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Chronic myeloid leukemia among patients with history of prior malignancies: a tale of dual survivorship

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Abstract

Background—Some patients with chronic-myeloid-leukemia have a history of previous malignancies. Chronic-myeloid-leukemia outcomes in these patients have not been well described.

Aims—To determine the outcome of patients with chronic-myeloid-leukemia and a history of prior-malignancies.

Methods—Included were patients enrolled in clinical trials of tyrosine-kinase-inhibitors as initial therapy for chronic-myeloid-leukemia in chronic phase from July 2000 to January 2014.

Results—Of the 630 chronic myeloid leukemia patients treated with frontline tyrosine-kinase-inhibitors, 626 had a known prior malignancy status. 45 (7%) had a prior malignancy other than non-melanoma skin cancer (PM) while 17 (3%) had a history of non-melanoma-skin-cancers alone. Chronic-myeloid-leukemia characteristics were similar between no-prior malignancy, prior-malignancy, and the non-melanoma-skin cancer groups. Patients in the prior-malignancy group were older (median age) than the other two groups. The most common prior malignancies were: non-melanoma-skin-cancer in 20 patients, breast cancer in 11, melanoma in 7, prostate cancer in 6, and colorectal cancer in 5. In regards to their chronic-myeloid-leukemia, the event-free-survival, transformation-free-survival, and the failure-free-survival were similar between the groups. There was a statistically significant decreased survival in the prior-malignancy group versus the no-prior-malignancy group versus the non-melanoma-skin-cancer group. In a multivariate-analysis

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advanced age and elevated creatinine were associated with worse survival after chronic-myeloid-leukemia diagnosis.

Conclusion—Patients with chronic-myeloid-leukemia with a history of prior-malignancies have the same excellent outcome as patients with no-prior-malignancies. In the few instances in which concomitant therapy for other malignancies was required during therapy with tyrosine-kinase-inhibitors this could be accomplished without significant toxicity.

Keywords

CML; second cancer; survivor; tyrosine kinase inhibitor; chronic myeloid leukemia

Introduction

The natural history of chronic-myeloid-leukemia (CML) has been irrevocably changed since the advent of tyrosine-kinase-inhibitors (TKIs). Imatinib, the first TKI, became standard therapy for patients with CML in 2001. Over 80% of patients with CML treated with imatinib as initial therapy achieve a complete-cytogenetic-response (CCyR) and approximately 70% achieve a major-molecular-response (MMR) by 5 years of therapy.¹

Use of TKIs as initial therapy has resulted in an improvement in survival² such that currently survival mimics that of the general population^{3, 4} and has resulted in an increase in the prevalence of the disease.⁵ With prolonged survival, questions arise about the effects of TKI treatment on prior medical conditions and the effect of such conditions on the management and outcome of patients with CML. In some instances, patients with CML may have a pre-existing diagnosis of another cancer, making CML the “second cancer”. Recent population studies suggest there is an increase prevalence of other malignancies prior to the diagnosis of CML compared to the incidence in the general population.⁶ The impact that a diagnosis of CML and the treatment with TKI may have on the prior-cancer, and the impact of the prior-malignancy on the outcome of patients with CML receiving treatment with TKI have not been described. Several hypothetical scenarios could be envisioned for patients with prior-malignancies that develop CML. One is reactivation of the prior malignancy because of the therapy for CML. The TKIs may have immunomodulatory effects as suggested by in-vitro inhibition of T-cell proliferation and activation by imatinib, nilotinib, and dasatinib.⁷⁻⁹ Some TKIs such as dasatinib also inhibit SRC kinases that are key regulators of immune responses.^{8, 10-13} An immunosuppressive effect of TKIs could potentially lead to reactivation of a prior malignancy. Another possible scenario is that having a prior malignancy adversely affects the prognosis of CML or the ability to tolerate TKIs. For instance, patients with secondary AML have inferior outcomes regardless of age or cytogenetics.¹⁴ Similarly, the history of prior- malignancies or the treatment for them could alter the clinical features or the clinical course of patients with CML.

