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The Role of New Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia

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Abstract

Imatinib mesylate was the first tyrosine kinase inhibitor (TKI) approved for the management of chronic myeloid leukemia (CML). Imatinib produces acceptable responses in ~ 60% of patients; with ~20% discontinuing therapy due to intolerance and ~20% developing drug resistance. The advent of newer TKIs' such as, nilotinib, dasatinib, bosutinib and ponatinib have provided multiple options for patients. These agents are more potent, have unique side effect profiles and are more likely to achieve relevant milestones such as, early molecular responses (3-6 months) and optimal molecular responses (12 months). The acquisition of BCR-ABL kinase domain mutations is also reportedly lower with these drugs. Thus far, none of the randomized phase III clinical trials have shown a clinically significant survival difference between frontline imatinib versus newer TKIs'. Cost and safety issues with the newer TKIs' such as, vascular disease with nilotinib and ponatinib and pulmonary hypertension with dasatinib have dampened the enthusiasm of using these drugs as frontline options. While the utility of new TKIs' in the setting of imatinib failure or intolerance is clear, their use as frontline agents should factor in the age of the patient, additional comorbidities, risk stratification (Sokal score) and cost. Combination therapies and newer agents with potential to eradicate quiescent CML stem cells offer future hope.

Keywords

Chronic myeloid leukemia; *BCR-ABL1*; Tyrosine kinase inhibitors

Introduction

Chronic myeloid leukemia (CML) is a clonal, hematopoietic stem cell disorder, characterized by a reciprocal translocation that involves fusion of the Abelson oncogene (ABL) located on chromosome 9q34 with the breakpoint cluster region (BCR) on chromosome 22q11.2.[1] This reciprocal translocation, t (9; 22) (q34; q11.2), results in a shortened chromosome 22 called the Philadelphia (Ph) chromosome, which encodes the BCR-ABL1 fusion oncoprotein [Figure 1]. [2-4] This protein has constitutive tyrosine kinase

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activity, which stimulates hematopoietic transformation and myeloproliferation.[5] The predominant isoform of BCR-ABL is a 210-kDa protein that is present in >90% of patients with CML.[6]

Prior to the advent of tyrosine kinase inhibitors (TKI), treatment options for patients with CML were limited to cytoreductive agents, Interferon alpha (INF-α) and allogeneic stem cell transplantation (HCT).[7] The use of cytoreductive agents such as, hydroxyurea, arsenic and busulfan, were largely palliative (symptom control), bearing no impact on the natural course of the disease. INF-α, was the first agent with disease modifying effect, with a favorable impact on over-all survival (OS).[7] In prospective, randomized studies, INF-α produced rates of major cytogenetic responses (Mcg) of 11 to 30% and complete cytogenetic responses (CCgR) in ~ 10% of patients.[8-10] Treatment with INF-α was however limited by poor tolerability and progressive disease.[11] Similarly, although allogeneic stem cell transplant is considered curative, it is associated with high morbidity (acute and chronic graft versus host disease) and mortality (non-relapse mortality), limiting generalized applicability.[7]

In 2003, the first major breakthrough was documented, with the results of the IRIS study (International Randomized Study of Interferon and STI571), demonstrating superiority of imatinib mesylate in comparison to combination therapy with INF-α and low dose cytarabine, in patients with chronic phase CML (CP-CML) [Table 1].[12] At 18 months, the rates of Mcg and CCgR were; 87.1% vs 34.7% and 76.2% vs 14.5% in the imatinib versus combination-therapy arms, respectively.[12] The estimated rate of freedom from progression to accelerated or blast phase CML (AP and BP) was 96.7% vs 91.5% in the imatinib vs combination-therapy arm respectively, and importantly imatinib was better tolerated.[12] The study was designed as a cross over study and given the success of imatinib, a large proportion of patients [65% (N=359), 26% due to intolerance to INF-α] crossed over to the imatinib arm.[13] At the 5-year follow up 87% of patients had achieved a CCgR, with an estimated OS of 89%.[13]

With the use of imatinib the survival of patients with CP-CML has dramatically improved. However, with time, 20-30% of patients develop TKI resistance, commonly attributable to *BCR-ABL1* kinase domain mutations.[14,15,16] Some patients fail therapy despite inhibition of BCR-ABL1, implicating activation of alternative resistance mechanisms.[15] Additionally, 5-10% discontinue therapy secondary to poor tolerability.[13] This has led to the development of newer TKIs' such as nilotinib, dasatinib, bosutinib and ponatinib [Tables 1, 2 and 3]. These agents inhibit a spectrum of tyrosine kinases apart from BCR-ABL1 and have differing potencies and side effect profiles. In this review, we attempt to discuss the role of newer TKIs' in the management of CML.

