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Treating early in the disease course: lessons from the CML model

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Abstract

The landscape of chronic myeloid leukemia (CML) management has changed with the advent of tyrosine kinase inhibitors (TKI) targeting BCR-ABL1 oncoprotein. Imatinib mesylate is the first TKI approved for frontline CML therapy, and it was followed by nilotinib and dasatinib. Now, oncologists have to make a challenging decision when choosing frontline therapy for CML, because none of the 3 available TKIs have shown obvious survival superiority. However, the rate of deeper and earlier response is higher with second generation TKIs than it is with imatinib, and such great response correlates with a clear survival advantage regardless of TKI type being used. Patients should be monitored carefully for compliance and response, and treatment failure should be recognized timely per suggested guidelines to allow a prompt switch to another TKI. Side effect profile and cost of the TKI are other important factors to be considered when choosing therapy, because, then, the case may be more favorable for a specific TKI. Cost of therapy will obviously constitute more significant part of the discussion with the patients once imatinib becomes generic. In several clinical studies, achieving undetectable and durable disease status allowed some patients to discontinue the TKI and enjoy long term treatment-free remission. Cure for CML may be possible with TKIs alone or TKI in combination with other investigational therapies. However, due to lack of long term outcome data and absence of consensus for the definition of optimal response and time to stop TKI, it is not recommended to discontinue treatment outside of a clinical trial.

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of the hematopoietic stem cell, and it is characterized by the overproduction of myeloid cells and presence of Philadelphia chromosome¹. A reciprocal translocation between the breakpoint cluster region (BCR) on chromosome 22 and the Abelson (ABL1) gene on chromosome 9 results constitutes Philadelphia chromosome which is translated as fused BCR-ABL1 protein. This chimeric oncoprotein is a constitutively active tyrosine kinase enzyme which suppresses apoptosis and induces replication via several downstream pathways^{2–3}.

In 2015, it is estimated that 6,660 new CML cases will be diagnosed, and 1,140 patients will die of CML⁴. With the widespread availability of tyrosine kinase inhibitors (TKIs), annual mortality decreased tremendously from 15–20% to 1–2%⁵. Up until early 2000, interferon-alpha (IFN) was the standard of care for CML treatment with modest complete cytogenetic response rate (CCyR; disappearance of Philadelphia chromosome) and improved overall survival (OS)^{6–7}. As CCyR was achieved in minority of the patients, no significant attention was paid to time to CCyR. Discovery and development of TKIs targeting BCR-ABL1 fusion protein changed the landscape of CML treatment by improving CCyR rates from 10–25% to 80–95%, and 10-year OS from 10–20% to 80–90%^{5, 8}.

In the early years of TKI era, the general thought was that the achieving CCyR was acceptable, regardless of when it happened. As some patients can achieve CCyR after 2–3 years on treatment, several analyses suggested that time to optimal response had minimal impact on survival⁹. However, with the longer follow-up and more data being available, it is now clear that not only achieving best response but time to such response also matters. It has been shown in a number studies that the achievement of an early and deep response is a surrogate marker for improved survival in chronic phase (CP) CML patients treated with TKIs^{10–15}. Regardless of which TKI being used, patients who achieved early and deep response had favorable outcome, but the amount of patients achieved such response was significantly higher among patients treated with second generation TKIs (nilotinib or dasatinib) compared to imatinib^{16–17}. On the other hand, randomized clinical trials comparing frontline use of second generation TKIs to imatinib in CML-CP patients have not shown any significant overall survival difference^{18–19}. Because subsequent use of second generation TKIs after imatinib failure or intolerance is still able to induce CCyR in almost half of the patients^{20–21}. In this review, we will discuss frontline therapy for CML-CP, and focus on early response to TKIs and its impact on outcome.

TKIs Tested in the Frontline Treatment

First Generation TKI

Imatinib Mesylate—Imatinib mesylate is the first TKI approved by FDA for CML therapy. It inhibits the phosphorylation of proteins involved in downstream pathways by binding to ATP-binding site of BCR-ABL1 oncoprotein²². IRIS trial was a landmark study showing the superiority of imatinib over IFN²³. Patients were randomized to imatinib (n=553) or IFN plus low dose cytarabine (n=553). With a median follow-up of 19 months, majority of patients in imatinib arm achieved CCyR (76% vs. 14%; p<0.001). IRIS trial was a crossover design, and after significant superiority of imatinib being demonstrated, 89% (n=493) of the patients on IFN and low dose cytarabine arm either crossed over to imatinib (57%) or discontinued therapy (32%). Overall, imatinib was tolerated better than the combination therapy. In imatinib arm, commonly observed adverse events were superficial edema (55%), nausea (44%), muscle cramps (38%), musculoskeletal pain (36%), fatigue (35%), rash (34%), diarrhea (33%) and headache (31%). Long term outcomes of 553 patients on imatinib arm have been reported, and at the eight-year data cut-off, 45% (n=304) of the patients were off the therapy due to adverse events (6%), poor therapeutic outcome (16%), stem cell transplant (3%), or other reasons (17%)²⁴. No new safety signals were

reported. Event-free survival (EFS), progression free survival (PFS) and overall survival (OS) were 81%, 92% and 85%, respectively.

