ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics

Available Online at www.jddt.in

CODEN: - JDDTBP (Source: - American Chemical Society)

Volume 5, Issue 8, August: 2017, 13-27

Review Article

GLEEVEC (IMATINIB): A BREAKTHROUGH IN CANCER TREATMENT

Sakshi Minocha[1], Saptarshi Das[2]

[1] Department of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences, Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan, India.

[2] Department of Pharmaceutical Sciences, Bengal College of Pharmaceutical Sciences and Research, Durgapur, West Bengal, India.

Received 07 may 2017; Accepted 15 August. 2017

ABSTRACT

Deregulated protein tyrosine kinase activity is central to the pathogenesis of human cancers. Targeted therapy in the form of selective tyrosine kinase inhibitors (TKIs) has transformed the approach to management of various cancers and represents a therapeutic breakthrough. Imatinib was one of the first cancer therapies to show the potential for such targeted action. Imatinib, an oral targeted therapy, inhibits tyrosine kinases specifically BCR-ABL, c-KIT, and PDGFRA. Apart from its remarkable success in CML and GIST, Imatinib benefits various other tumors caused by Imatinib-specific abnormalities of PDGFR and c-KIT. Imatinib has also been proven to be effective in steroid-refractory chronic graft-versus-host disease because of its anti-PDGFR action. Gleevec has been approved for the treatment of patients with positive inoperable and/or metastatic malignant gastrointestinal stromal tumors (GISTs). Gleevec is a signal transduction inhibitor that works by targeting the activity of enzymes called tyrosine kinases. The activity of one of these tyrosine kinases, known as c-kit, is thought to drive the growth and division of most GISTs.

Keywods: tyrosine kinase inhibitors (TKIs), Gleevec, metastatic malignant gastrointestinal stromal tumors (GISTs).

INTRODUCTION

Imatinib (also known as "Gleevec" or "Glivec"), a tyrosine kinase inhibitor, was called as "magical bullet," when it revolutionized the treatment of chronic myeloid leukemia (CML) in 2001. Imatinib was invented in the late 1990s by biochemist Nicholas Lyndon then working for Ciba-Geigy (now Novartis), and its use to treat CML was driven by Brian Druker, an oncologist at the Dana-Farber Institute. The first clinical trial of Imatinib took place in 1998 and the drug received FDA approval in May 2001. Lyndon, Druker, and the other colleagues were awarded the Lasker-DeBakey Clinical Medical Research Award in 2009 for "converting a fatal cancer into a manageable condition" and the Japan Prize in 2012 for their part in "the development of a new therapeutic drug targeting cancer-specific molecules." Encouraged by the success of Imatinib in treating CML patients, scientists explored its effect in other cancers and it was found to produce a similar miracle effect in other cancers where tyrosine kinases were over expressed.

Some say it's a miracle drug. Others call it a silver bullet. Gleevec, also marketed internationally as Glivec and sometimes referred to by its chemical name imatinib, entered the medical world with a bang. This medication was initially approved for use by the U.S. Food and Drug Administration (FDA) in 2001 for the treatment of chronic myelogenous leukemia (CML), a rare form of cancer that affects certain types of white blood cells. Since its initial approval, Gleevec has also been approved for use in patients with several types of gastrointestinal tumors. Currently, scientists continue to study the drug's effectiveness not only in various cancers, but also in other diseases, such as stroke.

DRUG DESCRIPTION

Imatinib is a small molecule kinase inhibitor. Gleevec film-coated tablets contain imatinib mesylate equivalent to 100 mg or 400 mg of imatinib free base. Imatinib mesylate is designated chemically as 4-[(4-Methyl-1-piperazinyl) methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methane sulfonate. Imatinib mesylate is a white to

*Corresponding author: Sakshi Minocha // E-mail: Saksmin7@gmail.com

off-white to brownish or yellowish tinged crystalline powder.

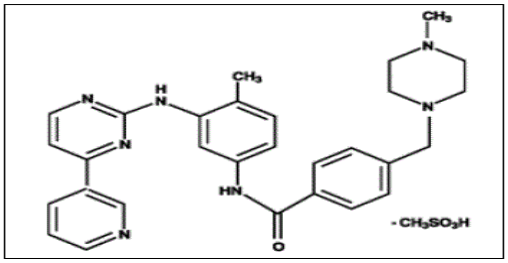

Figure 1: Structure of Imatinib mesylate (4-[(4-Methyl-1-piperazinyl) methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methane sulfonate)

Its molecular formula is $C_{29}H_{31}N_7OCH_4SO_3$ and its molecular weight is 589.7. Imatinib mesylate is soluble in aqueous buffers less than or equal to pH 5.5 but is very slightly soluble to insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol, and ethanol, but is insoluble in n-octanol, acetone, and acetonitrile. Inactive Ingredients: colloidal silicon dioxide (NF); crospovidone (NF); hydroxypropyl methylcellulose (USP); magnesium stearate (NF); and microcrystalline cellulose (NF). Tablet coating: ferric oxide, red (NF); ferric oxide, yellow (NF); hydroxypropyl methylcellulose (USP); polyethylene glycol (NF) and talc (USP).

Imatinib is used alone or together with other medicines to treat different types of cancer or bone marrow conditions. It prevents or stops the growth of cancer cells and is called an antineoplastic (cancer) agent. Imatinib is used for these conditions:

- Aggressive systemic mastocytosis (ASM)
- Chronic eosinophilic leukemia (CEL)
- Dermatofibrosarcoma protuberans (DFSP)
- Gastrointestinal stromal tumors (GIST)
- Hypereosinophilic syndrome (HES)
- Myelodysplastic syndrome (MDS)
- Myeloproliferative diseases (MPD)
- Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)
- Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML)

This medicine is available only with your doctor's prescription. This product is available in the following dosage forms:

- Tablet
- Capsule

Discovery of Imatinib

After working on many compounds the chemists landed on a 2-phenylaminopyrimidine derivative. This compound had low potency and poor specificity, inhibiting both serine/threonine and tyrosine kinases5. Using this as the parent molecule, they started designing a specific tyrosine kinase inhibiting molecule.

- By addition of a 3' pyridyl group, they found out the molecule will have enhanced cellular activity inside the cell. Introduction of Benzamide will increase the "anti-tyrosine kinase" activity.
- If "flag methyl" group is added to the 6 –position instead of anilino phenyl ring, it will lead to enhanced activity against tyrosine kinase.
- To overcome problems of oral bioavailability and water solubility a highly polar molecule called N-methylpiperazine was added.
- This drug was initially called CGP57148B (changed to STI571) later it was called Imatinib {IUPAC name 4-[(4-methylpiperazin-1-yl) methyl]-N-[4-methyl-3-[(4-pyridin-3-ylpyrimidin-2-yl) amino] phenyl] Benzamide} or Gleevec as it is more commonly known.

Pre-clinical tests: During the pre clinical tests, imatinib was assayed for inhibition of the enzyme.

