GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

Check for updates

Imatinib mesylate: Recent drug used in oncology

Nerella Bhavani * and M Sunitha Reddy

Centre for Pharmaceutical Sciences, Institute of Science and Technology, JNTU Hyderabad, Kukatpally, Hyderabad, Telangana state, India. Pin code: 500085.

GSC Biological and Pharmaceutical Sciences, 2023, 22(02), 173–186

Publication history: Received on 01 January 2023; revised on 16 February 2023; accepted on 18 February 2023

Article DOI: https://doi.org/10.30574/gscbps.2023.22.2.0059

Abstract

Background: The European Union and Canada have approved generic imatinib for the treatment of chronic myeloid leukaemia (EU). Anecdotal evidence suggests that generic imatinib performs less well than brand-name imatinib. MEDLINE and EMBASE were searched as methods. The European Medicines Agency (EMA) and Health Canada-approved generic imatinib product monographs were examined. We contacted Novartis, Teva, and Apotex's medical information.

Results: A number of issues have been brought up. First, generic imatinib approved outside of Canada and the EU has been linked to inconsistent results in two case series and lower efficacy in minor case reports. However, it is unclear whether these generic products' clinical bioequivalence has been established. Second, there have been concerns raised about generic imatinib's use in different populations. However, compared to adults with chronic myeloid leukaemia, imatinib absorption is not significantly different in children with chronic myeloid leukaemia or in patients with gastrointestinal tumours. Even though there have been reports of reduced absorption following gastric bypass and gastrectomy, the majority of imatinib is absorbed in the ileum, duodenum, colon, and jejunum. It has also been demonstrated that changes in stomach acidity have no impact on imatinib absorption. At room temperature, the beta-crystal form of brand-name imatinib is more stable than the alpha-crystal form of generic imatinib. However, the EMA discovered that both crystal forms were extremely soluble and that polymorphism would not materially affect the efficacy of generic imatinib.

Keywords: Imatinib Mesylate; High Bioavailability; Imatinib Absorption; Metabolism; Recent Drug Oncology; USFDA Drugs List

1. Introduction

Cancer will be the leading cause of death in the world in 2020, accounting for approximately 10 million deaths, or nearly one in every six. The most common types of cancer are breast, lung, colon, rectum, and prostate cancer. Tobacco use having a high BMI, drinking alcohol, eating few fruits and vegetables and not exercising account for roughly one-third of cancer-related deaths. Cancer-causing infections such as the human papillomavirus (HPV) and hepatitis are thought to be the cause of 30% of cancer cases in low- and lower-middle-income countries. Many tumours are curable if identified early and treated appropriately [1].

Cancer is a broad term that refers to a wide range of diseases that can affect any part of the body. Malignant tumours and neoplasms are other terms used. One distinguishing feature of cancer is the rapid formation of abnormal cells that grow beyond their normal boundaries and can then invade neighbouring parts of the body and spread to other organs; this process is known as metastasis. The primary cause of cancer death is widespread metastasis [1,2].

*Corresponding author: Nerella Bhavani

Imatinib belongs to the group of small molecules that selectively inhibit the tyrosine kinase of the Abl kinase. Imatinib is a powerful competitive inhibitor of ATP binding to the c-Kit, PDGF, and Abl kinase receptor tyrosine kinases as well as to these other enzymes. As a result, it particularly inhibits activated c-Kit mutants in gastrointestinal stromal tumours (GIST) Deininger and Druker as well as the Bcr-Abl fusion kinase originating from the Philadelphia chromosomal translocation, which is the main cause of chronic myelogenous leukaemia (2003). Imatinib is a pioneering instance of a selective target-based cancer therapy with good response rates and few adverse effects [2].

1.1. Prevalence

Cancer is the world's leading cause of death, accounting for nearly 10 million deaths in 2020[1]. In terms of new cancer cases in 2020, the most common were:

- Breast cancer (2.26 million cases);
- Lung (2.21 million cases); colon and rectum (1.93 million cases); prostate (1.41 million cases); skin (non-melanoma) (1.20 million cases); and stomach (1.20 million cases) (1.09 million cases).

In 2020, the most common causes of cancer death were: lung (1.80 million deaths); colon and rectum (916 000 deaths); liver (830 000 deaths); stomach (769 000 deaths); and breast (769 000 deaths) (685 000 deaths).Each year, approximately 400 000 children develop cancer. The most common cancers vary between countries. Cervical cancer is the most common in 23 countries. [1]

1.2. Pathophysiology

In many different ways, oncogenes stimulate cell development. A lot of people have the ability to make hormones, which act as "chemical messengers" between cells and promote mitosis. The impact of these hormones depends on how the receiving tissue or cells process the signals they receive. To put it another way, when a hormone receptor on a recipient cell is activated, a signal is transmitted from the cell's surface to the cell nucleus to affect a change in the nuclear regulation of gene transcription [3,4]. Some oncogenes are a part of the signal transduction system itself, or the signal receptors in cells and tissues themselves, influencing the sensitivity to such hormones. Oncogenes frequently generate mitogens or participate in DNA transcription during protein synthesis, which results in the production of the proteins and enzymes needed to make the goods and biochemicals that cells use and interact with.

Proto-oncogene mutations, which are oncogenes' typically dormant counterparts, can change how they express and function, hence boosting the quantity or activity of the resulting protein. When this occurs, the proto-oncogenes turn into oncogenes, upsetting the cell's usual balance of cell cycle regulation and opening the door to unchecked development. Even if it were possible, eliminating proto-oncogenes from the genome would not be able to lower the risk of cancer because they are essential for the body's growth, repair, and homeostasis. Only after they are altered do the signals for growth appear.The ras oncogene was one of the first to be identified in cancer research. 20% to 30% of all human tumours contain mutations in the Ras family of proto-oncogenes, which includes the H-Ras, N-Ras, and K-Ras. Researchers were shocked to discover that Ras was not only present in the human genome but also had the ability to cause cancer in cell line cultures when it was linked to a stimulating control element. Ras was first discovered in the genome of the Harvey sarcoma virus [5,6]

Table 1 USFDA Drugs list [2,3]

