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TPMT and ITPA Gene Polymorphism and Their Adverse Events during Chemotherapy of Acute Lymphoblastic Leukemia among Bangladeshi Children

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ABSTRACT

Background: The pharmacogenetic-oriented approach reduces the toxicity and increases the safety of chemotherapeutic agents. 6-mercaptopurin (6-MP) metabolizing enzymes such as thiopurine S-methyltransferase (TPMT) and inosine triphosphate pyrophosphatase (*ITPA*) contribute to variable responses and adverse effects among leukemia patients treated with 6-MP. The aim of our study was to identify the prevalence of TPMT and ITPA gene polymorphisms among Bangladeshi children with acute lymphoblastic leukemia (ALL) and their association with the adverse effects of 6-MP during the treatment.

Methods: We recruited 75 patients with ALL and 75 volunteers with minor illnesses as the control group. Genotyping for TPMT (TPMT*3C, *3B, *2) and ITPA (ITPAc.94C>.A) was performed. The relationship between genotypes and adverse effects of 6-MP was investigated.

Results: The frequency of *TPMT*3B*, *TPMT*3C* and *ITPA* polymorphisms among volunteers was 0.006, 0.020, and 0.093, respectively, whereas *TPMT*3C* and *ITPA* polymorphisms among ALL patients was 0.010 and 0.153, respectively. ALL patients with the *ITPA* variant developed fever (OR=6.9, 95% CI=1.99-23.91), neutropenia (OR=7.68, 95% CI=2.21-26.61), hyperbilirubinemia (OR=4.73, 95% CI=1.39-16.07) and raised serum ALT (OR=4.73, 95% CI=1.52-14.68) which were significant in comparison with those without polymorphism.

Conclusion: The frequency of *ITPA*c.94C>A among Bangladeshi children was high. Adverse effects of chemotherapy in patients with ALL suggests the importance of *ITPA* genotyping in ALL patients prior to starting chemotherapy.

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Introduction

The treatment of pediatric ALL as the most common malignancy in children has reached survival rates of up to 90% during the last three decades in the western countries and some industrialized countries.[1] Beside supportive care which plays an important role during chemotherapy for childhood malignancy to avoid and manage complications, pharmacogenetic intervention has been a new approach to achieve fewer side effects and accomplish better treatment outcomes.[2]

6-MP is one of the most widely used chemotherapeutic agents during maintenance therapy in childhood ALL which is administered as a daily oral dose for 2 years.[3, 4] Pharmacogenetic studies among children with ALL have shown an association between toxicity of 6-MP with single nucleotide polymorphisms (SNP) in genes

coding for 6-MP metabolizing enzyme such as thiopurine S-methyltransferase (*TPMT*) and inosine triphosphate pyrophosphatase (*ITPA*).[5] Pharmacogenetic-oriented approach has provided a molecular approach that guides individualization for the chemotherapeutic agents. This approach may reduce the toxicity and increase the safety of the treatment.[5]

Inosine triphosphatase catalyses the hydrolysis of *ITP* to inosine monophosphate, thereby trapping purines in the form of *ITP*.[6, 7] Deficiency of Inosine triphosphate pyrophosphohydrolase (*ITPa*se) has been reported to cause accumulation of the potentially toxic metabolite 6-thio-*ITP*.[8] At least 5 variants of the *ITPA* gene have been identified, among them two single nucleotide polymorphisms of *ITPA* c.94C>A and *ITPA*g. IVS2+21A>C are associated with decreased enzyme activity.[9] Individuals who are homozygous for the *ITPA* c.94C>A (P32T) mutation have complete deficiency of the enzyme activity which results in the accumulation of *ITP* intracellularly, whereas heterozygotes for *ITPA* c.94C>A mutation have decreased *ITPA* activity to 22.5% of the control mean value.[7]

