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Chronic Myeloid Leukemia – Mechanisms of Resistance and Treatment

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Abstract

Imatinib mesylate has revolutionized the treatment landscape for patients with newly diagnosed chronic myeloid leukemia (CML). Imatinib at a dose of 400 mg/day is considered the standard treatment for all newly diagnosed chronic phase CML. Follow-up on the pivotal International Randomized Study of Interfreron versus STI571 (IRIS) study has shown excellent response rates, progression-free survival and overall survival after 8 years of follow-up. However, some patients will develop resistance to imatinib treatment due to a multitude of reasons. Numerous strategies to overcome resistance are available including dose escalation of imatinib, switching to a second generation tyrosine kinase inhibitor or to one of the newer non-tyrosine kinase inhibitors. This review guides the treating physician with a rational approach in the management of CML patients who fail initial treatment with imatinib or lose response while on therapy with imatinib.

Keywords

myeloproliferative disorders; tyrosine kinase inhibitors; mutation screening; homoharringtonine; multikinase inhibitors

INTRODUCTION

Chronic myeloid leukemia (CML) is a pluripotent hematopoietic stem cell disorder leading to myeloproliferation and its attendant consequences. In the United States, it is estimated that approximately 5050 cases of CML will be diagnosed in 2010 with an annual incidence of 1–2 cases per 100,000 adult individuals.[1] The instigating factor in the pathogenesis of chronic myeloid leukemia (CML) is the formation of the Philadelphia chromosome resulting from the reciprocal translocation between chromosomes 9 and 22 (t(9;22)(q34;q11)), which is associated with the *de novo* creation of the *BCR-ABL* fusion oncogene.[2,3] The gene product of the *BCR-ABL* gene constitutively activates numerous downstream targets

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including *c-myc*, *Akt* and *Jun*, all of which cause uncontrolled proliferation and survival of CML cells.

IMATINIB MESYLATE

Imatinib mesylate (Gleevec™, STI-571), a 2-phenylaminopyrimidine, is a selective and potent inhibitor of *BCR-ABL* and few other tyrosine kinases, including *c-kit, PDGF-R* alpha and beta, and *ABL* related gene (ARG).[4] It is orally administered with 98% bioavailability and a half-life of 13–16 hours. Imatinib was first used in CML in patients who had developed resistance or intolerance to interferon-α (IFN-α). Among 532 such patients treated with imatinib, a complete cytogenetic response (CCyR) was achieved in 60%. The estimated 5-year survival rate was 76%.[5,6]

Based on these favorable results, a large, randomized trial was initiated among patients with CML in chronic phase (CML-CP) who had received no prior therapy. In this study, known as the International Randomized Study of Interfreron versus STI571 (IRIS) trial, patients were randomized to receive imatinib or IFN-α and ara-C which was the standard therapy at the time. Treatment with imatinib was significantly better in nearly all outcomes measured, including hematologic and cytogenetic response, toxicity and progression-free survival (PFS).[7] After 8 years, the cumulative CCyR rate for first-line imatinib-treated patients was 82%.[8] The event-free survival (EFS) was 81%, and the estimated rate of freedom from progression to accelerated phase (CML-AP) or blastic phase (CML-BP) was 92%. The estimated overall survival (OS) rate for patients treated with imatinib was 85%. At 8 years, 304 patients (55%) randomized to imatinib remained on treatment. The curves seem to plateau after the fourth year and yearly event rates have ranged from 0.3%–2%. With an annual mortality of 2%, the estimated survival of a newly diagnosed patient with CML may be in the range of 20–30 years.

MECHANISMS OF RESISTANCE

Despite the impressive results with imatinib, a subset of patients treated with imatinib will develop resistance. Failure to achieve a landmark response is considered primary resistance, and this is further subdivided into primary hematologic resistance, and primary cytogenetic resistance. Secondary resistance is defined by the achievement and then subsequent loss of a hematologic or cytogenetic response. Hematologic resistance occurs in 2–4% of cases, while cytogenetic resistance is more common, occurring in 15–25% of patients. Mutations in *BCR-ABL* are rarely responsible for primary resistance. Recent work suggests that primary resistance may be associated with increased transcript levels of the drug metabolism gene prostaglandin-endoperoxide synthase 1/cyclooxgenase 1 (PTGS1/COX1), and this may serve as a biomarker to distinguish patients with primary resistance to imatinib.[9]

