Major Adverse Cardiac, Arterial Occlusive, and Venous Occlusive Events among Chronic Myeloid Leukemia Patients Prescribed Ponatinib vs Bosutinib

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Background

- Chronic myeloid leukemia (CML) is a bone marrow and blood disorder accounting for 15% of adult leukemia.[1]
- Ponatinib, a tyrosine kinase inhibitor (TKI), was recently introduced for CML treatment in patients who may have failed previous treatments due to resistance, intolerance, or low clinical response.[2]
- Given the concerns for arterial occlusion, venous thromboembolism, heart failure, and hepatotoxicity, black box warnings in the prescribing information have been added for ponatinib.[3]
- However, an association between drug use and cardiovascular (CV) events has been observed with other TKIs used in the treatment of CML.[4]

Objectives

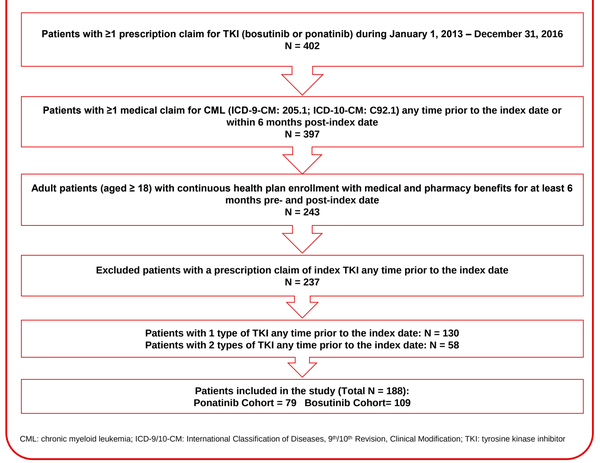
To assess the incidence of major adverse cardiac events (MACEs), arterial occlusive events (AOEs), and venous occlusive events (VOEs) among CML patients who were prescribed ponatinib vs bosutinib in routine clinical practice in the United States

Methods

Study Sample

- A retrospective observational study was conducted among CML patients with evidence of 1 or 2 prior TKI utilizations who were prescribed bosutinib or ponatinib. Study patients were selected from the IBM® MarketScan® Research ("MarketScan") database from July 1, 2012 through June 30, 2017.
- The index TKI prescription was identified in the following hierarchical order: (1) ponatinib and (2) bosutinib without ponatinib. Bosutinib was included as the reference because of its similar clinical use as ponatinib.
- Inclusion and exclusion criteria are shown in Figure 1.
- The follow-up period ranged from the index date to the earliest of index TKI discontinuation, switch to another TKI, end of continuous medical or pharmacy plan enrollment, or end of the study period.

Figure 1. Patient Flow Chart



CML: chronic myeloid leukemia; ICD-9/10-CM: International Classification of Diseases, 9th/10th Revision, Clinical Modification; TKI: tyrosine kinase inhibitor

Baseline Variables

- Patient demographics, including age, sex, and clinical characteristics were examined. The latter included CML disease severity, baseline comorbidities, and concomitant medication use.

Outcome Measures

- MACE was defined as a composite of stroke (hemorrhagic stroke and ischemic stroke), myocardial infarction, and inpatient death.
- AOEs were defined as CV events (transient ischemic attack, ischemic heart disease, and ischemic stroke), cerebrovascular events (precerebral and cerebral occlusion), and peripheral vascular events. VTEs were defined as pulmonary embolism and deep vein thrombosis. VOEs were defined as a composite of AOEs and VTEs.
- Numbers and percentages of patients with concomitant medication use during the follow-up period, such as anticoagulants and antiplatelets, were also examined.

