A Review on Imatinib: A wonder drug in Oncology

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Abstract

Imatinib is one of the first cancer therapies that has shown a potential for a novel approach in cancer treatment. Imatinib represents a therapeutic breakthrough as a targeted therapy in the form of selective tyrosine kinase inhibitors (TKIs) specifically BCR-ABL, c-KIT, PDGFRA. It has become the first line drug in management of several cancers. Apart from its remarkable success in CML, it has also shown promising results in the treatment of gastro-intestinal stromal tumors, clonal eosinophilic disorders, philadelphia chromosome positive acute lymphatic leukemia and in steroid-refractory chronic graft-versus-host disease because of its anti-PDGFR action. Introduction of Imatinib has radically improved the outcome of patients and has geared up further research into development of designer drugs with molecular targets. Apart from clinical profits of Imatinib in several cancers, it is associated with drug resistance and intolerance. This article gives a comprehensive review of the development, biology, utility, dosing, and limitations of Imatinib in oncology.

Keywords: Tyrosine kinase, oncology, leukemia, tumors, molecular target.

Introduction

Imatinib a tyrosine kinase inhibitor was called as “magical bullet,” in 2001 when it revolutionized the treatment of chronic myeloid leukemia (CML). Imatinib was well known by the names “Gleevec, Glivec and STI57” [1]. This was the beginning of the “Imatinib period.” Imatinib was perfect drug for targeted cancer therapy, in which only cancer phenotype, associated with BCR-ABL activity, was changed and normal features were unchanged. This gave new anticipation for prevention of unwanted side effects, which were usually associated with the use of chemotherapeutic drugs [2]. In May 2001 Imatinib was approved by the Food and Drug Administration for the treatment of CML that was refractory to interferon therapy and for the treatment of gastrointestinal stromal tumors in February 2002 [3]. Imatinib currently marketed by Novartis as Gleevec (USA) or Glivec (Europe/Australia) as mesylate salt (Imatinib mesilate INN), it was the first member of a new class of agents that act via inhibiting specific tyrosine kinase enzymes, in place of non-specifically inhibiting rapidly dividing cells. Celonib, Imalak, Lupitinib, Mesylonib, Mitinab were some of the brands of Imatinib which were available in market. These were manufactured by some of the leading pharmaceutical companies like Cipla, Lupin, Glenmark, etc. The average weight of Imatinib is 493.6027 and is represented by the chemical formula of C₂₉H₃₁N₇O.
Tyrosine kinases are essential mediators of the signaling cascade, and play key roles in growth, differentiation, metabolism, and apoptosis in response to external and internal stimuli [12, 13]. Several protein kinases are downregulated and several are overexpressed in human cancers [14-16]. Imatinib showed activities against ABL, BCR-ABL, PDGFRα, and c-KIT. It inhibited the constitutively active fusion product arising from the Philadelphia (Ph) chromosome of chronic myelogenous leukemia (CML) and c-kit (CD117), which was overexpressed in gastrointestinal stromal tumors.

Tyrosine kinases have an active site for binding ATP. Transfer of the terminal phosphate from ATP to tyrosine residues on its substrates, causes protein tyrosine phosphorylation which leads to the activation of signal-transduction pathways. Imatinib damages BCR-ABL-mediated transfer of phosphate to its substrates. Imatinib works by binding close to the ATP binding site, locking it in a closed or self-inhibited conformation, thus inhibiting the enzyme activity of the protein semi competently, ultimately resulting in “switching-off” of the downstream signaling pathways that support leukemogenesis [17]. Imatinib also obstructs these ABL proteins of non-cancer cells, but cells normally have extra redundant tyrosine kinases which let them to continue to function even if ABL tyrosine kinase is inhibited [18-21]. BCR-ABL tyrosine kinase inhibition also stimulates its entry into the nucleus, where it is incapable of performing any of its normal functions [4, 5]. Imatinib had extraordinary activity against CML and gastrointestinal stromal tumors in early trials [14, 22, 23].

