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Outcome of Treatment of CML with 2nd Generation Tyrosine Kinase Inhibitors After Imatinib Failure

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Abstract

Although imatinib revolutionized the management of chronic myeloid leukemia (CML), recent data indicate a transformation in the treatment approach likely in the near future. For patients who fail with standard-dose imatinib therapy, imatinib dose escalation is a second-line option. However, high-dose imatinib is not an appropriate approach for patients experiencing drug toxicity, and there remain questions over the durability of responses achieved with this strategy. Alternative second-line options include the newer tyrosine kinase inhibitors (TKIs) like dasatinib and nilotinib. A substantial amount of long-term data for these agents is available. Although both are potent and specific BCR-ABL TKIs, dasatinib and nilotinib exhibit unique pharmacological profiles and response patterns relative to different patient characteristics, such as disease stage and BCR-ABL mutational status. The superiority of second generation TKIs over imatinib in newly diagnosed disease has been recognized as well. They induce high and rapid rates of cytogenetic and molecular response, with less progression to advanced forms of disease in comparison with imatinib. Several investigational agents specific for those patients with the T315I mutation remain under evaluation. The future of CML therapy may include early use of these potent agents to help more patients achieve molecular remission and potentially be a path to a CML cure.

Keywords

CML; tyrosine kinase inhibitors; imatinib

Introduction

Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm with an incidence of 1-2 cases per 100,000 adults, with increasing incidence with age and a slight male predominance of 1.3:1. Thirty percent of patients are 60 years old or older, with the median age at presentation being 45-50 years old¹. The pathogenesis of CML involves a specific genetic abnormality involving the fusion of the Abelson murine leukemia (ABL) gene on chromosome 9 with the breakpoint cluster region (BCR) gene on chromosome 22². In 95% of cases, this fusion is the result of a balanced translocation between chromosomes 9 and 22 [t(9;22)(q34;q11)], termed the Philadelphia chromosome^{3,4}. The remaining 5% of cases are

a result of other genetic abnormalities that result in the fusion of these same genes⁴. The resultant BCR-ABL fusion protein contains the constitutively active tyrosine kinase region of ABL that produces a proliferative signal that regulates growth and replication through downstream pathways such as RAS⁵, RAF⁶, JUN kinase⁷, MYC⁸, and STAT^{9,10,11}. This contributes to leukemogenesis by creating a cytokine-independent cell cycle with aberrant apoptotic signals in response to cytokine withdrawal².

The causal role played by BCR-ABL in leukemogenesis, specifically as it relates to CML, has led to the development of tyrosine kinase inhibitors (TKIs) and represents the bulk of pharmaceutical research performed in this arena within the last decade. TKIs mitigate the oncogenic activity of the BCR-ABL protein through competitive inhibition at the ATP-binding site, leading to the inhibition of phosphorylation of proteins involved in BCR-ABL mediated intracellular signal transduction, and thereby causing the arrest of growth and apoptosis in CML cells^{12,13,14}.

Imatinib mesylate (Gleevec; Novartis Pharmaceuticals Corporation, NJ, USA) was the first of these drugs to receive the approval by the United States Food and Drug Administration (FDA) in 2001 for the treatment of patients with CML-CP at a dose of 400 mg/day; as well as for advanced phase (CML-AP) and blast phase (CML-BP) disease at a higher dose of 600 mg/day^{15,16,17}. The advent of imatinib revolutionized the treatment of CML and represented improved outcome over the previously well established gold standard of interferon-alpha (IFN- α) based treatments¹⁸. As a result, patients with CML in the chronic phase (CML-CP) can expect a lifespan of approximately 25 years and even beyond, transforming CML from a disease which was once fatal, with a 40% 7-year survival to one that is chronic, with a 90% 7-year survival.

Outcome with imatinib

The landmark phase III IRIS trial (International Randomized Study of Interferon versus STI571) was the first to clearly demonstrate the superiority of imatinib treatment in CML-CP as compared to IFN- α . Complete cytogenetic response (CCyR) rates were increased in the imatinib group over the IFN group (68% vs. 7% at 12 months; and 76.2% vs. 14.5% at 18 months)^{19,20}. Imatinib produced durable CCyR with rates of 87% and 85% at 5 years and 8 years respectively^{21,22}. Major molecular response (MMR) rates, defined as a 3 log reduction in BCR-ABL transcripts¹⁹, or BCR-ABL:control gene ratio of 0.10 or less²³, were also improved (39% vs. 2% at 12 months; $p < 0.001$)¹⁹, and remained durable at 5 years (92%) and 8 years (86%)^{21,22}. Freedom of progression from CP to AP or BP was increased in those who received imatinib as initial therapy as well (96.7% vs. 91.5% at 18 months)²⁰ and produced durable results (93% and 92%) at 5-years and 8-years respectively^{21,22}.