The purpose of this analysis was to investigate the frequency, characteristics, and outcome among patients with CML treated with TKIs who had prior malignancies.

Patients and Methods

We analyzed the records of all patients with Philadelphia chromosome (Ph)-positive-CML in chronic-phase treated with a TKI as initial therapy in clinical trials conducted at MD Anderson Cancer-Center from July 2000 to January 2014. The criteria for chronic phase CML was as previously described.¹⁵ These studies were approved by the Institutional-Review-Board, and all patients signed approved informed consents in accordance with the Declaration of Helsinki.

Evaluation of patients

All patients had a history and physical examination, complete blood counts, and blood chemistry panel before the start of therapy and at least once every month for the first 3 months, then every 3 months until 12 months from the start of therapy, and then every 6 months. Cytogenetic-response was assessed by G-banding in the bone marrow with 20 metaphases counted, and molecular-response was assessed by real-time-PCR and expressed as the BCR-ABL/ABL ratio on the international scale. Both cytogenetic and molecular response assessments were performed at baseline, every 3 months for the first 12 months, and then every 6 months. Definitions of cytogenetic and molecular-response were standard.¹⁵

The records of all patients were reviewed for a history of any malignancy diagnosed before CML was identified. All available clinical information related to the prior malignancy was collected, including the original diagnosis, stage, treatment, response to therapy (if any), status of the prior malignancy at the time of CML diagnosis, and any change in status of the prior malignancy after the start of CML therapy.

Statistical analysis

Summary statistics were used to describe the study population by groups. Overall survival (OS) was calculated as the number of months from the start of treatment to death or last follow-up date. Patients who were alive at their last follow-up were censored on that date. Event-free-survival (EFS) was determined from the start of therapy with TKI to loss of complete-hematologic-response (CHR), loss of major-cytogenetic-response (MCyR), transformation during treatment with the initial TKI, or death during therapy with first TKI. Failure-free-survival (FFS) was determined from the start of therapy with TKI to the occurrence of an event (as defined above for EFS), loss of CCyR, development of intolerance, or discontinuation of TKI therapy for any reason. Transformation-free-survival (TFS) was determined from the start of therapy with TKI to transformation to accelerated-phase (AP) or blast-phase (BP), or death during therapy with the original TKI. Pearson's chi-squared test (or Fisher's exact test) and t-test (or Wilcoxon's rank sum) were used to determine differences between the groups. The Kaplan-Meier product limit method was used to estimate the median OS, EFS, TFS, and FFS, respectively. Univariate-Cox proportional hazards regression models were used to identify any association with each of the variables and OS, EFS, TFS and FFS respectively. Univariate and multivariate Generalized-Linear-Models were used to model the relationship between response and demographic/clinical

characteristics. Statistical analysis was performed using STATA/SE version 14.1 statistical software (Stata Corp. LP, College Station, TX).

Results

During the study period, a total of 630 consecutive patients with CML in chronic phase were treated with a TKI as initial therapy. Of these, 626 had a documented prior malignancy status and they constitute the basis for this report. Among them, 73 (12%) were treated with imatinib 400mg/day, 204 (33%) with imatinib 800mg/day, 150 (24%) with dasatinib 100mg/day, 148 (24%) with nilotinib 400 mg twice daily, and 51 (8%) with ponatinib 30 or 45 mg/day. Among these 626 patients, 62 (10%) had a history of 72 malignancies prior to their diagnosis of CML. The patients were sub-divided into three groups for the sake of this analysis. Patients without a cancer diagnosis prior to their diagnosis of CML (nPM), patients who had a non-melanoma-skin-cancer (nMSC), and patients with a prior-malignancy, not a non-melanoma-skin-cancer (PM) were separated for this analysis. The clinical characteristics of these patients are shown in Table 1. Patients with prior malignancies, both the nMSC and the PM group, were older than the nPM group. There were no other clinically significant differences between the two groups.

