Novel Agents In CML Therapy: Tyrosine Kinase Inhibitors and Beyond

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Abstract

Treatment of Chronic myeloid leukemia represents one of cancer’s success stories. Deregulated tyrosine kinase activity of the BCR-ABL fusion protein has been established as the causative molecular event in CML. The drug Imatinib has revolutionized the treatment of CML and has become the gold standard of care in CML for it is a highly targeted BCR-ABL tyrosine kinase inhibitor (TKI) that induces complete hematologic response and sustained complete cytogenetic response in more than 80% of patients. Despite of such impressive response rates achieved with imatinib, some patients in the advanced stage of CML frequently obtain less modest responses. It may be due to resistance to the wonder drug imatinib, which in turn results in failure of treatment, even after large dose escalation. This has led to the development of novel treatment strategies which are currently being investigated in newly diagnosed CML and include upfront treatment with the next-generation tyrosine kinase inhibitors, such as dasatinib, nilotinib, or bosutinib, which also target the BCR-ABL but with increased in vitro potency as compared to imatinib, and possibly with a reduced potential for resistance. Such newer agents and combination approaches can improve treatment responses as compared with standard imatinib treatment. Such newer agents and combination approaches can improve treatment responses as compared with standard imatinib treatment. In addition, many other protein kinases implicated in signaling transduction downstream BCR-ABL also play critical roles in the pathogenesis of CML, thereby representing potential therapeutic targets as revealed from several clinical studies. While in many other cases, the CML cells develop mutations, which is a change in the amino acid sequence of the BCR-ABL oncogene, the most dangerous amongst them is the T315I mutation, which makes them resistant to the current targeted therapies (imatinib, dasatinib, and nilotinib). Newer drugs that work against T315I mutant cells are now being tested. Ponatinib, is one such pan-BCR-ABL inhibitor, which has shown ongoing strong efficacy in its continuing Phase 1 trial in treatment of the T315I mutation CML, as well as all other known mutations. Still other novel drugs in the pipeline, the farnesyl transferase inhibitors, such as lonafarnib and tipifarnib, seem to have some activity against CML and patients may respond favourably when such drugs are combined with imatinib. With many such novel drugs under development and many more in the pipe line, some of such drugs which are in various phases of clinical trials are being discussed.

Introduction

Chronic myeloid leukemia (CML), also known as chronic granulocytic leukemia (CGL), is one of the commonest hematological malignancies seen in clinical practice in Indian adults. It is a type of myeloproliferative disease linked to genetic abnormalities where there is a characteristic chromosomal translocation called the Philadelphia chromosome. The chromosomal defect is a translocation, in which parts of two chromosomes, 9 and 22, swap places. The result is a fusion gene that is created by juxta positioning the ABL 1 gene on chromosome 9 (region q34) to a part of the BCR (“breakpoint cluster region”) gene on chromosome 22 (region q11). Thus a part of the BCR gene from chromosome 22 is fused with the ABL gene on chromosome 9. This BCR-ABL fusion gene product functions as a constitutively activated tyrosine kinase for it has a domain that can add phosphate groups to its tyrosine residues but does not require activation by other cellular proteins. Thus it activates a number of cell cycle controlling proteins and enzymes, accelerates cell division, inhibits DNA repair, causes genomic instability and is responsible for the deadly blast crisis in CML.

TYROSINE KINASES:

The tyrosine kinases are a subgroup of a larger class of protein kinases that has an ATP binding site, which functions in several signaling pathways and can exist in an active or inactive state. These kinases are broadly divided into two main families:

