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TARGETING ONCOGENIC KINASE SIGNALING WITH SMALL MOLECULE KINASE INHIBITOR IMATINIB

Saad Farooq*, M.H. Qazi and Maria Fareed Siddiqui

Centre for Research in Molecular Medicine (CRiMM), The University of Lahore, 1 km Defense Road Lahore, Pakistan

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Correspondence to Author:

Saad farooq

Centre for Research in Molecular Medicine (CRiMM), The University of Lahore, 1 km Defense Road Lahore, Pakistan

E-mail: moonstar147@gmail.com

ABSTRACT: Protein tyrosine kinases (PTKs) are key players in cellular signal transduction events and have essential roles in cell growth, survival, differentiation and migration. Perturbations in protein tyrosine kinase activity have been implicated in a number of abnormalities, particularly cancer. Selective small molecule inhibitors are potential therapeutic agents targeting protein kinases involved in cancer and other diseases. The most dramatic clinical responses have been observed in cancer types that are strictly dependent on oncogenic kinases. In this case, targeting these kinases seems to be sufficient to provoke apoptotic response, thus limiting the process of tumorigenesis. Among tyrosine kinase inhibitors, imatinib mesylate (Gleevec®; Novartis) has demonstrated magnificent clinical efficacy in more than one type of cancer and received FDA approval for treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST). Imatinib has set a paradigm for the treatment and management of CML as BCR-ABL kinase inhibitor. It binds kinase domain of PTK as an ATP-competitive inhibitor thus preventing the interaction with effector proteins and subsequent signaling pathway. Imatinib has excellent pharmacokinetic profile and therapy is generally well tolerated with mild to moderate toxicity which is manageable on reduction or discontinuation of dosage. Despite its tremendous clinical outcome, patients with advanced disease harbor resistance which is perhaps multifactorial. Currently there is requisite of making strategies to overcome resistance mechanisms and adverse effects in order to provide maximum benefit to the patients.

INTRODUCTION: The human genome encodes more than 500 protein kinases virtually contributing in every signal transduction pathway through a phosphotransfer cascade.

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90 genes have been identified in human genome encoding tyrosine kinases, out of which 58 genes encode receptor tyrosine kinases and 32 are non-receptor tyrosine kinase encoding genes [1].

Receptor tyrosine kinases (RTKs) are cell surface receptors spanning through membrane and they contain N-terminal extracellular ligand binding domain and intracellular C-terminal domain with tyrosine kinase activity [2].

Members of receptor tyrosine kinase family have been implicated in critical cellular processes such as cell survival and metabolism, proliferation and differentiation, migration and cell cycle control (**Fig. 1**) [3, 4].

