Identifying the Time to Change BCR-ABL Inhibitor Therapy in Patients with Chronic Myeloid Leukemia

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Key Words

BCR-ABL inhibitor · Chronic myeloid leukemia · Dasatinib · Imatinib · Nilotinib

Abstract

Many patients newly diagnosed with chronic myeloid leukemia in the chronic phase (CML-CP) respond to imatinib. Those experiencing imatinib resistance/intolerance require alternative treatments. Delayed responses increase the risk of transformation to advanced disease, mutation development and loss of response. In retrospective analyses, achieving faster, deeper responses correlated with improved long-term response and outcome. Changing therapy to obtain early responses may improve the depth and speed of response, ultimately improving the outcome. Although trials are ongoing, there are no prospective data indicating that changing from imatinib to later-generation inhibitors reverses the inferior prognosis and improves the outcome. We describe the rationale behind early therapy change in CML-CP.

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Introduction

Many patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) are currently treated with imatinib, a BCR-ABL tyrosine kinase inhibitor, based on results from the pivotal phase III International

Randomized Study of Interferon versus STI571 (IRIS) trial [1, 2]. After 8 years, the cumulative complete cytogenetic response (CCyR) rate for patients receiving imatinib was 83% [3]. The 5- and 8-year overall survival (OS) rates were 89 and 85% [3, 4], respectively, compared with a 5-year OS rate of 57% [2, 5] in patients receiving interferon- α plus cytarabine in previous randomized studies performed before the availability of imatinib. This demonstrates one of the greatest achievements in modern allopathic medicine.

Nonetheless, approximately one third of patients develop resistance or do not respond to imatinib, which in many cases is because of the presence or emergence of BCR-ABL mutations for which imatinib has no inhibitory effect [2, 3, 6, 7]. Further, some patients are intolerant of imatinib therapy as they experience persistent low-grade adverse events (AEs) which impact their quality of life [2, 3, 6, 7]. After an 8-year follow-up of the imatinib arm of the IRIS trial, 8% of patients lost complete hematologic response (CHR), 18% lost CCyR, 8% transformed to accelerated-phase or blast-phase (AP/BP) CML, and 6% discontinued the trial based on treatment-related AEs [3, 8]. When IRIS was conducted, there were limited treatment options available for CML-CP, and more patients may have continued study treatment despite persistent low-grade AEs or other events.

Although imatinib is an effective treatment for most patients with newly diagnosed CML-CP, some patients require alternative treatments because of intolerance or re-

sistance. An understanding of the mechanisms of imatinib resistance led to the development of newer BCR-ABL inhibitors, dasatinib, nilotinib, bosutinib, and ponatinib, which have increased specificity and/or potency for BCR-ABL and are effective against a majority of clinically observed BCR-ABL mutations [9–15]. Dasatinib, nilotinib, bosutinib, and ponatinib have been approved for patients with imatinib-resistant or imatinib-intolerant CML-CP since 2006, 2007, September of 2012 (US only), and December of 2012 (US only), respectively [16–22].

Both dasatinib and nilotinib have superior response rates over imatinib in patients with newly diagnosed CML-CP as demonstrated in randomized, multicenter phase III trials [23, 24]. Following the phase III Dasatinib versus Imatinib Study in Treatment-Naïve CML patients (DASISION) and Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients (ENESTnd) trials, both dasatinib and nilotinib were approved in 2010 as first-line treatments for patients with newly diagnosed CML-CP [17, 20]. Although a survival benefit has not yet been detected, 2-year follow-up of the DASISION and the ENESTnd trials showed that significant improvements in molecular remission rates for dasatinib and nilotinib over imatinib are maintained. In DASISION, the rates of major molecular response (MMR) were 64 versus 46% ($p < 0.0001$), and rates of molecular response ≥ 4.5 log reduction in BCR-ABL levels ($MR^{4.5}$; BCR-ABL levels $\leq 0.0032\%$) were 17 versus 8% ($p = 0.0032$) for dasatinib 100 mg once daily versus imatinib 400 mg once daily, respectively [25, 26]. After a 2-year follow-up of the ENESTnd trial, for nilotinib 300 mg twice daily versus 400 mg twice daily versus imatinib 400 mg once daily, rates of MMR were 71 versus 67 versus 44% ($p < 0.0001$ for both comparisons), and rates of $MR^{4.5}$ were 25 versus 19 versus 9% ($p < 0.0001$ for nilotinib 300 mg versus imatinib; $p = 0.0006$ for nilotinib 400 mg versus imatinib), respectively [27]. These results demonstrate that dasatinib and nilotinib are effective treatments in the first-line setting for patients with CML-CP and are now included as first-line treatment options for patients with newly diagnosed CML-CP in the updated National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) guidelines [28, 29] and European LeukemiaNet (ELN) recommendations [30].