- **In-vitro analysis:** During the experiments it became clear that this specifically inhibited only tyrosine kinase and it did not affect threonine kinase or serine kinase or any growth receptors (Ex: Epidermal growth factor receptors or VEGF – R1 and R2).The experiments were repeated on cell lines. It showed inhibition with 50% inhibitory concentration being 0.1 – 0.35 µm. Since then numerous experiments have been done using Ph+ cell lines taken from patients and the IC50 values have been between 0.1 and 10 µm.
- **In vivo analysis**: To test the anti tumour activity of imatinib, syngeneic mice were transformed by transferring Bcr-Abl gene. Experiments done at Ciba Geigy showed that imatinib is orally absorbed effectively in mice and relevant concentration in plasma is seen with half life of 1.3 hrs. Use of 160mg/kg of imatinib on mice consecutively for 11 days showed assured continuous blocking of p210bcr/abl but it did not affect any other cancer type which is Bcr-Abl negative. Using protein structure predictions, they found out that imatinib intimately reacts with Abl Kinase. This binding will create conformational changes in the enzyme leading

to obstruction of ATP binding site (competitive inhibitor). Therefore, phosphorylation cannot take place and the tumour cells cannot proliferate.

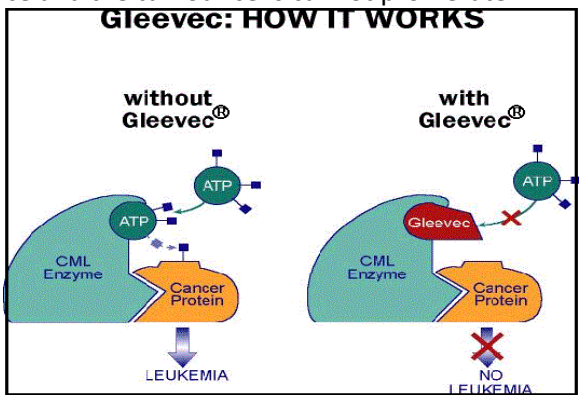

Figure 2: Working principle of Gleeevec

Clinical trials – Imatinib Monotherapy:

- **Phase I:** The phase I studies on the drug were done in June 1998, to determine the tolerated dosage level. Patients (diagnosed with CML in chronic stage and who had failed IFN treatment) were treated with 300mg of the drug and the results were very promising. Complete haematological response was shown by the patients. There were minimal side effects like Nausea, periorbital oedema and rashes.
- **Phase II:** Phase II trials started in late 1999. Tremendous improvement was shown by patients who were treated with imatinib on a daily basis. The disease progression free survival rate was as high as 89.2%. The drug was eliminated predominantly by hepatic metabolism and had a plasma half life period of 18 hours (hence daily dosage is recommended).
- **Phase III:** In the third phase studies, imatinib was administered along with IFN and cytarabine (anti-metabolic agent). The results were very positive showing 87% complete cytogenetic response. Imatinib not only has efficacy, but it also improved patients' quality of life.

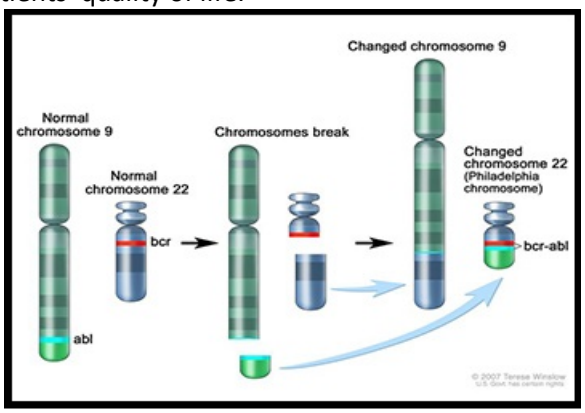

Figure 3: Normal Chrosome 9 changed to chrome 22

CLINICAL IMPLICATIONS:

1. **Chronic Myeloid Leukemia**: Chronic myeloid leukemia (CML) is characterized by the presence of a BCR-ABL fusion gene, which is the result of a reciprocal translocation between chromosomes 9 and 22. BCR-ABL is the driving force of leukemogenesis in CML .Being an inhibitor of BCR-ABL, the advent of Imatinib rapidly and dramatically modified the treatment of CML. When a patient is suffering from CML, there are three stages:

- The first stage is named chronic stage. In this stage 50% of the patients do not even have symptoms. Few complain about fatigue, pain and feeling full (loss of appetite). The blood workup of the patient will show 10% of abnormal white blood cells in the plasma and more than usual WBCs inside the bone marrow.
- The second phase is called accelerated phase, where up to 20% abnormal white cells are found in the blood. During this phase, patients generally complain about fatigue, bruising, fever, night sweats, infection, bone and abdominal pain.
- Third phase is blast crisis phase where the symptoms become much more noticeable. They include fatigue, bleeding, fever, weight loss, complications from infection and gout due to rapid cell turnover.

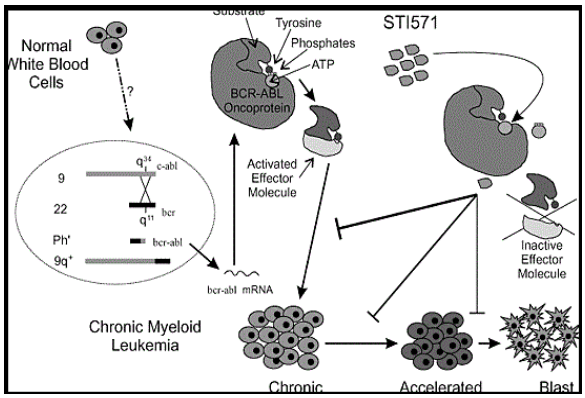

Figure 4: Normal WBC to blast crisis phase where the symptoms become much more noticeable

2. **Gastrointestinal Stromal Tumors**: Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms of the gastrointestinal (GI) tract accounting for <1% of primary gastrointestinal neoplasms. They are thought to arise from the interstitial cells of Cajal. GISTs are typically defined by the expression of c-KIT (CD117) in the tumor cells, as these activating KIT mutations are seen in 85–95% of GISTs. Imatinib potently inhibits the tyrosine kinase

activity of KIT. A number of clinical studies demonstrated the effectiveness of Imatinib in the treatment of unresectable or metastatic GIST .These include studies examining the efficacy and tolerability of different doses of Imatinib (400 mg/day, 600 mg/day, or 800 mg/day) and different dosing regimens.

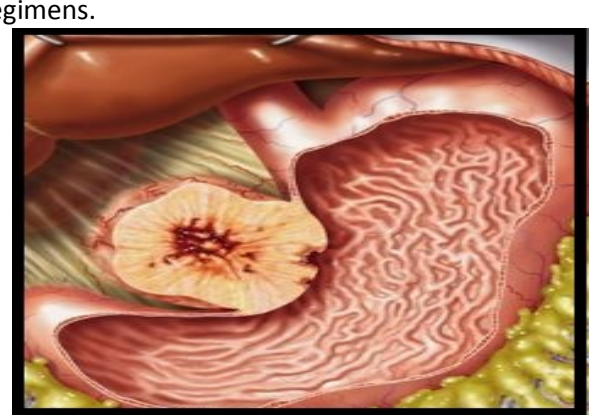

Figure 5: Gastrointestinal Stromal Tumors

3. **Dermato fibrosarcoma Protuberans**: Dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue tumor. DFSP is characterized by the presence of distinctive, reciprocal rearrangement of chromosomes 17 and 22. The rearrangement leads to the fusion of alpha chain type a (COL1A1) localized on 17q22 to the platelet-derived growth factor beta (PDGFB) localized on 22q13. DFSP has been reported to be treated with Imatinib, with doses between 400 and 800 mg daily for a period ranging from 2 to 24 months (median, 4 months), producing an average tumor reduction of 50% (range: 19%–100%) after a median follow-up time of 24 months (range: 88 days to 72 months). Several questions remain regarding the mechanism of action of Imatinib and possible resistance to this targeted therapy in DFSP. However, Imatinib is currently the gold standard in the treatment of locally advanced or metastatic DFSP.