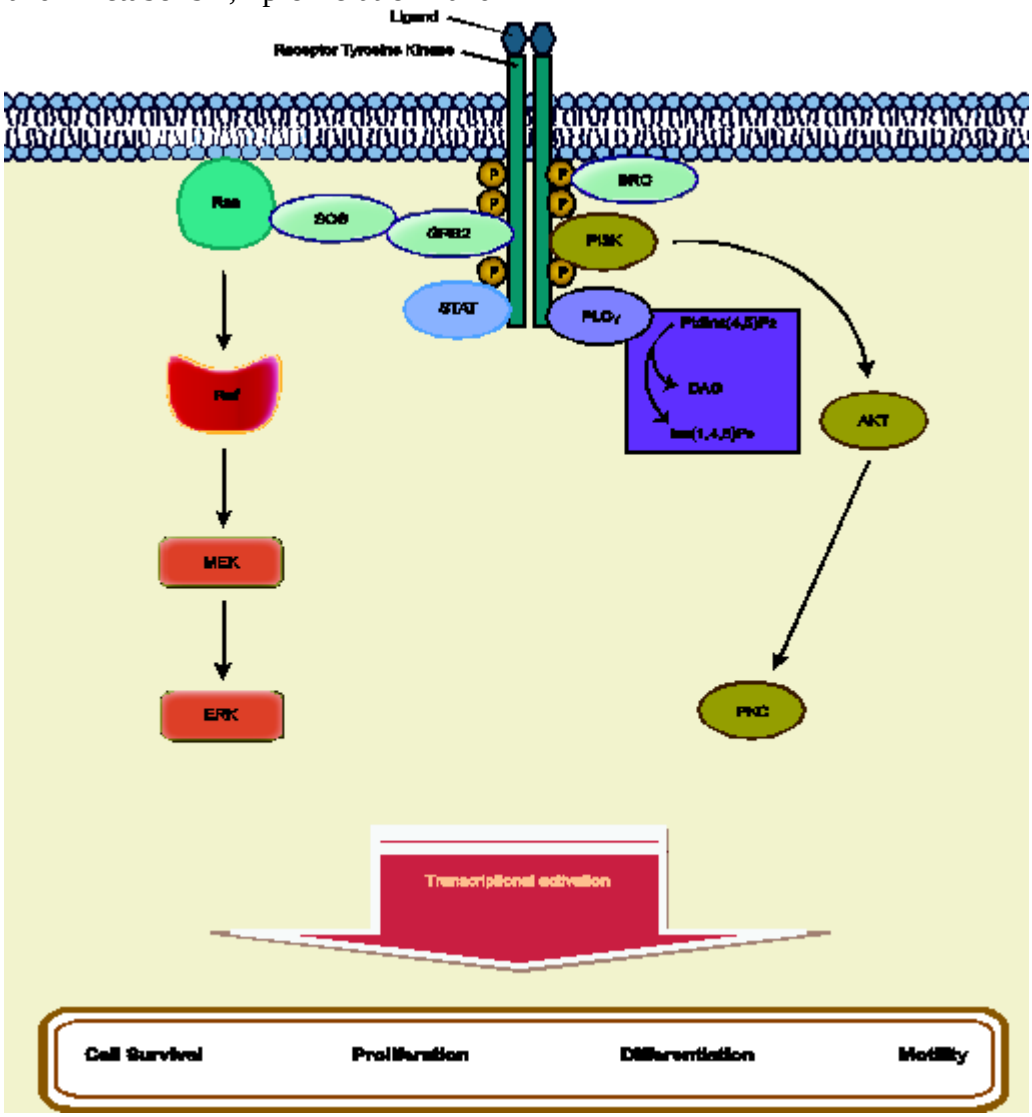

FIG. 1: RECEPTOR TYROSINE KINASE SIGNALLING NETWORK. Upon activation of RTKs, adaptor molecule GRB2 binds to receptor, followed by the recruitment of SOS which exchange GDP for GTP on Ras, enabling its attachment to Raf kinase. Activated Raf phosphorylates and activates MEK which in turn causes phosphorylation and activation of ERK. Furthermore, PLCγ interacts with activated RTK and causes hydrolysis of PIP_2 into two second messengers IP_3 and DAG, both carry out variety of responses. PI3K, AKT and STAT are also activated by RTKs and are involved in responses that are hallmarks of tumor cells.

There is involvement of nearly half of the protein tyrosine kinase (PTK) receptors in various human malignancies [3]. There are different mechanisms of abnormal PTK activity. Under such conditions, the receptors are constitutively activated by either amplification or mutational events. Constitutive dimerization of RTKs takes place due to mutations perturbing disulfide bonding in extracellular regions of receptor, thus forming covalent dimer. Mutations in transmembrane or juxtamembrane domains of receptor may also facilitate dimerization. In other mechanisms of aberrant tyrosine kinase activity, fusion proteins are formed between kinase domains of receptor and other proteins that occur normally as dimers or oligomers. This results in constitutively active kinase that promotes cell growth [5].

Development of Tyrosine Kinase Inhibitor: Interest in the development of tyrosine kinase inhibitors has been considerably enhanced for the treatment of malignant and non-malignant proliferative disorders [6]. This suggests the potential role of many of these kinases as therapeutic targets for design of anti-cancer drugs that can inhibit their tyrosine kinase activity. In past few years, there has been substantial attention in the development of

small inhibitors of protein kinases which are cell-permeable, diffusing across plasma membranes so that they can reach intracellular target sites. Small molecule kinase inhibitors are the class of drugs that can specifically bind and inhibit the activity of protein kinases. Most of the kinase inhibitors are developed for the purpose of the maximum selectivity towards a specific kinase of interest. Majority of these inhibitors target the ATP-binding site, but there is also a large number of non-ATP competitive kinase inhibitors that target unique allosteric sites [7].

The most exciting clinical response to the inhibitors of protein kinases has been noticed for cancer types that depict strict dependency of cell survival on the targeted kinase [8]. In such cases, complete blockage of kinase activity seems to be sufficient for the commencement of an apoptotic response in cancer cells, which can cause disease stabilization in patients under treatment [9]. The initial validation for this concept appeared with the success of imatinib as an inhibitor of BCR-ABL kinase in Chronic Myelogenous Leukemia (CML) [10].

CML is characterized cytogenetically by Philadelphia chromosome which is formed when ABL (Abelson) proto-oncogene is translocated from chromosome 9 and its 3' sequences combines with 5' sequences of BCR (breakpoint cluster region) gene on chromosome 22. The BCR-ABL fusion gene and its protein product with enhanced tyrosine kinase activity was found to be present in majority of CML patients and this 210-kD oncoprotein contains 902 or 927 amino acids of BCR fused with exons 2–11 of c-Abl [11, 12, 13].

This protein product of fusion BCR-ABL is found in more than 95% of CML patients and represents a major contributing factor of the disease (**Fig. 2**) [14].