1. The transmembrane receptor-linked tyrosine kinases family
2. And the cytoplasmic tyrosine kinases family

The receptor tyrosine kinases functions in transmembrane signaling, whereas the cytoplasmic tyrosine kinases is responsible for signal transduction to the nucleus.
transmembrane receptor-linked tyrosine kinase which is expressed in the leukemic clonal cells, activates many pro-growth and cell survival mechanisms, which confers resistance of such clonal cells to apoptosis. 7 Two of the major pathways activated by BCR-ABL are the class I PI3K and the Ras pathways, which are deregulated in most human cancers. 8 Since tyrosine kinase activity is essential for this transforming function of BCR-ABL, an inhibitor of this kinase could serve as an effective treatment for CML. ATP-competitive inhibitors like tyrosine kinase inhibitors (TKI) can prevent the binding of ATP, inhibit the phosphorylation of Bcr-Abl and can cause death of an apoptotic cell.9,10

1. 1st GENERATION BCR ABL KINASE INHIBITOR-IMATINIB MESYLATE:
Imatinib binds to the amino acids of the BCR/ABL tyrosine kinase ATP binding site and stabilizes the inactive form of the receptor thereby preventing tyrosine auto phosphorylation. This process ultimately results in "switching-off" the downstream signaling pathways that promote leukemogenesis. .11 However, approximately 20-25% of patients initially treated with imatinib will need alternative therapy, due to drug resistance.12 This resistance is usually due to two mechanisms, the Bcr-Abl dependent mechanisms like over expression or amplification of the Bcr-Ab1 gene, point mutations within the Bcr-Ab1 kinase domain that interfere with drug binding and Bcr-Ab1 independent mechanisms, like decreased intracellular concentration of imatinib, alterations in drug influx and efflux and activation of other independent pathways, like the Src kinase pathway.13 Within the Bcr-Ab1 kinase domain, around 40 point mutations have been described which have been linked to imatinib resistance in CML. These mutations are of two broad categories, those that directly interfere with the ability of imatinib to bind to the kinase domain (e.g., T315I), and those that impair the ability of Bcr-Ab1 to achieve inactive conformation required for binding to the drug. Imatinib binds only to the inactive or closed conformation of ABL. This fact explains why many BCR-ABL mutations can cause resistance to imatinib by shifting its equilibrium toward the open or active conformation. 14 Some of these resistant mutants are the M351T, E255V, F317L, Y253F, D276G and the highly resistant T3151 mutant. There is hence an urgent need for the development of novel compounds to prevent or overcome imatinib resistance.

2. 2nd GENERATION ABL KINASE INHIBITORS
These include nilotinib, bosutinib, dasatinib and INNO 406. Both nilotinib and bosutinib are approved as second-line treatments in all phases of CML and are highly effective in patients resistant to or intolerant to imatinib for these drugs target all the resistant BCR-ABL mutants, with the exception of the T3151 mutant.15

Nilotinib:
Substitution of the N-methylpiperazine moiety of imatinib by an amide moiety resulted in a more potent compound, Nilotinib which in addition to inhibition of tyrosine kinases also inhibited the activity of the Arg, Kit, and platelet-derived growth factor receptor (PDGFR), but not the Src-family kinases (SFK).16 Nilotinib is 10 to 50 times more selective and more potent than imatinib17 in inhibiting the proliferation and auto phosphorylation of the wild-type Bcr-Ab1 cell lines, most of the Bcr-Ab1 mutants, except the T315I mutant.18 Studies have shown it to be superior to imatinib in reducing the leukemic burden and prolonging the survival of mice transplanted with the wild-type Bcr-Ab1, the M351T and E255V mutants.19 Also nilotinib does not require a transporter mediated transport into cells, is well tolerated but the common adverse events includes myelosuppression, elevated bilirubin and lipase levels.

