Clinical Outcomes of CML Patients After Delayed Start of Nilotinib Treatment

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ABSTRACT

In developing countries, TKI is limited and many patients have delayed start of therapy. Superiority of nilotinib in delayed treatment is not well studied. We have previously recognized the possible superior effect of delayed nilotinib, and decided to analyse long-term effects. In this study we presented long-term outcomes of 70 CML patients categorized into Group 1 (n= 31, front-line nilotinib) and Group 2 (n= 39, front-line imatinib, second-line nilotinib). CCyR and MMR at 24 months on nilotinib were higher in Group 1 (88% vs. 75% and 81% vs. 59%, respectively). We further subcategorized Group 1 and 2 and also compared patients based on the length of delay between diagnosis and the start of front-line TKI treatment (Group 1A and 1B; Group 2A and 2B). Subgroup A were patients who immediately received therapy and subgroup B were patients who waited > 6 months for initial TKI. Regarding effects of delayed front-line nilotinib treatment, CCyR and MMR at 24 months did not differ significantly among in Groups 1A and 1B (83% vs. 77% and 78% vs. 69%, respectively; p= 0.924, p= 0.215, and p= 0.305). In Group 2B, the response was worse on front-line imatinib; however, clinical outcomes were improved after they received second-line nilotinib therapy. Thus, in Group 2, second-line nilotinib seemed to annul the deleterious effects of delayed start of front-line imatinib. CML patients treated with front- or second-line nilotinib had optimal responses regardless of the length of the wait period.

Keywords: Nilotinib, CML, Delayed treatment, Clinical outcomes

INTRODUCTION

Nilotinib is a aminopyrimidine-derivative BCR-ABL1 tyrosine kinase inhibitor used for the treatment of patients with newly diagnosed chronic myeloid leukemia (CML).[1] In the form of the hydrochloride monohydrate salt, nilotinib was first approved in the United States and elsewhere in 2007 for patients with CML in the chronic or accelerated phase who had resistance to or could not tolerate imatinib.[2,3] Even though the design of this second generation BCR–ABL inhibitor is based on the imatinib structure, in vitro studies showed that nilotinib has 20 to 50 times the inhibitory activity of imatinib in imatinib-sensitive CML cell lines and 3 to 7 times the activity in imatinib-resistant cell lines.[4,5] Although the conformation of ABL1 that is bound by nilotinib resembles that of the ABL1-imatinib complex, a much-improved topographic fit provides additional free energy, thereby moving many BCR-ABL1 mutants into the range of achievable nilotinib plasma concentrations.[6]

A randomized study, ENESTnd showed that rates of major molecular response (the primary end point) were significantly higher in patients receiving 300 mg of nilotinib (44%) or 400 mg of nilotinib (43%) twice daily than in those receiving imatinib (22%) at 12 months.[7]

Based on these results and later updates of ENESTnd with up to 5 and 6 years of follow-up, nilotinib was approved for the front-line treatment of CML.[8-10] Nilotinib is an effective option for the initial management of CML in early chronic phase, producing high rates of CCyR and MMR, with most patients reaching these responses early during their therapy.[11,12]

The safety profile of nilotinib is distinct from that of imatinib.[13] Cardiovascular toxicity, with focus on arterial occlusive events such as ischemic heart disease (IHD), peripheral arterial occlusive disease (PAOD) and ischemic cerebrovascular events (ICVEs) at 3, 5 and 6 years follow-up were more frequent with nilotinib.[7,8,10]

TKI therapy, including imatinib and nilotinib, was gradually introduced in Bosnia because of financial considerations and lack of insurance cover, which was highlighted in the study by Kurtovic-Kozaric.[14] Briefly, waiting lists existed, so patients had to wait for TKI therapy for months or even years. Nilotinib was introduced in 2011 and many patients who were on the waiting list were placed on front-line nilotinib. Thus, we wanted to analyze the outcomes of these patients in comparison to patients who received imatinib. This is particularly interesting because our previous study has shown that the waiting period has a very drastic effect on the outcome of patients treated with delayed imatinib; that study also showed a preliminary analysis that nilotinib might alleviate the effects of delayed start of treatment. So, our previous study recognized the superiority of nilotinib over imatinib in patients on delayed therapy.[14] However, the follow-up period was only 12 months, which is a very short time to make concrete conclusions regarding the superiority of nilotinib over imatinib. In this analysis we comprehensively analyzed long-term outcomes of patients treated with nilotinib after a delayed start of treatment.[14]

