Mediterranean Journal of Hematology and Infectious Diseases

Original Article

ITPA Polymorphisms and the Incidence of Toxicities in Children with Acute Lymphoblastic Leukemia

Patpetra Svasdisant[1], Waraporn Glomglao[1], Preeyanun Siraprapapat[1], Wiyakan Inthararujikul[1], Kalaya Tachavanich[1], Chetsada Boonthimat[1], Sakkarin Ardsiri[1], Kochpinchon Chansing[1], Suwimon Sriprach[1], Sasima Tongsai[2], Phakatip Sinlapamongkolkul[3], Kleebsabai Sanpakit[1] and Jassada Buaboonnam[1].

[1] Division of Hematology and Oncology, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.
[2] Research Department, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.
[3] Department of Pediatrics, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand.

Competing interests: The authors declare no conflict of Interest.

Abstract. ***Background:*** **6-Mercaptopurine (6-MP), a thiopurine agent, is a essential medication for treating pediatric acute lymphoblastic leukemia (ALL). However, its side effects of neutropenia and hepatotoxicity might interrupt treatment, resulting in poor outcomes. Inosine triphosphate pyrophosphatase (*ITPA*), an enzyme in the thiopurine pathway, may prevent the accumulation of toxic thiopurine metabolites. Studies on *ITPA* and thiopurine-associated toxicities are scarce.**
Methods: This study retrospectively investigated 1- to 15-year-old children with ALL who received 6-MP during the maintenance phase of treatment between 2000 and 2020. Toxicity during the first year of maintenance therapy and the mean dose of 6-MP were analyzed.
Results: The 209 patients had a median age of 4.8 (0.3-14.8) years. Of these, 124 patients (59.3%) had wild-type *ITPA*, 73 patients (34.9%) had heterozygous *ITPA 94C>A* (het*ITPA*), and 12 patients (5.7%) had homozygous *ITPA 94C>A* (hom*ITPA*), with an allele frequency of 0.23. The incidence of neutropenia among *ITPA* polymorphisms did not significantly differ (*P* = 0.813). In patients harboring hom*ITPA*, transaminitis was more frequent than other polymorphisms but without a significant difference (*P* = 0.063). The mean dose of 6-MP for patients with hom*ITPA* was significantly lower than that for patients with het*ITPA* or wild-type *ITPA* (*P* = 0.016).
Conclusions: Hom*ITPA* had a higher incidence of transaminitis and required a significantly larger dose reduction of 6-MP than wild-type *ITPA*. Further study is warranted to elucidate the effects of *ITPA* polymorphisms on toxicity in patients with ALL treated with 6-MP.

Keywords: Inosine triphosphate pyrophosphatase; Leukemia; Mercaptopurine; Neutropenia; Transaminitis.

Citation: Svasdisant P., Glomglao W., Siraprapapat P., Inthararujikul W., Tachavanich K., Boonthimat C., Ardsiri S., Chansing K., Sriprach S., Tongsai S., Sinlapamongkolkul P., Sanpakit K., Buaboonnam J. ITPA polymorphisms and the incidence of toxicities in children with acute lymphoblastic leukemia. Mediterr J Hematol Infect Dis 2023, 15(1): e2023024, DOI: http://dx.doi.org/10.4084/MJHID.2023.024

Published: March 1, 2023 **Received: January 10, 2023** **Accepted: February 28, 2023**

Correspondence to: Jassada Buaboonnam, MD. Associate Professor of Pediatrics, Division of Hematology and Oncology, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand. Tel*:* +66 2 419 5960; Fax*:* +66 2 411 3010. E-mail*:* onco008@yahoo.com