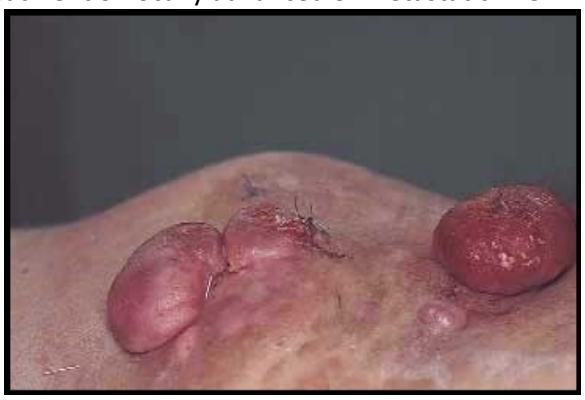

Figure 6: Dermato fibrosarcoma Protuberans

4. **Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia**: The Philadelphia chromosome (Ph) is a molecular abnormality present in approximately 30% of newly diagnosed cases of adult ALL. The occurrence of this disease subtype increases in an age-dependent manner and confers an unfavorable prognosis. Ph results from the translocation of chromosomes 9 and 22 producing a fusion gene, BCR-ABL.

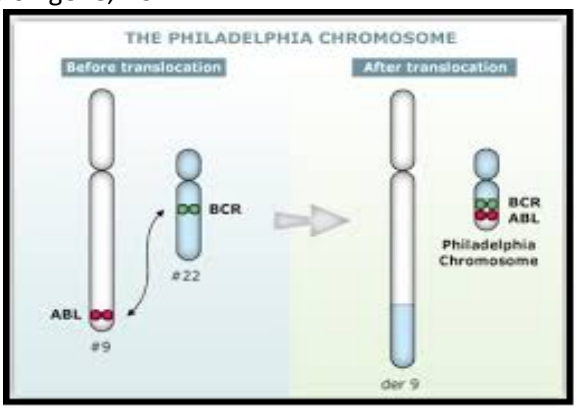

Figure 7: Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

5. **Systemic Mastocytosis**: Systemic mastocytosis (SM), a clonal neoplastic proliferation of mast cells, is defined by compact multifocal mast cell infiltrates in hematopoietic tissues with or without skin involvement [66]. SM is a heterogeneous spectrum of disorders; indolent to aggressive forms exist. Mastocytosis is frequently associated with somatic gain-of-function point mutation with KIT. The most common somatic point mutation is the KITD816V, resulting from substitution of valine for aspartic acid at codon 816 within KIT exon 17.

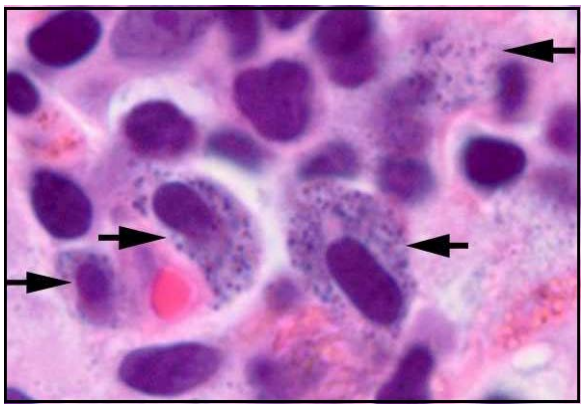

Figure 8: Systemic Mastocytosis

Apart from these cancers where Imatinib has already received FDA approval, various other cancers where

Imatinib has provided dramatic responses include the following:

1. **Aggressive Fibromatoses**: Aggressive fibromatoses (desmoid tumors) (AF) are clonal fibroblastic proliferations characterized by infiltrative growths with a locally aggressive behaviour and no known metastatic potential [73]. Because of local invasiveness and high recurrence rates, they are associated with significant morbidity. Primary surgery with negative surgical margins is the most successful treatment modality for desmoid tumors. Radiation therapy may be used in recurrent disease or as primary therapy in unresectable patients. The role of Imatinib in aggressive fibromatoses was explored by Mace and colleagues when they reported dramatic response to Imatinib in two patients with unresectable and progressive disease.

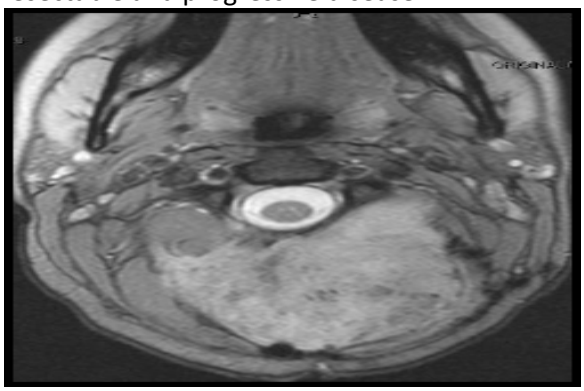

Figure 9: Aggressive Fibromatoses

2. **AIDS-Related Kaposi's Sarcoma**: Kaposi sarcoma (KS) is a spindle-cell tumor derived from endothelial cell lineage, associated with infection with human herpesvirus 8 (HHV-8). AIDS-related Kaposi sarcoma, unlike other forms of the disease, tends to have an aggressive clinical course. It is the most common presentation of Kaposi sarcoma [83]. Optimal control of HIV infection using HAART is an integral part of successful Kaposi sarcoma therapy.

3. **Chordoma**: Chordomas are rare tumors that arise from embryonic notochordal remnants, comprising less than 1% of CNS tumors. Surgery is the preferred treatment; however, local relapses occur in >50% of cases. Metastases occur in at least 20% of patients .A multicenter phase II clinical trial has confirmed the clinical efficacy of Imatinib in the treatment of chordoma. Treatment with Imatinib was successful in stabilizing tumor growth (84%) or shrinking tumor size (16%) in a cohort of patients with progressing, advanced chordoma. The largest phase II study in patients with platelet-derived growth factor beta-(PDGFB-) positive advanced chordoma treated with Imatinib (800 mg daily) failed to elicit an overall tumour response defined by RECIST.

4. **Recurrent Epithelial Ovarian Cancer**: Most patients with epithelial ovarian cancer (EOC) relapse. The second-line therapy includes drugs, such as taxanes, topotecan, pegylated liposomal doxorubicin, and/or gemcitabine .Platelet-derived growth factor (PDGF) and its receptor have been implicated in the early transformation and sustaining of tumor growth, their associated vascular endothelium, and signaling between tumor and stroma [90]. Various preclinical studies led to the use of Imatinib as a single agent for ovarian cancer, revealing some activity and some intolerance. In a phase II study, 14 patients with recurrent epithelial ovarian cancer (rEOC) were treated with Imatinib and weekly paclitaxel.

5. **Anaplastic Thyroid Cancer**: Anaplastic carcinoma of the thyroid (ATC) is the most aggressive thyroid gland malignancy. A preclinical study of Imatinib showed efficacy in inhibiting growth of ATC cell lines. Although the molecular target of this agent is not clearly defined, proposed mechanisms include inhibition of PDGF, KIT, and c-ABL. A single-institution study of Imatinib 400 mg twice daily orally in 11 patients with ATC was recently reported.