6-MP is an inactive pro-drug, which is metabolized into thioguanine nucleotides (TGN) in order to acquire its cytotoxic effects.[10] *TPMT* is involved in the methylation of 6-MP and is a key enzyme in the metabolism of 6-MP. The activity of *TPMT* is controlled by genetic polymorphisms which can alter the rate of the metabolism of 6-MP.[11] The cellular accumulation of TGN is inversely related to *TPMT* enzyme activity; presumably the higher *TPMT* activity shunts more drugs down the methylation pathway and resulting in less TGNs.[10] Studies have found that distribution of *TPMT* activity in erythrocytes is tri-modal; approximately 90% of persons have high activity, 10% have intermediate activity, and 0.3% have less or no detectable enzyme activity.[10, 12]

Three of these alleles (*TPMT**2, *3B and *3C) account for 80–95% of subjects with low to intermediate enzyme activity.[13, 14] It has been reported that toxicity due to 6-MPand its dose reduction was highest among patients who had homozygous variant alleles for *TMPT* (*TPMT* *2, *3C, *3B), intermediate among heterozygous patients and lowest among subjects with the wild type gene.[15, 16]

The knowledge of SNPs in 6-MP metabolizing enzymes and subsequent drug toxicity has developed more rational approaches to optimize chemotherapy in patients with ALL. *TPMT* and *ITPA* genetic variants differ from patient to patient and among different ethnic groups. Determination of the frequency of these genetic variants is necessary when considering pharmacogenetics as a tool to improve treatment outcome.

We aimed to determine the frequency of TPMT and ITPA variant alleles among Bangladeshi children with ALL and association of enzyme gene polymorphisms with adverse effects of 6-MP.

Materials and Methods

This descriptive study was conducted at two tertiary level hospitals in Dhaka city, the central part of Bangladesh. Seventy-five patients diagnosed with ALL were recruited from the pediatric hematology oncology department of Bangabandhu Sheikh Mujib Medical University (BSMMU) and 75 children who had referred to the outpatient unit of the Central Hospital with minor diseases such as common cold, diarrhea, or other minor illnesses were considered as the control group. All children with ALL were receiving maintenance therapy using 6-mercaptopurine 75 mg/m^2/day orally as per the UKALL-2003 protocol, version 7.[17] Drug administration was suspended if patients had developed any toxicity and lower doses were assigned for resuming the treatment when patients had recovered. Both groups were recruited for a one-year period between January-December 2013. Written informed consent was obtained from legal guardians and/or children prior to the enrollment into the study. This study was approved by the ethical review committees of BSMMU, Central Hospital Limited, and University of Tsukuba Hospital.

DNA Extraction and Genotyping

Genetic DNA was extracted from 0.2 ml peripheral blood using Genomic DNA Isolation Kit (QiAamp DNA Blood Mini Kit: Qiagen, Vealo, The Netherlands) following the instructions from the manufacturer. Polymorphisms of *TPMT**3C (c.719A>G, rs1142345), *TPMT**2(c.238G>C, rs1800462), *TPMT**3B (c.460G>A, rs1800460), and *ITPA*c.94C>A (rs1127354) were genotyped using the TaqMan SNP genotyping assay (Applied Bio Systems, Foster City, CA, USA). PCR was performed on a 384-well format with 3 ng of each DNA, and automatic allele calling was performed using ABI PRISM 7900HT detection system and analysis software, version 2.2.2 (Applied Bio systems).

Clinical and Laboratory Data Collection

Demography of the participants, signs and symptoms, disease state, toxicity profile, and results of blood biochemistries (complete blood count, serum bilirubin, liver transaminases (ALT) and serum creatinine were documented.

Adverse effects of 6-MP were defined as the occurrence of hematological toxicity, hepatotoxicity and other toxicities that resulted in suspending and delay in subsequent chemotherapy. Hematologic toxicity was defined as neutropenia (absolute neutrophil count (ANC) <1.0×10^9/L). Myelosuppression was defined as leucopenia (WBC<3.0×10^9/L), and/or thrombocytopenia (platelet <100×10^9/L). Hepatic toxicity was defined as a greater than two-fold increase in serum bilirubin and ALT. Fever was defined as temperature >38.0˚C. These definitions were set by our study group which are used by the hematology and oncology departments of BSMMU.