Introduction. Acute lymphoblastic leukemia (ALL) is children's most common hematologic malignancy. With advances in treatment, its event-free survival is approximately 90%.[1] 6-Mercaptopurine (6-MP) is one of

the key medications used during maintenance therapy, with the most extended phase of treatment being at least two years. Nevertheless, 6-MP's side effects of neutropenia and hepatotoxicity may interrupt treatment.[2] Two well-known thiopurine enzymatic genetic polymorphisms have demonstrated clinical significance for patients with 6-MP. They are thiopurine methyltransferase *(TPMT)*, prevalent in European populations, and nudix *(*nucleoside diphosphate linked moiety X*)* type motif 15 *(NUDT15)*, prevalent in Asian populations.[3,4] Inosine triphosphate pyrophosphatase *(ITPA)*, another enzyme in the multistep thiopurine pathway, prevents the accumulation of methylthioinosine triphosphate, a toxic thiopurine metabolite, thereby catalyzing inosine triphosphate to inosine monophosphate.[5,6] *ITPA 94 C>A* genotypes were found to have markedly decreased *ITPA* activity.[7] However, the clinical relevance between toxicities and such polymorphisms still needs to be well elucidated, and clinical recommendations for dose modifications according to the *ITPA* polymorphism need to be developed. Such studies on thiopurine enzymatic genetic polymorphisms apart from *TPMT* and *NUDT15* may better guide physicians in prescribing doses of thiopurine drugs, especially 6-MP, to prevent toxicity. The present investigation aimed to determine the effects of *ITPA* polymorphisms on (1) neutropenia and hepatotoxicity, (2) the modification of 6-MP dosage, and (3) survival for childhood ALL.

Patients and Methods. This retrospective study included patients aged 1 to 15 years diagnosed with ALL between January 2000 and December 2020. The patients were classified into risk groups according to the National Cancer Institute classifications and Thai Pediatric Oncology Group classification.[8,9] They were treated according to the national protocol of the Thai Pediatric Oncology Group.[9]

Treatment during maintenance therapy consisted of monthly pulse intravenous vincristine and 5-day oral prednisolone, weekly oral methotrexate (20 mg/m^2), and daily oral 6-MP (50 mg/m^2). Patients who experienced prolonged neutropenia or severe infection during previous therapy with 6-MP may have been administered a decreased 6-MP dosage, depending on the attending physician's assessment. Complete blood counts and liver function tests were performed monthly and trimonthly, respectively. The dose of 6-MP was adjusted to maintain an absolute neutrophil count between 500 and 1500 cells/mm^3. Treatment was temporarily interrupted if a patient developed cytopenia (an absolute neutrophil count < 500 cell/mm^3 or a platelet count < 50,000/mm^3) or hepatic dysfunction (direct hyperbilirubinemia or an elevated transaminase > 20 times the upper normal value). Patients with elevated transaminase > 5 times but < 20 times the upper normal value may have been prescribed a decreased dose of 6-MP at the attending physician's discretion. The mean dose of 6-MP at each interval was calculated using the sum of a 28-day dose (mg) divided by the product of 28 and the body surface area.

Neutropenia was defined as an absolute neutrophil count of fewer than 500 cells/mm^3. Transaminitis was defined as serum alanine aminotransferase more than five times the upper normal value.

As a retrospective study, the remaining blood specimens of patients during the diagnosis procedure were collected and subsequently evaluated for *ITPA 94C>A* polymorphisms using an allele-specific polymerase chain reaction method. The wildtype primer was 5′CGTTCAGATTCTAGGAGATAAGTTCC-3′. The mutant forward primer was 5′-CGTTCAGATTCTAGGAGATAAGTTCA-3'. For internal controls, 5'GCTTAGCACAAGCAGAGACCTGACG-3' and 5'TTCCACGAACATGTGTGAATGCAGC-3' were used. Patients harboring *TPMT* or *NUDT15* polymorphisms were excluded from this cohort.

Before this research began, its protocol was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si-479/2021).

