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Selecting the Best Frontline Treatment in Chronic Myeloid Leukemia

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Abstract

With the discovery of Philadelphia chromosome, understanding of chronic myeloid leukemia (CML) pathobiology has tremendously increased. Development of tyrosine kinase inhibitors (TKI) targeting the BCR/ABL1 oncoprotein has changed the landscape of the disease. Today, the expected survival of CML patients, if properly managed, is likely to be similar to the general population. Imatinib is the first approved TKI in CML treatment, and for several years, it was the only option in the frontline setting. Four years ago, second generation TKIs (nilotinib and dasatinib) were approved as alternative frontline options. Now, clinicians are faced the challenge of making decision for which TKI to chose upfront. Second generation TKIs have been demonstrated to induce deeper and faster responses compared to imatinib, however, none of 3 TKIs have been shown to have a clear survival advantage, they all are reasonable options. In contrast, when considering therapy in individual patients, the case may be stronger for a specific TKI. Co-morbidities of the patient and side effect profile of the TKI of interest should be an important consideration in decision making. At present, the cost nilotinib or dasatinib is not remarkably different from imatinib. However, patent for imatinib is expected to expire soon, and it will be available as a generic. Clinicians, then, need to weigh the advantages some patients gain with nilotinib or dasatinib in the frontline setting against the difference in cost. Whatever TKI is chosen as frontline, intolerance, non-compliance or treatment failure should be recognized early as a prompt intervention increases the chance of achieving best possible response.

Keywords

Chronic myeloid leukemia; Imatinib; Nilotinib; Dasatinib; Frontline Therapy

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm that is characterized by overproduction of myeloid cell lines and presence of Philadelphia chromosome (Ph)¹. The Ph chromosome results from a reciprocal translocation between the

Abelson (*ABL1*) gene on chromosome 9 and the breakpoint cluster region (BCR) on chromosome 22: t(9;22)(q34;q11). This leads to production of chimeric BCR-ABL1 oncoprotein with a molecular weight of 210 kD, which is a constitutively active tyrosine kinase enzyme that promotes replication and reduces apoptosis through downstream pathways such as JUN kinase, STAT, RAF and RAS²⁻⁹.

CML constitutes 15% of adult leukemia diagnosed in the United States¹⁰. It is estimated that 5,980 new cases will be diagnosed with CML in 2014¹¹. With the increased availability of newer treatment options, annual mortality has been decreased to 1–2% from 15 to 20% before 2000¹². As a result, CML prevalence gradually increased from 15,000 to 20,000 cases before 2000 to 70,000 in 2010. It is estimated to reach up to 144,000 cases by 2030 in the United States¹².

Before 2000, CML therapy was limited to hydroxyurea, busulphan, cytosine arabinoside (ara-C) and interferon-alfa (IFN- α) with modest complete cytogenetic response (CCyR: absence of Ph chromosome) rates (10% to 25%), and improved overall survival (OS) at the expense of significant toxicities¹³. Despite the high morbidity and mortality risk, allogeneic stem cell transplantation (allo-SCT) was the only modality to achieve long term remission or cure in CML patients with good performance status and an available donor. In early 2000, development of small molecule tyrosine kinase inhibitors (TKI) targeting BCR-ABL1 oncoprotein has revolutionized the treatment of CML. It has significantly changed the natural history of the disease, increasing 10 year OS from 10–20% to 80–90%¹².

Four years ago, frontline treatment of CML chronic phase (CP) was straightforward as imatinib was the only approved TKI. However, after approval of second generation TKIs (nilotinib and dasatinib) to be used in the frontline setting, physicians faced the challenge of making decision for which TKI to choose upfront. In this review, we will discuss the evidence supporting the frontline use of each of the available TKIs, including how to choose an agent in various clinical circumstances.

Frontline Treatment of Chronic Phase CML

To date, imatinib, nilotinib and dasatinib are the only TKIs have been approved by the United States Food and Drug Administration (FDA) as frontline therapies for CML. Current data shows that all three TKIs as reasonable options for frontline treatment of CML-CP (Table 1). Bosutinib and ponatinib are the other TKIs that have been evaluated in the frontline setting in newly diagnosed CML-CP patients. The former failed to show any response or survival superiority to imatinib, and the latter was stopped to be investigated in the frontline setting due to observation of arterial thrombotic events.

Imatinib Mesylate

Imatinib mesylate (Gleevec; formerly known as STI-571, Novartis Pharmaceutical Corporation, NJ, USA) is the first TKI approved by FDA for CML therapy. It is a signal transduction inhibitor which acts by binding to the ATP-binding site of the BCR-ABL1 oncoprotein thereby competitively inhibiting the phosphorylation of proteins involved in

downstream pathways. It also effects the off target kinases (PDGFR- α , PDGFR- β , KIT, DDR-1, DDR-2, and CSF1)^{14–16}.

IRIS (The International Randomized Study of IFN- α and STI571) is a breakthrough clinical trial for management of CML¹⁷. Investigators randomly assigned patients to receive imatinib (553 patients) or IFN- α and low dose ara-C (553 patients). After median follow up of 19 months, outcomes of patients receiving imatinib were remarkably superior than those treated with IFN- α and ara-C, particularly CCyR rate (76% vs. 14%, $p < 0.001$), and freedom from progression to accelerated phase (AP) or blast phase (BP) (96% VS 91%, $p < 0.001$) at 18 months. Eight-years follow up results of the IRIS study showed that the responses were also durable¹⁸. Event free survival (EFS) was 81%, progression free survival (PFS) was 92%, and OS was 85% (93%, when only CML-related deaths were considered).

