Title

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Prognostic factors and survival outcomes in patients with blast phase CML (CML-BP) in the tyrosine kinase inhibitor (TKI) era: cohort study of 477 patients

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Abstract

Background—Outcomes in blast phase CML (CML-BP) are historically dismal. We sought to analyse the characteristics, prognostic factors and survival outcomes in patients with CML-BP in the TKI era.

Methods—All patients with CML-BP (n=477) were treated with a TKI at some point during the course of their CML. Cox proportional hazard models identified characteristics which predicted for survival. Overall survival (OS) and failure free survival (FFS) were assessed. Optimal cut off points for specific parameters, were identified using CART (classification and regression tree).

Results—Median age was 53 years (range, 16 to 84); 64% were male. Eighty percent were initially diagnosed in chronic phase CML (CML-CP) median 41 months (0.7 to 298 months) before transformation to CML-BP. De-novo CML-BP occurred in 71 patients. Seventy two percent patients received TKI therapy prior to CML-BP. Initial therapy for CML-BP included, TKI alone (35%), TKI with chemotherapy (46%) and non-TKI therapies (19%). The median OS was 12 months and median FFS was 5 months. In multivariate analysis, myeloid immunophenotype, prior TKI, age 58 years, LDH 1227 IU/L, platelet count <102 K/µL, no stem cell transplantation (SCT), blast phase from CP/AP and presence of chromosome 15 aberrations predicted for a significantly increased risk of death. Achievement of major hematologic response and/or complete cytogenetic response to first line treatment predicted for better survival. Combination of TKI with intensive chemotherapy followed by stem cell transplant confer the best outcome.

Conclusions—Patients with CML-BP continue to pose a therapeutic challenge, have dismal outcomes and require newer treatment approaches.

Keywords

Chronic myeloid leukemia in blast phase; CML; CML-BP; Tyrosine kinase inhibitors (TKI); imatinib; nilotinib; dasatinib; ponatinib; bosutinib

Introduction

With the widespread use of tyrosine kinase inhibitors (TKI) for the treatment of chronic myeloid leukemia (CML), the risk of transformation to blast phase has markedly decreased. However a significant minority of patients transform to blast phase; this is less frequent in patients treated with second generation TKI as initial therapy.[1] The median survival in patients with CML-BP is less than 12 months.[2–4,5] The pathobiology of CML-BP involves multiple intermingling pathways with genetic and epigenetic aberrations involved in transformation, but is not fully understood.[6]

Although the poor prognosis of patients with CML-BP is well recognized, the predictive prognostic features in the era of TKI have been scantily addressed. One study with 51 patients in CML-BP (only a minority of whom were treated with TKI) suggested that low platelet count and age >60 years predict for poor survival.[2] Generally, patients with CML-BP are treated with TKI combined with intensive chemotherapy followed by allogenic stem cell transplantation (SCT); survival has improved with combined modality treatment as compared to that seen with TKI alone.[7–9] To the best of our knowledge, this is the largest analysis of CML-BP, describing the clinical characteristics, prognostic factors, survival outcomes and treatments for patients with CML-BP, who received a TKI at some point during the course of CML.

Patients and Methods

Four hundred seventy seven patients with blast phase CML (defined as 30% blasts in peripheral blood and/or bone marrow, or extramedullary disease) who were seen at MDACC from 1997 to 2016 were included in this analysis. A retrospective chart review protocol was approved by the institutional review board (IRB) and waiver of informed consent was

obtained. Response to treatment was assessed after initial treatment for CML-BP as defined previosuly.[10] Major hematologic response (MHR) encompasses both complete hematologic response (CHR) and no evidence of leukemia (NEL). Definitions of cytogenetic and molecular response were as previously described.[11] The pattern of clonal evolution was classified as previously described.[12] Only patients with available treatment and response information and who received frontline therapy for CML-BP were included in the final analysis. Overall survival (OS) was assessed from the date of diagnosis of BP until death or the date of last follow up. Failure free survival (FFS) was assessed from the time start of first line treatment for CML-BP to the date of first relapse, date of switch to second line therapy, date of death, or date of last follow up.

Statistical analysis

Univariate and multivariate Cox proportional hazard models were performed to identify specific characteristics of CML-BP which can predict for survival outcomes. Variables with p-value 0.25 in the univariate analysis were entered into a multivariate model. Median survival and survival probabilities were analyzed using the Kaplan-Meier methods and differences calculated by the log-rank test. We used classification and regression tree (CART) analysis to identify the optimal cut off points for specific parameters associated with survival, subsequently we identified prognostic factors which could independently predict survival in CML-BP. A p-value of <0.05 was considered significant. Statistical analyses were carried out using STATA/SE version 14.1 statistical software (Stata Corp. LP, College Station, Texas).

Results

Patients and disease characteristics

Patients with CML-BP (n=477) who were treated with TKI at some point during the course of their disease were included in this analysis. Among these patients, 343 (72%) were treated with TKI prior to developing CML-BP and 195 (57%) of them were evaluable for response. Response to prior TKI therapy was CHR in 97%, CCyR in 31% and MMR in 11%. The majority (n=381; 80%) of patients were in CML-CP at the time of initial CML diagnosis, with a median time from initial diagnosis of CML-CP to BP of 41 months (range 0.7 to 298 months). Twenty five patients (5%) were in accelerated phase at the time of initial diagnosis of CML; their median time from initial diagnosis of CML-AP to BP was 14 months (range 0.4 to 160 months). De-novo CML-BP was seen in 71 patients (15%). Types of first line treatment received by the patients at the time of initial diagnosis of CML, included – interferon based (37% and 16%), imatinib (26% and 48%), miscellaneous (21% and 16%), dasatinib (6% and 4%), chemotherapy alone (5%) and nilotinib (5% and 16%) for patients in CP and AP, respectively. For patients in CP who were initially treated with imatinib (n=99) and transformed to BP, 24 received imatinib as part of their initial therapy for CML-BP, while 31 received dasatinib, 7 nilotinib, 3 ponatinib and 2 bosutinib.

