Original Article

Application of a Pharmacokinetic Model of Metformin Clearance in a Population with Acute Myeloid Leukemia

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Abstract

Objective: We aimed to estimate the metformin-associated lactic acidosis (MALA) risk by assessing retrospectively the renal clearance variability and applying a pharmacokinetic (PK) model of metformin clearance in a population diagnosed with acute myeloid leukemia (AML) and diabetes mellitus (DM). **Methods:** All adults with preexisting DM and newly diagnosed AML at Roswell Park Cancer Institute were reviewed (January 2003–December 2010, n = 78). Creatinine clearance (CrCl) and total body weight distributions were used in a two-compartment PK model adapted for multiple dosing and modified to account for actual intra- and inter-individual variability. Based on this renal function variability evidence, 1000 PK profiles were simulated for multiple metformin regimens with the resultant PK profiles being assessed for safe CrCl thresholds. **Findings:** Metformin 500 mg up to three times daily was safe for all simulated profiles with CrCl ≥25 mL/min. Furthermore, the estimated overall MALA risk was below 10%, remaining under 5% for 500 mg given once daily. CrCl ≥65.25 mL/min was safe for administration in any of the tested regimens (500 mg or 850 mg up to three times daily or 1000 mg up to twice daily). **Conclusion:** PK simulation-guided prescribing can maximize metformin's beneficial effects on cancer outcomes while minimizing MALA risk.

Keywords: *Acute leukemia, Metformin, Metformin-associated lactic acidosis, pharmacokinetics*

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Introduction

Metformin is the first-line treatment for diabetes mellitus (DM) presenting itself with an unsurpassed safety profile. This molecule may also be the drug that has already prevented more cancer deaths than any other drug in human history.[1] Now highly sought after as both cancer treatment adjuvant and hypoglycemic agent,[2-4] metformin use in cancer patients raises new concerns for safety and risk of metformin-associated lactic acidosis (MALA). This concern is significant particularly in older patients with impaired renal function.[5,6] Despite the well-documented association between metformin use and improved cancer outcomes, the evidence evaluating our ability to estimate MALA risk in cancer patients is lacking. One major barrier for MALA estimation in this population at the time of cancer diagnosis is the intra- and inter-individual variability of renal clearance in patients with similar comorbidities at the time of MALA risk assessment.[1] According to the United States National Diabetes Statistics Report 2014, over 60% of the new DM cases were younger than 65 years.[7] By contrast, the National Cancer Institute indicated that roughly 75% of the new cancer cases were over 65 years.[8] Thus, prescribing metformin to a cancer patient should account for older age, declining renal function, drug-drug interactions, and other age-driven risks (e.g., ongoing comorbidities).

Acute myeloid leukemia (AML) is a hematologic malignancy with a dynamic disease course throughout

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which renal function concerns arise often[9] due to advanced median age at diagnosis,[8] potential occurrence of tumor lysis syndrome (TLS), and the systematic use of iodinated contrast dye – a renally excreted molecule used for diagnostic assessment. Instances as the ones listed above are thought to increase MALA risk in metformin users due to diminished metformin clearance, a fact leading prescribers to substitute metformin for insulin shortly after AML diagnosis rather than taking the risk of an adverse event. While specific data about insulin use and survival in AML is scarce,[10] premature insulin use in acute lymphoblastic leukemia was associated with worse survival.[11] This evidence led us to investigate whether or not continuing metformin would have been a safe clinical approach.

Lacking AML-specific evidence and given metformin's renal clearance,[6] we deemed necessary to conduct a retrospective evaluation of our population's longitudinal renal changes. We focused on using the calculated intra- and inter-individual variability to predict metformin's clearance in a previously published pharmacokinetic (PK) model.[12] In addition, for our MALA risk assessment, we took into consideration previously published reports of acute metformin overdose indicating an upper metformin level threshold of 100 μg/mL and a median reported level exceeding 50 μg/mL.[13] According to a report by Dell'Aglio *et al*., over 60% of the individuals with metformin levels over 50 μg/mL have survived.[13]

Methods

This retrospective cohort study was approved by Roswell Park Cancer Institute and University at Buffalo Institutional Review Boards (EDR193511). Included cases were adults with preexisting DM and emergent AML diagnosed between January 2003 and December 2010. Pathologically confirmed AML was determined as per institute's leukemia database while the International Classification of Diseases, Ninth Revision coding was used to determine the presence of diabetes (250.**). Out of the 78 patients identified to have been diagnosed with both diabetes and AML, 37 were excluded due to incomplete records (n_1 = 34) or unknown diabetes type (n_2 = 3). The remaining 41 cases were included in the final analyses. Longitudinal laboratory records (e.g., computed tomography scans and serum creatinine [SCr]) were automatically queried from electronic medical records while clinical history and demographic information were documented by chart review.