1. Imatinib mesylate

Imatinib mesylate was the first TKI, U.S. Food and Drug Administration (FDA) approved for the management of CML. Imatinib binds to the BCR-ABL1 kinase domain, which is in an inactive conformation in a pocket reserved for the ATP binding site, thus preventing the transfer of a phosphate group to tyrosine on the protein substrate and the subsequent activation of phosphorylated protein [Figure 1]. The pharmacokinetic properties and drug

interactions for imatinib are detailed in Table 2, while Table 3 lists the adverse effect profile. At 8 years of follow-up on the IRIS study, 45% of patients had discontinued treatment due to adverse events/safety (6%), unsatisfactory therapeutic outcomes (16%), allogeneic HCT (3%), death (3%) or other reasons.[17] The OS rate was 85%, with the annual rates of progression to AP or BP in years 4 to 8 after imatinib therapy being: 0.9%, 0.5%, 0%, 0%, and 0.4%, respectively. Progression to AP or BC was noted only in 3% of patients who achieved CCgR, and in none of patients who achieved major molecular response (MMR).[17] While conventional response criteria for CML have followed the optimal achievement of a complete hematological response (CHR) by 3 months, CCgR by 9-12 months and a MMR by 18 months [Table 4], there is increasing data suggesting that the achievement of BCR-ABL1 transcripts of ≤ 10% at 3 months (EMR- early molecular response) predicts for better OS, progression free survival (PFS), cumulative incidence of CCgR and MMR.[18,19] This goal seems to be better achieved by second generation TKI; with a recent study showing that 91.4% of patients receiving dasatinib achieved an EMR.[20] In addition, sub-optimal responses to imatinib and intolerance often lead to poor disease control with higher rates of AP or BP.

Imatinib is a highly effective TKI for ~60% of CML patients.[21] It is however, less potent than the second generation TKIs', an issue that can result in sub-optimal kinase inhibition leading to resistance and loss of responses.[22] Nearly all patients experience some impairment in quality of life, such as fluid retention (periorbital and peripheral), muscle cramps, or gastrointestinal disturbances (nausea, vomiting and diarrhea).[12,13,23] However, there are no worrying organ toxicity signals emerging after prolonged therapy with imatinib. The early concerns about an increase in cancer susceptibility and cardiac dysfunction have also not borne out.[24]

2. Nilotinib

Nilotinib is a more potent analogue of imatinib and was approved by the U.S. FDA in 2007 for the treatment of patients with CP or AP CML that were resistant to, or intolerant to imatinib. In *vitro* profiling has demonstrated that nilotinib is effective against most imatinib-resistant Abl kinase domain mutations. Clinically, five kinase domain mutations remain of major concern; T315I (gate keeper mutation), F359V, E255K/V, and Y253H [Table 4].[25] These mutations most frequently emerge on frontline or second-line nilotinib therapy and their presence is a contraindication to the use of nilotinib.[22] The Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENESTnd) study was a phase 3, randomized, open-label, multicenter study that assigned 846 patients with CP-CML in a 1:1:1 ratio to receive nilotinib (at a dose of either 300 mg or 400 mg twice daily) or imatinib (at a dose of 400 mg once daily) [Table 1].[26] At 12 months, the rates of MMR for nilotinib (44% for the 300-mg dose and 43% for the 400-mg dose) were nearly twice that for imatinib (22%) ($P<0.001$).[26] The rates of CCgR by 12 months were significantly higher for nilotinib (80% for the 300-mg dose and 78% for the 400-mg dose) than for imatinib (65%).[26] Patients receiving either the 300-mg dose or the 400-mg dose of nilotinib twice daily had a significant improvement in the time to progression to AP or BP. Gastrointestinal and fluid-retention events were more frequent among patients receiving imatinib, whereas dermatologic events and headache were more frequent in those receiving nilotinib.[26] This

study led to the frontline approval of nilotinib in the management of patients with newly diagnosed CML. At the 5-year follow up of the ENESTnd study, 60%, 62%, and 50% of pts in the nilotinib 300 mg BID, 400 mg BID, and imatinib arms, respectively, remained on core treatment.[27,28] Over half of pts in the nilotinib arms achieved $MR^{4.5}$ ($BCR\text{-}ABL^{IS} \leq$ 0.0032%) by 5 years. Rates of MMR, freedom from progression to AP and BP, and OS were higher with nilotinib in comparison to imatinib. An emerging concern related to the use of nilotinib is the occurrence of vascular events including peripheral arterial occlusive disease (PAOD), coronary artery disease (CAD), cerebrovascular disease (CVA), hyperglycemia and hypercholesterolemia.[27,28] In the ENESTnd trial, 20% of patients on the nilotinib 300 mg arm who were not diabetic at baseline were diabetic by 3 years, in comparison to 9% on the imatinib arm.[29]

3. Dasatinib

Dasatinib is a second-generation *BCR-ABL1* inhibitor that has a 325-fold higher potency *in vitro* in comparison to imatinib. Dasatinib is active against majority of the kinase domain mutations, with the exception of the T315I gatekeeper mutation.[30] In the CA180-034 trial of patients with imatinib-resistant or imatinib-intolerant CP-CML, dasatinib 100 mg once daily showed durable efficacy and safety, including a 6-year PFS of 49%, OS of 71%, and cumulative MMR rate of 43%.[31] In the phase 3 DASISION (DASatinib versus Imatinib Study In treatment-Naive CML patients) trial, patients with newly diagnosed CP-CML were randomized to receive dasatinib 100 mg (n = 259) or imatinib 400 mg (n = 260) once daily [Table 1]. [32] Cumulative response rates by 24 months in dasatinib and imatinib arms were: CCgR in 86% versus 82%, MMR in 64% versus 46%, and $MR^{4.5}$ in 17% versus 8%.[33] Transformation to AP/BP CML on study occurred in 2.3% with dasatinib versus 5.0% with imatinib. In safety analyses, fluid retention, superficial edema, myalgia, vomiting, and rash were less frequent with dasatinib compared with imatinib, whereas pleural effusion and grade 3/4 thrombocytopenia were more frequent with dasatinib.[33] This trial led to the frontline approval of dasatinib for newly diagnosed patients with CP-CML. At four years, 76% of patients on the dasatinib arm and 63% of patients on the imatinib arm had achieved a MMR.[34] In patients who achieved MMR, the median time to MMR for dasatinib and imatinib patients was 9.2 and 15.0 months, respectively. Through four years, transformation to AP and BP occurred in 12 patients receiving dasatinib and 18 patients receiving imatinib. PFS at four years was 90% in both arms and OS was 93% and 92% for dasatinib and imatinib respectively.[34] At three months, 84% of dasatinib treated patients vs. 64% of imatinib treated patients achieved an EMR. In the dasatinib arm, PFS and OS rates at four years for patients who had BCR-ABL ≤10% at three months vs. those who did not were 92% vs. 67% (p=0.0004) and 95% vs. 83% (p=0.0092), respectively. In the imatinib arm, PFS and OS rates at four years for patients who had BCR-ABL ≤10% at three months vs. those who did not were 95% vs. 70% (p<0.0001) and 96% vs. 84% (p=0.0021), respectively. Most drug-related adverse events occurred within the first year of treatment, and included myelosuppression, fluid retention (pleural effusion and superficial localized edema), diarrhea, headache, musculoskeletal pain, rash, and nausea. Of more concern are reports of pulmonary arterial hypertension, which by and large seems to resolve in most patients after discontinuing the medication. [34]