Patient and disease characteristics at the time of diagnosis of CML-BP are summarized in Table 1 *and in* supplemental figure-1. Overall, median age was 53 years (range, 16 to 84); 64% were male and 65% Caucasian. Extramedullary BP was identified in 128 patients

[27%; isolated extramedullary BP in 50 (39%)]. Distribution of patients according to immunophenotype was myeloid in 67%, lymphoid in 28%, mixed lineage 4%, megakaryocytic 0.5% and undifferentiated 0.5% immunophenotype occurred less frequently; the immunophenotype was unknown in 19 patients. The most common transcript type was e13a2 in 38% patients. Distribution of ABL mutations is shown in Table-1. Forty three percent of patients (n=200) had clonal evolution, of which 18% (n=85) were group 1 (trisomy 8, -Y and extra Philadelphia.), 15% (n=68) were group 2 (iso17, chromosome 3 aberration and -7/-7p), 10% (n=47) were an overlap of both groups, and 57% (n=263) did not belong to either group (Table-2 *and* supplemental figure-2). Six percent of patients had a variant Philadelphia chromosome. Using CART analysis, we identified the optimal cut off values for different continuous variables which correlated with survival outcomes including age (<58 years vs   58 years), hemoglobin (<13 gm/dL years vs   13 gm/dL), platelet count (<102 vs 102×10^9/L), bone marrow blast % (<5% vs   5%) and serum lactate dehydrogenase (LDH) (<1227 IU/L vs   1227 IU/L).

Type of treatments and response to first line therapy in patients with CML-BP

We then analysed the initial treatment for CML-BP and response to therapy in 426 (89%) patients with available information (Summarized in table-3). Treatment modalities were divided into TKI alone (n=149; 35%), TKI plus chemotherapy (n=195; 46%), and non-TKI based therapies (n=82; 19%). Non-TKI based therapies included ara-C-based regimens (non HyperCVAD; n=23), troxacitabine (n=13), Hyper-CVAD (n=6), omacetaxine (n=6), gemtuzumab-based (n=4) and miscellaneous (including investigational) therapies (n=30). Distribution of patients according to the type of TKI was imatinib (n=189; 55%), dasatinib (n=110; 32%), nilotinib (n=26; 7%), ponatinib (n=15; 4%) and bosutinib (n=5; 1%). The overall rates of MHR, CCyR and MMR were 50%, 21% and 12%, respectively. Patients treated with a combination of TKI with chemotherapy had significantly higher MHR compared to other modalities (p=0.0001). Similarly, rates of CCyR and MMR were higher with TKI combined with chemotherapy. Patient treated with dasatinib or ponatinib had a numerical trend for better response rates. MHR was not significantly higher with dasatinib compared to imatinib (p=0.08). Since few patients were treated with other TKI's, we could not compare dasatinib with other TKI's. Of the 149 patients who were treated with TKIs alone as a first line treatment for CML-BP, 80 patients (54%) were treated with imatinib and 76/80 (95%) progressed.

One hundred and four patients (22%) underwent stem cell transplantation (SCT) at some point after the diagnosis of CML-BP. The proportion of patients who received a SCT was higher among those treated with TKI-based combinations (21%) than those treated with TKI alone or non-TKI therapy (3% and 10%, respectively). Twenty five patients (35%) with de novo CML-BP underwent SCT compared to 79 (19%) of those who had transformed from CML-CP/AP. At the time of SCT, 12 patients remained in blast phase, 79 patients (76%) were in MHR and 45 (43%) in CCyR. The proportion of patients who underwent SCT according to the type of responses achieved were: MHR/no MHR (33% vs 16%), CCyR/no CCyR (40% vs 26%), and MMR/no MMR (43% vs 15%). Additional reasons for not undergoing SCT in 373 patients were disease progression/disease related complications in 46%, unknown and/or lost to follow up in 50%, and non-CML associated comorbidities in

4%. Of note, 56 (54%) of the patients who received a SCT required 2 or more therapies for CML-BP to be able to proceed to SCT. Overall, 56 patients (54%) needed second or subsequent therapies to get to stem cell transplant.

Prognostic factors and survival outcomes in patients with CML-BP

The median follow up was 11.5 months (range 0–195). The median overall survival was 12 months with 79% deaths; median FFS was 5 months with 87% failing first line treatment (Figure-1 A–B). We then analysed the impact of various patient characteristics at the time of CML-BP on OS and FFS. Patients with de novo blast phase had longer OS when compared to patients who transformed from CML-CP/CML-AP (p<0.0001) (Figure-1C). As shown in figure 1-D, overall survival has progressively improved since 2000 (i.e., the advent of imatinib) to the present date. Patients with lymphoid immunophenotype and patients who were not treated with TKI prior to CML-BP, had longer survival compared to patients with myeloid immunophenotype (p<0.001) and those who had received TKI prior to transformation to blast phase (p<0.0001) (Figure-1 E–F). We also identified a difference in overall survival with optimal cut off values determined by recursive partitioning for different variables. Patients age 58 years and those with LDH 1227IU/L (p<0.001 in both) had significantly inferior survival (Figure-1 G–H). Other variables (not shown) which showed significant correlation with inferior survival outcome were hemoglobin <13 g/dL, male gender, bone marrow blast at the time of blast phase 5% (compared to extramedullary disease only), platelet count <102 ×10^9/L, lack of isolated EMD, higher number of prior TKI and no SCT after CML-BP. OS was similar in patients exhibiting different transcript types, extramedullary disease (with or without blood/bone marrow disease) and patients with different ABL mutations (not shown). The grouping of chromosomal abnormalities per the classification of Wang et al had no bearing in OS (not shown). However, when survival was analyzed according to individual chromosomal aberrations, patients with trisomy 8, trisomy 19, trisomy 17, or Philadelphia chromosome with other cytogenetic abnormalities, or with chromosome 3 or chromosome 15 aberrations, had significantly inferior OS compared to patients without these aberrations (not shown).

