Criteria for Use of Imatinib Mesylate (Gleevec®)

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

These criteria were based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. These guidelines are intended to assist practitioners in providing consistent, high quality, cost effective drug therapy. They are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.

Introduction

Imatinib mesylate (Gleevec®) is a new class of drug called a protein tyrosine kinase inhibitor. Protein tyrosine kinases are a group of glycoproteins that are found on cell membranes (receptor tyrosine kinases) and in the cell cytoplasm (nonreceptor tyrosine kinases). Binding of their ligands activates protein tyrosine kinases and they transmit signals from the cytoplasm via phosphorylation of tyrosine on substrates and on downstream signaling proteins. Chronic Myelogenous Leukemia (CML) is a myeloproliferative disease with clonal proliferation and accumulation of myeloid cells. The Philadelphia chromosome abnormality (Ph+), present in greater than 95% of patients with CML, produces the abnormal gene bcr-abl. Imatinib inhibits the phosphorylation of substrate for the bcr-abl protein, as well as the receptor tyrosine kinases platelet-derived growth factor (PDGF) and c-Kit. C-Kit has been identified in cells from gastrointestinal stromal tumors (GIST).

1. Imatinib mesylate was approved in May of 2001 as the first tyrosine kinase inhibitor with approved indications for any phase of CML after failure of interferon therapy.

   Criteria for VA Use- Restricted to Hematology/Oncology Attending Physicians

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

   ** Intolerance as defined as ≥ Grade 3 non-hematologic interferon-related toxicity persisting for ≥ 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.

   OR

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

   OR

3. Patients with refractory or relapsed Ph^+ Acute Lymphoblastic Leukemia.

   OR

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

2 Dosing.

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 hematologic response.

Dose Increases:

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.

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**

3. Safety

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.. 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). Episodes of neutropenia noted in clinical trials lasted approximately 2-3 weeks, whereas the duration of thrombocytopenia ranged from 3-4 weeks.

Drug Interactions
Imatinib is metabolized by CYP3A4 and has many potential (but undocumented) drug interactions. Drugs that induce CYP3A4 (phenytoin, carbamazepine, Phenobarbital) may reduce imatinib plasma concentrations

Drugs that inhibit CYP3A4 (ketoconazole, erythromycin, intraconazole, etc) may increase imatinib plasma concentrations.

Imatinib decreases the C_{max} and AUC of simvastatin, probably by enzyme inhibition.

Warfarin is a substrate of CYP2C9 and caution is warranted for combined therapy with imatinib. The manufacturer suggests switching patients to a low molecular weight heparin product.

4. Summary of trials

CML chronic phase

- Phase I and Phase II trial in Ph+ patients who failed or didn't tolerate interferon
- Phase I- 83 patients Phase II- 184 patients
- Complete hematologic response in 93-98% at doses >300mg/day
- Complete cytogenetic response in 13-28%
- Toxicity primarily grade 1 &2 except hematologic toxicity was grade3
- Dose escalation in Phase I trial up to 1000mg/day
- Consistent results in both the Phase I and II trials; however data collection is ongoing

CML accelerated phase and blast crisis plus Ph+ ALL

- One pilot/dose escalation study and 2 Phase II multicenter studies (abstract only)
- 58 patients in dose escalation study (20 had ALL or lymphoid crisis), 374 patients in Phase II studies
- Complete hematologic response in 10-18% ; up to 78% had some decrease in counts
- Complete + major cytogenetic responses in 5-12%
- Toxicity included grade 1 & 2 non-hematologic events and 33-44% grade 3 or 4 hematologic toxicity
- Therapy was well tolerated; rapid responses (4 weeks) were common; more durable responses in myeloid crisis but no comparisons made to accelerated phase vs crisis
- Follow-up was very short <6 months and data is still being collected

Gastrointestinal Stromal Tumors

- Phase I and Phase II in abstract form only, 1 published case report
- Total of 56 patients
- Efficacy: decrease in tumor size on MRI or PET scans, decreased density of tumor cells when biopsied, 60-80% reported improvement of symptoms
- Toxicity was mostly mild (grade 1&2); some grade 3 or 4 hematologic and dermatologic toxicity
- Data collection is ongoing with relatively short follow-up
- Dose range from 400-800mg/day

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 to $\leq$ 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 to $\leq$ 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.

References

Blanke CD, von Mehren M, Joensuu H, et al. 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). *Proc Annu Meet Am Soc Clin Oncol.* 2001; 20. Abstract 1.

Druker BJ, Sawyers CL, Kantarjian H, et al. 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. New England Journal of Medicine 2001; 344(14): 1038-1042.

Druker BJ, et al. Efficacy and safety of a specific inhibitor of bcr-abl tyrosine kinase in CML NEJM 2001; 344: 1031-1037.

Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the Tyrosine Kinase Inhibitor, STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor. New England Journal of Medicine 2001; 344(14): 1052-1056.

Mahon FX, Faberes C, Pueyo S, et al. Response at Three Months is a Good Predictive Factor for Newly Diagnosed Chronic Myeloid Leukemia Patients Treated by Recombinant Interferon-α. Blood 1998; 11(December 1): 4059-4065.

O'Brien SG, Peng B, Dutreix C, et al. A Pharmacokinetic Interaction of Glivec and Simvastatin, a Cytochrome 3A4 Substrate, in Patients with Chronic Myeloid Leukemia. Blood 2001; 98(11, pt1): 141a. Abstract 593.

Rosti G, Alberti D, DeVivo A, et al. 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. Blood 2001; 98(11): 138a. Abstract 581.

Rosti G, Alberti D, DeVivo A, et al. 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. Blood 2001; 98(11): 138a. Abstract 582.

Talpaz M, Silver RT, Druker B, et al. A Phase II Study of STI 571 in Adult Patients with Philadelphia Chromosome Positive Chronic Myeloid Leukemia in Accelerated Phase. Blood 2000; 96(11, pt1): 469a. Abstract 2021.

Van Oosterom AT, Judson I, Verweij J, et al. STI571, an Active Drug in Metastatic Gastrointestinal Stromal Tumors (GIST), an EORTC Phase I Study. *Proc Annu Meet Am Soc Clin Oncol* 2001; 20. Abstract 2.