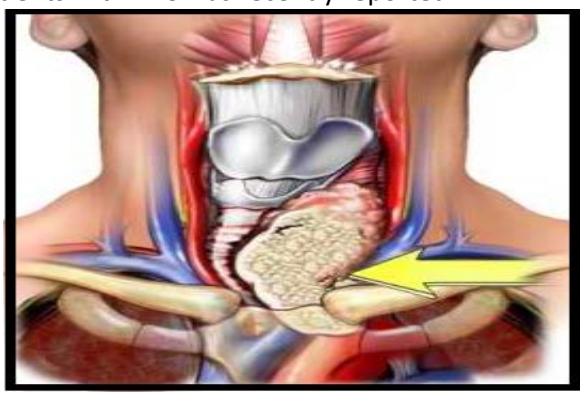

Figure 10: Anaplastic Thyroid Cancer

- **Biology of Abl gene and Bcr gene**: The Abl gene is responsible for production of a protein which works as a non-receptor for tyrosine kinase. The Abl gene is ubiquitously present in hematopoietic cells, but usually decreases with myeloid maturation. Tyrosine kinase is an enzyme which phosphorylates a substrate using phosphate group from ATPs. The Abl phosphorylation is tightly regulated process. If this controlling region is lost (as in case of fusion with Bcr), then it will lead to uncontrolled kinase activity.

Bcr gene is much more complex because they have many functional motifs. It is also involved in phosphorylation and GTP binding. The first exon present on this gene has oncogenic property because they have the codons responsible for production of proteins involved in Bcr-Abl fusion. It also has serine and threonine kinase enzymatic activity and it has autophosphorylation capability

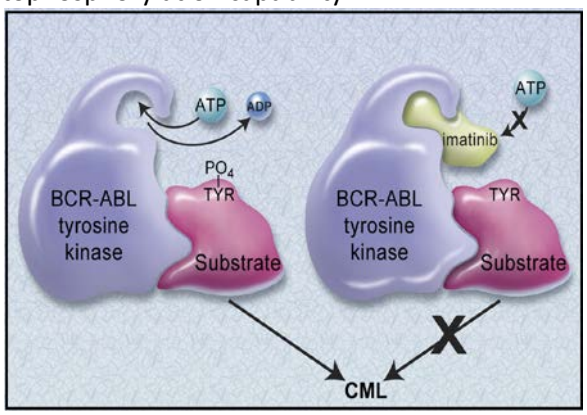

Figure 11: Biology of Abl gene and Bcr gene

- **Biology of Bcr-Abl gene**: Studies on p210bcr/abl shows that they are pleiotropic molecules critical for the development of CML and they have effect on DNA repair leading to instability (might lead to disease progression).
- **Inhibition of tyrosine kinase activity**: After the detailed study of Abl tyrosine kinase activity, medicinal chemists started working on inhibitors for this enzyme. They worked on several possible compounds which showed inhibitory effect. Some of the molecules that showed inhibition included benzopyranones and benzothiopyranones and the tyrphostin classes of compounds. However, they showed limited selectivity (affected normal tyrosine kinase present in the rest of the body) or showed less potency at cellular level.

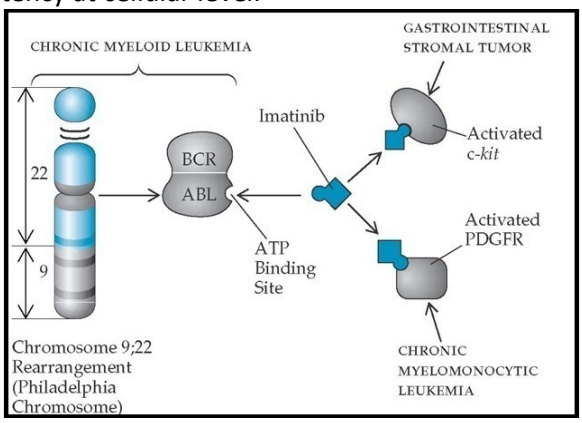

Figure 12: Inhibition of tyrosine kinase activity

MECHANISM OF ACTION:

Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in CML. Imatinib inhibits proliferation and induces apoptosis in BCR-ABL positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia. Imatinib inhibits colony formation in assays using ex vivo peripheral blood and bone marrow samples from CML patients. In vivo, imatinib inhibits tumor growth of BCR-ABL transfected murine myeloid cells as well as BCR-ABL positive leukemia lines derived from CML patients in blast crisis.

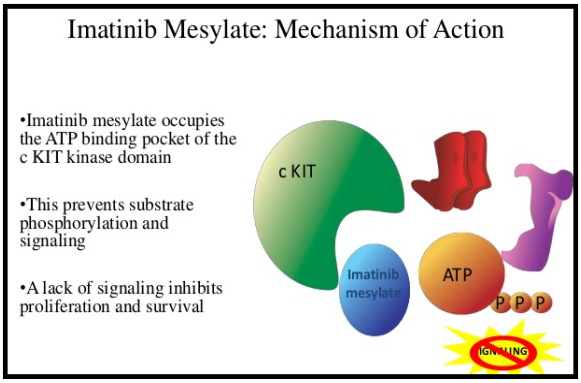

Figure 13: Mechanism of action of Imatinib mesylate

Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events. In vitro, imatinib inhibits proliferation and induces apoptosis in GIST cells, which express an activating c-kit mutation. Gleevec, (imatinib mesylate) competitively binds to the ATP binding pocket of both active and inactive Kit, preventing downstream signaling. Kit inhibition by imatinib may induce both apoptosis and quiescence in KIT+ GIST cells.

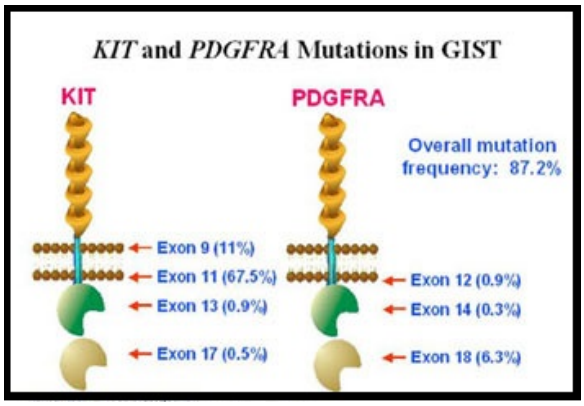

Figure 14: KIT and PDGFRA mutation in GIST

PHARMACOKINETICS: The pharmacokinetics of Gleevec have been evaluated in studies in healthy subjects and in population pharmacokinetic studies in over 900 patients. The pharmacokinetics of Gleevec are similar in CML and GIST patients.

❖ **Absorption And Distribution:** Imatinib is well absorbed after oral administration with Cmax achieved within 2-4 hours post-dose. Mean absolute bioavailability is 98%. Mean imatinib AUC increases proportionally with increasing doses ranging from 25 mg to 1,000 mg. There is no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5- to 2.5-fold at steady state when Gleevec is dosed once-daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in in vitro experiments is approximately 95%, mostly to albumin and α1-acid glycoprotein.

❖ **Metabolism:** CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is the N-demethylated piperazine derivative, formed predominantly by CYP3A4. It shows in vitro potency similar to the parent imatinib. The plasma AUC for this metabolite is about 15% of the AUC for imatinib.