Drug	Approval year	Therapeutic class	Target gene	Delivery type
Abiraterone acetate	2011	Prostate cancer	CYP17A1	Single
Brentuximab vedotin	2011	Lymphoma	TNFRSF8	Single
Crizotinib	2011	Lung cancer	ALK; MET	Single
Ipilimumab	2011	Melanoma	CTLA4	Single
Ruxolitinib phosphate	2011	Myelofibrosis	JAK1; JAK2	Single
Vandetanib	2011	Thyroid cancer	EGFR; PTK6; TEK; VEGFA	Single
Vemurafenib	2011	Melanoma	BRAF	Single
Pertuzumab	2012	Breast cancer	ERBB2	Both
Axitinib	2012	Kidney cancer	FLT1; FLT4; KDR	Single
Bosutinib	2012	Leukemia	BCR-ABL	Single
Cabozantinib	2012	Thyroid cancer	KDR; MET; RET	Single
Carfilzomib	2012	Multiple myeloma	PSMB1; PSMB10; PSMB2; PSMB5; PSMB8; PSMB9	Single
Enzalutamide	2012	Prostate cancer	AR	Single
Ponatinib hydrochloride	2012	Leukemia	BCR-ABL	Single
Regorafenib	2012	Colorectal cancer; Stomach cancer	RET; FLT1; KDR; FLT4; KIT; PDGFRA; PDGFRB; FGFR1; FGFR2; TEK; DDR2; NTRK1; EPHA2; RAF1; BRAF; MAPK11; FRK; ABL1	Single
Vismodegib	2012	Basal cell carcinoma	SMO	Single
Ziv-aflibercept	2012	Colorectal cancer	PGF; VEGFA; VEGFB	Single
Dabrafenib	2013	Melanoma	BRAF; LIMK1; NEK11; RAF1; SIK1	Both
Trametinib	2013	Melanoma	MAP2K1; MAP2K2	Both
Obinutuzumab	2013	Leukemia	MS4A1	Combination
Ado-trastuzumab emtansine	2013	Breast cancer	ERBB2	Single
Afatinib	2013	Lung cancer	EGFR; ERBB2; ERBB4	Single
Ibrutinib	2013	Lymphoma	BTK	Single
Pomalidomide	2013	Multiple myeloma	CRBN	Single
Idelalisib	2014	Leukemia; Lymphoma	PIK3CD	Both
Belinostat	2014	Lymphoma	HDAC1; HDAC2; HDAC3; HDAC6	Single
Ceritinib	2014	Lung cancer	ALK	Single
Pembrolizumab	2014	Melanoma	PDCD1	Single
Ramucirumab	2014	Stomach cancer	KDR	Single

1.3. Drug Profile of Imatinib mesylate

1.3.1. Structure

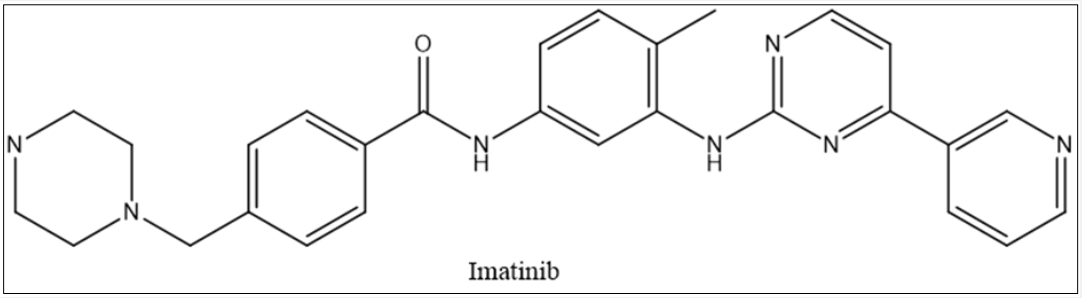

Figure 1 Structure of Imatinib

IUPAC Name:4-[(4-methylpiperazin-1-yl)methyl]-N-(4-methyl-3-{[4-(pyridin-3-yl) pyrimidin-2 yl]amino} phenyl) benzamide

Molecular Formula:$C_{29}H_{31}N_7O$

Molecular Weight: 493.6
Melting Point: 221-228 °C
Boiling Point: 754.9 °C
log P: 4.38
pKa: 1.52 ,2.56 ,3.73 ,8.07
Solubility: Soulable in water, DMSO and sparingly soluble in ethanol.
Trade name: Gleevec

1.4. Mechanism of Action

Imatinib is a 2-phenyl amino pyrimidine derivative with a specific inhibitory effect on a number of tyrosine kinase enzymes as its mode of action. It takes up the TK active site, which causes activity to drop [6,7].

The insulin receptor is one of many TK enzymes that are present in the body. The TK domain in abl (the Abelson proto-oncogene), c-kit, and PDGF-R is only recognised by imatinib (platelet-derived growth factor receptor).

The Philadelphia chromosome causes the fusion protein bcr-abl, also known as abl-bcr, to form in chronic myelogenous leukaemia. Imatinib is used to reduce bcr-abl activity since this tyrosine kinase is now constitutively active.

Tyrosine kinases feature ATP binding sites in each of their active sites. Tyrosine phosphorylation, also known as protein tyrosine phosphorylation, is the enzymatic activity that a tyrosine kinase catalyses when it transfers the terminal phosphate from ATP to tyrosine residues on its substrates. Imatinib inhibits the enzymatic activity of the protein semi-competitively by binding in close proximity to the ATP binding site of bcr-abl, trapping it in a closed or self-inhibited conformation. This information explains why several BCR-ABL mutations can result in imatinib resistance by causing the equilibrium to change in favour of the open or active conformation. Imatinib inhibits the above-mentioned targets (c-kit and PDGF-R), as well as the tyrosine kinases ABL2 (ARG), DDR1, and NQO2, an oxidoreductase, and is quite specific for the bcr-abl protein. Non-cancer cells' abl proteins are also inhibited by imatinib, but since these cells typically have extra redundant tyrosine kinases, they can still function even when abl tyrosine kinase is blocked. However, certain tumour cells are dependent on bcr-abl. Tumor cell death results from the inhibition of the bcr-abl tyrosine kinase, which also increases its entry into the nucleus where it is unable to carry out any of its typical anti-apoptopic actions. Other impacted routes include, The Ras/MapK route is one of the several downstream pathways of the Bcr-Abl pathway, which promotes growth factor-independent cell proliferation. The Src/Pax/Fak/Rac pathway is also impacted. This has an impact on the cytoskeleton, which causes a rise in cell motility and a fall in adhesion. Also impacted is the PI/PI3K/AKT/BCL-2 pathway. BCL-2 is in charge of maintaining the mitochondria's stability, which reduces apoptosis and boosts cell survival. The JAK/STAT pathway, which is in charge of proliferation, is the final pathway that Bcr-Abl influences[8,9,10].

1.4.1. Pharmacokinetics

When taken orally, imatinib is quickly absorbed and has a high bioavailability (98% of an oral dose reaches the bloodstream). Imatinib is metabolised in the liver by a number of cytochrome P450 system isozymes, primarily CYP3A4 and, to a lesser extent, CYP1A2, CYP2D6, CYP2C9, and CYP2C19. N-demethylated piperazine derivative, the primary metabolite, also has activity. Only a little amount of the medicine is excreted in the urine; the majority of the substance is eliminated through the bile and faeces. Only 25% of imatinib is removed intact; the majority is eliminated as metabolites. Imatinib and its primary metabolite have half-lives of 18 hours and 40 hours, respectively. It inhibits the action of the platelet-derived growth factor receptor, c-Kit, and Abelson cytoplasmic tyrosine kinase (ABL) (PDGFR). Imatinib mesylate looks to be useful in the treatment of a number of dermatological conditions as a PDGFR inhibitor. According to reports, imatinib is a successful treatment for dermatofibrosarcoma protuberans, hypereosinophilic syndrome, and FIP1L1-PDGFRalpha+ mast cell illness.[3]Imatinib's pharmacokinetic findings are fascinating. After oral dosing, imatinib is almost entirely absorbed (98%)—high solubility, high permeability, and a low hepatic extraction ratio[10].

The pharmacokinetics of imatinib have been investigated in healthy volunteers (extremely rare for an anticancer agent) and in patients with Philadelphia chromosomepositive CML or acute lymphocytic leukemia. To our knowledge, the data concerning the patients with GIST have not yet been reported.

