Criteria for Use of Imatinib Mesylate (Gleevec®)

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.

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). 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.

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

1. Chronic Phase, Interferon failures

   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.***

   * 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.

   OR

2. Newly diagnosed Ph+ CML, in chronic phase***

   *** Patient response to imatinib (hematologic and cytogenetic) should be documented at 6 months and 1 year following initiation to support continuation of therapy.

   OR

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

   OR

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

   OR

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

2 Dosing.

Indication	Imatinib Mesylate
CML: Chronic Phase	**400 mg once daily with meal**
CML: Accelerated Phase	**600 mg once daily with meal**
CML: Blast Crisis	**600 mg once daily with meal**
GIST	**400 mg or 600mg 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, lack of cytogenetic response at 12 months, loss of cytogenetic response.

Dose Increases:

Initial Dose	Imatinib Mesylate
400mg per day	**600 mg once daily with meal**
600mg per day	**400 mg 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

Initial Dose	Hematologic Toxicity	Adjustments
Starting at 400mg in CML Or Starting at 400mg or 600mg in GIST	**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 original dose of 400mg or 600mg 3. If recurrence of toxicity repeat step 1 and resume at reduced dose of 300mg (if started at 400mg) or 400mg (if started at 600mg for GIST)**
Starting at 600mg in Accelerated or Blast Crisis	**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

Chronic Phase Newly Diagnosed

O'Brien et al. 2003 N=1106 Phase III — Imatinib 400mg/d vs Interferon 5 MU/m^2/d + Cytarabine 20mg/m^2/d 10 days/month

Response	Initial Therapy		Crossover	
	Imatinib (N=553)	IFN+cytarabine (N=553)	Imatinib To IFN/cytarabine (N=11)	IFN/cytarabine To Imatinib (N=318)
CHR (%)	95.5	55.5*	27.3	82.4
Major Cytogenetic	85.5	22.1*	0	55.7
CGCR	73.8	8.5*	0	39.6
CGPR	11.4	13.6	0	16.0
PFS				
12 months	96.9	79.9*		
18 months	92.1	73.5*		
OS				
18 months	97.2	95.1		

*P<0.001

Kantarjian et al. 2003 N=50 — Imatinib 400mg/d

Median follow-up of 9 months

Response	Imatinib
CHR	98
Major Cytogenetic Response	90
CGCR	72
CGPR	18

Chronic Phase Interferon Failure

Druker et al. 2001 N=83 Phase I — Imatinib 25-1000mg/d (dose escalation)

Response	Imatinib (doses >300mg/day)
CHR	53/54
Major Cytogenetic Response	31%
CGCR	13%

Kantarjian et al. 2002 N=532 Phase II — Imatinib 400mg/d

Median Duration of Treatment 17.9 months

Response	Imatinib
CHR	95%
Major cytogenetic response	60%
CGCR	41
CGPR	19
PFS at 18 months	89%

Cortes et al. 2003 N=36 Phase II — Imatinib 400mg BID

CHR in 64% at start (interferon intolerance)

Response	Imatinib
CHR	11/11 (with abnormal peripheral counts at start)

	Cytogenetic Response CGCR Major response (CR+PR)	96% (6 with 0% Ph+ at start) 89 90
	BCR-ABL/ABL ratios Median at 3 months Median at 12 months Goal of <0.045%	 0.169 0.026 56%
	Time to progression	All alive in chronic phase with median f/u of 16 months

Kantarjian et al 2003
N=54

Imatinib Dose Escalation for poor Response or relapse on standard Dose
If on 300mg/d → 600mg/d
If on 400mg/d → 800mg/day (400mg BID)

Resistance/relapse Status	CGCR	CGPR
Loss of CGCR or CGPR (N=9)	3	2
Loss of minor CGR (N=4)	2	1
CG resistance (N=21)	1	5
Any CG resistance/relapse (N=34)	6	7

	CHR	PHR	CGCR	CGPR
Hematologic relapse (N=14)	6	4	0	0
Hematologic resistance (N=6)	3	0	0	1

Braziel et al 2002
N=19
(from phase I trial)

Imatinib 400mg/d

Minimum treatment/Follow-up of 14 months

Response	2 months	5 months	8 months	11 months	14 month
CHR	17/19	1/19		1/19	
CGCR		3/19	3/19		
CGPR	1/19		2/19	2/19	1/19

Accelerated Phase

Talpaz et al. 2002
N=235
Phase II

Imatinib 400mg/d (n=62)
600mg/d (n=119)

Median Duration of Treatment: 14 months for 400mg/d and 11 months for 600mg/d

Response	Imatinib
CHR Median duration of CHR 400mg 600mg	34% 13.4 months not yet reached
Major CGR Median time to CGR response 400mg 600mg	24% 2.4 months 2.9 months
Time to Progression 400mg 600mg	 8.8 months not yet reached
Overall survival (median survival not yet reached) Estimated at 12 months: 400mg 600mg	 65% 78%