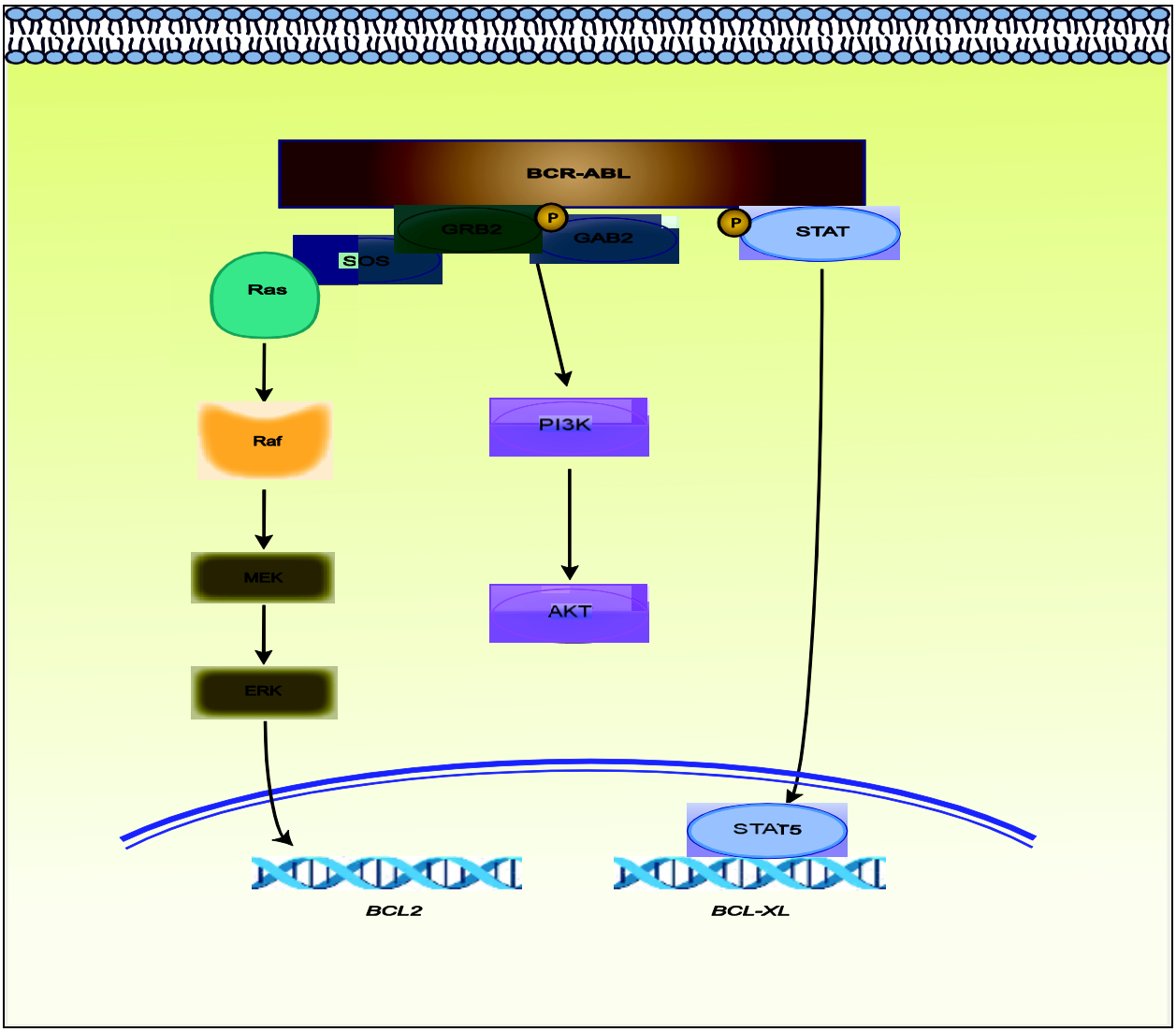

FIG. 2: TUMORIGENIC SIGNALING BY BCR-ABL KINASE. BCR-ABL kinase enables the cancer cells to evade apoptosis through Ras-MAPK pathway and PI3K-AKT survival pathway.

Additional studies indicated the significant protein tyrosine kinase (PTK) activity in the transformation function of BCR-ABL [15]. After identification of appropriate target the 2-phenylaminopyrimidines, the first reported potent PTK inhibitors with selectivity against the Abl and PDGF-R tyrosine kinases [16, 17], were optimized for inhibition of the Abl and PDGF-R by synthesizing a series of chemically related compounds and the relationship between their structure and activity was analyzed.