Dasatinib:
Dasatinib is a multi-target kinase inhibitor as it binds to other tyrosine and serine/threonine kinases, like the TEC family kinases, the mitogen activated protein kinases in addition to the receptor tyrosine kinase.20 Imatinib binds only the closed conformation of ABL whereas dasatinib binds to the open (active) conformation.21 Dasatinib once daily administration induces significantly higher and faster rates of complete cytogenetic and molecular response, better long term progression-free survival in patients as compared to imatinib. 22 It is well tolerated with adverse effects like grade 3–4 myelosuppression in advanced phases, diarrhea, nausea, headache, peripheral edema but with a higher incidence of pleural and pericardial effusions as compared to imatinib and nilotinib. However dasatinib is resistant in patients who harbor the T315I mutant and the novel F317L mutant.23

3. 3RD GENERATION TKI'S-HIGHLY ACTIVE AGAINST T315I MUTANT-PONATINIB
However, there still remains a small subset of patients who do not respond to TKIs because they harbor the BCR-ABL T315I mutant gene which confers them resistant to the first and second generation tyrosine kinase inhibitors. T315I represents about 15-20
percent of all clinically observed BCR-ABL mutations and is completely resistant to all currently approved pharmaceutical therapies.24, 25 This was the first mutation to be detected in imatinib-resistant patients and is due to the substitution of threonine with isoleucine at position 315 of the Abl protein.26 The prevalence of the T315I mutant is likely to increase with the increase in the use of the current second-generation BCR-ABL inhibitors. Therefore, development of a T315I inhibitor represents a significant unmet medical need in CML. A substrate-competitive inhibitor of Bcr-Abl, Ponatinib, was recently reported to have potent in vitro inhibitory activity in cell lines expressing wild-type Bcr-Abl and all the Bcr-Abl mutants, including the T315I mutant. It was also active in vivo in mice expressing the T315I mutant and caused decrease in leukemic cells.27 Ponatinib is currently in Phase II clinical trials in patients with resistant or intolerant CML and Ph+ ALL. Ponatinib was designed using ARIAD’s computational and structure-based drug design platform to inhibit not only the native BCR-ABL, but also its isoforms with very high potency and specificity. A Phase I study of ponatinib in patients with resistant and refractory chronic myeloid leukemia and Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) had demonstrated that about 66 % of patients in the trial had achieved a major cytogenetic response.28 Other third-generation TKIs which are under development include XL-228, a multi-kinase inhibitor with activity against the mutant type of BCR-ABL. DCC-2036 is another multi-kinase inhibitor in Phase I studies that impaires proliferation and induced apoptosis of cells transfected with unmutated or mutated BCR-ABL, including T315I.

4. DUAL SRC-FAMILY KINASE/ABL KINASE INHIBITORS:
The Src family kinases includes the nine structurally related, cytoplasmic non-receptor tyrosine kinases (Src, Fyn, Yes, Blk,Yrk, Fgr, Hck, Lck and Lyn), which are ubiquitous and display a tissue-specific expression pattern. Members of this family of kinases are important mediators of downstream signalling by ABL from cell-surface receptors. So inhibitors of these enzymes can therefore act synergistically with Bcr-Abl inhibitors and hence can potentially counteract the availability of alternative survival pathways which the CML cells utilise during Bcr-Abl inhibition. Consequently the combined inhibition of the tyrosine kinase activity of both Abl and Src-family kinases might have an added advantage over purely Abl inhibition by counteracting the drug-resistant mutant forms of Bcr Abl in the treatment of CML. Interestingly, much lower concentrations of the dual src/abl inhibitor are required to ablate the Bcr-Abl phosphorylation when compared to the first-generation tyrosine kinase inhibitor imatinib (IM).29

Bafetinib or INNO-406: Is a dual Abl/Lyn kinase inhibitor that is up to 55times more potent than imatinib as it inhibits the clonal proliferation of cells as well as of most of the Bcr-Abl mutants, except the T315I mutant.30 Unlike the other second-generation tyrosine kinase inhibitors, bafetinib inhibits Lyn kinase only with little or action against the other SFK.30 Since over expression of Lyn kinase has been implicated in Bcr-Abl independent resistance, this drug may have significant importance in imatinib-resistant CML patients.31 The drug is well tolerated with some elevation of serum transaminases.