The IRIS trial demonstrated that early response to therapy was related to improved long term outcomes. Of those who had achieved a partial cytogenetic response (PCyR) at 12 months, 80% had achieved a CCyR at 8 years of follow up, and no one who had achieved a MMR at 12 months had progression of disease to AP or BP at 8 years²². It also highlighted 2 important treatment endpoints, CCyR and MMR. At 12 months of follow up, overall freedom from progression for those who had attained a CCyR and MMR was 100%, as

compared with 95% for those with a CCyR and no MMR, which was not statistically significant. However, for those without CCyR, overall freedom of progression was significantly decreased when compared to those who did achieve CCyR in the first 12 months (85% vs. 95%; $p < 0.001$)¹⁹. Overall survival has been assessed by retrospective comparative analyses and shows a 3-year overall survival rate in imatinib-treated patients significantly improved over those treated with IFN- α at 3 years (92% vs. 84%; $P < 0.001$)²⁴ and 5 years of follow up (88% vs. 63%; $P = 0.001$)²⁵. Additionally, the 3-year overall survival rates for patients with CCyR at 12 months of follow up were shown to remain unchanged irrespective of the achievement of a MMR; however, the achievement of a major cytogenetic response (MCyR) by 12 months, as defined by 0-35% of cells in metaphase expressing the Ph chromosome) portended an improved 3-year survival rate over those that did not (99% vs 84%; $P < 0.001$)²⁵.

Milestones and monitoring on imatinib therapy

Throughout the course of treatment with imatinib, patients should routinely be reassessed for their response to therapy. This is imperative for the identification of suboptimal responses and failures to therapy in order to identify patients who may benefit from dose escalations or changes in therapy due to primary or secondary resistance. For this purpose, the European LeukemiaNet has set forth monitoring guidelines and validated criteria for identification of suboptimal responses and treatment failures^{23,26,27,28}.

Response to imatinib is judged relative to duration of therapy. Treatment failure is defined as follows: at 3 months, no hematologic response; at 6 months, no hematologic response and no cytogenetic response, with 95% or greater cells in metaphase still expressing the Ph chromosome; at 12 months, no cytogenetic response, irrespective of hematologic response; at 18 months, no CCyR; and finally, loss of response at any time²³. Suboptimal responses are those that do not meet criteria for response, nor those for failure, but represent a slow or inadequate response [Table 1]. Suboptimal response early in therapy is more prognostic than at later timepoints. Patients classified as suboptimal responders at 6 months have similar outcomes in terms of OS, PFS, and EFS as those with failure to therapy. However, suboptimal responders as identified at 12 months have similar rates of PFS as optimal responders, however, with worse EFS. Those with suboptimal response at 18 months of therapy have outcomes not statistically different than those classified as having an optimal response^{26,27,28}. The risk of loss of MCyR or CHR or progression to AP or BP is highest in the first 2-3 years of therapy, with decreases in rates of failure as therapy continues^{21,22,27}.

Hematologic response should be monitored by peripheral blood every 2 weeks until a CHR is achieved and confirmed, and every 3 months thereafter. CHR is defined as a platelet count less than 450×10^9 , WBC less than 10×10^9 , the absence of immature granulocytes and less than 5% basophils on differential, with no palpable spleen on exam²³. As the IRIS trial^{19,20,21,22}, and several independent retrospective reviews have confirmed^{24,25}, cytogenetic response is the gold standard for assessing optimal response and long term outcome. Thus, the bone marrow must be reassessed every 6 months until a CCyR is achieved and confirmed, and at least every 12 months thereafter. Molecular response should be assessed by RT-PCR in the peripheral blood every 3-6 months^{23,26,27,29}. The National

Comprehensive Cancer Network (NCCN) guidelines state that patients with a stable MMR can be monitored every 6 months²⁹. There are subsets of patients who appear to have rising levels of BCR-ABL transcripts while maintaining a cytogenetic response. This may indicate an increased risk for development of mutations or failure to therapy, however, this value should be considered with caution. It is inherently variable due to the fact that it is an international normalized ratio, and there is significant variability in values reported from different laboratories. Thus, a small increase in BCR-ABL transcript levels does not necessarily indicate treatment failure or loss of response. This is supported by the 3-year follow up of the IRIS trial in which CCyR, regardless of MMR, was associated with improved OS²⁵. If a patient who has previously achieved a MMR is noted to have a 1 log, or 5 fold increase in BCR-ABL transcripts, the value should be repeated and confirmed in 1-3 months to evaluate for loss of cytogenetic response. Patient compliance should be evaluated in both cases, and mutation analysis should be considered if the patient has been identified as having a suboptimal response within the first year of therapy or has had a loss of response at any time²⁹.

Resistance to imatinib

Despite the success of imatinib, a substantial proportion, 33%, of patients have been shown to be resistant to therapy^{30,31}. This resistance can be classified into two types: primary and secondary. Failure to achieve any of the ELN outlined criteria for response in accordance with the duration of therapy is considered primarily resistant; those who have previously achieved and subsequently lost their response in accordance with those guidelines are considered secondarily resistant^{18,29,30}. Primary resistance can be further divided into primary hematologic resistance, which occurs in 2%-4% of cases who fail to normalize peripheral counts; or primary cytogenetic resistance, which is more common and occurs in approximately 15%-25% of patients who fail to reduce their Ph+ cells to 35% or fewer of those sampled³².

Causal factors in imatinib resistance can be classified as either BCR-ABL dependent, or BCR-ABL independent. Point mutations are the most well-characterized BCR-ABL dependent factors and are responsible for 35-75% of cases of resistance^{30,33-38}. A key component to imatinib resistance centers around its ability to bind only to the closed, or inactive, conformation of the ABL kinase, and requires a very specific structural arrangement for entry and binding. Point mutations can cause steric hindrance as well as elimination of critical molecules required for hydrogen bonding between imatinib and ABL kinase, thus mitigating imatinib's efficacy^{30,38-40}. Examples of such mutations include T315I, Y253H, and F255K, among others³⁸.

