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POSTER ABSTRACTS

614.ACUTE LYMPHOBLASTIC LEUKEMIAS: THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Results of a Prospective Phase II Study of Individualized 6-Mercaptopurine Dosing Based on Pharmacogenomics in Childhood Acute Lymphoblastic Leukemia in East Asia

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Introduction Variations in the *NUDT15* and *TPMT* genes, which serve as pharmacogenomic markers for 6-mercaptopurine (6MP), contribute to individual differences in the optimal dosage of this medication. Nevertheless, given the observed difference in the tolerated dose of 6MP between East Asian and Western patients, it is essential to conduct a study to determine whether the same dosage guidelines are applicable to both populations. This study aimed to reduce treatment discontinuation and neutropenia during maintenance by adjusting the initial dose of 6MP based on the results of the *NUDT15* or *TPMT* variants.

M ethods

This is a prospective phase II trial being conducted at three institutions in Korea. Patients who initiated 6MP-based maintenance treatment for acute lymphoblastic leukemia (ALL) were included in the study. During the maintenance phase, 6MP was administered at an individualized starting dose based on the *NUDT15* and *TPMT* variants of each participant. Original dose (50 mg/m ^{2}/day) of 6MP was administered to patients with both *NUDT15* and *TPMT* wild-type, 30 mg/m ^{2}/day for *NUDT15* intermediate activity (*NUDT15* variant allele heterozygous) or TPMT heterozygosity, 10 mg/m ^{2}/day for *NUDT15* low activity (*NUDT15* variant allele homozygous), and 10 mg/m ^{2}/day three times per week for homozygous *TPMT* variants. The maintenance cycle consists of 12 weeks of daily 6MP at an individualized dosage, weekly methotrexate (MTX) at a dosage of 20 mg/m ^{2}, and monthly vincristine and steroid pulses. Lastly, intrathecally administered MTX is administered every three months. During treatment, the total white blood cell count was targeted to be between 2000/uL and 3000/uL, with an absolute neutrophil count greater than 500/uL and a platelet count greater than 50,000/uL. The whole exome was sequenced using genomic DNA extracted from peripheral blood at complete remission or hair follicles. As the primary and secondary endpoints, the duration of treatment discontinuation, the frequency of neutropenia, the presence of neutropenic fever during maintenance therapy, and the recurrence rate were compared to historical controls. A cohort of 254 patients who underwent maintenance therapy between the years 2001 and 2018 was chosen as the historical control group.

Results Total 72 patients were enrolled from July 2019 until Aril 2022. This analysis was conducted on 52 patients who finished maintenance therapy. There were 32 males, and 20 females. The median age of the patients was 5.6 years (range, 2.2˜15.9 years). The immunophenotypes of ALL was B-ALL in 40 patients, T-ALL in 10, Mixed phenotype in 1, and unspecified ALL in 1 patient. No patient had known pharmacogenetic variants in *TPMT*. The *NUDT15*phenotypes based on diplotypes included normal activity (n=41), intermediate activity (n=9), and low activity (n=2), occurring in 78.8%, 17.3%, and 3.8% respectively (Table 1). The number of days discontinued due to any toxicity during the 1 st cycle of maintenance therapy was average 7 days (max 59 days) in all patients, and that of the study group with intermediate enzyme activity phentypes was significantly shorter

than in historical controls, with an average 6 days vs. 12 days (*P*=0.03, Figure 1). The incidence of neutropenia during the 1 st cycle between two groups was not statistically different, however, among patients with *NUDT15* or *TPMT* intermediate activity, the frequency of neutropenia was significantly lower in the study group (*P*=0.03, Figure 2). The frequency of neutropenic fever (NF) and fever without neutropenia during the 1st cycle did not differ between the two groups. However, when patients with *NUDT15* or *TPMT* intermediate activity were analyzed, no fever occurred in the study group of 9 patients, while NF and fever occurred in 11 and 8 patients in the control group (Figure 3).

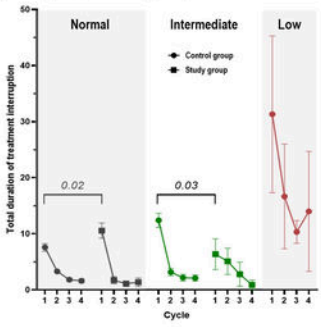
Conclusions Individualized administration of 6MP based on *NUDT15* and *TPMT* genotypes during maintenance therapy in Korean pediatric ALL patients significantly reduced treatment discontinuation and febrile toxicity. A decrease in the initial dosage from 50 mg/m ^{2}/day to 30 mg/m ^{2}/day has the potential to reduce febrile toxicity in the patient group exhibiting intermediate activity of the *NUDT15* enzyme, which is observed in approximately 20% of individuals in East Asia. Through this research, we expect to provide the dosing guidelines for 6MP in patients with ALL in East Asia.