Fisher's exact test, likelihood ratio statistics, or Pearson correlation were used where appropriate to assess associations between tested variables (nominal significance threshold of 0.05). Baseline metformin use was evaluated in relationship with gender, race, body mass index (BMI), smoking status, age, creatinine clearance (CrCl) categories, and instances of contrast dye administration. The assessed age categories were <50, 50–59, 60–69, 70–79, and 80+ years whereas studied BMI categories were 18.5–24.9 kg/m^2, 25.0–29.9 kg/m^2, ≥30 kg/m^2, and unknown. Analyses were carried out using SAS, version 9.4, statistical software (SAS Institute Inc., Cary, NC, USA).

Cockcroft-Gault method was used to estimate CrCl. Distributions, means, and variances of CrCl and total body weight (TBW) were used in a previously studied two-compartment PK model[12] adapted for multiple dosing. That PK model was modified to account for our population's actual intra- and inter-individual variability having no verified metformin clearance model defined for AML patients. This model involved the following parameters: the apparent clearance (CL) in L/h and volume of distribution (Vd) in L with respect to the central compartment, as per

$$CL = \left(\theta_{CL} \times [CrCl/6]\right) \times e^{Var(CL)}$$

$$Vd = \left(\theta_{Vd} \times [TBW/70]\right) \times e^{Var(Vd)}$$

Where θ_{CL} and θ_{Vd} are the mean population parameter estimates of CL and Vd. Var (CL) and Var (Vd) represent the sum of the inter- and intra-observation variability estimates of the respective population parameters. CrCl was simulated from a log-normal distribution while TBW was simulated from a normal distribution, each being representative of the respective observed population values. CrCl and TBW simulations were restricted to the lowest and highest values observed and normalized to the respective median population values.

1000 PK profiles were simulated for each of the following immediate-release metformin regimens: 500 mg or 850 mg once, twice, and three times daily and 1000 mg once and twice daily. The resultant PK profiles were assessed to identify the safe CrCl thresholds. All simulations were performed using R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The median age in our study was 71, with a majority of the cases being Caucasians (80%) and having no prior cancer history (68%) [Table 1]. Half of the participants were smokers. On average, during their treatment

course, each case had the renal function and evaluated 126 times (range: 10–396). The baseline renal function among all participants as depicted by CrCl calculation is summarized in Table 2. Overall, approximately 75% of the participants received iodinated contrast dye during the study interval. There were no significant differences in the distribution of gender, race, BMI, smoking status, age, CrCl categories, or instances of contrast dye administration between metformin users and nonusers.

Table 1: Study patients' demographics by utilization of oral diabetes mellitus treatment at baseline in patients with acute myeloid leukemia

Variable	Metformin users	Other DM drug users	Fisher's exact test (*P*)
Age at baseline (years)			
<50	3 (7.3)	3 (7.3)	0.485
50-59	1 (2.4)	3 (7.3)	
60-69	6 (14.6)	4 (9.8)	
70-79	6 (14.6)	11 (26.8)	
>80	3 (7.3)	1 (2.4)	
Gender			
Female	9 (47.4)	13 (59.1)	0.538
Male	10 (52.6)	9 (40.9)	
Ethnicity			
African American	1 (5.36)	2 (9.09)	0.610
Caucasian	16 (94.74)	18 (81.82)	
Other	0	2 (9.09)	
BMI at baseline			
18.5-24.9 (healthy)	2 (10.53)	1 (4.55)	0.428
25.0-29.9 (overweight)	6 (31.58)	5 (22.73)	
30+ (obese)	4 (21.05)	10 (45.45)	
Unknown	7 (36.84)	6 (27.27)	
Comorbidities at baseline			
Hypocholesterolemia	10 (52.63)	9 (40.91)	0.538
Cancer history	6 (31.58)	7 (31.82)	1
Hypertension	14 (73.68)	13 (59.09)	0.51
Smoking history	8 (42.11)	13 (59.09)	0.354
Chronic kidney disease	1 (5.26)	1 (4.55)	1
Insulin use at baseline			
Yes	1 (5.26)	8 (36.36)	0.024
No	18 (94.74)	14 (63.64)	

Data presented as *n* (%). BMI=Body mass index, DM=Diabetes mellitus

Table 2: Creatinine clearance categories by utilization of oral diabetes mellitus treatment at baseline in patients with acute myeloid leukemia

CrCl (mL/min)	Metformin users (%)	Other DM drug users (%)	Total (%)
<30	2 (10.53)	4 (18.18)	6 (14.63)
30-59.9	11 (57.89)	11 (50)	22 (53.66)
60-89.9	1 (5.26)	5 (22.73)	6 (14.63)
≥90	5 (26.32)	2 (9.09)	7 (17.07)

Data presented as *n* (%). CrCl=Creatinine clearance, DM=Diabetes mellitus

Upon AML diagnosis, ten metformin users were permanently switched to insulin due to MALA concerns while the remaining metformin users were place on indefinite hold and initiated on sliding scale insulin.

