Imatinib resistance: a review of alternative inhibitors in chronic myeloid leukemia

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The development of point mutations in the BCR-ABL kinase domain is the main reason for imatinib resistance in chronic myeloid leukemia. Different detection methods are used in chronic myeloid leukemia monitoring, such as direct sequencing, denaturing high performance liquid chromatography and allele specific polymerase chain reaction. Mutation analysis has become mandatory during patient workup of chronic myeloid leukemia in order for the physician to choose the most suitable tyrosine kinase inhibitor. This article, a review of possible therapies used to overcome imatinib resistance, investigates the current position by searching the PubMed electronic database using the following keywords: imatinib, dasatinib, nilotinib, aurora kinase, SRC kinase, mutation, treatment, drugs and resistance. New tyrosine kinase inhibitors include BCR-ABL kinase selective inhibitors, dual ABL/SRC kinase inhibitors and aurora kinase inhibitors. Awareness of the spectrum of new drugs against mutations, in particular the T315I mutation, makes it possible to properly select the best therapy for each patient.

Keywords: Leukemia, myelogenous, chronic, BCR-ABL positive/drug therapy; Protein-tyrosine kinases; Drug resistance, neoplasm; Antineoplastic agents/therapeutic use; Piperazines/therapeutic use; Pyrimidines/therapeutic use

Introduction

The eight-year IRIS study, which compared the therapeutic results of interferon and imatinib (Glivec®), confirmed the effectiveness of imatinib and its long-term safety in chronic myeloid leukemia (CML). Imatinib is a tyrosine-kinase inhibitor which binds to the inactive form of BCR-ABL tyrosine kinase, preventing adenosine triphosphate (ATP) from binding.

The complete cytogenetic response for patients treated with imatinib as the first line drug is 83% and the overall survival rate is 85% as revealed in the eight-year IRIS study. In addition, according to the European LeukemiaNet, achieving cytogenetic and molecular responses during the period reduces the risk of relapse, progression and death.

Nonetheless, some patients develop resistance to imatinib even after attaining a response. Resistance mechanisms are heterogeneous and may involve BCR-ABL gene amplification, gene mutation, incomplete inhibition and overexpression of the multidrug resistance gene (P-glycoprotein) which may favor the selection of resistant cells. Resistance is commonly due to mutations within the BCR-ABL kinase domain. More than seventy different amino acids substitutions in this domain have been described, but approximately 85% of all cases carry one of the following fifteen mutations: T315I, Y253F/H, E255K/V, M351T, G250E, F359C/V, H396R/P, M244V, E355G, F317L, M237I, Q252H/R, D276G, L248V, F486S.

If the patient reaches a suboptimal response or fails to respond to imatinib, the European LeukemiaNet recommends mutation identification before changing with another tyrosine kinase inhibitor or to another therapy (Table 1).

Different methods for mutation detection were introduced in CML handling, such as direct sequencing, denaturing high performance liquid chromatography (DHPLC) and allele specific polymerase chain reaction (ASO-PCR). Direct sequencing is the most used method; it is the gold standard in diagnostic routine, showing mutation detection sensitivity of 10-25% compared to DHPLC (5-10%) and ASO-PCR (0.1-1%).

More sensitive detection methods have identified that some mutations pre-exist before imatinib treatment, but are normally detected after clonal selection following tyrosine-kinase inhibition, showing that the tyrosine kinase inhibitor has a selective
influence over the total cell population. Other mutations can be acquired during disease progression in association with genetic instability.\(^9,10\) In vitro studies have identified mutations that can decrease tumor response to second generation tyrosine kinase inhibitors. Sensitivity is described by the concentration of drug necessary to inhibit 50% of wild type BCR-ABL tyrosine kinase (IC\(_{50}\)) in vitro, therefore, the smaller the IC50, the more powerful the drug is. Mutations are classified according to the IC50 of each tyrosine kinase inhibitor as sensitive, intermediately sensitive or insensitive.\(^11-16\)

Some studies have described that after treatment discontinuity, a proliferative disadvantage for the mutant clone (deselection) can occur. This effect seems to be less frequent in patients with the T315I mutation compared to mutations in the phosphate loop region.\(^17\)