Absorption: The absolute bioavailability of imatinib in its hard capsule form and in an oral solution (not commercially available) given as single doses has been determined in 12 healthy volunteers. When compared with an intravenous formulation (100 mg as a 1-h infusion, also not commercially available), the mean absolute bioavailability of the capsule (400 mg as 4 capsules) was 98.3% indicating a complete absorption and the lack of intestinal or hepatic first pass effects. The absolute bioavailability of the oral solution was 97.2%. The kinetic profiles of imatinib tablets and capsules, administered as a single dose of 400mg, have been evaluated over a sampling period of 4 days in 30 healthy volunteers. The 400 mg tablet form was developed to allow a single and more convenient intake of imatinib. Furthermore, the scored 100 mg tablet permits adjustments of dosage in children. The tablet form has replaced the capsule form in the United States and is about to gain approval in other parts of the world. The kinetic profiles of imatinib given in tablets (400mg or 4x100mg) or capsules (4x100mg) as a single dose are similar with a median time (Tmax) to reach the concentration peak (Cmax) of 2.5h (range 1.5-6h). The mean Cmax were 1.6 mg/l (Standard Deviation or SD: 0.6) and 1.7 mg/l (SD: 0.7) after ingestion of a 400mg tablet and 4x100 mg capsules, respectively. Data obtained in patients do not appear to differ from those of healthy subjects. Absorption parameters have been determined in 12 adult patients with CML who were given imatinib at a dose of 400 or 600mg per day. The mean Cmax were 2.02 mg/l (coefficient of variation or CV: 32%) and 6.76 mg/l (CV: 69%) and the mean Tmax were 4.07h (CV: 37%) and 3.84h (CV: 55%), after the first ingestion of 400 mg (n=6) or 600 mg (n=6), respectively. The most complete data are those derived from a phase I study which included 64 adult patients with CML. The kinetic characteristics were determined after the first administration and at steady state (day 7), with daily doses that ranged from 25 mg to 1g. The exposure to imatinib (the area under the plasma concentration-time curve or AUC calculated over 24h) was shown to increase proportionally to the dose both on day 1 and at steady state, suggesting the absence of saturation in the absorption and elimination processes. The Tmax ranged between 1.8 and 4h after a single dose and between 1 to 6.8h at steady state. At current label dose (400 mg), the Cmax increased from 1.9 mg/l (SD: 0.35) after the first dose (n=4) to 2.59mg/l (SD: 0.78) at steady state (n=5), respectively. The Tmax were comparable, around 3h. Similarly, the AUC0-24h increased from 24.8 mg.h/l (SD: 7.4) to 40.1 mg.h/l (SD: 15.7). Distribution: The activity of imatinib is related to the exposure of the body to the circulating free fraction (i.e. the AUC calculated with the unbound concentration). With regards to the blood distribution at therapeutic concentrations, the mean fraction of imatinib in plasma was around 70% when assessed, in vitro, with spiked blood samples of 3 healthy volunteers. In plasma from CML patients (n=5), imatinib was found to be highly bound to proteins (>99%). In vitro, imatinib binds to plasma proteins such ·1 acid glycoprotein and albumin. In animal bearers of human leukemic cells, high concentrations of ·1 acid glycoprotein have been associated with an absence of response to imatinib. It was suggested by the authors that high concentrations of the carrier decrease the active unbound fraction and prevent the diffusion of imatinib to the targets. Alpha1 acid glycoprotein is an acute phase reactant, the levels of which can rise after inflammatory stimuli such as cancer. Further, the same investigators reported a positive and significant correlation between ·1 acid glycoprotein levels and total (bound plus unbound) imatinib peak plasma concentrations at steady state in 19 patients with CML. On the other hand, the relationship between ·1 acid glycoprotein levels and the AUC was not significant. The addition of intravenous clindamycin, a drug known to bind with ·1 acid glycoprotein and hence potentially compete with imatinib binding, was shown to cause a decrease in exposure (bound plus unbound) of 2.9-fold in 5 patients. The percentage of imatinib bound at 3h decreased from 99% to 96%. Nevertheless, the concentrations of unbound imatinib determined at 3h were not significantly affected. Thus, the clinical relevance of variations of imatinib binding to plasma proteins due to displacement from its proteic binding sites by another drug or to changes in the concentrations of the plasma proteins (i.e. ·1 acid glycoprotein) is unknown. According

to Benet and Hoener, and given the elimination characteristics of imatinib, it is unlikely that changes in plasma protein binding influencethe clinical exposure of the patient. Imatinib is an oral drug with a predominant hepatic clearance (see below) and, in this case, the unbound drug exposure (the determinant of pharmacological effect) is independent of protein binding. Therefore, no clinical variation would be expected. Investigations have been conducted to assess the distribution of imatinib in the central nervous system (CNS) by determining its levels in the cerebrospinal fluid as a surrogate. CNS recurrence can occur in patients with CML during the late phase of the disease (the blast crisis) and rarely in patients with GIST. Furthermore, imatinib has raised interest in other types of CNS cancers such CNS relapses of acute lymphoblastic leukemia (ALL) with Philadelphia translocation or gliomas. Overall, determination of imatinib in the cerebrospinal fluid of treated patients with CNS involvement of ALL or CML has demonstrated marginal diffusion with concentrations below the IC50 (i.e. 0.15 mg/l). Levels of imatinib were found to be 74-fold lower in the CSF than in plasma of 4 patients (0.044 mg/l versus 3.27 mg/l). Similarly, 2 case reports indicated CSF concentrations less than 0.07 mg/l (< 3% of plasma levels) in one patient (600 mg per day) and 0.017 mg/l (versus 1.57 mg/l in the serum) in the other (200 mg per day). Finally, Le Coutre et al. reported mean imatinib concentrations of 0.038 mg/l in CSF from 17 patients with ALL (400 or 600 mg daily) versus 3.37 mg/l in the plasma. More complete CSF kinetics have been achieved in nonhuman primates (n=3) over 24h. Again, the penetration of imatinib in the CSF was weak with a mean ratio of CSF/plasma AUC of 5% (SD:2). Animal experiments suggest that the modest diffusion in the CNS is imputable to the transmembrane drug transporter Pglycoprotein (P-gp or ABCB1). P-gp encoded in man by the gene MDR1 was originally identified for its role in multidrug resistance to anticancer agents. P-gp is also a pharmacokinetic determinant acting as an efflux pump that prevents the passage of some oral drugs across the epithelial cells of the digestive tract and that is involved in the elimination processes (biliary excretion, renal and intestinal secretions). In addition, P-gp is expressed in brain capillary endothelial cells, participating in the concept of the blood brain barrier. In vitro, imatinib is transported by Pgp. Knock-out mice for the murine equivalent of MDR1 (no expression of P-gp) exibit a brain to plasma ratio 6-to 7-fold greater than that of wild-type mice (expressing P-gp) after intravenous injection. Hence, P-gp could limit the distribution of imatinib in the brain. It has to be stressed that P-gp expressed on the apical side of enterocytes and involved in the limited absorption of some oral drugs (i.e. ciclosporin) has apparently no impact on imatinib bioavailability since it is around 98%[11,12].

Metabolism: The metabolic profile of imatinib has not yet been published. According to the package insert, imatinib is mainly biotransformed by the isoenzyme cytochrome P450 (CYP) 3A4. Other isoforms such CYP1A2, CYP2D6, CYP2C9 and CYP2C19 appear to be involved in the metabolism.The main metabolite CGP 74588 or Ndesmethyl-imatinib exibits an in vitro activity comparable to that of the parent drug.