BCR-ABL independent mechanisms of resistance include amplification of the ABL kinase oncogene in response to high plasma imatinib levels^{30,41-44}; increased efflux of the drug by increased expression of P-glycoprotein (Pgp) efflux pumps^{30,45-47}; decreased drug uptake secondary to decreased expression of the drug uptake transporter, hOCT1^{30,48-51}; cytoplasmic sequestration of imatinib by increased serum protein alpha1-acid glycoprotein (AGP) which binds imatinib and impairs subsequent binding to ABL kinase^{30,52,53,54}; low serum drug concentration³⁰; and alternative signaling pathway activation, including

Ras/Raf/MEK kinase, STAT, Erk2, and SFK phosphorylation of BCR-ABL, all of which decrease susceptibility to imatinib³⁰.

Adherence is another BCR-ABL independent factor that has been shown to affect outcome. Rates of daily imatinib adherence have been estimated to range from 75% to 90%⁵⁵⁻⁵⁷ with higher adherence rates correlated to improved outcome. In one study of 87 patients with CML-CP treated with imatinib 400 mg daily, adherence was shown to correlate with MMR and CMR at 6 years. An adherence rate of 90% or less resulted in MMR in only 28.4% as compared to 94.5% in patients with greater than 90% adherence rates ($P<0.001$). CMR rates were 0% vs. 43.8% respectively ($P=0.002$). Notably, no molecular responses were observed when adherence rates were 80% or lower. Lower adherence rates have been described in younger patients, those with adverse effects of therapy, and those who have had dose escalations⁵⁵. This is an important consideration for treating physicians, as, with advancements in treatment, CML has evolved into a chronic condition requiring life-long daily oral therapy with efficacy inextricably tied to adherence.

Management of imatinib resistance

Imatinib dose escalation

Imatinib dose escalation is the first-line strategy to combat cytogenetic relapse or resistance^{23,26,29}. In a retrospective review of patients who underwent imatinib dose escalations as part of the IRIS trial according to IRIS protocol guidelines from a standard dose of 400 mg daily to doses of 600 or 800 mg daily, statistically significant improvement in responses were noted. IRIS protocol guidelines stipulated the following criteria for dose escalation: lack of CHR by 3 months; lack of minor CyR by 12 months (minor CyR is defined as 35-65% of cells in metaphase expressing the Ph chromosome); and loss of response at any time. In those who had not achieved a CHR by 3 months, 86% achieved a CHR 3 months after dose escalation and 29% went on to achieve a CCyR by 12 months. In patients who had not achieved a minor CyR by 12 months, 25% achieved a MCyR by 12 months after imatinib dose escalation, and 50% by 24 months. Of these patients, 50% went on to achieve a CCyR by 48 months. In patients with a loss of MCyR, 50% re-achieved a MCyR within 12.5 months, 33% of whom went on to achieve a CCyR. In those patients who exhibited progression of disease, 67% experienced normalization of WBC. Of note, dose escalations were not attempted for those who lost CCyR⁵⁸.

A subset of patients in the IRIS trial underwent dose escalations according to ELN guidelines, which did not necessarily overlap with protocol guidelines, and includes those without MCyR at 12 months and those without CCyR at 18 months. Dose escalation resulted in 55% of patients without MCyR at 12 months attaining MCyR 12 months after dose escalation, and 20% of patients without CCyR at 18 months attaining a CCyR 12 months after dose escalation. For the total population of dose-escalated patients, whether they qualified for dose escalation under IRIS protocol guidelines or under ELN guidelines, rates of freedom from progression were 89% and OS was 84% at 36 months of follow up⁵⁸.

In another study assessing 84 patients over 61 months with failure to standard-dose imatinib, doses were escalated to 600-800 mg daily. In 21 patients with hematologic failure, 48%

achieved a CHR, with only 14% achieving a cytogenetic response. In 63 patients with cytogenetic failure, 75% responded with CCyR. Two and 3-year EFS rates were 57% and 47%, respectively; with OS rates of 84% and 76%, respectively⁵⁹. Thus, while dose escalation after failure of standard-dose imatinib is an important and viable treatment option, it is likely to be effective only in the subset of patients with previous cytogenetic responses and is not indicated for patients with intolerance to the drug. Thus, clinical consideration should be given to 2nd generation TKIs.

Second generation tyrosine kinase inhibitors [Table2]

Dasatinib

Dasatinib was approved by the US FDA in 2006 for the 2nd line treatment of CML-CP, -AP, -BP, and Philadelphia-positive acute lymphoblastic leukemia [Ph (+) ALL] with resistance or intolerance to prior therapy with imatinib^{60,61}. Dasatinib is 325 times more potent than imatinib^{38,62}. Unlike imatinib, dasatinib binds to both the active and inactive forms of BCR-ABL³⁰.