In vitro sensitivity classifications are not completely accurate and need clinical validation. When validated, they are very useful to guide the proper therapeutic intervention after treatment failure. Furthermore, classification based on in vitro studies is not simple, since a particular mutation can be described as resistant or sensitive to the same inhibitor, for instance, the G250E mutation.\(^14\)

In vitro studies do not take into account in vivo variables such as drug absorption, distribution, metabolism, transportation and excretion, which greatly influence the overall clinical response to therapy. Moreover, clinical response also varies from patient to patient, depending on treatment adherence, interaction with food and/or medicines, as well as genetic background.\(^18\)

Therefore, mutation analysis becomes mandatory for the physician’s decision in order to choose the most adequate tyrosine kinase inhibitor, always taking into consideration other factors such as disease stage, patient characteristics, risk factors and co-morbidities.\(^19\)

This article, a review of possible therapies used to overcome imatinib resistance, investigates the current position by searching the PubMed electronic database using the following keywords: imatinib, dasatinib, nilotinib, aurora kinase, SRC kinase, mutation, treatment, drugs and resistance.

Novel BCR-ABL tyrosine kinase inhibitors

Novel tyrosine kinase inhibitors include selective inhibitors, dual ABL/SRC kinase inhibitors and aurora kinase inhibitors.\(^20,21\)

BCR-ABL tyrosine kinase

Tyrosine kinases participate in fundamental cell processes such as proliferation, adaptation and apoptosis through interactions with several proteins involved in oncogene signal transduction pathways, and are responsible for gene transcription activation or suppression. These interactions are mediated by adapter proteins such as the growth factor receptor-bound protein-2 (Grb2), growth factor receptor-binding protein complex (Gab2), SRC kinase family and focal adhesion kinases (FAK).\(^22\)

The main pathways involved in BCR-ABL signal transduction are: the Ras Sarcoma (RAS) pathway, mitogen-activated protein kinase pathway (MAPK), extracellular signal regulated kinase pathway (ERK), phosphatidyl-inositol-3-kinase pathway (PI3K), signal transduction and activator of transcription 5 (STAT5) and kB nuclear factor pathway (NFkB).\(^22-24\)

SRC kinase family

The SRC kinase family of proteins participates in signal transduction processes, contributing to cell growth regulation. This family structurally comprises nine homologous intracellular receptors (SRC, FYN, YES, BLK, YRK, HCK, LCK and LYN).\(^23\) There are multiple tyrosine residues in SH3-SH2 regions of BCR-ABL that are phosphorylated by HCK, LYN and FYN kinases (SRC family), increasing their activity. During CML progression, LYN and HCK overexpressions and/or activation can occur, suggesting a relationship with imatinib resistance.\(^25-27\)

Aurora kinase

The aurora kinase family is essential for mitotic progression. Aurora kinase A acts in the formation of the mitotic fuse and in the centromere maturation, allowing chromosome segregation into daughter cells. Aurora kinase B, in turn, is essential for the cytokinesis and aurora kinase C is mostly restricted to germinative cells.\(^28\)
Dasatinib

Dasatinib (Sprycel®, Bristol-Myers Squibb) is a multi-target inhibitor of BCR-ABL tyrosine kinase, SRC family kinases, platelet-derived growth factor (PDGF) and c-kit receptors. It acts on the adenosine triphosphate (ATP) binding site of ABL, regardless of the site activation state; it is 325 times more powerful than the imatinib in respect to wild type BCR-ABL cells and has a much smaller IC50. (32,29,30)

High response rates to dasatinib have been observed in patients with L248, Y253, E255, F359, H396 mutations. In comparison, T315, F317 and V299 mutations are associated with dasatinib resistance. (11)

While imatinib is a P-glycoprotein substrate which is highly expressed in hematopoietic stem-cells, dasatinib is not. (31) Similar to imatinib, dasatinib is metabolized in the liver, mainly by cytochrome P450 and thus potentially presents drug interactions. (32) Dasatinib is approved for second-line treatment in patients with CML who were not successfully treated using imatinib. Moreover, dasatinib is effective as initial treatment of CML patients in the chronic phase, rapidly reaching complete cytogenetic response. (33,34)

