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Estimated Glomerular Filtration Rate Changes in Patients with Chronic Myeloid Leukemia Treated with Tyrosine Kinase Inhibitors

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Abstract

Background—Chronic use of tyrosine kinase inhibitor (TKI) may lead to previously unrecognized adverse events. We evaluated the incidence of acute kidney injury (AKI) and chronic kidney disease (CKD) in chronic phase (CP) chronic myeloid leukemia (CML) patients treated with imatinib, dasatinib and nilotinib.

Methods—Four hundred and sixty-eight newly diagnosed CP CML patients treated with TKIs were analyzed. Molecular and cytogenetic response data, creatinine, glomerular filtration rate (GFR) were followed from start of therapy to last follow-up (median 52 months). GFR was estimated using the Modification of Diet in Renal Disease (MDRD) equation.

Results—Nineteen patients (4%) had TKI-associated AKI. Imatinib was associated with higher incidence of AKI compared to dasatinib and nilotinib (p=0.014). 58 patients (14%) developed CKD while receiving TKI, 49 of them (84%) while treated with imatinib (p<0.001). Besides imatinib, age, history of hypertension and diabetes mellitus were also associated with development of CKD. In patients with no CKD at baseline, imatinib was shown to decrease GFR overtime. Interestingly, imatinib did not cause significant decline in GFR of patients with history of CKD. Imatinib, dasatinib and nilotinib increased mean GFR after three months of treatment, and nilotinib led with the most significant increase (p<0.001). Acute or chronic kidney disease had no significant impact on overall cytogenetic and molecular response rates or survival.

Conclusion—Administration of TKI may be safe in the setting of CKD in CP CML patients, but close monitoring is still warranted.

Introduction

Tyrosine kinase inhibitors (TKI) have revolutionized the treatment of chronic myeloid leukemia (CML). Imatinib was the first TKI to be successfully used in clinical medicine providing not only progression-free and overall survival advantage but also fewer adverse effects compared with previous standard therapy with cytarabine and interferon (IFN)[1]. Second generation TKIs such as nilotinib, dasatinib and bosutinib, were later introduced demonstrating efficacy and safety for patients resistant to or intolerant of imatinib[2-3], and more recently as initial therapy[4-5].

Although TKIs are generally well tolerated and have fewer adverse events compared to IFN-based therapy, these drugs demonstrate off-target effects. TKIs were designed to target BCR-ABL, a chimeric protein, produced from the BCR-ABL fusion gene, originated from balanced translocation involving the chromosome 9 and 22, t(9;22)(q34;q11)[6]. However, off-target kinases (e.g., PDGFR-α, PDGFR-β, KIT, DDR-1, DDR-2, and CSF1) are also affected[7-8].

Overall, imatinib has been well tolerated in clinical trials, and the side effect profile has usually been mild to moderate. Gastrointestinal symptoms (nausea, vomiting and diarrhea), rash, muscle cramps and edema have been commonly occurring adverse effects[9]. A series of case reports propose that imatinib may be leading to acute kidney injury (AKI)[10-15]. Authors suggested that this side effect may be due to two mechanisms: toxic tubular damage and tumor lysis syndrome (TLS). Renal tubular cells are susceptible to the toxic effects of medications as tubular cells are exposed to high levels of toxins by concentrating and absorbing glomerular filtrate[16]. It has been shown that PDGF receptors are important in renal tubular cell regeneration after acute tubular necrosis (ATN)[17]. Thus, imatinib may interfere with PDGFR-mediated repair mechanisms.

There is lack of data regarding the effect of long term TKI treatment on kidney function and the incidence and prognosis of chronic kidney disease (CKD) in CML patients. One study has suggested decreased estimated glomerular filtration rate (GFR) in patients treated with imatinib[18], and there are no similar analysis for second generation TKIs. In our study, we aimed to evaluate the incidence of AKI and CKD in chronic phase (CP) CML patients being treated with imatinib (standard and high-dose), dasatinib and nilotinib as initial therapy. We also evaluated the GFR changes over time and its impact on outcome in these patients.

Patients and Methods

Study Group

We reviewed medical records of 475 consecutive patients with early CP CML treated with frontline TKI in consecutive prospective clinical trials at MD Anderson Cancer Center (MDACC) between 2001 and 2011. Seven patients were excluded from analysis as they received TKI for less than 3 months due to non-kidney related toxicities (n=2) and patient

preference (n=5). Starting dose of imatinib was 400 mg twice daily in 207 patients and 400 mg once daily in 49 patients. Patients treated with dasatinib received 100 mg (100 mg daily or 50 mg twice daily) and those treated with nilotinib received 800 mg (400 mg twice daily) total daily dose. In order to be eligible, patients should have been diagnosed with Philadelphia Chromosome positive (Ph (+)) or BCR-ABL positive early CP CML (time from diagnosis <12 months). Patients should have received no or minimal prior therapy which was defined as <1 month (30 days) of prior interferon alpha (with or without cytarabine) and or hydroxyurea. Other eligibility criteria included performance status 0-2, age 15 years, adequate end organ function (creatinine <1.5 × upper limit of normal (ULN), total bilirubin <1.5 × ULN, SGPT <2.5 × ULN). Patients with New York Heart Association (NYHA) class 3-4 heart disease, late CP (time from diagnosis >12 months), accelerated phase (AP) and blast phase (BP) were excluded. All treatment studies and this chart-review study were approved by Institutional Review Board of the MDACC. All patients signed an informed consent for the interventional studies; a waiver of informed consent was granted for the retrospective chart review.

Follow-Up

Patients had a complete blood count and complete metabolic profile every 1-2 weeks for the first three months and then every 6-12 weeks. Laboratory data from start of TKI were recorded and included in the analysis for all patients as long as they stayed on clinical trial. Information about other medications and clinical events that may be responsible for kidney function changes was also collected. Bone marrow aspiration with karyotype and reverse transcription polymerase chain reaction (RT-PCR) for BCR-ABL fusion transcripts from peripheral blood were performed at diagnosis, every 3 months for the first year, and every 6 months thereafter.

