NILOTINIB A NEW FDA APPROVED DRUG FOR THE TREATMENT OF CHRONIC MYELOGENOUS LEUKAEMIA

Shipra Sabherwal, Hitesh Kumar, Dipan Malhotra, Rajiv Sharma, Manav Malhotra, T. R. Bhardwaj*

Department of Pharmaceutical Chemistry, Indo-Soviet Friendship (ISF) College of Pharmacy, Ferozepur Road Moga-142 001, Punjab, India

***For correspondence**
Prof. T. R. Bhardwaj
Department of Pharmaceutical Chemistry,
ISF College of Pharmacy, Ferozepur Road,
Moga 142001, Punjab, India.
Phone no: +91 9872784844
email : bhardwajrtilak@yahoo.com

Summary

Chronic myelogenous leukaemia is one of the major chronic myeloproliferative diseases of pluipotential haematopoietic stem cells. Many therapeautic agents have failed to provide any relief to the patients suffering from chronic myelogenous leukaemia (CML). Imatinib was first ever developed drug for the treatment of (CML) but the problem associated with it is the resistant against this drug. Therefore, the development of new agents will remain an important challenging task for medicinal chemists. So, there is an urgent need for identification of new, potent, and less toxic agents which ideally shorten the duration of therapy and are effective against CML. Nilotinib which are found to be effective in patient with Imatinib – resistant chronic myelogenous leukaemia (CML). It is a second generation BCR-ABL tyrosine kinase inhibitor and found to be target specific kinase inhibitor as compare with Imatinib. This reviews article reflects development of Nolotinib, mechanism of action, preclinical, clinical studies and its FDA approval.

Keywords: Chronic myelogenous leukaemia, Imatinib, Nilotinib and Tyrosine kinase inhibitors.

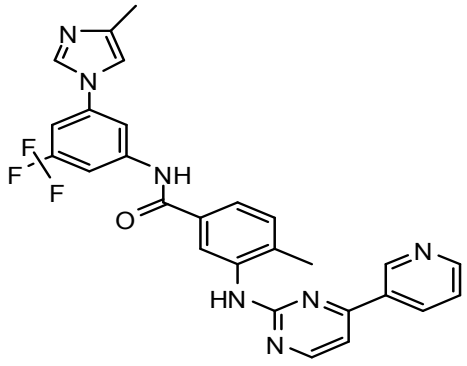
Introduction

Nilotinib (AMN107) has been developed by Novartis Pharmaceuticals Corporation, marketed under the trade name Tasigna. It was recently approved by U.S. Food and Drug Administration (FDA) on June 17, 2010. The drug was used for the treatment of newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (Ph^+CML) patient in chronic phase (CP-CML)[1]. Chronic myelogenous leukaemia (CML) is one of the major chronic myeloproliferative diseases of pluripotential hematopoietic stem cells. It has been reported that 1 out of 100 000 in the western countries is suffering from CML and its incidence increases steadily with age. It has been rarely found in children but more in men as compared to women[2]. The main cause of CML has been reciprocal chromosome translocation t (9; 22), in which the ABL proto-oncogene on chromosome 9 is translocated near the BCR gene on chromosome 22. This genetic alteration is known as the Philadelphia chromosome (Ph), results in the formation of a chimeric fusion protein, BCR-ABL. The presence of the Ph chromosome results in an uncontrolled protein phosphorylation of BCR-ABL,