❖ **Excretion:** Imatinib elimination is predominately in the feces, mostly as metabolites. Based on the recovery of compound(s) after an oral 14C-labeled dose of imatinib, approximately 81% of the dose was eliminated within 7 days, in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

MECHANISM OF RESISTANCE:

1. During disease progression, CML progenitor cells acquire a number of genetic alterations, most probably because of increased genomic instability, that may explain the aggressive phenotype, chemotherapeutic drug resistance, and poor prognosis of CML in BP. CML patients with imatinib mesylate resistance can be stratified into those with primary refractory disease, most frequently in accelerated or BPs, and those who relapse after initial response, who are most frequently in CP. On the basis of the presence or absence of BCR/ABL tyrosine kinase activity in leukemia cells, it is also possible to discriminate between cases with BCR/ABL-dependent and -independent mechanisms of imatinib mesylate resistance. The association of BCR/ABL gene amplification with resistance to imatinib mesylate is consistent with the reliance of CML blast crisis cells on BCR/ABL expression/activity for their proliferation and survival, and with the reported enhanced expression of BCR/ABL in these cells.

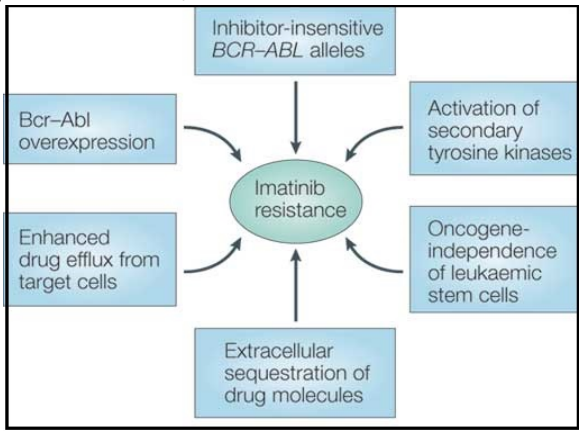

Figure 15: Mechanism of resistance

Other mechanisms of imatinib mesylate resistance involve mutations in the BCR/ABL gene itself. Several different mutations have been detected in at least 13 amino acids of the ATP-binding site or other regions of the tyrosine kinase domain, and the list is growing (23 , 28 , 29) . These mutations usually prevent imatinib mesylate from binding to BCR/ABL, thereby resulting in lack of inhibition of the tyrosine kinase activity.

2. A third mechanism of resistance relies on plasma levels of AGP. It has been shown that AGP binds imatinib mesylate at physiological concentrations in vitro and in vivo, and blocks the ability of imatinib mesylate to inhibit BCR/ABL kinase activity in a dose-dependent manner (reviewed in Ref. 23). Finally, in patients with primary refractoriness to imatinib mesylate, resistance more often occurs in absence of significant CRKL phosphorylation, suggesting activation of BCR/ABL-independent leukemogenic pathways.

DOSING AND ADMINISTRATION:

Refer to protocol by which patient is being treated.Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

1. Adults

❖ Oral: 400-600 mg (range 400-800mg) PO once daily. Administer with food.800 mg dose should be administered in two divided doses.

❖ Dosage in myelosuppression: CML chronic phase or GIST- If ANC < 1 x10^9/L or platelet < 50 x10^9/L, hold until ANC >1.5 and platelets >75:

- CML: if 1st, restart at 400 mg daily; if 2nd, restart at 300 mg daily.
- GIST: if 1st, restart at 600 mg daily; if 2nd, restart at 400 mg daily.

❖ Dosage in renal failure: no adjustment required.

❖ Dosage in hepatic failure: If bilirubin > 3 x ULN or ALT/AST > 5 x ULN:

- hold until bilirubin < 1.5 x ULN and ALT/AST < 2.5 x ULN
- restart at 300 mg (reduced from 400 mg) or 400 mg (reduced from 600 mg)
- full dose had been used in four patients with severe jaundice

2. **Children**:

❖ Oral: 260 mg/m^2 once daily or split daily into two (once in the morning and once in the evening).

❖ Dosage in myelosuppression: CML chronic phase- If ANC < 1 x109/L or platelet < 50 x109/L, hold until ANC >1.5 and platelets >75:

- If 1st episode, restart at 260 mg/m2 daily.
- If 2nd episode, restart at 200 mg/m2 daily.

❖ Dosage in hepatic failure: If bilirubin > 3 x ULN or ALT/AST > 5 x ULN:

- hold until bilirubin < 1.5 x ULN and ALT/AST < 2.5 x ULN
- Restart at 200 mg/m^2 daily (reduced from 260 mg/m2 daily) or 260 mg/m^2 daily (reduced from 340 mg/m^2 daily).

3. **Renal Dose Adjustments**: Patients with moderate renal impairment (CrCl = 20 to 39 mL/min) should receive a 50% decrease in the recommended starting dose and future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCl = 40 to 59 mL/min). For patients with moderate renal impairment doses greater than 400 mg are not recommended. Imatinib should be used with caution in patients with severe renal impairment. A dose of 100 mg/day has been tolerated in two patients with severe renal impairment.

4. **Liver Dose Adjustments**: Patients with mild and moderate hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment. If severe hepatotoxicity develops, the dose should be withheld until condition resolves. If elevations in bilirubin greater than 3 times the upper limit of normal (ULN) or liver transaminases greater than 5 times the ULN occur, the dose should be withheld until bilirubin returns to less than 1.5 ULN and transaminases to less than 2.5 ULN, at which time treatment may be resumed with a reduced dose (i.e. 400 mg reduced to 300 mg; 600 mg reduced to 400 mg).

INTERACTIONS:

It is difficult to determine the relevance of a particular drug interaction to any individual given the large number of variables.

Major	Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit.
Moderate	Moderately clinically significant. Usually avoid combinations; use it only under special circumstances.
Minor	Minimally clinically significant. Minimize risk; assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan.

1. Agents Inducing CYP3A Metabolism: Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of Gleevec, increased Gleevec oral-dose clearance by 3.8-fold, which significantly (p less than 0.05) decreased mean Cmax and AUC.Similar findings were observed in patients receiving 400 to 1200 mg/day Gleevec concomitantly with enzyme-inducing anti-epileptic drugs (EIAED) (e.g., carbamazepine, oxcarbamazepine, phenytoin, fosphenytoin, phenobarbital, and primidone).

2. Agents Inhibiting CYP3A Metabolism: There was a significant increase in exposure to imatinib (mean Cmax and AUC increased by 26% and 40%, respectively) in healthy subjects when Gleevec was coadministered with a single dose of ketoconazole (a

CYP3A4 inhibitor). Caution is recommended when administering Gleevec with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Grapefruit juice may also increase plasma concentrations of imatinib and should be avoided.

3. Interactions With Acetaminophen: In vitro, Gleevec inhibits the acetaminophen O-glucuronidate pathway (Ki 58.5 µM). Coadministration of Gleevec (400 mg/day for eight days) with acetaminophen (1000 mg single dose on day eight) in patients with CML did not result in any changes in the pharmacokinetics of acetaminophen. Gleevec pharmacokinetics were not altered in the presence of single-dose acetaminophen. There is no pharmacokinetic or safety data on the concomitant use of Gleevec at doses greater than 400 mg/day or the chronic use of concomitant acetaminophen and Gleevec.

