (Gleevec)	800mg PO qd	$95.20/day	$34,272.00/year
Drugs for comparison			
interferon alfa -2a	9 MU SQ qd	$35.35/day	$12,902.75/year

Conclusions

Imatinib works via tyrosine kinase inhibition, a novel mechanism for the treatment of CML and GIST. Treatment options available to patients with CML until this time included chemotherapy, interferon and stem cell transplantation. Stem cell transplant has been the only therapy to induce a durable remission (i.e. a complete cytogenetic response) in those patients with chronic phase CML. Interferon has produced cytogenetic responses in 10-20% and prolongs survival, especially when added to cytarabine therapy. Both hematologic and cytogenetic responses have been shown to occur with imatinib therapy albeit in limited published data. Updated response data indicate overall hematologic responses of 93%(CHR), 68%(CHR 37%, NEL 12%, return to chronic phase 20%), and 29%(CHR 7%, NEL 5%, return to chronic phase 19%) in chronic, accelerated, and blast phases, respectively. Major cytogenetic responses occur in 61% (53% confirmed with 2nd bone marrow biopsy), 25% (19% confirmed), and 15% (1.5% confirmed) of chronic, accelerated, and blast phases, respectively. There is not yet sufficient data on the durability of those responses or the impact on survival. The ease of treatment with an oral formulation coupled with a manageable adverse event profile as well as potential hematologic and cytogenetic response rates make imatinib an attractive therapeutic alternative. The cost of imatinib is significantly higher than other treatment options; when compared to interferon, the cost for imatinib is anywhere from 1.3 to 2.6 times more expensive. However, these figures do not include the cost for needles, syringes, patient teaching, follow-up calls, and monitoring needed for patients on subcutaneous interferon due to the dosage form and adverse effect profile. Imatinib will have a much smaller effect on a patient's quality of life, and with a higher response rate may turn out to be the most cost effective drug.

Although currently in progress, there is no data from randomized trials comparing imatinib to other therapeutic options in chronic phase CML. Because of this and the greater cost of imatinib, its use should be restricted to those patients in chronic phase CML who have failed interferon therapy. Imatinib should be offered as first-line therapy to patients in either accelerated or blastic phase CML. Because of the activity in accelerated phase and blast crisis, imatinib may be useful as a bridge therapy to induce partial responses prior to transplant. Also, there is some data recently presented at the American Society of Hematology meeting looking at using imatinib as first line therapy in CML, although the data is too new to draw meaningful conclusions at this time.

Finally, limited data has shown that imatinib is active in GIST and refractory Ph+ ALL, where treatment options become limited in these conditions with poor prognoses.

Recommendations

Add imatinib to the formulary.
Restrict prescribing privileges to the hematology/oncology attending physicians.
Restrict imatinib to patients who meet the following criteria:

1. Patients with Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML) in chronic phase who have failed interferon therapy with appropriate doses, due to lack of response* or due to severe intolerance**that resulted in discontinuation of interferon therapy; or patients who are poor candidates for interferon therapy due to poor performance or the inability to manage self-injections.***

   *Lack of response to interferon is defined as one of the following:
   - lack of complete hematologic response following three months of treatment
   - lack of a cytogenetic response following one year of treatment
   - hematologic or cytogenetic relapse following treatment

   Strength of Recommendation: A
   Quality of Evidence: II-2

2. Patients with Ph $^{+}$ CML in accelerated phase or blast phase.

   Strength of Recommendation: B
   Quality of Evidence: II-2

3. Patients with refractory or relapsed Ph+ Acute Lymphoblastic Leukemia.
   Strength of Recommendation: B
   Quality of Evidence: II-2

4. Patients diagnosed with advanced gastrointestinal stromal tumor (GIST) confirmed as CD117 positive via immunohistochemical staining.

   Strength of Recommendation: B
   Quality of Evidence: III

** Intolerance as defined as $\geq$ Grade 3 non-hematologic interferon-related toxicity persisting for $\geq$ one month.
*** Patient response to imatinib (hematologic and cytogenetic) should be documented at 6 months and 1 year following initiation to support continuation of therapy.

**Strength of Recommendation

A:	There is good evidence to support that the intervention be adopted.
B:	There is fair evidence to support that the intervention be adopted.
C:	There is insufficient evidence to recommend for or against the intervention, but recommendations may be made on other grounds.
D:	There is fair evidence to support that the intervention be excluded.
E:	There is good evidence to support that the intervention be excluded.

