Effects of Genetic Polymorphism on Pharmacokinetics of Cyclophosphamide in Conditioning Regimen for Adult Hematopoietic Cell Transplant Patients

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Introduction

- Cyclophosphamide (CY) is a commonly used chemotherapy agent in the conditioning regimen for hematopoietic cell transplant (HCT).

- Variable exposure of CY may affect the HCT outcomes [1,2], but its predictors are not well-studied.

- We aimed to explore potential single nucleoside polymorphisms (SNPs) that are associated with pharmacokinetics (PK) of CY.

Methods

Design: Observational pharmacogenomic-PK study
Patients: Adults HCT recipients on non-myeloablative regimen with CY on Day -6 (n = 85)

PK study:
- Blood sampling at 4, 6, 8, 26, 47 hours after the start of CY infusion
- Measured concentration of phosphamide mustard (PM), a final cytotoxic metabolite of CY
- Systemic PM exposure, as area-under-the-curve (AUC), was calcularated for three intervals (0-8 hour, 0-26 hours, and 0-infinity) by non-compartmental analysis.

Genotyping:
- Candidate genetic variants potentially associated with CY PK, toxicity and efficacy were identified from the literature.
- Genotyping was conducted for 141 SNPs.

Statistical analysis:
1. Excluded SNPs without association with PM AUCs (p ≥0.05)
2. Combined 3 genotypes into 2 groups when %AUC difference <10%
3. Eliminated highly correlated SNPs in linkage disequilibrium (R^2 >0.9)
4. Conducted stepwise multiple linear regression model selection by including the remaining SNPs, age, sex, and creatinine clearance (CrCL)
5. Final model included significant SNPs (p <0.05) and CrCL

Results

Table 1. Study population (n = 85)

	Total
Age, mean (SD)	61 (10)
Age <60, n (%)	28 (33%)
Age ≥60, n (%)	57 (67%)
Male, n (%)	47 (55%)
Female, n (%)	38 (45%)
Creatinine clearance, mean (SD)	79.5 (23.0)
Race/ethnicity	
White	82 (97%)
Native American	1 (1%)
Unknown	2 (2%)
Diagnosis	
Acute myeloid leukemia	29 (34%)
Myelodysplastic syndrome	16 (19%)
Multiple Myeloma	7 (8%)
Acute lymphoblastic luekemia	6 (7%)
Myeloproliferative disease	6 (7%)
Others	21 (24%)

Table 2. PK parameters of PM

Parameters	Median	Range
T_{max} (hour)	6	(4 – 23)
C_{max} (ng/mL)	5126	(2269 – 14248)
AUC 0-8 hour*	28494	(13285 – 66221)
AUC 0-26 hour*	73756	(36624 – 126512)
AUC 0-infinity*	83612	(40269 – 141270)
CL (L/hr)	49.1	(24.8 – 106.9)
CL (L/hr/kg)	0.58	(0.26 – 1.14)