**Pharmacokinetics**

After oral administration the bioavailability of drug was 90% [24], with Cmax achieved within 2-4 hours post-dose. The elimination half-lives of Imatinib and its active metabolite, the N-demethyl derivative (CGP74588), were approximately 18 and 40 hours, respectively. Increased doses ranges from 25 mg-1000 mg, also increases mean Imatinib AUC proportionally. Repeated dosing of Imatinib did not show any significant change in its pharmacokinetics. There is a 1.5- to 3-fold drug accumulation at steady-state after once-daily dose [25]. Plasma protein binding of Imatinib was approximately 95%, and is mostly to albumin and α1-acid glycoprotein. Imatinib metabolized in the liver and was facilitated by several isozymes of the cytochrome P450 system, including CYP3A4, CYP3A5 and, to a lesser extent, CYP1A2, CYP2D6, CYP2C9, and CYP2C19. The main enzyme responsible for metabolism of Imatinib is CYP3A4. Other cytochrome P450 enzymes, played a minor role in its metabolism. Interactions may occur between Imatinib and Inhibitors/inducers of these
enzymes, leading to changes in the plasma concentration of Imatinib as well as co-administered drugs [26].

The main metabolite, N-demethylated piperazine derivative, was also active, formed predominantly by CYP3A4. It showed potency similar to the Imatinib. The plasma AUC for this metabolite was about 15% of the AUC for Imatinib. The half-lives were 13.5 ± 0.9 h for Imatinib, 20.6 ± 1.7 h for N-desmethyl metabolite. Bile and feces was the major route of elimination and only a small portion of the drug was excreted in the urine. Most of Imatinib were eliminated as metabolites and only 25% was eliminated as unchanged (5% urine, and 20% feces) [24-26].

**Clinical Implication**

**Chronic Myeloid Leukemia**

As a result of a reciprocal translocation between chromosomes 9 and 22 (Philadelphia (Ph) chromosome), BCR-ABL (break point cluster region-abelson proto-oncogene) fusion gene was formed and were the [27, 28], driving force for leukemogenesis in CML [19]. Imatinib an inhibitor of BCR-ABL rapidly and dramatically modified the treatment of CML and led to important changes in management [29]. Imatinib was definite for the TK domain in abl (the Abelson proto-oncogene), c-kit and PDGF-R (platelet derived growth factor receptor) [30]. A phase II clinical trial was conducted in 39 Japanese patients in the first chronic phase of CML [31]. Hematologic complete response was achieved in 92.3% of the patients, complete cytogenetic response (CR) was achieved in 43.6%, and major partial CR was acquired in 20.5% of the patients. The early studies by Druker et al. indicated high response rates to Imatinib in patients with advanced CML and those pretreated with IFN-α [32]. The IRIS study, a milestone study in CML, by O’Brien et al. linked Imatinib and the combination of interferon-alpha (INF-α) with cytarabine in a randomized trial in 1106 CP-CML patients [33]. Imatinib induced broad haematological response (CHR) in 95.3% patients and complete cytogenetic response (CCR) in 73.8% patients [33]. In addition, patients on Imatinib had an improved quality of lifespan [34]. Imatinib received FDA approval in December 2001 on the basis of these results. Imatinib induced CHR in 98% of patients in chronic phase and CCR in 87% patients in 6 years follow up of IRIS trials [35]. The goal of treatment with Imatinib was the achievement of major molecular response (MMR). Gaining MMR was associated with significantly improved long term remission duration and progression-free survival (PFS). At 60-month follow-up, success of CCR and MMR by 12 months was associated with a PFS of 97% compared to 89% for patients with CCR but with less than MMR. Early molecular response projected better outcome, progression of disease correlated with disappointment to achieve a 1-log reduction in transcript level by 3 months and a 2-log reduction by 6 months [35]. Previously established poor prognostic significance of marrow fibrosis in CML was less related with Imatinib therapy [36]. There was limited data available on treatment of CML with Imatinib in pediatric patients. Imatinib was less costly and more efficacious than BMT in the 2-year treatment of Ph [+] CML [37].