Several studies have shown that dasatinib is highly effective in CML-CP. In the START-C trial, an international, multicenter, phase II trial assessing 387 patients with CML-CP who had demonstrated imatinib intolerance (n= 99) or resistance (n=288), patients were treated with dasatinib at an initial dose of 70 mg BID. Twenty four-month follow-up data showed overall rates of CyR 62%, CCyR 53%, CHR 91%, and MMR 47%. Two-year PFS was 80% and OS was 94%. Adverse events included grade 3 neutropenia (50%), grade 3 thrombocytopenia (49%), and grade 3 pleural effusions (9%). Nine percent of all adverse events were considered “severe⁶².” In another study assessed the efficacy of dasatinib in 445 imatinib-resistant or intolerant patients with CML-CP (n=186), CML-AP (n=107), CML-myeloid blast crisis (n=74), CML-lymphoid blast crisis (n=42), or Ph (+) ALL (n=36). Dasatinib produced MCyR rates of 45% and CCyR rates of 33% in patients with CML-CP, and major hematologic response rates in advanced stages of disease, including 59% in CML-AP; 39% in CML myeloid blast crisis; 31% in lymphoid blast crisis; and 42% in Ph (+) ALL⁶¹.

The dose optimization study CA180034 randomized 622 patients with imatinib resistant or intolerant CML-CP to 4 dasatinib treatment arms, including 100 mg daily, 50 mg BID, 140 mg daily, and 70 mg BID. Dasatinib dosed at 100 mg daily produced similar CyR and PFS rates as other dosing schedules, with significantly fewer occurrences of grade 3-4 neutropenia, thrombocytopenia, anemia, and pleural effusions. There were also fewer treatment interruptions, reductions, and discontinuations at 100 mg daily as compared to the other treatment groups⁶³.

Further evaluation of dasatinib therapy in imatinib-resistant patients with mutations by meta-analysis of 3 dasatinib studies, including the START-C, START-R, and CA180-034 dose optimization study, revealed that rates of response with dasatinib are favorable in a variety of genetic mutations including E255K/V (CCyR 38%), L248V (CCyR 40%), and G250E (CCyR 33%). CCyR rates were lower in F317L(7%), Q252H (17%), L384M(0%), and V299L (0%). Patients with T315I mutations did not respond to dasatinib⁶⁴.

Dasatinib has also been evaluated in patients with imatinib-resistant or intolerant CML-AP. One study assessed 174 such patients treated with dasatinib 70 mg BID. Major hematologic response rates were 64%, CHR rates were 45%; MCyR rates were 39% and CCyR rates were 32%. PFS at 12 months was 66% and OS was 82%. Adverse events included grade 3-4 thrombocytopenia (82%), neutropenia (76%), and diarrhea (52%, grade 3 or 4 in 8%)⁶⁵.

Appropriate dosing in CML-AP was evaluated in another study, in which 317 patients were randomized to receive dasatinib at 140 mg daily or 70 mg BID. The results at 2 years after initiation of treatment demonstrated similar efficacy in rates of hematologic and cytogenetic responses, as well as in PFS and OS rates. Dasatinib 140 mg once daily did demonstrate an improved safety profile with statistically fewer patients experiencing pleural effusions (20% vs. 39%; $P < 0.001$)⁶⁶.

Pleural effusions are the most common non-hematologic adverse events, occurring in up to 35% of patients with 17% of those classified as grade 3 or 4 toxicity. This occurs more commonly in CML-AP or -BP and at increased frequency in patients with comorbidities including a cardiac history, hypertension, a smoking history, and in those receiving BID dosing. This is thought to be a result of dasatinib's cross reaction with off-target tyrosine kinases⁶⁷. Platelet dysfunction resulting in bleeding has been described and is a function of platelet-derived growth factor receptor (PDGFR) inhibition⁶⁸.

Nilotinib

Another 2nd generation TKI is nilotinib, approved by the FDA in 2007 for treatment of patients with CML-CP and CML-AP who have proven resistant to imatinib therapy and in October of 2010 for the firstline treatment of patients with CML-CP⁶⁹. Nilotinib is an imatinib analogue with 30 times more potency than imatinib^{38,69,70}. Modifications in the molecular structure of nilotinib as compared to imatinib result in a better hydrophobic bond and translates into increased potency⁷⁰. This molecular modification also results in increased selectivity for the ABL protein, and less cross reactivity with KIT and PDGFR. This increased selectivity is most notable when comparing nilotinib to dasatinib, as kinases exhibit unique conformations in their inactive state and similar ones in the active state, leading to increased specificity of inhibitors that bind only to inactive conformations (nilotinib and imatinib) and increased potency in those that bind to both active and inactive forms (dasatinib)^{38,70}. This accounts for the less frequent rates of grade 3 or 4 pleural effusions seen with nilotinib^{70,71}. Nilotinib is more active against mutant BCR-ABL secondary to its increased potency, with a notable exception being the T315I mutation, against which nilotinib has no activity⁷⁰. The recommended dose for nilotinib, as determined by a phase I dose escalation study, is 400 mg BID⁶⁹.

Nilotinib is proven effective in CML-CP as a 2nd line therapy in imatinib-resistance. The pilot phase II trial assessed 321 patients with imatinib resistant CML-CP. MCyR rates were 59%, with durability of 78% at 24 month follow up. CCyR rates were 44%, with durability of 83% at 24 months. Overall survival was 88% at 24 months. Clinical efficacy of nilotinib was evaluated in a Phase II study in 137 patients with imatinib resistant CML-AP, demonstrating a 31% CHR at 1 month, and a 32% MCyR at 2.8 months. Twenty percent of

those who attained a MCyR attained a CCyR, with 70% maintaining a durable CCyR at 24 months. OS was 67% at 24 months, demonstrating clinical efficacy in CML-AP⁷².

