POLYMORPHISMS IN DRUG-METABOLISM GENES AND RISK ASSOCIATIONS FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction

Polymorphisms in genes that code for drug metabolism enzymes (DME) alter the risk for pediatric acute lymphoblastic leukemia (ALL) development and modulate the antineoplastic therapy efficacy in children with ALL, being a key cause of variability in ALL susceptibility and treatment response. The figure 1 shows the relation between DME and the treatment of ALL. Our aim is to investigate the risk associations between DME gene polymorphisms and ALL susceptibility and outcome.

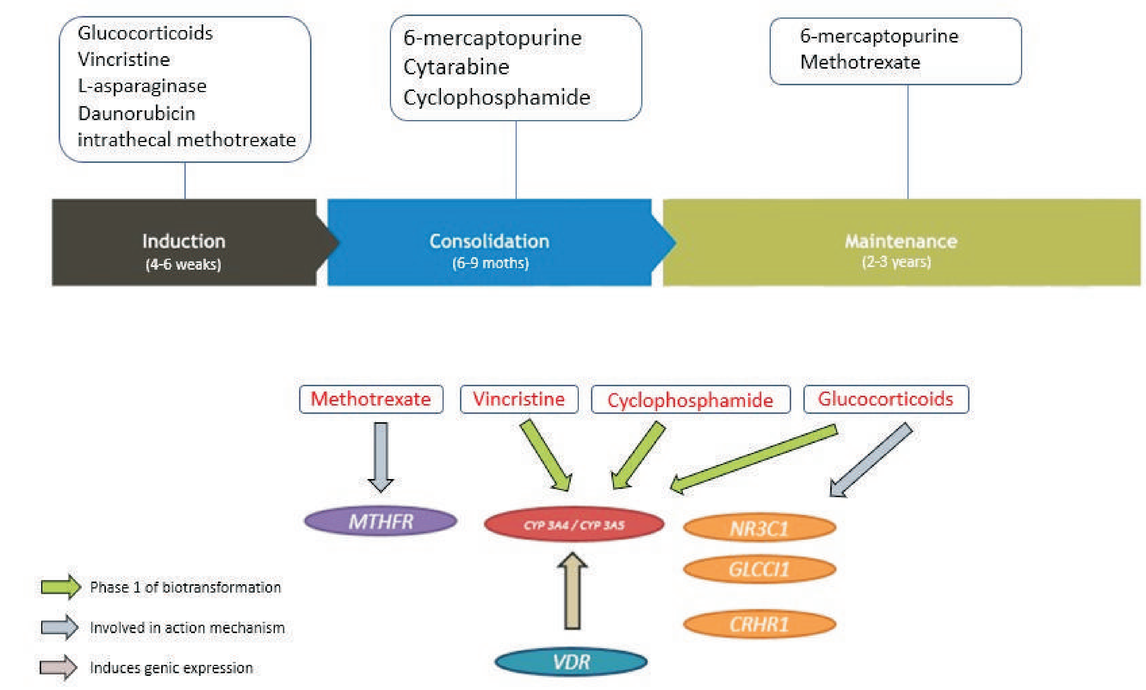

Figure 1. Pediatric ALL treatment and the relation between the studied genes and drug metabolism.

Methods

A genotyping study was designed (ALL and healthy controls; 1:1 ratio) in order to establish ALL susceptibility association. Then, a case-case analysis will be performed to access treatment responses. Patients have been treated following a modified Berlin-Frankfurt-Münster ALL protocol. The analyzed variables included in this model were demographic data, National Cancer Institute (NCI) risk stratification status, glucocorticoid responses at day 8 post-treatment (D8), minimal residual disease (MRD) at D30 and follow-up status. The genotyping is being performed by using high-resolution melting (HRM) technique for variants: *CYP3A4* rs2740574; *CYP3A5* rs776746; *VDR* rs2228570 and rs1544410; *MTHFR* rs1801133; *GLCCI1* rs37972; *CRHR1* rs242941; and *NR3C1* rs41423247. Statistical analysis will be performed in the dominant, recessive and co-dominant genotype models. For the case-control analysis, logistic regression was performed to access the odds ratio (OR) and 95% confidence interval (95% CI). In case-case analysis, Kaplan–Meier survival curves and log-rank test will be carried out to determinate the hazard ratios and 95% CI. The **Figure 2** shows the study design flowchart.