Note: T_{max}, time at maximum concentration; C_{max}, maximum concentration; CL, clearance; *unit is (ng•hr/mL)
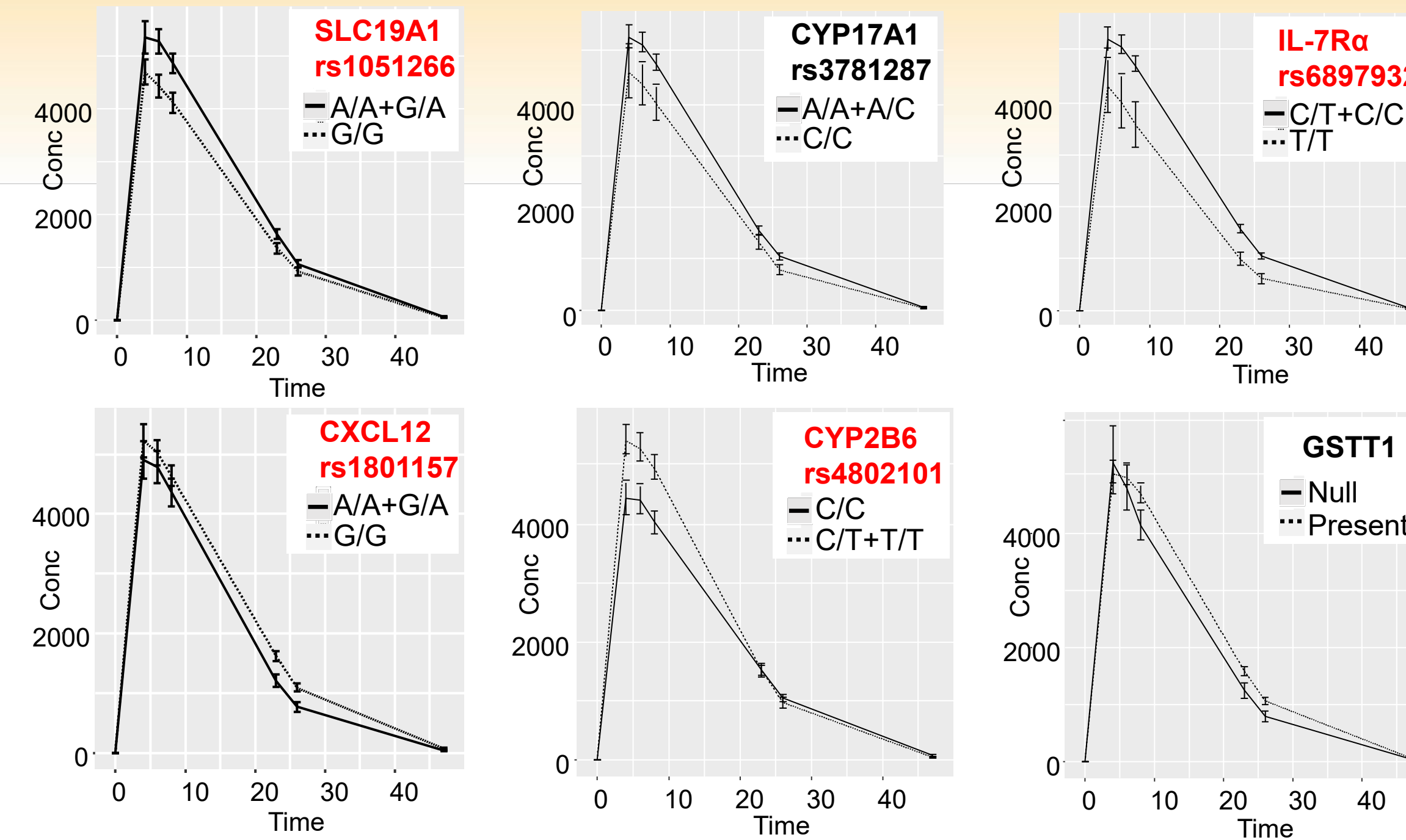

Figure 1. Time-concentration data by genotypes

Table 4. Multiple linear regression analysis

	AUC 0-8			AUC 0-26			AUC 0-inf		
	Estimate	(95%CI)	p	Estimate	(95%CI)	p	Estimate	(95%CI)	p
Creatinine clearance	32	(-59 – 123)	0.48	110	(-55 – 274)	0.19	136	(-49 – 322)	0.15
rs1051266: G>A (SLC19A1) G/G (vs. G/A+A/A)				-12449	(-20023 – -4875)	<0.01	-15119	(-23651 – -6587)	<0.01
rs1801157: A>G (CXCL12) A/A+A/G (vs. G/G)				-13566	(-21364 – -5768)	<0.01	-17677	(-26461 – -8893)	<0.01
rs3781287: C>A (CYP17A1) C/C (vs. C/A+A/A)				-12955	(-22729 – -3181)	0.010	-13487	(-24497 – -2476)	0.02
rs4802101: C>T (CYP2B6) C/C (vs. C/T+T/T)	-5691	(-9871 – -1511)	0.008	-7855	(-15674 – -35)	0.049	-5970	(-14779 – 2838)	0.18
rs6897932: T>C (IL-7Rα) T/T (vs. T/C+C/C)				-14410	(-24980 – -3839)	0.008	-20022	(-31929 – -8115)	<0.01
GSTT1: Null (vs. Present)				-6255	(-15315 – 2806)	0.17	-11130	(-21336 – -924)	0.03

Discussion

CYP2B6
- Lower PM AUC $_{0-8}$ and AUC$_{0-26}$ were associated with a 2KB upstream variant (rs4802101) of CYP2B6, which is a major enzyme of CY to form PM.
- This variant was reported to have 2-fold lower exposure of a CY active metabolite in patients with systemic lupus erythematousus [3].

SLC19A1, IL7Rα, CXCL12
- Two functional variants were associated with low PM AUC$_{0-26}$ and/or AUC$_{0-inf}$; rs1051266 in SLC19A1 (p.His27Arg) and rs6897932 in IL7Rα (p.Thr244Ile).
- An intron variant of CXCL12 (rs1801157) also showed low PM AUC$_{0-26}$ and/or AUC$_{0-inf}$.
- These genes were not known to be involved in CY metabolism.

Conclusion

- We confirmed a previously reported effect of a *CYP2B6* variant on CY PK in a different population.

- We identified novel SNPs that are associated with PM exposure. These variants need to be validated in other populations and their functionality needs to be assessed.

References: [1] McDonald, et al. Blood. 2003 Mar 1;101(5):2043-8. [2] McCune, et al. Clin Pharmacol Ther. 2009 Jun;85(6):615-22. [3] Shu, et al. Br J Clin Pharmacol. 2016 Feb;81(2):327-40.