The safety profile for nilotinib is relatively benign, with rates of grade 3 hematologic adverse events including neutropenia and thrombocytopenia⁷³ (which are noted to occur more frequently in advanced stages of CML)⁷⁰, and anemia. Grade 3 elevations in lipase were seen in 5% of treated patients with grade 1 and 2 pancreatitis observed⁷³. Other biochemical abnormalities included hyperglycemia, hypophosphatemia, and hyperbilirubinemia⁷⁰. Grade 3-4 nonhematologic malignancies, including pleural effusion, GI bleeding, arrhythmia, and pneumonia have also been observed⁷³. Nilotinib offers the additional benefit of a low rate of cross-intolerance to imatinib, with only 3% experiencing recurrence of non-hematologic intolerance, and only 21% experienced recurrence of hematologic intolerance such as neutropenia and thrombocytopenia⁷⁴.

Bosutinib

Bosutinib is an orally administered Src/ABL inhibitor, estimated to be 45-50 times more potent than imatinib, with minimal inhibitory activity of PDGFR and c-KIT⁷⁵. This increased specificity is expected to produce less myelosuppression and fluid retention than other TKIs. 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 bosutinib 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 being assessed in the frontline setting for treatment of patients with CML-CP.

Investigational agents for use after failures with 2 TKIs or in the presence of T315I mutations

Ponatinib

Ponatinib is a multikinase inhibitor that has shown inhibitory activity of BCR-ABL wild type, BCR-ABL-T315I, and all other tested variants. Initial dose escalation data showed efficacy at 30 mg daily with no dose limiting toxicities. Preliminary data are available on 32 patients with CML, Ph (+) ALL, and other hematologic malignancies. Twelve of the 32 patients exhibited T315I mutations. Of the twelve patients, 7 (58%) with CML-CP attained a CHR; 2 (17%) attained a CCyR (1 with CML-CP and 1 CML-AP); and 1 (8%) with CML-CP attained a PCyR. One patient with CML-CP with the nilotinib-resistant F359C mutation attained a CCyR and MMR on AP24534⁷⁶.

Omacetaxine mepesuccinate

The development of resistance to TKIs has led to the development of Omacetaxine, a cetaxine with a mechanism of action independent of tyrosine kinase inhibition. Phase II/III studies in patients with CML status post failed therapy with multiple TKIs, and a significant

proportion with baseline mutations, are ongoing. Preliminary data in patients without T315I mutations demonstrate 80% CHR rates, 20% MCyR rates, and 10% MMR rates in CML-CP patients; 75% hematologic response rates including return to chronic phase (RCP) and CHR, and 5% CCyR rates in CML-AP; and 8% hematologic response rate including RCP and CHR in CML-BP⁷⁷. In those with CML-CP with T315I mutations, results show achievement of an 85% CHR rate, 28% CyR rate, 15% MCyR rate, 15% MMR rate, and 57% reduction in the T315I clone. OS was not met in this group of patients. In CML-AP, 37.5% showed hematologic response with OS of 18.8 months. In CML-BP, hematologic response was demonstrated in 30% with OS of 1.8 months⁷⁸.

An update combining both of the above study populations was presented at ASH 2010. Thirty six of the 93 chronic phase patients had been treated previously with 3 or more TKIs. Over a median followup of 7.5 months, 27/36 (75%) achieved or maintained a CHR and 7 (19%) achieved a major CyR (4 complete and 3 partial) with omacetaxine, with a median duration of at least 4 months. These findings support the further investigation of this agent in patients failing other TKI therapy⁷⁹. Grade 3 to 4 hematologic adverse events included thrombocytopenia (65%), neutropenia (48%), and anemia (40%), febrile neutropenia (12%), bone marrow failure (12%), pancytopenia (7%) and febrile bone marrow aplasia (6%). Grade 3 to 4 nonhematologic adverse events included fatigue (6%). Grade 1-2 adverse events included diarrhea, fatigue, nausea, vomiting, fever, headache, and asthenia^{77,78,79}.

Predictors of outcome

The primary goal of therapy for patients with CML is still achievement of CCyR. Those who achieve this goal, have a low probability of eventually progressing. Achieving a major molecular response is desirable as it further improves the long-term outcome, but patients who have a CCyR are not considered to have failure to imatinib if they do not have a major molecular response. This is because the difference in EFS probability is small, although significant. The timing of this response is also important. Despite initial suggestions from the IRIS trial that a MMR at 12 months improved long-term outcome, compared to CCyR but no MMR, the 8-year follow-up data has shown no difference in outcome using this hallmark. By 18 months, patients who have a CCyR and MMR have a better probability of EFS than those with CCyR but no MMR, but the difference is small (95% vs. 86%), and even smaller if considering only transformation to AP or BP or death as an event (99% vs 96%)⁸⁰.