**Gastrointestinal Stromal Tumors**

Gastrointestinal stromal tumors (GISTs) were mesenchymal neoplasms of the gastrointestinal (GI) tract, mesentery, or omentum that expressed the protein-tyrosine kinase KI and responsible for <1% of primary gastrointestinal neoplasms. They were believed to arise from the interstitial cells of cajal. GISTs were classically defined by the expression of c-KIT (CD117) in the tumor cells; in 85-95% of GISTs these activated KIT mutations was seen. About 3–5% of the remainder of KIT-negative GISTs covered PDGFRA mutations [38, 39]. Imatinib inhibits the tyrosine kinase activity of KIT.

A number of clinical studies confirmed the effectiveness of Imatinib in the management of unresectable or metastatic GIST [40-44]. These studies include examining the efficacy, tolerability and different dosing regimens of Imatinib. In a phase III randomized trial, 746 patients with advanced incurable GIST, 800 mg Imatinib was not found to be greater to 400 mg Imatinib as primary systemic therapy; no statistically significant changes in objective response rates, progression-free survival (PFS), or overall survival (OS) were observed [42]. However, in a phase II randomized trial examining dose choice in 946 patients with advanced GIST, patients whose tumors expressed an exon 9KIT mutation, treated with a daily dose of 800 mg of Imatinib (versus 400mg), experienced a significantly superior PFS (P = 0.0013) with a fall of relative risk of 61% [45].

Surgery was the basis of curative treatment for primary resectable GIST patients. However, GIST tumors had a high risk of relapse and can be considered for adjuvant therapy [46, 47]. At least three phase III trials had assessed the benefit of adjuvant Imatinib. In one randomized, double-blinded phase III trial, 713 patients who had undergone complete gross resection of a primary GIST measuring at least 3 cm and expressing KIT had been treated with Imatinib (400mg daily) or placebo for 1 year.
The 1-year relapse-free survival (RFS) rate was 98 versus 83% supporting Imatinib. The absolute benefit was greatest in those with high-risk disease (relapse rate 47 versus 19% for placebo and Imatinib, respectively); for moderate risk disease it was 14 versus 5%, respectively. Overall survival benefit was not found. In another phase III trial, 908 patients with intermediate or high-risk GIST and with tumor rupture or intraoperative tumor spillage were randomly assigned to 2 years of Imatinib or observation alone [49].

At a median follow-up of 4.7 years, 5-year Imatinib-free survival (IFS) was 87% in the Imatinib arm related to 84% in the control arm, 3-year RFS was 84 versus 66%, and 5-year overall survival was 100 versus 99%. The Scandinavian Sarcoma Group (SSG) XVIII trial compared 36 versus 12 months of adjuvant Imatinib (400mg daily) in 400 patients associated with high-risk GIST [50]. At a median follow-up of 54 months, prolonged treatment was associated with a significant improvement in RFS and the primary endpoint (5-year RFS 66 versus 48%) as well as overall survival (92 versus 82%) at a median follow up of 54 months. It had amplified the 1-year survival rates in high risk GISTS to more than 90% and also improved the 5-year survival rates after surgical resection [51]. After CML, Imatinib dramatically improved both the management and prognosis for this rare disease [52].

**Dermato fibro sarcoma Protubersans**

(DFSP) is a rare soft tissue tumor and represents approximately 1% of sarcomas with an indolent growth and a less than 5% probability of metastases [53]. DFSP was categorized by the presence of distinctive, reciprocal rearrangement of chromosomes 17 and 22. The reorganization leads to the fusion of alpha chain type a (COL1A1) localized on 17q22 to the platelet-derived growth factor beta (PDGFB) localized on 22q13. The development of COL1A1-PDGFB fusion gene resulted in the constitutional up regulation of PDGFB expression, leading to constant autocrine stimulation of PDGF receptor B (PDGFRB) which was a key pathogenetic factor [54]. In various in vitro and in vivo studies [55] initial case reports showed the benefit of Imatinib in metastatic and locally advanced DFSP [56, 57]. In neo adjuvant setting also, DFSP has been testified to be treated with Imatinib, with doses between 400 and 800mg daily for a period ranging from 2 to 24 months (median, 4 months), produced an average tumor decline of 50% (range: 19%–100%) after a median follow-up time of 24 months (range: 88 days to 72 months) [58-61].

**Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (ALL)**

ALL is a molecular abnormality present in approximately 30% of newly diagnosed cases of adult ALL. The occurrence of this disease is age-dependent and conferred an unfavorable prognosis. This disease results from the translocation of chromosomes 9 and 22 producing a fusion gene, BCRABL [62] and expression of which results in two different sized proteins, p190 and p210. While p190 protein is responsible for Ph-positive (Ph+) ALL, and p210 protein is predominant in chronic myelogenous leukemia (CML) [63]. However, Imatinib has been found to be a favorable drug in this type of ALL. In a latest study by Lee and colleagues on 18 patients with Ph+ ALL, sequential chemotherapy and Imatinib was given prior to transplantation. Later a median follow-up duration of 25 months revealed that the probability of disease free survival and overall survival was 78% and relapse rate was low at 4%. Researchers studied the long-term outcome of 335 patients on three diverse treatment schedules of Imatinib (600 mg/day) [64]. In the first cohort patients received Imatinib between induction and first consolidation as well as after the first consolidation therapy. The second cohort was treated during the second half of induction chemotherapy with Imatinib and continued till allo-SCT. The third cohort patients started receiving Imatinib with induction chemotherapy and continued until allo-SCT. At 4-year assessment, total survival was found to be highest (50%) in patients in the third cohort. These results suggest that Imatinib treatment should be started early with prolonged duration. The single huge multinational, prospective study on two cohorts of Ph+ ALL patients exhibited analogous results [65]. Patients in Cohort 1 received Imatinib following induction, while Cohort 2 patients received Imatinib in the second phase of induction. Patients who were treated early with Imatinib showed improved response in terms of overall survival, event-free survival, and relapse-free survival. These results again support the observation of treating Ph+ ALL patients earlier in therapy with Imatinib and hence approved as a first line therapy for Ph+ ALL.

**Hypereosinophilic Syndromes/Chronic Eosinophilic Leukemia**

The hypereosinophilic syndromes (HES) are a rare group of disorders described by the overproduction of eosinophils, which is characterised by a blood eosinophil count >1.5 × 109/L for at least 6 months without any detectable cause and related organ damage [66]. HES is an analysis of exclusion, once clonal eosinophilia (such as leukemia) and reactive eosinophilia (in response to
infection, autoimmune disease, tropical eosinophilia, or cancer) had been ruled out [67]. Some HES patients were linked with an omission in chromosome 4, which fuses the FIP1-like-1 gene (FIP1L1) to the PDGFRA gene, leads to FIP1L1-PDGFRα rearrangement. The patients with a FIP1L1-PDGFRα rearrangement were now renamed as chronic eosinophilic leukemia (CEL), as this gene had become a marker of disease clonality [68]. The first-line and second line treatment of HES was prednisone with a response rate of nearly 70% and interferon-α or hydroxyurea [69, 70]. The frequency of this fusion gene was variable between 3 and 56% [71, 72]. In 100% of patients (15/15) within three months, Imatinib induced complete hematological remission [73]. Imatinib as a first-line therapy in HES patients with FIP1L1-PDGFRα fusion protein, is approved by FDA.