Statistical analysis was performed using SPSS software, version 21.0 (IBM Corporation, NY, USA). Data were expressed as number %, mean±SD. Deviation from Hardy-Weinberg expectations was examined by chi-square test or Fisher's exact test. Chi-square test was performed to compare the relationship between polymorphisms and development of toxicity. Univariate and multivariate logistic regression analysis was performed to assess the

association between *ITPA* polymorphism and toxicity. A two-sided p-value less than 0.05 was considered to be statistically significant.

Results

75 patients with childhood ALL and 75 children as control group at the age of 5±2.5 and 3.1±1.6 years old, respectively were enrolled into the study. Among all participants, *TPMT* and *ITPA* genetic polymorphisms were found in 4% (6) and 22.7% (34), respectively. In control group, the minor allele frequency of *TPMT**3B (rs1800460), *TPMT**3C (rs1142345), and *ITPA*94C>A (rs1127354) was 0.006, 0.020, and 0.093, respectively. In children with ALL, the frequency of *TPMT**3C and *ITPA*c.94C>A was 0.010 and 0.153, respectively. We found 3 homozygous variants for *ITPA* c.94C>A (rs1127354) genes but no homozygous variant for *TPMT**3C, *TPMT**3B and *TPMT**2 alleles. All 3 homozygous variants were among the ALL patients. We also found 37 heterozygous variants for the *ITPA* gene, among which 19 were in the case group and 18 were in the control group. *ITPA*c.94C>A was the most common variant in the subjects screened, while no *TPMT**2 variant was detected (Table 1). Minor allele frequency of *ITPA*c.94C>A was 22.7% among all participants (34/150).

It was observed that children with ALL who had *ITPA*c.94C>A polymorphism had a higher chance of having neutropenia in 20 (9 CC variant and 11 CA/AA variant), raised serum bilirubin in 22 (12 CC variant and 10 CA/AA variant), raised ALT in 29 (16 CC variant and 13 CA/AA variant) and fever in 36 patients (20 CC variant and 16 CA/AA variant) (Table 2).

In univariate logistic regression analysis, it was observed that patients with *ITPA*c.94C>A polymorphism had a 6 times higher chance of absolute neutropenia (OR=6.25, 95%CI=2.01–19.42), a times higher chance of hyperbilirubinemia (OR=3.58, 95% CI=1.21–10.61), a 4 times higher chance of increased ALT (OR=4.53, 95% CI=1.53–13.43), and a 7 times higher chance of fever (OR=7.00, 95% CI=2.05–23.84) in comparison to patients without this polymorphism. After adjusting for age, sex, height, and weight in multivariate logistic regression analysis, the association remained significant (Table 2).

Discussion

Use of genomic sequence information for providing safe and effective medication for developing "personalized/individualized medicine" is bridging the gap between the basic research and clinical practice.[18, 19] There are no molecular analyses on the Bangladeshi population to identify the pharmacogenomic determinants of 6-MP associated drug toxicity. We conducted this study because of growing interest in employing pharmacogenetics to refine and better individualize treatment for childhood ALL.

TPMT is a gene related to the anti-leukemic and side effects of 6-MP. It is mentioned as a potential gene suggested for polymorphism studies.[20] Prevalence of *TPMT* polymorphisms vary among different ethnic groups ranging from 2-14%.[5] In this study, allelic frequency of TPMT*3C and TPMT*3B polymorphism among Bangladeshi children were found to be 3.3% (5) and 0.7% (1), respectively (Table 1). We did not find the *TPMT**2 allele, most likely due to the small sample size and the known low frequency of some *TPMT*

Table 1: Frequency of *TPMT and ITPA* alleles in children with ALL and control group