Several mechanisms of resistance to imatinib have been described. These can be classified into two categories: *BCR-ABL*-dependent and *BCR-ABL* independent. The first group includes amplification or overexpression of *BCR-ABL* or its protein product,[10] and point mutations of the *ABL* sequence.[11] The second group includes multidrug-resistance (MDR) expression and overexpression of Src kinases.[12] *BCR-ABL*-dependent mechanisms are more common, particularly point mutations, which have been identified in approximately 50% of

patients who develop clinical resistance to imatinib.[13,14] More than 90 different mutations have been described and occur in any of the different relevant domains of the kinase, including the ATP-binding domain (also known as P-loop), the catalytic domain, the activation loop, and amino acids that make direct contact with imatinib. The significance of these mutations varies. While some retain some sensitivity to imatinib at concentrations similar to those of the wild type sequence, others, particularly T315I, are nearly completely insensitive to imatinib.[15] Most of the clinically relevant mutations develop in a few residues in the in the P-loop (G250E, Y253F/H, and E255K/V), the contact site (T315I), and the catalytic domain (M351T and F359V).[16] The P-loop mutations have been suggested to carry an increased risk of rapid blastic transformation and short survival[13] although the M.D. Anderson Cancer Center (MDACC) experience does not support this notion.[17] In some patients, more than one mutation may be present at the same time. This phenomenon appears to increase in frequency after treatment with more than one tyrosine kinase mutation. Mutations are quantified by direct sequencing and the sensitivity of such assay varies between 10%–25%.[18,19] Other methods, such as denatured high-performance liquid chromatography increase the sensitivity to 1% to 10%.[19,20] However, it is unclear at this time if identification of small mutated clones with these highly sensitive methods is clinically relevant.

Other mechanisms of resistance due to intrinsic factors include: *BCR-ABL* gene amplification, *BCR-ABL* overexpression, aberrations in other oncogenetic signaling pathways, and the persistence of leukemic stem cells.[14,21,22] Extrinsic factors contributing to resistance include those that decrease the blood levels or bioavailability of imatinib, such as: patient compliance, drug–drug interactions, drug influx and efflux and multidrug resistance in sanctuary sites, as well as microenvironmental factors.[21]

MUTATION SCREENING DURING IMATINIB THERAPY

The European LeukemiaNet (ELN) and the National Comprehensive Cancer Network (NCCN) provide guidance for the monitoring of patients with CML.[23,24] The criteria for defining optimal response, sub-optimal response and failure to respond are outlined in Table 1. The ELN recommends mutational analysis in instances of suboptimal response or failure to therapy, and always before changing therapy to a second-generation tyrosine kinase inhibitor (TKI). Patients failing TKI therapy should potentially be assessed for compliance to therapy before switch, as it has been shown that patient reported compliance and actual compliance reported can be discordant, and this may be a reason for treatment failure. The magnitude of increase in *BCR-ABL* transcript levels which should prompt mutation testing is a topic of debate. Five to 10-fold rises have been proposed as a reasonable trigger for mutation testing. A recent study demonstrated that increases in *BCR-ABL* mRNA levels of 5-fold or more were not sufficiently sensitive in detecting mutations, and that a 2.6-fold increase in *BCR-ABL* transcripts is a better threshold.[25] In most clinics, however, it may be more reasonable to consider mutation testing when *BCR-ABL* levels increase at least 5-fold, confirmed in an independent test in the same laboratory to confirm that the observed increase is real, and not due to assay or laboratory variability.

STRATEGIES TO OVERCOME IMATINIB RESISTANCE

Multiple strategies to overcome failure to standard dose (400 mg/day) imatinib are under investigation. These include dose escalation of imatinib, switch to a second-generation TKI, other novel TKIs in a clinical trial, non-TKI based therapy and allogeneic stem cell transplant (SCT) in eligible patients.