4. Bosutinib

Bosutinib is an oral Src/Abl tyrosine kinase inhibitor. The phase III Bosutinib Efficacy and Safety in Newly Diagnosed CML (BELA) trial compared bosutinib with imatinib in newly diagnosed, CP-CML [Table 1].[35] A total of 502 patients were randomly assigned 1:1 to bosutinib 500 mg per day or imatinib 400 mg per day. The CCgR rate at 12 months was not different for bosutinib (70%; 95% CI, 64% to 76%) versus imatinib (68%; 95% CI, 62% to 74%; two-sided P = .601); hence, the study did not achieve its primary end point.[35] The MMR rate at 12 months was higher with bosutinib (41%; 95% CI, 35% to 47%) compared with imatinib (27%; 95% CI, 22% to 33%; two-sided P < .001). Time to CCgR and MMR was faster with bosutinib compared with imatinib (two-sided P < .001 for both). On-treatment transformation to AP/BP occurred in four patients (2%) on bosutinib compared with 10 patients (4%) on imatinib. The safety profiles of bosutinib and imatinib were distinct; GI and liver-related events were more frequent with bosutinib, whereas neutropenia, musculoskeletal disorders, and edema were more frequent with imatinib. Bosutinib, compared with imatinib, was associated with higher incidences of diarrhea (68% *v* 21%, respectively), vomiting (32% *v* 13%, respectively), and abdominal pain (11% *v* 5%, respectively).[35] Conversely, bosutinib, compared with imatinib, was associated with lower incidences of edema (11% *v* 38%, respectively), bone pain (4% *v* 10%, respectively), and muscle spasms (2% *v* 20%, respectively). The aggregate incidence of grade 3 or 4 AEs was 64% in the bosutinib arm and 48% in the imatinib arm (*P* < .001).[35]

5. Ponatinib

Ponatinib, a highly potent third generation TKI was granted accelerated approval by the U.S FDA in December 2012 for the treatment of patients with CML that were resistant to, or intolerant of prior TKI therapy. Ponatinib is effective against a vast spectrum of kinase domain mutations, including the T315I gatekeeper mutation.[36] In a phase II study (PACE-Ponatinib in patients with CML or Ph+ ALL), among 267 patients with CP-CML, 56% had a MCgR (including 70% of patients with the T315I mutation), 46% had a CCgR (66% with the T315I mutation), and 34% had a MMR (56% of patients with the T315I mutation).[37] Responses were observed regardless of the baseline kinase domain mutation status. No single *BCR-ABL1* mutation conferring resistance to ponatinib was detected. Among 83 patients with AP-CML and 62 with BP-CML, 55% and 23% had a MCgR. Common adverse events reported were thrombocytopenia (37%), skin rash (34%), dry skin (32%), and abdominal pain (22%). Serious arterial thrombotic events were observed in 9% of patients; these events were considered to be treatment-related in 3%.[37] Additional follow-up from these ponatinib trials has since revealed a much higher frequency of serious adverse vascular events (48% and 24% in the phase I and II trials, respectively). [38]This concern led the U.S. FDA and Ariad Pharmaceuticals to abruptly withdraw ponatinib from the market in October 2013. Importantly, an ongoing phase III trial (EPIC- Exploring Ponatinib In untreated patients with CML) comparing ponatinib to imatinib for the first-line treatment of CML was also closed, patients were crossed over to imatinib, and their follow-up was terminated.[38]

In January 2014, the US FDA allowed Ariad Pharmaceuticals to resume the marketing of ponatinib with new safety measures. The current indications for ponatinib include; treatment of adult patients with T315I-positive CML (CP, AP and BP), or T315I-positive Ph+ ALL,

and the treatment of adult patients with CP, AP or BP CML or Ph+ ALL for whom no other TKI therapy is indicated. The warnings and precautions in the label were revised to describe the vascular occlusion events, including venous thromboembolism, PAOD, CAD and CVA. The optimal starting dose for ponatinib was decreased to 30 mg daily. Additional side effects include, pancreatitis (biochemical and clinical), hepatic transaminitis and treatment emergent hypertension [Table 3].