Bosutinib: Bosutinib (SKI-606) is 7-alkoxy-3-quinoline carbonitrile, which functions as a dual inhibitor of both Src and Abl kinases has a 10- to 20-fold higher potent antiproliferative activity against imatinib-sensitive as well as the resistant Bcr-Abl–positive cell lines, like the Y253F, E255K and D276G mutants, but not the T315I mutant.22 It can bind to both inactive and intermediate conformations of Bcr-Abl tyrosine kinase receptor and is currently in phase II studies.22 Bosutinib inhibits the proliferation of the CML progenitors but is moderately effective in inducing apoptosis.32 Unlike dasatinib, bosutinib does not significantly inhibit Kit or PDGFR but has a more favorable toxicity profile in comparison.22

5. AURORA KINASE INHIBITORS:
Apart from TKIs, the next promising group of molecules are the inhibitors of the Aurora family of serine/threonine kinases that are essential for cell proliferation. Aurora kinases play a crucial role in cellular division by controlling the segregation of the chromatids. Defects in this segregation can cause genetic instability, which is associated with tumorigenesis. They are hence found over expressed in various cancers like leukemia, colon cancer, prostate cancer and carcinoma of the breast. There are three mammalian aurora kinase, A, B and C out of which the first two play an important role in oncogenesis.33 Aurora A kinase has a crucial role in mitotic spindle formation and centrosome maturation, so its inhibition can disrupt the progression of a cell-cycle. On the other hand Aurora B is a chromosomal passenger protein essential for chromosomal congression and cytokinesis associated with centromeres during prometaphase and with the spindle mid zone during anaphase and telophase. On
the contrary the expression of Aurora C kinase is predominantly restricted to the germ cells, whose function is unclear.35

**TOZASERTIB:** Is a potent inhibitor of all the three Aurora kinases in a nanomolar range, a moderate to strong inhibitor of other kinases, like the ABL and JAK2, which are also the targets for a range of myeloproliferative disorders.36 It also inhibits the autophosphorylation of T315I mutant BCR-ABL in transformed cells.36 Dasatinib with tozasertib in combination resulted in higher attenuation of phosphorylation and increased apoptosis and prolonged survival in athymic nude mice as compared to treatment with either agent alone.37 These results provide the rationale for combination trials of tozasertib and dasatinib in patients with BCR-ABL T315I-positive CML.37

**DANUSERTIB:** PHA-739538 - which is currently in phase II clinical trials in patients who have relapsed after imatinib therapy is an orally bioavailable inhibitor of all the types of Aurora kinases with additional activity against the T315 BCR-ABL kinase.38 Treatment with danusertib in T315I mutants revealed significantly decreased phosphorylation of histone H3 Ser10, a marker of Aurora B activity, indicating that this compound simultaneously inhibits Aurora B and the mutants of BCR-ABL. It also has potent anti-proliferative activity on a wide range of other cancer cell lines, where it significantly inhibits tumour growth in different animal tumour models and at well-tolerated doses.38

**BARASERTIB:** Is yet another selective Aurora-B inhibitor which is a highly soluble acetonilide-substituted pyrazole aminoquinazolone pro-drug that is cleaved completely in the human plasma to yield the active drug substance.39

**6. NON-ATP-COMPETITIVE INHIBITORS OF BCR-ABL -ALLOSTERIC INHIBITORS:** A potential alternative approach to ATP-competitive BCR-ABL inhibition is to use molecules that inhibit the kinase activity either by a non-ATP competitive allosteric mechanism potentially involving binding to the myristate pocket in the C-lobe of the Bcr-Abl kinase domain 40 or by preventing the binding of substrates to the kinase through covalent interactions. This strategy has the advantage that imatinib-resistant mutants are unlikely to be resistant to such inhibitors, owing to the different binding sites and hence can provide an important pharmacological tool to overcome mutations that cause resistance to the conventional ATP-competitive inhibitors. The ability of these compounds to synergize with ATP-competitive inhibitors to inhibit the growth of transformed cells in Bcr-Abl mutants is also likely to prevent or delay the emergence of resistance mutations. A major advantage of such non competitive kinase inhibitors is that they can be highly selective for a particular kinase. GNF-2(3-[6-[[4-(trifluoromethoxy)phenyl]amino]-4-pyrimidinyl]benzamide) is the lead compound in this class which has no activity against most kinases but inhibit the activity of imatinib-resistant BCR-ABL kinase-domain mutants.41