Excretion: The elimination pathways of imatinib remain mostly unpublished. When determined in 2 patients with CML, the amount of imatinib in urine represented 2.7 and 4.1% of the administered dose. In addition, N-desmethyl-imatinib was also found in very low amounts (1.7 and 2% of the administered dose in the urine). The biliary excretion has been investigated in one patient with normal liver tests receiving imatinib (400 mg daily). The amount of the parent drug and the CGP 74588 metabolite represented 17.7 and 2.1% of the daily dose, respectively[13].

Pharmacokinetic parameters: The pharmacokinetic parameters of imatinib given at therapeutic dosages in adult patients are presented in Table I. The exposition to imatinib administered once-daily appeared to increase on chronic administration. Hence, the AUC calculated over 24h were 24.8 mg/l.h (SD:7.4) on day 1 and 40.1 mg/l.h (SD:15.7) at steady state in patients receiving a daily dose of 400 mg. Overall, the kinetics of imatinib in patients with CML receiving a daily dose of 400 mg or 600mg are characterized, at steady state, by a Cmax ranging from 2.6 to 3.5 mg/l, a terminal half-life of 15h to 19h (calculated over a 2-day period) and a total body clearance of around 200ml/min. With regard to the IC50 for Bcr-Abl (0.15 mg/l), the plasma through concentrations were well above, around 1.2 mg/l in 14 patients receiving 400mg or 600mg. According to the product label, the kinetics of imatinib are comparable in GIST and CML patients[14,15].

2. Clinical Implications

2.1. Myeloid Leukemia Chronica

The BCR-ABL fusion gene, which is the outcome of a reciprocal translocation between chromosomes 9 and 22 (the Philadelphia (Ph) chromosome), is what distinguishes chronic myeloid leukaemia (CML)from other types of leukaemia. The cause of leukemogenesis in CML is BCR-ABL. Imatinib, a BCR-ABL inhibitor, has significantly changed the way that CML is treated and is managed as a result of its rapid and dramatic introduction[12;11].

High response rates to imatinib were observed in patients with advanced CML who had received IFN- pretreatment in the pioneering study by Druker et al. Imatinib and the combination of interferon-alpha (INF-) and cytarabine were

compared in the seminal CML study IRIS by O'Brien et al., which had 1106 CP-CML patients. Imatinib caused a complete cytogenetic response (CCR) in 73.8% of patients and a complete haematological response (CHR) in 95.3% of patients. Additionally, patients taking imatinib reported a higher quality of life. Imatinib was given FDA approval in December 2001 as a result of these findings. Imatinib caused CHR in 98% of chronic phase patients and CCR in 87% during the 6-year follow-up of the IRIS study. Achieving these objectives is the aim of Imatinib therapy. A considerably greater long-term remission duration and progression-free survival were linked to receiving MMR (PFS). At 60-month follow-up, patients who achieved CCR and MMR at 12 months had a PFS of 97% compared to 89% for patients who had achieved CCR but fell short of MMR. Early molecular response indicated better results; illness progression was associated with failure to reduce transcript levels by 1 log by 3 months and 2 log by 6 months[13,14].

Imatinib resistance has grown to be a difficult issue despite a significant advancement in clinical CML treatment. Soon after imatinib was first used in clinical practise, it became clear that there were patients who were resistant to the treatment. Patients with advanced-phase disease experienced lower initial responses, and majority of those patients with initial responses had temporary responses. When CHR and MCR cannot be reached after three months and six months, respectively, it is said to be primary resistance. Different drug transport and/or metabolism may be the root of primary resistance. A 5–10-fold rise in BCR–ABL transcripts indicates acquired resistance, which is defined as the development of the disease to an advanced stage or lack of response. Amplification of the BCR-ABL fusion gene, mutations in the BCR-ABL kinase domain, overexpression of drug transporter genes, and overexpression of tyrosine kinases such the SRC family kinases can all contribute to acquired resistance. Higher doses of Imatinib, a second-generation tyrosine kinase inhibitor (TKI), or an allogeneic stem cell transplant are two alternatives for second-line therapy. In phase III studies, second-generation TKIs like Nilotinib and Dasatinib, which had faster and greater rates of CCRs and molecular responses than Imatinib, have also been found to be more effective than this drug in treating newly diagnosed CML. As a result, the Food and Drug Administration has given both medications their approval for use in patients with newly diagnosed chronic CML[11,13].

2.2. 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. About 3–5% of the remainder of KIT-negative GISTs contain PDGFRA mutations[15,16].

Imatinib significantly changed the treatment and prognosis for this rare condition after CML. Imatinib has a strong inhibitory effect on KIT's tyrosine kinase activity. Imatinib has been shown to be beneficial in treating metastatic or unresectable GIST in a number of clinical investigations. These include investigations of the effectiveness and tolerance of various Imatinib dosages (400 mg daily, 600 mg daily, or 800 mg daily), as well as various dosing schedules. 800 mg of Imatinib was not found to be superior to 400 mg of Imatinib as the primary systemic therapy in a phase III randomised trial involving 746 patients with advanced incurable GIST; no statistically significant differences in objective response rates, progression-free survival (PFS), or overall survival (OS) were found. However, patients whose tumours expressed an exon 9 KIT mutation, treated with a daily dose of 800 mg of Imatinib (versus 400 mg), experienced a significantly better PFS () with a reduction of relative risk of 61% in a phase II randomised trial examining dose selection in 946 patients with advanced GIST[16,17].

Patients with primary resectable GIST typically receive surgery as their primary curative treatment. A significant majority of GIST tumours, however, have a high risk of recurrence and may benefit from adjuvant therapy. The advantages of adjuvant imatinib have been examined in at least three phase III trials. Imatinib (400 mg daily for one year) or a placebo was administered to 713 patients who had undergone complete gross resection of a primary GIST measuring at least 3 cm and expressing KIT in one randomised, double-blinded phase III trial. The rate of 1-year relapse-free survival (RFS) favouring imatinib was 98 percent as opposed to 83 percent. The absolute benefit was highest in patients with high-risk disease (relapse rate was 47 versus 19 % for Imatinib and placebo, respectively); for patients with moderate risk disease, it was 14 versus 5%. There was no overall survival advantage. 908 patients with moderate or high-risk GIST who had tumour rupture or intraoperative tumour leakage were randomly assigned to two years of imatinib treatment or observation alone in a different phase III trial. At a median follow-up of 4.7 years, the Imatinib arm had a 5-year Imatinib-free survival (IFS) rate of 87% compared to the control arm's 84 percent, a 3-year RFS rate of 84% compared to 66%, and a 5-year overall survival rate of 100% versus 99%. In 400 patients with high-risk resected GIST, the Scandinavian Sarcoma Group (SSG) XVIII study evaluated 36 versus 12 months of adjuvant imatinib (400 mg daily). Prolonged treatment was linked to a significant improvement in RFS and the primary outcome (5-year RFS, 66 versus 48%) as well as overall survival at a median follow-up of 54 months (92 versus 82 percent)[15,16].

Resistance to imatinib has emerged as a major issue in GIST, similar to CML, as all GIST patients receiving imatinib for advanced disease would unavoidably experience progressive disease. In the randomised European trial comparing two dosages of imatinib, primary resistance was observed in 12% of the 934 patients and was more common in those with lung metastases but not liver metastases (41 percent). There have been several pathways for Imatinib resistance in GIST explained. The occurrence of new secondary mutations is the resistance mechanism that is most frequently seen. Amplification of KIT, pharmacokinetic resistance, which may involve altered drug transporter activity, activation of the cytochrome P450 (CYP) 3A4 isoenzyme, and subpar patient compliance are other pathways of acquired resistance that have been found.Dose-escalation of Imatinib or second-generation tyrosine kinase inhibitors (TKIs) may be considered in these settings[1,17].