INDICATIONS

- Newly diagnosed adult and pediatric patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in the chronic phase
- Patients with Ph+ CML in blast crisis (BC), accelerated phase (AP), or in the chronic phase (CP) after failure of interferon-alpha therapy
- Adult patients with relapsed or refractory Ph+ acute lymphoblastic leukemia (Ph+ ALL)
- Pediatric patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene rearrangements as determined with an FDA-approved test
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-KIT mutation as determined with an FDA-approved test or with c-KIT mutational status unknown
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown
- Adult patients with unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP)
- Patients with KIT (CD117)-positive gastrointestinal stromal tumors (GIST) that cannot be surgically removed and/or have spread to other parts of the body
- Adult patients after surgery who have had their KIT (CD117)-positive GIST completely removed

HOW SUPPLIED

- ❖ Gleevec is a pill, taken by mouth, once or twice daily.
- ❖ Gleevec should be taken with a large glass of water, after a meal.
- ❖ The amount of Gleevec that you will receive depends on many factors, including your general health or other health problems, and the type of cancer or condition being treated.

Dosage Forms and Strengths:

1. **100 mg Film Coated Tablets:** Very dark yellow to brownish orange, film-coated tablets, round, biconvex with bevelled edges, debossed with “NVR” on one side, and “SA” with score on the other side.
2. **400 mg Film Coated Tablets:** Very dark yellow to brownish orange, film-coated tablets, ovaloid, biconvex with bevelled edges, debossed with “400” on one side with score on the other side, and “SL” on each side of the score.
3. **400 mg Film Coated Tablets:** Very dark yellow to brownish orange, film-coated tablets, ovaloid, biconvex with bevelled edges, debossed with “gleevec” on one side and score on the other side.

Storage and Handling:

Each film-coated tablet contains 100 mg or 400 mg of imatinib free base.

1. 100 mg Tablets: Very dark yellow to brownish orange, film-coated tablets, round, biconvex with bevelled edges, debossed with “NVR” on one side, and “SA” with score on the other side.

Bottles of 90 tablets.

2. 400 mg Tablets: Very dark yellow to brownish orange, film-coated tablets, ovaloid, biconvex with bevelled edges, debossed with “400” on one side with score on the other side, and “SL” on each side of the score.

Bottles of 30 tablets.

3. 400 mg Tablets: Very dark yellow to brownish orange, film-coated tablets, ovaloid, biconvex with bevelled edges, debossed with “gleevec” on one side and score on the other side.

Unit Dose (blister pack of 30).

❖ Store at 25°C (77°F); excursions permitted to 15°C-30cC (59°F-86°F) [see USP Controlled Room Temperature]. Protect from moisture.

❖ Dispense in a tight container, USP.

❖ Do not crush Gleevec tablets. Avoid direct contact of crushed tablets with the skin or mucous membranes. If such contact occurs, wash thoroughly as outlined in the references. Avoid exposure to crushed tablets.

OVERDOSE

Experience with doses greater than 800 mg is limited. Isolated cases of Gleevec overdose have been reported. In the event of overdosage, observe the patient and give appropriate supportive treatment.

➢ **Adult Overdose:**

*1. **1,200 To 1,600 mg (Duration Varying Between 1 To 10 Days):** Nausea, vomiting, diarrhea, rash erythema, edema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite.*

*2. **1,800 to 3,200 mg (As High As 3,200 mg Daily For 6 Days):** Weakness, myalgia, increased CPK, increased bilirubin, gastrointestinal pain.*

*3. **6,400 mg (Single Dose):** One case in the literature reported one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, neutrophil count decreased, increase transaminases.*

*4. **8 to 10 g (Single Dose):** Vomiting and gastrointestinal pain have been reported.*

❖ *A patient with myeloid blast crisis experienced Grade 1 elevations of serum creatinine, Grade 2 ascites and elevated liver transaminase levels, and Grade 3 elevations of bilirubin after inadvertently taking 1,200 mg of Gleevec daily for 6 days. Therapy was temporarily interrupted and complete reversal of all abnormalities occurred within 1 week. Treatment was resumed at a dose of 400 mg daily without recurrence of adverse reactions. Another patient developed severe muscle cramps after taking 1,600 mg of Gleevec daily for 6 days. Complete resolution of muscle cramps occurred following interruption of therapy and treatment was subsequently resumed. Another patient that was prescribed 400 mg daily, took 800 mg of Gleevec on Day 1 and 1,200 mg on Day 2. Therapy was interrupted, no adverse reactions occurred and the patient resumed therapy.*

➢ **Pediatric Overdose:**

❖ One 3-year-old male exposed to a single dose of 400 mg experienced vomiting, diarrhea and anorexia and another 3-year-old male exposed to a single dose of 980 mg experienced decreased white blood cell count and diarrhea.

SIDE EFFECTS

- Minor Side Effects: Some of the side effects that can occur with imatinib may not need medical attention. As your body adjusts to the medicine during treatment these side effects may go away.
  - Acid or sour stomach, belching , difficulty having a bowel movement (stool)
  - difficulty with moving , discouragement
  - fear or nervousness
  - feeling sad or empty
  - feeling unusually cold
  - full or bloated feeling
  - irritability
  - lack or loss of strength
  - muscle stiffness
  - night sweats
  - swollen joints
  - weight loss
  - Back pain
  - bad, unusual, or unpleasant (after) taste
  - watering of the eyes
- Major Side Effects: You should check with your doctor immediately if any of these side effects occur when taking imatinib:

❖ fluid retention - shortness of breath (even while lying down), swelling, rapid weight gain (especially in your face and midsection);

❖ fluid build-up in the lungs - pain when you breathe, wheezing, gasping for breath, cough with foamy mucus;

❖ liver problems - upper stomach pain, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes);

❖ low blood cell counts - fever, chills, flu-like symptoms, swollen gums, mouth sores, skin sores, rapid heart rate, pale skin, easy bruising, unusual bleeding, feeling light-headed;

❖ signs of stomach bleeding - bloody or tarry stools, coughing up blood or vomit that looks like coffee grounds;

❖ signs of tumor cell breakdown - lower back pain, blood in your urine, little or no urinating; numbness or tingly feeling around your mouth; muscle weakness or tightness; fast or slow heart rate, weak pulse; confusion, fainting;

❖ thyroid symptoms - extreme tired feeling, dry skin, joint pain or stiffness, muscle pain or weakness, hoarse voice, feeling more sensitive to cold temperatures; or

❖ severe skin reaction - fever, sore throat, swelling in your face or tongue, burning in your eyes, skin pain, followed by a red or purple skin rash that spreads (especially in the face or upper body) and causes blistering and peeling.

WHAT OTHER DRUGS WILL AFFECT GLEEVEC

Many drugs can interact with imatinib-

✓ bosentan;
✓ dihydroergotamine or ergotamine;
✓ fentanyl (Abstral, Actiq, Fentora, Duragesic, Lazanda, Onsolis);
✓ nefazodone;
✓ pimozide;
✓ St. John's wort;
✓ an antibiotic - clarithromycin, erythromycin, telithromycin;
✓ antifungal medicine - itraconazole, ketoconazole, posaconazole, voriconazole;
✓ antiviral medicine to treat hepatitis C or HIV/AIDS - atazanavir, boceprevir, cobicistat (Stribild, Tybost), delavirdine, efavirenz, fosamprenavir, indinavir, nelfinavir, nevirapine, ritonavir, saquinavir, telaprevir;
✓ a blood thinner - warfarin, Coumadin, Jantoven;
✓ heart medicine - nicardipine, quinidine;
✓ medicine to prevent organ transplant rejection - cyclosporine, sirolimus, tacrolimus;
✓ seizure medication - carbamazepine, fosphenytoin, oxcarbazepine, phenobarbital, phenytoin, primidone; or
✓ tuberculosis medication - isoniazid, rifabutin, rifampin, rifapentine.