The most striking feature of these compounds was inhibition of both v-Abl and the PDGF-R kinases. Among them, Imatinib (formerly known as STI571 or CGP 57148B) emerged as the lead compound for preclinical trials [18].The in vitro screening employed a set of assays of isolated protein kinase enzymes for initial chemical optimization. Although this sounds straightforward now, this was too difficult in the late 1980s, when techniques for the recombinant expression of active tyrosine protein kinase enzymes were in their infancy [19, 20].

After the development of imatinib by rational drug design, it was tested several times in preclinical models. It was found that submicromolar concentrations of this compound inhibited v-Abl, PDGF receptor, and KIT receptor autophosphorylation and signalling pathways in which these kinases were involved [16, 17]. The targeting of KIT and PDGFR, other than BCR-ABL, has broadened the clinical applications of imatinib in diseases that involved deregulated PDGFR or KIT kinases. Imatinib have had high profile achievement exhibiting up to 80% response rates in chronic phase-CML patients [21].

Moreover, clinical efficacy of BCR-ABL tyrosine kinase inhibitor imatinib in Chronic Myeloid Leukemia provides a proof that BCR-ABL oncoprotein is the primary cause of CML [10, 22].

TABLE 1: APPROVED KINASE INHIBITORS. There are hundreds of chemical compounds with unique structure that selectively inhibit the variety of kinases. Some of the kinase inhibitors which are approved for their use in humans as anti-cancer agents are listed in table [7]

Name	Known Targets	Indication
Imatinib (Gleevec; Novartis)	Bcr-Abl, c-Abl, PDGFR, c-KIT,	CML, GIST
Nilotinib (Tasigna; Novartis)	Bcr-Abl, c-Abl, PDGFR, c-KIT, DDR1	Imatinib- refractory CML
Sorafenib (Nexavar; Bayer/Onyx)	c-KIT, PDGFR, VEGFR	Renal cancer
Sunitinib (Sutent; Pfizer)	c-KIT, PDGR, VEGFR	Renal cancer, imatinib-resistant GIST
Dasatinib (Sprycel; Bristol–Myers Squibb)	Bcr-Abl, SRC family, TEC family	Imatinib-resistant CML

Clinical Studies: Series of experiments showed the potency and selectivity of imatinib towards Abl tyrosine kinase, including BCR-ABL tyrosine kinase [23]. Imatinib specifically inhibited the proliferation of myeloid cell lines that contained BCR-ABL as colony forming assays taken from CML patients when incubated with 1µM imatinib showed remarkable reduction (92-98%) in BCR-ABL colonies while normal colony formation was not affected [24, 25].

A phase I clinical trial with imatinib started in June 1998 [10]. Patients eligible for study were in the chronic phase of CML and had failed therapy with interferon-α. After 300 mg or greater doses of orally administered imatinib, 53 out of 54 patients achieved a complete hematologic response. Clinical responses were experienced within first three weeks of imatinib therapy and maintained in 96% of patients with median duration of 310 days follow up. At this dose level of 300 mg or greater, major cytogenic responses were appeared in 53% of patients and 13% patients achieved a complete cytogenic response.

Phase I study was expanded after the success of imatinib in chronic phase patients who had failed with IFN-α therapy and CML patients with myeloid and lymphoid blast crisis and those with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (ALL) were included [22]. Patients were treated daily with doses ranging from 300-1000 mg of imatinib. Of these patients, 55% with myeloid blast crisis responded to the therapy. 21% of these patients had cleared bone marrow blasts to <5%. These and other clinical evidences indicated the remarkable single agent activity of imatinib in CML blast crisis and Ph positive ALL but response were not inclined to be long-lasting.

Success of phase I studies promoted the initiation of the phase II studies of imatinib in late 1999. Imatinib was administered as a single agent in the interferon-resistant patients, in all phases of CML. In these studies, imatinib was tested in more than 1000 patients over a time period of 6 to 9 months. The results obtained from phase II studies were sufficient to confirm the results seen in phase I studies and led to the FDA approval of imatinib [26].

Physiochemical Properties: Imatinib is a synthetic 2-phenylaminopyrimidine derivative and structural formula of imatinib free base is shown in **fig. 3** [27].

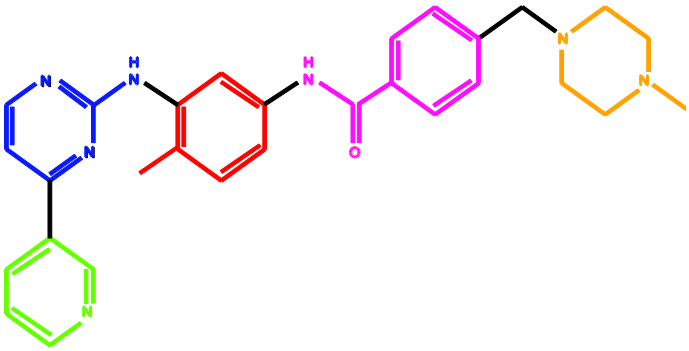

FIG. 3: IMATINIB CONSISTS OF A PYRIDINE RING (COLORED *GREEN*), AN AMINOPYRIMIDINE RING (IN *BLUE*), A METHYLBENZENE RING (*RED*), A BENZAMIDE RING (*MAGENTA*), AND AN N-METHYLPIPERAZINE RING (*ORANGE*).