Statistical analysis. Demographic data were determined using descriptive statistics. Categorical variables are presented as a number and percentage, and continuous variables are given as a mean ± standard deviation *(*SD*)* or a median *(*range*)*, as appropriate. The associations between *ITPA* polymorphisms, neutropenia, and transaminitis were determined using Pearson's chi-squared test. Simple and multiple binary logistic regression analyses assessed the associations between *ITPA* polymorphisms, 6-MP doses, and transaminitis. The odds ratio (OR) with a corresponding 95% confidence interval (95% CI) was used to evaluate the strengths and directions of associations. Differences in 6-MP doses among the heterozygous and homozygous *ITPA* polymorphisms and wild-type *ITPA* at baseline and each follow-up were evaluated using 1-way ANOVA, followed by Bonferroni corrections for multiple post hoc comparisons of means. The Kaplan-Meier method was used to estimate the 3-year overall survival (OS) and event-free survival rates. A log-rank test was constructed to compare the 3-year OS and event-free survival rates. IBM SPSS Statistics for Windows, version 23 (IBM Corp, Armonk, NY, USA) was used for the data analyses. Probability (*P*) values of less than 0.05 were considered statistically significant.

Results. The study cohort consisted of 209 patients with ALL. There were 112 boys and 97 girls; their median age was 4.8 (0.3-14.8) years. The median duration of follow-

up was 36 (16–36) months. As for risk, 114 patients were classified as standard risk, 69 patients were high risk, and 26 patients were very high risk.

In terms of genotype, 124 patients (59.3%) had wild-type *ITPA 94C>A*, 73 patients (34.9%) showed heterozygous *ITPA 94C>A* (het*ITPA*), and 12 patients (5.7%) showed homozygous *ITPA 94C>A* (hom*ITPA*). The allele frequency of *ITPA 94C>A* was 23%. The percentage of standard risk, high risk, and very high risk in wild-type ITPA are 55.6%, 30.6%, and 13.7%, respectively. Those in hetITPA are 53.4%, 37%, and 9.6%, respectively, while those in homITPA are 50%, 33.3%, and 16.7%, respectively.

Univariable analysis was undertaken for *ITPA 94C>A*, the 1-year mean dose of 6-MP, and side effects. No association was revealed between *ITPA 94C>A* and neutropenia during one year of maintenance therapy (P = 0.813; **Table 1**). The incidences of neutropenia during one year of maintenance therapy in patients harboring wild-type *ITPA*, het*ITPA*, and hom*ITPA* were 33.9%, 37.0%, and 41.7%, respectively. The association between *ITPA 94C>A* and transaminitis during one year of maintenance therapy (P = 0.063) is demonstrated in **Table 2**. Pairwise comparisons using Bonferroni correction showed a significant difference between patients with and without transaminitis in hom*ITPA* (12.2% vs. 3.8%; P = 0.036). The incidences of transaminitis during one year of maintenance therapy in patients harboring wild-type *ITPA*, het*ITPA*, and hom*ITPA* were 20.2%, 24.7%, and 50.0%, respectively.

The 1-year mean doses of 6-MP for wild-type *ITPA*, het*ITPA*, and hom*ITPA* were 39.11 ± 14.19 mg/m^2, 39.40 ± 14.21 mg/m^2, and 27.08 ± 12.58 mg/m^2, respectively (P = 0.016). The Bonferroni post hoc test revealed a significantly lower 1-year mean dose of 6-MP for hom*ITPA* than for the wild-type and het*ITPA* groups (P < 0.05).

Two factors were significantly associated with transaminitis in univariable binary logistic regression analysis of factors and transaminitis. They were *ITPA 94C>A* and a 1-year mean dose of 6-MP. Patients with het*ITPA* and hom*ITPA* developed transaminitis more frequently than those harboring wild-type *ITPA* (het*ITPA*: OR, 1.296; 95% CI, 1.650–2.583; P = 0.461; hom*ITPA*: OR, 3.960; 95% CI, 1.177–13.328; P = 0.026). Higher doses of 6-MP were associated with no incidence of transaminitis (OR, 0.943; 95% CI, 0.919–0.968; P < 0.001). In multivariable binary logistic regression analysis, there was no statistically significant association between *ITPA 94C>A* and transaminitis.