Statistical Analysis

- Descriptive analysis was conducted to compare the outcomes between the ponatinib and bosutinib cohorts. Chi-square tests and Student's t-tests were used to generate p-values for categorical and continuous variables, respectively. Kaplan-Meier curves were provided for the study outcomes.
- The unadjusted incidence rates and p-values were calculated using Poisson regression with the cohort indicator as the only independent variable.
- Inverse probability of treatment weighting (IPTW) was applied to compare MACEs, VOEs, and AOEs between the ponatinib and bosutinib cohorts. The propensity score was calculated using a multinomial logistic model; baseline covariates (including demographic and clinical characteristics) and two treatment cohorts (reference: Bosutinib cohort) were included in the model.
- Cox proportional hazards models with stepwise selection were used to calculate the hazard ratios (HRs) with stabilized propensity score weights and robust standard errors. Imbalanced baseline covariates with profound clinical impact after IPTW were included in the model.

Sensitivity Analysis

- To test the robustness of the results, a sensitivity analysis was conducted using Optum® Clinformatics® ("Optum") data from October 1, 2012 through September 30, 2017. The same patient selection criteria and variables were applied and assessed. Due to the small sample size, however, only descriptive analysis was conducted for the Optum data population.

Results

- After applying the selection criteria, 79 and 109 patients were included in the ponatinib and bosutinib cohorts, respectively (Figure 1).
- The mean ages were 53 years (ponatinib cohort) and 58 years (bosutinib cohort) (Table 1).
- Most ponatinib patients initiated treatment with a dose of 45mg (61%), and most bosutinib patients initiated with a 500mg dose (55%; Table 1).
- The average CCI scores were 1.23 for ponatinib and 1.81 for bosutinib patients (Table 1).
- The most common baseline comorbid conditions included anemia (ponatinib: 49%; bosutinib: 34%), hypertension (ponatinib: 33%; bosutinib: 46%), and diabetes (ponatinib: 15%; bosutinib: 29%; Table 1).
- Some patients were observed to have CV events before index ponatinib or bosutinib use:
  - MACE (ponatinib: 8%; bosutinib: 16%);
  - AOEs (ponatinib: 15%; bosutinib: 28%); and
  - VTE (ponatinib: 1%; bosutinib: 6%; Table 1).
- Similar percentages of patients with ponatinib or bosutinib had evidence of anticoagulant use (11%). More bosutinib patients (12%) had baseline use of antiplatelets than ponatinib patients (0%; Table 1).

Table 1. Descriptive Baseline Characteristics for CML Patients with Use of 1 or 2 TKI Types Pre-index Date

	Ponatinib (N = 79)		Bosutinib (N = 109)		
	N/Mean	%/SD	N/Mean	%/SD	P-value
Age	52.56	13.64	57.61	13.74	**0.013**
Female	41	52%	52	48%	0.570
CML Disease Severity					
Low	1	1%	2	2%	0.759
Moderate	60	76%	101	93%	**0.001**
High	17	22%	5	5%	**<0.001**
Unknown	1	1%	1	1%	0.818
Baseline Comorbid Indices					
Quan-Charlson Comorbidity Index	1.23	2.04	1.81	2.33	0.078
Chronic Disease Score	4.14	3.85	5.58	4.18	**0.017**
Starting Daily Dose					
Low Starting Dose	0	0%	41	38%	**<0.001**
Standard Starting Dose	31	39%	60	55%	**0.032**
High Starting Dose	48	61%	8	7%	**<0.001**
Baseline Comorbidities					
Anemia	39	49%	37	34%	**0.033**
Diabetes	12	15%	32	29%	**0.024**
Chronic Pulmonary Disease	8	10%	20	18%	0.118
Congestive Heart Failure	8	10%	20	18%	0.118
Hypertension	26	33%	50	46%	0.074
Hypercholesterolemia	7	9%	15	14%	0.302
Obesity	6	8%	10	9%	0.702
Renal Disease	10	13%	19	17%	0.371
MACE	6	8%	17	16%	0.098
Myocardial Infarction	4	5%	11	10%	0.209
Ischemic Stroke	1	1%	5	5%	0.201
AOE	12	15%	30	28%	**0.045**
Cardiovascular Events	10	13%	29	27%	**0.020**
Cerebrovascular Events	0	0%	10	9%	**0.006**
Peripheral Vascular Arterial Events	2	3%	5	5%	0.462
VTE	1	1%	7	6%	0.084
Concomitant Medications					
Anticoagulants	9	11%	13	12%	0.910
Antiplatelet	0	0%	13	12%	**0.001**
Angiotensin Converting Enzyme Inhibitor	11	14%	20	18%	0.420
Angiotensin Receptor Blocker	11	14%	15	14%	0.975
Beta Blockers	13	16%	41	38%	**0.002**
Statins	8	10%	46	42%	**<0.001**
Anti-diabetics	12	15%	25	23%	0.187
Bone Marrow Stem Cell Transplant (anytime pre-index date)	11	14%	2	2%	**0.001**