Imatinib is marketed by its brand name Gleevec® in USA and by Glivec® in Europe by Novartis Pharmaceuticals as its mesylate salt. Gleevec film-coated tablet contains imatinib mesylate (active ingredient) equivalent to 400 mg of imatinib free base. Imatinib mesylate is chemically designated as 4-((4-Methyl-1-piperazinyl)methyl)-N-(4-methyl-3-((4-(3-pyridinyl)-2-pyrimidinyl)amino)-phenyl) benzamide methanesulfonate [28].

Molecular weight of Imatinib mesylate is 589.7084 and molecular formula is $C_{29}H_{31}N_7O \bullet CH_4SO_3$. It is quadrivalent base with pKa (acid dissociation constant) values ranging from 1.52–8.07, thus easily soluble in water at pH 5.5 or less and solubility decreases in aqueous buffer as the pH increases. The drug substance is sparingly soluble at physiological pH (50µg/mL at pH 7.4) and is nearly insoluble in neutral/alkaline aqueous buffers (≤pH 8.0). In polar organic solvents, such as methyl alcohol (methanol) and ethyl alcohol (ethanol), imatinib readily dissolves. But in organic solvents of low polarity, it is nearly insoluble and completely insoluble in n-octanol, acetone and acetonitrile.

Imatinib mesylate is physically white to off-white to brownish/yellowish tinged crystalline powder. Hydrolysis of amide bond does not takes place in artificial gastric fluid at temperature of 37°C and pH 1.2 for one hour, indicating the stability of imatinib under these conditions [29].

Pharmacology of Imatinib: Imatinib is a small molecule kinase inhibitor that blocks the tyrosine kinase activity of the proteins involved in the pathogenesis of Chronic Myelogenous Leukemia (CML) and gastrointestinal stromal tumor (GIST) by competing the ATP binding site on enzyme domain. Hence, imatinib inhibits the BCR-ABL kinase, the constitutive abnormal tyrosine kinase fusion protein created by reciprocal translocation between the chromosome 9 and chromosome 22, called Philadelphia translocation. 95% of the patients affected by CML are reported Philadelphia chromosome positive.

Similarly, imatinib is a potent inhibitor of the Kit receptor tyrosine kinase and displays activity towards GIST by suppressing the tyrosine kinase activity of mutated c-kit receptor broadly expressed (85%) in GIST, a subgroup of soft-tissue sarcomas [30]. Many studies demonstrate that imatinib is not entirely specific; it is also active against the mutated receptor tyrosine kinase for platelet-derived growth factor (PDGF) [31] and encourages the activation of natural killer (NK) cells [32].

Imatinib is given orally and is prepared in hard capsules or tablets (United States) as its salt (imatinib mesylate or methane sulfonic acid). Each tablet of Gleevec contains 100 or 400 mg of imatinib free base. The recommended dosage for adult Chronic Myelogenous Leukemia patients in its various stages (chronic, accelerated or blast crisis) and for Kit-positive GIST that become metastatic and/or unresectable, once daily dose of 400 mg or 600 mg is given with a meal.

In children with CML, range of daily doses is from 260 mg/m^2 to 340 mg/m^2. The treatment is continued until progression of disease or intolerable toxicity [30]. Dosage of Gleevec increases from 400 mg to 600 mg for patients suffering from chronic phase disease. For patients in accelerated phase or blast crisis, dosage increases from 600 mg to 800 mg, given as 400 mg twice a day [28].

In vitro studies indicate that the contents of the capsule can be dissolved and are stable in water and apple juice but not in milk, orange juice or cola [33]. Imatinib should be stored at 25° C (77°F); excursions are tolerable from 15 to 30°C (59-86°F) and dispense it in a tight container [28].

Pharmacodynamics of Imatinib:

Mechanism of Action: Imatinib functions as an ATP-competitive inhibitor with a *K*i value of 85 nM [16]. Imatinib binds to ATP site of kinases and an adjacent small hydrophobic pocket, hence blocking the kinase activity and preventing the transfer of phosphate group from ATP to target substrates. The crystal structure of Abl kinase domain in complex with imatinib reveals that it binds to inactive conformation of Abl (**Fig. 4**) [34]. In this way, imatinib induces cytogenetic responses in patients with CML in chronic phase.