Imatinib Dose Escalation

Dose escalation can improve the response in a subset of patients with resistance to standard dose imatinib and was the main option for managing suboptimal responses and treatment failures before the introduction of second generation TKIs. In a retrospective analysis of patients enrolled in the IRIS trial, Kantarjian et al reported that among 106 patients who required dose escalation due to resistance to standard dose therapy, freedom-from-progression and OS rates were 89% and 84%, respectively, at 3 years from dose escalation.[26] In another study from MDACC, 84 patients with CML-CP were dose escalated to imatinib 600–800 mg/day after developing hematologic failure (n = 21), or cytogenetic failure (n = 63) to standard dose imatinib.[27] Among patients that met the criteria for cytogenetic failure, 75% (47/63) responded to imatinib dose escalation. In contrast, in patients where imatinib was dose escalated because of hematologic failure, 48% achieved a complete hematologic response and only 14% (3/21) achieved a cytogenetic response. Patients more likely to respond to imatinib dose increase are those that have previously achieved a cytogenetic response and then lost it and who have not developed any mutations unresponsive to imatinib. Even in these cases, a switch to a 2nd generation TKI is preferable unless the patient has no access to these agents.

Several Phase II studies examined the role of a higher dose of imatinib (800mg) upfront in the treatment of patients with CML. The Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study was a phase 3 trial comparing the efficacy and safety of high-dose (800 mg/day) with standard-dose imatinib (400 mg/day) in patients with newly diagnosed CML-CP.[28] The primary endpoint of the study was rate of major molecular response (MMR) at 12 months of therapy. A 24-month update on the TOPS data was recently reported.[29] It appears that there was no significant difference between the 800 mg/day and 400 mg/day arms for either the CCyR (76% vs 76%, respectively; $P = 1.00$) or MMR rate (51% vs 54%, respectively; $P = .626$) Most importantly, thus far at 24 months there were no differences between arms with respect to EFS (95% vs 95%, respectively; $P = .71$), PFS (98% vs 97%; $P = .64$), and OS (98% vs 97%, respectively; $P = .70$), although it is still relatively early. Adverse events tended to be more common among patients in the 800-mg/day arm vs the 400-mg/day arm, as was the rate of discontinuation due to adverse events (12% vs 5%, respectively). The results from TOPS study were confirmed in a randomized trial Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) 021/ELN (021/ELN) assessing the efficacy of imatinib 800 mg/day vs 400 mg/day as front line therapy in high-risk Sokal patients.[30] The primary study endpoint of CCyR at one year was not significantly different between patients treated with imatinib 400 mg/day (61%) vs 800 mg/day (64%). There was a trend toward higher rates of MMR with 800 mg/day compared with 400 mg/day, but the differences were not statistically significant. Adverse events were not

significantly different between treatment arms, but compliance was lower in the 800-mg arm (62% received doses >600 mg) compared with the 400-mg arm (87% received doses >350 mg).

Although the aforementioned studies have shown improved CCyR and MMR with a higher dose of imatinib, the follow-up of these studies is short to evaluate for EFS and OS. Hence, at the writing of this chapter, imatinib at a dose of 400mg daily is still the preferred regimen of choice in newly diagnosed patients with CML-CP.

Dasatinib

Dasatinib (Sprycel®, Bristol-Myers Squib, Princeton, NJ) is an orally bioavailable, multi-kinase inhibitor that is be 325 fold more potent than imatinib against unmutated *BCR-ABL*.[31] It is currently approved for the treatment of imatinib-resistant or imatininb-intolerant CML in all phases and Ph-positive acute lymphoblastic leukemia (Ph+ ALL). The response to dasatinib among patients in chronic, accelerated and blast phase (myeloid and lymphoid) after imatinib failure are summarized in Table 2.[32–34] Dasatinib is overall well tolerated. Myelosuppression occurs frequently, with grade 3 or 4 neutropenia or thrombocytopenia occurring in nearly 50% of patients treated at a dose of 70mg twice daily. The most common non-hematologic grade 3–4 toxicities at a dose of 70 mg twice daily were pleural effusion (9%), dyspnea (6%), bleeding (4%), diarrhea (3%), and fatigue (3%). In an open-label phase III trial, 670 patients with imatinib-resistant/intolerant CML-CP were randomly assigned between four dasatinib treatment schedules: 100 mg once daily, 50 mg twice daily, 140 mg once daily, or 70 mg twice daily.[35] Results of this trial showed that 100 mg once daily retained its activity and was associated with less toxicity, particularly pleural effusion and myelosuppression, with grade 3–4 neutropenia or thrombocytopenia occurring in approximately 30% each.

Based on these results, a Phase II trial from MDACC was recently reported in 50 patients with newly diagnosed chronic phase CML.[36] Ninety-eight percent achieved CCyR, and 41 patients (82%) achieved a MMR. Responses occurred rapidly, with 94% of patients achieving CCyR by 6 months. The projected EFS rate at 24 months was 88%. A randomized phase 3 trial comparing the efficacy of dasatinib and imatinib in the first-line has completed accrual, and results are expected in late 2010.