Quality of Evidence

I:	Evidence obtained from at least one properly randomized controlled trial.
II-1:	Evidence obtained from well-designed controlled trials without randomization.
II-2:	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3:	Evidence obtained from multiple time series studies with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.
III:	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

Appendix A

Common Toxicity Criteria		
Effect	**Grade 3**	**Grade 4**
Nausea	No significant intake, requires IV fluids	**
Fluid retention *		
Ascites	Symptomatic, requiring therapeutic paracentesis	Life-threatening physiologic consequences
Pleural effusion	Symptomatic, requiring O_2 or therapeutic thoracentesis	Life-threatening (eg. Requiring intubation)
Pericardial effusion	Physiologic consequences resulting from symptoms	Tamponade (drainage or pericardial window required)
Muscle cramps	Severe pain: pain or analgesics severely interfering with activities of daily living	Disabling
Diarrhea	Increase of > 7 stools/day or incontinence; or need for parenteral support for dehydration	Physiologic consequences requiring intensive care; or hemodynamic collapse
Vomiting	$\geq$ 6 episodes in 24 hours over pretreatment; or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Neutropenia	$\geq$ 0.5- <1.0 x 10^9 /L ANC $\geq$ 500 - <1000/mm^3	< 0.5 x 10^9 /L <500/mm^3
Thrombocytopenia	$\geq$ 10.0 - <50.0 x 10^9 /L	<10.0 x 10^9 /L
Anemia	$\geq$ 65 – 80 g/L	< 65 g/L

***** Fluid retention events include pleural effusion, ascites, pulmonary edema, pericardial effusion, anasarca, edema aggravated and fluid retention not otherwise specified.

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National PBM Drug Monograph

Imatinib Mesylate (Gleevec™)

Addendum April 2003

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

http://www.vapbm.org/monograph/imatinibcmonograph.pdf

Introduction

Imatinib is a potent inhibitor of tyrosine kinases associated with the abnormal BCR-ABL gene fusion product. The BCR-ABL gene is the result of a translocation of t(9,22), also known as the Philadelphia chromosome (Ph), and is found in more than 90% of patients diagnosed with chronic myelogenous leukemia (CML). Previously, imatinib has demonstrated the ability to induce complete hematologic responses and major cytogenetic responses in patients who had failed to respond to interferon and cytarabine during the chronic phase of CML. Recently, a phase 3 trial comparing imatinib to interferon and cytarabine in newly diagnosed, untreated patients with CML in chronic phase was completed.

Study goals

The primary endpoint was progression, defined as: death from any cause during treatment, development of accelerated-phase CML or blast phase, loss of hematologic response, loss of major cytogenetic response, or an increasing white blood cell count.

Secondary endpoints: rate of complete hematologic response, rate of major cytogenetic response, safety, and tolerability.

Methods

In a prospective, phase 3, multi-centered, randomized trial patients received either interferon and cytarabine or imatinib.

Interferon: Gradually escalating SQ doses to the target of 5 million units/m^2 per day (if toxicities were <grade 3).
Cytarabine: SQ doses of 20mg/m^2 (maximum dose of 40mg) for 10 days each month when maximally tolerated dose of interferon was achieved.

Imatinib: 400mg orally every day.

N.B. Hydroxyurea was allowed for both arms during the first six months to help keep white blood cell counts <20,000/mm^3

Dose Modifications

Imatinib: If no complete hematologic response by 3 months or at least a minor cytogenetic response at 12 months, increase dose to 400mg bid.

Cytarabine: If receiving the maximally tolerated interferon dose, and no complete hematologic response at 3 months or at least a minor cytogenetic response at 12 months, increase up to 40mg/day for 15 days each month.

Crossover

Patients were allowed to crossover if: there was no response, a loss of response, an increase in the white blood cell count, or could not tolerate therapy (recurrence of nonhematologic toxicity of at least a grade 3 despite dose reductions and symptom management).

Data Analysis

The primary endpoint was analyzed by an intention-to-treat analysis; all other parameters were analyzed only until patients crossed over or discontinued therapy.