PATIENTS AND METHODS

Patients in chronic phase of chronic myeloid leukemia (n= 70) who started their TKI treatment in period from June 2005 to August 2016 were included in this multicentre retrospective cohort study. Four Clinical Centers in the Federation of Bosnia and Herzegovina (Sarajevo, Tuzla, Mostar and Zenica) participated. Procedures performed in the study were in accordance with the 1964 Helsinki declaration and with the ethical standards of the Ethical Committee of the University Clinical Centre Sarajevo. Even though branded imatinib became available as front-line therapy in June 2005, not all of patients received drug. Due to the limited availability of imatinib, newly diagnosed patients were placed on the waiting list and received cytostatic hydroxycarbamide in the order to reduce leukemic mass. In September 2013, Federal Health Insurance Agency approved generic imatinib as front- and second-line therapy and since then, there is no waiting list for CML patients in Bosnia. Nilotinib was introduced in March 2011 as front-line therapy and as alternative therapy for patients who failed on imatinib therapy (second-line therapy). Diagnosis was conducted according to the standard procedures of the participating instututions because of the availability of cytogenetic and molecular testing. The period from onset to diagnosis was short due to standard clinical procedures, which did not significantly affect the time between diagnosis and start of therapy.

Patients were categorized into two study groups: Group 1 (n= 31) contained patients receiving nilotinib as front-line therapy and Group 2 (n= 39) included patients who started with imatinib (branded imatinib or generic imatinib) and then were switched to nilotinib at a certain time during their follow-up. Groups 1 and 2 were further subcategorized based on the amount of delay between time of diagnosis and the start of front-line nilotinib or front-line imatinib treatment (Group 1A and 1B; Group 2A and 2B). Subgroup A were patient who immediately received therapy (less than 6 months between diagnosis and the start of treatment) and subgroup B were patients who waited more than 6 months for initial nilotinib or imatinib therapy. Among patients in Group 2, five patients stopped TKI therapy after treatment failure on branded imatinib and were without treatment for median period of 19.5 months (range 6-36 months) before nilotinib was available. One patient voluntarily stopped treatment.

Imatinib was administered orally at dosage of 300, 400 and 600 mg/day. Front-line nilotinib patients

received orally 300 mg twice daily and second line nilotinib-treated patients received 400 mg or 600 mg twice daily. Nilotinib treatment was continued until disease progression or unacceptable toxicity. Disease progression was established as loss of CCyR and MMR. Cardiovascular toxicity included ischemic heart disease and peripheral arterial occlusive disease. Also, patients were categorized based on the waiting period between time of diagnosis and start of TKI therapy in two groups: patients who immediately started TKI therapy (0-5 months wait) and patients who waited 6 and more months for TKI therapy.

Patient variables that were collected included age, gender, town, canton, date of diagnosis, date of start of therapy, wait period for TKI treatment, monthly TKI dosage, adverse side effects and overall survival (events were defined by death from any cause). Patient data was collected from the database of the Federal Solidarity Fund. In order to assess clinical outcome, complete cytogenetic response (CCyR, defined as < 1% BCR-ABL1-positive nuclei of at least 200) and major molecular response (MMR, defined as ≤ 0-1% BCR-ABL1 expression) were evaluated.[15,16] Fluorescent in situ hybridization (FISH) for detection BCR-ABL1 positive nuclei and peripheral-blood reverse transcription real time polymerase chain reaction (RQ-PCR) for the BCR-ABL1 fusion transcript were performed at baseline, every 3 months until patients were achieved CCyR or MMR, and every 6 months thereafter.[17]

Survival probabilities were estimated with the Kaplan-Meier method and compared using the log-rank test. Data were analyzed using IBM SPSS v.21 (IBM Corp., Armonk, NY, USA). The probability of the achievement of a first CCyR was calculated by a cumulative incidence function (CIF).[18]

RESULTS

Seventy patients were enrolled in this study between June 2005 and August 2016, treated at four Clinical Centers in Federation of Bosnia and Herzegovina. The median age of enrolled patients was 54.5 years (range 18-76; Group 1= 54; Group 2= 55). Sixty one percent of patients were males. Additional chromosomal abnormalities in Ph+ cells were reported in 4% of patients (3/70). The median follow-up from the time of diagnosis was 51 months (range 3-135 months) and from the start of therapy was 39 months (range 3-51 months). Patient characteristics at the last contact are shown in Table 1.