AOE: arterial occlusive event; CI: confidence interval; CML: chronic myeloid leukemia; IPTW: inverse probability of treatment weighting; MACE: major adverse cardiac event; SD: standard deviation; TKI: tyrosine kinase inhibitor; VOE: venous occlusive event; VTE: venous thromboembolism

Outcomes

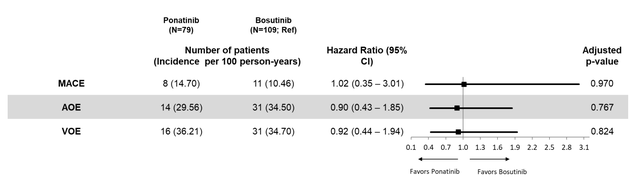
- The mean duration of follow-up was ~23 months across the two cohorts, and the median follow-up was ~19 months (Table 2).
- Consistent with the baseline results, in the follow-up period, similar percentages of patients with ponatinib and bosutinib use also had use of anticoagulants (14%-23%); more bosutinib patients (13%) had evidence of antiplatelet use than ponatinib patients (4%; Table 2).
- In the follow-up period, ponatinib patients were associated with similar incidence of MACEs (14.70 vs 10.46 per 100 PYs; p=0.464), AOEs (29.56 vs 34.50 per 100 PYs; p=0.632), and VOEs (36.21 vs 34.70 per 100 PYs; p=0.890) compared with bosutinib patients (Figure 2).
- Inpatient ponatinib and bosutinib patients also had similar incidence of inpatient MACEs (9.03 vs 5.55 per 100 PYs; p=0.422), AOEs (20.26 vs 16.78 per 100 PYs; p=0.636), and VOEs (22.30 vs 17.77 per 100 PYs; p=0.553).

Table 2. Descriptive Outcomes for CML Patients with 1 or 2 Types of TKI Use Pre-index Date

	Ponatinib (N = 79)		Bosutinib (N = 109)		
	N/Mean	%/SD	N/Mean	%/SD	P-value
Duration of Follow-up Time (in days)					
Mean, SD	692.03	439.65	673.09	415.63	0.764
Median	598		579		
Duration of Index Treatment (in days)					
Mean, SD	255.76	302.63	383.41	410.37	**0.015**
Median	152		249		
Concomitant Medications					
Anticoagulants	18	23%	15	14%	0.108
Antiplatelet	3	4%	14	13%	**0.033**
Angiotensin Converting Enzyme Inhibitor	17	22%	20	18%	0.589
Angiotensin Receptor Blocker	9	11%	15	14%	0.631
Beta Blockers	20	25%	41	38%	0.075
Statins	11	14%	36	33%	**0.003**
Anti-diabetics	15	19%	21	19%	0.962

CML: chronic myeloid leukemia; SD: standard deviation; TKI: tyrosine kinase inhibitor

Figure 2. Unadjusted Incidence Rates and IPTW Hazard Ratios* of MACEs, AOEs, and VOEs (IBM MarketScan population)