Disclosures No relevant conflicts of interest to declare.

Table 1. The results of NUDT15 and TPMT variants

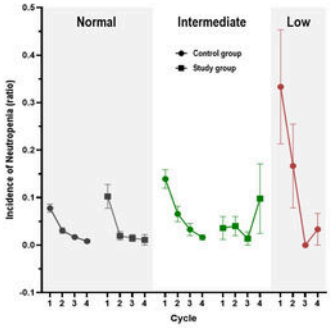
Enrolled Patients (N=52)					Control group (N=254)				P-value
NUDT15 Diplotype	TPMT Diplotype	Phenotypes	Number of Patients	6MP starting dose	NUDT15 Diplotype	TPMT Diplotype	Phenotypes	Number of Patients	
						*1/*1	Normal	189 (74.4%)	
					*1/*1	*1/*3C		1	
*1/*1		Normal	41 (78.8%)	50mg/m²/day		*1/*6		2	
					*1/*2	*1/*1		8	
					*1/*3	*1/*1	Intermediate	41 62 (24.4%)	
	*1/*1				*1/*4	*1/*1		4	0.59
*1/*3			9	30mg/m²/day	*1/*5	*1/*1		3	
					*1/*6	*1/*1		3	
		Intermediate	11 (21.2%)		*2/*3	*1/*1		1	
*1/*5§			2	30mg/m²/day	*3/*3	*1/*1	Low	1 3 (1.2%)	
					*3/*5	*1/*1		1	

Figure 1. The number of days discontinued due to any toxicity during Cycle 1-4. In cycle 1 of patients with intermediate phenotypes, the study group had fewer medication discontinuation days than the control group.



Cycle	Normal phenotype days, average (range)			Intermediate days, average (range)			Low days, average (range)
	Control	Study	P-Value	Control	Study	P-Value	Control
1	8 (0-56)	11 (0-28)	**0.02**	12 (0-39)	6 (0-28)	**0.03**	31 (14-59)
2	3 (0-35)	2 (0-21)	0.20	3 (0-21)	5 (0-21)	0.66	17 (2-34)
3	2 (0-31)	1 (0-14)	0.22	2 (0-21)	3 (0-21)	0.97	10 (7-14)
4	2 (0-41)	1 (0-21)	0.54	2 (0-17)	1 (0-7)	0.53	14 (0-35)
1-4	14 (0-78)	14 (0-35)	0.53	20 (0-54)	15 (0-49)	0.15	72 (33-135)

Figure 2. The incidence of neutropenia (CBCs with neutropenia / Total CBCs) due to any toxicity during Cycle 1-4. Among patients with *NUDT15* intermediate activity, the frequency of neutropenia was significantly lower in the study group during cycle 1.



Cycle	Normal phenotype ratio, average			Intermediate ratio, average			Low ratio, average
	Control	Study	P-Value	Control	Study	P-Value	Control
1	0.08	0.1	0.39	0.15	0.03	**0.03**	0.33
2	0.03	0.02	0.50	0.07	0.03	0.85	0.17
3	0.02	0.01	0.90	0.03	0.01	0.79	0
4	0.01	0.01	0.72	0.02	0.07	0.05	0.03
1-4	0.04	0.04	0.99	0.07	0.04	0.88	0.13

Figure 3. The frequency of neutropenic fever (left), the frequency of fever without neutropenia (right). No fever occurred in the study group of 9 patients with *NUDT15* intermediate activity, while NF and fever occurred in 11 and 8 patients in the control group, respectively.

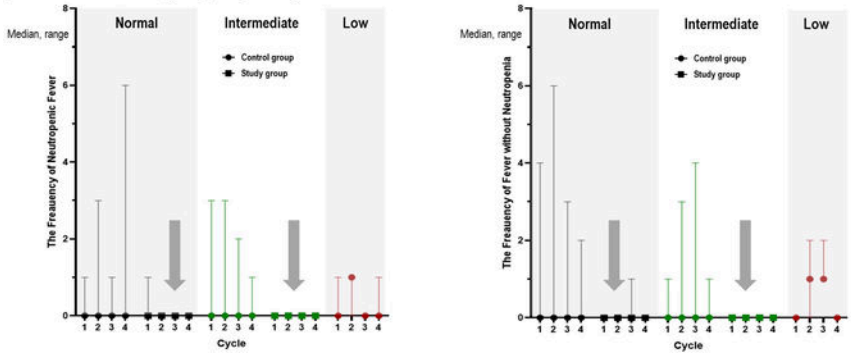


Figure 1

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