Choosing the optimal TKI

Imatinib was the first TKI approved for the management of CML and has >15 years of safety and efficacy data associated with it.[24] It is generally well tolerated and all the randomized studies comparing imatinib with second generation TKIs' have not demonstrated a clinically significant survival difference (both for OS and PFS). Therefore, while considering frontline therapy in patients in whom survival is the predominant goal, imatinib still remains an excellent option. This is especially relevant if patients have a low Sokal score or a low EUTOS (European Treatment and Outcome Study Score) score.[39] One strategy designed to maximize the use of imatinib and only use more potent TKIs where there is evidence of a high risk of progression is to use frontline imatinib and rely on the molecular responses at 3 and/or 6 months to identify the high-risk patients and switch them to a second generation TKI (lack of EMR at 3-6 months or lack of an optimal molecular response at 12 months). This concept is supported in part by the recent TIDEL-II (Therapeutic Intensification in De Novo Leukemia-II) study. Two-hundred and ten patients with CP-CML were enrolled in two equal, sequential cohorts.[40] All patients started treatment with imatinib 600 mg/day. Imatinib plasma trough level was performed at day 22 and if <1000 ng/mL, the dose of imatinib was escalated to 800 mg/day. Patients were then assessed against molecular targets: *BCR-ABL1* ≤10%, ≤1%, and ≤0.1% at 3, 6, and 12 months, respectively. Cohort 1 patients failing any target escalated to imatinib 800 mg/day, and subsequently switched to nilotinib 400 mg twice daily for failing the same target 3 months later. Cohort 2 patients failing any target were switched to nilotinib directly, as did patients with intolerance or loss of response in either cohort. At 2 years, 55% of patients remained on imatinib, and 30% on nilotinib. Only 12% had >10% *BCR-ABL1* at 3 months. Confirmed MMR was achieved in 64% at 12 months and 73% at 24 months. At 3 years, OS was 96% and transformation-free survival was 95%. [40]

In contrast to imatinib, the front line use of second-generation TKIs result in faster and deeper molecular responses (MMR/MR^3 and $MR^{4.5}$), [26,33,41] lower risks of AP/BC transformation,[33] and in the case of nilotinib, lower risk of acquired kinase domain mutations.[22] Hence these agents can be used preferentially in younger patients and in those with high Sokal or EUTOS scores (studies need further validation). However, outstanding questions remain over the long-term safety profile of these drugs. The development of vascular side effects such as PAOD, CVA, CAD and VTE with nilotinib and ponatinib and cardiopulmonary toxicities such as pleural effusions, interstitial pneumonitis and pulmonary hypertension with dasatinib warrant caution while prescribing these agents for frontline therapy. These toxicities may, in part, contribute to the lack of significant differences in OS between patients treated with imatinib and those receiving second generation TKIs'.

Newer TKIs' have a distinct role in patients who have known mutations precluding the use of imatinib or other second generation TKIs' [Table 5] and in the setting of intolerance to imatinib therapy. Co-morbidities of the patient and side effect profile of the TKI of interest should be an important consideration in decision making. For example, nilotinib and ponatinib should be avoided in someone who has preexisting peripheral vascular disease or cardiovascular disease, while dasatinib should be avoided in someone with pre-existing pleural effusions or pulmonary hypertension. At present, the cost of second generation TKIs' is not remarkably different from imatinib. However, the patent for imatinib is expected to expire soon, and it will be available as a generic product. Clinicians, then, need to weigh the advantages some patients gain with nilotinib or dasatinib in the frontline setting against the difference in cost.[42]

Newer Agents for CML

Although TKIs' have offered much in terms of OS and quality of life for patients with CML, the ability of these agents to cure CML is limited. In the prospective, multicentre, Stop Imatinib (STIM) study, imatinib treatment (of >2 years duration) was discontinued in patients with CML who had molecularly undetectable leukemia (CMR= >5-log reduction in BCR-ABL). 100 patients were enrolled and 69 patients had at least 12 months follow-up. Forty-two (61%) of these 69 patients relapsed.[43] At 12 months, the probability of persistent CMR for these 69 patients was 41% (95% CI 29-52). All patients who relapsed responded to reintroduction of imatinib.[43] This failure results from the inability of TKIs' to eradicate quiescent CML stem cells. In a recent study, the activation of peroxisome proliferator-activated receptor-gamma (PPAR-γ) by glitazones (anti-diabetic drugs), decreased the expression of STAT5 and its downstream targets HIF2α and CITED2, which are key guardians of quiescence in stem cells.[44] When pioglitazone was given temporarily to three patients with CML with chronic residual disease in spite of imatinib therapy, all of them achieved sustained CMRs' up to 4.7 years after withdrawal of pioglitazone.[44] These exciting results need validation in larger prospective studies.

Newer TKIs' with higher potencies and activity against the gatekeeper mutation, such as danusertib (PHA-739358)[45-47] and rebastinib (DCC-2036) are undergoing clinical development [Table 6]. ABL001 is a potent, specific BCR-ABL inhibitor with a distinct, allosteric mechanism of action that recently entered phase I development.[48] It has been developed for use in combination with nilotinib to provide greater coverage of BCR-ABL and in order to avoid the development of resistance. In contrast to TKIs that bind to the ATP-site of the ABL1 kinase domain, ABL001 binds to a pocket on the BCR-ABL kinase domain that is normally occupied by the myristoylated N-terminus of ABL1 [Figure 1]. ABL001 functionally mimics the role of the myristoylated N-terminus by occupying its vacant binding site and restores the negative regulation of the kinase activity.[48] Given that it does not act on the ATP binding site of the kinase domain; it has demonstrable *in vitro* activity against the T315I gatekeeper mutation.