The role of high dose imatinib as initial therapy is controversial. Efficacy and safety of high dose imatinib (800 mg daily) was compared to standard dose (400 mg daily) imatinib in several randomized clinical trials. In one randomized study, at 12 months, CCyR rates were 63% and 50% for patients treated with 800 mg and 400 mg imatinib, respectively²⁵. Patients who achieved CCyR at 1 year landmark had better OS (96% vs 91%, $p=0.015$). Major molecular response (BCR-ABL1 transcript level $< 0.1\%$ international scale [IS]) rates were higher in high dose imatinib group compared to standard dose, 59% and 44%, respectively ($p<0.001$). In contrast, similarly designed another randomized trial showed comparable CCyR rates at 12 months for patients treated with high dose and standard dose imatinib, 70% and 66%, respectively ($p=\text{not significant}$). In another trial, investigators randomized 216 patients with high risk (Sokal score) CML to receive 800 mg or 400 mg imatinib in the frontline setting²⁶. At 1 year, CCyR rate was 64% and 58% for patients treated with 800 mg and 400 mg imatinib, respectively ($p=0.435$). None of the randomized clinical trials were able to show any OS benefit with high dose imatinib. Recently, final results of TOPS clinical trial were reported, and suggested that initial dose in CML did not affect the long term response to imatinib²⁷. In that study, patients were randomized 2:1 to imatinib 800 mg ($n=319$) and 400 mg ($n=157$) daily dose and had minimum follow-up of 42 months. MMR rates were similar among high dose and standard dose groups, 79% and 76%, respectively ($p=0.408$). The median time from randomization to CCyR was 5.8 and 5.9 months, in 800 mg and 400 mg arm, respectively. The CCyR rates were not different at 12, 24, 36 and 42 months as well. Similarly, no significant EFS, PFS, and OS difference was reported.

Imatinib and IFN combinations have been investigated by number clinical trials, and no OS benefit demonstrated compared to imatinib alone^{25, 28–31}. In SPIRIT trial, 636 patients with CML-CP were randomized four different treatment groups; imatinib 400 mg daily, imatinib 400 mg daily and cytarabine or IFN, and imatinib 600 mg daily²⁸. At 12 months, CCyR rates were similar across all groups, however, MMR rate was found to be higher in patients treated with imatinib 400 mg plus IFN arm compared to imatinib 400 mg arm, 57% and 38%, respectively ($p=0.005$). Nevertheless, with a minimum follow-up of 24 months, superior MMR rates in imatinib plus IFN did not translate into better PFS or OS. Forty-five percent of the patients treated with imatinib plus IFN combination had to stop therapy due to toxicity, and only 7% of the patients in imatinib 400 mg arm had to discontinue therapy. Most common toxicities in imatinib plus IFN group were as follows; neutropenia (69%), thrombocytopenia (30%), rash (30%) and edema (25%). Grade 3 or 4 neutropenia was significantly higher in imatinib and IFN arm compared to imatinib 400 mg arm, 49% and 7%, respectively ($p<0.001$), and similarly grade 3 or 4 thrombocytopenia were also more common (11% vs 2%, $p=0.002$). CML IV study as well as a randomized clinical study at the MD Anderson Cancer Center demonstrated no cytogenetic, molecular response or survival superiority of imatinib plus IFN combination to imatinib alone^{25, 29}. In most studies, addition of IFN to imatinib appeared to increase only cost of therapy and toxicity.