Group 1 (n= 31) consisted of newly diagnosed CML patients on front-line nilotinib; 84% of patients (26/31) were treated with the initial 300 mg dose twice daily. In five patients, nilotinib dose was escalated to 400 mg due to the absence of an optimal response; one patient was still on nilotinib treatment with an optimal response and four patients were without significant improvements and subsequently discontinued nilotinib and switched to imatinib. Among those four patients, three patients were switched to imatinib as a result of treatment failure and one patient had side effects (heart failure). One patient on imatinib as second-line therapy died due to TKI resistance (mutations were detected). Besides this patient, three more patients who stayed on front-line nilotinib died (Table 2). Estimated overall survival at cut-off date for this study was 85% for patients in Group 1 (Table 2). Results regarding the achievement and loss of CCyR and MMR on nilotinib therapy during the follow-up are presented in Table 2. After 6 months of follow-up on nilotinib, 55% (17/31) of patients achieved CCyR and 6% (2/31) achieved MMR. After 12 and 24 months, 81% (25/31) was in CCyR and achievement of MMR was 39% (12/31) and 74% (23/31), respectively (Table 3). Overall, in Group 1, 24/31 patients (77%) achieved a MR4.0 at least once and 21/24 (88%) achieved a sustained MR4.0; 14/31 patients (45%) achieved a MR4.5 and 14/14 (100%) a sustained MR4.5; 8/31 patients (26%) achieved MR5.0 and all of them sustained MR5.0.

Group 2 (n= 39) consisted of patients treated with front-line imatinib therapy who were switched to nilotinib as second-line therapy due to treatment failure (n= 36), side effects (n= 2), and other reasons (n= 1). Patients were treated with both, branded and generic imatinib, prior to nilotinib therapy (27 and 12 patients, respectively). Median follow-up on imatinib therapy was 24 months (range 3-93). Reasons for switch to nilotinib were treatment failure 79% (31/39) and side effects of imatinib thera-

Table 1. Patient characteristics based on the tyrosine kinase inhibitor (TKI) therapy and treatment delay

Characteristics		GROUP 1 Front-line nilotinib	GROUP 2 Second-line nilotinib	
			Without pause between imatinib and nilotinib	Pause between imatinib and nilotinib
Patients (n= 70)		31/70 (44%)	39/70 (56%)	
			33/39 (85%)	6/39 (15%)
Median follow-up on nilotinib in months (range)		39 (3-48)	18 (3-51)	
			15 (3-48)	45 (39-51)
Median follow-up in months on imatinib, in months (range)		–	24 (3-93)	
			18 (3-93)	46.5 (12-63)
Follow-up on imatinib, after nilotinib	Patients (n)	4/31 (13%)	2/39 (5%)	0/39 (0%)
	Median in months (range)	12 (12-18)	13.5 (3-24)	
			13.5 (3-24)	0
Discontinued imatinib	Patients (n)	–	–	6/39 (15%)
	Median length of discontinuance in months (range)	–	–	19.5 (6-36)
Wait period 0-6 months	Patients (n)	18/31 (58%)	26/33 (79%)	5/6 (83%)
	Median (range)	0 (0-6)	0 (0-6)	0
	EUTOS score (median)*	38.5	40	
Wait period > 6 months	Patients (n)	13/31 (42%)	7/33 (21%)	1/6 (17%)
	Median (range)	15 (9-60)	18 (9-36)	48
	EUTOS score (median)	38.1	10.15	

* We did not find statistically significant difference between EUTOS scores in Group 1 and Group 2 (p> 0.05)

py 5% (2/39). Remaining five patients (6/39, 15%) had suboptimal response on front-line imatinib and discontinued therapy and one patient voluntarily stopped treatment despite achieving MMR (Table 1, Group 2B). Median period of discontinuation was 19.5 months (range 6-36). These patients were covered with cytostatic hydroxycarbamide and started with nilotinib when it became available as second-generation therapy in Bosnia and Herzegovina. Two patients in Group 2 (2/39) were switched back to imatinib (third-line therapy) because of side effects of nilotinib therapy. Estimated overall survival at cut-off date in Group 2 was 85% at cut-off date for this study (Table 2). Results regarding the achievement and loss of CCyR and MMR on imatinib and nilotinib therapy during the follow-up are presented in Table 2. Five patients (5/39) died due to treatment failure (3/5) and side effects of nilotinib therapy like heart failure (2/5). After 6 months of follow-up, 41% (16/39) was in CCyR and 28% (11/39) in MMR. At 12 months of follow-up, 62% (24/39) of patients was in CCyR, and 31% (12/39) was in MMR. Achievement of CCyR and MMR at 24 months on nilotinib therapy was 67% (26/39) and 49% (19/39), respectively (Table 3). In Group 2, 18/39 patients (46%) achieved a MR4.0 at least once and 13/18 (72%) achieved a sustained MR4.0; 5/39 patients (13%) achieved a MR4.5 and 4/5 (80%) sustained MR4.5; 4/39 patients (10%) achieved MR5.0 and all of them sustained MR5.0. If we compare the estimated achievement of CCyR and MMR of Group 1 and Group 2, we find no statistical difference.