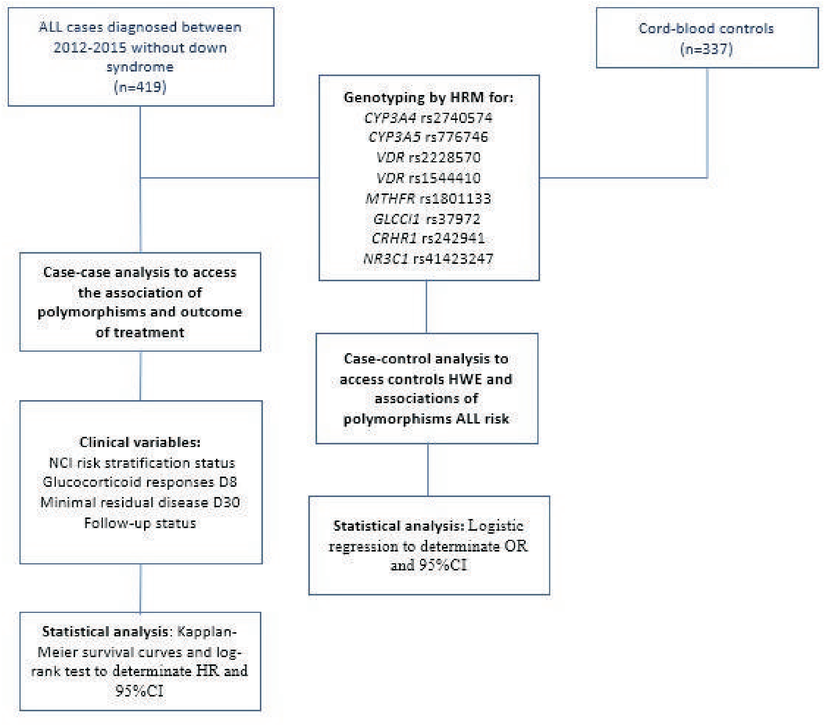

Figure 2. Study design flowchart.

Results

First, the efficacy of HRM for genotyping was tested. Direct sequencing validated the melting curve patterns of heterozygous, wild-type and homozygous variants. Patient cases eligible for this study (n=419) have median age of 5 years, being B-cell precursor ALL (82.9%) and T-cell ALL (17.1%). Cases and controls were similar in sex and differed in skin color. The clinical and demographic characteristics of cases and are summarized in the **Table 1.** So far, the most of sample were genotyped for *VDR* rs2228570 and rs1544410; *MTHFR* rs1801133; *GLCCI1*, rs37972; *CRHR1* rs242941. The control group are in Hardy-Weinberg Equilibrium for all these polymorphisms. No genotype was associated with ALL risk, as shown in **Table 2**.

Table 1. Demographic and clinical characteristics of cases and controls.

		Cases, n (%)	Controls, n (%)	p-value
Total		419	337	NA
Age median (years)		5.0	NA	
Sex				
	Male	254 (60.6)	178 (56.3)	0.24
	Female	165 (39.4)	138 (43.7)	
Skin color				
	White	199 (47.4)	81 (32.5)	0.0001
	Non-white	220 (52.5)	168 (67.5)	
ALL subtype				
	T-ALL	72 (17.1%)	NA	NA
	BCP-ALL	347 (82.9%)	NA	

Abbreviations: n, number; ALL, Acute lymphoblastic leukemia; T-ALL, T-cell ALL; BCP-ALL, B-cell precursor AL; NA, not applicable.

Table 2. Genotyping partial results.

	Cases, n (%)	Controls, n (%)	OR (95%CI)
***MTHFR* rs1801133**	106	337	
CC	46 (43.4)	181 (53.7)	1.0
CT	53 (50.0)	124 (36.8)	1.27 (0.80 - 2.00)
TT	7 (6.6)	32 (9.5)	0.75 (0.31 - 1.80)
***GLCCI1* rs37972**	297	84	
CC	118 (39.7)	38 (45.3)	1.0
CT	137 (46.2)	39 (46.4)	1.13 (0.68 - 1.88)
TT	42 (14.1)	7 (8.3)	1.93 (0.80 - 4.65)
***VDR* rs1544410**	297	231	
GG	130 (43.7)	114 (49.3)	1.0
GA	135 (45.4)	91 (39.2)	1.30 (0.90 - 1.87)
AA	32 (11.2)	26 (11.3)	1.08 (0.61 - 1.92)
***VDR* rs2228570**	272	279	
CC	120 (44.1)	130 (46.6)	1.0
CT	117 (43.0)	123 (44.1)	1.03 (0.72 - 1.47)
TT	35 (12.9)	26 (9.3)	1.46 (0.83 - 2.57)
***CRHR1* rs242941**	192	272	
CC	66 (34.4)	104 (38.2)	1.0
CT	94 (48.9)	125 (46.0)	1.18 (0.78 - 1.78)
TT	32 (16.7)	43 (15.8)	1.17 (0.67 - 2.03)

Abbreviation: n, number; OR, odds ratio; 95%CI, 95% confidence interval.

Conclusions

In perspective, the remaining cases and controls samples will be genotyped soon and the survival curves will be performed.

Projeto Gráfico: Setor de Edição e Informação Técnico-Científica / INCA

MINISTÉRIO DA SAÚDE