Table 1: Many drugs can interact with imatinib-effect, mechanism and management

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit or grapefruit juice[64]	may increase plasma level of imatinib	may inhibit CYP3A4 metabolism of imatinib in the intestinal wall	avoid grapefruit and grapefruit juice
ketoconazole[64]	increases plasma level of imatinib	inhibits CYP 3A4 metabolism of imatinib	use with caution
levothyroxine[65]	imatinib may increase thyroid-stimulating hormone level and symptoms of hypothyroidism	imatinib may increase hepatic clearance of levothyroxine	closely monitor thyroid function during concurrent use and adjust levothyroxine dose as needed
rifampin	decreases plasma level of imatinib	induces CYP3A4 metabolism of imatinib	avoid concurrent use
simvastatin	increases plasma level of simvastatin	inhibits CYP3A4 metabolism of simvastatin	avoid concurrent use
warfarin	prolongs bleeding time	possibly inhibits CYP2C9 and CYP3A4 metabolism of warfarin	closely monitor bleeding parameters during concurrent use and adjust warfarin dose as needed, or consider other alternatives (eg, low-molecular weight or standard heparin)

PRECAUTIONS

- Imatinib has often been associated with edema and occasionally serious fluid retention. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. Unexpected rapid weight gain should be carefully investigated and appropriate treatment should be provided.
- Cases of cardiogenic shock / left ventricular dysfunction have been associated with the initiation of imatinib therapy in patients with hypereosinophilic syndrome and cardiac involvement. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD or ASM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1 to 2 mg/kg) for one to two weeks concomitantly with imatinib should be considered at the initiation of therapy.
- Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully and any

patient with signs or symptoms consistent with cardiac failure should be evaluated and treated.

- Thrombocytopenia, neutropenia and anemia often occur during treatment and are more frequent in accelerated phase CML and blast crisis. Complete blood counts should be obtained weekly during the first month, biweekly during the second month, and thereafter as clinically appropriate.
- Imatinib has occasionally been associated with severe hepatotoxicity. Liver function tests (transaminases, bilirubin, and alkaline phosphatase) should be monitored at baseline and at monthly intervals or as clinically appropriate. Abnormal results may be managed by interrupting treatment or decreasing the dose.
- Growth retardation occurring in children receiving imatinib has been reported. Close monitoring of growth in children under imatinib treatment is recommended. Growth retardation occurring in children receiving imatinib has been reported. Close monitoring of growth in children under imatinib treatment is recommended.
- Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with imatinib. TSH levels should be closely monitored in such patients.
- Tumor Lysis Syndrome, including fatal cases, have been reported. Close monitoring is recommended.Safety and efficacy have not been established in children less than 2 years old.
- This medicine may cause blurred vision and may impair your thinking or reactions. Be careful if you drive or do anything that requires you to be alert and able to see clearly. Dizziness or severe drowsiness can cause falls, accidents, or severe injuries.
- Grapefruit and grapefruit juice may interact with imatinib and lead to potentially dangerous effects. Avoid the use of grapefruit products while taking Gleevec.
- Others: Fluid Accumulation in the Brain, Relapse of Hepatitis B Infection Symptoms, High Blood Pressure, Disease of the Arteries of the Heart, Fluid in the Covering of the Heart or Pericardium, Heart Valve Disease, Chronic Heart Failure, Failure of the Left Ventricle of the Heart, Inflammation of the Middle Tissue Heart Muscle, Hemorrhage, Escape of Fluid into the Lungs, Fluid in the Lungs, Liver Problems, Severe Liver Disease, Bleeding of the Stomach or Intestines, Kidney Disease, Heart Disease Present at Birth, Visible Water Retention, Blood Circulation Failure due to Serious Heart Condition, Ascites, Pregnancy, A Mother who is Producing Milk and Breastfeeding, Diabetes, A Rupture in the Wall of the Stomach or Intestine, Overweight, Anemia, Decreased Blood Platelets, Decreased Neutrophils a Type of White Blood Cell.

➢ **Do not use Gleevec if you are pregnant**:

- It could harm the unborn baby. Use effective birth control to prevent pregnancy, and tell your doctor if you become pregnant during treatment.
- It is not known whether imatinib passes into breast milk or if it could harm a nursing baby. You should not breast-feed while using this medicine.
- Gleevec can affect growth in children. Talk with your doctor if you think your child is not growing at a normal rate while using this medicine.

OTHER COMMENTS:

✓ Therapy should be initiated by a physician experienced in the treatment of patients with hematological malignancies or malignant sarcomas, as appropriate.

✓ Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

✓ The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day. For daily dosing of 800 mg and above, dosing should be accomplished using the 400-mg tablet to reduce exposure to iron.

✓ In children, imatinib treatment can be given as a once-daily dose or alternatively the daily dose may be split into two, once in the morning and once in the evening. There is no experience with imatinib treatment in children less than 2 years of age.

✓ For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 mL for a 100 mg tablet, and 200 mL for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

✓ This medicine may cause blurred vision and may impair your thinking or reactions. Be careful if you

drive or do anything that requires you to be alert and able to see clearly. Dizziness or severe drowsiness can cause falls, accidents, or severe injuries.

✓ Grapefruit and grapefruit juice may interact with imatinib and lead to potentially dangerous effects. Avoid the use of grapefruit products while taking Gleevec.

✓ Avoid being near people who are sick or have infections. Tell your doctor at once if you develop signs of infection.

✓ Avoid activities that may increase your risk of bleeding or injury. Use extra care to prevent bleeding while shaving or brushing your teeth.

✓ Imatinib can pass into body fluids (including urine, feces, vomit). Caregivers should wear rubber gloves while cleaning up a patient's body fluids, handling contaminated trash or laundry or changing diapers. Wash hands before and after removing gloves. Wash soiled clothing and linens separately from other laundry.

CONCLUSION

The tyrosine kinase (TK) inhibitor, Imatinib, has revolutionized the therapy of malignancies that are addicted to one of its target kinases, c-ABL, c-KIT, and PDGFR. Currently, Imatinib is the standard of care in CML and GIST as it has dramatically changed the outlook of these diseases. Its use has extended to various other cancers and has achieved firstline position in cancers like Ph+ ALL, advanced dermatofibrosarcoma protuberans, hypereosinophilic syndrome, and systemic mastocytosis. Imatinib has also provided a valuable option in patients with SR-cGVHD who cannot access other treatments like extracorporeal photopheresis. No other targeted therapies have contributed so much to therapeutic armamentarium in oncology as Imatinib. Not only as therapy, Imatinib also acted as a tool for understanding the mechanisms of the diseases like CML and GIST. Various studies are ongoing to explore its benefits in other cancers also. The major drawback with Imatinib is development of resistance which is therapeutically challenging. Second- and third-generation TKIs have come up to overcome this resistance. Despite these limitations, Imatinib has contributed immensely to the field of oncology so that it should still be called a “wonder drug.”

REFERENCES

1. Reckmann AH, Fischer T, Peng B, et al. Effect of food on STI571 Glivec pharmacokinetics and bioavailability. Proc Am Soc Clin Oncol 2001;20(Part 1 of 2):(abstract 1223).