We then looked at the impact of type of treatment and responses achieved in CML-BP. Patients treated with a combination of TKI with chemotherapy had superior outcome compared to TKI alone (p=0.005) (Figure-2A) or with non-TKI based treatments. This correlates with a more frequent use of combination of TKI with chemotherapy (74% of patients treated in 2010–2016 compared to 36% in 2000–2004). Because of the small numbers of patients treated with some individual TKI, no firm conclusions can be drawn about the impact of individual TKI, but there was a suggestion of a better survival for patients treated with dasatinib compared to imatinib (p=0.06) (Figure-2B). Other TKI cohorts have too few patients to evaluate. Patients who received SCT after their initial treatment for CML-BP had a significantly longer survival than patients who did not receive SCT after their initial therapy (Figure-2C). Moreover, patients who achieved MHR or CCyR or MMR after initial blast phase treatment had better survival outcome (Supplemental figure- 3A–C).

We also analysed the impact of patient characteristics on FFS. Patients with myeloid immunophenotype, prior TKI therapy, age 58 years and LDH 1227 IU/L (p<0.001 in both) had significantly inferior FFS. (Supplemental figure-4 A–D). Chromosomal aberrations which showed significant correlation with inferior FFS were chromosome 3 aberrations, trisomy 8, Philadelphia chromosome with other cytogenetic abnormalities, chromosome 15, chromosome 17 aberrations and minus Y (not shown). Patients age 58 years, those with LDH 1227 IU/L hemoglobin <13 g/dL, bone marrow blast 5%, platelet count <102 ×10^9/L, lack of isolated EMD, or with no SCT after CML-BP had a significantly inferior FFS. Patients who achieved MHR or CCyR or MMR after initial blast phase treatment had significantly longer FFS (p<0.0001) (Supplemental figure 3 D-F). Furthermore, patients treated with a combination of TKI with chemotherapy had superior FFS compared to patients treated with TKI alone (p<0.001) (Figure-3A) or with non-TKI based treatments. Similar to OS, there was a trend for longer FFS with dasatinib compared to imatinib (p=0.06) (Figure-3B). Patients who received SCT after their initial treatment for CML-BP had a significantly longer FFS then those patients who did not receive SCT after their initial therapy (Figure-3C).

First-line treatment for patients with de novo CML-BP included TKI alone (n=24; 34%), TKI plus chemotherapy (n=41; 58%), non-TKI based therapies (n=2; 3%) and 4 unknown. Outcomes by type of first line therapy for denovo BP and in patients who progressed from CP/AP is shown in supplemental figure-5 (A–D).

Factors predictive for survival outcomes – multivariate analysis (MVA)

We then created cox regression models for OS (Table-4) and FFS (Supplemental table-1) and identified factors which were associated with survival. In multivariate analysis (MVA) for OS, adjusting for different variables, age 58 years (HR=1.41, p=0.004), platelet count 102 ×10^9/L (HR=0.65, p=0.001), treatment with TKI prior to transformation to CML-BP (HR=1.51, p=0.004), LDH 1227 IU/L (HR 1.32, p=0.01), myeloid immunophenotype (HR=1.67, p<0.001), chromosome 15 aberrations (HR 2.20, p=0.02), transformation from CML-CP/AP (vs. de novo CML-BP; HR 1.43, p=0.06), and treatment with SCT after CML-BP (HR 0.40, p<0.001) were significantly associated with OS. In a separate MVA, we noted that the achievement of MHR and/or CCyR emerged as the most significant independent predictor for survival while isolated EMD was no longer associated with survival (not shown). Type of clonal evolution by group 1, group 2, both or neither groups did not predict for OS.

We then analysed FFS in patients on which we had the available information for their frontline therapy for CML-BP (n=426). The following factors significantly predicted for the increased risk of failure in MVA: myeloid immunophenotype, prior TKI therapy, presence of chromosome 3 aberrations, lack of SCT after CML-BP, non-TKI based therapy and platelet count <102 ×10^9/L (Supplemental Table-1). Similar to the OS, achievement of MHR and/or CCyR predicted for longer FFS, while isolated EMD did not predict for FFS after adjusting for response. In addition, a higher number of TKI therapies prior to progressing to CML-BP was also associated with inferior survival in MVA (OS, p=0.055; FFS p=0.019).

Discussion

Despite the marked progress in therapy for CML, patients who transform to CML-BP have a dismal outcome, particularly if previously treated with TKI. To the best of our knowledge, this is the largest study describing the characteristics and outcome of patients with CML-BP treated with TKI. We have identified that myeloid immunophenotype, treatment with TKI prior to transformation to CML-BP, age ≥ 58 years, LDH ≥ 1227 IU/L, platelet count <102 ×10^9/L, no treatment with SCT after blast phase, transformed CML from CP/AP and the presence of chromosome 15 aberrations were predictive for poor survival in CML-BP.