New evidence supports initial use of more potent second-generation BCR-ABL inhibitors to achieve improved long-term outcomes [23–25, 27, 31, 32]. A delayed reduction in BCR-ABL level or other measures of tumor burden, as determined by cytogenetic and molecular response, increases the risk of disease progression whereas

a rapid reduction in tumor burden may have an additive value in reducing this risk [33–37]. Additionally, second-generation BCR-ABL inhibitors, which have notably broader mutational coverage than imatinib, may reduce the likelihood of emergent resistance, thereby further decreasing the risk of progression [37, 38].

With the advent of second-generation BCR-ABL inhibitors, the importance of achieving early, deep molecular and cytogenetic responses for long-term outcomes has received significant attention based on a number of exploratory, retrospective analyses in the first- and second-line treatment settings [31, 39–47]. The most recent NCCN and ESMO guidelines advise a change in treatment [alternative BCR-ABL inhibitor or allogeneic hematopoietic stem cell transplant (alloHSCT)] or clinical trial (NCCN) if a patient does not reach a deep level of molecular response [BCR-ABL transcript level $\leq 10\%$ on the International Scale (IS)] by 3 months [28, 29] or by 6 months according to the updated ELN recommendations [30]. Although a strong association between an early reduction in BCR-ABL transcript levels and improved survival has been indicated by several independent retrospective analyses, the benefit of changing treatments at these early time points has yet to be validated in a randomized clinical trial.

In this article, we review the current evidence for determining when to change BCR-ABL inhibitor therapy based on certain clinical indicators or measures of response, to support achievement of the best long-term outcomes and reduce the risk of transformation to advanced disease.

Achieving an Early, Deep Response May Be Associated with Improved Long-Term Response and Outcome

CML treatment recommendations incorporate the principle of achieving a specific level of response within a defined time frame [28–30]. Current CML treatment guidelines (NCCN, ESMO and ELN) define an optimal response, warning or suboptimal response and failure during first- and second-line treatment at specific treatment landmarks from 3 months up to and including 12–18 months (table 1) [28–30].

Independent studies have confirmed that patients on imatinib classified as having failure or suboptimal response at 3, 6 or 12 months, according to the 2009 ELN recommendations, have significantly worse outcomes than optimally responding patients [49–52]. These data suggest that increasing the proportion of patients who

Table 1. Definitions of response during treatment with BCR-ABL inhibitors according to ELN recommendations (a), NCCN guidelines (b) and ESMO guidelines (c) [28–30]

a ELN recommendations [30]

	Response		
	Optimal ¹	Warning ²	Failure ³
<i>First-line BCR-ABL inhibitor therapy and second-line when first-line treatment changed for intolerance</i>			
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%	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%
Then, at any time	BCR-ABL1 ≤0.1%	CCA/Ph– (–7, or 7q–)	Loss of CHR; loss of CCyR; confirmed loss of MMR ⁴ ; mutations; CCA/Ph+
<i>Second-line BCR-ABL inhibitor therapy</i>			
Baseline	NA	No CHR or loss of CHR on imatinib, or lack of CyR to first-line TKI, or high risk	NA
3 months	BCR-ABL1 ≤10% and/or Ph+ <65%	BCR-ABL1 >10% and/or Ph+ 65–95%	No CHR, or Ph+ >95%, or new mutations
6 months	BCR-ABL1 ≤10% and/or Ph+ <35%	Ph+ 35–65%	BCR-ABL1 >10%, and/or Ph+ >65%, and/or new mutations
12 months	BCR-ABL1 <1% and/or Ph+ 0	BCR-ABL1 1–10% and/or Ph+ 1–35%	BCR-ABL1 >10%, and/or Ph+ >35%, and/or new mutations
Then, at any time	BCR-ABL1 ≤0.1%	CCA/Ph– (–7 or 7q–) or BCR-ABL1 >0.1%	Loss of CHR, or loss of CCyR or PCyR; new mutations; confirmed loss of MMR ⁴ ; CCA/Ph+