Phase II and III studies on dasatinib showed faster and more prominent molecular and cytogenetic responses compared to imatinib. (35)

Nilotinib

Nilotinib (Tasigna®, Novartis) has an imatinib-derived structure. Therefore, nilotinib binds to a BCR-ABL inactive conformation, occupying the same site as ATP in the enzyme active conformation. It also inhibits the platelet-derived growth factor tyrosine kinase (PDGF) and c-kit receptors, showing an efficiency similar to imatinib and having a higher selectivity for BCR-ABL. (36,37)

In wild type BCR-ABL cells, nilotinib is 20 times more potent than imatinib, inducing apoptosis with significantly smaller concentrations compared to imatinib. Nilotinib is effective in patients with most mutations, except for E255K/V,F359C/V, Y253H and T315I mutations. (12,13)

Nilotinib presents differences in efflux patterns as it does not use organic cation transporters (OCT-1). (38) Similar to imatinib and dasatinib, nilotinib is metabolized in the liver, mainly by the cytochrome P450 and thus potentially presents drug interactions. (32)

Nilotinib is approved as a second-line treatment in the chronic and accelerated phases of CML, in CML patients resistant or intolerant to imatinib, minimal cross-intolerance to imatinib and in the presence of few adverse effects. (32,39)

Nilotinib presents a fast and complete cytogenetic response in the initial chronic phase of almost all patients, with a low toxicity profile. (40)

Nilotinib phase II studies showed faster and more intense molecular and cytogenetic responses when compared to imatinib and only one patient in this study advanced to the accelerated or blastic phase. Phase III nilotinib studies showed greater molecular and cytogenetic responses and more patients reached undetectable levels of the disease. (35)

Bosutinib

Bosutinib (SKI-606, Wyeth), originally identified as a SRC inhibitor, is a potent anti-proliferative and pro-apoptotic agent of BCR-ABL cell lines. It is similar to dasatinib, but it does not inhibit growth factor tyrosine kinase receptors, such as PDGFR and epidermal growth factor receptor (EGFR). This feature may turn bosutinib less toxic than dasatinib, but a clinical comparison is necessary to confirm this. (41,42)

Tyrosine kinase inhibition by bosutinib was similar to that observed with imatinib, but demanding lower concentrations. At high concentrations bosutinib can inhibit the multiple drug-resistance protein, which has contributed to improved pharmacokinetic effects. (42,43) In vitro studies suggest that T315I and V299L mutations are resistant to bosutinib. (16)

In phase II trials, bosutinib was effective in patients who were resistant or intolerant to imatinib, including patients with mutations in the kinase domain. Currently, bosutinib is in phase III trials. (44)

Ponatinib

Ponatinib (AP24534) was developed to interact with the inactive ABL conformation at multiple sites and with the T315I mutation, providing high affinity and efficacy. Therefore, it also works against other imatinib-resistant mutations. (45)

Ponatinib has been shown to inhibit SRC family kinases, PDGFRα and c-KIT, but not Aurora kinases, which distinguishes it from other T315I inhibitors in development. (45)

In a phase I clinical trial ponatinib was used to treat 67 patients resistant to imatinib, dasatinib and nilotinib and passed safety requirements. Among these patients, 72% presented mutations in BCR-ABL at the beginning of the study or had a documented mutation story, including the T315I and F317L mutations. Moreover, 82% of patients were in the chronic phase, presented the T315I mutation and achieved a greater CgR. (46)

Saracatinib

Saracatinib (AZD0530, Astra-Zeneca) is a dual SRC/ABL kinase inhibitor. Saracatinib is able to overcome Y253F and E255K but not T315I mutations. If its inhibitory effect is a result of a direct effect on SRC, on ABL kinases or on both of them, is still a matter of debate. (47,48)

Saracatinib has been tested in CML animal models and in clinical trials for solid tumors such as recurrent or...
metastatic head and neck squamous cell carcinoma. It has not entered CML clinical trials yet.\(^{(49,50)}\)