While the long term outcomes of imatinib therapy were impressive, by the end of 8 years, 45% of the patients had to be taken off the drug due to failure or intolerance¹⁸. Alternative treatment options were needed. Efficacy and tolerability of high dose (800 mg per day) imatinib has been investigated in two randomized clinical trials, one in all patients¹⁹ and another in high risk patients²⁰, and both suggested no survival superiority of patients treated with higher dose imatinib in frontline. The former study showed that patients achieved major molecular response (MMR: BCR/ABL1 transcript level $< 0.1\%$ [international scale (IS)] and CCyR earlier with high dose (6 months CCyR 57% vs 45% with standard dose; $p = 0.0145$), however the rates ultimately reached the same level at 12 months (CCyR rates 70% vs 66%, respectively; $p =$ not significant). In contrast, another randomized study showed higher rates of MMR and CCyR for patients treated with high dose imatinib, with MMR rates at 12 months 59% and 44% for patients treated with 800 mg versus 400 mg imatinib, respectively ($p < 0.001$)²¹. At 3 year follow up, the MMR rates became comparable, 82% and 79%, respectively. Most recently, TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) study reported no significant difference in EFS, PFS and OS in CML-CP patients treated with imatinib 800 mg (319 patients) or 400 mg (157 patients) daily dose with a minimum follow up of 42 months²². MMR rates were comparable between groups (79 vs 76% for 800 and 400 mg/day, respectively; $p = 0.480$) by 42 months. The frontline use of high dose imatinib is possibly not applicable to all patients but may be an option for patients with high risk disease who have no access to second generation TKIs²³.

Several studies have been conducted to evaluate the efficacy of combining imatinib with pegylated IFN- α (pegIFN) or ara-C showed no significant survival benefit^{21,24–28}. In a phase III trial, SPIRIT (STI571 Prospective Randomized Trial), 636 patients with newly diagnosed CML-CP were randomized to four arms: imatinib 400 mg/day; imatinib (400 mg/day) plus cytarabine; imatinib plus pegIFN; imatinib 600 mg/day²⁴. At 12 months, CCyR rates were similar in all arms, but MMR rate was higher in imatinib/pegIFN arm compared to the imatinib (400 mg/day) alone arm, 57% and 38%, respectively ($p < 0.001$). However, the increased MMR rate with imatinib-pegIFN combination did not translate into better survival. Importantly, 45% of the patients receiving imatinib/pegIFN discontinued the therapy during the first year mostly due to toxicity, and discontinuation rate was only 7% in patients treated with imatinib (400 mg/day) alone. A randomized clinical trial at the MD Anderson Cancer Center²⁵ as well as CML IV study²¹ showed no response (cytogenetic or

molecular) or survival advantage of combining pegIFN and imatinib. In addition, combining pegIFN with imatinib increased toxicity and cost of therapy.

Nilotinib

Nilotinib (Tasigna; formerly known as AMN-107, Novartis Pharmaceutical Corporation, NJ, USA) is a close relative of imatinib designed to fit into ATP binding site of BCR/ABL1 oncoprotein with higher affinity²⁹. In vitro studies showed that it inhibits proliferation of cell lines expressing BCR/ABL1 with 20 fold greater potency than imatinib³⁰. It was initially tested in patients with imatinib failure. In a phase II study, 321 CML-CP patients who were resistant or intolerant to imatinib were treated with nilotinib (800 mg daily)³¹. With a median follow-up of 24 months, overall, 44% of the patients achieved CCyR (41% of imatinib resistant and 51% of imatinib intolerant patients). Eighty-four percent of the patients who achieved CCyR maintained response at last follow-up. The PFS and OS were 64% and 87% at 24 months, respectively. In another similarly designed study, 1422 CML CP or AP patients who failed or became intolerant to imatinib were treated with nilotinib (800 mg daily)³². With a median follow-up of 18 months, rate of CCyR was 50%, and PFS was reported as 80%. Following these favorable results as salvage therapy, nilotinib was investigated in the frontline setting.

The ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinic Trials Newly Diagnosed Patients) trial is a phase III, randomized study comparing two doses of nilotinib (300 or 400 mg twice daily) with imatinib 400 mg daily^{33••}. MMR rate at 12 months was the primary endpoint of this trial and it was superior in patients treated with nilotinib (44% for 300 mg dose and 43% for nilotinib 400 mg dose) compared to imatinib (22%) ($p<0.001$). Similarly, CCyR rates by 12 months were higher with nilotinib (80% for 300 mg dose and 78% for 400 mg dose) than with imatinib (65%) ($p<0.001$). Progression to AP or BP was significantly lower in patients receiving nilotinib compared to those receiving imatinib (<1% and 11% respectively). In this trial, achieving BCR/ABL1^{IS} <10% at 3 months (early molecular response) was shown to be correlated with favorable clinical outcomes in CML-CP patients treated with nilotinib or imatinib. At 3 months, 91% (300 mg twice daily) and 89% (400 mg twice daily) of nilotinib arm achieved early molecular response (EMR) compared to 67% of imatinib arm (p value not reported). Patients who achieved EMR had better PFS rates at 4 years than those who did not, respectively, 95% and 83% (nilotinib 300 mg twice daily; $p=0.006$), 97% and 89% (nilotinib 400 mg twice daily; $p=0.039$), and 98% and 83% (imatinib; $p<0.001$)³⁴. Similarly, OS rates at 4 years were higher in patients achieved EMR compared to those who did not, respectively, 97% and 87% (nilotinib 300 mg twice daily; $p=0.011$), 97% and 93% (nilotinib 400 mg twice daily; $p=0.248$), and 99% and 84% (imatinib; $p<0.001$). A 5 year follow-up showed that the depth of the molecular response increased over time in favor of nilotinib³⁵. Rates of MMR were 77% with nilotinib (300 or 400 mg twice daily) and 60% with imatinib ($p<0.001$). Similarly, MR^{4.5} (BCR-ABL1^{IS} transcript 0.0032%) rates were higher with nilotinib (54% and 52%, 300 mg and 400 mg twice daily dose, respectively) than imatinib (31%, $p<0.001$). There were less AP or BP with nilotinib 300 and 400 mg twice daily than imatinib ($n=2$ and 3 vs. 12, $p<0.006$ and 0.018). However, no OS difference was observed across the arms. Side effect profile was not similar, cardiovascular events (8%, nilotinib 300mg; 13%, nilotinib 400 mg; 2%, imatinib) and