Nilotinib

Nilotinib (Tasigna®; Novartis Pharmaceuticals, East Hanover, NJ) is a rationally-designed *BCR-ABL* inhibitor that is 30-fold more potent than imatinib in vitro, with greater specificity for *BCR-ABL*.[37,38] It is currently approved for treatment of imatinib-resistant/intolerant patients with CML-CP and CML–AP (but not BP or Ph+ ALL) at a dose of 400 mg twice daily (BID). The response to nilotinib among patients in chronic, accelerated and blast phase (myeloid and lymphoid) after imatinib failure are summarized in Table 2.[39,40] The most common grade 3 or 4 laboratory abnormalities were elevated lipase (17%), hypophosphatemia (16%), hyperglycemia (12%), and elevated total bilirubin (8%). Grade 3 or 4 non-hematologic adverse events were infrequent, with rash, headache, and diarrhea occurring in 2% of patients. The most common grade 3 or 4 hematological adverse events

were neutropenia (31%), thrombocytopenia (31%), and anemia (10%). Pleural or pericardial effusions (all grades) occurred in 2% of patients, and grade 3 or 4 pleural or pericardial effusions were rare (<1%).

Nilotinib has also demonstrated promise as a front-line therapy in patients with CML-CP.[41–43] In the first head-to-head comparison of a second-generation TKI (nilotinib at 300 mg BID or 400 mg BID) to imatinib (400 mg/day), nilotinib 300 mg BID and 400 mg BID showed higher rates of MMR (44% and 43% respectively) and CCyR (80% and 78% respectively) than imatinib at 400 mg/day (MMR: 22% [$P < 0.0001$ vs. both nilotinib doses), CCyR: 65% [$P < 0.0001$ vs. nilotinib 300 mg BID; $P < .0005$ vs. nilotinib 400 mg BID) at 12 months of follow-up.[42] In a Phase II study from MDACC, 51 patients with newly diagnosed CML-CP were treated with nilotinib at 400mg BID. Ninety-eight percent patients achieved CCyR, while 76% (39/51) achieved MMR. Rapid responses were observed, with 96% and 98% of patients in CCyR by 3 and 6 months respectively.[41] A randomized phase 3 trial comparing the efficacy of nilotinib and imatinib in the first-line has completed accrual, and results are expected in late 2010.

Bosutinib

Bosutinib (SKI606), an orally available dual *SRC/ABL* inhibitor, is 30 to 50 times more potent than imatinib, with minimal inhibitory activity against *C-Kit* and *PDGFR*, therefore expected to produce less myelosuppression and fluid retention.[44] The phase I study identified a treatment dose of 500 mg daily and showed evidence of clinical efficacy. Phase II studies in patients with CML-CP who have failed imatinib and second generation TKIs therapy are ongoing.[45,46] Preliminary data for response to nilotinib among patients in chronic, accelerated and blast phase (myeloid and lymphoid) after imatinib failure are summarized in Table 2. The most common adverse events with bosutinib were gastrointestinal (nausea, vomiting, diarrhea); these were usually grade 1–2, manageable and transient, diminishing in frequency and severity after the first 3–4 weeks of treatment. Bosutinib is currently being assessed in the frontline setting for treatment of patients with CML-CP.

OTHER MULTIKINASE INHIBITORS

One of the most promising agents for treatment of T315I mutation in clinical trials is AP24534, an orally available multi-TKI designed using a structure-based approach as a pan-*BCR-ABL* inhibitor.[47] AP24534 potently inhibits the enzymatic activity *of BCR-ABL*-T315I, the native enzyme and all other tested mutants. It also prevents the emergence of resistant mutants at concentrations of 40 nM. In a Phase 1 clinical trial of AP24534 at doses from 2–60 mg in 27 patients with CML (19 with CP, 4 AP and 4 BP), complete hematologic response (CHR) was achieved or maintained in 83% of patients treated in CP; major hematologic responses were also achieved in 38% of patients treated in advanced stages of the disease.[48] More importantly, 9 of 20 patients treated in CP achieved a MCyR (including 5 CCyR), including 3 of 7 with T315I (2 CCyR). The most common drug-related adverse events were elevations of lipase and amylase at a dose of 60mg daily. Grade 3 or 4 thrombocytopenia occurred in 9% of patients, with no grade 3–4 drug-related neutropenia.