The recommendations by the ELN have provided a clear framework for decision making and the significance of the definitions of failure and suboptimal response have been demonstrated in two independent series^{27,81}. Patients with suboptimal response to therapy have an inferior outcome, although the significance appears to be heterogeneous, with a more profound adverse prognostic effect for patients with suboptimal response to therapy at earlier time points (6 months) and than at later time points (18 months). It is however reasonable to consider treatment modifications for patients who have a suboptimal response to therapy. Treatment guidelines recommend dose escalation of imatinib to 600 or 800 mg/day in cases of suboptimal response^{38,70}. However, it should be acknowledged that there is minimal data available regarding the effectiveness of this approach^{58,59}. For patients with

clear failure to imatinib therapy, the current approach is to change therapy to a second generation TKI, although ASCT is also an option following treatment failure^{17,82}. Clinical trial data have confirmed the efficacy of dasatinib and nilotinib in patients with imatinib resistance or intolerance and the superiority of dasatinib versus imatinib dose escalation following imatinib resistance^{70,81,83}. It is possible that earlier treatment switch to second-line agents, i.e. after suboptimal response, could result in more favorable long-term outcomes than with dose-escalated imatinib, but there are currently no clinical data to support this hypothesis.

In addition to efficacy outcomes, mutational data should be considered when selecting TKI therapy⁸⁴. The BCR-ABL genotype can be used to guide treatment decisions since it is a prognostic factor for disease progression⁸⁴⁻⁸⁶. Patients with T315A/I, F317I/L, and V299L mutations do not appear to respond consistently to therapy with dasatinib⁸⁶⁻⁸⁹, whereas patients with the F359C/V substitution do benefit from dasatinib⁸⁶. In an analysis of 1043 patients who underwent mutational assessment in phase II/III studies in CP CML, 14 patients had baseline F317L mutations, and just one patient had a baseline V299L mutation⁸⁹. It was found that patients bearing F317L mutations achieved a high CHR rate (93%), but cytogenetic response rates (MCyR, 14%; CCyR, 7%) were lower than in patients without these mutations. Importantly, in patients treated with dasatinib, high response rates were obtained with the common imatinib-resistant mutations in Y253, E255 and E359 residues.

Nilotinib resistance is associated with mutations in the T315, Y253, and E255 residues⁸⁴⁻⁸⁶. Indeed, recently it was shown that the presence of E255K/V, Y253H, or F359C/V mutations at baseline are independent predictors of worsened PFS in patients with CP CML⁸⁶. Therefore, dasatinib therapy may be more appropriate for patients with these common mutations, whereas nilotinib may be better suited for those patients with F317L mutations⁸⁸. Although both dasatinib and nilotinib are ineffective against T315I BCR-ABL⁸⁵, this mutation is more likely to affect patients in the advanced phases of CML⁸⁵. Patients with T315I may achieve favorable outcomes with therapies other than the available second-line TKIs, e.g AP24534, omacetaxine, and others^{90,91}.

A recent study has explored factors that may predict response and outcome in patients with chronic-phase CML receiving dasatinib or nilotinib after failing imatinib^{92,93}. The analysis included 123 patients in chronic phase post imatinib failure: 78 treated with dasatinib and 45 treated with nilotinib. Multivariate analysis for predictive factors was performed for event-free survival, overall survival, and 12-month major cytogenetic response (MCyR). Investigators found that event-free survival in response to a second TKI in CML depends on achieving a prior cytogenetic response to imatinib and on the patient's performance status. In the study, patients with performance status 1 and no prior cytogenetic response to imatinib had a high likelihood of responding to a second TKI with poor event-free survival and overall survival. Patients with both risk factors had a 24-month overall survival of only 40% compared with 95% for patients with neither risk factor. Therefore, patients with no previous cytogenetic response to imatinib should be offered additional treatment approaches including allogeneic stem cell transplantation and clinical trials. However, the achievement

of MCyR with a second TKI by 12 months may compensate for the presence unfavorable baseline factors⁹³.

Safety and tolerability are also important considerations in choosing a TKI. The potential impact of the drug's AE profile on any of the patient's preexisting conditions should be considered in choosing between second generation BCR-ABL inhibitors. Since pleural effusion is more common for patients receiving dasatinib therapy, patients with risk factors for pleural effusion such as a prior cardiac history, chronic obstructive pulmonary disease and hypertension are at greater risk for developing these complications⁶⁷. Risk factors for developing pleural effusions while taking dasatinib also include disease stage (BC > AP > CP), previous lung problems such as smoking or infections and those patients maintained on starting doses of dasatinib⁹⁴.

Blood glucose elevations have been observed in 11% of CML-CP, and 4% of CML-AP patients treated with nilotinib^{72,95}. While no CML-CP or CML-AP patients required dose adjustments, dose interruption or discontinued nilotinib therapy due to elevated blood glucose, preexisting hyperglycemia should be carefully monitored to ensure that the condition is not exacerbated by nilotinib treatment. Prior severe pancreatitis may also be a concern on nilotinib therapy, and patients with a history should be closely monitored on nilotinib therapy.

Cardiac events, including congestive heart failure, left ventricular dysfunction and QT prolongation have all been reported with dasatinib and nilotinib. Though they occurred in <5% of the patient population, a literature review of clinical trials in CML-CP for dasatinib 70 mg twice daily and nilotinib 400 mg twice daily revealed grade 3/4 nonhematologic AEs, including arrhythmias, for both agents⁷³.