biochemical abnormalities were higher among patients treated with nilotinib. In contrast, more patient developed diarrhea (22%, nilotinib 300mg; 31%, nilotinib 400 mg; 41%, imatinib) and muscle cramps (12%, nilotinib 300mg; 12%, nilotinib 400 mg; 34%, imatinib) with imatinib.

Dasatinib

Dasatinib (Sprycel; formerly known as BMS-354825, Bristol Myers Squibb, New York, USA) is a potent tyrosine kinase inhibitor with activity against both active and inactive conformation of BCR-ABL1 kinase domain, Src kinases, PDGFR, and c-Kit³⁶. Dasatinib is 325 times more potent than imatinib and 16 times more potent than nilotinib against wild type BCR/ABL1 oncoprotein³⁶. It shows inhibitory activity in all BCR-ABL1 mutant cell lines resistant to imatinib except for those harboring the T315I mutation^{37–38}. Like nilotinib, dasatinib resulted in hematologic and cytogenetic responses in patients who had failed imatinib. In a phase III trial, 670 CML-CP patients who were resistant (74%) or intolerant (24%) to imatinib were randomized to receive dasatinib 100 mg once daily, 50 mg twice daily, 140 mg once daily or 70 mg twice daily. At 6 years, PFS rates were 49%, 51%, 50% and 47%, respectively, and OS rates were 71%, 74%, 77% and 70%, respectively. Forty-three percent of patients in 100 mg once daily arm and 40% of the all other arms achieved MMR by 6 years³⁹. Favorable results of dasatinib in the salvage setting provided the rationale for this potent drug to be tested in newly diagnosed CML-CP patients.

In DASISION (Dasatinib versus Imatinib Study in Treatment-Naïve CML Patients) trial, 519 newly diagnosed CMP-CP patients were randomized to receive to imatinib 400 mg or dasatinib 100 mg once daily, and dose escalations were allowed for both drugs in case of suboptimal response as defined per protocol. In this phase III trial, the primary end point was confirmed CCyR at 12 months. This end point was achieved at higher rate in dasatinib arm compared to imatinib arm (77% and 66% respectively, $p=0.007$)⁴⁰. Recently, 5-year follow-up results of the study were reported showing that the statistically significant CCyR observed at 12 and 24 months was no longer present at 60 months(83% and 78%, respectively; $p=0.187$)⁴¹. In contrast, the rates of molecular responses remained significantly higher in dasatinib arm (MMR:76% and 64%, $p=0.002$; MR^{4.5}:42% and 33%, $p=0.025$). At 5 years, no PFS and OS difference was noted. Dasatinib induced deeper responses at early time points (3, 6, or 12 months) compared to imatinib. For instance, at 3 months, 84% of dasatinib arm achieved EMR compared to 64% of imatinib arm ($p<0.001$). Achievement of EMR in both arms was predictive for better PFS (dasatinib:89% vs. 72%, $p=0.001$; imatinib: 93% and 72%, $p<0.001$) and OS (dasatinib:94% vs. 81%, $p=0.003$; imatinib: 95% vs. 81%, $p<0.001$). Rate of transformation to AP or BP was lower in patients treated with dasatinib compared to imatinib, 4.6 % (n=12/259) and 7.3% (19/260), respectively. Twenty-nine percent of the dasatinib arm experienced pleural effusion, and most of them were grade 1 or 2 (67 of 74 patients). Only 20% of those patients (n=15) discontinued dasatinib due to pleural effusion. Arterial ischemic events were slightly higher in dasatinib group compared to imatinib, 5% and 2%, respectively. Fourteen pulmonary hypertension cases were reported in dasatinib arm, and 6 of them discontinued the drug. In this long term follow-up, overall no new safety signals were seen with dasatinib, and it remains to be a standard of care in the frontline setting.

Dasatinib (100 mg daily) and imatinib (400 mg daily) have also been evaluated in another phase III randomized (406 patients in each arm) clinic trial by an independent group. Recently, first results of this large study were reported with a median follow-up of 34 months⁴². At 12 months, both CCyR and MMR rates were found to be higher in patients treated with dasatinib compared to imatinib (CCyR: 51% vs. 40%, $p=0.002$; MMR: 58% vs. 43%, $p<0.001$). Forty patients discontinued therapy due to suboptimal response, 9% (37 of 406) of imatinib and 1% (3 of 406) of dasatinib arm. The PFS and OS were not significantly different among patients treated with dasatinib or imatinib. Grade 3 or 4 thrombocytopenia was higher in patients receiving dasatinib (13%) compared to imatinib (4%). So far, pleural effusions were seen in 19% (78 of 406) of patients treated with dasatinib, and 17% (13 of 78) required drainage. Cardiovascular events were slightly higher in dasatinib (2%, 8 of 406 patients) than imatinib arm (0.5%, 2 of 406 patients). EMR rates were not reported but, at 1 year, clearly dasatinib provided better molecular and cytogenetic responses. Further follow-up is required to better compare survival.