2.3. Dermatofibrosarcoma Protuberans

A uncommon soft tissue tumour called dermatofibrosarcoma protuberans (DFSP), which makes up around 1% of all sarcomas, grows slowly and has a less than 5% chance of spreading to other organs. Chromosomes 17 and 22 have a specific, reciprocal rearrangement that is a hallmark of DFSP. Alpha chain type a (COL1A1), which is located on 17q22, merges with platelet-derived growth factor beta (PDGFB), which is located on 22q13, as a result of the rearrangement. A crucial pathogenetic factor, persistent autocrine activation of PDGF receptor B (PDGFRB) is caused by the constitutional elevation of PDGFB expression that comes from the creation of the COL1A1-PDGFB fusion gene. Initial case reports demonstrated the effectiveness of Imatinib in patients with metastatic and locally advanced DFSP based on the inhibitory effects of Imatinib on DFSP cell development in several in vitro and in vivo studies. In the biggest retrospective series, Imatinib 800 mg was given daily to 10 patients with locally progressed or metastatic DFSP. Eight patients with locally advanced illness all had t(17;22) evidence in their karyotypes or through fluorescence in situ hybridization (FISH), and two of them entirely responded to treatment. The karyotypes of the two patients with metastatic illness were more intricate. While the second lacked the normal t(17;22) and did not respond, the first exhibited a partial response lasting seven months. It is unknown if Imatinib has the same effect on conventional DFSP cancers lacking t(17;22). Imatinib has been reported to be used to treat DFSP in the neoadjuvant context as well, with doses between 400 and 800 mg daily for a period of 2 to 24 months (median, 4 months), resulting in an average tumour decrease of 50% (range: 19%-100%) after a median follow-up duration of 24 months (range: 88 days to 72 months). Regarding Imatinib's mode of action and potential DFSP resistance to this targeted therapy, there are still many unanswered questions. The gold standard for the treatment of locally progressed or metastatic DFSP is now imatinib[15,16,18].

2.4. Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

A molecular aberration known as the Philadelphia chromosome (Ph) is seen in about 30% of adult ALL cases that have just received a new diagnosis. This disease subtype has a bad prognosis and occurs more frequently as people age. Chromosomes 9 and 22 are translocated, resulting in the fusion gene BCR-ABL, which causes Ph. BCR-ABL expression yields the two distinct proteins, p190 and p210. While p210 protein predominates in chronic myelogenous leukaemia, p190 protein is only produced in Ph-positive (Ph+) ALL (CML). Treatment outcomes for this illness have been transformed by TKI-based therapy, which is now considered the gold standard of care. Imatinib was given along with the same induction and consolidation chemotherapy in a prospective, multicenter trial enrolling patients with recently discovered Ph+ ALL. Both treatment plans enabled allo-SCT in the majority of patients and resulted in manageable side effects, while concurrent use of imatinib and chemotherapy had stronger anticancer effects[11,12,17].

The long-term results of 335 patients receiving Imatinib (600 mg/day) treatment according to three distinct regimens were examined by the same study team. Patients in the first cohort got imatinib prior to the first consolidation therapy as well as following it. Imatinib was administered to the second cohort throughout the second half of induction chemotherapy and up until allo-SCT. Imatinib was administered to the third cohort along with induction chemotherapy and continued until allo-SCT. In patients in the third cohort, overall survival was reported to be at its maximum level (50%) at the 4-year review. These results imply that imatinib therapy should begin at a young age and last for a long time.Similar findings were seen in the largest international prospective study conducted on two cohorts of Ph+ ALL patients [57]. Following induction, patients in Cohort 1 received imatinib. Imatinib was administered to individuals in Cohort 2 during the second induction phase. Patients who received Imatinib treatment early had higher overall, event-free, and relapse-free survival outcomes. These results confirm the notion that Imatinib should be administered earlier in therapy to Ph+ ALL patients. Imatinib has therefore been approved as a first-line treatment for Ph+ ALL[13,14].

2.5. Hypereosinophilic Syndromes/Chronic Eosinophilic Leukemia

The hypereosinophilic syndromes (HES), a rare class of illnesses characterised by a persistent overproduction of eosinophils and accompanied organ damage, are characterised by blood eosinophil counts >1.5 109/L for at least 6

months without any apparent explanation. Once clonal eosinophilia (such as leukaemia) and reactive eosinophilia (due to infection, autoimmune disease, tropical eosinophilia, or malignancy) have been ruled out, HES is a diagnosis of exclusion. The FIP1-like-1 gene (FIP1L1) and the PDGFRA gene are fused in some HES patients due to a loss in chromosome 4, which results in the FIP1L1-PDGFRA rearrangement. As this gene has evolved into a marker of disease clonality, HES patients with a FIP1L1-PDGFRA rearrangement are now classed as having chronic eosinophilic leukaemia (CEL). The PDGFRA TK is constitutively activated by this fusion gene. Patients with asymptomatic HES who don't show signs of organ damage are attentively watched, but there is no accepted standard of care for them. Prednisone has historically been the first-line treatment for HES, with a response rate of close to 70%. However, relapses frequently happen, necessitating the patient's search for second-line medication choices such interferon or hydroxyurea. Tyrosine kinase inhibitor is developed as a potential therapeutic target as a result of the finding of the FIP1L1-PDGFRA oncogene. Studies have found that this fusion gene occurs between 3 and 56% of the time, which is a variable frequency. In 100% of patients (15/15), imatinib completely brought about haematological remission after three months. Within six months, 83% (10/12) of patients with FIP1L1-PDGFRA positivity experienced complete molecular remission, which is shown by a negative nested reverse transcriptase polymerase chain reaction (RT-PCR) for FIP1L1-PDGFRA fusion transcripts in peripheral blood. Comparatively, just three (21%) of the 14 individuals lacking this marker responded to imatinib, whereas six (43%) had partial or full clinical and haematological improvements. As a first-line treatment for HES patients with FIP1L1-PDGFRA fusion protein, Imatinib has FDA approval[17,19].