The most common prior malignancy was non-melanoma-skin-cancer with 20 instances in 18 patients, representing 28% of all prior cancers. Three patients had a recurrence of their nMSC and were all treated with surgery. Of the 20 instances of non-melanoma-skin cancer, 2 patients had 2 instances of nMSC and one patient that had both nMSC and breast cancer. The patient with both breast cancer and nMSC was included in the PM group for this analysis.

Forty-five patients with a prior cancer had 52 instances of a malignancy that was not a nMSC. Three patients in the PM group had 2 different PMs (thyroid cancer + Hodgkin lymphoma, transitional bladder cancer + clear-cell kidney cancer, and colon cancer + prostate cancer, respectively). Two patients had 3 PMs other than nMSC (renal cell + prostate + colon cancer in one, and melanoma + adenocarcinoma of the lung + mucosa-associated lymphoid tissue [MALT] lymphoma in the other). A listing of all prior malignancies and the treatments are shown in Supplement Table 1. The median time from diagnosis of the prior malignancy to the diagnosis of CML was 65 months (6-517) in the PM group and 49 months (15-452) in the nMSC group.

One patient with nMSC was treated with radiation therapy. All other nMSCs were treated with simple or wide excision and were considered cured. Twenty-four (46%) of the 52 remaining malignancies were treated with chemotherapy, 20 (38%) had received radiotherapy, and 44 (84%) had surgery. Combined therapy was common, including 10 patients with surgery, chemotherapy and radiotherapy, 6 patients treated with surgery and radiotherapy, 9 with surgery and chemotherapy, and 1 with chemotherapy and radiotherapy (Supplement Table 1).

Status of PM at time of CML Diagnosis

Forty-two of the forty-five patients (93%) in the PM group had no active disease and were receiving no treatment for cancer at the time of their CML diagnosis. Two patients (4%) were still receiving treatment for their prior malignancy at the time of diagnosis with CML. Both were receiving tamoxifen for breast cancer and had no evidence of disease. One patient (2%) had active disease at the time of CML diagnosis (defined as diagnosis or documented treatment for prior cancer within 6 months before or after diagnosis of CML). This patient had been operated on for an early stage melanoma 6 months prior to the diagnosis of CML and was being followed with observation only at the time of CML diagnosis (Supplement Table 1).

Outcome of prior malignancy after diagnosis of CML

After treatment for CML was initiated, 41 of 45 patients (91%) in the PM group remained free of recurrence or progression of their non-CML malignancy. This includes one patient with active stable melanoma on imaging, who had not been treated in 23 months prior to the diagnosis of CML; all others had no evidence of recurrence of their disease. Four patients had recurrence of their prior malignancy. These included the following: One patient with recurrent melanoma diagnosed 13 months after the original diagnosis of melanoma and 6 months after starting imatinib 800 mg/day was treated with chemotherapy for relapsed melanoma; one patient had recurrence of breast cancer treated with chemotherapy and radiation diagnosed 151 months after the initial diagnosis of breast cancer and 40 months after starting treatment with imatinib 800 mg/day. One patient with recurrence of MALT lymphoma 113 months after initial diagnosis and 11 months after starting nilotinib was treated with radiation. And one patient with recurrent prostate cancer 49 months after initial diagnosis and 25 months after starting dasatinib that was treated with radiation. (Supplement Table 2) Three of these four patients continued treatment for CML with a TKI while being treated for the recurrence of the prior malignancy. The one patient that did not continue therapy had his imatinib 800mg/day held while he was being treated for metastatic malignant melanoma at an outside institution and died of unknown causes prior to being able to restart his TKI. Twelve of forty-five patients (27%) in the PM group have died. All died while taking their TKI. Two deaths were considered related to the PM (breast and melanoma, respectively) and there were no CML-related deaths.