Summary

TKIs' have revolutionized the management of patients with CML and have markedly improved their OS. Imatinib was the first TKI approved and is currently considered a very

effective front line option for most patients. With more than a decade of safety data, the long term use of imatinib is generally safe and no major safety concerns have emerged. With time, a fair number of patients discontinue imatinib, either due to disease progression/ resistance or secondary to intolerance. For this group of patients newer TKIs' have revolutionized care. The newer TKIs' are more potent than imatinib and have unique side effect profiles. These agents are more likely than imatinib to achieve optimal molecular responses, especially EMR, leading to a considerable debate on which TKI is the best frontline option. While there is no doubting their efficacy, especially in patients with kinase domain mutations, their safety profiles are somewhat controversial and continue to evolve. Serious vascular side effects such as PAOD, CVA and CAD with nilotinib and ponatinib and the development of pulmonary hypertension with dasatinib, currently continue to dampen the enthusiasm for using these drugs as frontline agents. Newer TKIs' with enhanced potencies and safety profiles and drugs acting at alternate sites optimizing responses are exciting prospects.

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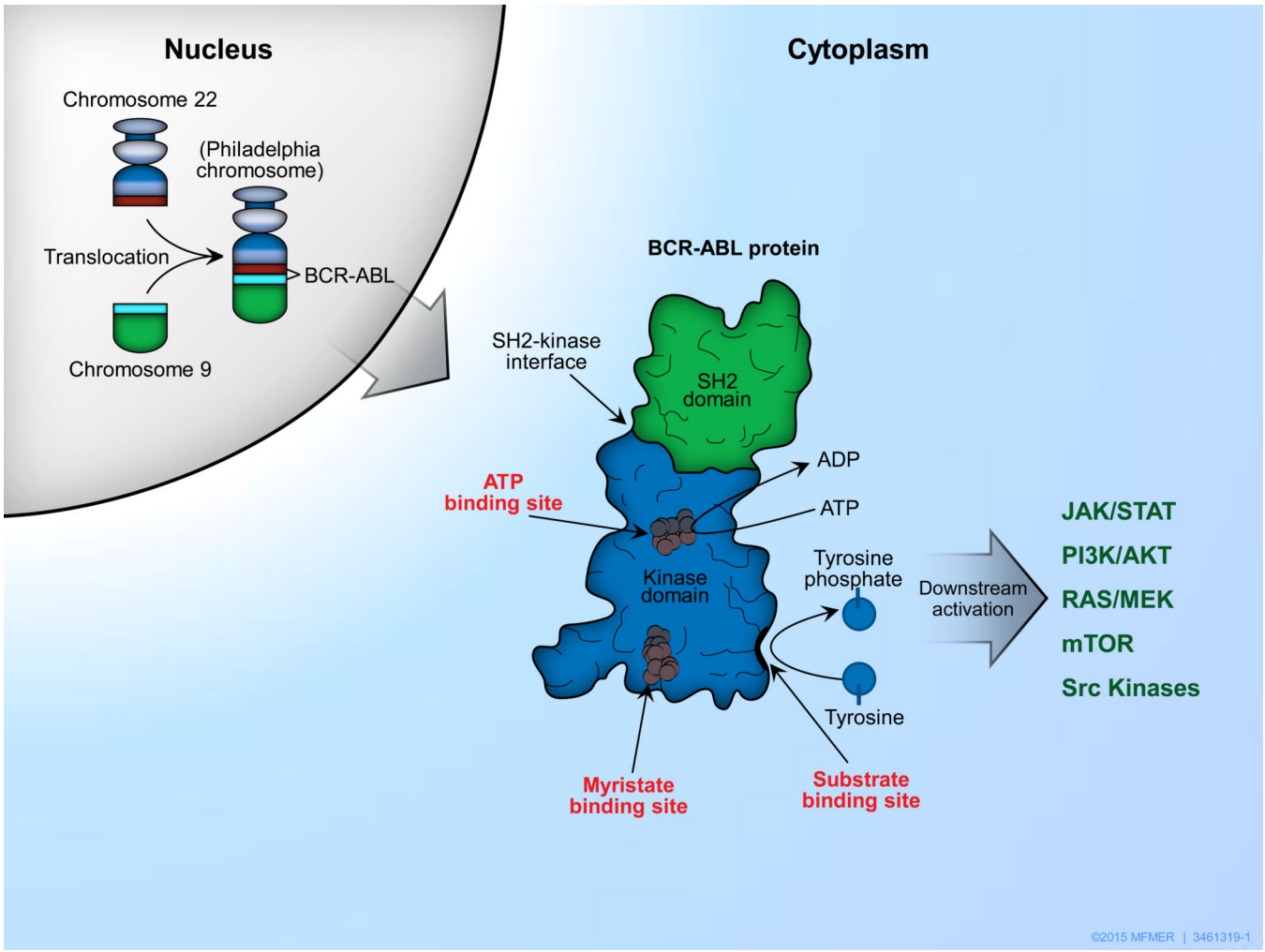

Figure 1.