2.6. Systemic Mastocytosis

A clonal neoplastic growth of mast cells known as systemic mastocytosis (SM) is characterised by compact multifocal mast cell infiltrates in hematopoietic organs, with or without skin involvement. A wide range of illnesses, including indolent and aggressive types, make up SM. ISM (indolent SM) patients typically have a normal life expectancy. Aggressive SM (ASM), mast cell leukaemia (MCL), SM with an associated clonal haematological nonmast cell lineage disease (SM-AHNMD), and mast cell sarcoma are examples of advanced forms of mastocytosis (MSC). Mastocytosis and somatic gain-of-function point mutations in KIT are frequently linked. The KITD816V, which occurs when valine is substituted for aspartic acid at codon 816 within KIT exon 17, is the most prevalent somatic point mutation. The first TKI to be tested in SM in vitro was imatinib, but the outcomes were underwhelming. Five out of ten patients in a trial had an overall response (OR), and all responses were seen in patients who tested negative for the KITD816V mutation. In several case studies, patients with KIT mutations other than those involving KITD816V were found to benefit from imatinib. The FDA initially approved imatinib, and it is still the sole TKI, for the treatment of adult patients with ASM who do not have the KITD816V mutation or whose KIT mutational status is unknown.Apart from these cancers where Imatinib has already received FDA approval, various other cancers where Imatinib has provided dramatic responses include the following[16,17]

2.7. Fibromas that are aggressive

Desmoid tumours (desmoid tumours) are clonal fibroblastic proliferations classified as aggressive fibromatoses (AF), which are characterised by infiltrative growths with a locally aggressive behaviour and no known metastatic potential. They are linked to severe morbidity due to their local invasiveness and high recurrence rates. The most effective form of treatment for desmoid tumours is primary surgery with unfavourable surgical margins. In patients with incurable disease or as the main treatment, radiation therapy may be employed. When Mace and colleagues observed remarkable responses to imatinib in two patients with unresectable and progressing illness, they investigated the drug's potential function in aggressive fibromatoses[8,9,14]. Imatinib demonstrated outstanding response rates in 51 AF patients with or without prior treatment in a phase II Multicenter Sarcoma Alliance for Research through Collaboration (SARC) trial. At one year and three years, the PFS was 66% and 58%, respectively. Imatinib 400 mg once a day for a year was administered to 40 patients with unresectable and progressing symptoms of AF by Penel et al. While overall survival was 95%, the 1- and 2-year PFS rates were 67% and 55%, respectively. None of the investigations found a connection between the expression of Imatinib sensitive tyrosine kinase and/or its mutations with response[19].

2.8. Cancerous melanoma

A neoplasm of melanocytes is malignant melanoma (MM). Malignant melanoma incidence is rising by 4% year. Surgery is the only effective treatment for cutaneous melanoma; adjuvant therapy is only used for patients with advanced melanoma. Patients with melanomas that originate from mucosal surfaces (such as the sinuses, mouth, and vagina) or acral surfaces (such as the palms, soles, and nail beds that do not contain hair) have extremely few treatment choices and have a very short prognosis of less than a year for advanced illness. Compared to cutaneous melanomas, mucosal and acral melanomas exhibit different biologic characteristics and genetic changes. KIT-activating mutations were recently discovered in 16.7% of melanomas developing in skin with chronic UV exposure, 21% of mucosal melanomas, and 11% of acral melanomas**.** Additional cases revealed amplification or a rise in KIT copy number. A KIT mutation was

found in 15% of anal melanomas in a different publication. Studies on the usage of imatinib were started as a result of the lack of efficient treatments and the identification of KIT abnormalities. According to a study by Carvajal et al., Imatinib treatment produced a clinically significant response in this population of patients. Recent studies have also demonstrated Imatinib's efficacy in treating metastatic melanoma patients who had KIT protooncogene mutations or amplified tumours. Imatinib was used to treat 24 evaluable patients with KIT-mutant (), KIT-amplified (), or both () melanoma among 50 individuals. Out of these 24 patients, 7 experienced a partial response to therapy, and 5 had their responses confirmed by further imaging tests, for an overall response rate of 50%. Imatinib can be tried in MM having KIT aberrations[18,19].

2.9. AIDS-Related Kaposi's Sarcoma

Human herpesvirus 8 infection is linked to the spindle-cell tumour known as Kaposi sarcoma (KS), which arises from the lineage of endothelial cells (HHV-8). In contrast to other types of the illness, AIDS-related Kaposi sarcoma typically has a severe clinical course. It is the Kaposi sarcoma's most typical manifestation. A key component of effective Kaposi sarcoma treatment is achieving the best possible control of HIV infection utilising HAART. Patients with Kaposi sarcoma at low risk, however, hardly ever react to HAART alone. Following Kaposi sarcoma herpes virus (KSHV) infection of endothelial cells, autocrine and paracrine processes activate the c-KIT and platelet-derived growth factor (PDGF) receptors. Imatinib showed efficacy and was well tolerated in patients with AIDS-related Kaposi's sarcoma in a recent phase II research. 30 individuals took 400 mg of imatinib every day for up to 12 months as part of the research. Six patients (20%) showed stable illness, whereas 10 patients (33%) had partial responses. The median response time was 21 weeks, and the median response time was 36 weeks. However, neither c-KIT nor PDGF mutations, nor any variations in the potential cytokines, were shown to be correlated with response. Some individuals who respond well to traditional therapy may be given the option of imatinib as a substitute[19,20].

2.10. Chordoma

Less than 1% of CNS cancers are chordomas, which are rare tumours that develop from embryonic notochordal remains. Surgery is the primary course of action, however >50% of patients experience local relapses. At least 20% of patients have metastatic disease[20].

The therapeutic effectiveness of imatinib in the treatment of chordoma has been proven by a multicenter phase II clinical trial. In a group of patients with advanced chordoma that was advancing, imatinib treatment was beneficial in stabilising tumour growth (84%) or reducing tumour size (16%). The largest phase II study of patients with advanced chordoma and positive platelet-derived growth factor beta (PDGFB) treated with imatinib (800 mg daily) did not produce an overall tumour response as measured by RECIST. At 6 months, however, 64% of patients had shown a therapeutic improvement, 18% had some evidence of tumour size decrease, and 70% of patients had stayed stable during treatment. Imatinib may be taken into consideration in advanced chordoma due to the lack of any therapy[12,21].

3. Preparations and storage

The pills should be kept dry and should be maintained at a temperature of 25 °C (77 °F), with excursions allowed to 15 °C (30 °C) (59 °F-86 °F). A strip of 10 capsules or pills costs roughly Rs 600–1000[12].

3.1. Side Effects

Despite the fact that imatinib is typically well tolerated, it is nonetheless linked to several of the usual adverse effects, such as symptoms of fluid retention include headache, diarrhoea, weakness, nausea, vomiting, abdominal distention, edoema, rash, disorientation, and cramping. Hepatic function, cardiac failure, and myelosuppression. After receiving Imatinib treatment for six weeks, a 46-year-old lady with chronic phase CML had acute pancytopenia, fever, a chest infection, and bleeding. She later passed away from pulmonary mucormycosis. An Indian study has suggested that Imatinib use may have a negative impact on the skin. In the case of toxicity, a dose change or temporary suspension of therapy may be required. If a serious non-hematologic side event manifests (such as severe hepatotoxicity or significant fluid retention), imatinib should be discontinued until the problem is resolved. More common side effects include Bleeding from surgical wounds, bleeding gums, bloating or swelling of the face, hands, lower legs, or feet, blood in the urine, bloodshot eyes, bloodshot noses, blue lips and fingernails, blurred vision, body aches or pain, chest pain or discomfort, chills, clay-colored stools, and coughing are all symptoms of the flu. [8] Long-term effects of imatinib include cariac toxicity, abnormal bone and mineral metabolism, gynecomastia, hypothyroidism, cutaneous toxicity, hepatotoxicity, pulmonary toxicity and Secondary malignancies[20,21].