Improving frontline therapy

Improving imatinib in the frontline setting

The TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity Study) phase 3 trial randomized 476 patients 2:1 to receive high dose imatinib of 800 mg (n = 319) or standard dose of 400 mg (n = 157) daily. The study showed that high dose imatinib of 800 mg improved the rate of responses and eventually showed a trend towards better event free survival. However, at 12 months, differences in MMR and CCyR rates were not statistically significant (MMR, 46% vs. 40%; $P = .2035$; CCyR, 70% vs. 66%; $P = .3470$)⁹⁶.

The SPIRIT trial, a phase III multicenter open-label prospective randomized trial, compared the efficacy of high dose imatinib (600 mg) or combination therapy using standard doses of imatinib (400 mg) combined with either Ara-C or pegylated IFN- α (PegIFN); to standard dose imatinib (400 mg daily). Six hundred thirty six patients with CML-CP were evaluated and randomized to receive imatinib 400 mg daily (n=159), imatinib 600 mg daily (n=160), imatinib 400 mg daily in combination with Ara-C (n=158), or imatinib 400 mg daily in combination with pegylated IFN- α (n=159). The primary endpoint was overall survival and secondary endpoints included rate and duration of hematologic and cytogenetic responses, molecular responses, and tolerability. Median follow up was 36 months. Rates of MMR at 6

months were significantly higher in the imatinib + PegIFN arm vs. the standard dose imatinib arm (39% vs. 21%; $p < .001$). Grade 3/4 neutropenia and/or thrombocytopenia occurred in 8% of patients treated with imatinib 400 mg, 14% of patients treated with imatinib 600 mg, in 41% of imatinib + Ara-C patients and in 40% of imatinib-PegIFN patients respectively. Grade 3/4 non hematological events were reported in 19% of patients treated with imatinib 400 mg, in 30% of patients treated with imatinib 600 mg, in 27% of patients treated with imatinib 400 mg + Ara-C, and in 31% of imatinib + PegIFN. Discontinuation of experimental treatment occurred within the first 6 and 12 months in 26% and 18% of imatinib + Ara-c patients and in 35% and 11% of imatinib + PegIFN patients respectively. These results indicate that there is a potential benefit for combination therapy with imatinib and PegIFN in the treatment of patients with newly diagnosed CML-CP⁹⁷.

Nilotinib in the frontline setting [Table 3]

Cortes et al at MD Anderson assessed 51 patients with newly diagnosed CML-CP treated with nilotinib 400 mg twice daily in the frontline setting. Fifty (98%) attained a CCyR and 39 (76%) attained a MMR. Ninety six percent attained CCyR by 3 months and 98% attained CCyR by 6 months. The projected event-free survival at 24 months was 90%. Grade 3/4 hematologic toxicities included neutropenia (12%), and thrombocytopenia (11%). Nonhematologic toxicity was grade 1-2 and manageable. The median dose at 12 months was 800 mg. The results of this study point to nilotinib as being an effective option for frontline treatment of patients with CML-CP⁹⁸.

In the phase II GIMEMA trial, 73 patients were treated with nilotinib at a dose of 400 mg twice daily with a median follow up of 30 months. Rates of CCyR, MMR, and CMR at 24 months were 92%, 82%, and 12%, respectively. One patient showed progression to advanced disease and was shown to have the T315I mutation. The discontinuation rate due to adverse events was 5%. These results confirm that nilotinib is highly efficacious in the frontline setting⁹⁹.

The phase III ENESTnd trial randomized patients to compare imatinib 400 mg twice daily to nilotinib 300 mg twice daily or nilotinib 400 mg twice daily in the frontline setting in patients with early chronic phase CML. In the current analysis of 24-month data, nilotinib at 400 mg twice daily resulted in superior progression-free survival compared with imatinib (97.9% vs 95.2%; $P = .0437$). Nilotinib also significantly improved the rates of CCyR and MMR at 24 months. CCyR at 24 months was 87% with 400 mg twice daily nilotinib compared with 77% with imatinib ($P = .0018$). Likewise, MMR at 24 months was 59% with 400 mg nilotinib vs 37% with imatinib ($P < .0001$). There were also significantly fewer progressions to advanced phase and blast crisis with nilotinib. Based on these data, nilotinib has been approved for the frontline therapy of CML. The gap in efficacy in favor of nilotinib has persisted over time and it appears that nilotinib may improve both short-term and long-term outcomes compared with imatinib¹⁰⁰.

In the ENESTnd trial, nilotinib was also shown to be safe and well-tolerated with no increase in side-effects compared with imatinib. By contrast, treatment-related gastrointestinal toxicity and fluid retention of all grades were more frequent with imatinib than they were in either nilotinib arm¹⁰⁰.

Dasatinib in the frontline setting [Table 4]

Cortes et al at MD Anderson Cancer Center published a study in which 50 patients with newly diagnosed CML-CP were randomized to dasatinib 100 mg once daily or 50 mg twice daily in the frontline setting. Median follow up was 24 months. Of the 50 patients enrolled in the study, 49 (98%) attained a CCyR and 41 (82%) attained a MMR. Ninety four percent of patients attained CCyR by 6 months. There was no difference in response rate by treatment arm. The projected event-free survival rate at 24 months was 88%. Grade 3/4 hematologic toxicities included neutropenia and thrombocytopenia, and occurred in 21% and 10% of patients, respectively. Nonhematologic toxicity was usually grade 1 to 2. There was no significant difference in toxicity between the two arms, and the actual median dose at 12 months was 100 mg (range, 20 to 100 mg). These results lead to the conclusion that the management of CML-CP in the frontline setting with dasatinib is an effective approach, yielding high rates of CCyR and MMR¹⁰¹.