CML outcome

The median follow-up for all patients included in this analysis was 84 months (0-180) from the start of TKI therapy. Among them, 563 (90%) achieved CCyR, 529 patients (85%) achieved MMR, and 425 (68%) achieved a molecular response with 4.5-log reduction (MR 4.5). After 3 months of TKI therapy, 538 patients (86%) had achieved a major-cytogenetic-response (MCyR). Overall, the 5-year EFS is 85% (95%CI, 0.81-0.87), 5-year failure free survival (FFS) is 68% (95%CI, 0.64-0.72), 5-year TFS is 92% (95% CI, 0.89-0.94), and the 5-year OS is 92%, (95% CI, 0.89-0.94).

The 564 patients with no prior malignancies had a median follow-up of 86 months (0-180) from the start of TKI therapy. Among them, 505 (90%) achieved a CCyR, 475 (84%) achieved MMR, and 381 (68%) achieved MR4.5. After 3 months with TKI therapy, 482

patients (85%) had achieved a MCyR. For this group of patients, the 5-year EFS is 84% (95%CI, 0.81-0.88), 5-year FFS is 68% (95%CI, 0.64-0.72), the 5-year TFS is 93%, (95%CI, 0.90-0.95) and the 5-year OS is 93% (95%CI, 0.90-0.95).

The 45 patients with prior malignancies had a median follow-up of 78 months (12-172) from the start of TKI therapy. Among them, 43 (96%) achieved a CCyR, 41 (91%) achieved MMR, and 36 (76%) achieved MR4.5. After 3 months with TKI therapy, 41 (91%) had achieved a MCyR. For this cohort of patients, the 5-year EFS is 85% (95%CI, 0.66-0.94), the 5-year FFS is 63% (95%CI, 0.46-0.76), the 5-year TFS is 82% (95%CI, 0.69-0.96), and the 5-year OS is 79% (95%CI, 0.63-0.89).

The nMSC group of 17 patients had a median follow-up of 68 months (9-157) from the start of TKI therapy. In this cohort 15 (88%) achieved a CCyR, 13 (76%) achieved MMR, and 8 (47%) achieved a MR 4.5. After 3 months with TKI therapy, 16 (94%) had achieved a MCyR. In the nMSC group the 5-year EFS is 86% (95%CI, 0.33-0.98), the 5-year FFS is 70% (95%CI, 0.32-0.90), the 5-year TFS is 88% (95%CI, 0.33-0.98), and the 5 year OS is 100%.

Response rates were similar across all cohorts. Additionally, the long-term CML outcomes (EFS, FFS, and TFS) were equivalent between the three groups (Figure 1a-c). There was however, a statistically significant difference in overall survival between the groups (Figure 1d). In the PM group, 12 (27%) patients have died (median age at time of death 72 years (range, 52-91). In contrast, in the nPM group, 65 (12%) patients died (median age at time of death 63 years (range, 23-92) and in the nMSC group, only 1(6%) patient (age 80 years) died (HR 2.40, 95%CI 1.29-4.44) (Supplement Table 3).

Univariate / Multivariate Analysis

We performed a generalized-linear-model analysis to evaluate the features associated with achieving MR 4.5. In a univariate-analysis the variables that negatively predicted for achieving MR4.5 were platelets <400K/uL, creatinine >1.3mg/dL, aspartate aminotransferase (AST) >46 IU/L, and treatment with imatinib 400mg/day as the frontline TKI (versus all other options). In the multivariate-analysis the following variables were independently negatively associated with achievement of MR4.5: history of nMSC (OR,0.34 [95%CI, 0.13-0.94], p=0.037), platelets <400K/uL (OR,0.58 [95%CI, 0.39-0.86] p=0.007), creatinine>1.3mg/dL (OR,0.28 [95%CI, 0.11-0.73] p=0.01), and imatinib 400mg/day (OR, 0.43 [95%CI, 0.24-0.79] p=0.007) (Supplement Table 4).