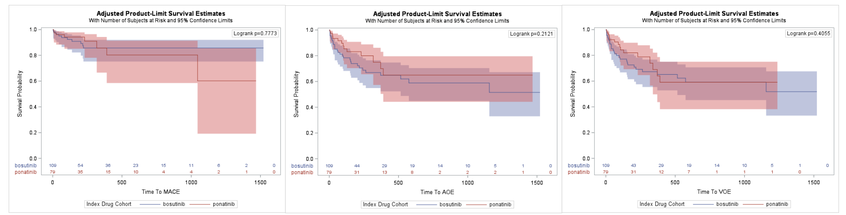


AOE: arterial occlusive event; CI: confidence interval; IPTW: inverse probability of treatment weighting; MACE: major adverse cardiac event; VOE: venous occlusive event

* Cox proportional hazards models with stepwise selection were used to calculate the hazard ratios and adjusted p-values.

- The Kaplan-Meier curves for CV events (MACE, AOEs, VOEs) are shown in Figure 3. Patients with ponatinib and bosutinib use had similar time to MACEs, AOEs, and VOEs (all logrank p-values>0.05).
- After applying IPTW and further adjusting for additional confounders using Cox models, compared to those with bosutinib use, ponatinib patients were associated with similar rate of MACEs (HR: 1.02; 95% CI: 0.35, 3.01; adjusted p-value=0.970), AOEs (HR: 0.90; 95% CI: 0.43, 1.85; adjusted p-value=0.767), and VOEs (HR: 0.92; 95% CI: 0.44, 1.94; adjusted p-value=0.824) (Figure 2).

Figure 3. Cumulative Incidence of MACE, AOE, and VOE between Ponatinib and Bosutinib Patients in the MarketScan Population

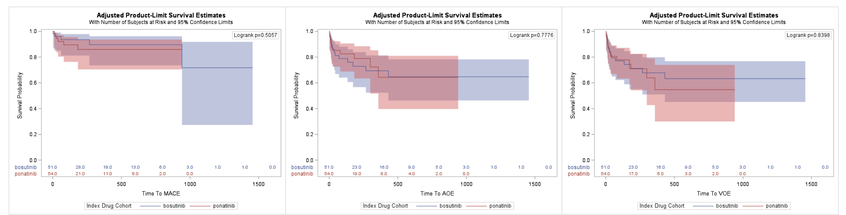


AOE: arterial occlusive event; MACE: major adverse cardiac event; VOE: venous occlusive event

Sensitivity Analysis

- In the Optum data population, similar descriptive baseline and outcome results were observed for the two cohorts (data not shown). The Kaplan-Meier curves are shown in Figure 4. No significant difference was observed between ponatinib and bosutinib patients for MACE, AOE, and VOE outcomes.

Figure 4. Sensitivity Analysis: Cumulative Incidence of MACE, AOE, and VOE between Ponatinib and Bosutinib Patients in the Optum Population



AOE: arterial occlusive event; MACE: major adverse cardiac event; VOE: venous occlusive event

Limitations

- As a retrospective observational study, the data only support conclusions about associations, not causation.
- As events were assessed during TKI treatment, specific associations between treatment and long-term events cannot be ascertained.
- Given the nature of claims data, laboratory test results and biomarkers were not available. Diagnoses and drug prescriptions were neither identified nor verified beyond claims entries. Missing values, coding errors, and lack of clinical accuracy may have introduced bias into the data.
- The analysis was conducted in a US commercial claims database with a relatively small sample size; the results may have limited applicability to other populations. However, the robustness of the results was tested in two different datasets; and the results are consistent.

Conclusions

Among CML patients treated with second- or third-line ponatinib or bosutinib, similar risk of CV events (MACE, AOEs, VTEs) were observed in the follow-up in this study in a community setting.

References

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Disclosures

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M. Levy is a paid consultant to Millennium Pharmaceuticals, Inc., the study sponsor.
F. Neumann, S. Srivastava, D. Naranjo, J. Xu, and M. Dalal are employees of Millennium Pharmaceuticals, Inc., the study sponsor.
L. Xie, Y. Wang, and Q. Zhang are employees of STATinMED Research, which is a paid consultant to Millennium Pharmaceuticals, Inc., the study sponsor.

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