CrCl and TBW varied between 4.7 and 120 mL/min and 52.3 and 130 kg, respectively. The observed mean CrCl was 61 ± 37.67 mL/min. No association was noted between SCr changes and white blood count changes, suggesting a limited TLS contribution (Spearman's correlation estimate = −0.0764, 95% confidence interval: 0.1054 to −0.0472, $P < 0.0001$). In this study, metformin levels >5 μg/mL, as identified by our model simulation, were considered instances of increased MALA risk.[12,13] The upper unsafe limit of CrCl (metformin levels >5 μg/mL) varied with dose and schedule [Table 1], with a mean observed unsafe CrCl in the lower than 25 mL/min category regardless of the simulated regimen. Table 3 summarizes the simulated metformin profiles and analyzed serum concentrations. Specifically for 500 mg daily regimen, the MALA risk was 4.2% (42 out of 1000 simulated profiles) and occurred in those profiles with $CrCl_{max}$ ≤20.69 mL/min (mean ± standard error: 14.58 ± 1.98). The MALA risk increased to 5.7% and 7.3% in the simulations of 500 mg taken twice and three times daily but only in the profiles with $CrCl_{max}$ ≤25.48 mL/min (12.72 ± 1.55 and 13.55 ± 1.42, respectively). The 850 mg dose taken daily revealed a MALA risk of 7.3%, while for the three times, a day schedule was 9.3% among individuals with $CrCl_{max}$ ≤65.25 mL/min (20.16 ± 2.85 and 19.72 ± 2.31, respectively). The MALA risk remained below 10% for both 1000 mg once and twice daily simulations and only among cases with $CrCl_{max}$ ≤65.25 mL/min (22.80 ± 2.97 and 19.60 ± 2.63, respectively). The mean simulated steady-state concentration of metformin for each of the described regimens remained at safe levels.

Discussion

Specific PK models of metformin clearance in cancer patients are currently lacking, modeling reports published to date being limited to healthy participants only. Based on our knowledge, this PK simulation is the first conducted in cancer patients, relying on actual retrospectively acquired clinical evidence. The main limitations of this study were as follows: the inclusion of immediate-release metformin doses only and the absence of a covariance matrix in the simulation, given the borderline significant positive correlation between TBW and CrCl ($P = 0.094$). As a result, our approach did not restrict moderate or high CL values from being simulated in conjunction with a low Vd. Thus, the

Table 3: Metformin pharmacokinetic parameters by dose and schedule

Dose (mg) and schedule	Dose interval AUC_{ss}	C_{ss}	Profiles >5 µg/mL		C_{max} (µg/mL)	Mean CrCl (95% CI)
			$CrCl_{max}$ (mL/min)	Count		
500 daily	16.65	0.69	20.69	42	23.04	14.58 (10.94-19.45)
500 every 12 h		1.39	25.48	57	43.79	12.72 (10.25-15.80)
500 every 8 h		2.08	25.48	73	65.41	13.55 (11.74-15.65)
850 daily	28.30	1.18	65.25	73	39.17	20.16 (15.62-26.02)
850 every 12 h		2.36	65.25	86	74.43	18.23 (14.76-22.52)
850 every 8 h		3.54	65.25	93	111.20	19.72 (16.16-24.05)
1000 daily	33.30	1.39	65.25	82	46.09	22.80 (17.71-29.36)
1000 every 12 h		2.77	65.25	88	87.57	19.60 (15.75-24.39)

AUC_{ss}=Area under the curve at steady state, C_{ss}=Steady-state concentration, $CrCl_{max}$=Maximum creatinine clearance, C_{max}=Maximum concentration, CrCl=Creatinine clearance CI=Confidence interval

possibility of simulating a profile exceeding 5 µg/mL, despite having a higher CrCl, was maximized.

Our data indicate a low MALA risk in most of the profiles generated from the present AML patient database. These findings are in agreement with the current metformin label updates regarding renal adjustments[13] which could, potentially, be extrapolated to individuals diagnosed with DM and other malignancies. However, for a more precise risk calculation, PK validation studies will be necessary to establish the exact relationship between estimated CrCl, considered metformin regimen, and the expected blood level.

Authors' Contribution

ACC was responsible for the study concept, study design, definition of intellectual content, supervision of the data acquisition and analysis, and manuscript preparation; GWB and HAM were responsible for data acquisition, literature search, manuscript editing, and review; ZAPW was responsible for statistical analysis, manuscript editing, and review and has contributed to the study design. ACC takes full responsibility for the integrity of the work from the inception to the published article and is designated as "Guarantor."

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Conflicts of interest

There are no conflicts of interest.

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