Bosutinib

Bosutinib (Bosulif, formerly known as SKI-606, Pfizer, Inc.), similarly to dasatinib, is a dual Src-ABL inhibitor. At difference with other TKIs, bosutinib produces no significant inhibition of PDGFR and KIT⁴³. It is more potent than imatinib and active against most of the mutations associated with imatinib resistance. In a phase I/2 study, 288 patients with CML-CP who were resistant or intolerant to imatinib were treated with bosutinib⁴⁴. At 24 months, overall CCyR rate was 41%, and 64% of those achieving CCyR had MMR. PFS and OS were 79% and 92%, respectively. In another trial, 118 patients with CML-CP who had been pretreated with imatinib followed by nilotinib and/or dasatinib were treated with bosutinib as 3rd or 4th line of therapy⁴⁵. With a median follow-up of 28 months, bosutinib induced CCyR in 24% of this heavily treated population. By 2 years, PFS and OS were 73% and 83%, respectively. Proven clinical efficacy in the relapsed setting led this drug to be tested as frontline therapy.

In BELA (Bosutinib Efficacy and Safety in Newly Diagnosed CML) trial, efficacy of bosutinib has been evaluated in the frontline setting⁴⁶. In this phase III study, 502 newly diagnosed CML-CP patients were randomized to receive bosutinib 500 mg or imatinib 400 mg daily. The primary end point was CCyR at 12 months. However, this end point was not different for bosutinib (70%) versus imatinib (68%) ($p=0.601$). Overall toxicity profile of bosutinib was distinct from imatinib. Gastrointestinal side effects were more common with bosutinib, such as diarrhea (70% vs. 26%; $p<0.001$), vomiting (33% vs. 16%; $p<0.001$), and alanine aminotransferase elevation (33% vs. 9%; $p<0.001$). In contrast, the side effects that were less common with bosutinib were edema (peripheral, 5% vs. 12%; $p=0.006$; periorbital, 2% vs. 14%; $p<0.001$), musculoskeletal complaints (muscle cramps, 5% vs. 22%; $p<0.001$; myalgia, 5% vs. 12%; $p=0.010$; bone pain, 4% vs. 11%; $p=0.003$) and neutropenia (13% vs. 30%; $p<0.001$)⁴⁷. Overall toxicity related discontinuation rate was higher in patients received bosutinib compared to imatinib, 19% (48 patients) and 6% (14 patients), respectively. Fifteen (31%) of 48 patients were discontinued from bosutinib before their first baseline assessment. Thus, authors suggested that early discontinuations may have contributed the lower CCyR rates in bosutinib arm. As a result dasatinib was not approved in

the frontline setting, but it is still a reasonable option in the salvage setting. Currently, a multicenter phase III randomized study is ongoing to compare lower dose (400 mg daily) of bosutinib and standard dose (400 mg) imatinib in patients with newly diagnosed CML-CP.

Ponatinib

Ponatinib (Iclusig, formerly known as AP24534, Ariad Pharmaceuticals), is a pan-BCR/ABL inhibitor retaining potency against all ABL mutations including T315I⁴⁸. In a phase II clinical trial, 449 patients with CML-CP, AP, BP and Ph positive acute lymphoblastic leukemia (ALL) who were intolerant or failed to prior TKI (dasatinib or nilotinib) or developed T315I mutation were treated with ponatinib⁴⁹. Among 267 CML-CP patients, 46% achieved CCyR (40% of those with resistance or intolerance to dasatinib or nilotinib, and 66% of those with T315I mutation). Overall MMR rate was 34%, and patients with T315I mutation achieved higher MMR rate (56%) compared to those with resistance or intolerance to dasatinib or nilotinib (27%) in CML-CP group. Responses were durable; sustained major cytogenetic response at least for 12 months in 91% patients. Similarly, ponatinib showed significant antileukemic activity in patients with CML-AP, BP and Ph positive ALL as well. No single BCR/ABL1 mutation was found to be resistant to ponatinib. Overall, the common side effects were thrombocytopenia (37%), rash (34%), dry skin (32%), abdominal pain (22%) and serious arterial thrombotic events (9%)⁴⁹. In 3% of the patients, these events were considered to be related with ponatinib. Twelve percent of the patients discontinued the treatment due to adverse events, and most common reason was thrombocytopenia (18 patients, 4%). Successful results in the salvage setting provided the rationale for ponatinib to be evaluated as a frontline agent in newly diagnosed CML-CP patients.

In EPIC (Ponatinib in Newly Diagnosed Chronic Myeloid Leukemia) trial, 307 patients were randomized to receive ponatinib 45 mg daily (154 patients) or imatinib 400 mg daily (152 patients)⁵⁰. However, this phase III trial was terminated in October 2013 due to observation of arterial thrombotic events. As a result, prospectively defined endpoints were not able to be analyzed. However, at a median follow-up of 5 months, investigators reported the end points that could be analyzed: BCR/ABL1^{IS} < 10% at 3 months, MMR and CCyR. The percentage of patients with < 10% BCR/ABL1^{IS} at 3 months was higher in ponatinib (94%) than imatinib arm (68%). The proportion of patients who achieved MMR at any time was higher for ponatinib than imatinib. Common side effects with ponatinib were skin rash (38%), abdominal pain (36%), headache (33%), constipation (27%), elevated lipase (27%), myalgia (26%), and thrombocytopenia (25%); with imatinib, they were muscle spasms (34%), nausea (34%), and diarrhea (27%). Arterial thrombotic events were more common with ponatinib (11 patients, 7%) than imatinib (3 patients, 2%). Authors suggested that future trials will need to take into account the relevant risk factors and use lower doses of ponatinib. In a single institution and single arm study, 51 patients with newly diagnosed CML-CP were treated with ponatinib was also reported recently⁵¹. With a median follow-up of 15 months, overall CCyR and MMR rates were 95% and 80%, respectively. Patients were able to achieve deep and fast responses. At 3 months, 90% and 50% of the patients achieved CCyR and MMR, respectively. At 6 months, 22% of the patients achieved undetectable BCR/ABL1 levels. None of the patients progressed to AP or BP, and all patients were alive

at last follow-up. Eighty-five percent (43 of 51) of the patients needed treatment interruption. By June 2014, all patients taken off the study (38 patients per FDA recommendation and 13 patients due to side effects). Among these 13 patients, 7 of them had arterial occlusive events.