Definitions

Primary laboratory outcomes were creatinine and GFR changes. Creatinine is not a sensitive test to determine kidney function as a significant portion of kidney function needs to be affected before it detects any decline in GFR[18]. In this study, GFR was estimated using the Modification of Diet in Renal Disease (MDRD) equation, which was shown to be a more accurate estimate compared to the Cockcroft-Gault method and other commonly used equations[19]. Primary clinical end points were AKI and CKD. AKI[20] was defined as an increase in serum creatinine of 0.3 mg/dl, and CKD[21] defined as an estimated GFR <60 ml/min/1.73 m² persisting for at least 90 days.

Molecular responses were defined as follows: Deep molecular response (MR[4.5]) BCR-ABL1 transcript level 0.0032% international scale (IS), major molecular response (MMR) BCR-AB1[IS] transcript level 0.1%. BCR-ABL1 transcript levels were calculated by IS since 2005 when this standardization became available. Karyotype analysis was performed by G-banding in bone marrow cells with 20 metaphases analyzed. Cytogenetic response was defined as follows: minor cytogenetic response Ph-positive metaphases >35%, major cytogenetic response (MCyR) Ph-positive metaphases between 0-35%, and complete cytogenetic response (CCyR) 0% Ph-positive metaphases[22].

Statistical Analysis

The statistical analysis was performed by using SPSS software (Version 21.0. Armonk, NY: IBM Corp) and Statistical analysis was performed using STATA/SE version 13.1 statistical software (Stata Corp. LP, College Station, TX). Categorical variables were reported as percentages and counts. Continuous variables reported as median (minimum-maximum) or mean. Kruskal-Wallis test and Chi-square tests were used to evaluate associations between TKI types. Univariate and multivariate logistic regression analysis was used to determine the relationship between clinical features (diabetes mellitus (DM), coronary artery disease (CAD), hypertension (HTN), age and type of TKI) and the development of AKI or CKD. Repeated-measures ANOVA was used to evaluate the effects of TKI type over time on GFR changes. Survival probabilities and medians were estimated by the Kaplan-Meier limit product method. Event-free survival (EFS) was calculated from beginning of treatment to the date of any of the following events: transformation to AP or BP, loss of MCyR or death while on TKI. Transformation-free survival (TFS) was calculated from the start of treatment to the date of progression to AP/BP during therapy, last follow-up, or death from any cause. Overall survival (OS) was calculated until death from any cause at any time. Univariate and multivariate Cox proportional hazard models were used to identify any association with each potential clinical features and survival (EFS, TFS and OS). All tests are 2 sided and a p-value   0.05 was considered as statistically significant.

Results

A total of 468 early CP CML patients consecutively enrolled in trials with imatinib (n=253), dasatinib (n=99) and nilotinib (n=116) were included in this analysis. Clinical characteristics of patients treated with the different modalities were similar as eligibility criteria were nearly identical for all clinical trials (Table 1). Sokal[23] risk score was calculated for all patients, and no significant difference was noted among the three groups (p=0.493). Median duration on TKI treatment was 52 months and it was longest in the imatinib group (87 months) as clinical trials testing imatinib started earlier than the ones testing other TKIs.

Medical co-morbidities, such as HTN, DM and CAD, were found at similar rates among patients in each of the three cohorts. Median baseline creatinine levels were the same (0.9 mg/dL) for patients treated with imatinib, dasatinib, or nilotinib. No difference in baseline GFR was observed among all three cohorts (p=0.106).

Nineteen patients (4%) had TKI-associated AKI during follow up (Table 2). Baseline creatinine increased at least 1.5 fold in 79% of these patients. Median time interval from start of TKI to first occurrence of AKI was 9 days (range 4-84 days). TKI was held in 4 of 19 patients (21%) for a median of 10 days. No patient had to discontinue or switch TKI due to AKI. Factors possibly contributing to the development of AKI were identified in 8 patients: 4 patients were documented to have dehydration due to poor oral intake (n=2) or diarrhea (n=2), two patients were on furosemide for fluid retention, and two other patients were on prophylactic allopurinol at the time of AKI. No possible contributing factors were identified for the remaining 11 patients. Among 19 patients who developed AKI, 16 (84%) were treated with imatinib and three (16%) with other TKIs (1 with dasatinib and 2 with nilotinib (p=0.014) (Table 3). Overall, 6%, 1% and 2% of patients treated with imatinib,

dasatinib, and nilotinib developed AKI, respectively. Among the 16 patients who developed AKI on imatinib, 15 were on 800 mg and 1 patient was on 400 mg total daily dose. Patients who had AKI were older (p=0.006) and more likely to carry prior diagnoses of DM, HTN or CAD (p<0.05). TKI type was the only statistically significant factor (OR: 5.7, p=0.010) associated with the development of AKI while adjusting for the other clinical factors (Table 3).

Forty-eight patients had a prior diagnosis of CKD at the start of TKI treatment. The distribution of patients with history of CKD were similar among all three TKI groups (p=0.241). Although the specific cause of this was not purposely investigated, 60% (29/48) of them had underlying DM, HTN and/or CAD, and 48% were above the age of 65 years. Fifty-eight patients (14%) developed new onset CKD over the course of TKI therapy. Overall, 22% (49/ 226), 5% (5/ 93) and 4% (4/101) of CML patients treated with imatinib, dasatinib, and nilotinib developed CKD, respectively. Five percent of instances of CKD were classified as stage IV, and the rest were stage III disease per KDOQI criteria[21]. Median time interval from start of TKI to diagnosis of CKD was 12 months (range: 3-108 months). No TKI dose change was made for patients who developed CKD. Forty-nine of these 58 patients (84%) were on imatinib and nine (16%) were on other TKIs (5 dasatinib, 4 nilotinib) (p<0.001). Incidence of CKD was similar for patients on imatinib 400 mg or 800 mg (p=0.711). Median age was 60 years and 45 years in patients with CKD and without CKD, respectively (p<0.001) (Table 3). DM, HTN or CAD were also associated with development of CKD (p<0.010). In multivariate analysis, age, treatment with imatinib, and coexistence of DM or HTN were found to be associated with development of CKD (p<0.01). Among them, treatment with imatinib was the most significant factor associated with the development of CKD with an odds ratio of 8.3 (95%CI 3.5-19.4; p<0.001).