rendering it constitutively activated. The BCR - ABL fusion protein has been found to be present in more than 90% of CML patients. CML was characterized by an over production of immature myeloid cells and mature granulocytes in the spleen, bone marrow and peripheral blood. However, if untreated CML progresses it ultimately may lead to a disorder associated with bone marrow failure or transformation to acute leukaemia. There are three phases of the disease: chronic phase, accelerated phase and the blast crisis phase. The initial chronic phase is of 4-6 years with CML progresses into the accelerated phase marked by the presence of primitive blast cells in the bone marrow and peripheral blood. Finally, the terminal blast crisis phase is characterized by the presence of undifferentiated blasts in the bone marrow and peripheral blood. Usually, patients in the blast crisis phase have a median survival of 18 weeks. The BCR-ABL inhibitor Imatinib mesylate (Glivec) is now the choice of drug for the treatment of CML. After five years of therapy with Imatinib high percentage (89%) of newly diagnosed patients with CML are alive and the median survival of patients with accelerated CML is 42.6 months. The annual rate of progression to accelerated phase/ blast crisis phase ranges from 1.5% in the first year, 2.8% in the second year to 0.6% in the fifth year in newly diagnosed patients. In patients with accelerated phase, the estimated rate of progression is 73% from last 4 years and all the patients with blast crisis phase will ultimately progress to death[3].

Nilotinib has been developed as second-generation drug and it act by inhibiting BCR-ABL tyrosine kinase that would be effective in patients with Imatinib-resistant CML. Imatinib resistance results into the emergence of point mutations within the kinase domain of BCR-ABL and lead decreased binding affinity of the drug. Nilotinib is synthetic aminopyrimidine derivative which act as competitive ATP- inhibitor for BCR-ABL[4]. Nilotinib is highly selective for BCR-ABL, binding to wild-type BCR-ABL with 20 times more as compared to the affinity of imatinib, and has *in vitro* activity against many imatinib-resistant mutants. Nilotinib is highly potent drug as compared to imatinib having a broader spectrum of activity against BCR-ABL. This has resulted in a clinical use of nilotinib for CML-CP and CML-AP patients who have developed resistance to imatinib. Nilotinib is an analogue of imatinib with similar multiple kinase targets, but without inhibition of the Src, gene the gene which regulates tyrosine kinase proteins that in turn affect cell multiplication. Nilotinib is of great interest to the scientists who want to use it as an option to treat cancer. The binding approach of nilotinib is energetically more favourable than imatinib. This has resulted in a more selective targeting for the malignancy. This is in particular significant for the older patients as they have problem in tolerating imatinib treatment. The higher dose required for imatinib make it hard for its further clinical use. Therefore, nilotinib is considered to be better substitute for the treatment of CML.

CHEMISTRY



4-Methyl-3-((4-(3-pyridinyl)-2-pyrimidinyl) amino)-N-(5-(4-methyl-1H-imidazol-1-yl)-

3-(trifluoromethyl) phenyl) benzamide hydrochloride monohydrate

Nilotinib is chemically: 4-methyl-3-((4-(3-pyridinyl)-2-pyrimidinyl)amino)-N-(5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)phenyl)benzamide hydrochloride monohydrate and corresponds to the molecular formula: $C_{28}H_{22}F_3N_7O.HCl.\ H_2O$. The molecular mass of nilotinib hydrochloride is 583.99(monohydrate) and 565.98(anhydrate). As it lacks chiral centre, therefore, no stereoisomers are possible. It appears as a white to slightly yellowish or slightly green-yellowish powder. It exists in three crystalline forms form A (dihydrate), B, C (monohydrate) form and amorphous forms. Monohydrate form is the most stable and least hygroscopic in nature and exhibits many medicinal properties. The crystalline forms are least hygroscopic in nature and show no transformation even on storage for several months. Solubility of nilotinib hydrochloride monohydrate in water at 25°C strongly decreases with increasing pH. It is practically insoluble in buffer solutions of pH 4.5 and higher pH values. Nilotinib is sparingly soluble in ethanol and methanol[5]. Many modifications had been done in imatinib by different drug companies to improve its efficacy such as replacement of the piperazine ring with a trifluorinated imidazole which fits well into a hydrophobic pocket and eliminated the unwanted hydrogen bonds between N-methylpiperazine and Ile^{360} and His^{361} of ABL. The have shown results in a better topological fitting and the molecule has been found to be inhibit ABL with 30-fold increased potency.