We also compared the efficacy of front-line and second-line nilotinib in this study by categorizing the treatment delay into two subgroups: patients who waited less and more than 6 months for TKI therapy (Group 1A and 1B; Group 2A and 2B). Pa-

Table 2. Clinical outcomes of CML patients on front-line and second-line nilotinib at cut-off date of the study

Characteristics		GROUP 1 Front-line nilotinib	GROUP 2 Second-line nilotinib	
			Without pause between imatinib and nilotinib	Pause between imatinib and nilotinib
Death		4/31 (13 %)	5/39 (13%)	
			5/33 (15%)	0/6 (0%)
CCyR on imatinib prior to nilotinib	Patients (n)	-	20/39 (51%)	
			17/33 (52%)	3/6 (50%)
	Achievement of CCyR in months (range)	-	12 (2-81)	
			12 (2-81)	28.5 (9-54)
Lost CCyR on imatinib prior to nilotinib (after they achieved CCyR)	Patients (n)	-	3/20 (15 %)	
			2/17 (12%)	1/3 (33%)
	Median loss of CCyR in months (range)	-	27 (3-38)	
			27 (3-38)	27
	Median duration of CCyR loss in months (range)	-	9 (1-27)	
			9 (1-27)	9
MMR on imatinib prior nilotinib	Patients (n)	-	12/39 (31%)	
			10/33 (30%)	2/6 (33%)
	Achievement of MMR in months (range)	-	15 (3-81)	
			15 (3-81)	28.5 (9-63)
Lost MMR on imatinib prior to nilotinib (after they achieved MMR)	Patients (n)	-	6/12 (50 %)	
			5/10 (50%)	1/2 (50%)
	Loss of MMR (months, range)	-	25.5 (3-63)	
			24 (3-63)	27
	Median duration of MMR loss in months (range)	-	9 (1-27)	
			9 (1-27)	9
CCyR on nilotinib	Patients (n)	25/31 (80%)	*26/39 (67%)	
			24/33 (73%)	2/6 (33%)
	Time to CCyR from therapy (median in months, range)	6 (3-33)	6 (3-45)	
			6 (3-18)	45 (15-45)
	Duration of CCyR (median in months, range)	36 (27-36)	12 (12-21)	
			12	21
Lost CCyR on nilotinib) (after they achieved CCyR	Patients (n)	3/25 (12%)	4/26 (15%)	
			3/24 (13%)	1/2 (50%)
	Median loss of CCyR in months (range)	36 (27-36)	6 (6-36)	
			6 (6-36)	6
	Duration of CCyR loss in months (range)	6 (3-21)	4.5 (1-9)	
			3 (1-9)	6
MMR on nilotinib	Patients (n)	25/31 (80%)	**22/39 (56%)	
			20/33 (61%)	2/6 (33%)
	Achievement of MMR in months (range)	15 (3-45)	9 (3-45)	
			8 (3-42)	45 (27-45)
Lost MMR on nilotinib (after they achieved MMR)	Patients (n)	5/25 (20%)	4/22 (18%)	
			4/20 (20%)	0/2 (0%)
	Median loss of MMR in months (range)	27 (15-33)	9 (6-33)	
			9 (6-33)	-
	Median duration of MMR loss in months (range)	15 (6-24)	4.5 (3-9)	
			4.5 (3-9)	-

* Seven patients have already achieved CCyR on imatinib (six patients in subgroup without pause and one in subgroup with the pause between treatments)
** Four patients have already achieved MMR on imatinib (three patients in subgroup without pause and one in subgroup with the pause between treatments)

tients in Group 1B were placed on the waiting list for front-line nilotinib therapy and waited for more than 6 months to start the treatment. However, patients in Group 2B waited for more than 6 months to start with the front-line imatinib therapy, and they were immediately switched to second-line nilotinib after treatment failure or side effects of front-line therapy. Patients on second-line nilotinib who achieved CCyR (four patients; Table 2) and MMR (seven patients; Table 2) on imatinib and patients who discontinued TKI therapy (long lag time between front-line and second line TKI; n= 6; Table 2) were excluded from this analysis.