We then calculated the mean GFR for all patients at baseline, 3, 6, 12 months and annually for as long as they remained on study. Patients with normal renal function (Figure 1A) and with history of CKD (Figure 2A) were evaluated separately to understand the effect of TKIs in these two cohorts. Among patients with no CKD at baseline, the GFR changes were significantly associated with the TKI used over time (p<0.001). The mean GFR declined significantly in patients treated with imatinib or dasatinib, and this decline was more prominent in patients treated with imatinib (Figure 1B). In imatinib group, at 3 and 6 months, mean GFR declined from baseline by 8 and 10 ml/min/1.73 m^2, respectively. This downward trend continued for 4 years then stabilized. We also analyzed whether the GFR change was affected by the starting dose of imatinib. The changes were similar in both groups suggesting there was no dose effect within the tested doses (p=0.319) (Figure 3). In the dasatinib group, mean GFR decline was modest (3 and 4 ml/min/1.73 m^2) at 3 and 6 months, respectively, and it stabilized after 1 year. Interestingly, mean GFR increased slightly in patients treated with nilotinib. Mean increase from baseline was 4 ml/min/1.73m2 after 3 months of therapy with nilotinib (p<0.001), and GFR remained above the baseline throughout treatment.

Among patients with CKD at baseline, the mean GFR changes were significantly associated with the TKI type over time (p<0.001). The mean GFR increased after 3 months of treatment in all TKI groups (Figure 2A). It increased by 14 ml/min/1.73m^2 among patients

treated with nilotinib, and by 3 and 6 ml/min/1.73m^2 in patients treated with imatinib and dasatinib, respectively (Figure 2B). At 6 month follow-up, mean GFR trended down in all groups, but it was still above the baseline. By the end of the 24 months, mean GFR difference from baseline was slightly lower (1 ml/min/1.73m^2) for imatinib and higher (4 ml/min/1.73m^2) for the dasatinib cohort. In contrast, among nilotinib-treated patients, the mean GFR increased from baseline by 8 and 10 ml/min/1.73m2, at 12 and 24 month follow-up, respectively.

CCyR, MMR and MR$^{4.5}$ rates were not significantly different among patients who developed AKI or who did not.(Table 3). In contrast, patients who developed CKD while on TKI were found to have higher rates of CCyR (98% and 89%, p=0.063) and MMR (97% and 84%, p=0.021) compared to the patients who did not have CKD, respectively. Similarly, deep molecular response rates (MR$^{4.5}$) were 86% and 63% in patients who developed CKD and no CKD, respectively (p=0.001). However, in multivariate analysis, no association was found between cytogenetic or molecular responses and CKD.

EFS proportion rates were found to be lower in AKI patients compared to the patients without AKI (p=0.030). TFS and OS proportion rates were similar (Figures 4a-4c). Five of 19 patients (26%) with AKI had an event (3 loss of MCyR, 1 BP, 1 death) at some point during their follow-up. Among five patients, only one required TKI interruption due to AKI (held for 5 days). There were no association between development of CKD and EFS, TFS, and OS (Figures 5a-5c). AKI, age, and CAD are significantly associated with the risk of dying (Table 4). Patients who developed CKD appeared to have better OS (HR: 0.32, 95%CI: 0.10-0.97; p=0.044), but CKD had no association with EFS or TFS.

Discussion

This analysis suggests that treatment with imatinib and to a lesser degree with dasatinib, in CML patients with relatively normal kidney function is associated with decline in GFR over time. In contrast, CML patients with CKD at baseline did not experience any further decline in GFR, regardless of the TKI used. Nilotinib was the only TKI associated with modest but significant increase of GFR from baseline. Interestingly, this increment was more obvious in CML patients with CKD. Among these TKIs, only imatinib was found to be associated with development of AKI. It should be acknowledged that the larger proportion of patients treated with imatinib in our imatinib cohort received a higher starting dose (i.e., 800 mg daily). When comparing the changes in GFR between patients treated at the standard and the higher dose of imatinib, we did not identify any difference in the changes of GFR suggesting there might not be a dose effect. However, this would have to be confirmed in patients more uniformly treated at the standard dose.

As most patients with CML are likely to receive TKI for prolonged periods of time and possibly indefinitely, it has become important to understand the long term consequences of exposure to these drugs[24]. This is the first study evaluating and comparing the renal function in CML patients receiving imatinib, dasatinib or nilotinib. In this analysis, patients who developed AKI were older and more likely to have DM, HTN or CAD. Age and these medical co-morbidities are known risk factors for renal disease. However, in our study,

multivariate analyses showed that imatinib was an independent factor for the development of AKI. In some reports, TLS has been suggested as a risk factor for development of AKI in patients treated with imatinib[25-26]. This could be an important consideration especially in CML with AP or BP. However, in our study population, none of the patients that developed AKI had changes in uric acid or potassium levels or any other clinical features that may be considered diagnostic or suggestive of TLS. TKIs are also inhibitors of PDGFR-α, PDGFR-β receptors. It has been shown that PDGFRs are involved in tubulogenesis and are distributed mainly in renal tubules and to a lesser extent in the glomerulus of a normal rat kidney. mRNA expression of PDGFRs is enhanced after ischemic injury[17]. Although, the molecular mechanisms of TKI renal toxicity have not been thoroughly recognized or investigated, it has been suggested that inhibition of the PDGF B-Chain/PDGRF axis by PDGFR-β selective agents like trapidil may worsen renal ischemia-perfusion injury in rats[27]. Based on these observations it has been proposed that PDGF blockage should be avoided during ischemia-reperfusion injury of the renal tubules[17, 27]. In a handful of the patients reported here there was some suggestion of concomitant dehydration that may have caused poor renal perfusion. However, most patients did not have such identifiable factors that could have triggered poor perfusion.