Second Generation TKI

Nilotinib—Nilotinib is the second TKI approved for the frontline treatment of CML-CP. It is a close relative of imatinib mesylate designed to bind BCR-ABL1 with higher affinity³². In vitro studies suggested that nilotinib inhibits the cell lines expressing BCR-ABL1 with greater potency (20 fold) than imatinib³³. FDA granted accelerated approval of nilotinib after its efficacy and safety was demonstrated in newly diagnosed CML-CP patients in a randomized, open-label clinical trial (ENESTnd)¹⁷. In this phase III trial, 846 patients were assigned 1:1:1 ratio to receive nilotinib (400 mg or 300 mg twice daily) or imatinib (400 mg once daily). At 12 months, CCyR rates were higher for nilotinib (400 mg dose; 78%, 300 mg dose; 80%) than for imatinib (65%) ($p<0.001$). Similarly, MMR rates were higher for nilotinib (400 mg dose; 43%, 300 mg dose; 44%) than for imatinib (22%) by 12 months. One percent of the patients treated with nilotinib progressed in to AP or BP compared to 11% with imatinib. Five-year follow up data showed that patients treated with nilotinib had superior overall molecular response rate³⁴. Overall MMR rates were 77% for nilotinib and 60% for imatinib ($p<0.001$). MR^{4.5} (BCR-ABL1^{IS} transcript 0.0032%) rates were found to be higher for nilotinib than imatinib, 53% and 31%, respectively ($p<0.001$). Progression to AP or BP were less common in patients treated with nilotinib (400 mg dose; 3 patients, 300 mg dose; 2 patients) than those treated with imatinib (12 patients) by 5 years ($p=0.005$, $p=0.018$). No OS difference was demonstrated across the arms. Cardiovascular events were higher among patients in nilotinib group (13%, nilotinib 400 mg; 8%, nilotinib 300 mg; 2%, imatinib). On the other hand, imatinib caused more diarrheas (31%, nilotinib 400 mg; 22%, nilotinib 300 mg; 41%, imatinib) and muscle cramps (12%, nilotinib 400mg; 12%, nilotinib 300 mg; 34%, imatinib) than nilotinib did.

Dasatinib—Dasatinib is the third and last TKI approved by FDA for frontline treatment of CML-CP patients. It has BCR-ABL1, Src kinase, PDGFR and c-Kit inhibitory activity, and 16 times more potent than nilotinib and 325 times more potent than imatinib against BCR-ABL1 oncoprotein³⁵. Except T315I mutation, it has inhibitory activity on all imatinib resistant BCR-ABL1 mutant cell lines³⁶. Dasatinib was approved for frontline CML treatment by FDA after its efficacy has been shown in a randomized, open-label multinational study¹⁶. In DASISION trial, 519 newly diagnosed CML-CP patients were randomized to receive dasatinib (100 mg daily) or imatinib (400 mg daily). With a minimum follow-up of 12 months, CCyR rate was higher for dasatinib than for imatinib, 83% and 72%, respectively ($p=0.001$). MMR rates were also found to be superior in patients treated with dasatinib (46% vs 28%, $p<0.001$). Five-year follow up data was presented recently, when 61% and 63% of dasatinib and imatinib arm were still on their initial study drug, respectively¹⁹. Statistically significant CCyR superiority of the dasatinib arm was no longer present by the end of five years (83% and 78%; dasatinib and imatinib, respectively, $p=0.187$). However, patients treated with dasatinib achieved deeper molecular responses (MR^{4.5}: 42% and 33%, $p=0.025$, MMR: 76% and 64%, $p=0.002$). At 5 years, no OS or PFS difference were reported across treatment arms (OS: 91% and 90%, PFS: 85% and 86%, dasatinib and imatinib, respectively). Progression to AP or BP was less common in dasatinib arm compared with imatinib arm, 4.6 % (12 patients) and 7.3% (19 patients), respectively. Grade 3 or 4 neutropenia were similar in dasatinib and imatinib arms, 21% and 20%, respectively¹⁶. In contrast, rate of grade 3 or 4 thrombocytopenia was higher for dasatinib

(19%) than for imatinib (10%). Incidence of fluid retention (all grades) was more frequent with imatinib (42%) than with dasatinib (19%). However, pleural effusion was reported only in dasatinib arm (10%). With a longer follow up, incidence of pleural effusion continued to increase every year, and reached up to 29% (overall) in dasatinib-treated patients by 5 years¹⁹. Overall 15 patients had to discontinue dasatinib due to pleural effusion (20% of patients who developed pleural effusion). Arterial ischemic event were uncommon in both arms (dasatinib; 12 patients, imatinib; 6 patients).