PHARMACOKINETICS

Nilotinib is well absorbed after oral administration but food and fatty meals increases the absorption of drug. It has high plasma protein binding (93.4% to 93.9%) to human serum albumin and to α-1 acid glycoprotein and its half life is 17 h. Higher plasma levels are achieved with dose of 400 mg twice a day as compared to 800 mg once a day. So the drug should be taken in empty stomach because higher plasma level has resulted into impairment of ventricular repolarization[6]. Nilotinib is mainly metabolised by oxidation, glucuronic acid conjugation and hydrolysis of amide. In oxidation reactions involve oxidation of methyl-imidazole ring, oxidation of pyridinyl-pyrimidinyl-amino methyl-benzamide moiety and degradation of oxidized imidazole. There are 74 different metabolites that have been detected in the plasma, urine and faeces. Nilotinib is potent inhibitor of CYP2C9 (Ki of 0.132μM and CYP3A4/5(Ki of 0.448μM), CYP2C8 (Ki of 0.236 μM). The oxidative metabolism of nilotinib decreased by >95% with CYP3A4 inhibitors with apparent IC_{50} values of 0.012 (ketoconazole) and 1.2μM (troleandomycin). It is also potent inhibitor of *in vitro* human uridine diphosphosphate-glucuronosyl transferase 1A1 (UGT1A1) (Ki of 0.19μM). Nilotinib is well distributed in plasma and its apparent volume of distribution (Vz/f) was 579 litres. Nilotinib is excreted primarily into the faeces as unchanged drug (69% of the dose), 21% of the remaining drug is distributed between 18 different metabolites and 4.5% of the dose was excreted by the kidneys[7].

MECHANISM OF INHIBITION OF ABL TYROSINE KINASE BY NILOTINIB

Nilotinib act by binding to the inactive conformation of the ABL Tyrosine kinase, with p-loop folding over the ATP-binding site and activation loop that involve pyridyl-N and backbone –NH of methionine 318, the anilino-NH and side chain hydroxyl of threonine 315 , the amido-NH and side chain carboxylate of Glu 286 as well as the amido -C=O and backbone –NH of Asp 381 by blocking the substrate binding site and inhibiting the catalytic activity of the enzyme[8]. This better fit between Nilotinib and the kinase binding site decreases the proliferation and viability of wild-type Bcr/Abl and Imatinib–resistant Bcr-Abl mutant expressing cells *in vitro* by selectively inhibiting the Bcr/Abl auto-phosphorylation. It inhibits the kinase activity of the most BCR/ABL mutants; except for T315I and Src kinase[9].

PRECLINICAL STUDIES

Preclinical studies suggest that Nilotinib is very effective in the treatment of BCR/ABL. The effectiveness of the drug was tested against a small number of highly malignant cells which were

injected in both transplant and transgenic mouse models used. In Transplant model, fifteen C57Bl/6J mice male, 6 weeks old were transplanted with $1X10^{48093}$ cells via a tail vein injection. Eight mice the vehicle group were fed a mixture of 8 parts peanut butter and 2 parts vegetable oil and the remaining 7 mice treatment group were treated with 75 mg of Nilotinib per kg body weight added to the same mixture daily. Nilotinib and mixture was fed five days after the transplantation. This was carried out for fifty days after the first day of transplantation[10]. Vehicle treated mice became dead within three weeks of the transplantation. They showed symptoms of acute lymphoblastic leukemia (ALL). Nilotinib treated mice live longer than the vehicle treated mice. This clearly indicated that Nilotinib is very effective in inhibiting the proliferation of leukemic cells, *in vivo*[11]. In Transgenic model, five P190 Bcr/Abl mice were treated with 75 mg/kg of Nilotinib on daily basis. These mice were analysed by examining their peripheral blood by Flow cytometry using a FAC Scan (BD Biosystems, Germany) to identify the markers which were suitable to detect the leukemic cells. It was observed that Nilotinib treatment led to a complete regression of the lymphomas within six days for all of the five BCR/ABL transgenic mice. There was significant improvement in the health of all five mice. Their mobility was restored within one week of treatment. Thus, during Pre clinical studies, Nilotinib was found to eliminate the cancer cells both *in vivo* and *in vitro*[12,13].