**Heat Shock Protein 90 Inhibitors**

The BCR-ABL tyrosine kinase is a client protein of the heat shock protein (hsp) 90. HSP90 proteins play important roles in the regulation of the cell cycle, cell growth, cell survival, apoptosis, angiogenesis and oncogenesis. They function as molecular chaperone that interacts with proteins like Raf, Akt, FLT-3 and Bcr-Abl and keeps these proteins in a stable and functional conformation inside the cell. HSP90 inhibitors can inhibit the ability of the protein to function as a chaperone, thereby leading to the down regulation of Bcr-Ab1 mutants including the E255K and T315I mutants and can also induce apoptosis in CML cell lines preferentially over their normal cellular counterparts.42

**Geldanamycin:** Is a naturally existing HSP90 inhibitor that belongs to the class of benzoquinone ansamycin antibiotic. Hepatotoxicity is a dreadful adverse effect for which GA has not moved forward in clinical trials but development of its analogues show higher affinity to HSP90 in tumor cells as compared to normal tissues and constitute a class of potential antitumor drugs (2-3). These include 17-allylamino-demethoxygeldamycin (17-AAG) and 17-dimethylamino- geldanamycin (17-DMAG) that have completed phase I and are currently entering phase II clinical trials. In addition, the analogue 17-AAG targets and inhibits the P-glycoprotein multidrug resistance pump and thereby can inhibit drug efflux, one of the common cause of imatinib resistance.43

**7. INDEPENDENT OF TYROSINE KINASE INHIBITION -Homoharringtonine:** Homoharringtonine (HHT) is a plant alkaloid derived from an evergreen tree of the genus Cephalotaxus. It inhibits multiple pathways, which includes the up-regulation of genes associated with apoptosis, angiogenesis in CML. HHT in combination with imatinib, is synergistic in CML cell lines as it results in a reduction in BCR-ABL transcript levels in 50% of patients 44 and a reduction or disappearance of the
8. HISTONE DEACETYLASE INHIBITORS – VORINOSTAT:

For gene expression the control of the coiling and uncoiling of DNA in a cell is accomplished with the help of histone acetylases (HAT), which acetylate the lysine residues in the core histone moiety leading to a less compact and more transcriptionally active chromatin. On the other hand, the actions of histone deacetylases (HDAC), is to remove these acetyl groups from the lysine residues leading to the formation of a condensed and transcriptionally silenced chromatin, thereby affecting gene expression.47 It also causes transcriptional upregulation of cyclin-dependent kinase inhibitor, cell-cycle arrest and apoptosis in tumor cells.48 It also induces expression of p27, a key cell-cycle regulator, and is associated with downregulation of Bcr-Abl protein. In CML cells the activity of the Bcr-Abl tyrosine kinase (TK) in the cytosol activates several molecular mechanisms which inhibits apoptosis.49 These mechanisms include increased expression of the antiapoptotic Bcl-xL protein and increased activity of AKT kinase that confers resistance to apoptosis through several known mechanisms. Vorinostat or SAHA is a HDAC inhibitor, treatment with which leads to increased levels of p21 and p27 which are genes involved in cell cycle regulation, generation of reactive oxygen species (ROS), upregulation of the levels of the pro-death proteins, e.g., Bax, Bak and Bim. Collectively, these effects inhibit cell-cycle growth, lower the threshold to apoptotic stimuli and induce apoptosis of CML cells. By inducing acetylation of hsp90 it also inhibits the ATP-binding and chaperone function of hsp90. This leads to poly ubiquitylation, proteasomal degradation and depletion of hsp90 client proteins, including Bcr-Abl itself and its downstream effectors c-Raf and AKT. 50 Combination treatment with imatinib resulted in a greater level of apoptosis than that was achieved with either agent alone50 whereas co-treatment with nilotinib was synergistic in inducing apoptosis in imatinib-resistant cell lines expressing the T315I and E255K mutants leading to the depletion of the Bcr-Abl levels.51 Collectively, these findings generate the rationale to investigate the clinical efficacy of the combined treatment with SAHA and imatinib against the advanced phases of CML as well as test the antileukemia effects of SAHA against imatinib-refractory CML.