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b NCCN guidelines [28]

	Response		
	Optimal ¹	Suboptimal ²	Failure ³
<i>First-line BCR-ABL inhibitor therapy</i>			
3 months	BCR-ABL ≤10%; PCyR (1–35%)	–	BCR-ABL >10%; <PCyR
12 months	CCyR and MMR	PCyR (1–35%)	No MMR; <PCyR (>35%); cytogenetic relapse
18 months	CCyR and MMR	–	No MMR with no CCyR at 12 months; PCyR (1–35%); cytogenetic relapse

Table 1. (continued)**c** ESMO guidelines [29]

	Response		
	Optimal ¹	Warning ²	Failure ³
<i>First-line BCR-ABL inhibitor therapy</i>			
3 months	Ph+ ≤95%; BCR-ABL <10%	–	Ph+ >95%; BCR-ABL >10%
6 months	Ph+ ≤35%; BCR-ABL <10%	Ph+ 35–65%	Ph+ >65%; BCR-ABL >10%
12 months	Ph+ 0; BCR-ABL ≤1%	–	Ph+ ≥1%; BCR-ABL >1%
Any time	–	Loss of MMR	Loss of CHR; loss of CCyR; mutations

Adapted with permission from Baccarani et al. [29]. These definitions are an adaptation of the ELN definitions of response to first-line imatinib.

NA = Not applicable; CCA/Ph+ = clonal chromosome abnormalities in Philadelphia chromosome-positive cells; CHR = complete hematologic response; CCA/Ph– = clonal chromosome abnormalities in Philadelphia chromosome-negative cells; CCyR = complete cytogenetic response; MMR = major molecular response (BCR-ABL1 ≤0.1% = MR³ or better); PCyR = partial cytogenetic response.

¹ Optimal response: continue treatment.

² Suboptimal response/warning: monitor patients more carefully, some patients may benefit from change in therapy (no confirmed evidence that a change in therapy will improve response).

³ Failure: change treatment.

⁴ In two consecutive tests, of which one with a BCR-ABL1 transcripts level ≥1%.

achieve a deeper response to therapy early has the potential to decrease the rate of transformation to AP/BP and other negative outcomes. In patients receiving second-line dasatinib after imatinib resistance or intolerance, those with an optimal versus suboptimal response versus treatment failure at 3 months had a higher probability of achieving CCyR (91, 51 and 9%, respectively) and MMR (71, 31 and 5%, respectively) within 2 years and a higher probability of 2-year OS (90, 80 and 67%, respectively) and progression-free survival (PFS; 97, 93 and 88%, respectively) [40]. In patients receiving second-line nilotinib after imatinib resistance or intolerance, those with a better than suboptimal versus suboptimal response versus treatment failure at 3 months had a higher probability of PFS at 12 months (93, 76 and 71%, respectively) and 24 months (79, 59 and 41%, respectively) [39].

The lack of early response may be a surrogate marker for poorer long-term response and outcome. Early achievement of cytogenetic and/or molecular response can lead to subsequent improved responses and long-term outcomes in CML-CP [3, 48] (table 2). Several studies indicate that achievement of CCyR or MMR within 12 months is associated with a higher probability of sta-

ble response, event-free survival (EFS), transformation-free survival, and OS [3, 6].

Reaching response milestones as early as 3 months from the initiation of BCR-ABL inhibitor treatment may further improve future responses and reduce transformation to advanced disease (table 3). In a study of patients receiving imatinib, the optimal predictive BCR-ABL transcript level cutoffs at 3, 6 and 12 months were established based on outcomes observed for the patient population, rather than using arbitrary predefined levels of log reduction. Data suggested that the transcript level cutoff of ≤9.84% at 3 months was the most informative for identifying patients with a high risk of progression and poor survival, compared with the 6- and 12-month cutoffs [46]. In patients treated with imatinib, achieving BCR-ABL transcript levels of ≤10% compared with >10% at 3 months was associated with improved 8-year OS (93.3 vs. 56.9%; $p < 0.001$), improved 8-year PFS (92.8 vs. 57.0%; $p < 0.001$), a lower risk of treatment failure by 18 months (5.8 vs. 20.7%; $p = 0.0003$), and a lower risk of disease progression (2.7 vs. 8.1%; $p = 0.0156$) [41, 46].