Table 1. Comparison of homozygous *ITPA*, heterozygous *ITPA*, and wildtype *ITPA* for cases with and without neutropenia in Thai pediatric acute lymphoblastic leukemia patients.

Events	All patients)n = 209(	Neutropenia)ANC < 500( )n = 74(	No neutropenia)ANC ≥ 500( )n = 125(	*P* value
***ITPA*94C>A, n)%(**				0.813
Wildtype	124)59.3(	42)56.8(	82)60.7(	
Heterozygous	73)34.9(	27)36.5(	46)34.1(	
Homozygous	12)5.7(	5)6.8(	7)5.2(	

ANC, absolute neutrophil count; *ITPA*, inosine triphosphate pyrophosphatase.

Table 2. Comparison of homozygous *ITPA*, heterozygous *ITPA*, and wildtype *ITPA* for cases with and without transaminitis in Thai pediatric acute lymphoblastic leukemia patients.

Events	All patients)n = 209(	Transaminitis)n = 49(	No transaminitis)n = 160(	*P* value
***ITPA*94C>A, n)%(**				0.063
Wildtype	124)59.3(	25)51.0(	99)61.9(	
Heterozygous	73)34.9(	18)36.7(	55)34.4(	
Homozygous	12)5.7(	6)12.2(	6)3.8(	

ITPA, inosine triphosphate pyrophosphatase.

Table 3. Univariable and multivariable binary logistic regression analysis of factors and transaminitis.

Factors	Crude OR)95% CI(	*P* value	Adjusted OR)95% CI(	*P* value
***ITPA*94C>A**				
Wildtype	Reference		Reference	
Heterozygous	1.296)0.650–2.583(	0.461	1.357)0.657–2.804)	0.410
Homozygous	3.960)1.177–13.328(	0.026	2.376)0.655–8.627(	0.188
1-year dose of 6-MP	0.943 (0.919–0.968)	< 0.001	0.946 (0.921–0.971)	< 0.001

6-MP, 6-mercaptopurine; *ITPA*, inosine triphosphate pyrophosphatase.

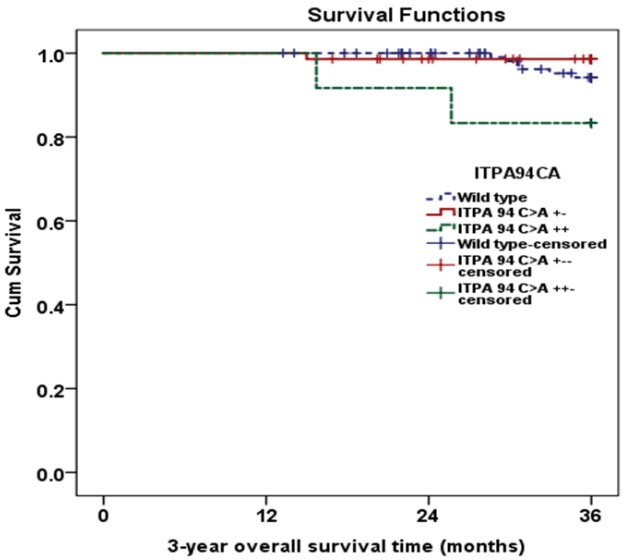

Figure 1. Comparison of 3-year overall survival rates in Thai children with acute lymphoblastic leukemia by inosine triphosphate pyrophosphatase (*ITPA*) polymorphism status.