Criteria

Inclusion:

- 18-70 years old
- chronic-phase, PH-positive CML
- previously untreated except for hydroxyurea or anagrelide
- liver aminotransferases, serum bilirubin, serum creatinine no higher than 1.5 times ULN

Exclusion:

- extramedullary disease other than hepatosplenomegaly
- <100,000 platelets unrelated to therapy
- women who were breast feeding, pregnant, or of childbearing potential without a negative pregnancy test
- ECOG performance status of 3 or more
- Other uncontrolled serious medical conditions
- Prior chemotherapy or any investigational drug
- Prior hematopoietic stem cell transplant
- Surgery within the past 4 weeks
- HIV positive
- History of another cancer within 5 years

Results

Table 1. Baseline Criteria

Characteristic	Imatinib (n = 553)	Interferon plus cytarabine (n = 553)
Age- median	50	51
Sex (%)		
Male	61.7	56.1
Female	38.3	43.9
ECOG performance status (%)		
0	76.9	74
1	20.8	21.9
2	1.4	2.0
missing	0.9	2.2
Interval since diagnosis (mo)		
Median	2.1	1.8
Chromosomal abnormalities in addition to Ph (%)		
No	82.5	88.2
Yes	12.1	7.6
Splenomegaly (%)	23.0	27.1
WBC $x10^{-3}/mm^3$		
Median	17.9	20.2
Platelet count $x10^{-3}/mm^3$		
Median	336	340

Table 2. Treatment Status[†]

Variable	Imatinib	Interferon plus cytarabine
Continued initial treatment (%)	85.7	10.8
Discontinued initial treatment	12.3	31.6
Disease Progression (no. of pts)	18	29
Adverse events	12	33
Proceed to allogeneic transplant	8	7
Withdrew consent	12	75
Crossed over to alternative arm (%)	2	57.5
Disease Progression (No. of pts)	6	63
Intolerance of treatment	4	136
No CHR at 6 mo	0	41

No CHR or MCR at 12 ms	1	53
Continued alternative treatment (No.)	6	284
Discontinued alternative treatment	5	34

† Median follow-up of 19 months

Table 3. Observed Hematologic and Cytogenetic Responses

Response	Initial Treatment		Crossover Treatment	
	Imatinib (n=553)	IFN + cytarabine (n=553)	From Imatinib to IFN + cytarabine (n=11)	From IFN + cytarabine To imatinib (n=318)
Complete hematologic	95.3 (93.2-96.9)	55.5 (51.3-59.7)†	27.3 (6.0-61.0)	82.4 (77.7-86.4)
Major cytogenetic	85.2 (81.9-88.0)	22.1 (18.7-25.8)†	0 (0-28.5)	55.7 (50.0-61.2)
Complete	73.8 (69.9-77.4)	8.5 (6.3-11.1)†	0 (0-28.5)	39.6 (34.2-45.2)
Partial	11.4 (8.9-14.3)	13.6 (10.8-16.7)	0 (0-28.5)	16.0 (12.2-20.5)

†p<0.001 for comparison to imatinib group

Table 4. Disease Progression and Survival

Outcome	Imatinib	Interferon + cytarabine
Progression-Free Survival		
12 months	96.6	79.9†
18 months	92.1	73.5†
Survival Rate		
18 months	97.2	95.1

† p<0.001

Adverse Events

Adverse events were consistent with previous clinical trials. Patients in the imatinib group had primarily grade 1 or 2 events with rare grade 3 or 4 toxicities. Patients in the interferon + cytarabine group had more grade 3 or 4 toxicities consistent with the high number of crossovers to the imatinib arm.

Conclusion/Recommendation

The management of newly diagnosed patients with Chronic Myelogenous Leukemia has changed. Until this time, the gold standard for treatment has been the combination regimen of cytarabine and interferon. Recent data from a Phase III trial comparing imatinib vs. cytarabine and interferon has shown superior outcomes with imatinib therapy. These outcomes include cytogenetic response, hematologic response, tolerability and freedom from progression to advanced phases of CML. Based on this data, imatinib should be considered first-line therapy for CML.

Allogeneic stem cell transplantation, a procedure with significant morbidity and mortality, is still considered the only curative treatment. For this reason, patients who may be potential candidates for transplant should be offered this option due to the potential for imatinib-failure or loss of response. The durability of response with imatinib is unknown at this time, but maturity of this data and others will provide insight on this issue.

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