**Systemic Mastocytosis**

Systemic mastocytosis (SM) is defined by compact multifocal mast cell infiltrates in hematopoietic tissues with or without skin involvement. It is a clonal neoplastic proliferation of mast cells [74]. SM is a mixed spectrum of disorders: indolent to aggressive forms occur. Most patients had a normal life expectancy with indolent SM (ISM). Advanced forms of mastocytosis consist of aggressive SM (ASM), mast cell leukemia (MCL), SM with an associated clonal hematological non-mast cell lineage disease (SM-AHNMD), and mast cell sarcoma (MSC) [74]. Mastocytosis is frequently connected with somatic gain of-function point mutation with KIT. The utmost common somatic point mutation is KITD816V, which results from substitution of valine for aspartic acid at codon 816 within KIT exon 17 [75-77]. A study demonstrated an overall response of imatinib in 5 out of 10 patients, and two were seen in patients negative for KITD816V mutation, the result were disappointing [78]. Imatinib was found to be effective in patients carrying KIT mutations without involving KITD816V in some case reports [79, 80]. Imatinib was approved by the FDA for treatment of adult patients with ASM without the KITD816V.

**Aggressive Fibromatoses**

Aggressive fibromatoses (desmoid tumors) (AF) is the clonal fibroblastic proliferations described by infiltrative growths with a locally aggressive behavior and no known metastatic potential [81]. Because of local invasiveness and high relapse rates, they are linked with significant morbidity. Mace and colleagues explained the role of Imatinib in aggressive fibromatoses when they reported dramatic response to Imatinib in two patients with unresectable and progressive disease [82]. In a phase II Multicenter Sarcoma Alliance for Research through Collaboration (SARC) trial, Imatinib showed remarkable response rates in 51 AF patients with or without previous treatment and locally advanced disease [83]. Penel et al. treated patients with unresectable and progressive symptomatic AF with Imatinib 400 mg daily for 1 year [84]. PFS rates were 67% and 55%, for 1 and 2 years respectively, while overall survival rate was 95%.

**Malignant Melanoma**

Malignant melanoma (MM) is a neoplasm of melanocytes and its incidence were increased by 4% every year. Patients with melanomas arise from mucosal surfaces (e.g., sinuses, mouth, and vagina) or acral surfaces (e.g., non-hair-containing palms, soles, and nail beds) survive less than 12 months in advanced disease due to limited treatment options. As compared with cutaneous melanomas, mucosal and acral melanoma has different genetic alterations and biologic behavior. Due to a deficiency of effective therapies and detection of KIT aberrations, studies on the use of Imatinib were initiated. A study by Carvajal et al. noticed that treatment with Imatinib in this subset of patients resulted in clinically significant response [85]. Recent studies also proved the effectiveness of Imatinib in patients with advanced melanoma harboring mutations or amplification of the KIT protooncogene [86, 87]. Of 50 patients with melanomas, 24 evaluable patients with KIT-mutant of these 24 patients, 7 achieved a partial response to therapy, with 5 patients’ responses confirmed on subsequent imaging studies, for an overall confirmed response rate of 21% [86, 87]. Imatinib can be effective in MM having KIT aberrations.

**AIDS-Related Kaposi’s Sarcoma**

Kaposi sarcoma (KS) is a spindle-cell tumor resulting from endothelial cell lineage, linked with infection with human herpes virus 8 (HHV-8). AIDS-related Kaposi sarcoma tends to have an aggressive clinical course representing the most common presentation of Kaposi sarcoma [88]. The integral part of successful Kaposi sarcoma therapy was optimal control of HIV infection using HAART [89]. However activation of c-KIT and platelet-derived growth factor (PDGF) receptors by autocrine and paracrine mechanisms follows Kaposi Sarcoma herpes virus (KSHV) infection. During phase II study, Imatinib demonstrated activity and was well tolerated in patients with AIDS-related Kaposi’s sarcoma [90]. The study included patients who received 400 mg Imatinib daily for up to 12 months. Overall, 33% patients achieved partial response and 20% patient’s demonstrated stable disease. Imatinib may be considered as an alternative therapy in some patients who progress on conventional therapy.
Chordoma

Phase II clinical trial had confirmed the efficacy of Imatinib in the treatment of chordoma. These are rare tumors that arise from embryonic notochordal remnants, comprising less than 1% of CNS tumors [91]. Treatment with Imatinib was 84% successful in stabilizing tumor growth and 16% in shrinking tumor size 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 produce an overall tumor response defined by RECIST. However, at 6 months, 70% of patients stayed stable during treatment, 64% showed a clinical advantage, and 18% showed some decline in tumour size [92]. Imatinib may be considered in advanced chordoma due to lack of any therapy.