Variations	rs number	Wild type	Heterozygous	Homozygous	Minor allele frequency
Children with ALL					
*TPMT**2	rs1800462	75	0	0	0.000
*TPMT**3B	rs1800460	75	0	0	0.000
*TPMT**3C	rs1142345	73	2	0	0.010
ITPAc.94C>A	rs1127345	55	17	3	0.153
Control group					
*TPMT**2	rs1800462	75	0	0	0.000
*TPMT**3B	rs1800460	74	1	0	0.006
*TPMT**3C	rs1142345	72	3	0	0.020
ITPAc.94C>A	rs1127345	61	14	0	0.093

TPMT, thiopurine S-methyltransferase; *ITPA*, inosine triphosphate pyrophosphatase; Allele frequency was calculated by using Hardy-Weinberg principle.

Table 2: Univariate and multivariate logistic regression analysis showing the association of ITPA polymorphism (*ITPA*c.94C>A) with toxicity

	CC	CA/AA	Crude OR	95% CI	Adjusted OR	95% CI
Leukopenia (<3×10^9/L)	6	8	1.62	0.56-4.72	2.18	0.65-7.23
Absolute neutropenia (<1.0×10^9/L)	9	11	6.25	2.01-19.42	7.68	2.21-26.61
Thrombocytopenia (<100×10^9/L)	12	5	1.19	0.36-3.96	1.11	0.33-3.77
Hyperbilirubinemia (>17.3µmol/L)	12	10	3.58	1.21-10.61	4.73	1.39-16.07
Raised serum ALT (>36U/L)	16	13	4.53	1.53-13.43	4.73	1.52-14.68
Fever (≥101°F)	20	16	7.00	2.05-23.84	6.89	1.99-23.91

OR, Odds ratio; CI, Confidence interval. Adjusted by age, sex, height, and weight.

variants among the Asian populations. The frequency and distribution of *TPMT* alleles in our study among Bangladeshi were similar to that of Iranians,[21] Turkish,[22] and Japanese populations.[23]

ITPA is an enzyme involved in the metabolism of 6-MP. Genetic polymorphisms in the *ITPA* gene are associated with reduced activity of the *ITPA* enzyme and increased toxicity of 6-MP. There are several polymorphisms described for *ITPA*, but the P32T (proline to threonine substitution at amino acid 32) variant is the most common SNP.[24] *ITPA*c.94C>A frequency has been investigated in various populations. Studies on Asian populations have revealed a higher frequency of this variant allele than among American Caucasians, British Caucasians or Africans. [19, 24] The incidence of *ITPA*c.94C>A variant among Southwest Asians and Chinese were found to be 2.0% (2/99), and 4.7% (9/192).[25]

This is the first report from Bangladesh showing the effect of *TPMT* and *ITPA* genotypes in optimizing 6-MP therapy based on genetic constitution.

Several previous studies indicated that *TPMT* polymorphisms are associated with 6-MP toxicity.[26-28] In our study, patients with deficiency in *ITP*ase enzyme tended to be more likely to develop fever and or neutropenia and more likely experienced liver toxicity (raised serum bilirubin and ALT) during treatment with 6-mercaptopurine.

Our study found that 6-MP toxicities tended to be higher among homozygous and heterozygous variant alleles of *ITPA* in comparison to the wild type.

Conclusion

The frequency of *ITPA*c.94C>A mutation among Bangladeshi children was high. In concordance with other studies, our study also showed that *ITPA*c.94C>A polymorphisms have a higher chance of developing hematopoietic and hepatic toxicity during treatment with 6-MP.

We propose the importance of *ITPA* genotyping in patients with ALL to design more rational and cost-effective treatment strategy for children with ALL. As polymorphism of *ITPA* is more frequent in comparison to *TPMT* among the Bangladeshi population, it should be prioritized during the screening process. Furthermore, we recommend a larger nationwide study for more precise estimation of *TPMT* allele frequency.

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Conflict of Interest: None declared.

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