AP24534 will be tested in a large, multicenter study focusing on patients with imatinib-, nilotinib-, and dasatinib-resistant disease, including a subset with the T315I mutation.

XL228 *(Exelixis Inc, San Francisco, USA)* is a potent, multitargeted kinase inhibitor with potent activity against wild-type and T315I isoforms of *BCR-ABL*.[49] In a prelim Phase 1 clinical study, XL228 was administered to 27 patients in six cohorts with a once-weekly dosing schedule (dose range from 0.45 mg/kg to 10.8 mg/kg). All patients were resistant or intolerant to at least two prior standard therapies (including imatinib, dasatinib, and nilotinib) or had a known *BCR-ABL* T315I mutation. Preliminary evidence of clinical activity was observed in patients treated at doses of 3.6 mg/kg and higher, including stable or decreasing white blood cell and/or platelet count within 2 months (in 14 patients, 5 with T315I), and/or >1-log reduction in *BCR-ABL* transcript levels by reverse transcriptase-polymerase chain reaction (RT-PCR) within 3 months (in 3 patients, 2 with T315I). XL 228 has been generally well tolerated. Dose limiting toxicities observed with once weekly dosing included grade 3 syncope and hyperglycemia in two patients dosed at 10.8 mg/kg. The most commonly reported grade 2 adverse effects were hyperglycemia, fatigue, nausea, vomiting, and bradycardia.

NON-TYROSINE KINASE INHIBITORS

Homoharringtonine is a plant alkaloid that has been used in China for many years in the treatment of patients with acute myeloid leukemia. Before the introduction of imatinib, it was the best treatment option for patients who failed IFN-α and were not transplant candidates, with cytogenetic responses in approximately 30% of patients.[50,51] Omacetaxine mepesuccinate, a cephalotaxine ester and a derivative of homoharringtonine that has excellent bioavailability through the subcutaneous route, is a multitargeted protein synthase inhibitor that has been in clinical development for several years. Omacetaxine shows clinical activity against CML with a mechanism of action independent of tyrosine kinase inhibition and is thus not affected by the presence of mutations.[52,53] In a recently reported Phase 2/3 clinical study of omacetaxine administered at a dose of 1.25 mg/m^2 sc twice daily for 7 days (every 28 days) to 89 patients with CML (44 CP, 25 AP and 20 BP) who are either intolerant or resistant to at least 2 TKI's (imatinib, dasatinib or nilotinib), the rates of CHR and MCyR were 82% and 23% in CP, respectively.[54] In a similar trial enrolling 81 patients (49 CP, 17 AP and 15 BP) with T315I mutation who did not respond to imatinib; omacetaxine led to a CHR in 86% and MCyR in 27% among patients treated in CCyR. These responses were durable.[55] The most commonly reported events were thrombocytopenia (58%), anemia (36%) and neutropenia (33%). Non-hematologic toxicities were primarily grade ½ with the most frequently reported events of diarrhea (44%), fatigue (35%), pyrexia (32%), nausea (26%), and asthenia (21%).

MUTATION STATUS AND CHOICE OF THERAPY

Although more than 100 BCR-ABL mutations have been identified in clinical samples,[18] the presence of a mutation does not typically lead to resistance. Baseline mutation screening for newly diagnosed patients with CML has shown no benefit for predicting response, [56] and should not be routinely employed. In a study using highly sensitive DNA sequencing

techniques, patients treated with imatinib showed no correlation between baseline mutation status and response, PFS or OS. Other studies have confirmed that the identification of mutations pre-therapy does not predict insensitivity to imatinib.[57–59]

The utility of using *in vitro* mutation data to select a second generation TKI remains a matter of controversy. In their seminal paper, Redaelli et al. report on the *in vitro* activity of nilotinib, dasatinib and bosutinib against 18 *BCR-ABL* mutations (Table 3).[44] The 8 most common mutations (T315I, Y253F/H, E255D/K/R/V, M351T, G250A/E, F359C/L/V, H396P/R, M244V); found in 85% of patients with mutations were included in the analysis. The mutations were stratified using half maximal inhibitory concentration (IC_{50}) values into sensitive, moderately resistant, resistant, or highly resistant. The authors conclude that this data offers physicians a tool for selecting a patient tailored TKI therapy. One of the major criticisms for using *in vitro* data in selecting the next line of therapy is that it does not fully predict the *in vivo* response.[60] In a recent publication, Laneuville et al. report that adequate drug exposure to inhibit the *BCR-ABL* kinase located in the cytoplasm of leukemic cells requires satisfactory pharmacokinetics, which are affected by independent variables that might be related to molecular structure of the drug itself. They also note that the table as constructed in the Redaelli article does not allow a side-by-side comparison of data, as columns for each inhibitor are normalized to the data within that column. Indeed, none of these studies take into account factors such as protein binding and cell influx/efflux or a variety of other *in vivo* factors that could affect results. Therefore, until more definitive results are published, treating physicians must not solely rely on *in vitro* data to select the next TKI for their patients who are imatinib-resistant/intolerant.