**INNO-46 (NS-187, Nippon-Shinyaku)**

INNO-46 (NS-187, Nippon-Shinyaku) is a potent dual BCR-ABL/LYN tyrosine kinase inhibitor. It is 25-55 times more powerful than imatinib regarding the BCR-ABL self-phosphorylation block. It also inhibits PDGFR and c-Kit receptor phosphorylation with a potency similar to imatinib. Studies suggest that LYN kinase inhibition can break the imatinib-resistant disease progression, being less sensitive to mutations in ABL kinase domain than other inhibitors, such as imatinib. However, it does not inhibit the T315I mutation and additional studies are needed to better evaluate the effectiveness of INNO-406 in patients who have developed resistance or intolerance to imatinib and to other tyrosine kinase inhibitors.\(^{(27,51-53)}\)

In INNO-406 phase I studies, tolerance was for 240 mg doses twice a day and a high CgR was reached by six patients. From the 56 patients in the study, 71% were resistant and 29% were intolerant to imatinib, 26 patients were intolerant or resistant to dasatinib and 20 patients presented resistance or intolerance to nilotinib. Because it is a third-line treatment, a lower response rate is expected.\(^{(53)}\)

**MK-0457**

MK-0457 (Merck, originally developed by Vertex Pharmaceutical as VX-680) is an aurora kinase inhibitor, which presents anti-proliferative and pro-apoptotic effects in a series of tumor cell lines.\(^{(59)}\) It has been shown to bind to 37 of 119 tested kinases and to imatinib-resistant mutant forms.\(^{(54)}\)

Different from imatinib, which binds deeply into the ABL kinase domain, MK-0457 is anchored by four hydrogen bridges, suggesting a mechanism for T315I mutation inhibition and an eventual clinical application.\(^{(55)}\)

During MK-0457 phase I and phase II performance studies, important cardiac events, such as prolongation of the QT interval, were observed, causing additional MK-0457 trials to be cancelled and drug development was interrupted.\(^{(56)}\)

**ON012380**

ON012380 (Onconova) is a BCR-ABL inhibitor, active against 100% of imatinib-resistant mutations including the T315I mutation. This is because ON012380 does not compete with ATP to inhibit BCR-ABL, but with its substrates suggesting that molecules with action sites out of the kinase domain can be good therapeutic agents against imatinib-resistant leukemias.\(^{(57)}\)

In comparison to imatinib, ON012380 is 10 times more powerful. Besides being selective against BCR-ABL, it is likely that ON012380 is also effective against cells in which resistance to imatinib is due to overexpression or activation of LYN kinases.\(^{(57,27)}\)

ON012380 has not entered clinical trials and so its effectiveness and safety in vivo have not been confirmed yet.\(^{(58)}\)

**Conclusion**

Mutation analysis is important to guide clinical decisions regarding treatment, especially for patients who suspend imatinib due to intolerance or resistance. It would be ideal for all services to have access to mutation analysis tests before choosing the second or third tyrosine kinase inhibitors, since the identified mutation can influence the response to tyrosine kinase inhibitors. It is mandatory to know the action spectrum of new drugs against mutations, mainly T315I and to always take into account other variables involved in patient care, such as the individual characteristics of patients, clinical condition, comorbidities and treatment adaptation.