Recurrent Epithelial Ovarian Cancer

Most patients relapse with epithelial ovarian cancer (EOC). The second-line drug therapy includes, taxanes, topotecan, pegylated liposomal doxorubicin, and/or gemcitabine [93]. Platelet derived growth factor (PDGF) and its receptor has been occupied in the early transformation and sustaining of tumor growth, their linked vascular endothelium, and signaling between tumor and stroma [94]. Numerous preclinical studies [95, 96] directed to the use of Imatinib as a single agent for ovarian cancer, revealed some activity and some intolerance. During phase II study, 14 patients with recurrent epithelial ovarian cancer (rEOC) were treated with Imatinib and weekly paclitaxel. The objective responses occurred in 4 patients and 5 of the 12 patients treated had a PFS of more than 6 months with negligible toxicities [97]. However it was found to have some response, further studies on the role of Imatinib in rEOC are warranted.

Anaplastic Thyroid Cancer

Anaplastic Thyroid Cancer the most aggressive thyroid gland malignancy was anaplastic carcinoma of the thyroid (ATC). Imatinib showed efficacy in inhibiting growth of ATC cell lines during preclinical studies [98]. Even though the molecular target of this agent is not clearly defined, proposed mechanisms contain inhibition of PDGF, KIT, and c-ABL. A single-institution study of Imatinib 400mg twice daily orally in 11 patients with ATC was recently informed [99, 100] however the trial was prematurely terminated.

Steroid-Refactory Chronic Graft-versus-Host Disease

(SRcGVHD) Management for SR-cGVHD is challenging. Imatinib is a strong dual inhibitor of both transforming growth factor-b and platelet-derived growth factor receptor (PDGF-R) pathways, which is accountable for fibrosis and inflammation in cGVHD [101]. It also inhibits T-cell proliferation [102]. In phase II study, Imatinib was tried in 40 patients with SR-Cgyvd [103]. After 6 months, 14 had partial responses (PR), 4 minor responses (MR) with relevant steroid sparing (46%) according to Courriel criteria, and 20 additional than or equal to PR (51.3%), as per the National Institutes of Health (NIH) criteria and NIH severity score changes. The best responses were seen in the lungs, gut, and skin. After a median follow-up of 40 months, 28 patients were alive, with a 3-year overall survival (OS) and event-free survival of 72% and 46%, respectively. There was a significant reduction in PDGF-R stimulatory activity in 7 responders, whereas it stayed high in 4 non responders. So, Imatinib signifies a valuable option for patients with SR-cGVHD [103].

Dosage and Administration

The recommended dose of Imatinib mesylate for adult patients in CML chronic phase is 400 mg/day [25] and for CML accelerated phase/blast crisis is 600 mg/day. The recommended dose is 260 mg/m2/day for children with Ph+ chronic phase CML, recurrent after transplantation or who are resistant to interferon-alpha therapy, 400 mg/day is the recommended dose for gastrointestinal stromal tumors or for adults with unresectable and/or metastatic, malignant GISTs is 600 mg/day. The dose of Imatinib should be given with glass of water. In children once daily dose may be given or it can be split into two. The dose may be dissolved in water or apple juice (50-100ml) if patient is unable to swallow the tablet. The dose may be increased/ doubled in adult CML cases, in the absence of severe adverse events and severe non-leukemia related neutropenia/ thrombocytopenia in the following circumstances:

- Progression of disease (at any time);
- Failure to achieve a satisfactory hematologic response after at least 3 months of therapy;
- Cytogenetic response after 6-12 months of therapy;
- Loss of an earlier hematologic
- Cytogenetic response.