The incidence of CML-BP has markedly decreased after the introduction of TKI for the treatment of CML, particularly with the use of second and third generation inhibitors.[5,13] However, our data suggests that although the outcome is poor with a median survival of only 12 months, the survival has progressively improved over time. As shown in Figure-1D, there is an improvement in outcome after the introduction of TKI and after 2005, when second generation TKI became increasingly available, first through clinical trials and later through standard of care, it has further improved. This could potentially be due to the increased use of TKI combined with chemotherapy followed by SCT after diagnosis of CML-BP.[9,14] Our results are similar to those reported in previous smaller series treated mostly with imatinib.[7,15] This is despite more patients having received prior TKI before transformation, an adverse prognostic factor identified in our analysis. Our data also suggests that treatment with dasatinib may confer a survival benefit when compared to treatment with imatinib. This is perhaps not unexpected considering the higher potency, wider coverage of abl mutants, and the reported significant albeit modest success for patients treated with dasatinib after imatinib failure.[10] Although it would be expected that similar benefit would be observed with other newer agents, our cohort included too few patients with each individual TKI to draw firm conclusions in this regard. Similarly, we cannot make any inferences regarding the relative benefit of the different second generation TKI. One of the caveats of our data is that the study is retrospective and the treatment, kinase domain mutation data and the response data were not available for all patients. Furthermore, in our analysis, as therapy became more effective, the rate of transformation decreased over time. For example, only 36 patients were diagnosed with CML-BP after 2013. This affected the exposure to newer TKI such as ponatinib which was approved in December 2012. Only 8 of these 36 patients were treated with ponatinib-based regimen as a first line therapy of CML-BP (including both patients with documented T315I), as combination therapies with other TKI were better known and preferred over single agent TKI by that time. Eventually, 2 additional patients received ponatinib for CML-BP as this therapy and combinations based on ponatinib became more established.[16] We further identified that use of non-TKI based therapies was independently predictive of poor failure free survival compared to TKI based treatments. In our analysis, the median time from initial diagnosis of CML-CP to BP was 41 months (range 0.7 to 298 months) which is perhaps longer than would be expected. The precise reasons for these longer than expected time to transformation is not clear, but we hypothesize that the availability of TKIs and other treatment options, many of them in clinical trials before they were widely available, allowed patients to remain in CP longer even if not having an optimal response.

The pathogenesis of CML-BP in the TKI era has received little attention[17] and precise molecular mechanisms/mutational/epigenetic changes delineating the transition from chronic phase CML to accelerated phase and blast phase CML are still unclear. It is possible that treatment with TKI exerts a selection pressure over CML cells which can then evolve over time and develop into an overt BP.[18] Our data could be viewed as supportive of this hypothesis since we have shown that prior TKI therapy was a poor prognostic factor in CML-BP. Whether this transition is dependent upon exposure to TKI or is secondary to an inherent mutation profile of various sub clones which evolve over time is unclear.[19] Existence of these sub clones which could predispose to an overt BP is supported by one study which showed that the presence of cells with aberrant immunophenotype - myeloid or lymphoid in CML-CP patients can predispose CML patients to CML-BP.[20] Whether the sub clones give rise to a more resistant disease is not known, but since we show that denovo CML-BP had better outcome than those who transformed from CP/AP (supplemental figure-5), our results would be compatible with this hypothesis. Our study also shows a very high incidence of clonal evolution, more frequently observed than ABL kinase domain mutations, suggesting that transformation is the result of complex molecular processes rather than the mere development of resistance to TKI. One recent study suggested the presence of novel fusions in *MLL* gene and in *ANKRD11* gene in patients with CML-BP, using RNA sequencing.[21] Previously, *ABL, RUNX1, ASXL1*[22] *and IDH1* mutations were described in patients with CML-BP,[23] however paired sample analysis from several patients on TKI therapy was not reported. In contrast, the presence and type of ABL kinase domain mutations had minimal prognostic consequences as we had previously reported.[24]

Our analysis generated some novel findings. We identified that chromosome 15 aberrations, which are uncommon in CML, constitutes a poor prognostic risk factor in CML-BP. Chromosome 15 abnormalities are identified as a minor route abnormality in CML.[25] The long arm of chromosome 15 contains a tumor suppressor gene *CCNDBP1*[26] which is down regulated in different cancers, but its role in CML is unknown. In addition we identified the optimal cut off points for various parameters which indicated high disease burden in CML-BP such as elevated serum LDH levels, low platelet count and low hemoglobin level. Advanced age and low hemoglobin were shown to predict for poor survival in another study from 51 patients with CML-BP, most of them not treated with TKI.[2] Some chromosomal abnormalities were significantly correlated to survival in univariate but not in MVA such as trisomy 8, trisomy 19. Interestingly, the type of clonal evolution[12] and chromosome 17 abnormalities did not predict for survival. In addition, age 58 years and lack of SCT after the diagnosis of BP were also predictive for poor OS. Our analysis also showed that prognostic factors for FFS were similar to those for OS, except that non-TKI based therapy and chromosome 3 aberrations significantly predicted for increased risk of failure of first line therapy. Chromosome 3 aberrations were previously reported to have poor prognostic impact in patients with CML.[27] Importantly, response to therapy is incorporated into the MVA, achievement of MHR or CCyR after first line treatment for CML-BP was a stronger predictor for longer survival compared to other prognostic factors. We also identified isolated EMD as a favorable factor for survival compared to patients with bone marrow involvement with or without EMD.