The pathogenesis of chronic myeloid leukemia (CML) involves reciprocal translocation t (9; 22) (q34; q11.2) forming an abnormal chromosome 22- the Philadelphia chromosome. Fusion of the Abelson gene (ABL) located on chromosome 9 with the breakpoint cluster region (BCR) on chromosome 22 leads to the formation of an oncogene which encodes the BCR-ABL1 fusion oncoprotein. This protein has constitutively upregulated tyrosine kinase activity and by phosphorylation of substrates causes downstream activation of various molecular pathways such as JAK/STAT, PI3K/AKT, RAS/MEK, mTOR, Src kinases. These in turn dysregulate the adhesion, proliferation, transformation, and apoptotic behavior of hematopoietic cells.[5]

The BCR-ABL protein has been described as a complex coiled molecular structure with spatial domains: Src-homology-2 (SH2) and SH3 domains which bind adapter proteins; and the kinase domain which has the ATP, substrate and allosteric myristate-binding pockets. These different binding sites as well as downstream pathways are potential therapeutic targets for drug development against CML.[87,88]

Table 1

Summary of major TKI trials

Phase III trial	**IRIS [12]**			**DASISION [32]**			**ENEST [26]**			**BELA [35]**		
Study design												
Number of study arms	Two			Two			Three: Imatinib 400 mg OD/ Nilotinib 300mg/400mg BID[¥]			Two		
Crossover	Allowed if treatment failure or intolerance			No			No			No		
Dose modification	Dose escalation allowed			Interruptions, dose reductions or escalations allowed			Allowed escalation in Imatinib dose; not Nilotinib			Allowed escalation for both Bosutinib and Imatinib		
Total number of patients	1106			519			846			502		
	Interferon +low dose cytarabine	**Imatinib**	**P-value**	**Dasatinib**	**Imatinib**	**P-value**	**Nilotinib**	**Imatinib**	**P-value**	**Bosutinib**	**Imatinib**	**P-value**
Study dosage	Interferon: max tolerated. Cytarabine: 20 mg/m2	400 mg daily		100 mg daily	400 mg daily		300 mg BID[¥]	400 mg daily		500 mg daily	400 mg daily	
Follow-up at initial analysis	**12 mo**			**12 mo**			**12 mo**			**12 mo**		
CHR	56%	95%	<.001	NA	NA					71%	85%	NS
CCR	9%	74%	<.001	83%	72%	0.001	80%	65%	<.001	70%	68%	NS
MMR	NA	39%		46%	28%	<.001	44%	22%	<.001	41%	27%	<.001
Median time to first CHR	2.5 mo	1 mo		NA	NA		NA	NA		4.4 wk	4.6 wk	NS
Median time to first CCR	NA	NA		NA	NA		NA	NA		12.9 wk	24.6 wk	<.001
Median time to first MMR	NA	NA		HR 2.0		<.001	8.6 mo	NA		37.1 wk	72.3 wk	<.001
Progression to AP/BP	7%	1%	<.001	2%	4%		<1%	4%	0.01	2%	4%	
Event free survival	NA	NA		NA	NA		NA	NA		94%	93%	
Progression free survival	80%	97%	<.001	96%	97%	NS	NA	NA		NA	NA	

Overall survival	95%*	97%*	NS*	97%	99%	NS	NA	NA		99%	97%	
Follow-up last reported	**8 year [17]**			**5 year [49]**			**5 year [27,28]**			**2 year [50]**		
Patients on study	NA	55%		61%	63%		60%	50%		63%	71%	
CCR	NA	NA		83%	78%	NS	NA	NA		58%	65%	NS
MMR	NA	86%		76%	64%	.002	77%	60%	<.001	47%	41%	NS
$MR^{4.5}$	NA	NA		42%	33%	0.025	54%	31%	<.001	NA	NA	
Progression to AP/BP	NA	8%		5%	7%		4%	8%	0.04	2%	5%	0.019
Event free survival	NA	81%		NA	NA		NA	NA		92%	88%	
Progression free survival	NA	NA		85%	86%	NS	NA	NA		NA	NA	
Overall survival	NA	85%		91%	90%	NS	94%	92%	NS	97%	95%	

Abbreviations: CHR: Complete hematologic response; CCR: Complete cytogenetic response; MMR: Major molecular response BCR-ABL1 PCR ≤ 0.01% on International Scale; MR4.5: BCR-ABL1 PCR ≤ 0.0032% on International Scale; AP: Accelerated phase; BP: Blast phase; NA: Not available; NS: Not significant;

* at 18 months.

¥ there was no significant difference in results between the two Nilotinib arms so we include the more commonly used dose of 300mg BID in this table.