Arsenic Trioxide (ATO):

Arsenic trioxide (As2O3, Trisenox) induces apoptosis in Bcr-Abl–positive cell lines and reduces the proliferation of CML blasts.52 It causes down regulation and auto phosphorylation of the Bcr-Abl protein in imatinib-resistant cell lines that are characterized by Bcr-Abl dependent resistance.53 Combination with imatinib induces synergistic inhibition of the growth of Bcr-Abl–expressing cell lines,50 cell death in imatinib-resistant cell lines that over expressed Bcr-Abl or had the M351T or Y253F, but not the T315I mutants.53 A recent report showed that As2O3, via the degradation of the promyelocytic leukemia protein, was able to sensitize quiescent CML leukemia-initiating cells to cytosine arabinoside–mediated induction of apoptosis.54 make imatinib resistant cell lines and primary cells susceptible to imatinib-induced growth inhibition and apoptosis.

Proteasome Inhibitors:

The ubiquitin-proteasome system (UPS) is the principle pathway for diverse intracellular protein degradation so it is critical for normal cell survival and function.55 Proteasome is a large proteolytic complex that consists of a 20S catalytic complex and two 19S regulatory subunits. Proteins that are to be degraded are tagged with ubiquitin chains and bind to a receptor on the 19S complex and the protein is denatured and presented to the 20S proteasome for degradation.55 Proteasome inhibitors target the catalytic 20S core of the proteasome and suppress the proteasomal degradation of numerous cellular proteins.56 Inhibition of transcription activated by nuclear factor B (NF- B) has been implicated as the mechanism responsible for the antitumor effect of proteasome inhibitors. The proteasome inhibitor, bortezomib inhibits proliferation, induces G2/M phase cell cycle arrest and promotes apoptosis of imatinib-sensitive and resistant CML cell lines.57 Synergism between bortezomib and the HDI vorinostat and between bortezomib and flavopiridol has been reported in in vitro studies of growth inhibition of CML cell lines.56 They also exert synergic effects with histone deacetylase inhibitors and cyclin-dependent kinase inhibitor flavopiridol 58. Thus it offers a potential therapeutic option in CML by targeting both
TKI-insensitive stem cells and TKI-resistant BCR-ABL mutations. Hence combined use of tyrosine kinase inhibitor and proteasome inhibitor might be helpful for optimizing CML treatment.

**CYCLIN-DEPENDENT KINASE INHIBITORS- FLAVOPIRIDOL:**
They are a family of protein kinases that regulates the cell cycle and whose aberrant upregulation can lead to oncogenic effects. Consequently, cyclin-dependent kinase inhibitors (CDKNI) are the negative cell regulatory proteins that can block this kinase activity in response to signals from the environment or from a damaged DNA, and can cause selective interruption of the cell cycle usually during the G1 phase which eventually results in death of these cells. The CDKNI family contains three members which are CDKNIA (also known as p21CIP), CDKNIB (also known as p27KIP1) and CDKNIC (also known as p57KIP2). A number of oncogenes like c-myc and ras target these pathways causing inappropriate activation of CDKs. The BcrAbl tyrosine kinase activates the mitogenic signaling pathways by activation of the RAS, Erk, and JNK pathways which stimulates the G1-to-S phase transition in hematopoietic cells. The chronic myelogenous leukemic cell proliferation also depends on the nucleo-cytoplasmic ratio of the cyclin-dependent kinase inhibitor p27. There is also an associated Bcr-Abl driven activation of cyclin dependent kinase 2 (CDK2) in cells. Thus there is a defective checkpoint combined with increased survival which causes clonal evolution of the disease in CML. Flavopiridol a semi-synthetic flavone, is the first CDK inhibitor to be tested in clinical trials after being identified in an anti-cancer agent screen in 1992. Studies report that reatment with imatinib and flavopiridol leads to an increased mitochondrial damage, activation of caspases and enhanced apoptosis in imatinib-resistant CML cell line.