In a retrospective analysis of the phase III DASISION trial, achieving BCR-ABL transcript levels of ≤10% at

Table 2. Probability of achieving MMR and the risk of developing a progression event according to reduction in BCR-ABL transcript levels at fixed time points [48]

BCR-ABL1:ABL1 transcript ratio	Percentage probability of outcome according to transcript ratio at specified time points					
	MMR (BCR-ABL1:ABL1 <0.05%)			Event		
	3 months	6 months	12 months	3 months	6 months	12 months
≤0.1%	100 (3)	96 (6)	97 (12)	4 (13)	1 (38)	3 (40)
>0.1–1%	84 (6)	69 (12)	61 (18)	3 (46)	7 (30)	2 (48)
>1–10%	53 (17)	44 (18)	20 (33)	11 (21)	9 (34)	8 (47)
>10%	33 (15)	15 (18)	7 (46)	13 (47)	23 (14)	50 (19)

Adapted with permission from Quintas-Cardama et al. [48]. Figures in parentheses are median months to outcome. MMR = Major molecular response.

3 months, compared with levels of >10%, in both the dasatinib and imatinib arms, provided increased probability of achieving MMR by 2 years (dasatinib 76 and 16%, imatinib 66 and 19%, respectively), decreased risk of transformation to AP/BP CML within 3 years (dasatinib 3 and 14%, imatinib 3 and 13%, respectively) and increased probability of 3-year PFS (dasatinib 93 and 68%, $p = 0.0003$; imatinib 96 and 75%, $p < 0.0001$) and OS (dasatinib 96 and 86%, $p = 0.0348$; imatinib 96 and 88%, $p = 0.0036$, respectively) [44, 47]. Furthermore, deeper levels of response were achieved earlier with dasatinib compared with imatinib as equivalent BCR-ABL/ABL ratios were achieved 6 months earlier with dasatinib [44], and a higher proportion of patients treated with dasatinib achieved a BCR-ABL level of ≤10% at 3 months compared with imatinib (84 vs. 64%, respectively) [44, 47]. Similar results were observed with earlier and deeper cytogenetic responses in DASISION [47]. In the phase III STI571 Prospective International Randomised Trial 2 (SPIRIT 2) study of dasatinib 100 mg once daily versus imatinib 400 mg once daily for newly diagnosed CML-CP, after a median follow-up of 18.4 months, an early and deep response with first-line dasatinib (BCR-ABL ≤10% after 3 months) was associated with an increased probability of eventually achieving a CCyR. Patients with ≤10% BCR-ABL levels at 3 months had significantly improved cumulative rates of CCyR, MMR and MR^{4.5} by 2 years [45]. BCR-ABL transcript cutoff levels predictive of long-term response with dasatinib were significantly lower compared with those for imatinib (e.g. 2 vs. 10%), highlighting that response kinetics in patients receiving second-generation BCR-ABL inhibitors may differ from those in patients receiving imatinib [45].

Similarly, in a retrospective analysis of the ENESTnd trial, a more rapid decline in BCR-ABL levels was also dem-

onstrated. Median BCR-ABL levels for patients receiving nilotinib at 6 months (both arms; BCR-ABL ratio 0.19 IS) were similar to those for patients receiving imatinib at 18 months (BCR-ABL ratio 0.21 IS), and more patients receiving nilotinib 300 and 400 mg twice daily had BCR-ABL levels of ≤10% at 3 months compared with patients receiving imatinib (74, 78 and 61%, respectively) [31, 43].

These retrospective studies indicate that early achievement of a response with BCR-ABL inhibitor therapies is predictive of improved long-term outcome and reduced risk of transformation to advanced disease (table 3). Delaying treatment response may decrease the chance of achieving these longer-term outcomes. For patients failing to achieve an early molecular or cytogenetic response, an early change in therapy to a second-line treatment may increase the probability of long-term response and survival. Based on these findings from retrospective analyses, NCCN and ESMO guidelines were updated to include provisions to allow change in treatment for patients failing to achieve BCR-ABL levels of ≤10% (or partial CyR) after 3 months of BCR-ABL inhibitor therapy (table 1b, c) [28, 29]. The ELN recommendations suggest a change in treatment for patients failing to achieve BCR-ABL levels of ≤10% after 6 months of treatment (table 1a) [30].