CLINICAL STUDIES

In a monotherapy trial with Nilotinib the total number of 119 subjects with Chronic myelogenous leukemia (CML); (17-Chronic phase (CP), 56-Acute phase (AP), 10 of whom with only clonal evolution, 24 myeloid Blast crisis phase (BC) and 22 lymphoid BC/ALL Ph^+) inadequately controlled on diet participated for 385 days. Drug dose levels ranging from 50mg to 1200 mg oral dose were administered. Intra-patient dose escalation was done only in patients with inadequate response and no-dose limiting toxicities[14] 92% of CP patients reached haematological response and 53% cytogenetic response. 90% of AP patients achieved cytogenetic response while AP patients (without clonal evolution), while 72% of them reached haematological response and 48% cytogenetic response. 42% of myeloid BC obtained haematological response and 29% cytogenetic response. In phase II trials, 321 patients (with resistance or intolerance to Imatinib) were treated with Nilotinib at 400mg TD. 72% of the patients had been already treated with Imatinib (> 600mg/day). Where as 59% of the patients achieved a major cytogenetic response (MCyR) in a median time of 2.8 months and 44% reached complete cytogenetic response (CCyR)[15].

In Phase III B, an open-label multicentred study was undertaken with 1793 subjects (resistance or intolerance after Imatinib in all CML phases (CP, AP and BC). Patients received 400 mg twice a day (TD) of Nilotinib and dose escalation was not permitted. Chronic haematological response rate was obtained in 40% CP, 10% AP and 3% BC patients. Major cytogenetic response rate was 41% in CP, 7% in AP and 14% in BC patients. 76% of patients experienced grade 3/4 toxicities (haematological, thrombocytopenia and neutropenia). It was observed that Nilotinib appeared active in patients who were resistant or intolerant to both Imatinib and Dasatinib. Nilotinib is well tolerated and does not appear to be associated with adverse effect such as fluid retention, oedema, weight gain or pleural effusions. In early chronic phase patients too, it appears to have great Efficacy and a limited spectrum of manageable toxicity[16]. It is found to be an inhibitor of CYP3A4, CYP2C8, CYP2C9 and CYP2D6 and it may also induce CYP2B6, CYP2C8 and CYP2C9. Therefore, it alters serum concentration of other drugs[17,18].

FDA APPROVAL AND MARKET AUTHORIZATION

The FDA approval for Nilotinib was based on the single randomized, active-control, open-label multinational clinical trial. Eight hundred and forty six patients were randomly assigned to receive imatinib 400 mg once daily, nilotinib 300 mg or 400 mg twice a day. The primary objective was to