The inhibitory effect of PDGF B-Chain/PDGRF axis blockage on tubular regeneration has been mainly shown in ischemia-reperfusion animal models[28]. In contrast, in all other animal injury models the blockage of PDGF appeared to have the opposite effect, with an improvement of renal function[29-38]. For instance, several studies have shown there is an improvement in renal function with TKI therapy in animal models of nephropathies such as diabetic nephropathy[37], nephroangiosclerosis[39], lupus nephritis[38] and chronic allograft nephropathy[40]. Inhibition of PDGFR in some of these models was associated with decreased mesenchymal proliferation and matrix accumulation. PDGF has been commonly implicated in the pathogenesis of progressive kidney injury in human disease and experimental models[41]. PDGF is synthesized by renal cells and infiltrating macrophages that are frequently associated with progressive renal injury[36, 42-43]. PDGF plays a role in nephropathy by stimulating mesengial cell proliferation and increasing extracellular matrix synthesis,[44] and PDGF blockage has been suggested as a possible mechanism to attenuate progression of CKD[28]. Iyoda et. al. reported that nilotinib treated rats have less proteinuria and attenuated glomerulosclerosis in experimental renal disease[45]. This observation is concordant with our observation that patients treated with nilotinib had stable or improved GFR in patients with normal kidney function or CKD. It does not however explain the differences observed between the three inhibitors considering all three are PDGFR inhibitors (Figure 1). It is likely that the renal dysfunction associated with TKI therapy is multifactorial. Further studies are required to understand the mechanism by which TKI may adversely affect renal function.

Interestingly, patients with a history of CKD had no significant decline in GFR after being treated with imatinib or dasatinib, and a modest increase in GFR in patients treated with nilotinib (Figure 2B). This observation should be considered with caution since patients with higher levels of creatinine were excluded from the trials. Still, some patients had modest renal dysfunction as assessed by GFR but this should not be considered as proof of the safety of these agents in patients with more significant renal dysfunction. Studies

specifically directed at such patients are required to better define the safety of different TKIs in that patient population.

Age is an important factor in renal function as average GFR declines over time[46]. Wetzels et. al reports 0.4 ml/min/year decline in estimated GFR in 869 healthy individuals[47]. In our analysis, we do not have a control group. However, the mean decline in GFR observed in our study population was remarkably greater than that proposed in the aforementioned study, making it less likely that the observed decline in GFR was entirely due to aging. In the first 5 years, the mean decline in GFR was approximately 3 and 1 ml/min/year for imatinib and dasatinib, respectively. GFR then remained relatively stable after the 5th year in the imatinib group (Figure 1A). This may suggest that imatinib use beyond 5 years may not be a risk factor for further GFR decline.

In conclusion, AKI occurs in a small percentage of patients treated with TKI, particularly those treated with imatinib. The effect tends to be mild and usually requires no treatment interruptions or changes in TKI. Still, it is important to monitor renal function particularly early during the course of therapy as most AKI cases occur during the first 3 months of therapy. Imatinib and to a lesser extent dasatinib may decrease GFR levels early during the course of treatment, but this GFR change was not clinically significant and was not associated with any significant impact on response rates or survival. Thus, administration of these drugs may be safe in the setting of CKD in CP CML patients but further studies are needed in this patient population to confirm this observation.

Acknowledgments

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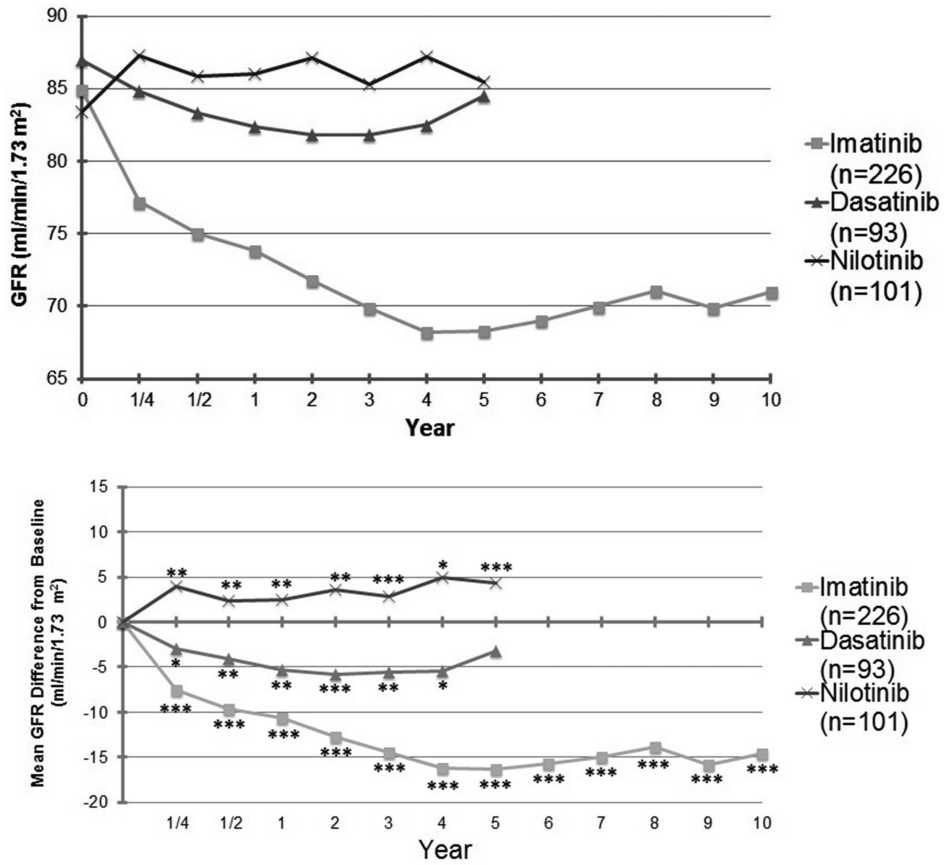
Figure 1. GFR Changes in CML Patients without CKD at Baseline