Blast Crisis/ALL

Druker et al. 2001
N=58
Phase I with
Dose escalation

Imatinib 300-1000mg/d

38 patients with myeloid blast crisis
10 with lymphoid blast crisis
10 with ALL

Response	Myeloid Blast crisis	Lymphoid Blast crisis + ALL
CHR	4/38	4/20
Median duration of therapy	74 days (1-349)	74 days (1-349)
Median duration of response	84 days	58 days

Kantarjian et al. 2002
N=75

Imatinib 300-1000mg/d

65 patients with myeloid blast crisis
10 with lymphoid blast crisis

Response	Total	Myeloid	Lymphoid
CHR	21%	23%	10%

		CHR	21%	23%	10%
		CGCR	6	5	10
		CGPR	3	3	0
		Overall survival		6.5 months	7 months
		Median follow-up 11 months 57 patients died 8 are still on imatinib therapy			
Sawyers et al. 2002 N=260 Phase II Blast Crisis	Imatinib 400mg/d (n=37) 600mg/d (n=223)	Response	Total (n=229)	Previously Untreated (n=148)	Previously Treated (n=81)
		CHR	7.9%	8.8%	6.8%
		CGCR	7.4	8.1	6.2
		CGPR	8.7	7.4	11.1
Ottmann et al. 2002 N=56 Phase II	Imatinib 400mg or 600mg/d	48 patients with ALL 8 patients with lymphoid blast crisis			
		Response	ALL	Lymphoid Blast Crisis	
		CHR	19%	50	
		CGCR	17		
		TTP	2.2 months		
		OS	4.9 months		
GIST Demetri et al. 2002 N=147	Imatinib 400mg/d (n=73) Imatinib 600mg/d (n=74)	Best Response	400mg	600mg	Either
		CR	0	0	0
		PR	36 (49.3%)	43 (58.1%)	79 (53.7%[CI45.3-62])
		SD	23 (31.5)	18 (24.3)	41 (27.9[CI20.8-35.9])
		PD	12 (16.4)	8 (10.8)	20 (13.6)
		Could not be evaluated	2 (2.7)	5 (6.8)	7 (4.8)
		Median time to OR 13 weeks Median follow-up 288 days Median TTP and OS not yet reached			
van Oosterom et al. 2002 N=40 (n=35 with GIST; 5 with other advanced soft tissue sarcomas) Phase I	Imatinib 400-1000mg/d	Response	GIST		
		PR	19 (54%)		
		SD	13 (37%)		
		Minimum follow-up 10 months			

CHR=Complete Hematologic Response; CGCR=Cytogenetic Complete Response; CGPR=Cytogenetic Partial Response; PFS= Progression Free Survival; OS=Overall Survival; IFN=Interferon; TTP=Time To Progression; CR= Complete Response; PR= Partial Response; SD= Stable Disease; PD= Progressive Disease

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

Braziel RM, Launder TM, Druker BJ, Olson SB, Magenis RE, Mauro MJ, et al. Hematologic and cytogenetic findings in imatinib mesylate-treated chronic myelogenous leukemia patients: 14 months' experience. Blood 2002;100:435-441.

Cortes J, Giles F, O'Brien S, Thomas D, Garcia-Manero G, Rios MB, et al. Result of high-dose imatinib meslyate in patients with Philadelphia chromosome-positive chronic myeloid leukemia after failure of interferon-α. Blood 2003; Mar 13 (epub ahead of print).

Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. NEJM 2002;347:472-80.

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.

Kantarjian H, Sawyers C, Hichhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, et al. for the International STI571 CML Study Group. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. NEJM 2002;346:645-52.

Kantarjian HM, Cortes JE, O'Brien S, Giles F, Garcia-Manero G, Faderl S, et al. Imatinib mesylate therapy in newly diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia: high incidence of early complete and major cytogenetic responses. Blood 2003:101:97-100.

Kantarjian HM, Talpaz M, O'Brien S, Giles F, Garcia-Manero G, Faderl S, et al. Dose escalation o f imatinib mesylate can overcome resistance to standard-dose therapy in patients with chronic myelogenous leukemia. Blood 2003;101:473-475.

Kantarjian HM, Cortes J, O'Brien S, Giles FJ, Albitar M, Rios MB, et al. Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast crisis. Blood 2002;99:3547-3553.

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, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. for the IRIS Investigators. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. NEJM 2003;348:994-1004.

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.

Ottman OG, Druker BJ, Sawyers CL, Goldman JM, Reiffers J, Silver RT, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood 2002;100:1965-1971.

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.

Sawyers CL, Hochhaus A, Feldman E, Goldman Jm, Miller CB, Ottmann OG, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood 2002;99:3530-3539.

Talpaz M, Silver RT, Druker B, Goldman JM, Gambacorti-Passerini C, Guilhot F, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood 2002;99:1928-1937.

van Oosterom AT, Judson IR, Verweij J, Stroobants S, Dumez H, Donato di Paola E, et al. for the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Update of phase I study of imatinib (STI571) in advanced soft tissue sarcomas and gastrointestinal stromal tumors: a report of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer 2002;38 Suppl 5:S83-7.

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