Prospective clinical studies evaluating the choice of second generation TKI's based on in vitro sensitivity data in imatinib intolerant/resistant patients are limited. In a retrospective analysis of 169 imatinib-resistant patients treated with a second generation TKI at MDACC, 86 were found to have a mutation.[61] Forty-one patients were treated with dasatinib and 45 with nilotinib. Mutations were stratified on the basis of IC_{50} values into high (n=42), intermediate (n=25), low (T315I, n=9), and unknown (n=10). Although response rates tended to be higher in patients without baseline mutations, there were no significant differences in CHR, MCyR, or CCyR between patients with and without baseline mutations. Response rates were higher in patients with CML-CP with low IC_{50} mutations, compared with intermediate IC_{50} mutations. The existence of a mutation at baseline was not shown to impact overall survival, but the presence of intermediate IC_{50} mutations was significantly associated with poorer EFS ($p = 0.0006$) and OS ($p = 0.03$).

Among 1043 patients treated with second-line dasatinib in phase 2/3 trials, 39% had a preexisting *BCR-ABL* mutation, including 48% of 805 patients with imatinib resistance or suboptimal response.[62] Sixty-three different *BCR-ABL* mutations affecting 49 amino acids were detected at baseline, with G250, M351, M244, and F359 most frequently affected. After 2 years of follow-up, dasatinib treatment of imatinib-resistant patients with or without a mutation resulted in notable response rates (CCyR: 43% vs 47%) and durable PFS (70% vs 80%). Impaired responses were observed with some mutations with a dasatinib median IC_{50} greater than 3nM; among patients with mutations with lower or unknown IC_{50}, efficacy was comparable with those with no mutation. In a subanalysis of a phase II study of nilotinib in

patients with imatinib-resistant or imatinib-intolerant CML-CP, baseline mutation data were assessed in 281 (88%) of 321 patients.[63] Among imatinib-resistant patients, the frequency of mutations at baseline was 55%. After 12 months of therapy, MCyR was achieved in 60%, CCyR in 40%, and MMR in 29% of patients without baseline mutations versus 49% (P = 0.145), 32% (P = 0.285), and 22% (P = 0.366), respectively, of patients with mutations. Patients with mutations that were less sensitive to nilotinib in vitro (IC_{50} > 150 nM; Y253H, E255V/K, F359V/C) had less favorable responses, as 13%, 43%, and 9% of patients with each of these mutations, respectively, achieved MCyR; none achieved CCyR.

CURRENT RECOMMENDATIONS FOR TREATMENT OF CML

A proposed approach to the management of patients with CML is depicted in Figure 1. Imatinib at a dose of 400 mg/day is considered the standard treatment. If patients do not achieve the landmarks as established by the ELN, modification to this therapy should be strongly considered. Dose escalation of imatinib can be considered, but is not likely to be effective in patients who never achieved a cytogenetic response on imatinib or those with known imatinib-resistant mutations. A change to a second-generation therapy may be a better option for most patients. *In vitro* and *in vivo* data have demonstrated that both dasatinib and nilotinib have a small and distinct set of mutants that confer decreased sensitivity: Y253H, E255K/V, and F359C/V for nilotinib and Q252H, E255K/V, V299L, and F317L for dasatinib. Therefore, if the mutation analysis reveals any of these mutations, that particular second generation TKI should be avoided.