compare the rate of major molecular response (MMR) at 12 months of each nilotinib dose with that of imatinib 400 mg QD. MMR was defined as BCR-ABL transcript level of $\leq$ 0.1 percent in peripheral blood by international scale measured by RQ-PCR, which corresponds to a $\geq$ 3 log reduction of BCR-ABL transcripts from the standardized baseline. The rate of complete cytogenetic response (CCyR) by month 12 was the key secondary endpoint[19]. The primary efficacy endpoint, MMR at 12 months, was achieved in 63 patients [22 percent (95 percent CI: 18, 28)] treated with imatinib, 125 patients [44 percent (95 percent CI: 38, 50)] treated with the lower dose of nilotinib, and 120 patients [43 percent (95 percent CI: 37, 49)] treated with the higher dose of nilotinib. The differences were statistically significant for both groups of nilotinib-treated patients compared with imatinib-treated patients ($p < .001$). CCyR rates by 12 months were 65 percent (95 percent CI: 59, 71) for patients treated with imatinib, 80 percent (95 percent CI: 75, 85) for patients treated with the lower dose of nilotinib and 78 percent (95 percent CI: 73, 83) for patients who received the higher dose of nilotinib[20]. More than 98 percent of patients in all three treatment groups experienced at least one adverse drug reaction (ADR). Overall incidences of Grade 3-4 toxicity were 46 percent in patients treated with nilotinib 300 mg twice-daily compared to 52 percent of patients treated with nilotinib 400 mg twice-daily. Common ADRs reported more frequently on nilotinib treatment compared to the imatinib treatment included rash, abnormalities of liver function (AST, ALT and bilirubin), hyperglycemia, hypercholesterolemia, elevated serum lipase, and headache. The incidence and severity of myelosuppression e.g. neutropenia, anemia, and/or thrombocytopenia) appeared similar in with both imatinib and nilotinib. The most common electrolyte imbalances in patients receiving nilotinib during were hypophosphatemia, hypokalemia, and hypocalcemia[21]. The safety profile of the 300 mg twice-daily dosing regimen appeared more favourable than that of the 400 mg twice-daily regimen, while the efficacy appeared comparable. The recommended dose of nilotinib for patients with newly diagnosed CP-CML is 300 mg twice a day. Tasigna is a trademark of the Novartis Pharmaceuticals Corporation and on June 17, 2010 it was approved by FDA for its manufacturing and marketing in various countries[22].

DOSAGE

Nilotinib is available in 150 mg and 200 mg hard gelatine capsules for oral administration. 150 mg capsules are red opaque with black axial imprint "NVR/BCR" and 200 mg capsules are light yellow with red axial imprint "NVR/TKI". Nilotinib capsules for oral use contain 150 mg or 200 mg nilotinib base as anhydrous hydrochloride and monohydrate). It also contain inactive ingredients colloidal silicon dioxide, crosspovidone, lactose monohydrate, magnesium stearate, polyoxamer 188 gelatine, iron oxide (red), iron oxide yellow, iron oxide black and titanium dioxide. The recommended dose for a newly diagnosed patient with Ph^+CML-CP is 300 mg orally twice a day and the same for resistant patients with Ph^+CML-CP/AP is 400 mg orally twice a day is required[23]. Nilotinib should be taken twice daily at approximately 12 h intervals and must not be taken with food. The capsules should be taken with water and no food should be consumed for at least 2 h before the dose and one hour after the dose. If a dose is missed the patient should not worry but should resume taking the next prescribed daily dose. Nilotinib may be given in combination with hematopoietic growth factors such as erythropoietin or GCSF or it may be given with hydroxyurea or anagrelide if clinically indicated[24].

ADVERSE EFFECTS

Although the drug has been introduced for the beneficial of the patients, still it cause thrombocytopenia, neutropenia and anemia. Nilotinib has been shown to prolong cardiac ventricular repolarization as measured by the QT interval on the surface ECG in a concentration-dependent manner. It can result in ventricular tachycardia. Its use may result in elevations in bilirubin,

AST/ALT and alkaline phosphatase. It can also cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcaemia, and hyponatremia. Electrolyte abnormalities must be corrected prior to initiating Nilotinib and these electrolytes should be monitored periodically during therapy[25]. It also cause increase in serum lipase. Sudden deaths have been reported in patients with resistant or intolerant Ph^+ CML receiving nilotinib (n=867; 0.6%). A similar incidence was also reported in the expanded access program for patients with resistance or intolerant Ph^+ CML. The relative early occurrence of some of these deaths relative to the initiation of nilotinib suggests the possibility that ventricular repolarization abnormalities may have contributed to their occurrence[26,27].