**DNA-METHYLTRANSFERASE INHIBITORS:**
The methylation of DNA a process occurring both in eukaryotic and prokaryotic cells, carried out by DNA methyl transferases (DNMT) plays an important role in the normal embryological development, genomic stability and also in carcinogenesis, and hence is a novel target for the treatment of malignancy. Cancers are usually hypomethylated due to inhibition of the inhibitory effects of homologous recombination and transcription of the normally repressed genes. DNA methyl transferase hence can theoretically serve as a reasonable target for antineoplastic drugs by preventing methylation they can limit the damaging recombination and also prevent transposon transcription and can silence the suppressor genes, ultimately inhibiting tumor growth and possibly inducing involution. Such novel agents in clinical trials which prevent methylation are 5-azacytidine (azacitidine), 5-aza-2’-deoxycytidine (decitabine), 1-β-Darabinofuranosyl-5-azacytosine (fazarabine) and dihydro-5-azacytidine (DHAC). After phosphorylation, they are incorporated into the DNA or RNA and are covalently linked with DNMT where they induce cell death by structural instability at the site of incorporation and by inhibition of DNA synthesis. The may be useful in CML. An in vitro study revealed that a combination of combination of decitabine with imatinib had additive to synergistic growth inhibitory effects upon cells containing Bcr-Abl with the M351T and Y253Fmutants.

**TUMOR SUPPRESSOR PP2A:**
Increased expression of Bcr-Abl protein leads to inactivation of tumor suppression gene protein phosphatase 2A (PP2A) tumor suppressor by enhancing the expression of one inhibitor. The molecular or pharmacologic reactivation of PP2A activity suppresses Bcr-Abl expression and function, resulting in growth inhibition, increased apoptosis, impaired clonogenicity and decreased in vivo leukemogenesis in CML cell lines and primary CML cells. Some PP2A activators like FTY720 is now in the phase of clinical trials in the management of patients with multiple sclerosis or undergoing renal transplantation. This agent also suppresses the growth, abolishes Bcr-Abl phosphorylation and induced Bcr-Abl down-regulation via the activation of PP2Ain imatinib-sensitive and T315I-expressing cell lines.

**Conclusion**
Without doubt, imatinib represents a major achievement for the treatment of CML but resistance to this drug has become and will continue to be a therapeutic challenge. Single agent therapy with imatinib may not be the best long-term option in CML, at least for a proportion of patients and other strategies need to be explored. Many novel compounds are currently being investigated preclinically and clinically, and therapeutic approaches to circumvent the problem of imatinib resistance are now possible. Dasatinib and nilotinib represent the first of the newer generation TKIs which are effective and safe in patients with imatinib resistant and intolerant CML. It is likely, however, that sub clones with novel
Bcr-Abl mutants will again develop in response to these new small-molecule inhibitors. Although it is nowadays emphasized as a clinical emergency, the problem of resistance driven by the T315I mutant is likely to be resolved soon. Therefore, alternative therapeutic approaches are required and these may involve the combination of Bcr-Abl TKIs with inhibitors of non-Bcr-Abl targets or targets downstream of Bcr-Abl to achieve a synergistic effect and possibly prevent or overcome resistance.

References


Illustrations
Illustration 1

Signalling Pathway In CML
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