Results of SPIRIT 2 trial were presented recently³⁷. In this largest phase III, open-label clinical trial, 814 newly diagnosed CML-CP patients were randomized to receive dasatinib (100 mg daily) and imatinib (400 mg daily). With a median 34 months follow-up, 64% of the patients were still on initial study drug. By 12 months, dasatinib induced superior CCyR and MMR rates compared to imatinib (CCyR: 51% vs. 40%, $p=0.002$; MMR: 58% vs. 43%, $p<0.001$). The PFS and OS were similar across treatment arms. Pleural effusions occurred in 78 dasatinib-treated patients (19%), and 13 of 78 patients (17%) required therapeutic drainage. Development of pleural effusion among patients treated with dasatinib was not found to effect molecular responses. By 12 months, MMR rate was 65% among patients who developed pleural effusion and 56% in those without ($p=0.148$). Early molecular response rates were not reported, however, at 12 months, dasatinib induced superior cytogenetic and molecular responses. Longer follow-up needed to better compare arms.

Bosutinib—Bosutinib is a fairly specific inhibitor of Src-ABL tyrosine kinase, and has no substantial inhibition of PDGFR and KIT³⁸. It sustains activity against most mutations related with imatinib resistance except V299L and T315I. Pharmacokinetics, efficacy and safety of this TKI were evaluated in a phase I/II study³⁹. Part I was a dose-escalation study which led to determination of 500 mg daily dosing. Part II evaluated the efficacy and safety of bosutinib 500 mg once-daily dosing. In total, 288 imatinib-resistant ($n=200$) or imatinib-intolerant ($n=88$) CML-CP patients were enrolled. With a median 24 follow-up, 86% and 41% had complete hematologic and cytogenetic response, respectively. PFS and OS were 79% and 92%, respectively. Proven clinical benefit in relapsed and refractory setting allowed this drug to be tested in frontline setting. In BELA trial, 502 newly diagnosed CML-CP patients were randomized to be treated with bosutinib 500 mg daily or imatinib 400 mg daily⁴⁰. Achievement of CCyR by 12 month was determined as the primary end-point. However, the study did not achieve its primary end-point as CCyR rate was 70% and 68% for bosutinib and imatinib, respectively ($p=0.601$). By 12 months, MMR rate was higher for bosutinib (41%) than for imatinib (35%, $p<0.001$). Side effect profile of bosutinib is distinct from imatinib. With a minimum follow up of 30 months, compared to imatinib, bosutinib was associated with more gastrointestinal side effects (diarrhea, 70% vs. 26%; $p<0.001$; vomiting, 33% vs. 16%), elevated alanine aminotransferase (33% vs. 9%; $p<0.001$), and fever (19% vs. 12%; $p=0.046$)⁴¹. However, the following side effects were more common with imatinib compared to bosutinib; edema (periorbital; 14% vs 2%, $p<0.001$; peripheral; 12% vs. 5%, $p=0.006$), musculoskeletal (myalgia; 12% vs 5%, $p=0.010$; muscle cramps 22% vs 5%, $p<0.001$), and neutropenia (30% vs 13%, $p<0.001$). Twenty-one percent of the patients who had diarrhea with bosutinib received dose interruption, however, none of them had to discontinue the drug because of diarrhea. Bosutinib could not get approval to be used

in frontline setting, but it is a reasonable choice for patients with relapsed disease. Currently, a randomized multicenter Phase III trial is ongoing to compare bosutinib 400 mg daily dose and imatinib 400 mg daily dose in newly diagnosed CML-CP patients.