Recommendations for Changing Treatment

The ELN recommendations and the NCCN and ESMO guidelines recommend either imatinib 400 mg once daily, dasatinib 100 mg once daily or nilotinib 300 mg twice daily for the first-line treatment of CML-CP [28–30]. For patients who are or become intolerant or resistant to first-

Table 3. Probability of long-term outcomes and responses according to 3-month BCR-ABL levels across several clinical trials [31, 41, 42, 44–47]

	BCR-ABL levels ≤10% at 3 months	Patients, %																		
		PFS		OS	Progression or transformation to AP/BP				MMR		MR ^{4,5}		CMR ^a							
		≤10%	>10%		p value	≤10%	>10%	p value	≤10%	>10%	p value	≤10%	>10%	p value						
DASISION [44, 47] 3-year follow-up																				
Imatinib	64	95.9	75.3	<0.0001	96.0	88.0	0.0036	2.6	12.9	-	2-year	66	19	-	-	-	-	-	-	-
Dasatinib	84	93.1	68.2	0.0003	95.9	85.9	0.0348	3.0	13.5		2-year	76	16							
ENESTnd [31] 2-year follow-up																				
Imatinib	61	-	-	-	-	-	-	-	-	-	>1-10%	52	20	-	-	-	-	-	-	-
Nilotinib 300 mg	74											67	29							
Hammersmith ^b [46] 8-year follow-up																				
Imatinib	-	≤9.54% 92.8	>9.54% 57.0	<0.001	≤9.84% 93.3	>9.84% 56.9	<0.001	-	-	-	≤2.81% 82.5	>2.81% 21.1	<0.001	-	≤0.61% 84.7 ^b	>0.61% 1.5 ^b	<0.001	<0.001	<0.001	<0.001
CML-IV [41, 42] 5-year follow-up																				
Imatinib	72	>1-10% 92	87	0.037	95.2	87.0	<0.001	2.7	8.1	0.0156	-	-	-	-	-	-	-	-	-	-
SPIRIT [45] 2-year follow-up																				
Dasatinib	91.4	-	-	-	-	-	-	-	-	-	79.8	14.3	<0.001	45.7	0	<0.001	6.1	0	0.45	0.45
AP/BP = Accelerated phase/blast phase; CMR = complete molecular response; MMR = major molecular response; MR ^{4,5} = molecular response of ≥4.5 log reduction in BCR-ABL levels (BCR-ABL levels of ≤0.0032%).																				
^a CMR was defined by finding two consecutive samples with no detectable transcripts having an ABL1 control with more than 40,000 copies.																				
^b For the Hammersmith study, the table shows the cutoff in BCR-ABL transcript levels that distinguish low- and high-risk groups with maximal sensitivity and specificity for each outcome.																				

AP/BP = Accelerated phase/blast phase; CMR = complete molecular response; MMR = major molecular response; MR^{4,5} = molecular response of ≥4.5 log reduction in BCR-ABL levels (BCR-ABL levels of ≤0.0032%).

^a CMR was defined by finding two consecutive samples with no detectable transcripts having an ABL1 control with more than 40,000 copies.

^b For the Hammersmith study, the table shows the cutoff in BCR-ABL transcript levels that distinguish low- and high-risk groups with maximal sensitivity and specificity for each outcome.

line BCR-ABL inhibitor treatment and do not achieve an optimal response, guidelines and recommendations suggest enrollment into a clinical trial, an increase in the imatinib dose, a change in BCR-ABL inhibitor therapy, or alloHSCT as alternative treatment options [28–30, 53, 54]. Given the recent data showing superior efficacy of nilotinib and dasatinib in patients with CML-CP, currently, high-dose imatinib has an uncertain role given the high rates of toxicity and risk of reduced adherence to treatment. AlloHSCT is a potentially curative treatment for patients with CML; however, considerable treatment-related mortality and morbidity and practical issues associated with alloHSCT, such as donor availability, have limited its utility. The tremendous long-term outcomes observed with first- and second-line BCR-ABL inhibitor therapy and the increasing number of available targeted therapies challenges the role of alloHSCT as second-line therapy.