Which TKI is best for my patient?

Balancing TKI toxicity profile and patient co-morbidities

TKIs are generally well tolerated medications when adequate supportive care and monitoring are employed. Each TKI has a distinct side effect profile which should be taken into consideration when choosing a therapy (Table 2).

Dasatinib has been associated with developing pleural effusion (14% vs. 0% with dasatinib and imatinib, respectively)⁵², and physicians may need to select another TKI for patients who already have pleural effusion or for the ones who have high risk of developing pleural effusion due to underlying cardiac disease (congestive heart failure), lung disease (chronic obstructive pulmonary disease), kidney or liver failure. Pulmonary arterial hypertension (PAH) is an uncommon but serious side effect of dasatinib⁵³. Dasatinib related PAH improves after discontinuation of the drug but likely does not result in complete hemodynamic recovery. Patients with known PAH may be started on alternative TKI. Dasatinib has been shown to induce platelet inhibition⁵⁴. Patients taking concomitant anti-platelet agents (e.g. aspirin clopidogrel) should be followed carefully due to increased risk of bleeding⁵⁵.

Lower extremity and periorbital edema are the most common side effects of the imatinib therapy. Even though edema usually tends to be a mild complication that can be managed with diuretics or fluid restriction, occasionally, it may be severe and require treatment interruptions or dose reductions^{56–58}. For patients with clinically significant peripheral edema due to venous insufficiency or any other chronic etiology, dasatinib or nilotinib may be considered as better first line options

For patients with poorly controlled diabetes mellitus, nilotinib should be started in caution as it may worsen the hyperglycemia³³. This unique side effect has not been reported with imatinib or dasatinib. QT prolongation is known to increase lethal cardiac arrhythmias, and it is a rare but noteworthy side effect of nilotinib³³. In vitro and in vivo preclinical studies suggested QT prolongation with this drug, and it became one of the parameters that needed to be monitored at baseline and while on therapy. In a chart review of 81 patients receiving nilotinib (baseline corrected QTc < 450 msec), the QT interval has not been found to be significantly prolonged at any time point during therapy⁵⁹. None of the patients developed a QTc interval > 500 msec. However, in patients with baseline prolonged QT or long QT syndrome, caution should be exercised as risk of cardiac event increases significantly in these patients, especially when QTc > 470 at baseline⁶⁰. Nilotinib has also been found to be associated with a low, but remarkable cardiac or vascular problems. In the frontline study evaluating efficacy of nilotinib and imatinib, cumulative incidence of cardiovascular events in patients treated with nilotinib was found to be higher compared to imatinib (8%, nilotinib 300mg; 13%, nilotinib 400 mg; 2%, imatinib)³⁴. Even though its frequency is not very

common, avoiding nilotinib in patients with significant cardiovascular disorders may be justified if there is viable alternative.

Cost

Over the last decade, the cost of anticancer therapy has increased from \$4,500 to more than \$10,000 per month⁶¹. Eleven of the 12 cancer drugs approved by FDA in 2012 were priced above \$100,000 per year⁶². The annual price for imatinib was nearly \$30,000 once approved by FDA in 2001. This original price was set to make all research and commercialization for imatinib profitable expecting the average patient would take the drug for 5–10 years⁶³. Now, however, as long as a patient is compliant with the medication, they can live close to normal lifespan. Consequently, prevalence of CML and the number patients requiring imatinib to stay alive have increased significantly. New indications for this drug were also developed and approved by FDA⁶⁴. Ironically though, the annual price of imatinib increased to \$92,000 in 2013⁶². This price is in the same range with nilotinib (\$115,000) and dasatinib (\$123,000).

Patent for imatinib is expected to expire by 2015, and it will be available as a generic drug with the anticipation that the price will fall significantly. Clinicians, then, need to weigh the advantages some patients gain with nilotinib or dasatinib in the frontline setting against the difference in cost⁶⁵. This will be especially important in countries, such as United States, where patients may pay an average one-fifth of drug costs out of pocket, and health expenditures are the most common reason of personal bankruptcies⁶⁶.

Any of the three TKIs, imatinib, nilotinib or dasatinib, may be selected in the frontline setting. Nilotinib and dasatinib have been shown to be superior to imatinib in achieving earlier response and lesser transformations, but do not appear to improve OS. Imatinib is still highly effective in significant number of CML patients and potentially cheaper than the alternatives. When selecting an agent, clinician should consider side effect profile and comorbidities along with the cost to make the best decision for the patient.