Third Generation TKI

Ponatinib—Ponatinib is a pan-BCR-ABL1 inhibitor with a novel molecular structure allowing inhibition of both wild type and mutant BCR-ABL1 including T315I⁴². Clinical activity of ponatinib has been initially shown in a phase I clinical trial, 43 heavily treated CML-CP patients were treated and 98% and 72% achieved complete hematologic and major cytogenetic response (Philadelphia chromosome < 35%), respectively⁴³. Of the 12 patients with T315I mutant CML, all achieved complete hematologic response and 92% achieved major cytogenetic response. This was followed by a phase II clinical trial in which 267 CML-CP patients who had unacceptable side effects (16%) or resistant to dasatinib or nilotinib (84%) were treated with ponatinib 45 mg daily⁴⁴. Forty-six percent of the patients achieved CCyR, and 70% of those were harboring T315I mutation. No single BCR-ABL1 mutation demonstrated resistance to ponatinib. In Epic trial, 307 newly diagnosed CML-CP patients were randomized to ponatinib 45 mg daily or imatinib 400 mg daily⁴⁵. However, this study was terminated due to the observation of arterial thrombotic events in the ponatinib arm. With a median follow-up of 5 months, investigators were able to analyze BCR-ABL1 < 10% at 3 months, CCyR and MMR. Almost all patients in the ponatinib arm (94%) were able to achieve BCR-ABL1 levels < 10% within 3 months. In imatinib arm 68% of the patients achieved the same goal. MMR and deeper molecular response rates were significantly higher in ponatinib compared to imatinib arm at all time points when the response was evaluated. Common (>25%) toxicities with ponatinib therapy were rash (38%), abdominal pain (36%), headache (33%), constipation (27%), lipase elevation (27%), muscle pain (26%), and low platelets (25%); with imatinib, there were muscle spasms (34%), nausea (34%), and diarrhea (27%). Grade 3 or 4 thrombocytopenia was more common for ponatinib than for imatinib, 12% and 7%, respectively. In ponatinib arm, 10 patients (7%) developed serious arterial thrombotic events, whereas only 1 patient (0.7%) developed the same condition in imatinib arm. In a single arm clinical trial, 51 newly diagnosed CML-CP patients were treated with ponatinib (45 mg daily). Patients were able to achieve fast and deep responses. By 3 months, 90% and 50% of the patients achieved CCyR and MMR, respectively. With a median follow-up of 16 months, none of the patients progressed to AP or BP, and all patients were alive. Forty-three patients (85%) required treatment interruptions, and median duration of treatment interruption was 9 days. All patients were taken off clinical trial, 38 per FDA recommendation due to the concerns of arterial thrombosis risk, and 13 due to side effects. Among these 13 patients, seven discontinued ponatinib after arterial ischemic events.

Which TKI to Choose for Frontline Therapy?

Factors Effecting Decision Making

Toxicity Profile—Compared to majority of antineoplastic drugs, TKIs are fairly well tolerated when appropriate monitoring and supportive care are employed. Each TKI carries a

distinct toxicity profile which should be considered carefully when making frontline treatment decision.

Peripheral and periorbital edema are the common side effects of imatinib, and reported in up to 40% of the patients treated with this agent^{16–17}. Edema is usually managed with diuresis or fluid restriction as it tends to be mild for the most of the patients. However, in certain cases, clinicians may need to reduce the dose or interrupt treatment^{46–48}. Imatinib may not be considered as a first choice for patients with severe edema due to venous insufficiency or any other chronic condition.

Hyperglycemia is known side effect of nilotinib or imatinib, however grade 3 or 4 hyperglycemia appears to be unique to nilotinib and not reported with other TKIs^{16–17}. Patients with poorly controlled diabetes should take nilotinib cautiously as it may potentially deteriorate glucose control. Largest frontline study evaluating the safety of nilotinib suggested low but considerable risk of cardiovascular events (CVE). CVEs were defined as ischemic cerebrovascular events, ischemic heart disease or peripheral artery disease. Five-year follow up data of ENESTnd trial showed that up to 13% of the patients treated with nilotinib developed CVEs compared to 2% with imatinib-treated patients. Despite the low frequency of CVEs, if there is any viable alternative, nilotinib may be avoided for patients with underlying CVEs.

Pleural effusion is a unique side effect of dasatinib. In the final update of DASISION trial (minimum follow-up of five years), pleural effusion was reported in almost 30% of the patients treated with dasatinib, and close to a 20% of those with pleural effusion required therapeutic drainage¹⁹. Overall 6% of dasatinib-treated patients had to discontinue the drug due to pleural effusion. TKIs other than dasatinib might be a better choice for the patients with pleural effusion (underlying primary lung disease) or for the ones who are likely to develop pleural effusion due underlying heart, liver or kidney failure. Dasatinib has been associated with the development of pulmonary arterial hypertension (PAH). In a case series, nine patients with no known underlying chronic cardiac or lung disease were reported to develop moderate to severe PAH after being treated with dasatinib (median 34 months)⁴⁹. Clinical and hemodynamic improvements were noted in eight patients after discontinuation of dasatinib. In DASSISION trial, 14 patients (5%) developed PAH in dasatinib arm, and six of them had to discontinue the therapy. Patients with underlying PAH may be required to avoid dasatinib if alternatives are available. Dasatinib has also been found to inhibit platelet function by impairing epinephrine- and arachidonic acid-induced aggregation⁵⁰. Even though less frequent, similar impaired platelet aggregation was observed with imatinib as well. Patients who need to take anti-platelet drugs such as aspirin or clopidogrel and dasatinib concomitantly should be monitored carefully for increased risk of bleeding.