(A) Mean GFR Trend Over time

(B) Mean GFR Difference from Baseline

GFR, glomerular filtration fate; CML, chronic myeloid leukemia; CKD, chronic kidney disease; n, number of patients (at the start of treatment) . Data are mean [95% CI]. * $p < 0.05$ vs. baseline, * * $p < 0.01$ vs. baseline, * * * $p < 0.001$ vs. baseline by paired t–test.
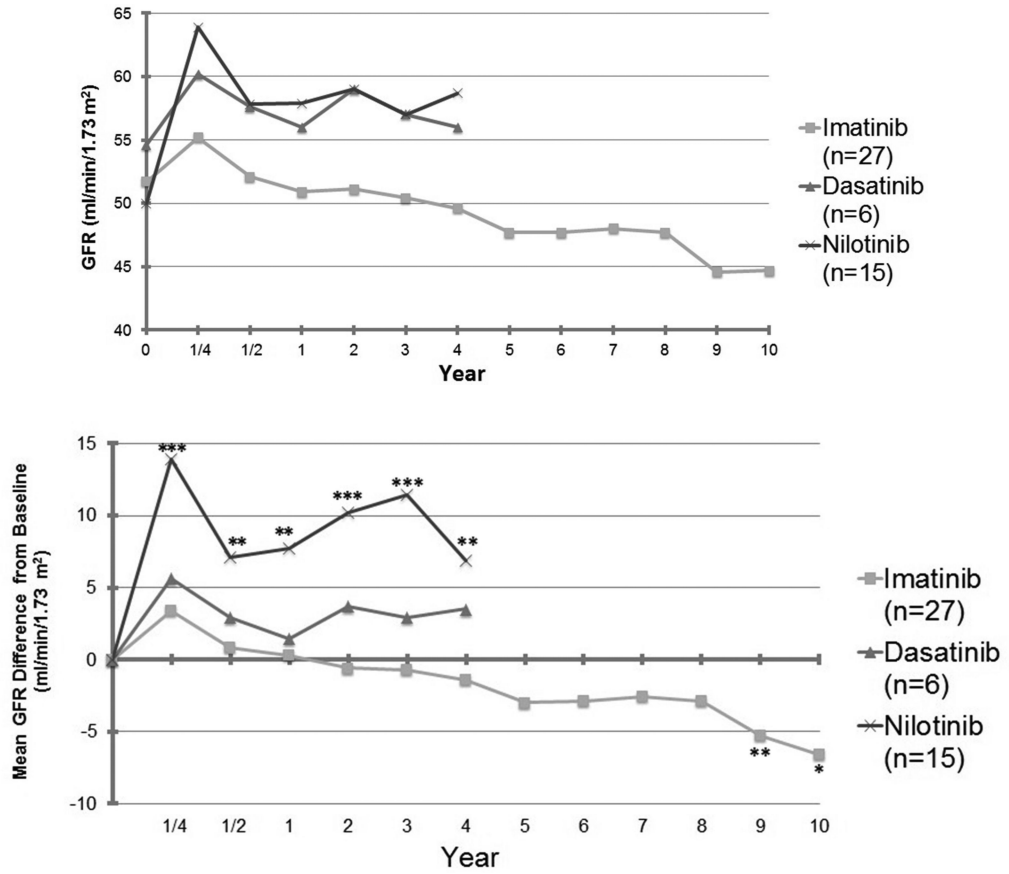
Figure 2. GFR Changes in CML Patients with CKD at Baseline

(A) Mean GFR Trend Over time

(B) Mean GFR Difference from Baseline

GFR, glomerular filtration rate; CML, chronic myeloid leukemia; CKD, chronic kidney disease; n, number of patients (at the start of treatment). Data are mean [95% CI]. * $p < 0.05$ vs. baseline by paired t–test.
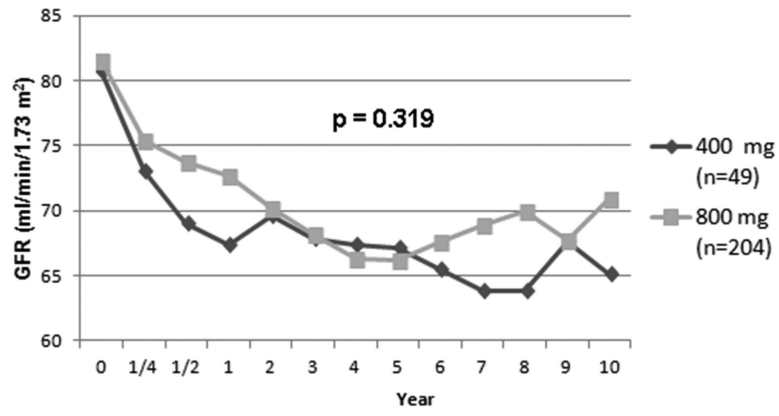
Figure 3.
GFR Changes in CML Patients Treated with High or Standard Dose of Imatinib

GFR, glomerular filtration rate; CML, chronic myeloid leukemia; n, number of patients (at the start of treatment)