If clinically indicated the dose may be increased to 340 mg/ m2/day in children. Increased iron level can be developed in Patients on high doses of Imatinib.
Preparations and storage

The tablets are stored at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) and should be protected from moisture. The cost of strip of 10 capsules/tablets is approximate Rs 600-1000.

Side effects of Imatinib therapy

Though Imatinib is generally well tolerated, it is still associated with some of the common side effects including fluid retention, headache, diarrhea, loss of appetite, weakness, nausea, vomiting, abdominal distention, edema, rash, dizziness, and muscle cramps, myelosuppression, heart failure, and liver function [104]. Lokeshwar et al reported a case of 46-year-old woman with chronic phase CML, who developed severe pancytopenia associated with fever, chest infection and bleeding after 6 weeks of therapy with Imatinib, she died of pulmonary mucormycosis. The use of Imatinib may causes dermatological toxicity has been reported in an Indian study [105]. Dose adjustment or temporary stoppage of therapy may be needed in the event of toxicity. Imatinib should be withheld until the event is resolved if a severe non hematologic adverse event develops (such as severe hepatotoxicity or severe fluid retention). If rises in serum bilirubin >3 times upper limit of normal (ULN) or in hepatic transaminases >5 times ULN occur, Imatinib should be withdrawn until bilirubin values had resumed to a <1.5 x ULN and transaminase levels to <2.5 x ULN. If ANC is <1.0 x 10^9/L and/or platelets <50 x 10^9/L, discontinue Imatinib until ANC >1.5 x 10^9/L and platelets >75 x 10^9/L. If reappearance happens, discontinued and restart at reduced dose. If cytopenia continued for 4 weeks and was still unrelated to leukemia, discontinued Imatinib until ANC >1 x 10^9/L and platelets >20 x 10^9/L and then restart at 300 mg daily dose. Unexpected late side effects may be gynecomastia and low testosterone and are common in males treated with Imatinib [104, 106].

Precautions

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 [104]. 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 likeitraconazole 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 agents like alprazolam, diazepam, or triazolam;
- Cholesterol lowering drugs likelovastatin, atorvastatin, or simvastatin and cyclosporin, pimozone, warfarin etc [11].

Imatinib resistance

Although a major clinical advance in the treatment of CML, Imatinib resistance has turn out to be a challenging problem. Resistance to Imatinib had been reported [107, 108] soon after the introduction of the drug into clinical practice. Reasons contributed to primary resistance are poorly identified and investigation of routes underlying has begun [109]. Clinically, it would be beneficial to recognize patients prior to the resistance onset, since they may benefit from additional aggressive therapy [110-112]. Durability of responses and response rates to Imatinib are highly dependent on the stage of disease at which treatment is introduced [113-116]. Preliminary responses were poorer in patients with advanced-phase disease and responses tended to be transient inmost responders with advanced-phase disease. Approximately 10–15% of patients were associated with therapeutic resistance to Imatinib and can be classified according to the time of onset as primary or secondary [109]. Primary (intrinsic) resistance was found to be due to the lack of efficacy from the onset of treatment with Imatinib. It was as an inability to achieve CHR at 3 months and MCR at 6 months and may be caused by differential drug metabolism and/or drug transport. Secondary (acquired) resistance was due to the initial response followed by a loss of efficacy with the time of exposure to Imatinib [108-110]. It may also be caused by mutations in the BCR-ABL kinase domain, amplification of the BCR-ABL fusion gene, overexpression of drug transporter genes, enhanced expression of the multi-drug resistance gene, excessive binding of Imatinib by protein [117-123] and over
expression of tyrosine kinases such as the SRC family kinases [112,124]. It was a progression to advanced disease with a 5–10-fold increase in BCR-ABL transcripts. Studies showed that mutations consulting resistance to Imatinib, including T315I, were found irregularly in them [125]. Another study showed that P-loop mutations were not linked with poor effect and recommended that the prognosis was dependent on several other factors [112]. It turns out to be evident that the existence of mutations did not describe all cases of Imatinib resistance and the evolving problem was the primary resistance linked with BCR-ABL-independent mechanisms [126,127]. Nevertheless, Gorre and colleagues revealed that point mutations in BCR-ABL may be the primary mechanism of acquired resistance to Imatinib, advising that the tyrosine kinase activity of BCRABL remained crucial in progressive disease.