Cost—The global cancer burden continues to increase due the growth and aging population, and it is expected to nearly double by 2030⁵¹. Likewise, the health care spending for cancer continues to increase. AHRQ (The agency for Healthcare research and Quality) estimates that the total of all health care costs for cancer in the United States in 2011 were \$88.7 billion. Within the last 10 years, the cost range of new anticancer drugs increased tremendously, from \$4,500 to \$10,000 per month⁵². In 2001, the price for imatinib was close

to \$30,000 per year, and this price was set to make all commercialization and research for this drug profitable considering the fact that average patient would be on it for 5–10 years⁵³. The use of imatinib has increased 10-year survival in CML patients from 20% to 85%. As a result, the prevalence of CML increased from 20,000 cases in 2000 to 70,000 cases in 2010. By 2030, it is predicted to reach up to 144,000 cases in the United States⁵. Consequently, the number of patients taking imatinib has increased. FDA also approved several other new indications for imatinib. Though, paradoxically, the annual price of imatinib tripled within a decade, and reached up to \$92,000 by 2013. The annual cost of dasatinib and nilotinib appeared to be slightly expensive than imatinib, \$123,000 and \$115,000, respectively⁵⁴. Imatinib may become generically available in 2016, and the price difference between newer TKIs and imatinib will become significant. Use of cheaper drugs is especially considerable in countries, such as United States, where health expenditures are one of the most common reasons for personal bankruptcies⁵⁵. To justify the cost difference of newer TKIs in the frontline setting in CML patients, a significant clinical benefit, such as survival, must be demonstrated. So far, the longest follow-up data for second generation TKIs shows no overall survival superiority to imatinib. Oncologists, then, need to weigh the advantages that some CML patients gain with dasatinib or nilotinib against the difference in the price.

Monitoring

Careful monitoring and compliance with the TKIs highly correlate with favorable responses to the treatment⁵⁶. Bone marrow examination is recommended every 3 months during first year of therapy, and it may be repeated every 1–3 years⁵⁷. In patients with durable CCyR, monitoring can only be performed by real-time quantitative polymerase chain reaction (RT-PCR) from peripheral blood every 3–6 months. In case of TKI intolerance or failure, patient compliance must be investigated carefully to prevent unnecessary changes in TKI therapy. European Leukemia Network (ELN) defines failure as following; not achieving complete hematologic or minor cytogenetic response (Philadelphia chromosome < 95%) by 3 months, not achieving major cytogenetic response or BCR-ABL1 > 10% by 6 months, and not achieving CCyR or BCR-ABL > 1% by 12 months⁵⁸ (Table 1). ELN recently designated a new response category called as “warning”. Patients fit into this category are not required to change TKI but need to undergo more frequent monitoring to allow timely change of treatment in case of failure.

Not Only Response but an Earlier and Deeper Response

Prior to the TKI era, only a minority of the patients was able to achieve CCyR with the IFN therapy, and time to achieve such response did not receive much attention⁵⁹. Similarly, in the early years of TKI era, the general thought was that achieving CCyR is good enough, regardless of when it happened. However, with the introduction of newer TKIs, it is now clear that the achieving response at an earlier time point correlates with superior outcome. Overall, second or third generation TKIs are more successful at inducing earlier responses compared to imatinib. In ENESTnd trial, at 3 months, 89% (400 mg dose) and 91% (300 mg dose) of nilotinib arm and 67% of imatinib arm achieved <10% BCR-ABL1 transcript level (no p value reported). Patients who achieved such response had better PFS and OS rates at four years than those who did not^{18, 60} (Table 2). In DASISION trial, at 3 months, dasatinib

induced deep molecular responses in higher proportion of patients. BCR-ABL1 transcript level was 10% in 84% of patients on dasatinib compared with 64% on imatinib. Patients with BCR-ABL1 transcript level 10% by 3 or 6 months had superior PFS and OS regardless of the TKI type. In another study with 8-year follow-up, 282 CML-CP patients were treated with frontline imatinib 400 mg daily⁶¹. Patients who achieved BCR-ABL1 < 9.8% at 3 months had significantly better OS (93% vs 57%, $p < 0.001$) and EFS (65% vs 7%, $p < 0.001$). Several other studies also reproduced similar findings, which brought up a reasonable question as what to do for patients who could not reduce BCR-ABL1 transcript level <10% by 3 months of TKI therapy^{62–65}. Current literature is controversial for those who fail to achieve optimal response by 3 months. In an analysis of 528 CML-CP patients treated with frontline imatinib, achieving BCR-ABL1 level <10% by 3 or 6 months was associated with superior outcome⁶⁶. Progression before the 6-month landmark occurred in only 4% of the patients who failed to achieve BCR-ABL1 < 10% at 3 months. Patients who continued therapy and achieved BCR-ABL1 <10% at 6-month landmark had superior outcomes, approximating those with BCR-ABL1 <10% at 3 months. However, patients who failed to have a transcript level <10% at both 3 and 6 months had significantly inferior survival. ELN suggests that in case of failure to achieve 3-month optimal response, a confirmatory test should be performed and patient should be monitored carefully. TKI switch might be warranted if BCR-ABL1 is still > 10% by 6 months.