Table 2
Pharmacological properties of Tyrosine Kinase Inhibitors

	Imatinib [51]	Dasatinib [52]	Nilotinib [53]	Bosutinib [54]	Ponatinib [55]
Year of FDA/EMA approval	2001/2001	2006/2006	2007/2007	2012/2013	2012/2013
Kinases inhibited	BCR-ABL, PDGF, SCF, c-kit	BCR-ABL, SRC family kinases, c-kit, EPHA2, PDGFRβ	BCR-ABL, c-kit, PDGFR, CSF-1R, DDR1	BCR-ABL, SRC family kinases, Minimal activity against c-kit or PDGFR	Native/mutant BCR-ABL, including T315I, VEGFR, PDGFR, FGFR, EPH receptors, SRC family kinases, KIT,RET, TIE2, FLT3
Indications and usage in CML	First line	First or second line	First or second line	Resistance or intolerance to prior therapy	T315I-positive or when no other TKI is indicated
Absolute oral bioavailability	98%	14-34% (animal studies) [56]	50-82%	23-64% (animal studies)	Not determined
Time to maximum concentration (hours)	2-4	0.5- 6	3	4-6	6
Volume of distribution (liters)	435	2505	273 [57]	6080	1223
Half-life (hours)	18	3- 5	17	22.5	24
CNS penetration	0.5-2% [58]	5-28% [59]	0.23-1.5% [60]	~50% [61]	Not determined
Metabolism	Major: CYP3A4 Minor: CYP1A2, CYP2D6, CYP2C9, and CYP2C19	Major: CYP3A4	Major: CYP3A4	Major: CYP3A4	Major: CYP3A4 Minor: CYP2C8, CYP2D6, CYP3A5 esterases and/or amidases
Mode of elimination	~81% in feces, mostly as metabolites	~85% in feces, mostly as metabolites	~93% in feces, mostly as parent drug	~91% in feces	~ 87% in feces
Recommended dosage	CP: 400-800 mg/day AP/BP: 600-800 mg/day	CP: 100 mg OD AP/BP:140 mg OD With/without food	First line in CP: 300 mg BID Second line in CP/AP: 400 mg BID Without food	CP/AP/BP: 500-600 mg OD With food	CP/AP/BP: 45 mg OD With food
Dose adjustment: Hepatic impairment Renal impairment	Yes Yes	No No	Yes No	Yes No	Yes No
Important drug interactions	CYP3A4 inducers CYP3A4 inhibitors Warfarin	CYP3A4 inducers CYP3A4 inhibitors Proton pump inhibitors Antacids H2 Antagonists	CYP3A4 inducers CYP3A4 inhibitors Proton pump inhibitors Anti-arrhythmics	CYP3A4 inducers CYP3A4 inhibitors Proton pump inhibitors	Strong CYP3A inhibitors Strong CYP3A inducers
Use in Pregnancy	Category D	Category D	Category D	Category D	Category D
Use in breast feeding mothers	Not known	Not known	Not known	Not known	Not known
Contraindications			Hypokalemia Hypomagnesemia Long QT syndrome	Hypersensitivity to Bosutinib*	

	Imatinib [51]	Dasatinib [52]	Nilotinib [53]	Bosutinib [54]	Ponatinib [55]
Approximate cost for one month supply	$11053	$12428	$12433	$13078	$13536
Other indications	Ph+ ALL; MDS/MPD; Aggressive systemic mastocytosis; Hypereosinophilic syndrome and/or chronic eosinophilic leukemia; Dermatofibrosarcoma protuberans; GIST	Ph+ ALL GIST	GIST		Ph+ ALL when no other TKI is indicated or T315I positive

Abbreviations: FDA: US Food and Drug Administration; EMA: European Medicines Agency; CP: Chronic phase; AP: Accelerated phase; BP: Blast phase; OD: Once daily; BID: Twice daily;

Strong CYP3A inducers: rifampin, phenytoin, carbamazepine, St. John's Wort, rifabutin and phenobarbital.

Moderate CYP3A inducers include bosentan, nafcillin, efavirenz, modafinil and etravirine

Strong CYP3A inhibitors include ritonavir, indinavir, nelfinavir, saquinavir, ketoconazole, boceprevir, telaprevir, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and conivaptan.

Moderate CYP3A inhibitors include fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, grapefruit products and ciprofloxacin

* In the BOSULIF clinical trials, anaphylactic shock occurred in less than 0.2% of treated patients.

Table 3
Adverse effects of Tyrosine Kinase Inhibitors

	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib
Laboratory:					
Neutropenia	++++++	++++++	++++++	++++	+++++
Thrombocytopenia	+++++	+++++	++++++	+++++	++++++
Anemia	+++	++++	++++	++++	+++
Elevations in ALT/AST	+++	+	+++	++++	++++
Elevated lipase	++		++++	+++	++++++
Elevated bilirubin	+	++	+++	++	++
Elevated alkaline phosphatase	+		+		++
Elevated Creatinine	++	++	+	++	+
Hypophosphatemia	++++++	++++	++++	+++	+++
Hyperglycemia	+		++++		+++
Hyperkalemia	++		+++		++
Hyponatremia	+		+++		+++
Hypokalemia	++	++	++		++
Hypocalcemia	++	++	++		++
Clinical:					
Sudden death			+		
Hypersensitivity				+	
Abdominal pain	++	++	++	++	++++
Clinical pancreatitis					+++
Nausea	++	++	++	++	++
Vomiting	++		+	++	++
Diarrhea	++	++	++	+++	++
Constipation	+	++	+		++
Hemorrhage	++	++	++		+++
GI bleed	+	++	+		++
CNS bleed	++				++
Hypertension	+		++		++++++
Myocardial ischemia	++	++	+++		++++
Stroke/TIA	+	+	++		+++
Peripheral arterial occlusion	+		++		+++
Venous thromboembolism					+++
Ocular toxicity					++
QTc prolongation		+	+		
Tachyarrhythmias	+++	+++			+++
Bradyarrhythmias					++
Pulmonary hypertension		++			

	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib
Heart failure	++	**+++**			**+++**
Pericardial effusion		**++**			++
Pleural effusion	++	**+++**			++
Dyspnea	+	++	++	++	++
Skin rash	**++**	**++**	+	+++	+++
Muscle cramps/spasms	++		+		++
Musculoskeletal Pain	**+++**	++	++	+	++
Headache	+		++	++	++
Peripheral neuropathy					**++**
Fluid retention/edema	**++**	**+++**	+	+	++
Fatigue	++	++	++	++	++
Fever	++		+	+	++

Grade 3/4 toxicity from the clinical trial data available for first/second line use of the TKI in CP-CML.