P value calculated by repeated-measures ANOVA
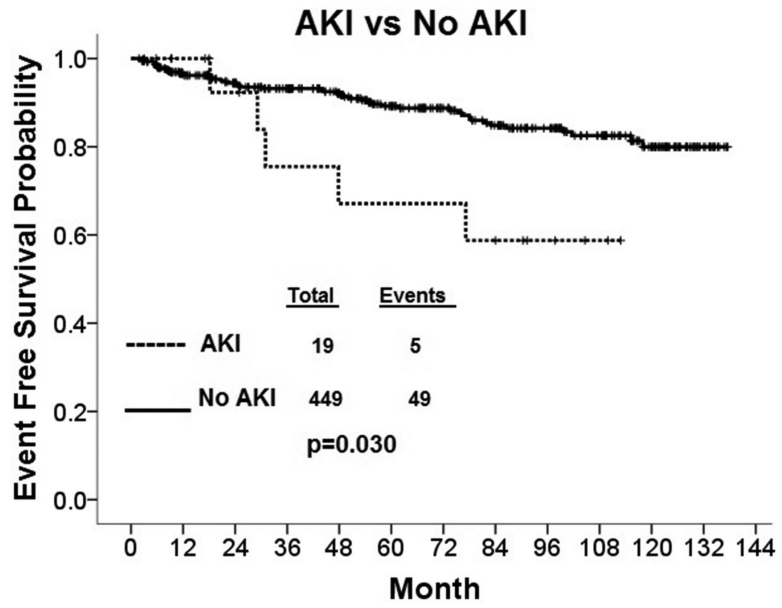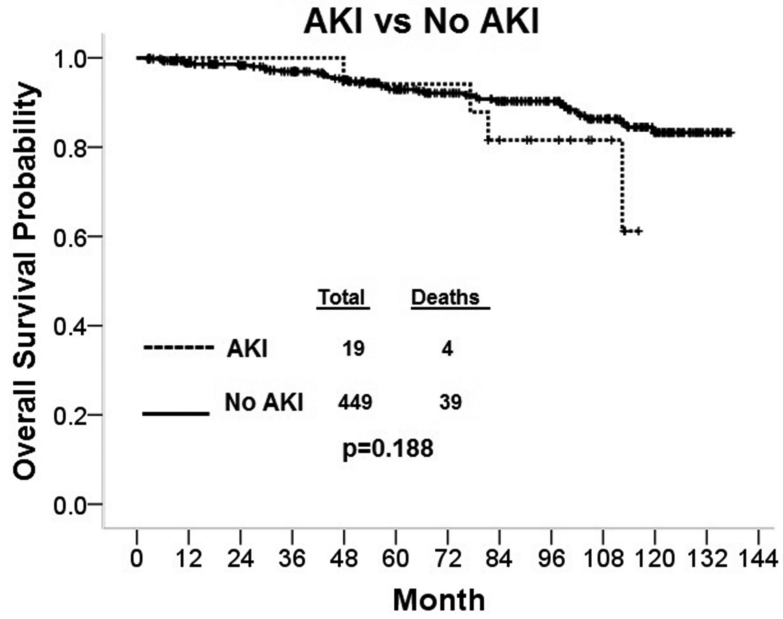
Figure 4.
Overall (A), Event Free (B) and Transformation Free (C) Survival of CML patients with or without AKI determined by Kaplan-Meier survival method.
CML, chronic myeloid leukemia; AKI, acute kidney injury

CKD vs No CKD

CKD vs No CKD

Figure 5.
Overall (A), Event Free (B) and Transformation Free (C) Survival of CML patients with or without CKD determined by Kaplan-Meier survival method