3.2. Precautions

When taking this medication, serious skin responses can happen. [10]During pregnancy the use of this medication is not recommended. Women are advised not to conceive while on treatment as Imatinib is teratogenic in rats. Until more data is acquired, the decisions must be individualized, if pregnancy occurs. There is no relevant data whether this drug passes into breast milk or not, so breast-feeding is not recommended, while using this drug. Patients on this drug should avoid activities which may cause the risk of getting cut, bruised or injured. The drugs that may require dosage adjustment or special monitoring during therapy include;

- Antifungals like itraconazole or ketoconazole;
- Antibiotics like clarithromycin, erythromycin or

Troleandomycin, Rifampicin/Rifabutin, prednisolone and dexamethasone, anticonvulsants like phenytoin, carbamazepine, clonazepam, or phenobarbital, antihypertensives like nifedipine, amlodipine, felodipine, isradipine, nimodipine, anti-anxiety medications like alpra[7]. Some inactive components in imatinib mesylate may result in allergic reactions or other severe issues[11].

3.3. Imatinib resistance

Most results of imatinib resistance arise from experiences in GISTs and chronic myeloid leukemias (CMLs). [12] Despite being a significant clinical development in the treatment of CML, imatinib resistance has proven to be a difficult issue. Resistance to Imatinib had been reported [107, \s108] soon after the introduction of the drug into clinical \spractice. Poor efforts have been made to pinpoint the causes of the primary resistance, and research into the possible causes has already started. Clinically, it would be advantageous to identify patients before the emergence of resistance, since they may benefit from more vigorous treatment[9,10].The disease stage at which treatment is started has a significant impact on the longevity of responses and response rates to imatinib. Patients with advanced-phase disease had worse preliminary responses, and most responders with advanced-phase disease tended to have temporary responses. Therapeutic resistance to imatinib was seen in approximately 10-15% of patients, and these patients can be divided into two categories based on the timing of either primary or secondary onset. It was discovered that the lack of efficacy with Imatinib treatment from the start was the cause of primary (intrinsic) resistance. It was described as an inability to reach CHR at 3 months and MCR at 6 months, and it might have been brought on by altered drug transport and/or metabolism. The initial response to Imatinib was followed by a decline of efficacy over time, which led to secondary (acquired) resistance. Overexpression of drug transporter genes, increased expression of the multi-drug resistance gene, amplification of the BCR-ABL fusion gene, mutations in the BCR-ABL kinase domain, increased protein binding of imatinib and over 233 Volume 3 Issue 4 of Advances in Biomedicine and Pharmacy (2016) Expression of tyrosine kinases like those in the SRC family was reported by Husain A et al. With a rise in BCR-ABL transcripts of 5–10 fold, the disease had progressed to an advanced stage[18,19].

Studies revealed that irregularly occurring mutations, such as T315I, were detected in them that conferred Imatinib resistance. Another study concluded that P-loop mutations were not associated with bad outcomes and that the prognosis depended on a number of additional factors. It has become clear that not all instances of imatinib resistance were caused by mutations, and the main issue was the development of resistance associated to BCR-ABL-independent pathways[21,22].

However, Gorre and colleagues suggested that BCR-ABL point mutations might be the main cause of acquired resistance to imatinib and insisted that the tyrosine kinase activity of BCRABL was still essential for the progression of disease.

In leukemic cells, DNA methyl transferases (DNMTs) were found to be overexpressed in a leukaemia type- and stage-specific way, suggesting that upregulated DNMTs may play a role in the pathogenesis of CML. This held true regardless of the information provided by Jelinek et al. They discovered that each patient had an average of 4.5 methylated genes in the CP, 6.2 methylated genes in the AP, and 6.4 methylated genes in the BC. Additionally, it was shown that individuals who were unable to tolerate or were resistant to imatinib had more methylation genes. Thus, it was discovered that DNA methylation was associated with the development of CML and Imatinib resistance. Other research largely concentrated on genes whose expression differs between Imatinib responders and non-responders. Another study suggests that Imatinib resistance in CPCML patients may be related to the transcriptional regulation of genes involved in apoptosis and anti-apoptosis, disease progression, oxidative stress, DNA repair, and genes whose products are known to interact with centrosomes[22,23].

The most frequently discovered mechanism associated with recurrence is alterations in the kinase domain, and the mutation T315I, which replaces the amino acid threonine with the amino acid isoleucine, was most frequently found in patients who were resistant to imatinib.

However, it was noted that just one patient had a point mutation and none of the 12 CML patients isolated for mutation in the BCR-ABL kinase domain had the T315I mutation[23].

Therapeutic strategies include dose escalation to reach each patient's optimal level, combination therapy, and treatment interruption may be used to control imatinib resistance.

PKC 412 is a FLT3 inhibitor that has been discovered to be effective against mutants that are Imatinib-resistant. Given the significant prevalence of resistance, it is recommended that Imatinib be used in combination with additional chemotherapeutics. These findings suggested that initial resistance to imatinib is caused by intricate mechanisms, many of which are BCR-ABL independent. The idea of combining treatment with demethylating drugs seems to be acceptable; it is also suggested that the resistance to imatinib may be multifactorial as a result. According to preliminary research, the combination of rapamycin with imatinib works synergistically to overcome mild resistance to the drug[18,19].

Table 2 Clinical trials

S.No	Study Title	Conditon or Disease	Outcome Measures
1	Docetaxel+ Imatinab Mesylate	Breast cancer	Symptomatic Deterioration
2	Imatinib Mesylate + Capecitabine in	Breast Cancer	Symptomatic Deterioration
3	Imatinib+Capecitabine + Cisplatin in	Metastatic Stomach Cancer	Safety ,Tolerability ,Overall tumor response as assessed by RECIST
4	Imatinib Mesylate (Gleevac +Sorafenib in)	Androgen-independent Prostate Cancer (AIPC)	Overall clinical benefits were measured(complete response and stable disease)
5	Imatinib Mesylate +Irinotecan +Cisplatin in	Lung Cancer	Progression-free survival
6	Imatinib Mesylate + Gemcitabine in	Recurrent Pancreatic Cancer	Determine maximum tolerated dose according to toxicity
7	Gleevec+ Gemzar	Ovarian cancer	TO Determine the safety and Torelability
8	Imatinib Mesylate + Gemcitabine	Lung Cancer	Percentage of Patients Who Meet Critieria for Response(Partial response , complete response and stable disease
9	Gleevac + Paclitaxel	Ovarian and other Cancers of Mullerian Origin	Progression-free-tolerance and the Best Overall Clinical Response

4. Conclusion

A common example of targeted therapy including tyrosine kinase inhibition is imatinib mesylate. It has transformed the treatment of cancers associated with one of its target kinases, such as c-ABL, c-KIT, and PDGFR. It has an easy method of administration and is the norm of care for CML and GIST since it has significantly altered how these diseases are perceived. Imatinib has a noteworthy function in many additional cancers and is currently the first line treatment for cancers including Ph+ ALL, advanced dermatofibrosarcoma protuberans, hypereosinophilic syndrome, and systemic mastocytosis.Imatinib also demonstrated its value for SR- cGVHD patients who lack access to other therapies including extracorporeal photopheresis.A proper follow-up reduces side effects and aids in the identification of imatinib resistance. Tyrosine kinases are crucial in the neoplastic development of several human malignancies. Imatinib's success has sparked a remarkable effort to create tailored PTK therapy based on the discovery of over 40 chromosomal translocations that result in the deregulation of 12 different PTK associated to diverse hematologic malignancies. No other targeted medicines, compared to imatinib, have made a significant contribution to the therapeutic arsenal in cancer. It also served as a tool for figuring out how diseases like CML and GIST work. Despite the positive outcome,

Imatinib encountered the nascent issue of resistance, while combinatory therapy appears to hold promise for addressing this issue. Imatinib is considered as a wonder drug‖ as it has contributed greatly to the field of oncology.