Achievement of CCyR at 24 months for patients on front-line nilotinib (no wait, Group 1A), patients on second-line nilotinib (no wait, Group 2A), patients on front-line nilotinib > 6 months wait (Group 1B) and patients on second- line nilotinib > 6 months wait (Group 2B), was not statistically different (91%, 84%, 87 %, and 100%, respectively. Also, at 24 months, 85% of patients on front-line nilotinib (no wait, Group 1A), 71% of patients on second-line nilotinib (no wait, Group 2A), 75% of patients front-line nilotinib > 6 months wait (Group 1B) and 100% of patients on second-line nilotinib > 6 months wait (Group 2B) achieved MMR. When we compared Group 1A and 1B we did not find statistically significant differences regarding OS, CCyR and MMR (p= 0.924, p= 0.215, and p= 0.305, respectively).

DISCUSSION

Nilotinib as second generation TKI was rationally designed to be a more potent and selective BCR–ABL1 inhibitor than imatinib and to address the unmet needs of patients who did not achieve optimum responses or became resistant to imatinib treatment. Nilotinib was introduced in Bosnia and Herzegovina as front-line and second-line therapy in March 2011. Many patients who were on the waiting list to start TKI therapy were placed on front-line nilotinib. Our previous study showed that front-line nilotinib may alleviate deleterious effects of delayed front-line imatinib; however, the follow-up period was only 12 months.[14] Thus, we conducted this long-term study, which analyzed newly diagnosed CML patients on nilotinib as front-line (Group 1) or second-line therapy (Group 2), where 35 patients waited for front-line TKI therapy (imatinib or nilotinib) for median period of 12 months (range 1-62) from diagnosis.

When we analyzed effects of delayed treatment, our results showed that the achievement of CCyR at 24 months for patients on immediate front-line nilotinib therapy and patients on delayed front-line nilotinib was 91% and 84%, respectively. At 24 months, 85% of patients on immediate front-line nilotinib and 75% of patients on delayed front-line nilotinib achieved MMR. In study by Kurtovic-Kozaric et al., at 12 months, CCyR and MMR achievement on nilotinib therapy was superior compared to imatinib treatment (80% in immediate and 91% in > 13 months wait group achieved CCyR; 43% of patients with immediate treatment achieved MMR and 38% of patients who waited >13 months), which is similar to results obtained in our study.[14]

The waiting lists for targeted cancer therapies have existed since 2004 in Bosnia and Herzegovina, and the wait period could be from several months to years. CML patients who can be treated with the available drugs have to wait for the therapy.[19] Generic imatinib therapy became available in 2013 and since then there are no waiting lists for CML and GIST patients. Results from previous studies in Bosnia showed that there was no significant difference in the overall survival and achievement of CCyR between front-line branded imatinib and front-line generic imatinib.[20-22]

Delayed targeted treatment significantly affected all CML patient outcomes, including survival and cytogenetic and molecular response. However, recent study that analyzed effects of delayed therapy in GIST patients showed that patients who received immediate imatinib therapy for < 1 year did not show better clinical outcomes compared to patients who received the same duration of therapy but had to wait > 6 months for the start of therapy.[23] Differences in the effects of delayed treatment are probably due to the biology of the disease.

Several studies confirmed a high and rapid efficacy of immediate nilotinib treatment. Results from the European ENEST1st (The Evaluating Nilotinib Efficacy and Safety in Clinical Trials

Table 3. Clinical outcomes of CML patients on front-line and second-line nilotinib at 24 months of follow-up