In summary, this study provides the most comprehensive analysis of the disease characteristics and outcome of patients with CML-BP in the TKI era. It identifies novel leads into the prognostication and survival outcomes of patients with CML-BP in the TKI era. Treatment with a combination of TKI and chemotherapy followed by SCT remains the backbone in the management of these patients. New approaches to treat patients with CML-BP that address the molecular complexity of CML-BP are needed.[28,2930]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Condensed Abstract

Myeloid immunophenotype, prior TKI use, older age, higher LDH, low platelet count, stem cell transplantation (SCT) after blast phase, transformed CML from CP/AP and presence of chromosome 15 abnormalities were predictive for poor survival in CML-BP. Patients with CML-BP treated with a combination of TKI with chemotherapy have superior survival then TKI alone.
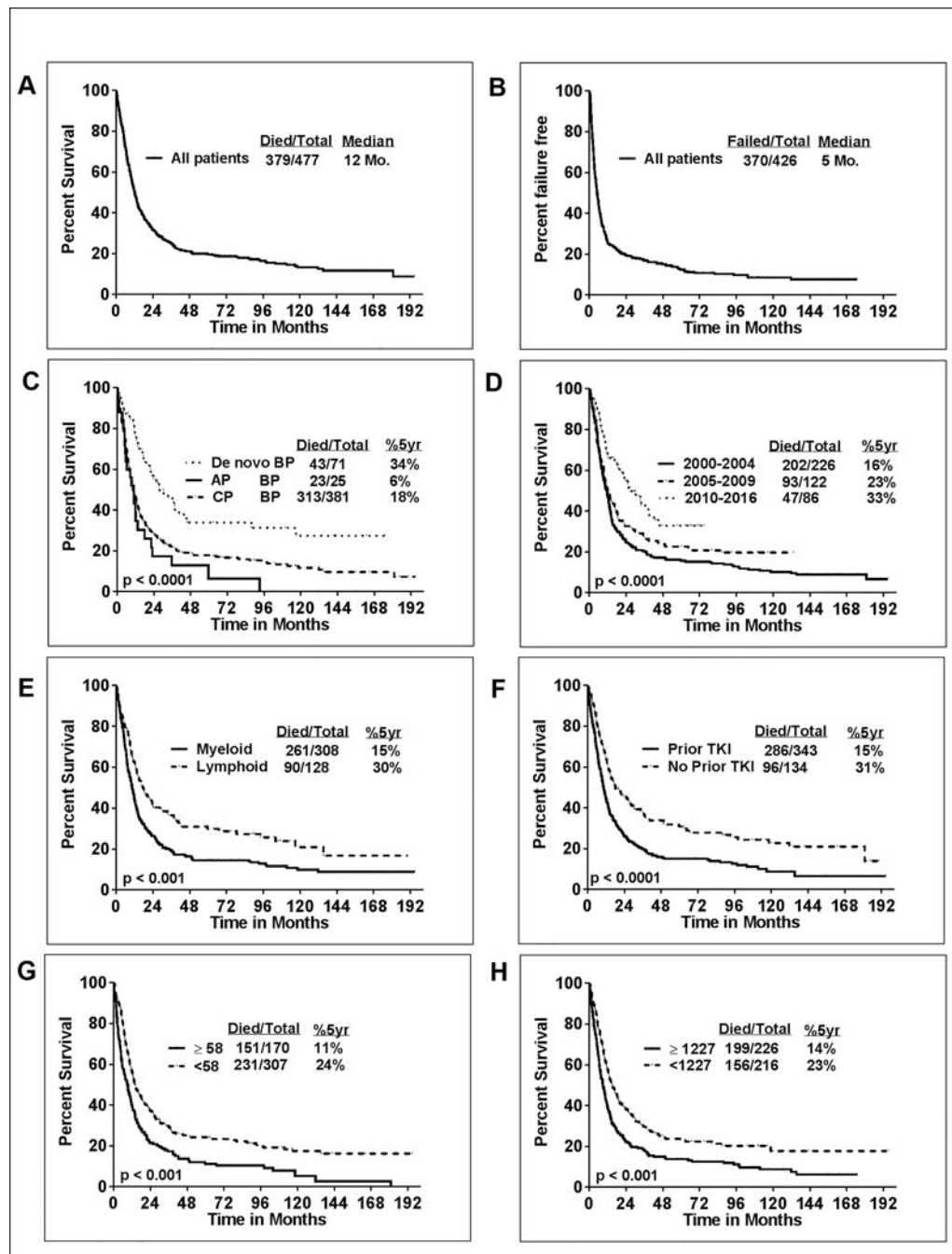
Figure-1. Survival outcome in patients with CML-BP – Overall and according to patient characteristics

A) Overall survival (OS) for all patients. The median overall survival was 12 months with 79% deaths. **B)** Failure free survival (FFS) for all patients. The median FFS was 5 months with 87% failing first line treatment **C)** Patients with de novo blast phase had better OS compared to patients who transformed from chronic/accelerated phase CML; p<0.0001 **D)** Survival has progressively improved after the advent of imatinib in 2000 and is significantly better in the current era; p<0.0001 **E)** Patients with myeloid immunophenotype of CML-BP