We then performed a multivariate-Cox-proportional-hazards-analysis to investigate features associated with survival. In a univariate-analysis for OS: age, Sokal score, serum albumin, blood urea nitrogen (BUN)>20 mg/dL, and creatinine>1.3 mg/dL were associated with outcome. In a multivariate-analysis, only older age (HR, 1.05 [95%CI 1.03-1.07], p<0.001) and creatinine>1.3 mg/dL (HR, 3.09 [1.45-6.57], p=0.003) were independently associated with inferior survival probability. Importantly, a history of prior malignancy was not independently associated with OS probability (Table 2).

Competing Risk Regression Analysis

We then performed a competing-risk-regression analysis to investigate whether the risk of death due to CML or another cause of death not related to CML was different when given variables were no longer competing for relevance. Age was not statistically significant in regards to cause of death between CML deaths and deaths from other causes (HR 1.01[95%CI 0.97-1.06], $p=0.546$). Risk of death from non-CML causes was statistically significantly increased compared to the incidence of death from CML in the PM group (HR 4.69E-07 [95%CI 2.26E-07-9.71E-07], $p<0.001$). The risk of death from CML vs other causes was statistically significantly increased when baseline bone marrow blasts were $>10\%$ (HR2.54 [95%CI 7.05-139.87], $p<0.001$) (Supplement Table 5). In an analysis of cumulative incidence of death, there were no CML related deaths in the PM group and there was only one event in the nMSC group, preventing a comparison with this group. In the nPM group, the 5-year cumulative incidence of non-CML specific death was 3.65% (95%CI, 2.20-5.66). In the PM group the 5-year cumulative incidence of non-CML specific death was 15.80% (95%, 6.35-29.09) (Figure 2).

Discussion

With better understanding of cancer biology and ever-improving cancer therapies, the outcome for patients with various cancers has improved significantly in recent years. The death rate for all cancers in 1991 was 215.22 per 100,000, and declined to 175.86 per 100,000 in 2008.¹⁶ The annual percent change during this period ranges from -0.46 to -1.61. A natural consequence of the prolonged survival of patients with cancer is the possibility of developing a second cancer. Second cancers may develop as a consequence of exposure to agents used for the treatment of the primary cancer. Exposure to some therapeutic modalities such as alkylating agents and radiotherapy, may result in a significant increase in the risk of developing second cancers.¹⁷ In many instances, however, no common etiologic link can be identified and a second cancer may occur as a result of prolonged survival with persistence of a constant annual risk of development of seemingly unrelated malignancies. In the latter scenario, the incidence of a second cancer would be expected to be similar to that seen in the general population. We have previously reported on the occurrence of second cancers among patients with CML treated with a TKI. The incidence we reported was somewhat lower than expected in the general population, suggesting that TKIs do not increase the risk of second malignancies.¹⁸ However, Scandinavian registry studies have reported different findings suggesting an increased risk of secondary malignancies among patients with CML treated with TKIs.^{19, 20}

Herein we present the first analysis of the outcome of prior malignancies among a large group of patients with CML that had such prior history, as well as the outcome of CML among these patients. Patients with prior malignancies were older than their counterparts with no prior malignancies. Aside from this, there were no clinically significant differences in the characteristics of patients with or without prior malignancies.