Bold font indicates clinically important adverse events noted on post-marketing surveillance.

Key Reported frequency of toxicity

+ <1 %

++ 1-5 %

+++ 5-10 %

++++ 10-20 %

+++++ 20-30 %

++++++ >30 %

Table 4

Response criteria

Time on TKI therapy	Current ELN [62]/NCCN [63] recommendations			Older criteria		
	Optimal	Warning	Failure	Optimal	Suboptimal	Failure
Baseline	NA	High risk or CCA/ Ph +, major route	NA			
3 months	BCR-ABL1 ≤ 10% and/or Ph+ ≤ 35%	BCR-ABL1 > 10% and/or Ph+ 36-95%	Non-CHR and/or Ph+ >95%	CHR, minor CHR (<65%)	No CHR	Less than CHR
6 months	BCR-ABL1 ≤ 1% and/or Ph+ 0	BCR-ABL1 1- 10% and/or Ph+ 1-35%	BCR-ABL1 > 10% and/or Ph+ >35%	PCgR (<35%)	Less than PCgR (>35%)	No CgR
12 months	BCR-ABL1 ≤ 0.1%	BCR-ABL1>0.1-1%	BCR-ABL1 >1% and/or Ph+ >0	CCgR	PCgR (1-35%)	Less than PCgR (>35%)
18 months				MMR	Less than MMR	Less than CCgR
Then, and at any time	BCR-ABL1 ≤ 0.1%	CCA / Ph- (−7, or 7q-)	Loss of CHR Loss of CCgR Confirmed loss of MMR Mutations CCA/ Ph+	Stable or improving MMR	Loss of MMR	2 fold increase in transcripts

ELN: European LeukemiaNet

NCCN: National Comprehensive Cancer Network

CCA: Clonal Chromosome Abnormalities

CHR: Complete Hematological Response defined as WBC < 10×10^9/L, Basophils <5%, No myelocytes, promyelocytes, myeloblasts in the differential, Platelet count <450×10^9/L, Spleen nonpalpable.

CCgR: Complete Cytogenetic Response defined as no Ph+ metaphases on chromosome banding analysis (at least 20 bone marrow cell metaphases) or <1% BCR-ABL1 positive nuclei of at least 200 nuclei on fluorescence in situ hybridization.

PCgR: Partial Cytogenetic Response defined as 1 to 35% Ph+ metaphases

MMR: Major Molecular Response defined as BCR-ABL1 expression of ≤0.1% on the international scale

Table 5

BCR-ABL mutations and therapeutic options [64-70*]

Mutation	Drug resistance	Therapeutic options
Wild type M244V Q252H M315T F311L L387M H396P	-	Imatinib Dasatinib Nilotinib Bosutinib
G250E F311I H396R	Imatinib	Dasatinib Nilotinib Bosutinib
V299L T315A F317L/V/I/C	Dasatinib Bosutinib	Nilotinib Imatinib
Y253H/F E255K/V E355G V379I F359V/C/I	Imatinib Nilotinib	Dasatinib
T315I	Imatinib Dasatinib Nilotinib Bosutinib	Ponatinib
T315M	All TKIs	-

*This table compiles the mutations and sensitivities from studies reporting IC50 values derived using a cell line model. It suggests sensitivity to TKIs based on mutations but firm clinical data is not currently available.

Table 6
Newer TKIs & non-TKIs under study for CML

Agent	Mode of action	Activity in the presence of mutations/ Preliminary data	Phase of development	References
Omacetaxine mepesuccinate (Synribo)	Semisynthetic formulation of homoharringtonine. The mechanism of action includes inhibition of protein synthesis leading to cell death.	Not known/ CML-CP 18% MCR.	Phase 3	71-74
MK 0457	Aurora kinase inhibitor	T315I/ Minimal response in clinical trials	Phase 2	75
PHA-739358 (Danusertib)	Pan aurora kinase inhibitor and third generation TKI	T315I	Phase 2	45
ABL001	Allosteric inhibitor of BCR-ABL prevents emergence of resistant disease when administered in combination with nilotinib	Yes	Phase 1	48
DCC-2036 (Rebastinib)	TIE2, VEGFR1, BCR-ABL kinase inhibitor	T315I	Phase 1	46,47
AT9283	Aurora kinase inhibitor	Yes	Phase 1	76
BP5-087	STAT3 SH2 domain inhibitor combines with bcr-abl1 inhibition to overcome kinase-independent resistance in chronic myeloid leukemia	Yes	Pre-clinical	77,78
ON012380	Non-ATP competitive inhibitor of BCR-ABL	Unknown	Pre-clinical	79
SGX70393	Azapyridine-based inhibitor of native and T315I-mutant BCR-ABL kinase	T315I	Pre-clinical	80
TG101223	Small molecule BCR-ABL inhibitor	T315I	Pre-clinical	81
GNF-2/ GNF-5	Allosteric inhibitors of BCR-ABL	T315I	Pre-clinical	82
ESKM	Human IgG1 T-cell receptor mimic monoclonal antibody used alone or in combination with TKIs	T315I	Pre-clinical	83
U0126	MEK1/2 inhibitor reverses imatinib resistance through down-regulating activation of Lyn/ERK signaling pathway in imatinib-resistant K562R leukemia cells	Yes	Pre-clinical	84
KW-2449	Dual BCR-ABL Aurora kinase inhibitor	Yes	Pre-clinical	85,86