Monitoring Response to Therapy

Response to TKI therapy is highly correlated with careful monitoring and compliance with the drug. Patients treated outside of a clinical trial might have the same excellent outcome as the ones treated in a clinical trial once they are monitored and managed with the same rigor⁶⁷. Response to TKI has been classified as hematologic, cytogenetic, and molecular⁶⁸. Complete hematologic response (CHR) is defined as normalization of peripheral blood with no immature cell such as promyelocytes, myelocytes or blasts, and disappearance of splenomegaly. Cytogenetic response is categorized as minor cytogenetic response (Ph chromosome-positive metaphases > 35%), partial cytogenetic response (Ph chromosome-positive metaphases between 1% and 35%), and CCyR (Absence of Ph chromosome-positive metaphase). Major cytogenetic response (MCyR) is the range of response including PCyR and CCyR. Real-time quantitative polymerase chain reaction (RT-PCR) is used to measure BCR-ABL1 transcripts. Complete molecular response (CMR) is the absence of detectable BCR-ABL1^{IS} transcript (MR^{4.5}, minimal sensitivity of 4.5-log). It should be kept in mind that the results of molecular testing can vary depending on the laboratory and techniques being used. Advances in technology allows bone marrow aspiration and biopsy to

be avoided in certain situations, however, it is recommended that all suspected CML patients should undergo biopsy for diagnosis and proper staging in terms of CP, AP or BP. Current guidelines recommend bone marrow examinations at 3, 6 and 12 months of therapy⁶⁹. Once achieved CCyR, bone marrow biopsies every 1–3 years is useful in patients with stable CCyR. Alternatively, monitoring response in patients with durable CCyR can be continued with RT-PCR from peripheral blood every 3–6 months or more often if any inconsistency or increase noted in BCR/ABL1 transcript levels⁷⁰.

When to Switch TKI

In case of treatment failure, patient compliance, drug-drug interaction, and mutation analysis have to be investigated before making any change in treatment. This approach will prevent any unnecessary TKI switching and labeling a potentially effective drug as “failed”. Treatment failure is defined by European Leukemia Network (ELN) and National Comprehensive Cancer Network (NCCN) as not achieving certain level of response at specific time points⁶⁹ (Table 3). ELN categorizes responses as optimal, warning and failure. Warning means that the response to treatment requires more often monitoring to detect failure earlier and allow timely changes in therapy.

Earlier and deeper response to TKI has been associated with better outcomes. The controversial point is that the level of molecular or cytogenetic response, especially at 3 months of therapy. In a study, 477 CML patients treated with imatinib, dasatinib or nilotinib in the frontline setting have been evaluated for their response and survival with a median follow-up of 72 months⁷¹. Patients who could not achieve MCyR at 3 months had significantly lower 3-year EFS (81% vs 95%, $p<0.001$), transformation free survival (93% vs 97%, $p<0.026$) and OS (92% vs 96%, $p=0.01$) compared to those achieved MCyR, respectively. In the same study, similar favorable survival was shown in patients achieving MCyR at 6 months as well. In another study, outcome of 282 newly diagnosed CML-CP patients who were treated with imatinib 400 mg daily as frontline therapy followed by nilotinib or dasatinib were reported⁷². Patients with a BCR/ABL1^{IS} transcript levels more than 9.84% at 3 months had significantly lower 8-year EFS (7% vs 65%, $p<0.001$), PFS (57% vs 93%, $p<0.001$) and OS (57% vs 93%, $p<0.001$), respectively. These two retrospective analyses and several others^{73–75} brought up a question as what to do with patients who failed to achieve 3-month milestone. Current data on switching TKI at 3 month is still controversial. The results from two independent groups have shown that patients with a BCR/ABL1^{IS} transcript level $> 10\%$ at 3 months have the same favorable outcome as the patients with transcript level $< 10\%$, when they continued the therapy and achieved BCR/ABL1^{IS} transcript level $< 10\%$ at 6 months^{76–77}. ELN suggest that a single measurement of BCR/ABL1 transcript level should not be sufficient to define treatment failure, whereas supplementary tests should be performed in between 3 and 6 month landmarks to monitor the trend and confirm the failure⁶⁹. However, if the level of BCR/ABL1^{IS} is still $> 10\%$ by 6 months, switching TKI might be needed.

Achieving CCyR, especially latest by 12 months, is the gold standard of CML therapy as it is associated with improved survival⁷⁸. With the development of more potent drugs, there is an interest in inducing deeper molecular responses. MMR has been considered as a possible

therapeutic goal in CML therapy. In a long term analysis of the IRIS study, it has been shown that patients who achieved CCyR and MMR at 18 months had more durable responses. The probability of losing CCyR by 7 years was 26% for patients who achieved CCyR but not MMR at 18 months, and it was only 3% for patients who achieved both CCyR and MMR. There was also significant improvement in the 7-year EFS probability for patients achieving MMR at 18 compared with no MMR (95% vs 86%, respectively). However, TFS and OS were not significantly different. Patients who achieved CCyR by 12 months can be monitored with molecular testing, and bone marrow biopsy with cytogenetic assessment is only needed if there is any suspicion of progression. Patients who lost CHR or CCyR need a different TKI unless the reason of failure is non-compliance. Postponing treatment change in a patient who lost cytogenetic response is associated with poor EFS and decreased response probability⁷⁹. Fluctuations in BCR/ABL1 levels during CCyR should only dictate careful compliance assessment and closer follow-up. There is no need to change therapy in patients who achieved CCyR and no MMR or who lost MMR but maintains CCyR. Uptitrating the imatinib dose or switching TKI may lead to lower transcript levels in those patients, but there is still no data proving that such intervention improves the long term outcome⁸⁰.

Can we safely discontinue TKI?