The DASISION trial, an international, multicenter, randomized phase III trial on frontline dasatinib therapy, randomized 519 patients to receive dasatinib 100 mg once daily or imatinib 400 mg once daily. Findings from this trial were recently published¹⁰². The current data presented at ASH 2010 represented an 18-month follow-up showing that dasatinib was superior to imatinib with respect to the primary endpoint, the rate of CCyR. The likelihood of achieving a CCyR at any time was higher with dasatinib vs imatinib (85% vs 80%; hazard ratio [HR] = 1.5; $P < .0001$)¹⁰³.

In addition, the secondary endpoint, the rate of MMR, was also significantly improved with dasatinib compared with imatinib. The likelihood of achieving MMR at any time with dasatinib was significantly higher than with imatinib (57% vs 41%; HR = 1.8; $P < .0001$). Based on these data, dasatinib was approved by the US Food and Drug Administration as a standard of care for CML patients. Dasatinib was also shown to be well tolerated, with low rates of grade 3/4 hematologic and nonhematologic toxicity, as well as a low rate of discontinuation due to adverse events although, pleural effusion occurred only in patients treated with dasatinib (in 12% of 258 patients, nearly all grade 1 and 2)^{102,103}.

Another study by the Southwest Oncology Group (S0325) compared dasatinib 100 mg to imatinib 400 mg in newly diagnosed CML in chronic phase. The study showed that dasatinib was associated with greater MMR compared with imatinib at 12 months. However, the 12-month rates of complete hematologic response (CHR), CCyR, OS, or PFS were comparable between treatment groups. The lack of statistical significance in rates of CCyR was likely due to the fact that patients who were not evaluable were considered non-responders¹⁰⁴.

Bosutinib in the frontline setting

The BELA trial, an international, multicenter, open-label phase III trial, compares bosutinib with imatinib in the frontline setting using CCyR as a primary endpoint and MMR as a secondary endpoint¹⁰⁵. In this study, non-evaluable patients were considered non-responders. Consequently, bosutinib was associated with a similar rate of CCyR compared with imatinib at 12 months (70% vs 68%; $P = .601$), and the primary endpoint was not met.

In evaluable patients only, bosutinib did induce a significantly higher rate of CCyR compared with imatinib (78% vs 68%; $P = .026$). In addition, there was a significantly higher MMR with bosutinib in both the intent-to-treat and evaluable populations (intent-to-treat patients: 39% vs 26%, $P = .002$; evaluable patients: 43% vs 27%, $P < .001$). More follow-up on these studies is needed to determine whether these responses are sustained and whether bosutinib is truly superior to imatinib.

Conclusion

The treatment of CML has progressed significantly since the approval of imatinib in 2001. With the advent of TKIs, the focus of the scientific community has shifted to the molecular management of disease, which has had a considerable impact on the approach to cancer treatment to date. Imatinib has transformed CML from an immediately life-threatening disease to one that is treatable with daily oral medication that makes it possible to improve both overall survival and maintain quality of life. However, increasing incidence of imatinib-resistance and intolerance necessitates the development of alternative therapies. There is a substantial amount of data supporting the improvement in outcome in long term follow up of the 2nd generation TKIs, nilotinib and dasatinib. Improving outcome in the frontline setting should be the direction of further scientific research, including the implementation of 2nd generation TKIs as frontline therapy.

Despite extraordinary progress, a true cure for CML is not generally achieved by Abl kinase inhibitors. TKIs are potent inhibitors of Bcr-Abl kinases (among others), resulting in rapid reduction of the majority of cells carrying the Ph chromosomal marker. However, suppression of Abl-driven hematopoiesis may be insufficient to eradicate quiescent stem cells. Studies assessing the combination of TKIs with promising agents are ongoing. These combinations include TKI and hedgehog inhibitors, omacetaxine, vaccines, and hypomethylating agents. If successful, this strategy could lead to a safe and permanent discontinuation of therapy in patients with a good response. The impact of using more potent agents in the frontline setting on the potential to discontinue TKI therapy remains to be determined. The future of CML therapy may include early use of these potent agents, perhaps in combination with new molecules, to help more patients achieve CMR, which could lead to therapy discontinuation and cure.

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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 hematolog Legend: 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

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

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

Nilotinib for newly diagnosed CML-CP

Phase of Study	Number of patients (n)	Dose	CCyR (%)	MMR (%)
II	51	400 mg twice daily	98	76
II	73	400 mg twice daily	96	85
III	846	300 mg (nilotinib) (n=282)	80	44
		400 mg (nilotinib) (n=281)	78	43
		400 mg (imatinib) (n=283)	65	22

CCyR: complete cytogenetic response, MMR: major molecular response

Table 4

Response rates with frontline dasatinib.

Study	Number of patients	CCyR (%)	MMR (%)	PFS (%)	OS (%)
MDACC	50	98	82	--	--
DASISION	259	78	57	94.9 (18 months)	96 (18 months)
S0325	123	82	59	99 (12 months)	100 (12 months)

CCyR: complete cytogenetic response, MMR: major molecular response, PFS: progression free survival, OS: overall survival, MDACC: MD Anderson Cancer Center

* cCCyR (confirmed complete cytogenetic response) is reported for DASISION study.