Considering the various types of cancers involved in these patients, and considering the retrospective nature of this analysis, we cannot identify an obvious link between the prior malignancies and CML, whether related to common genetic predisposition, from exposure

to common predisposing environmental or other factors, or resulting from exposure to chemotherapy or radiotherapy used to manage the first malignancy. Interestingly, a registry report from the Swedish CML Registry reported an increased prevalence of prior cancers among patients with CML compared to what is observed in the general population with an odds ratio of 1.47 (95% CI 1.20 – 1.82). The investigators commented that this link suggests a possible hereditary or acquired predisposition to cancer.⁶ There were 52 incidences of cancer prior to treatment of CML, most commonly these were breast, melanoma, other hematologic malignancies, prostate, and colorectal cancer. There is some parallel in this with the Swedish registry study that noted a significantly increased incidence of breast cancer, gastrointestinal cancer, malignant melanoma, urinary tract cancers and endocrine cancer.⁶ In our study there was no difference in response to CML therapy in patients with a prior malignancy as compared to patients without such malignancies. The wide variability of tumor types (and likely stages at diagnosis, although this information was frequently inaccessible) preclude expectations of outcome for these patients. By definition, they were all survivors of their prior cancer at least long enough to develop CML. Only 4 of 45 patients experienced a recurrence of their prior cancer. Thus, it appears that most of these patients had been cured of their prior malignancy. With the excellent outcome achieved with TKI for their CML, most of these patients appear to have survived two (and in a few instances more) separate cancers.

The response to therapy with TKI for patients with prior malignancies was excellent and similar to that observed among patients with no prior malignancies. Over 90% of patients achieved a CCyR and more than two thirds achieved a MMR. This resulted in an excellent overall survival, with no instances of transformation to accelerated or blast phase. There was a trend for lower MR4.5 among patients with nMSC of unknown significance that may represent only a statistical artifact.

Acute myeloid leukemia (AML) is most frequently cited as a secondary malignancy, however, there are intermittent reports of CML as a second malignancy. A recently published report in JAMA Oncology describes 3 cases of CML following treatment for germ cell tumors (GCT). All three received alkylating chemotherapeutic agents and of the 3, 1 died of his GCT and the other 2 had at least some response to TKIs.²¹ Case series and reports are all that are described in the literature in any detail.²² Patients with such secondary AML have usually a very poor prognosis, with low rates of response and cure, even after stem cell-transplant.²³ The prognosis is inferior even for patients with core-binding factor leukemias.²⁴ According to our analysis, patients with CML have a similarly favorable outcome whether they have received prior therapy or not.

Our results suggest that while CML outcomes are excellent, patients with CML as a second malignancy have shorter survival. The multivariate analysis suggests that age and renal function (creatinine) are the best predictors of OS, whereas a history of prior malignancy is not independently associated with survival. Interestingly however, a competing-risk-analysis of the groups shows that the PM and the nPM groups were more likely to die of causes other than CML (Figure 2).

These results suggest that survivors of prior malignancies that acquire CML as a second (or later) malignancy may have a similarly excellent outcome with TKI therapy as patients in whom CML is their first malignancy. In fact, this data stresses the importance of the control of other comorbid conditions after the diagnosis and treatment of CML. Therefore, these patients should be offered treatment with TKI aiming for the best possible outcome leading to survivorship from a second malignancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Outcome Kaplan Meier Curve
 (A) Event-Free-Survival, (B) Transformation-Free- Survival, (C) Failure-Free-Survival, (D) Overall-Survival

Figure 2. Cumulative Incidence of Death by PM status

Table 1
Clinical characteristics at the time of CML diagnosis of all patients with and without a prior malignancy