Achieving a CMR has not been shown to provide any long term benefit for CML patients. However, such a great response brings the possibility of discontinuation of TKI. Several international clinical trials evaluated that possibility in CML patients who achieved deep molecular responses (Table 4). In STIM (Stop Imatinib) trial, imatinib was discontinued in 100 patients who had remained in MR^{4.5} for 2 years or more while on therapy⁸¹. With a median follow-up of 50 months, 61 patients had molecular relapse, and 58 of them relapsed within 7 months. Three late relapses occurred at month 19, 20 and 22⁸². All patients with molecular relapse were sensitive to TKI re-challenge. This study suggested that approximately 40% of the patients with durable CMR might be cured with TKI alone. In TWISTER trial, similarly, imatinib was discontinued in 40 CML patients who achieved MR^{4.5} and maintained it for 2 years⁸³. With a median follow-up of 43 months, treatment-free remission rate was 45% (18 of 40 patients). Most relapses (15 of 22) occurred within the first 6 months after stopping imatinib. None of the relapsing patients developed kinase domain mutation, AP or BP. Interim analysis of another TKI discontinuation therapy was reported in 200 CML patients with 6 month follow-up molecular data⁸⁴. Majority of the patients (97%) were treated with imatinib and others (3%) with nilotinib or dasatinib. Eligibility criteria for this trial were to receive TKI for at least 3 years and achievement of persistent deep molecular response (MR⁴, BCR-ABL1^{IS} transcript 0.01%) for at least a year. In this study with a short follow-up, treatment free remission rate was reported as 72%. More recently, the feasibility of nilotinib or dasatinib discontinuation has also been tested in patients treated with these TKIs as frontline or after imatinib failure or intolerance. This study reported interim outcome of 52 patients with at least 12 months follow-up⁸⁵. Twenty-four months persistent MR^{4.5} was also a requirement for discontinuation of TKI. Patients were followed with monthly RT-PCR during first year, every 3 months during second year and every 6 months thereafter. With a median follow-up of 32 months, treatment-free

survival was reported as 54% (28 of 52 patients). Similarly, majority of relapses occurred early with a median duration of 4 months. However, at present, discontinuation of the TKI should not be recommended outside the context of a clinical trial, due to lack of long term results of those studies, and the uncertainty in selecting best candidate patients.

Future Perspectives and Conclusion

Imatinib, nilotinib and dasatinib are very effective treatment options for CML in the frontline setting. However, there is a group of patients who will be resistant to these therapies and eventually fail. Unfortunately, in CML, we could not develop an ideal staging and prognosticating system which may allow us to detect high-risk patients at diagnosis or shortly after starting therapy and intervene accordingly. At present, there are 3 risk stratification systems used in CML, the EUTOS, Sokal and Hasford. These scoring systems are developed based on patients' clinical features such as age, as spleen size, platelet number and differential of peripheral blood. It doesn't appear as one being clearly superior to other. Two of these scoring systems were developed in pre-TKI era; Sokal risk score was developed when the conventional chemotherapy was the standard of care, and similarly Hasford scoring emerged in the era of IFN- α . EUTOS has been developed in imatinib era but its validity or superiority has not been confirmed by 2 independent studies^{86–87}. There is little evidence suggesting that current risk scoring systems may be helpful in tailoring TKI therapy²³.

A better approach might be to choose the most favorable therapy on the basis of biomarkers. By this way, patients with a high risk of drug resistance or disease progression could be recognized at diagnosis and treated on clinical trials or with intensive therapies. In order to be useful in this setting, biomarkers or assay(s) should be able to discriminate the patients who are likely to respond poorly to a particular TKI⁸⁸. Several assays have been developed; however, it is not clear if any of them will be able to predict the outcome with high degree of accuracy and guide CML management^{89–91}. In vitro inhibitory concentration 50% for imatinib (IC₅₀^{imatinib}) has been shown to be a predictive of molecular response in patients with previously untreated CML-CP⁸⁹. Phosphorylation of adaptor protein Crkl (CT10 regulator of kinase-like), in CML cells which were collected diagnosis, determined the response to imatinib. Patients with low IC₅₀^{imatinib} were more likely to achieve 1% BCR/ABL^{1S} by 3 months compared to the patients with high IC₅₀^{imatinib}, 36% and 8%, respectively (p=0.01). Similarly, low IC₅₀^{imatinib} predicted the superior MMR at 12 months as well. This assay could be used for other TKIs as well, but no published information exists correlating the IC₅₀ for nilotinib or dasatinib⁸⁸. Consequently, as of now, IC₅₀ analysis cannot be used to tailor the frontline therapy in CML patients. Another potential biomarker is OCT-1 (organic cation transporter 1), which is an active influx pump for imatinib into target cells^{90,92}. Reduced OCT-1 activity is associated with poor PFS and EFS as well as inferior molecular response in patients treated with imatinib^{93–95}. Patients with reduced OCT-1 activity who failed to achieve optimal response with imatinib may also have suboptimal responses when salvaged with nilotinib⁹⁶. However, currently, no frontline clinical trials of nilotinib or dasatinib are available to test this assumption.

Cancerous inhibitor of PP2A (CIP2A) is an important determinant of progressive CML. PP2A is a tumor suppressor phosphatase that regulates cell differentiation, proliferation and survival, and CIP2A has recently been shown to inhibit PP2A in gastric and breast cancer⁹⁷. Patients who will later transform into BP were found to have higher CIP2A protein levels ($p<0.001$) than patients who will not transform⁹¹. Although, its use as a biomarker of BP needs further validation and prospective testing, CIP2A may be a target in CML treatment. Growth factor independence 1 (GFI1) is another potential biomarker in CML, it is a transcription factor with a critical role in hematopoiesis including granulocytic differentiation and stem cell quiescence⁹⁸. Soliera et al has shown that ectopic GFI1 expression inhibited the colony formation and proliferation both in CD34⁺ cells and p210 BCR/ABL1-expressing cell lines through the repression of Mcl-1 and/or STAT5B⁹⁹. In an analysis of CP-CML patients, low GFI1 expression at diagnosis was demonstrated as highly associated with transformation into BP¹⁰⁰. These results support the previously described function of GFI1 in the suppression of proliferation and colony formation of p210 BCR/ABL1 transformed cells, and suggest GFI1 as a potential prognostic marker for high-risk CML.