DRUG INTERACTIONS

The administration of Nilotinib with strong CYP3A4 inhibitors or anti-arrhythmic drugs including amiodarone, disopyramide, procainamide, quinidine, sotalol and other drugs that may prolong QT interval including chloroquine, clarithromycin, haloperidol, methadone, moxifloxacin and pimozide should be avoided. Treatment with any of these agents is required, if it is recommended that therapy with Nilotinib be interrupted. If interruption of treatment with Nilotinib is not possible, patients who require treatment with a drug that prolongs QT or strongly inhibits CYP3A4 should be closely monitored for prolongation of the QT interval[28].

Conclusion

Nilotinib is the best drug ever developed for the treatment of Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia. It is considered as second generation BCR-ABL tyrosine kinase inhibitor. It was created with the idea of improving the target specificity of an earlier kinase inhibitor, Imatinib. It inhibits the receptor kinases platelet derived growth factor receptor (PDGF-R) and c-kit, a receptor tyrosine kinase mutated which is activated in most of the gastrointestinal stromal tumours (GISTs) the drug is boon for those suffering patient who have developed resistance for other anticancer drugs. Although, its safety profile is not so good but it will be useful for the patients which are resistant to Imatinib.

References

1. Cowan-Jacob SW, Guez V, Fendrich G, Griffin JD, Fabbro D, Furet P, Liebetanz J, Mestan J, Manley PW. Imatinib (STI571) resistance in chronic myelogenous leukemia: molecular basis of the underlying mechanisms and potential strategies for treatment. Mini Rev Med Chem. 2004; 4: 285-289.
2. Alvarez RH, Kantarjian H, Cortes JE. The biology of chronic myelogenous leukemia: implications for imatinib therapy. Semin Hematol. 2007; 44: 4-14.
3. Kantarjian H, Talpaz M. Definition of the accelerated phase of chronic myelogenous leukemia. J Clin Oncol. 1988; 6: 180-182.
4. Rosti G, Palandri F, Castagnetti F, Breccia M, Levato L, Gugliotta G, Capucci A, Cedrone M, Fava C, Intermesoli T, Cambrin GR, Stagno F, Tiribelli M, Amabile M, Luatti S, Poerio A, Soverini S, Testoni N, Martinelli G, Alimena G, Pane F, Saglio G, Baccarani M; GIMEMA CML Working Party. Nilotinib for the frontline treatment of Ph (+) chronic myeloid leukemia. Blood. 2009, 114, 4933-4938.
5. Druker BJ, Sawyers CL, Kantarjian HN. Efficacy and Safety of a Specific Inhibitor of the BCR-ABL Tyrosine Kinase in Chronic Myeloid Leukemia. Engl J. Med. 2001; 344: 1031-1037.
6. Shah NP, Tran C, Lee FY, Chen P, Norris D. Overriding Imatinib resistance with a novel ABL kinase inhibitor. Science. 2004; 305: 399-401.
7. Gorre ME, Mohammed M, Ellwood K, Hsu N. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science. 2001; 293: 876-880.