	CML Initial Malignancy (n= 564)	Prior Malignancy (n= 45)	Non-melanoma skin cancer (n = 17)	p-value
Age at diagnosis of CML	47.4 (14.8-86.4)	61.1 (30.1-84.7)	57.9 (36.1-73.5)	<0.001
Followup after CML diagnosis (months)	88 (0-178)	75 (5-175)	67 (14-171)	
Age at diagnosis of prior malignancy (years)		54.3 (21.2-81.6)	50.8 (5.7-68.9)	
Followup after diagnosis of prior malignancy (months)		152 (15-685)	135 (63-1407)	
Time from prior malignancy to CML (months)		65 (6-517)	49 (15-452)	
% Male	60.1	53.3	52.9	0.578
Race				0.162
% Asian	3.5	0	0	
% Black	7.3	2.2	0	
% Hispanic	11.9	4.4	0	
% White	77.3	93.3	100	
Albumin (g/dL)	4.2 (2-6.8)	4.3 (2.5-5.2)	4.3 (3.6-5.5)	0.774
Blood urea nitrogen (mg/dL)	15 (5-39)	16 (9-26)	16 (10-21)	0.039
Creatinine (mg/dL)	0.9 (0.5-4.5)	0.9 (0.5-1.5)	0.8 (0.6-1.4)	0.254
Lactate dehydrogenase (IU/L)	894 (252-5805)	927 (331-2884)	1042 (374-3102)	0.665
Total bilirubin (mg/dL)	0.4 (0.1-3.4)	0.3 (0.1- 0.9)	0.4 (0.2-0.8)	0.019
Alanine aminotransferase (IU/L)	26 (9-166)	22 (11-68)	20 (11-48)	0.025
Aspartate aminotransferase (IU/L)	32 (10-223)	31 (11-75)	24.5 (12-47)	0.232
White blood cell count (K/uL)	27 (0.8-342.5)	35.3 (3.5-128.4)	40.9 (5.7-119.4)	0.409
Hemoglobin (g/dL)	12.1 (6.2-16.7)	12.3 (9-15.9)	11.8 (8.1-14.8)	0.434
Platelets (K/uL)	334.5 (22-3000)	363 (50-2928)	291 (103-1411)	0.732
Spleen (cm)	0 (0-30)	0 (0-7)	0 (0-16)	0.426
Peripheral Blood Blasts (%)	0 (0-20)	0 (0-5)	0 (0-2)	0.506
Peripheral Blood Basophils (%)	3 (0-38)	4 (0-18)	4 (0-14)	0.470
Bone Marrow Blasts (%)	2 (0-25)	1 (0-9)	2 (0-5)	0.723
Bone Marrow Basophils (%)	2 (0-35)	2 (0-8)	2 (0-8)	0.892
Sokal Risk Score	No (%)			0.200
Low	378 (67)	27 (60)	8 (47)	
Intermediate	141 (25)	12 (27)	6 (35)	
High	45 (8)	6 (13)	3 (18)	
CML Treatment	No (%)			0.151
Imatinib 400 mg/day	69 (12)	4 (7%)	0 (0)	
Imatinib 800 mg/day	189 (34)	12 (27)	3 (18)	
Dasatinib	132 (23)	9 (20)	9 (53)	
Nilotinib	129 (23)	15 (33)	4 (24)	

	CML Initial Malignancy (n= 564)	Prior Malignancy (n= 45)	Non-melanoma skin cancer (n = 17)	p-value
Ponatanib	45 (8)	5 (11)	1 (6)	
Clonal Evolution at diagnosis	33 (6)	5 (15)	0 (0)	0.21

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Table 2
Multivariate Cox Proportional Hazards Analysis for OS

	HR	95%CI		p-value
Age @ CML DX	1.05	1.03	1.07	<0.001
Groups				
CML Initial Malignancy				
Prior Malignancy	1.44	0.75	2.76	0.276
Non-melanoma skin cancer	0.46	0.06	3.37	0.442
Bun>20 mg/dL				
No				
Yes	0.81	0.42	1.56	0.523
Albumin>3.4 g/dL				
No				
Yes	0.51	0.23	1.10	0.087
Creatine>1.3 mg/dL				
No				
Yes	3.09	1.45	6.57	0.003
TKI				
Dasatinib				
Imatinib 400 mg/day	1.57	0.59	4.20	0.366
Imatinib 800 mg/day	1.16	0.47	2.89	0.742
Nilotinib	1.72	0.65	4.56	0.271
Ponatinib	1.26	0.14	11.17	0.835
Sokal Score				
Low				
Int	1.04	0.60	1.82	0.891
High	1.77	0.86	3.61	0.119