Timing to initiation of a different BCR-ABL inhibitor following first-line treatment failure may affect long-term outcomes. Patients treated with dasatinib or nilotinib after cytogenetic relapse on imatinib have higher survival rates compared with patients treated after hematologic relapse (3-year survival: 92 vs. 52%), supporting the idea that an early change of therapy may be advantageous although patients with hematologic relapse most likely have worse disease [55]. A retrospective analysis of imatinib-resistant patients receiving dasatinib attempted to establish the optimal time for initiating dasatinib after loss of response [56]. Overall, 72% of patients who received dasatinib after loss of a major cytogenetic response (MCyR) on imatinib achieved a CCyR compared with 42% of patients who were treated after loss of both MCyR and CHR. EFS was also higher after earlier dasatinib treatment (24-month EFS rates: 89% after loss of MCyR on imatinib versus 29% after loss of both MCyR and CHR) [56]. An observational study (Factors Impacting on Response to Dasatinib in Europe) showed that in patients with CML-CP who had imatinib resistance/intolerance, delaying the time to dasatinib initiation negatively impacted the response to dasatinib [57]. A significant effect of time from imatinib failure to dasatinib initiation on the achievement of a better response to dasatinib was observed ($p < 0.023$). Furthermore, a 6- and 12-month delay in starting dasatinib resulted in a respective 7.5 and 14.4% decrease in the odds of achieving a better response (including CCyR/MMR). These studies suggest that optimal responses may be achieved earlier and the probability of improved long-term outcomes increased when a second-line BCR-ABL inhibitor is administered early after imatinib resistance or intolerance. Patients who have

clinical indicators or surrogate markers for poor responses and outcomes on imatinib may also benefit from changing to a different BCR-ABL inhibitor earlier.

The presence of low-grade AEs in patients treated with imatinib may also influence the speed of remission and long-term outcome. For example, lowering the imatinib dose to manage such AEs in patients who reached specific levels of response but have persistent low-grade nonhematologic toxicities could potentially risk a loss of response. This provides a rationale for changing to an alternative therapy (dasatinib, nilotinib, bosutinib, ponatinib) in these patients rather than lowering the imatinib dose. However, it must be recognized that dasatinib, nilotinib, bosutinib, and ponatinib have their own specific AE profiles and there is always concern with changing an effective therapy, particularly if the low-grade AEs are not impeding adherence to the prescribed treatment regimen. With more treatment options available for CML-CP, it is more likely that physicians will alter treatment to improve quality of life especially as CML typically requires lifelong treatment [58].

For second-line treatment of CML, BCR-ABL inhibitor selection should be based on disease phase, primary or secondary resistance, mutations, likelihood of patient adherence, comorbidities, side effect profile, and physician experience [53]. BCR-ABL mutational analysis at the time of treatment failure provides additional guidance in the selection of optimal second-line BCR-ABL inhibitor therapy in patients with identifiable mutations; furthermore, mutation testing is recommended in patients experiencing treatment failure and before changing therapy to a second-line BCR-ABL inhibitor [28–30, 53]. In patients with no identifiable mutations, the following should be considered when choosing second-line therapy: prior response to BCR-ABL inhibitors; BCR-ABL inhibitor used in the first-line setting; safety profile of each agent; comorbid conditions; likelihood of adherence to the prescribed regimen, and physician experience [28–30, 53]. In patients with a suboptimal response, but no identifiable imatinib-resistant mutations, imatinib dose escalation may be an option, but these patients should be closely monitored for toxicities. This option may become more favorable once imatinib becomes generically available, especially in patients with low-grade toxicities [59].