For the vast majority of patients who do not harbor a mutation, choice for a second generation TKI is based on co-morbid conditions present. Dasatinib use is associated with the development of pleural and pericardial effusion,[64] bleeding[65] and infection[66]. Therefore, caution should be exercised before prescribing dasatinib in patients with hypertension, asthma, pneumonia, gastrointestinal bleeding, chronic obstructive pulmonary disease, chest wall injury, congestive heart failure, auto-immune disorders and concomitant aspirin use. Severe, uncontrolled diabetes and past pancreatitis are considered risk factors for nilotinib use due to the occurrence of grade 3/4 lipase elevation (18%), bilirubin elevation (7%) and hyperglycemia (12%). QT prolongation is a concern with both agents, and the simultaneous use of agents prolonging the QT interval should be avoided. Although both dasatinib and nilotinib are ineffective against T315I *BCR-ABL*, this mutation is more likely to affect patients in the advanced phases of CML. Patients with T315I may achieve favorable outcomes with other therapies, e.g AP24534, omacetaxine. SCT is generally reserved for patients who have not responded to a second or third generation TKI and for those patients with T315I mutation who have not responded to newer agents.

CONCLUSION

Imatinib has dramatically altered the landscape of treatment for patients with CML. For most patients, the long-term outcomes including the PFS and OS are excellent. For a few subset of patients who are intolerant to or are resistant to imatinib, newer second generation TKI's are becoming excellent choices of therapy. The mechanisms of resistance, *in vivo* and *in vitro* sensitivities and choice of agents are rapidly evolving. It is hoped that in the near

future preclinical and clinical data will become available that will guide the treating physician to select the best TKI, both in the frontline and relapsed setting, for an individual patient with CML.

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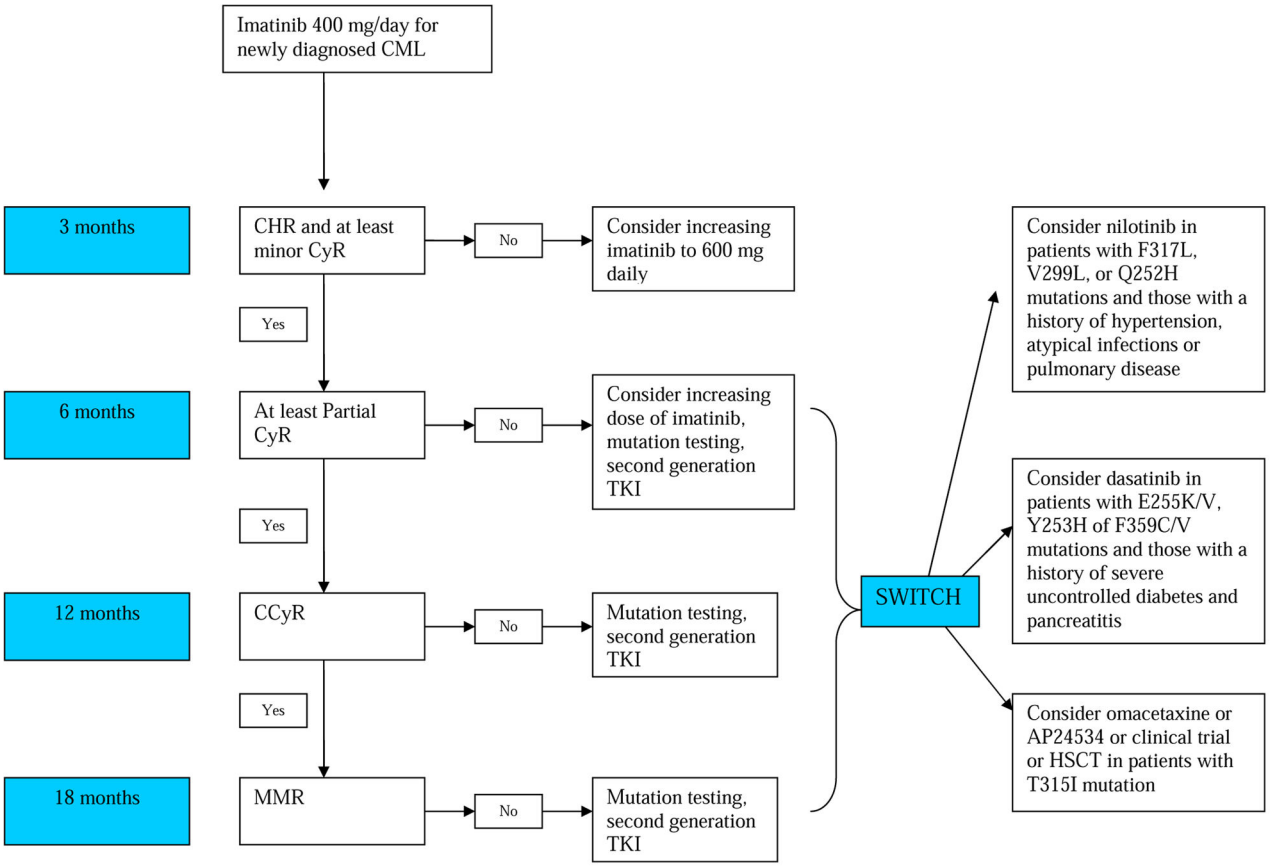