**References**

1. Fava C, Saglio G. Can we should improve on frontline imatinib therapy for chronic myeloid leukemia? Semin Hematol. 2010;47 (4):319-26.
2. Druker BJ, Guilhot F, O’Brien SG, Gathmann I, Kantarjian H, Gattermann N, Deininger MW, Silber RT, Goldman JM, Stone RM, Cervantes F, Hochhaus A, Powell BL, Gabrilove JL, Rousselet P, Reiffers J, Cornelissen JJ, Hughes T, Agis H, Fischer T, Verhoeft G, Shepherd J, Saglio G, Gratwohl A, Nielsen JL, Radich JP, Simonsson B, Taylor K, Baccarani M, So C, Letvak L, Larson RA; IRIS Investigators. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. 2006;355(23):2408-17. Comment in: N Engl J Med. 2007;356 (17):1780; author reply 1780.
3. Baccarani M, Cortes J, Pane F, Niedierwieser D, Saglio G, Apperley J, Cervantes F, Deininger M, Gratwohl A, Guhilott F, Hochhaus A, Horowitz M, Hughes T, Kantarjian H, Larson R, Radich J, Simonsson B, Silver RT, Goldman J, Hehmman R; European LeukemiaNet. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol. 2009;27(35):6041-51. Comment in: J Clin Oncol. 2010;28(18):e310; author reply e311.
4. Gambacorti-Passerini CB, Gunby RH, Piazza R, Galieta A, Rostagno R, Scapozza L. Molecular mechanisms of resistance to imatinib in Philadelphia-chromosome-positive leukemias. Lancet Oncol. 2003;4(2):75-85.
5. Hochhaus A, Kreil S, Corbin AS, La Rosée P, Muller MC, Lahaye T, et al. Molecular and chromosomal mechanisms of resistance to imatinib (STI571) therapy. Leukemia. 2002;16(11):2190-6.
6. Apperley JF. Part I: mechanisms of resistance to imatinib in chronic myeloid leukemia. Lancet Oncol. 2007;8(11):1018-29.
7. Shah NP, Nicoll JM, Nagar B, Gorre ME, Paquette RL, Kuriyan J, et al. Multiple BCR-ABL kinase domain mutations confer polycyonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. Cancer Cell. 2002;2(2):117-25. Comment on: Cancer Cell. 2002;2(2):99-102.
8. Kantarjian H, Schiffer C, Jones D, Cortes J. Monitoring the response and course of chronic myeloid leukemia in the modern era of BCR-ABL tyrosine inhibitors: practical advice on the
use and interpretation of monitoring methods. Blood. 2008;111(4):1774-80.
9. Roche-Lestienne C, Soenen-Cornu V, Grardel-Duflos N, Lai JL, Philippe N, Facon T, et al. Several types of mutations of the Abl gene can be found in chronic myeloid leukemia patients resistant to STI571, and they can pre-exist to the onset of treatment. Blood. 2002;100(3):1014-8.
10. Soverini S, Martineelli G, Rosti G, Bassi S, Amabile M, Poerio A, et al. ABL mutations in late chronic phase chronic myeloid leukemia patients with up-front cytogenetic resistance to imatinib are associated with a greater likelihood of progression to blast crisis and shorter survival: a study by the GIMEMA Working Party on Chronic Myeloid Leukemia. J Clin Oncol. 2005;23(18):4100-9.
11. Muller MC, Cortes JE, Kim DW, Druker BJ, Erben P, Pasquini R, et al. Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting BCR-ABL mutations. Blood. 2009;114(24):4944-53. Comment in: Blood. 2009;114(24):4914-5.
12. Hughes T, Saglio G, Branford S, Soverini S, Kim DW, Muller MC, et al. Impact of baseline BCR-ABL mutations on response to nilotinib in patients with chronic myeloid leukemia in chronic phase. J Clin Oncol. 2009;27(25):4204-10.
13. O’Hare T, Walters DK, Stoffregen EP, Jia T, Manley PW, Mestan J, et al. In vitro activity of BCR-ABL inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. Cancer Res. 2005;65(11):4500-05.
14. Brandford S, Melo JV, Hughes TP. Selecting optimal second line tyrosine kinase therapy for chronic myeloid leukemia patients after imatinib failure: does the BCR-ABL mutation status really matter? Blood. 2009;114(27):5426-34.
15. O’Hare T, Eide CA, Deininger MW. BCR-ABL kinase domain mutations, drug resistance, and the road to a cure for chronic myeloid leukemia. Blood. 2007;110(7):2242-9.
16. Redaelli S, Piazza R, Rostagno R, Magistroni V, Perini P, Marega M, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009;27(3):469-71. Comment in: J Clin Oncol. 2010;28(11):e169-71; author reply e172.
17. Hanfstein B, Müller MC, Kreil S, Ernst T, Schenk T, Lorentz C, et al. Dynamics of mutant BCR-ABL-positive clones after cessation of tyrosine kinase inhibitor therapy. Haematologica. 2011;96(3):360-6. Comment in: Haematologica. 2011;96(3):347-9.
18. Soverini S, Rosti G, Iacobucci I, Baccarani M, Martineelli G. Choosing the best second-line tyrosine kinase inhibitor in imatinib-resistant chronic myeloid leukemia patients harboring BCR-abl kinase domain mutations: how reliable is the IC50? Oncologist. 2011;16(6):686-76.