have inferior survival compared to CML-BP with lymphoid immunophenotype (p<0.001; 5 year survival % is 15% vs 30%) **F)** Patients previously treated with tyrosine kinase inhibitor (TKI) had poor survival (p<0.0001; 5 year survival % is 15% vs 31%) **G)** Patients age   58 years had poor survival (p<0.001; 5 year survival % is 11% vs 24%). The cut off of 58 years is derived from recursive partitioning **H)** Patients with LDH levels   1227 IU/L had poor survival (p<0.001; 5 year survival % is 14% vs 23%). The cut off of 1227 for serum LDH is derived from recursive partitioning method
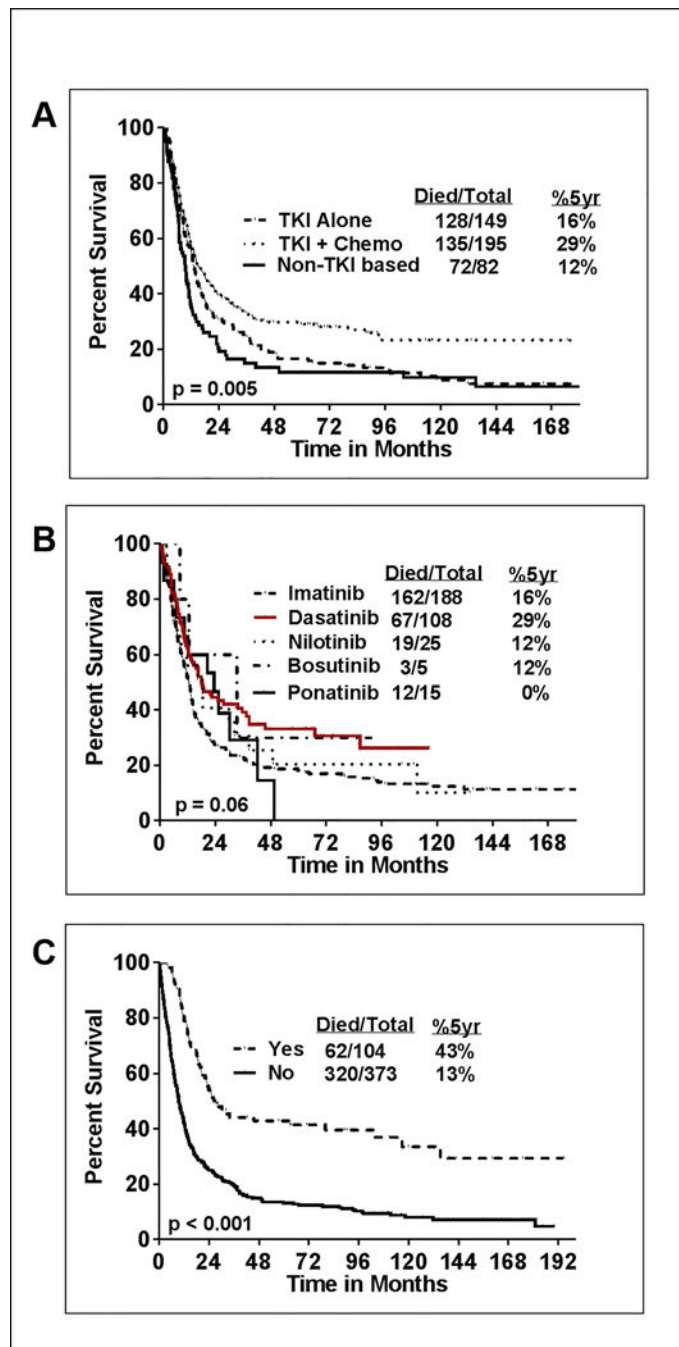
Figure-2. Overall survival (OS) in patients with CML-BP according to treatment modality
A) Patients who are treated with frontline tyrosine kinase inhibitor (TKI) in combination
with chemotherapy had superior survival (p=0.005; 5 year survival % is 30% vs 14% vs 9%)
compared to patients who were treated with TKI alone and non-TKI based therapies as the
first line treatment for CML-BP **B)** Patients treated with various TKI's are shown. Dasatinib
therapy appears to have a better survival compared to other TKI's (p=0.06; 5 year survival %
with dasatinib is 29%. Too few patients to evaluate in nilotinib, ponatinib and bosutinib

cohorts. **C)** Patients who are not treated with stem cell transplantation (SCT) after the diagnosis of CML-BP had inferior survival (p<0.001; 5 year survival % is 13% vs 43%)
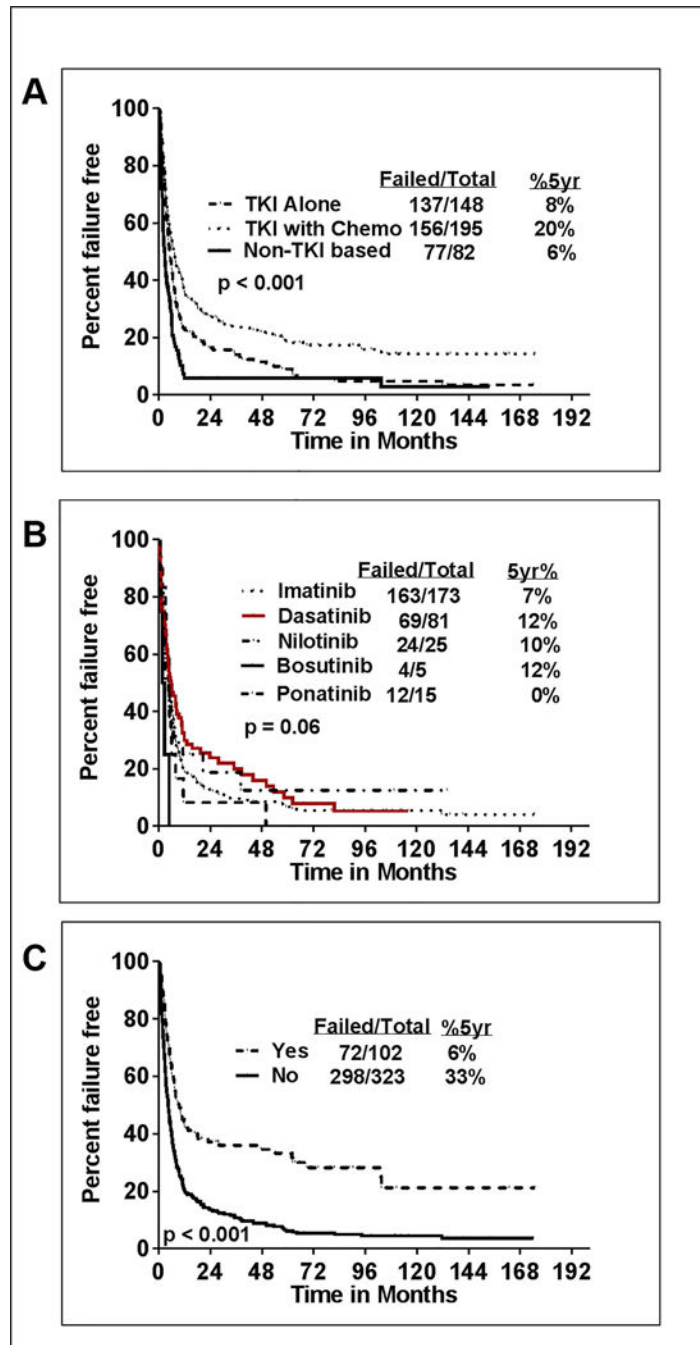
Figure-3. Failure free survival (FFS) in patients with CML-BP according to treatment
A) Patients who are treated with frontline tyrosine kinase inhibitor (TKI) in combination with chemotherapy had superior FFS (p<0.001; 5 year FFS % is 20% vs 8% vs 6%) compared to patients who were treated with TKI alone and non-TKI based therapies as the first line treatment for CML-BP **B)** Patients treated with dasatinib therapy had better survival compared to other TKI's, imatinib, nilotinib, ponatinib, bosutinib (p=0.06; 5 year FFS %