CML, chronic myeloid leukemia; CKD, chronic kidney

Table 1

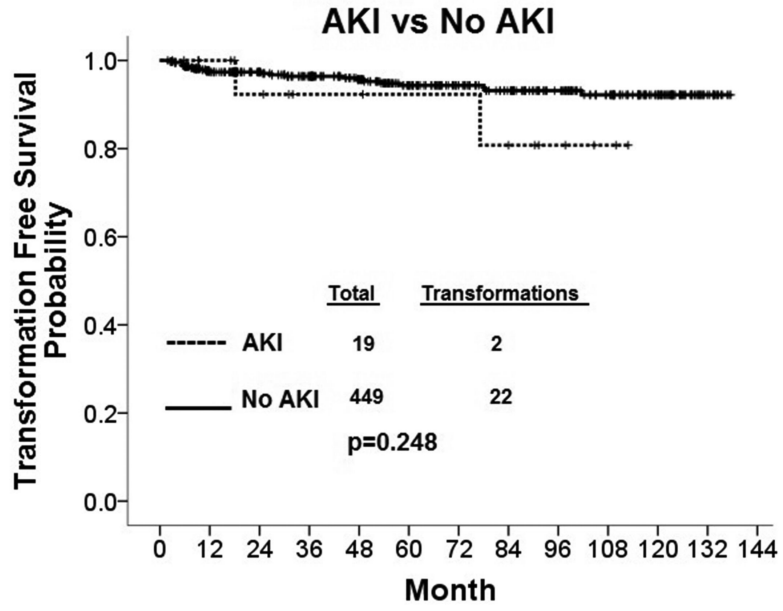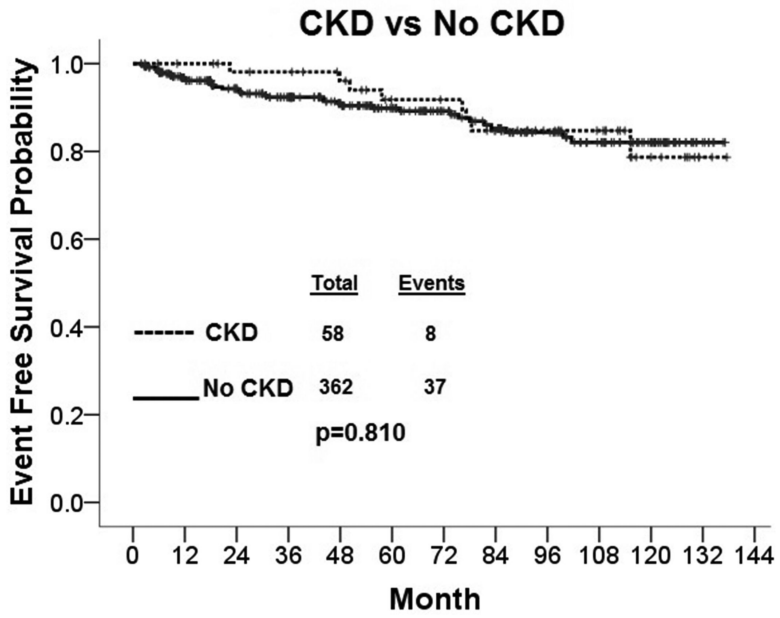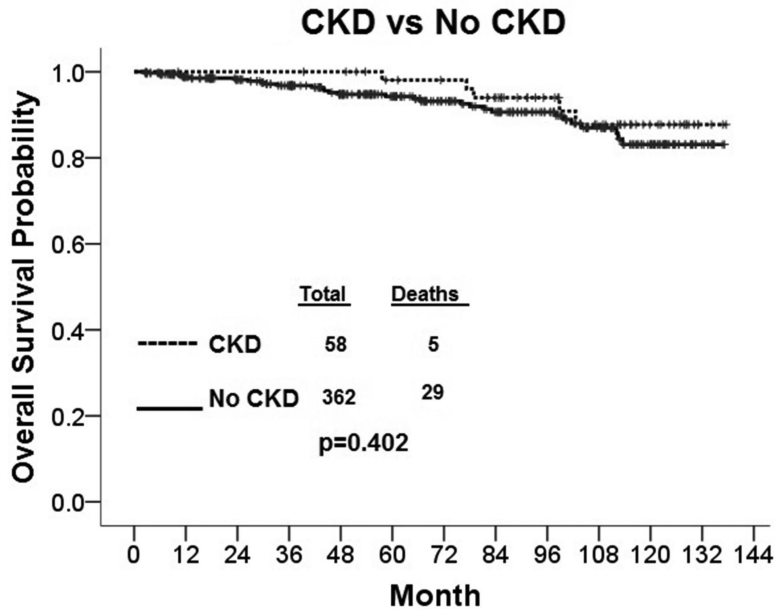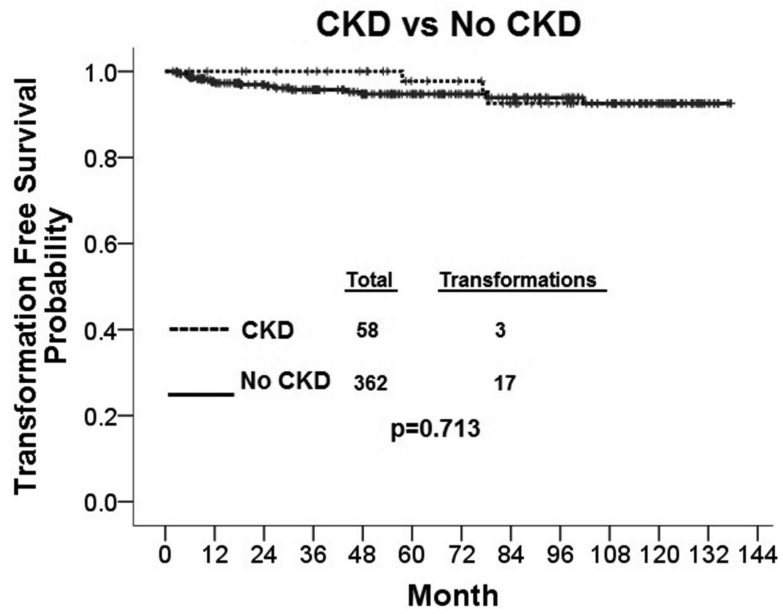Clinical Characteristics of the Patients at the Start of Treatment

Characteristics	Imatinib n=253 Median	Range	Dasatinib n=99 Median	Range	Nilotinib n=116 Median	Range	P value
Age	48	15-85	48	18-82	50	17-86	0.382
Hemoglobin, g/dL	12.4	6.2-16.7	11.9	6.7-16.2	12.3	8-15.8	0.100
WBC, ×10⁹/L	26.9	2.2-283	26.4	0.8-294.7	40	1.4-342	0.405
Platelets, ×10⁹/L	365	58-1476	333	84-2000	304	70-3000	0.058
PB basophils,%	3	0-19	3	0-19	3	0-38	0.447
PB blasts,%	0	0-12	0	0-5	0	0-20	0.372
BM basophils, %	3	0-15	2	0-12	2	0-35	0.073
BM blasts, %	2	0-14	2	0-8	2	0-25	0.937
Baseline Creatinine, mg/dL	0.9	0.5-1.7	0.9	0.6-1.5	0.9	0.6-1.8	0.067
Baseline GFR	80	34-168	81	48-166	80	28-138	0.106
Splenomegaly, No. of pts (%)	67 (26)		26 (26)		25 (22)		0.577
Sokal, No. of pts (%)							
Low	140 (55)		65 (66)		66 (57)		
Intermediate	83 (33)		25 (25)		35 (30)		0.493
High	30 (12)		9 (9)		15 (13)		
Gender, No. of pts (%)							
Male	149 (59)		57 (58)		75 (64)		0.492
Female	104 (41)		42 (42)		41 (35)		
Co-Morbidities, No. of pts (%)							
DM	17 (7)		8 (8)		11 (9)		0.643
HTN	63 (25)		27 (27)		32 (28)		0.822
CAD	22 (9)		6 (6)		4 (3)		0.169
CKD at baseline, No. of pts (%)	27 (11)		6 (6)		15 (13)		0.241
Duration on study, months	87	2-130	36	2-72	28	2-77	<0.001
Duration of follow up, months	105	4-138	39	3-74	31	2-79	<0.001

