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**

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by-nc/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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