19. Jabbour E, Jones D, Kantarjian HM, O’Brien S, Tam C, Koller C, et al. Long-term outcome of patients with chronic myeloid leukemia treated with second-generation tyrosine kinase inhibitors after imatinib failure is predicted by the in vitro sensitivity of BCR-ABL kinase domain mutations. Blood. 2009;114(10):2037-43.
20. Bumbea H, Vladareanu AM, Voican I, Cîșteanu D, Barsan L, Onisai M. Chronic myeloid leukemia therapy in the era of tyrosine kinase inhibitors - the first molecular targeted treatment. J Med Life. 2010;3(2):162-6.
21. Weisberg E, Manley PW, Cowan-Jacob SW, Hochhaus A, Griffin JD. Second generation inhibitors of BCR-ABL for the treatment of imatinib-resistant chronic myeloid leukemia. Nat Rev Cancer. 2007;7(5):345-56.
22. Alvarez RH, Jantarjian H, Cortes JE. The biology of chronic myelogenous leukaemia: implications for imatinib therapy. Semin Hematol. 2007;(1 Suppl 1):S4-S14.
23. Ren R. Mechanisms of BCR-ABL in the pathogenesis of chronic myelogenous leukemia. Nat Rev Cancer. 2005;5(3):172-83.
24. Steelman LS, Pohner SC, Shelton JG, Franklin RA, Bertrand FE, McCubrey JA. JAK/STAT, Raf/MEK/ERK, PI3K/Akt and BCR-ABL in cell cycle progression and leukemogenesis. Leukemia. 2004;18(2):189-218.
25. Kantarjian HM, Giles F, Cardama AQ, Cortes J. Important therapeutic targets in chronic myelogenous leukemia. Clin Cancer Res. 2007;13(4):1089-97.
26. Li S. Src-family kinases in the development and therapy of Philadelphia chromosome-positive chronic myeloid leukemia and acute lymphoblastic leukemia. Leuk Lymphoma. 2008;49(1):19-26.
27. Donato NJ, Wu YJ, Staple J, Gallick G, Lin H, Aリングhaus R, et al. BCR-ABL independence and LYN kinase overexpression in chronic myelogenous leukemia cells selected for resistance to STI571. Blood. 2003;101(2):690-8.
28. Harrington EA, Bebbington D, Moore J, Rasmussen RK, Ajose-Adeogun AO, Nakayama T, et al. VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth in vivo. Nat Med. 2004;10(3):262-7. Erratum in: Nat Med. 2007;13(4):511. Comment in: Nat Med. 2004;10(3):234-5.
29. Schittenhelm MM, Shiraga S, Schroeder A, Corbin AS, Griffith D, Lee FY, et al. Dasatinib (BMS-354825), a dual SRC/ABL kinase inhibitor, inhibits the kinase activity of wild-type, Juxtamembrane, and activation loop mutant KIT isoforms associated with human malignancies. Cancer Res. 2006;66(1):473-81.
30. Shah NR, Tran C, Lee FY, Chen P, Norris D, Sawyer CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science. 2004;305(5682):399-401. Comment in: Science. 2004;305(5682):319-21.
31. Talpaz M, Shah NP, Kantarjian H, Donato N, Nicolli J, Paquette R, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. N Engl J Med. 2006;355(24):2531-41. Comment in: N Engl J Med. 2006;354(24):2594-6. N Engl J Med. 2006;355(10):1062-3; author reply 1063-4.
32. McFarland KL, Wetzstein GA. Chronic myeloid leukemia therapy: focus on second-generation tyrosine kinase inhibitors. Cancer Control. 2009;16(2):132-40.
33. Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362(24):2260-70. Comment in: N Engl J Med. 2010;363(17):1672-3; author reply 1673-5. Expert Opin Pharmacother. 2011;12(1):157-63. N Engl J Med. 2010;363(17):1672-3; author reply 1673-5. N Engl J Med. 2010;362(24):2314-5.
34. Cortes JE, Jones D, O'Brien S, Jabbour E, Ravandi F, Koller C, et al. Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. J Clin Oncol. 2010;28(3):398-404. Comment in: J Clin Oncol. 2010;28(3):363-5.
35. Kantarjian HM, Baccarani M, Jabbour E, Saglio G, Cortes JE. Second-generation tyrosine kinase inhibitors: the future of frontline CML therapy. Clin Cancer Res. 2011;17(7):1674-83.
36. Weisberg E, Manley PW, Breitenstein W, Brüggé J, Cowan-Jacob SW, Ray A, et al. Characterization of AMN107, a selective inhibitor of native and mutant BCR-ABL. Cancer Cell. 2005;7(2):129-41. Erratum in: Cancer Cell. 2005;7(4):399. Mohammed, Azam [corrected to Azam, Mohammad].
37. Golemovic M, Verstovsek S, Giles F, Cortes J, Manshouri T, Manley PW, et al. AMN107, a novel aminopyrimidine inhibitor of BCR-ABL, has in vitro activity against imatinib-resistant chronicmyeloid leukemia. Clin Cancer Res. 2005;11(13):4941-7.
38. White DL, Saunders VA, Dang P, Engler J, Zannettino AC, Cambarerí AC, et al. OCT-1-mediated influx is a key determinant...
of the intracellular uptake of imatinib but not nilotinib (AMN107): reduced OCT-1 activity is the cause of low in vitro sensitivity to imatinib. Blood. 2006;108(2):697-704.