Data are presented as median (minimum-maximum) or number (%). PB, peripheral blood; BM, bone marrow; GFR, estimated glomerular filtration rate (ml/min/1.73 m2); No. of pts, number of patients; Sokal, Sokal Risk Score; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CKD, chronic kidney disease

Table 2

Clinical Characteristics of Patients Developed Acute Kidney Injury

TKI	Dose (mg/day)	Age	Sex	DM	HTN	CAD	CKD	TKI Held	Baseline GFR	Time Interval (days)
Imatinib	400	49	M	–	–	–	–	–	79	84
Imatinib	800	79	F	–	+	+	+	+	39	4
Imatinib	800	24	M	–	–	–	–	–	119	8
Imatinib	800	85	M	–	+	+	–	+	64	8
Imatinib	800	52	M	–	–	–	–	–	70	11
Imatinib	800	43	M	–	–	–	–	–	92	12
Imatinib	800	80	F	–	+	+	+	+	48	9
Imatinib	800	55	M	–	+	–	–	–	69	9
Imatinib	800	26	M	+	+	+	–	–	73	48
Imatinib	800	66	M	–	–	+	–	–	97	7
Imatinib	800	58	M	–	+	–	+	–	48	8
Imatinib	800	45	F	+	–	–	+	–	90	9
Imatinib	800	80	M	–	+	–	–	–	58	4
Imatinib	800	62	M	+	+	–	–	–	76	6
Imatinib	800	57	M	–	+	–	+	+	69	10
Imatinib	800	70	M	–	–	–	–	–	55	18
Dasatinib	100	58	F	–	+	–	–	–	81	7
Nilotinib	800	52	M	+	+	+	–	–	70	84
Nilotinib	800	58	M	–	–	–	–	–	78	13

TKI, tyrosine kinase inhibitor; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; GFR, estimated glomerular filtration rate (ml/min/1.73 m^2)

Table 3

Comparison of Clinical Characteristics of Patients with or without Acute or Chronic Kidney Disease

Characteristics	Acute Kidney Injury						Chronic Kidney Disease					
	AKI n=19 (%)	No AKI n=449 (%)	Univariate Analysis p value	Multivariate Analysis OR	C.I. (95%)	p value	CKD n=58 (%)	No CKD n=362 (%)	Univariate Analysis p value	Multivariate Analysis OR	C.I (95%)	p value
Age, median	58	48	0.006	1.0	0.98-1.1	0.384	60	45	<0.001	1.1	1.0-1.1	<0.001
Gender												
Male	15 (79)	266 (59)	0.097				32 (55)	223 (62)	0.353			
Female	4 (21)	183 (41)		0.4	0.1-1.2	0.107	26 (45)	139 (38)		1.5	0.7-2.9	0.288
TKI												
Imatinib	16 (84)	237 (53)	0.014	5.7	1.5-21	0.010	49 (84)	177 (49)	<0.001	8.3		<0.001
Nilotinib or Dasatinib	3 (16)	212 (47)					9 (16)	185 (51)				
Co-Morbidities Prior to TKI Therapy												
DM	4 (21)	32 (7)	0.035	2.3	0.6-8.5	0.203	11 (19)	17 (5)	<0.001	3.8	1.3-10.7	0.012
HTN	11 (58)	111 (25)	0.003	2.3	0.7-7.8	0.180	30 (52)	63 (17)	<0.001	3.0	1.4-6.4	0.003
CAD	6 (32)	26 (6)	<0.001	2.0	0.5-75	0.325	8 (14)	17 (5)	0.010	0.6	0.2-1.9	0.346
CKD	5 (26)	43 (10)	0.026	2.0	0.2-4.1	0.283						
AKI after TKI Therapy												
AKI							6 (10)	8 (2)	0.004	2.9	0.7-11.5	0.135
Response Rates												
CCyR	17 (89)	406 (90)	0.891	0.8	0.2-4.1	0.830	57 (98)	324 (89)	0.063	6.5	0.8-53.9	0.085
MMR	15 (79)	382 (85)	0.469				56 (97)	303 (84)	0.021			
MR$^{4.5}$	12 (63)	292 (65)	0.867				50 (86)	228 (63)	0.001			

Data are presented as median or number (%)

Univariate Analysis: Mann-Whitney U test or chi-square test; Multivariate Analysis: Multivariate logistic regression analysis; OR, odds ratio; C.I, confidence interval

AKI, acute kidney injury; CKD, chronic kidney disease; TKI, tyrosine kinase inhibitor; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CCyR, complete cytogenetic response;

MMR, major molecular response; MR$^{4.5}$, BCR-ABL1 transcript levels 0.0032 (international scale);

Table 4

Multivariate Analysis of Survival

Clinical Features	HR	C.I. (95%)	p value
Event-free Survival			
AKI	6.14	2.0-18.6	0.001
CKD	0.68	0.3-1.5	0.353
CCyR	0.04	0.02-0.1	<0.001
Transformation-free Survival			
AKI	7.2	1.5-35.1	0.015
CKD	0.63	0.17-2.4	0.502
CCyR	0.04	0.01-0.1	<0.001
Overall Survival			
AKI	4.02	1.1-15.0	0.041
CKD	0.32	0.1-0.97	0.044
CCyR	0.08	0.04-0.2	<0.001
Age	1.05	1.02-1.1	0.001
HTN	0.5	0.2-1.5	0.220
CAD	4.4	1.4-14.0	0.013

HR, hazard ratio; C.I., confidence interval; AKI, acute kidney injury; CKD, chronic kidney disease; CCyR, complete cytogenetic response; HTN, hypertension; CAD, coronary artery disease