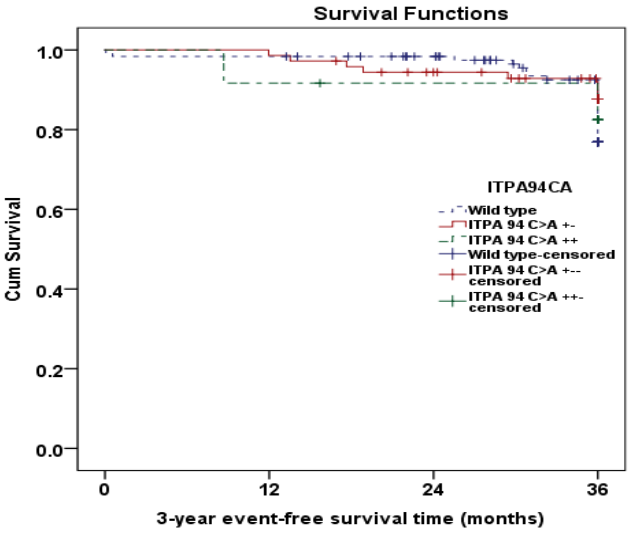

Figure 2. Comparison of 3-year event-free survival rates in Thai children with acute lymphoblastic leukemia by inosine triphosphate pyrophosphatase (*ITPA*) polymorphism status

However, there was a significant association between the 1-year mean dose of 6-MP and no incidence of transaminitis *(*adjusted OR = 0.958; 95*%* CI, 0.930–0.987; *P* = 0.005; **Table 3***)*.

All patients' estimated 3-year OS rate was 95*.1%*, while the estimated 3-year event-free survival rate was 81.1*%*. The 3-year OS rates of patients harboring wild-type *ITPA*, het*ITPA*, and hom*ITPA* were 90*.8%*, 92*.8%*, and 83*.*3*%*, respectively *(P* = 0.370; **Figure 1***)*. The 3-year event-free survival rates for wild-type *ITPA*, het*ITPA*, and hom*ITPA* were 76.9*.*1*%*, 87*.7%*, and 82*.5%*, respectively (*P* = 0.375; **Figure 2***)*.

Discussion. Genetic polymorphisms in thiopurine metabolism pathways increase the accumulation of toxic metabolites. The increased accumulation might account for the varied responses and toxicities among patients receiving thiopurine drugs such as 6-MP. The polymorphisms vary among ethnicities. *ITPA* is a catalytic enzyme that hydrolyzes inosine triphosphate, a toxic noncanonical nucleotide, to less toxic metabolites.[10] The allele frequency of 2 well-known polymorphisms, *TPMT* and *NUDT15*, varies among ethnicities, with the latter prevalent in Asian populations.[11] As for *ITPA*, its allele frequency in this study was 0.23, consistent with other studies on Asian populations.[4,12]

Neutropenia is among the most common complications for those treated with thiopurine agents. The polymorphisms of the genes involved in thiopurine metabolism account for the neutropenia of patients treated with such agents. Currently, thiopurine doses are based on the TPMT and NUDT15 polymorphisms.[2] However, the recommended thiopurine doses for patients harboring *ITPA* polymorphisms need to be better established. Additionally, research findings on the association of *ITPA* and neutropenia in patients treated with thiopurine are controversial. Several studies have demonstrated a significant risk of neutropenia or neutropenic fever with decreased doses of thiopurine[13,14] in patients with *ITPA* polymorphisms. Conversely, some studies did not identify any association between neutropenia and *ITPA* polymorphisms.[15,16] In the present study's cohort, the incidences of neutropenia in patients harboring *ITPA* polymorphisms were not significantly different from those with wild-type *ITPA*. The heterogeneity of the results might be due to the different 6-MP doses used by studies (range: 50-75 mg/m^2) and pharmacogenomic variations related to different ethnic or racial groups.

Transaminitis during treatment with combined 6-MP and MTX is common in pediatric ALL.[17] The methylated metabolites of 6-MP account for hepatotoxicity. Therefore, the genetic polymorphisms leading to excessive methylated metabolites are considered plausible causes of hepatotoxicity.[18] The correlation between *ITPA* polymorphisms and elevated transaminase is uncertain.[4,6,14] In the univariate analysis of the current investigation, the incidence of transaminitis in patients with hom*ITPA* was significantly higher than in those with het*ITPA* and wild-type *ITPA*. Fortunately, this cohort did not exhibit severe transaminitis (> 20 times) or severe hepatic dysfunction, including coagulopathy. Careful monitoring of liver function tests may be necessary for individuals harboring hom*ITPA*.