39. Swords R, Mahalingam D, Padmanabhan S, Carew J, Giles F. Nilotinib: optimal therapy for patients with chronic myeloid leukemia and resistance or intolerance to imatinib. Drug Des Devel Ther. 2009; 3:89-101.

40. Cortes JE, Jones D, O’Brien S, Jabbour E, Konopleva M, Ferrajoli A, et al. Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. J Clin Oncol. 2010; 28(3):392-7. Comment in: J Clin Oncol. 2010; 28(3):363-5.

41. Puttini M, Coluccia AM, Boschelli F, Cleris L, Marchesi E, Donella-Deana A, et al. In vitro and In vivo activity of SKI-606, a novel Src-Ab1 Inhibitor, against imatinib-resistant BCR-ABL+ neoplastic cells. Cancer Res. 2006;66(23):11314-22.

42. Golas JM, Arndt K, Etienne C, Lucas J, Nardin D, Gibbons J, et al. Nilotinib: a review of alternative inhibitors in chronic myeloid leukemia

43. O’Hare T, Shakespeare WC, Zhu X, Eide CA, Rivera VM, Wang F, et al. AP24534, a Pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the t315i mutant and overrides mutation-based resistance. Cancer Cell. 2009;16(5):401-12.

44. Brummendorf TH, Cervantes F, Kim D, Chandy M, Fischer T, Hochhaus A, et al. Bosutinib is safe and active in patients with chronic phase chronic myeloid leukemia with resistance or intolerance to imatinib. Blood. 2006;108(31):11011-6.

45. Kantarjian H, le Coutre P, Cortes J, Pinilla-Ibarz J, Nagler A, Hochhaus A, et al. A non-A TP-competitive inhibitor of BCR-ABL overrides imatinib resistance. Proc Natl Acad Sci U S A. 2005;102(31):10987-92.

46. Schenone S, Brullo C, Musumeci F, Botta M. Novel dual Src/Ab1 inhibitors for hematologic and solid malignancies. Expert Opin Investig Drugs. 2010;19(8):931-45.

47. Nowak D, Boehrser S, Hochmuth S, Trephol B, Hofmann W, Hoelzer D, et al. Src kinase inhibitors induce apoptosis and mediate cell cycle arrest in lymphoma cells. Anticancer Drugs. 2007;18 (9):981-95.

48. Gwannessia PM, Romanski A, Schwarz K, Bacie B, Ruthardt M, Ottmann OG. The effect of the dual Src/Abl kinase inhibitor AZD0530 on Philadelphia positive leukaemia cell lines. BMC Cancer. 2009;9:53.