Clinical outcomes		GROUP 1 Front-line nilotinib	GROUP 2 Second-line nilotinib	
			Without pause between imatinib and nilotinib	Pause between imatinib and nilotinib
Death		0/31 (0%)	4/39 (10%)	
			4/33 (12%)	0/6 (0%)
CCyR on imatinib prior to nilotinib	Patients (n)	–	13/39 (39%)	
			11/33 (33%)	2/6 (33%)
	Achievement of CCyR in months (range)	–	9 (2-18)	
			11 (2-18)	9
MMR on imatinib prior nilotinib	Patients (n)	–	6/39 (15%)	
			4/33 (12%)	2/6 (33%)
	Achievement of MMR	–	10.5 (9-15)	
	in months (range)		13 (9-15)	9
CCyR on nilotinib	Patients (n)	25/31 (81%)	26/39 (67%)	
			25/33 (76%)	1/6 (17%)
	Achievement of CCyR	6 (3-12)	6 (3-15)	
	in months (range)		6 (3-15)	15
MMR on nilotinib	Patients (n)	23/31 (74%)	19/39 (49%)	
			18/33 (55%)	1/6 (17%)
	Achievement of MMR	12 (3-21)	9 (3-24)	
	in months (range)		9 (3-24)	–

as First-Line Treatment) study showed that by 24 months, 55.2% of 1089 patients achieved MR4.0 and 38.6% achieved MR4.5, which is similar to our results (67% of patients achieved and sustained MR4.0 and 45% of patients achieved a MR4.5).[13] In a study conducted on 130 CML patients in early chronic phase, nilotinib were administered in dose 300 mg twice daily, a deep molecular response was achieved in 46% (MR4.0) and 17% (MR4.5) of patients at 2 years, which is lower than our results.[12] Another study by Cortes et al. showed that out of 51 patients with newly diagnosed CML-CP who were treated with nilotinib 400 mg twice, 93% achieved CCyR and 79% achieved MMR at 24 months, similar to our results (81% of patients was in CCyR and 74% was in MMR at 24 months).[11] Results from 6-year follow-up of ENESTnd showed that MMR rate on nilotinib 300 mg twice daily was 77.3% and it is similar to results given in our study where 77% of patients on front-line nilotinib achieved MR4.0.[10] In Turkish national Phase II study of nilotinib as effective front-line treatment option for CML-CP patients, MMR and MR4.5 rates at 24 months were higher compared to results obtained in our study (83% and 50.9 %, respectively).[24]

With a median observation of 39 months (range 3-48 months), in Group 1 87% (27/31) of patients were still on treatment with front-line nilotinib. In Group 1 (front-line nilotinib treatment) four patients died (4/31). One patient who died due to TKI resistance was on imatinib as second-line therapy (mutations T315I, E315I and E255K were detected). Other three patients were on nilotinib when they died. One of these patients progressed to accelerated phase after 27 months of therapy, lost hematological response and died. Other one patient, a 53 year old man, was diagnosed with amyotrophic syndrome, and this patient died due to progressive muscular dystrophy (lung insufficiency). Remaining one patient died without disease progression and without detectable BCR-ABL1 mutations, due to a worsening of general clinical conditions.

In Group 2, five patients died (three of them had suboptimal response, and two due to heart failure). Also, five patients had suboptimal response to imatinib as front-line therapy and they had to

discontinue therapy (median period of discontinuation was 19.5 months) until nilotinib has become available in Bosnia, when they were switched. Interestingly, none of these patients died. Two patients from Group 2 were again switched to imatinib therapy due to adverse reaction on nilotinib therapy. Among them, one patient achieved complete cytogenetic response and the other one had durable molecular response after the second switch.

Compared to results from our previous study, CCyR occurred at a higher overall rate and considerably faster with nilotinib than with standard-dose imatinib (24-month CCyR: 81% with nilotinib vs. 69% with branded imatinib and 70% with generic imatinib).[19]

Our study also showed that nilotinib is a more potent TKI inhibitor than imatinib. In general, higher achievement of CCyR and MMR were detected in group of patients on front-line nilotinib compared to front-line imatinib. Also, patients on front-line nilotinib achieved CCyR and MMR in shorter period of time (Table 3). Possible reason could be that mutations that accumulate during wait period are responsible for resistance to imatinib, but are sensitive to nilotinib therapy.[25] Otherwise, it could be due to gene expression changes that occur as the result of disease progression. Studies of CML patients who relapsed after initially successful treatment with imatinib demonstrated a gene expression pattern closely related to advanced phase disease.[26]

In conclusion, patients treated with nilotinib who waited for therapy had optimal response regardless of the length of the wait period prior to the start of therapy, unlike patients treated with front-line imatinib. Similar to the cytogenetic responses, the achievement of MMR in patients treated with nilotinib in the different wait groups was indistinguishable.

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