The dose of 6-MP in patients harboring hom*ITPA* was significantly lower than that for patients with het*ITPA* or wild-type *ITPA* in this cohort. This finding may signify a clinically meaningful effect of *ITPA* polymorphisms, even though the incidences of neutropenia were not significantly different. Furthermore, dose reduction of 6-

MP did not appear to worsen ALL treatment outcomes, given that the survival rates of patients with *ITPA* and wild-type *ITPA* were not significantly different. However, further study with a larger cohort is warranted to determine whether dose reduction and *ITPA* do not affect such patients' relapse risk.

Some limitations need to be mentioned. First, as a retrospective study, some data might be missing or incomplete. Second, the number of cases with hom*ITPA* was low, which might impact the analysis of the outcomes of these patients. Third, the data were restricted to a single center. Consequently, the generalizability of our data and findings might be limited.

Conclusions. Patients harboring *ITPA*, especially homozygous *ITPA*, seemed to have transaminitis and significantly required a greater dose reduction of 6-MP than patients with wild-type *ITPA*. Nevertheless, the neutrophil count did not appear to be affected. Further study is needed to elucidate the effects of *ITPA* polymorphisms on toxicity in patients with ALL treated with 6-MP.

Acknowledgements. The authors are indebted to Mrs. Sam Ormond from the Clinical Research Centre, Faculty of Medicine, Thammasat University, and Mr. David Park for editorial assistance.

Conflict of Interest Declaration. All authors declare no personal or professional conflicts of interest and no financial support from companies that produce and/or distribute the drugs, devices, or materials described in this report.

References:

1. Maloney KW, Devidas M, Wang C, Mattano LA, Friedmann AM, Buckley P, et al. Outcome in children with standard-risk B-cell acute lymphoblastic leukemia: Results of Children's Oncology Group trial AALL0331. J Clin Oncol. 2020;38:602-12. https://doi.org/10.1200/JCO.19.01086 PMid:31825704 PMCid:PMC7030893
2. Relling MV, Schwab M. Clinical pharmacogenetics implementation consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105:1095-1105. https://doi.org/10.1002/cpt.1304 PMid:30447069 PMCid:PMC6576267
3. Buaboonnam J, Sripatanatadasakul P, Treesucon A, Glomglao W, Siraprapapat P, Narkbunnam N, et al. Effect of NUDT15 on incidence of neutropenia in children with acute lymphoblastic leukemia. Pediatr Int. 2019;61:754-758. https://doi.org/10.1111/ped.13905 PMid:31166660
4. Mao X, Yin R, Sun G, Zhou Y, Yang C, Fang C, et al. Effects of TPMT, NUDT15, and ITPA genetic variants on 6-mercaptopurine toxicity for pediatric patients with acute lymphoblastic leukemia in Yunnan of China. Front Pediatr. 2021;9:719803. https://doi.org/10.3389/fped.2021.719803 PMid:34660484 PMCid:PMC8518605
5. Sumi S, Marinaki AM, Arenas M, Fairbanks L, Shobowale-Bakre M, Rees DC, et al. Genetic basis of inosine triphosphate pyrophosphohydrolase deficiency. Hum Genet. 2002;111:360-7. https://doi.org/10.1007/s00439-002-0798-z PMid:12384777
6. Citterio-Quentin A, Moulsma M, Gustin M-P, Lachaux A, Boulieu R. ITPA activity in children treated by azathioprine: Relationship to the occurrence of adverse drug reactions and inflammatory response. Basic Clin Pharmacol Toxicol. 2018;122:588-595. https://doi.org/10.1111/bcpt.12958 PMid:29327413
7. Arenas M, Duley J, Sumi S, Sanderson J, Marinaki A. The ITPA c.94C>A and g.IVS2+21A>C sequence variants contribute to missplicing of the ITPA gene. Biochim Biophys Acta. 2007;1772:96-102. https://doi.org/10.1016/j.bbadis.2006.10.006 PMid:17113761
8. Smith MA, Arthur DC, Camitta BM, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. J Clin Oncol. 1996;14 1:18-24. https://doi.org/10.1200/JCO.1996.14.1.18 PMid:8558195
9. The Thai Pediatric Oncology Group. Treatment protocol for acute lymphoblastic leukemia. In: National protocol for treatment of childhood cancers, 1st ed. Bangkok: M Print Cooperation. 2016:1-83
10. Zamzami MA. Inosine triphosphate pyrophosphatase (ITPase): Functions, mutations, polymorphisms and its impact on cancer therapies. Cells. 2022;11:384. https://doi.org/10.3390/cells11030384 PMid:35159194 PMCid:PMC8833965
11. Yang JJ, Whirl-Carrillo M, Scott SA. Pharmacogene variation consortium gene introduction: NUDT15. Clin Pharmacol Ther. 2019;105:1091-4. https://doi.org/10.1002/cpt.1268 PMid:30515762 PMCid:PMC6465081
12. Jantararoungtong T, Wiwattanakul S, Tiyasirichokchai R, Prommas S, Sukprasong R, Koomdee N, et al. TPMT*3C as a predictor of 6-mercaptopurine-induced myelotoxicity in Thai children with acute lymphoblastic leukemia. J Pers Med. 2021;11. https://doi.org/10.3390/jpm11080783 PMid:34442427 PMCid:PMC8400562
13. Moradveisi B, Muwakkit S, Zamani F, Ghaderi E, Mohammadi E, Zgheib NK. ITPA, TPMT, and NUDT15 genetic polymorphisms predict 6-mercaptopurine toxicity in middle eastern children with acute lymphoblastic leukemia. Front Pharmacol. 2019;10. https://doi.org/10.3389/fphar.2019.00916 PMid:31507415 PMCid:PMC6718715
14. Azimi F, Mortazavi Y, Alavi S, Khalili M, Ramazani A. Frequency of ITPA gene polymorphisms in Iranian patients with acute lymphoblastic leukemia and prediction of its myelosuppressive effects. Leuk Res. 2015;39:1048-1054. https://doi.org/10.1016/j.leukres.2015.06.016 PMid:26242828
15. Wahlund M, Nilsson A, Kahlin AZ, Broliden K, Myrberg IH, Appell ML, et al. The role of TPMT, ITPA, and NUDT15 variants during mercaptopurine treatment of Swedish pediatric patients with acute lymphoblastic leukemia. J Pediatr. 2020;216:150-7.e1. https://doi.org/10.1016/j.jpeds.2019.09.024 PMid:31635813
16. Boonyawat B, Monsereenusorn C. ITPA:c.94C>A and NUDT15:c.415C>T polymorphisms and Their relation to mercaptopurine-related myelotoxicity in childhood leukemia in Thailand. Appl Clin Genet. 2021;14:341-51. https://doi.org/10.2147/TACG.S318912 PMid:34349542 PMCid:PMC8326781
17. Ebbesen MS, Nygaard U, Rosthøj S, Sørensen D, Nersting J, Vettenranta K, et al. Hepatotoxicity during maintenance therapy and prognosis in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2017;39. https://doi.org/10.1097/MPH.0000000000000733 PMid:28060115
18. Vasta LM, Zanetti RC, Parekh DS, Warwick AB, Lieuw K. A Retrospective review of mercaptopurine metabolism reveals high rate of patients with suboptimal metabolites successfully corrected with allopurinol. J Pediatr Hematol Oncol. 2021;43:e1003-e9. https://doi.org/10.22541/au.158921477.78208996