Achieving CCyR, latest at 12 months, is another important goal as it correlates with improved survival⁷. Prompt TKI switch is the standard of care for patients who fail to achieve such response. In TKI era, our goals became more ambitious, aiming for deeper molecular responses. Achievement of MMR has been evaluated as another potential therapeutic goal in CML treatment. In a long term analysis of the IRIS trial, achieving both CCyR and MMR at 18 months was correlated with durable response⁶⁷. The possibility of losing CCyR by 7 years was 3% for patients who achieved MMR and CCyR at 18 months compared to 26% for patients who achieved CCyR but not MMR. Seven-year EFS probability was significantly superior for patients with MMR at 18 months compared to those without MMR (95% vs 86%, respectively). In contrast, OS and TFS were similar in both groups.

Patients who achieved CCyR at 12 months or earlier should be monitored with RT-PCR, bone marrow biopsy and cytogenetic analysis might be needed if disease progression was suspected. Patients who lost the complete hematologic response, CCyR or developed clonal evolution should switch TKI therapy. Delays in TKI switch in patients with loss of CCyR are associated with inferior EFS⁶⁸. Currently, there is no solid evidence suggesting TKI switch for patients with CCyR but no MMR or for those who lost MMR but remain in CCyR. However, fluctuations in BCR-ABL1 transcript levels during CCyR should be monitored closely, and may be evaluated for BCR-ABL1 kinase domain mutations⁶⁹.

Can We Cure CML?

With access to the TKIs, most patients with CML could have a near normal life expectancy⁷⁰. Current standard of care is to continue the treatment indefinitely as the ability of a TKI to eradicate the CML is unclear. In clinical practice, complete molecular remission

is defined as undetectable BCR-ABL1 transcript on quantitative RT-PCR. Achievement of a sustained CMR in some CML patients brought the possibility of TKI discontinuation. This idea was first evaluated in STIM trial by stopping imatinib in 100 CML patients who remained in CMR for 2 years or more while receiving therapy⁷¹. With a median follow-up of 50 months, 61 patients had molecular relapse. Fifty-eight patients relapsed within the first 7 months of discontinuation, and remaining 3 relapse were observed later at 19, 20 and 22 months. None of the relapsed patients progressed into AP or BP, and all were sensitive to TKI re-challenge. This study suggested that overall 40% of the patients with sustained CMR may not need indefinite TKI therapy. Similar outcome was also reported by the Australian TWISTER study⁷². In this prospective clinical trial, 40 CML-CP patients who had sustained CMR for 2 years or more discontinued imatinib. With a minimum follow-up of 15 months (median 43 months), 22 (55%) of 40 patients had molecular relapse. Of the 22 relapses, 15 (68%) occurred, early, 3 months (median) after discontinuation. Remaining 7 relapses occurred later (median 14 months). All patients with relapsed disease restarted on imatinib, and achieved CMR status at least in one measurement after restarting. None of the patients developed a kinase domain mutation or progressed to AP or BP. An interim analysis of the EURO-SKI trial, another TKI discontinuation study, has recently been reported with 6 months follow-up data⁷³. Patients who had sustained deep molecular response (BCR-ABL1 < 0.01%) for at least 1 year and under TKI therapy for at least 3 years were considered as eligible. Of the eligible 200 CML patients, 97% received imatinib, and 3% received second generation TKIs as frontline therapy. The median time to TKI discontinuation was 8 years. Relapse was defined as loss of MMR, and observed in 77 (39%) patients. In another recent trial, STOP 2G-Study, discontinuation of second generation TKIs has been reported with at least 12-month follow-up in 52 CML patients⁷⁴. Patients who had sustained CMR for at least 2 years were eligible, and loss of MMR was defined as relapse. Second generation TKIs were given due to imatinib intolerance (67%), imatinib failure (23%) or as frontline therapy (10%). With a median follow-up of 32 months, 24 patients relapsed (46%). None of the patients lost complete hematologic response or progressed to AP or BP. Prior history of imatinib failure was associated with remarkably lower chance of successful TKI discontinuation. Twelve-month probability of treatment-free survival was 42% in patients with history of imatinib failure compared to 67% in those with no history of imatinib failure (p=0.04). As of now, discontinuation of TKI is not part of routine CML management due to lack of standardized molecular testing for patient selection and relapse definition, and absence of long term results of mentioned clinical studies