Compliance with ethical standards

Acknowledgments

I would like to thanks ms. K. A. Vijetha (Assistant professor) for proper Guidence and centre for pharmaceutical sciences, IST for providing all necessory assessory lab chemical and e-library.

Disclosure of conflict of interest

Both author have equal contributed in the manuscript and No conflict of interest.

References

[1] Van den Abbeele AD, Badawi RD. Use of positron emission tomography in oncology and its potential role to assess response to imatinib mesylate therapy in gastrointestinal stromal tumors (GISTs). European journal of cancer. 2002 Sep 1;38:S60-5.

[2] Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, Chen LL, Podoloff DA, Benjamin RS. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. Journal of clinical Oncology. 2007 May 1;25(13):1753-9.

[3] Burger K, Nooter K. Pharmacokinetic resistance to imatinib mesylate: role of the ABC drug pumps ABCG2 (BCRP) and ABCB1 (MDR1) in the oral bioavailability of imatinib. Cell cycle. 2004 Dec 1;3(12):1502-5.

[4] Huse DM, Von Mehren M, Lenhart G, Joensuu H, Blanke C, Feng W, Finkelstein S, Demetri G. Cost effectiveness of imatinib mesylate in the treatment of advanced gastrointestinal stromal tumours. Clinical drug investigation. 2007 Feb;27:85-93.

[5] Weigel MT, Dahmke L, Schem C, Bauerschlag DO, Weber K, Niehoff P, Bauer M, Strauss A, Jonat W, Maass N, Mundhenke C. In vitro effects of imatinib mesylate on radiosensitivity and chemosensitivity of breast cancer cells. BMC cancer. 2010 Dec;10:1-4.

[6] Ramanathan RK, Egorin MJ, Takimoto CH, Remick SC, Doroshow JH, LoRusso PA, Mulkerin DL, Grem JL, Hamilton A, Murgo AJ, Potter DM. Phase I and Pharmacokinetic Study of Imatinib Mesylate in Patients With Advanced Malignancies and Varying Degrees of Liver Dysfunction: A Study by the National Cancer Institute Organ Dysfunction. Journal of Clinical Oncology. 2008 Feb 1;26(4):563-9.

[7] Dagher R, Cohen M, Williams G, Rothmann M, Gobburu J, Robbie G, Rahman A, Chen G, Staten A, Griebel D, Pazdur R. Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clinical Cancer Research. 2002 Oct;8(10):3034-8.

[8] Choi H, Charnsangavej C, de Castro Faria S, Tamm EP, Benjamin RS, Johnson MM, Macapinlac HA, Podoloff DA. CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment. Am J Roentgenol. 2004 May 18;183:1619-28.

[9] Cohen MH, Williams G, Johnson JR, Duan J, Gobburu J, Rahman A, Benson K, Leighton J, Kim SK, Wood R, Rothmann M. Approval summary for imatinib mesylate capsules in the treatment of chronic myelogenous leukemia. Clinical cancer research. 2002 May;8(5):935-42.

[10] Le Cesne A, Van Glabbeke M, Verweij J, Casali PG, Findlay M, Reichardt P, Issels R, Judson I, Schoffski P, Leyvraz S, Bui B. Absence of progression as assessed by response evaluation criteria in solid tumors predicts survival in advanced GI stromal tumors treated with imatinib mesylate: the intergroup EORTC-ISG-AGITG phase III trial. Journal of clinical oncology. 2009 Aug 8;27(24):3969.

[11] Mundhenke C, Weigel MT, Sturner KH, Roesel F, Meinhold-Heerlein I, Bauerschlag DO, Schem C, Hilpert F, Jonat W, Maass N. Novel treatment of ovarian cancer cell lines with Imatinib mesylate combined with Paclitaxel and Carboplatin leads to receptor-mediated antiproliferative effects. Journal of cancer research and clinical oncology. 2008 Dec;134:1397-405.

[12] Champagne MA, Capdeville R, Krailo M, Qu W, Peng B, Rosamilia M, Therrien M, Zoellner U, Blaney SM, Bernstein M. Imatinib mesylate (STI571) for treatment of children with Philadelphia chromosome-positive leukemia: results from a Children's Oncology Group phase 1 study. Blood. 2004 Nov 1;104(9):2655-60.

[13] Burger H, van Tol H, Boersma AW, Brok M, Wiemer EA, Stoter G, Nooter K. Imatinib mesylate (STI571) is a substrate for the breast cancer resistance protein (BCRP)/ABCG2 drug pump. Blood. 2004 Nov 1;104(9):2940-2.

[14] Trent JC, Patel SS, Zhang J, Araujo DM, Plana JC, Lenihan DJ, Fan D, Patel SR, Benjamin RS, Khakoo AY. Rare incidence of congestive heart failure in gastrointestinal stromal tumor and other sarcoma patients receiving imatinib mesylate. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2010 Jan 1;116(1):184-92.

[15] Strebhardt K, Ullrich A. Another look at imatinib mesylate. New England Journal of Medicine. 2006 Dec 7;355(23):2481.

[16] George DJ. Receptor tyrosine kinases as rational targets for prostate cancer treatment: platelet-derived growth factor receptor and imatinib mesylate. Urology. 2002 Sep 1;60(3):115-21.

[17] Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. Journal of Pharmacology and Experimental Therapeutics. 2005 Dec 1;315(3):971-9.

[18] Holdsworth CH, Badawi RD, Manola JB, Kijewski MF, Israel DA, Demetri GD, Van den Abbeele AD. CT and PET: early prognostic indicators of response to imatinib mesylate in patients with gastrointestinal stromal tumor. American Journal of Roentgenology. 2007 Dec;189(6):W324-30.

[19] Force T. In reply to'Cardiotoxicity of the cancer therapeutic agent imatinib mesylate'. Nature medicine. 2007 Jan 1;13(1):15-6.

[20] Stroobants S, Goeminne J, Seegers M, Dimitrijevic S, Dupont P, Nuyts J, Martens M, Van den Borne B, Cole P, Sciot R, Dumez H. 18FDG-Positron emission tomography for the early prediction of response in advanced soft tissue sarcoma treated with imatinib mesylate (Glivec®). European journal of cancer. 2003 Sep 1;39(14):2012-20.

[21] Blanke CD, Demetri GD, Von Mehren M, Heinrich MC, Eisenberg B, Fletcher JA, Corless CL, Fletcher CD, Roberts PJ, Heinz D, Wehre E. Long-term results from a randomized phase II trial of standard-versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. Journal of clinical oncology. 2008 Feb 1;26(4):620-5.

[22] Candelaria M, Arias-Bonfill D, Chávez-Blanco A, Chanona J, Cantú D, Pérez C, Dueñas-González A. Lack in efficacy for imatinib mesylate as second-line treatment of recurrent or metastatic cervical cancer expressing platelet-derived growth factor receptor α. International Journal of Gynecologic Cancer. 2009 Nov 1;19(9).

[23] Kubo T, Piperdi S, Rosenblum J, Antonescu CR, Chen W, Kim HS, Huvos AG, Sowers R, Meyers PA, Healey JH, Gorlick R. Platelet-derived growth factor receptor as a prognostic marker and a therapeutic target for imatinib mesylate therapy in osteosarcoma. Cancer. 2008 May 15;112(10):2119-29.