8. Hare OT, Walters KD, Deininger WNM, Druker BJ. AMN107: Tightening the grip of imatinib. Cancer Cell. 2005; 7: 117-121.
9. Breccia M, Alimena G. Nilotinib: a second-generation tyrosine kinase inhibitor for chronic myeloid leukemia. Leukemia research. 2010; 34: 129-134.
10. Weisberg E, Manley PW, Breitenstein W, Brüggen J, Cowan-Jacob SW, Ray A, Huntly B, Fabbro D, Fendrich G, Hall-Meyers E, Kung AL, Mestan J, Daley GQ, Callahan L, Catley L, Cavazza C, Azam M, Neuberg D, Wright RD, Gilliland DG, Griffin JD Weisberg E, Manley WP, Breitenstein W, Bruggen J. Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. Cancer Cell. 2005; 7: 129-141.
11. Deininger WM. Clin Cancer Res. Currently, the most advanced HSP90 inhibitors in clinical trials are used as the standard of care in patients with ER-positive breast cancer. 2008; 14: 4026.
12. Palandri F, Castagnetti F, Gugliotta G, Poerio A. Haematology meeting reports. 2008; 2, 22-27.
13. Nicolini F, Alimena G, Turkina AT, Shen ZS. Nilotinib: A second-generation tyrosine kinase inhibitor for chronic myeloid leukemia. Haematologica. 2009; 94: 119-227.
14. Weisberg E, Manley P.; Mestan, J.; Cowan-Jacob, C.; Ray, A. AMN107 (nilotinib): a novel and selective inhibitor of BCR-ABL. British journal of Cancer. 2006; 94: 1765-1769.
15. Faderl S, Talpas M, Estrov Z, Kantarjian H. Chronic myelogenous leukemia: biology and therapy. Ann Intern Med. 1999; 131: 207-219.
16. Bradeen HA, Eide CA, O'Hare T, Johnson KJ, Willis SG, Lee FY, Druker BJ, Deininger MW. Comparison of imatinib mesylate, dasatinib (BMS-354825), and nilotinib (AMN107) in an N-ethyl-N-nitrosourea (ENU)-based mutagenesis screen: high efficacy of drug combinations. Blood. 2006; 108: 2332-2338.
17. Hochhaus A, Giles F, Apperley J, Wang J. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. Haematologica. 2009; 94: 631-635.
18. Kantarjian H, Giles FG, Bhalla KNP, Pinilla J. Long-term outcomes in the second-line treatment of chronic myeloid leukemia. Haematologica. 2009; 94: 627635.
19. Nilotinib Information – Nilotinib, leukemia, diagnosis of leukemia, nilotinib treatment, side-effects [Online]. Available online on URL: http:www.nilotinib.org.
20. Erpvan PN, Gelderblom H, Guchelaar JK. Clinical pharmacokinetics of tyrosine kinase inhibitors. Cancer Treatment Reviews. 2006; 35: 692-706.
21. Fava C, Kantarjian H, Cortes J, Jabbour E. Development and targeted use of nilotinib in chronic myeloid leukemia. Drug design, Development and Therapy. 2009; 2: 233-243.
22. Corbin AS, Buchdunger E, Pascal F. Druker BJ. Analysis of the structural basis of specificity of inhibition of the Abl kinase by STI571. J Biol Chem. 2002; 277: 32214-32219.
23. Hochhaus A, Hughes T. Clinical resistance to Imatinib: mechanisms and implications. Hematol Oncl. Clin North Am. 2004; 18: 641-656.
24. Kaur P, Feldhahn N, Zhang B, Trageser D, Trageser D, Muschen M, Pertz V, Groffen J, Heisterkamp N. Nilotinib treatment in mouse models of P190 Bcr/Abl lymphoblastic leukemia. Molecular Cancer. 2007; 6: 67-73.
25. Verstovsek S, Golemovic M, Kantarjian H, Manshouri T, Estrov Z, Manley P, Sun T, Arlinghaus RB, Alland L, Dugan M, Cortes J, Giles F, Beran M. AMN107, a novel aminopyrimidine inhibitor of p190 Bcr-Abl activation and of in vitro proliferation of Philadelphia-positive acute lymphoblastic leukemia cells. Cancer. 2005; 104: 1230-1236.
26. Voncken JW, Griffiths S, Greaves MF, Pattengale PK, Heisterkamp N, Groffen J. Restricted oncogenicity of BCR/ABL p190 in transgenic mice. Cancer Res. 1992; 52: 4534-4539.
27. Giles F, Larson RA, Kantarjian H. Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia Is There an Optimal Treatment Plan. Blood. 2007; 25: 110-117.
28. Heisterkamp N, Jenster G, Zovich D, Pattengale PK, Groffen J. Acute leukaemia in bcr/abl transgenic mice. Nature. 1990; 344: 251-253.