with dasatinib is 20%. **C)** Patients who are not treated with stem cell transplantation (SCT) after the diagnosis of CML-BP had inferior outcome (p<0.001; 5 year FFS % is 6% vs 33%)

Table-1

Patient characteristics at blast phase CML (CML-BP)

Characteristic	No. (%), or Median [Range]
N	477
Age at BP, years [range] [*]	53 [16–84]
Gender (Male/Female)	305 (64)/172 (36)
Ethnicity (Caucasian/Others)	312 (65)/165 (35)
Hemoglobin [g/dL] [*]	10 (0–16)
WBC (K/μL) [*]	19 (0–768)
Platelet (K/μL) [*]	77 (0–2750)
Peripheral blood blast %	21 (0–145)
Bone Marrow blast % [*]	40 (0–99)
Serum LDH (IU/L) [*]	1242 (0–21874)
Serum Uric Acid (mg/dL)	5.6 (0.7–20)
Myeloid/Lymphoid immunophenotype	308 (67)/128 (28)
Prior TKI (Yes/No)	343 (72)/134 (28)
Transcript Type	
e13a2	182 (41)
e14a2	170 (39)
e13a2 +e14a2	74 (17)
e1a2	14 (3)
Extramedullary disease	128 (27)
Isolated extramedullary disease	50 (39)
CNS involvement at any point (Yes/No)	50 (13)/327 (87)
SCT after BP (Yes/No)	104 (22)/373 (78)
Characteristic	**No. (%), or Median [Range]**
Patients with ABL mutation testing	187 (39)
T315I	28 (15)
E255K	15 (8)
F317L	12 (6)
Miscellaneous [#]	39 (21)
Negative	93 (50)
Initial Treatment Type [**]	426 (89)
TKI Alone	149 (35)
TKI with chemotherapy	195 (46)
Others Non-TKI therapies	82 (19)
Type of TKI's used	
Imatinib	189 (55)

Characteristic	No. (%), or Median [Range]
Dasatinib	110 (32)
Nilotinib	26 (7)
Bosutinib	5 (1)
Ponatinib	15 (4)
CML phase at initial diagnosis	
Chronic Phase (CP)	381 (80)
Accelerated phase (AP)	25 (5)
Blast phase (BP)	71 (15)
Time from initial diagnosis to BP (months)	26 [0–298]
CP to BP	381 (80), 41 [0.7–298]
AP to BP	25 (5), 14 [0.4–160]
Median follow-up (months)	11.5 (0–195)
Last follow up status (Alive/Died)	95 (20)/382 (80)

[*] Optimal cut off values identified by CART analysis for different variables were – age (<58 years vs 58 years), hemoglobin (<13 gm/dL years vs 13 gm/dL), white blood cell count (WBP) none identified, platelet count 102 K/μL, bone marrow blast % (<5% vs 5%), serum lactate dehydrogenase (LDH) (<1227 IU/L vs 1227 IU/L),

[#]* ABL mutations (n) – Y253H (8), G250E (4), Q252H (3), E255V (3), M351T (3), V299L (2), F311L (2), H396R (2), other mutations (12, 1 each),

[**] Among those patients who had initial treatment information available

Table-2

Distribution of various chromosomal aberrations at the time of CML-BP

Chromosomal abnormalities	N	%
No. of non-Ph+ chromosomal abnormalities n [Median (range)]	463 [1.0 (0–19)]	97
Classic Philadelphia Chromosome (Ph+) alone		
No	356	76.7
Yes	108	23.3
Double Ph+		
No	382	82.5
Yes	81	17.5
iso17 (i17)		
No	429	92.5
Yes	35	7.5
Trisomy 8		
No	386	83.2
Yes	78	16.8
Trisomy 19		
No	447	96.3
Yes	17	3.7
-Y aberration		
No	448	96.6
Yes	16	3.4
Trisomy 21		
No	446	96.1
Yes	18	3.9
Trisomy 17		
No	457	98.5
Yes	7	1.5
Del7		
No	424	91.4
Yes	40	8.6
Chromosome 3 aberrations		
No	410	88.4
Yes	54	11.6
Variant Ph		
No	435	93.8
Yes	29	6.3
Chromosome 15 aberrations		
No	454	97.8

Chromosomal abnormalities	N	%
Yes	10	2.2
Chromosome 17 aberrations		
No	390	88.4
Yes	70	11.6
Type of clonal evolution, n (%)	200	43
Group 1 (Trisomy 8, -Y and Double Ph.)	85	18
Group 2 (iso17, chr. 3 aberration and -7/-7p)	68	15
Group 1 + 2	47	10
Neither group	263	57