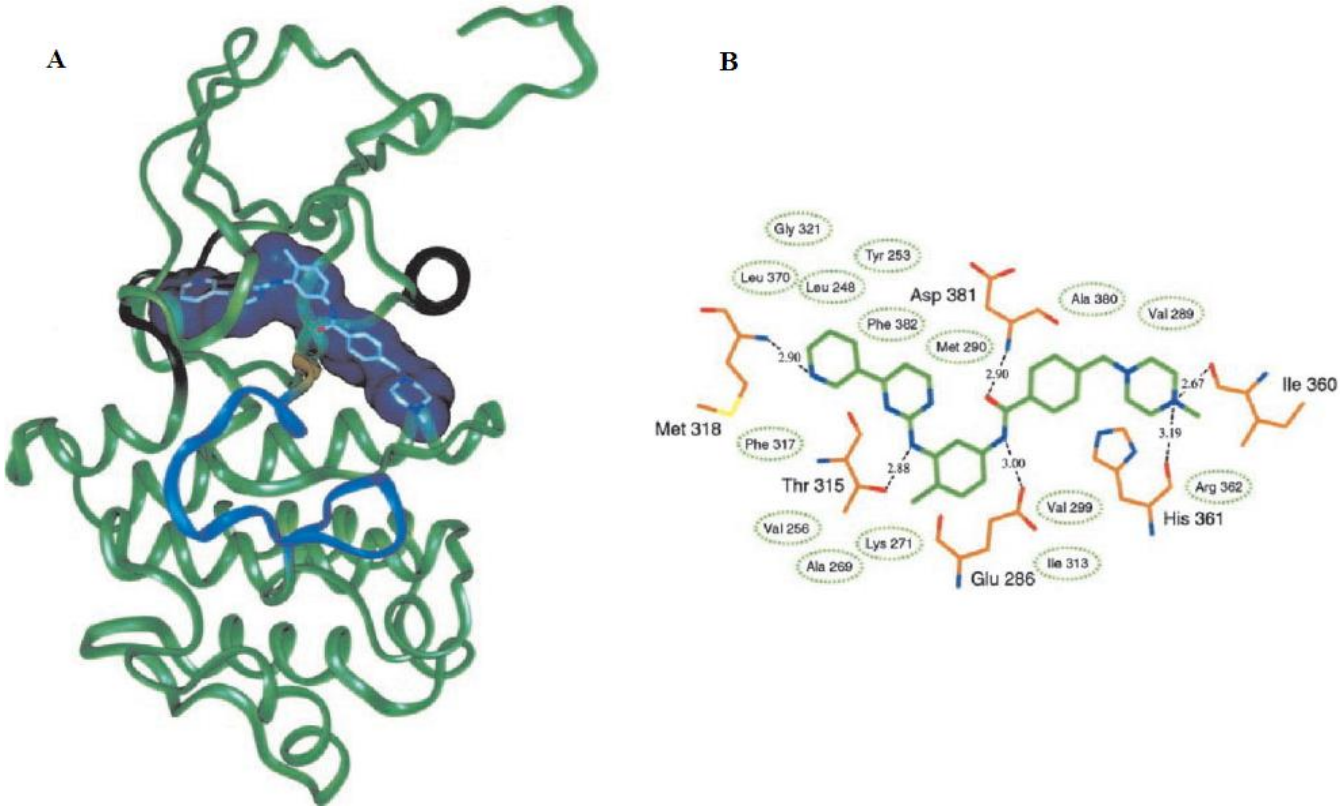

FIG. 4: BINDING OF TYROSINE KINASE INHIBITOR IMATINIB TO ABL KINASE: a) The ribbon representation of Abl kinase domain bound to imatinib. b) This schematic diagram depicts interactions made by imatinib with Abl. Dotted lines indicate hydrogen bonds along with their distances. Residues making van der Waals interactions with imatinib are *circled* with *dotted lines*.

Drug Interactions: Imatinib is mainly metabolized by CYP3A4 and CYP3A5 isozymes. So when imatinib is co-administered with drugs that inhibit the activity of CYP3A4 and CYP3A5, its metabolism can be reduced and plasma concentrations increased.

Major activator of CYP3A4 and CYP3A5 isozyme system may increase metabolism and reduce exposure to imatinib (e.g. carbamazepine, barbiturates, dexamethasone, rifampicin, phenytoin, and St John's Wort (hypericum)) [29]. Drug-drug interaction analyses of imatinib have focused on the potential alteration in activity of CYP3A4 and CYP3A5. In general, precautionary measures should be taken for drug interactions while administering imatinib with substrates or modulators of the CYP3A family.

Adverse effects of Imatinib and their Clinical Management: In clinical studies, there is good tolerance of imatinib. Along with many benefits of imatinib treatment, adverse effects are also accompanied that must be managed in order to the adherence of patients to treatment. Adverse effects for imatinib are reported mild to moderate (grade 1 or 2) and appears to be easily manageable and reversible without reduction in dosage or permanent discontinuation of therapy. Most commonly occurring adverse reactions that patients may experience are gastrointestinal reactions (nausea,

vomiting, and diarrhea), lethargic conditions edema, muscle cramps, and different types of rashes are developed [35, 36].