Figure 1. A proposed schema for the management of patients with imatinib resistant or imatinib intolerant chronic phase CML

CHR: complete hematologic response; CyR; cytogenetic response; CCyR: complete cytogenetic response; MMR: major molecular response; TKI: tyrosine kinase inhibitor

Table 1

Response Definitions to Imatinib in Chronic Phase CML (European Leukemia Net guidelines)

Evaluation Time	Response		
	Optimal	Suboptimal	Failure
3 months	CHR and at least minor CyR	No CyR	No CHR
6 months	At least partial CyR	Less than partial CyR	No CyR
12 months	CCyR	Partial CyR	Less than partial CyR
18 months	MMR	Less than MMR	Less than CCyR
Any time	Stable or improving MMR	Loss of MMR, presence of mutations	Loss of CHR, loss of CCyR, clonal evolution

CHR: complete hematologic response; CyR: cytogenetic response; CCyR: complete cytogenetic response; MMR: major molecular response

Table 2

Response to second generation tyrosine kinase inhibitors (dasatinib, nilotinib and bosutinib) in patients who are imatinib-resistant or intolerant in chronic phase, accelerated phase and blast phase CML

Response	Percent Response										
	Dasatinib				Nilotinib				Bosutinib		
	CP N=387	AP n=174	MyBP n=109	LyBP n=48	CP n=321	AP N=137	MyBP N=105	LyBP N=31	CP N=146	AP N=51	BP N=38
Median follow-up (mo)	15	14	12+	12+	24	9	3	3	7	6	3
% Resistant to imatinib	74	93	91	88	70	80	82	82	69	NR*	NR*
% Hematologic Response	-	79	50	40	94	56	22	19	85	54	36
CHR	91	45	27	29	76	31	11	13	81	54	36
NEL	-	19	7	6	-	12	1	0	-	0	0
% Cytogenetic Response	NR	44	36	52	NR	NR	NR	NR	-	NR	NR
Complete	49	32	26	46	46	20	29	32	34	27	35
Partial	11	7	7	6	15	12	10	16	13	20	18
% Survival (at 12 months)	96 (15)	82 (12)	50 (12)	50 (5)	87 (24)	67 (24)	42 (12)	42 (12)	98 (12)	60 (12)	50 (10)

CP: chronic phase; AP: accelerated phase; MyBP: myeloid blast phase; LyBP: lymphoid blast phase, mo: months; CHR: complete hematologic response; NEL: no evidence of leukemia

Table 3

In Vitro Sensitivity of Different BCR-ABL Mutants to Different Tyrosine Kinase Inhibitors

	IC50-fold increase (WT=1)			
	Imatinib	**Bosutinib**	**Dasatinib**	**Nilotinib**
WT	1	1	1	1
L248V	3.54	2.97	5.11	2.80
G250E	6.86	4.31	4.45	4.56
Q252H	1.39	0.31	3.05	2.64
Y253F	3.58	0.96	1.58	3.23
E255K	6.02	9.47	5.61	6.69
E255V	16.99	5.53	3.44	10.31
D276G	2.18	0.60	1.44	2.00
E279K	3.55	0.95	1.64	2.05
V299L	1.54	26.10	8.65	1.34
T315I	**17.50**	**45.42**	**75.03**	**39.41**
F317L	2.60	2.42	4.46	2.22
M351T	1.76	0.70	0.88	0.44
F359V	2.86	0.93	1.49	5.16
L384M	1.28	0.47	2.21	2.33
H396P	2.43	0.43	1.07	2.41
H396R	3.91	0.81	1.63	3.10
G398R	0.35	1.16	0.69	0.49
F486S	8.10	2.31	3.04	1.85

Mutations can be classified as sensitive (IC50 fold increase ≤2), resistant (between 2.01 and 10) or highly resistant (>10; T315I mutation)