Table-3

Summary of responses and type of frontline treatments for CML-BP

Overall Response with frontline therapies (ITT)	N (%)
Major hematologic response (MHR)	206 (50)
Complete cytogenetic response (CCyR)	88 (21)
Major Molecular response (MMR)	48 (12)
Type of therapies and responses according to type of therapy	

Initial treatment	426 (89)	% Response		
		MHR	CCyR	MMR
TKI alone	149 (35)	43	17	10
TKI with chemotherapy^	195 (46)	64	29	16
Others (non-TKI) therapies	82 (19)	29	13	4
TKIs used for CML-BP				
Imatinib	189 (55)	53	17	10
Dasatinib‡	110 (32)	64	34	22
Nilotinib*	26 (7)	35	15	15
Bosutinib	5 (1)	40	–	–
Ponatinib	15 (4)	67	33	27

^
MHR p=0.001,

‡MHR p=0.08,

*
No. of patients with available response data was <5

Table-4

Factors predictive for overall survival (OS) in patients with blast phase CML (CML-BP) - Cox proportional hazard model

	N	Events	Log-rank	HR	95% CI HR	P-value
#^$ **Univariate**						
Age at transformation	477	382		1.02	(1.01–1.02)	<0.001
Hemoglobin (g/dL)	447	358		0.93	(0.89–0.97)	0.001
Serum LDH (IU/L)	442	355		1.00	(1.00–1.00)	<0.001
BP Immunophenotype			<0.001			
Lymphoid	128	90				
Myeloid	308	261		1.57	(1.23–1.99)	<0.001
CML phase at initial diagnosis			<0.001			
De Novo BP	71	43				
AP	25	23		2.56	(1.54–4.25)	<0.001
CP	381	316		2.01	(1.46–2.77)	<0.001
Chromosome 15 aberration			0.125			
No	454	363				
Yes	10	9		1.67	(0.86–3.24)	0.129
Prior TKI			<0.001			
No	134	96				
Yes	343	286		1.68	(1.33–2.12)	<0.001
SCT after BP			<0.001			
No	373	320				
Yes	104	62		0.39	(0.30–0.51)	<0.001
Type of initial treatment			0.001			
Non-TKI based	82	72				
TKI Alone	149	128		0.78	(0.58–1.04)	0.085
TKI with Chemotherapy	195	135		0.58	(0.43–0.77)	<0.001
Age 58 years [*]			<0.001			
No	307	231		1.64	(1.34–2.02)	<0.001
Yes	170	151				
LDH 1227 IU/L [*]			<0.001			
No	216	156		1.56	(1.26–1.92)	<0.001
Yes	226	199				
Hemoglobin 13 g/dL [*]			<0.001			
No	404	332		0.48	(0.32–0.72)	<0.001
Yes	43	26				
BM blast % 5 [*]			<0.001			
No	46	24		2.13	(1.41–3.23)	<0.001

	N	Events	Log-rank	HR	95% CI HR	P-value
#^$ **Univariate**						
Yes	394	327				
Platelet count 102 K/μL*			<0.001			
No	257	220				
Yes	192	141		0.68	(0.55–0.84)	<0.001

	N	Events	Log-rank	HR	95% CI HR	P-value
# **Multivariate**	N	Events	Log-rank	HR	95% CI HR	P-value
BP Immunophenotype						
Lymphoid	128	90				
Myeloid	308	261		1.70	1.30–2.22	<0.001
CML phase at initial diagnosis						
De Novo BP	71	43				
AP	25	23		1.83	1.01–3.32	0.047
CP	381	316		1.43	0.97–2.11	0.069
Chromosome 15 aberration						
No	454	363				
Yes	10	9		2.20	1.12–4.32	0.021
Prior TKI						
No	134	96				
Yes	343	286		1.51	1.14–2.00	0.004
SCT after BP						
No	373	320				
Yes	104	62		0.40	0.29–0.55	<0.001
Age 58 years*						
No	307	231				
Yes	170	151		1.41	1.11–1.78	0.004
LDH 1227 IU/L*						
No	216	156				
Yes	226	199		1.32	1.05–1.65	0.018
Platelet count 102 K/μL*						
No	257	220				
Yes	192	141		0.65	0.51–0.83	0.001

*
Optimal cut off values identified by CART (classification and regression tree) for different variables were – age (<58 years vs 58 years), hemoglobin (<13 gm/dL years vs 13 gm/dL), platelet count (<102 vs 102 K/μL), bone marrow blast % (<5% vs 5%), serum lactate dehydrogenase (LDH) (<1227 IU/L vs 1227 IU/L);

#
Platelet count, white blood cell count, peripheral blood blast %, BCR-ABL transcript type, spleen size, gender type, race, type of treatments, type of TKI used, number of prior TKI, extramedullary disease, LDH levels, bone marrow blast % were not significant in multivariate analysis;

^
Chromosomal aberrations which were significantly predictive of overall survival in univariate but not in multivariate analysis were trisomy 8, trisomy 19, trisomy 17, Philadelphia chromosome with other cytogenetic abnormalities, chromosome 3 aberrations;

$^{\$}$Variables which were significantly predictive for longer survival in univariate analysis but not included in this MVA model due to >20% missing values were achievement of major hematologic response (MHR), complete cytogenetic response (CCyR) and isolated extramedullary disease (EMD). Inclusion of only patients with available MHR or CCyR to the baseline characteristics model predicted for longer survival while isolated EMD did not predict for longer survival in MVA (not shown). Type of clonal evolution by group 1, group 2, both or neither groups did not predict for OS.