Resistance to Imatinib: In spite of significant clinical efficacy of imatinib in treating CML, resistance to therapy occurs in patients with advanced disease. Clinical studies indicated that patients in chronic phase show long lasting responses whereas most patients responding in blast crisis relapse despite persistent therapy [10, 22, 37]. Mechanisms of resistance to imatinib therapy identified from in vitro studies include several-fold increase in quantity of BCR-ABL oncoprotein, BRC-ABL gene amplification, and multidrug resistance P-glycoprotein overexpression [38, 39, 40].

The most frequent mechanism of resistance found in these studies was overexpression of BCR-ABL mRNA and its protein product. In patients who acquired resistance to imatinib showed mutations in Abl tyrosine kinase domain [41] sequencing of ATP-binding site and activation loop of Abl kinase domain indicated point mutation of cytosine to thymidine, resulting in replacement of single amino acid residue at position 315 designated as T315I.

Threonine 315 is essential for the formation of hydrogen bond with imatinib. The substituted isoleucine lacks oxygen atom thus preventing the bond formation and this isoleucine was also predicted to produce steric clash with imatinib, so this residue was termed gatekeeper for imatinib.

Imatinib in Combinations:

Combination with Taxane therapy: As imatinib inhibits tyrosine kinase signaling by PDGFR, imatinib was used with injected paclitaxel in a study and the inhibition of PDGFR signaling pathway in a mouse model was examined to produce substantial therapeutic effects against prostate cancer bone metastases [42]. Impact of paclitaxel and imatinib on mice under experiment was observed as monotherapy as well as in conjunction. In mice treated with paclitaxel, tumor prevalence was 17 of 20 and in mice treated with imatinib, incidence of tumor was found to be 10 of 20 with median weight of 1.8g.

Tumor incidence was 7 out of 20 in mice which were treated with the combination of imatinib and paclitaxel and the median weight of tumor was 0.6g. The smaller tumor size among mice treated with imatinib reflects decreased cell divisions of tumor cells and increased apoptosis or both.

Analysis of PDGFR status in bone marrow biopsies of androgen-independent prostate cancer (AIPC) revealed no readily discernible alteration in PDGFR expression after 30 days of imatinib therapy alone [43]. However, in combination therapy of imatinib plus docetaxel, there was noticeable decline in tumor expressing PDGFR.

Secondary type glioblastomas are associated with over activity of PDGFR forming autocrine loop, which participate in tumor progression and leads to transformation process, manifesting more malignant phenotype [44, 45].

Clinical trials using only imatinib therapy for recurrent glioblastomas resulted in increased progression free survival for only a few patients after six months [46, 47]. Docetaxel is used in different types of cancers and its therapy for treatment of glioblastomas has shown negligible or no significant response [48, 49].

The combine effect of docetaxel and imatinib was observed in primary glioma cell lines [50]. Docetaxel alone induced apoptosis in 4.3-10% cells, whereas imatinib alone caused apoptosis in 4.7-7% cells, but docetaxel and imatinib when introduced together induced apoptosis in 13.8-40.1% cells. Imatinib and taxol induce apoptosis via different signaling pathways (**Fig. 5**).

An experiment was set in which human breast cancer cell lines were incubated with ascending concentrations of doxorubicin and imatinib used alone or in combination [51].

Both drugs revealed their additive therapeutic effects on cell growth inhibition which was enhanced as compared to their individual effect. Combination of Imatinib with radiation on breast cancer cells was also evaluated and the surviving fraction of cancerous cells was reduced [51].