It was reported that DNA methyl transferases (DNMTs) were over expressed in leukemic cells in a leukemia type- and stage-specific manner and therefore up regulated DNMTs may contribute to the pathogenesis of CML [128,129]. This was constant with the data offered by Jelinek et al. [130]. They observed that the average number of methylated genes was 4.5 per patient in the CP, increasing to 6.2 in the AP and 6.4 in the BC. A greater number of methylated genes were also detected in patients resistant or intolerant to Imatinib. Thus, DNA methylation was linked with CML progression and resistance to Imatinib. Other studies focused mainly on genes whose expression varies between responders and non-responders to Imatinib [131–133]. Another study propose that the transcriptional regulation of apoptotic and anti-apoptotic genes, disease progression genes, oxidative stress genes, genes for DNA repair and genes whose products were known to interact with centrosomes was connected with Imatinib resistance in CPCML patients [132]. Subsequently kinase domain mutations are the most regularly identified mechanism linked with relapse and the substitution of threonine with isoleucine at residue 315 (T315I) was the utmost frequently detected mutation in Imatinib resistant patient [134]. Though, it was reported that none of 12CML patients separated for mutation in the BCR-ABL kinase domain had the T315I mutation and only single patient had a point mutation [135]. Imatinib resistance could be manage by therapeutic approaches such as dose escalation to attain individual optimal levels, combination therapy, as well as treatment interruption.

PKC 412 is an fms-like tyrosine kinase 3 (FLT3) inhibitor found to be effective against Imatinib-resistant mutants [136]. The high incidence of resistance suggests that Imatinib should be combined with other chemotherapeutic agents [32, 137-139, 140]. These data proposed that primary resistance to Imatinib is mediated by complex mechanisms, which is mostly BCR-ABL independent. It is also proposed that the resistance to Imatinib could be multi factorial as a result; the idea of combined treatment with de methylating agents seems to be acceptable. Preliminary studies showed that the combination of rapamycin to Imatinib acts synergistically, to overcome moderate resistance to imatinib [141–143].

Conclusion

Imatinib mesylate is a standard example of targeted therapy through tyrosine kinase inhibition. It has revolutionized the therapy of malignancies that are linked to one of its target kinases, c-ABL, c-KIT, and PDGFR. It has convenient mode of administration and is the standard of care in CML and GIST as it has noticeably changed the viewpoint of these diseases. The remarkable role of Imatinib can be seen in various other cancers and has achieved first line position in cancers like Ph+ ALL, advanced dermatofibrosarcoma protubersans, hypereosinophilic syndrome, and systemic mastocytosis. Imatinib also proved it’s important in patients with SR-cGVHD who cannot access other treatments like extracorporeal photopheresis. An appropriate follow up minimizes side effects and helps in detection Imatinib resistance. In many human cancers, tyrosine kinases play critical role in neoplastic process. The achievement of Imatinib has instigated an incredible effort to develop targeted PTK therapy based on the existence of over 40 chromosomal translocations that lead to deregulation of 12 different PTK linked with various hematologic malignancies. As compare to Imatinib no other targeted therapies have contributed to a great extent to therapeutic armamentarium in oncology, it also acted as a tool for understanding the mechanisms of the diseases like CML and GIST. Despite the satisfactory outcome, Imatinib faced the budding problem of resistance, although combinatorial treatment seems promising to solve the problem of Imatinib resistance, Imatinib is considered as a “wonder drug” as it has contributed greatly to the field of oncology.

Conflict of interest

Authors declare that there is no conflict of interest to reveal.
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