As of now, none of the proposed assays or biomarkers can clearly direct optimal therapy for CML patients at diagnosis. However, investigation of the biomarkers led to better understanding of fundamental biologies that can be monitored and targeted. As our knowledge of CML pathobiology grows, therapeutic approaches combining tyrosine kinase inhibitors and other effective agents attacking novel targets may become the focus of the clinical trials in the future. Such strategies may result in deeper responses and eradicate minimal residual disease, and potentially allow more patients to be cured.

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Table 1

Comparison of Frontline Therapy Outcomes in Chronic Phase CML

Clinical Outcome (%)	TOPS ²²		ENESTnd ³⁴		DASISION ^{d1}	
	IM 400 (n=157)	IM 800 (n=319)	NIL 600 (n=282)	NIL 800 (n=281)	IM 400 (n=283)	IM 400 (n=260)
BCR-ABL <10% by 3 mo	NR	NR	91	89	84	64
BCR-ABL <10% by 6 mo	NR	NR	97	93	89	83
CCyR by 12 mo	67	70	80	78	83	72
MMR by 12 mo	39	45	44	43	46	28
Cumulative MR ^{4,5}	NR	NR	40	37	42	33
Minimum f/u (months)	42	42	48	48	60	60
Still on study drug at last f/u	73	68	66	69	61	63
Progression-free survival	92	94	93	96	85	86
Overall Survival	94	94	94	97	91	90

CML, chronic myeloid leukemia; IM 400 or 800, imatinib total daily dose of 400 or 800 mg; NIL 600 or 800, nilotinib total daily dose of 600 or 800 mg; DAS 100, dasatinib total daily dose of 100 mg; n, number of patients randomized to the particular arm; f/u, follow-up; BCR/ABL1 transcript level in international scale(IS); CCyR (complete cytogenetic response), absence of Ph chromosome-positive metaphase; MMR (major molecular response), BCR-ABL1/ABL1 transcript ratio 0.1% (IS); MR^{4,5}, BCR-ABL1 transcript 0.0032%

Table 2

Comparison of Adverse Events of TKIs Used in the Frontline Setting for Patients with Chronic Phase CML

Standard Daily Dosage	Imatinib 400 mg	Nilotinib 600 mg or 800 mg	Dasatinib 100 mg
Nonhematologic (all grades)			
Fatigue	+	+	+
Headache	+	++	+
Nausea	+++	++	+
Vomiting	+	+	+
Diarrhea	++	+	++
Rash	++	+++	++
Muscle Spasm	+++	+	+/-
Myalgia	+	+	+
Peripheral Edema	++	+	+
Periorbital Edema	++	+/-	+/-
Pleural Effusion	-	-	++
QTc > 500 msec	+/-	+/-	+/-
Laboratory Abnormalities (grade 3 or 4)			
Neutropenia	++	++	+++
Anemia	+	++	+
Thrombocytopenia	+	++	+++
Hyperglycemia	-	+	-
Hypophosphatemia	++	+	+
Elevated Transaminases	+/-	+	+/-
Hyperbilirubinemia	+/-	+	+/-

Data based on frontline TKI studies in CML patients (Kantarjian et.al N Engl J Med. 2010⁴⁰; Saglio et al. N Engl J Med. 2010³³).

Key: +++ = more than 20%; ++ = 10%–20%; + = 5%–10%; +/- = less than 5%; - = rare or no information. Values are approximations in some cases.

Table 3Response Evaluation and Management of CML in the Frontline Setting (ELN 2013)⁶⁹

Milestones	Continue Current TKI		Closer Monitoring		Switch TKI
3 months	BCR/ABL1	10% and/or Ph+ 35%	BCR/ABL1 > 10% and/or Ph+36–95%		No CHR and/or Ph+ >95%
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%
12 months	BCR/ABL1	0.1%	BCR-ABL1 0.1–1%		BCR/ABL1 > 1% and/or Ph >0%

CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor; Ph +, % of Philadelphia chromosome positive metaphases on bone marrow examination; BCR/ABL1 transcript level in international scale; CHR, complete hematologic response

At any time loss of CHR, loss of complete cytogenetic response (Ph + 0%), loss of confirmed major molecular response (BCR/ABL1 0.1%), and clonal evolution in Ph positive cells means failure

Table 4

Summary of Major Clinical Trials Evaluating TKI Discontinuation in CML Patients

Clinical Characteristics	STIM ⁸²	TWISTER ⁸³	French CML Group ⁸⁵	EURO-SKI ⁸⁴
Number of pts	100	40	52	200
Eligibility Criteria	MR ^{4.5}	MR ^{4.5}	MR ^{4.5}	MR ⁴
Discontinued TKI	IM	IM	NIL/DAS	IM/NIL/DAS
Median follow-up (months)	50	43	32	NR [*]
Definition of relapse	Loss of MMR	Loss of MMR	Loss of MMR	Loss of MMR
Number of pts in remission (%)	39 (39)	18 (45)	28 (54)	123 (72)
Number of relapsed pts (%)	61 (61)	22 (55)	24 (46)	67 (38)
early relapse [‡]	58 (95)	15 (68)	19 (80)	67
late relapse [‡]	3 (5)	7 (32)	5 (20)	NR [*]
Incidence of AP or BP	0	0	0	0

TKI, tyrosine kinase inhibitor; Pts, patients; MR^{4.5}, BCR-ABL1 transcript 0.0032%; MR⁴, BCR-ABL1 transcript 0.01%; IM, imatinib; NIL, nilotinib; DAS, dasatinib; NR, not reported; MMR, BCR-ABL1 transcript 0.1%; AP, accelerated phase; BP, blast phase

^{*} Median follow-up was not reported in this interim analysis but all patients had at least 6 months molecular response data

[‡] Depending on trial, early relapse reflects the ones that occurred within 6 or 12 months, and late relapses after 6 or 12 months