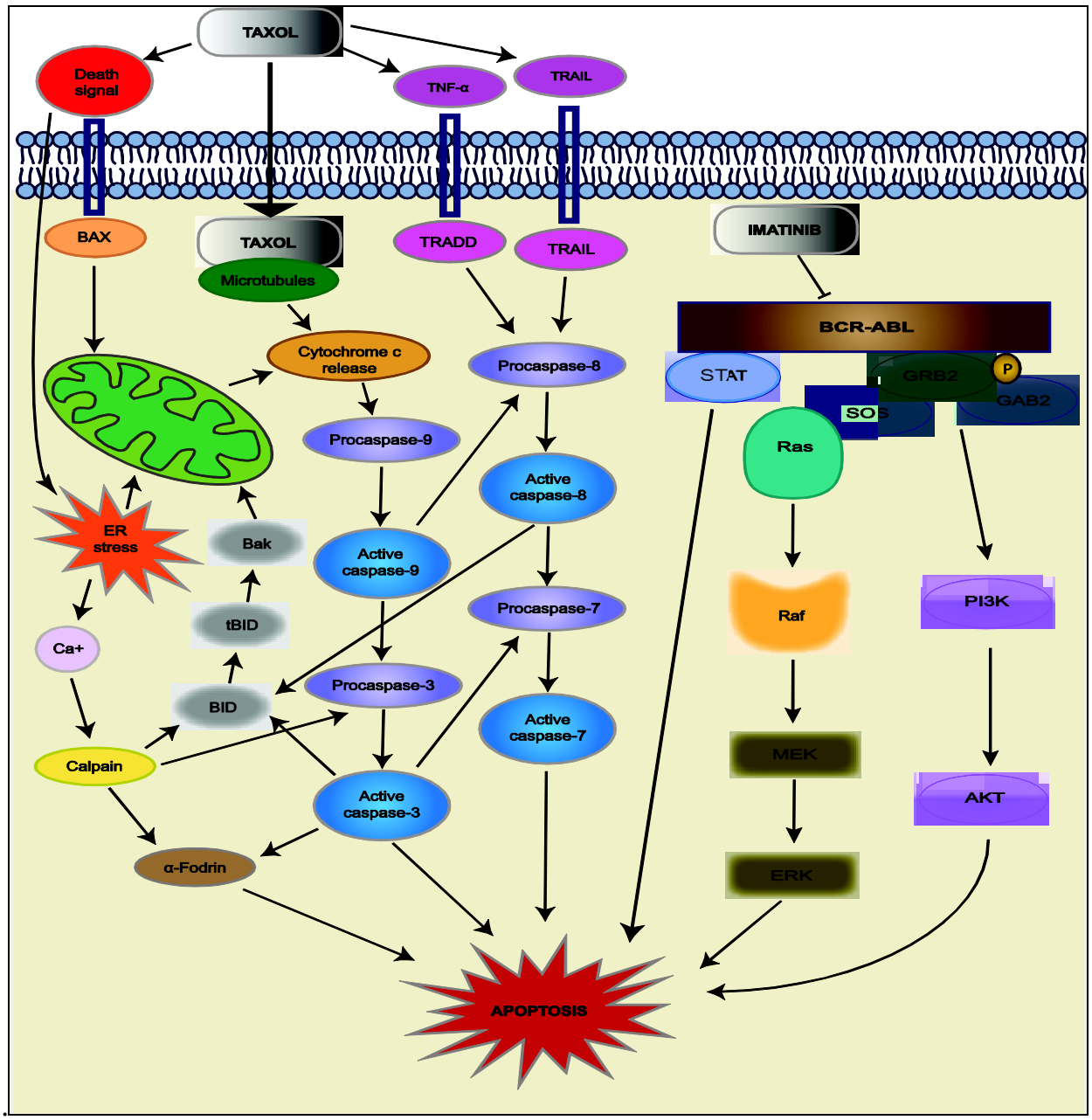

FIG. 5. **ILLUSTRATION OF ADDITIVE EFFECTS OF IMATINIB AND TAXOL.** *In vitro*, paclitaxel (taxol) polymerizes tubulin and stabilize the microtubules. This causes the cell cycle arrest in the G2/M phase and ultimately apoptosis. Taxol initiates death signals that causes upregulation of BAX and ER stress, increasing intracellular Ca^{++} that upregulates calpain. Taxol also triggers extrinsic caspase pathway by upregulating TNF-α and TRAIL. Bcl-xL phosphorylation promotes cytochrome c release from mitochondria which associates with apaf-1 and procaspase-9, thus activating intrinsic apoptotic pathway. Calpain cleaves and activates procaspase-3 which in turn cleaves α–fodrin, PARP and DFF45 leading to apoptosis.

CONCLUSION AND PERSPECTIVES: Imatinib mesylate revolutionized the treatment and outcome of chronic myeloid leukemia and certain other cancer types. It is very effective against some types of leukemia that express BCR-ABL1 gene product whose tyrosine kinase domain is best known target of imatinib. This drug has many possible targets and can be given in some combinations which expand its usage in several abnormalities. Other possible combination therapies can be made optimum by considering the signalling pathways affected by imatinib and other drugs. Although clinical efficacy of this drug is significant in Philadelphia chromosome positive CML patients, some patients become resistant to the therapy due to several reasons mainly mutations in Abl kinase domain. In order to overcome its drawbacks, amendments can be made in its chemical structure where certain functional groups can be added or substituted. Another option is the development of similar and improved small molecules with inhibitory activity against tyrosine kinases.

A new wave of tyrosine kinase inhibitors is currently under clinical practices and enabled the imatinib-resistant CML patients to respond to the therapy. With the development of new kinase inhibitors, there could be chance of discovery of new possible kinase targets which may broaden the application of tyrosine kinase inhibitors (TKIs).

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