Conclusions

Imatinib, nilotinib and dasatinib are great frontline therapy options for CML patients. As the treatment paradigm for CML continues to progress, most patients do well and expected to live close to normal lifespans. As a result, long-term quality of life measures and potential toxicities with chronic TKI use should be part of CML research. Imatinib is expected to be generic in 2016, and it is likely to be a cheap therapeutic option compared to the other TKIs approved for frontline use. Then, generic imatinib will obviously be more used unless the price for second generation TKIs drops substantially to a comparable level. Compliance with TKI therapy and monitoring per suggested guidelines are two most important factors for

success in CML therapy. With the advance of technology, now, we can detect very low level of residual disease. However, achieving CCyR by 12 months is still a major milestone in CML therapy. As of now, there is no strong recommendation to change TKI based on BCR-ABL1 levels alone measured at 3 months. Though, it has been showed repeatedly by several clinical studies that patients with deep molecular responses (BCR-ABL1 < 10%) at 3 or 6 months had significantly better survival regardless of TKI type being used. Increased incidence of CMR rates with newer TKIs brought the possibility of permanently discontinuation of the therapy in patients with durable responses. There are obviously several benefits of stopping TKI treatment, not the least of which is the avoiding cost burden of this expensive drug. However, due to lack of long term outcome data from TKI discontinuation trials and absence of consensus for the definition of optimal response and time to stop TKI, it not recommended discontinuing TKI outside of a clinical trial. It is essential to continue investigating therapies that increase deep and durable responses. Cure for CML may be achieved with more potent TKIs alone or TKI in combination with other investigational therapies such as check point inhibitors, JAK2 inhibitors, hedgehog inhibitors or vaccines. Upfront treatment with TKI plus a novel agent may improve the eradication of residual disease, and potentially avoid the need for life-long therapy with TKIs.

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Table 1Evaluation of Response to the Frontline CML Treatment (ELN 2013)⁵⁸

Landmarks	Switch TKI	Warning	Optimal Response
3-month	No CHR and/or Philadelphia chromosome > 95%	BCR-ABL1 > 10% and/or Philadelphia chromosome 36–95%	BCR-ABL1 10% and/or Philadelphia chromosome 35%
6-month	BCR-ABL1 > 10% and/or Philadelphia chromosome > 35%	BCR/ABL1 = 1–10% and/or Philadelphia chromosome 1–35%	BCR-ABL1 1% and/or Philadelphia chromosome 0%
12-month	BCR-ABL1 > 1% and/or Philadelphia chromosome > 0%	BCR-ABL1 = 0.1–1%	BCR-ABL1 0.1%

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

At any time; loss of CCyR (Philadelphia chromosome 0%), loss of CHR, loss of confirmed (in 2 consecutive tests) MMR (BCR-ABL1 0.1%), and emergence of clonal evolution in Philadelphia chromosome positive cells mean failure

Table 2

Early Molecular Responses with Frontline TKI Therapy and Associated Outcomes

Clinical Trial	BCR-ABL1	3-month Landmark Analysis				6-month Landmark Analysis			
		Patients, n (%)	PFS	p	OS	Patients (%)	PFS	p	OS
ENESTnd ¹⁸ (4-year follow-up)	Nilotinib 300 mg BID	234 (91)	95%	0.06	97%	250 (97)	95%	0.06	96%
	> 10%	24 (9)	83%		87%	7 (3)	75%		75%
	Nilotinib 400 mg BID	232 (89)	97%	0.04	97%	236 (93)	97%	<0.01	97%
	> 10%	28 (11)	89%		93%	17 (7)	82%		82%
DASISION ⁶⁰ (3-year follow-up)	Imatinib 400 mg QD	176 (67)	98%	<0.01	99%	216 (84)	97%	<0.01	98%
	> 10%	43 (16)	83%		84%	40 (16)	79%		70%
	Dasatinib 100 mg QD	198 (84)	93%	<0.01	96%	210 (89)	94%	<0.01	97%
	> 10%	37 (16)	68%		86%	26 (11)	66%		84%
	Imatinib 400 mg QD	154 (64)	96%	<0.01	96%	197 (83)	95%	<0.01	96%
	> 10%	85 (36)	75%		88%	41 (17)	65%		88%

TKI, tyrosine kinase inhibitor; n, number; PFS, progression free survival; p, p value; OS, overall survival; BID, twice daily; QD, daily