2. Senior K. Gleevec does not cross blood-brain barrier. Lancet Oncol 2003;4(4):198.

3. Peng B, Hayes M, Resta D, et al. Pharmacokinetics and Pharmacodynamics of imatinib in a phase I trial with chronic myeloid leukemia patients. J Clin Oncol 2004;22(5):935-42.

4. Ford JM. STI571 (formerly CGP 57 148 B) investigators brochure. Basel: Novartis Pharma AG; 23 June 2000. p. 77.

5. Gleevec (Imatinib) safety and efficacy evaluation report. East Hanover NJ: Novartis Pharmaceuticals Corporation; 2001. p. 71.

6. Druker BJ. STI571 (Gleevec/Glivec, imatinib) versus interferon (IFN) + cytarabine as initial therapy for patients with CML: results of a randomized study. Proc Am Soc Clin Oncol 2002;21 (Part 1 of 2):1a (abstract).

7. Wassmann B, Gokbuget N, Scheuring UJ, et al. A randomized multicenter open label phase II study to determine the safety and efficacy of induction therapy with imatinib (Glivec, formerly STI571) in comparison with standard induction chemotherapy in elderly (>55 years) patients with Philadelphia chromosome-positive (Ph+/BCR-ABL+) acute lymphoblastic leukemia (ALL) (CSTI571ADE 10). Ann Hematol 2003;82(11):716-20.

8. Wassmann B, Scheuring U, Pfeifer H, et al. Efficacy and safety of imatinib mesylate (Glivec) in combination with interferon-alpha (IFN-alpha) in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). Leukemia 2003;17(10):1919-24.

9. Wassmann B, Pfeifer H, Scheuring U, et al. Therapy with imatinib mesylate (Glivec) preceding allogeneic stem cell transplantation (SCT) in relapsed or refractory Philadelphia-positive acute lymphoblastic leukemia (Ph+ALL). Leukemia 2002;16(12):2358-65.

10. Ottmann OG, Druker BJ, Sawyers CL, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood 2002;100(6):1965-71.

11. 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. N Engl J Med 2001;344(14):1052-6.

12. Novartis Pharmaceuticals Canada Inc. Gleevec product monograph. Dorval, QC; 16 June, 2006.

13. Novaretti MC, Fonseca GH, Conchon M, et al. First case of immune-mediated haemolytic anaemia associated to imatinib mesylate. Eur J Haematol 2003;71(6):455-8.

14. De Arriba JJ, Nerin C, Garcia E, et al. Severe hemolytic anemia and skin reaction in a patient treated with imatinib. Ann Oncol 2003;14(6):962.

15. Burton C, Azzi A, Kerridge I. Adverse events after imatinib mesylate therapy. N Engl J Med 2002;346(9):712-3.

16. Mozziconacci MJ, Cailleres S, Maurice C, et al. Myelodysplastic features developing in Philadephia-negative cells during imatinib mesylate therapy for CML: report of a new case.[comment]. Leukemia 2003;17(9):1901-2.

17. Chee YL, Vickers MA, Stevenson D, et al. Fatal myelodysplastic syndrome developing during therapy with imatinib mesylate and characterised by the emergence of complex Philadelphia negative clones.[see comment][comment]. Leukemia 2003;17(3):634-5.

18. Elliott MA, Mesa RA, Tefferi A. Adverse events after imatinib mesylate therapy. N Engl J Med 2002;346(9):712-3.

19. Barton JC, Jones SC, Lamberth WC, et al. Cardiac tamponade associated with imatinib mesylate therapy of chronic myelogenous leukemia. Am J Hematol 2002;71(2):139-40.

20. C. H. Takimoto and E. Calvo, "Principles of oncological pharmacotherapy," in Cancer Management: A Multidisciplinary Approach, R. Pazdur, L. D. Wagman, K. A. Camphausen, and W. J. Hoskins, Eds., 11th edition, 2008.

21. M.W. Deininger and B. J. Druker, "Specific targeted therapy of chronicmyelogenous leukemia with imatinib," Pharmacological Reviews, vol. 55, no. 3, pp. 401–423, 2003.

22. P. Vigneri and J. Y. Wang, "Induction of apoptosis in chronic myelogenous leukemia cells through nuclear entrapment of BCR-ABL tyrosine kinase," Nature Medicine, vol. 7, no. 2, pp. 228–234, 2001.

23. B. Peng, C. Dutreix, G. Mehring et al., "Absolute bioavailability of Imatinib (Glivec®) orally versus intravenous infusion," Journal of Clinical Pharmacology, vol. 44, no. 2, pp. 158–162, 2004.

24. B. Peng, P. Lloyd, and H. Schran, "Clinical pharmacokinetics of imatinib," Clinical Pharmacokinetics, vol. 44, no. 9, pp. 879–894, 2005.

25. M. L. Hensley and J. M. Ford, "Imatinib treatment: specific issues related to safety, fertility, and pregnancy," Seminars in Hematology, vol. 40, no. 2, pp. 21–25, 2003.

26. J. D. Rowley, "A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining," Nature, vol. 243, no. 5405, pp. 290–293, 1973.

27. T. G. Lugo, A.-M. Pendergast, A. J. Muller, and O. N. Witte, "Tyrosine kinase activity and transformation potency of bcr-abl oncogene products," Science, vol. 247, no. 4946, pp. 1079–1082, 1990.

28. B. J. Druker, S. Tamura, E. Buchdunger et al., "Effects of a selective inhibitor of the ABL tyrosine kinase on the growth of BCR-ABL—positive cells," Nature Medicine, vol. 2, pp. 561–566, 1996.

29. B. J. Druker, C. L. Sawyers, H. Kantarjian et al., "Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome," New England Journal of Medicine, vol. 344, no. 14, pp. 1038–1042, 2001.

30. B. J. Druker, M. Talpaz, D. J. Resta et al., "Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia," New England Journal of Medicine, vol. 344, no. 14, pp. 1031–1037, 2001.

31. S.G.O'Brien,F.Guilhot, R. A. Larsonet al., "Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronicmyeloid leukemia,"New England Journal of Medicine, vol. 348, no. 11, pp. 994–1004, 2003.

32. E. A. Hahn, G. A. Glendenning, M. V. Sorensen et al., "Quality of life in patients with newly diagnosed chronic phase chronic myeloid leukemia on imatinib versus interferon alfa plus low dose cytarabine: results from the IRIS study," Journal of Clinical Oncology, vol. 21, no. 11, pp. 2138–2146, 2003.

33. B. J. Druker, F. Guilhot, S. G. O'Brien et al., "Five-year followup of patients receiving imatinib for

chronicmyeloid leukemia," The New England Journal of Medicine, vol. 355, pp. 2408–2417, 2006.

34. van Rhee F., Szydlo R. M., Hermans J., Devergie A., Frassoni F., Arcese W., de Witte T., Kolb H. J., Niederwiser D., Jacobsen N., Gahrton G., Bandini G., Carreras E., Bacigalupo A., Michallet M., Ruutu T., Reiffers J., Goldman J. M., Apperley J., Gratwohl A. Long-term results after allogeneic bone marrow transplantation for chronic myelogenous leukemia in chronic phase: a report from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant, 20: 553-560, 1997.

35. Trotta R., Vignudelli T., Candini C., Intine R., Pecorari L., Guerzoni C., Santilli G., Byrom B., Goldoni G., Ford L., Caligiuri M., Maraia R., Perrotti D., Calabretta B. BCR/ABL activates mdm2 mRNA translation via the La antigen. Cancer Cell, 3: 145-160, 2003.