Future Directions

As noted, there are accumulating data to suggest that a change from imatinib therapy to second-generation BCR-ABL inhibitors in patients with suboptimal re-

sponse may improve long-term responses and outcome; however, these data are retrospective and still immature. There is also no direct evidence that a change from imatinib therapy to dasatinib, nilotinib, bosutinib, or ponatinib can reverse the inferior prognosis of these patients and provide better responses and outcomes comparable with patients who received first-line treatment with the second-generation BCR-ABL inhibitor. An open-label, randomized, prospective, multi-center, phase IIb trial has been designed to assess the benefits of an early change from imatinib to dasatinib in patients with >10% BCR-ABL levels at 3 months [60]. This study is being conducted in patients with CML-CP who have achieved CHR but have not achieved $\leq 10\%$ BCR-ABL levels at 3 months after first-line treatment with imatinib 400 mg once daily. Recruited patients are randomized to receive either dasatinib 100 mg once daily or imatinib, with the option to dose increase following a standard of care approach. The rate of MMR at 12 months from the start of first-line imatinib has been established as the primary endpoint. This trial may prospectively identify patients who should change therapy early to achieve maximal molecular response and improved survival. In addition, the trial may serve as a steward of continued imatinib use in the first-line setting for patients who tolerate the drug and have $\leq 10\%$ BCR-ABL levels after 3 months of treatment.

Discussion

Although most patients with newly diagnosed CML-CP respond to imatinib, others experience resistance or intolerance necessitating a change in treatment. Delaying responses to imatinib (failing to achieve $\leq 10\%$ BCR-ABL levels by 3 months or CCyR or MMR by 12 months) decreases PFS and OS and increases the risk of transformation to AP/BP and the loss of response [3, 6, 45, 46].

Changing Therapies

Achieving early molecular and cytogenetic response is correlated with improved response and long-term outcomes. Changing therapies upon failure to reach early response landmarks may allow patients to achieve optimal responses earlier. A randomized trial will enable a prospective analysis of the potential benefits of changing treatment to dasatinib in patients not achieving $\leq 10\%$ BCR-ABL levels after 3 months receiving imatinib. This will be of interest to physicians and payers and may guide future treatment recommendations.

For some patients, optimal responses are achieved with imatinib but persistent low-grade or acute grade 3/4 AEs become a problem. AEs and intolerance can reduce adherence to treatment leading to decreased response and transformation to AP/BP [61]. For patients who experience low-grade chronic AEs with imatinib, two phase IV clinical trials are investigating changing therapy to dasatinib (NCT01660906; CA180-400) or nilotinib (NCT00980018; MAC S0999). It is hoped that AEs will improve or resolve with a change in therapy and an optimal response will be maintained.

Beyond Second-Line Treatment

Salvage therapy with alternative second-generation BCR-ABL inhibitors may be successful in patients who are resistant to second-line dasatinib or nilotinib, according to the different spectra of mutations associated with clinical resistance [62, 63]. In a phase II study, patients who were resistant to both imatinib and dasatinib responded to third-line nilotinib treatment [64]. Similarly, bosutinib and ponatinib have demonstrated efficacy in patients who are resistant to imatinib and dasatinib and/or nilotinib [19, 21, 22, 65, 66]. Ponatinib has shown activity in patients harboring the highly resistant T315I BCR-ABL mutation [22, 65, 66]. Other novel agents (SGX393 and PHA-739358) capable of inhibiting the T315I-mutated BCR-ABL are being developed [67, 68]. With more effective first-line therapy, fewer patients may require salvage.

First-Line Treatment Selection

Optimizing first-line treatment is essential to achieving better long-term outcomes [69]. Therapy should be tailored to ensure patients achieve a deep, early response associated with improved long-term survival. More patients achieve a deeper, faster response in the first-line setting with second-generation BCR-ABL inhibitors compared with imatinib [23, 24]. Long-term follow-up is needed to determine if this correlates with a survival benefit and an improvement in PFS. Once generic imatinib is available, one possibility to reduce treatment cost may be identifying subgroups of patients who have poorer outcomes on imatinib who might derive greater benefit using dasatinib or nilotinib as first-line treatments.

Final Considerations

In both second- and first-line settings, choosing between dasatinib and nilotinib requires consideration on a patient-to-patient basis, as there is no comparative clinical trial evidence to direct this decision. Economic con-

siderations are anticipated to become a significant factor for treatment selection when generic imatinib becomes available in 2015. A prospective early change trial would help define a population of patients with equivalent response and survival when continuing on imatinib treatment compared with changing to a second-generation BCR-ABL inhibitor. For the remaining patients, this trial would present definitive evidence for the required level and timing of response, indicating a need to change from imatinib to a more potent BCR-ABL inhibitor and thus providing the best possibility of achieving improved long-term outcomes.

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