in vivo *38*: 2041-2048 (2024)
doi:10.21873/invivo.13662

NUDT15 Polymorphism and Its Association With Mercaptopurine Hematotoxicity in Acute Lymphoblastic Leukemia in Indonesian Children

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Abstract. *Background/Aim: Hematotoxicity is a life-threatening condition that has become the major cause of drug discontinuation in patients with acute lymphoblastic leukemia (ALL). The nudix hydrolase 15 (NUDT15) gene polymorphism (c.415C>T) is reported to have an association with the hematotoxicity of 6-mercaptopurine (6-MP) as maintenance therapy in patients with ALL. However, the prevalence of this genetic polymorphism in the Indonesian population is unknown. This study aimed to assess the frequency of NUDT15 polymorphism among Indonesian pediatric patients with ALL and its association with the hematotoxicity of 6-MP. Patients and Methods: A total of 101 stored DNA samples from pediatric patients with ALL receiving 6-MP treatment were used for genetic testing. Direct sequencing was conducted to determine the NUDT15 c.415C>T genotype. Chi-square or Fisher's exact test were employed to examine the association between the NUDT15 c.415C>T genotype and hematotoxicity. Results: All (100%) of the DNA samples from patients with ALL treated with 6-MP exhibited a homozygous variant of the NUDT15 c.415C>T genotype, 70.3% of which showed hematotoxicity to some extent. We found no significant differences in NUDT15 gene polymorphism among patients with ALL with different states of hematotoxicity. Conclusion: The observed high frequency of NUDT15 c.415C>T in our study population might explain the elevated prevalence of 6-MP-associated hematotoxicity in pediatric patients with ALL within the Indonesian population. Our study provides new insight regarding the NUDT15 gene polymorphism and its relation to hematotoxicity. Further studies are required to determine the necessity of adjusting the initial dose of 6-MP for Indonesian pediatric patients with ALL.*

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Key Words: NUDT15, mercaptopurine, ALL, hematotoxicity, polymorphism.

Mercaptopurine (6-MP) is a thiopurine drug frequently used in standard therapy for autoimmune disease and hematological malignancies, including acute lymphoblastic leukemia (ALL) (1, 2). The pharmacogenetics of 6-MP have been studied extensively. Polymorphisms in the thiopurine methyltransferase (*TPMT*) gene have a well-established effect on myelosuppression of 6-MP in the Caucasian population (1, 3), but neither in the Asian population nor in the Indonesian population (4-8). *TPMT* polymorphisms has been investigated in our population and we found a very small frequency of *TPMT* mutant allele (0.95%) and no association with 6-MP hematotoxicity (8). Despite the lower frequency of *TPMT* mutations observed in Asians, the incidence of 6-MP-induced hematotoxicity is common, suggesting the presence of other possible genetic or enzymatic factors causing hematotoxicity (4-9). Another possible source of genetic variants that may cause hematotoxicity is nudix hydrolase 15 (*NUDT15*) gene (previously nucleoside diphosphate-linked moiety X-type motif 15) (9-11).

NUDT15 genetic polymorphism was reported to be associated with thiopurine hematotoxicity. *NUDT15* is an important enzyme that converts the cytotoxic thioguanine triphosphate (TGTP) metabolite of thiopurines to the less toxic thioguanine monophosphate. Dysfunction in TGTP degradation by *NUDT15* leads to an accumulation of TGTP, promoting its binding to DNA, resulting in DNA damage and apoptosis. Patients carrying mutant *NUDT15* alleles exhibit increased levels of DNA-bound thioguanine (DNA-TG) and severe myelosuppression. Homozygous carriers of

mutant *NUDT15* alleles can only endure 8% of the standard 6-MP dose, while those with heterozygous alleles can tolerate up to 63% (10). Among various mutant alleles, *NUDT15 c.415C>T* (rs116855232) is the most common variant that has been significantly correlated with thiopurine-induced leukopenia (12-16). Since the frequency of mutant *NUDT15* alleles in Asia was found to be more than 10%, the Clinical Pharmacogenetics Implementation Consortium recommends testing the *NUDT15* genotype for initial dose adjustment of 6-MP to mitigate the risk of hematotoxicity in Asian patients (13). The recommendation was made based on previous studies in Korea, Japan, and Taiwan showing the association of *NUDT15* polymorphism with the hematotoxicity of 6-MP (9, 14-17). However, prevalence of the *NUDT15* polymorphism in the Indonesia population is unknown. Thus, we aimed to determine the prevalence of *NUDT15 c.415C>T* allele mutation among a population of Indonesian patients with ALL receiving 6-MP and its association with hematotoxicity events.

Patients and Methods

Study design. This was a cross-sectional study that was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (Registration number: KET-1259/UN2.F1/ETIK/PPM.00.02/2020). We used stored DNA samples from pediatric patients with ALL recruited in our previous study (8). In brief, we recruited pediatric patients with ALL who came to Cipto Mangunkusumo Hospital and Dharmais Cancer Hospital from June 2017 to October 2018 with the following eligibility criteria: aged 1-18 years, underwent treatment with 50 mg/m^2 6-MP/day for at least 1 month in maintenance-phase therapy according to the Indonesian ALL Protocol 2013 (18). Patients who had a severe infection, received colony-stimulating factors, allopurinol, mesalazine, olsalazine, or sulfasalazine on their treatment regimen were excluded. We recorded the demography of all eligible patients. The peripheral blood sample from each patient was drawn at a single time point and separated for hematological analysis and genomic DNA isolation to evaluate the genotype. Hematological data were recorded and categorized according to the Common Terminology Criteria for Adverse Events v3.0. (19). Genomic DNA was isolated from the blood sample of each patient using Genomic DNA Mini Kit (Geneaid Biotech Ltd, Taipei, Taiwan, ROC) following the manufacturer's instruction and stored at –80˚C until further use. The samples from five patients were excluded due to insufficient DNA volume for analysis. In total, we included 101 patients (Figure 1).

Based on the Indonesian protocol for ALL, after finishing induction-phase therapy, the maintenance phase was started at treatment week 18 for high-risk ALL or week 13 for standard-risk ALL and this continued until 2.5 years after diagnosis. The maintenance-phase regimen consists of oral 6-MP with a starting dose of 50 mg/m^2/day; pulse methotrexate at 20 mg/m^2/week orally; intravenous vincristine every fifth and sixth week with dexamethasone orally at 4 mg/m^2/day (standard-risk ALL) or 6 mg/m^2/day (high-risk ALL) for 2 weeks. Patients also received pulses of methotrexate intrathecally at 7-week intervals for six courses during the first year of the maintenance-phase therapy (8).

NUDT15 genotyping. A Nanodrop 2000 Spectrophotometer (Thermo Fisher Scientific Inc., Waltham, MA, USA) was used for genomic DNA quantification of the stored samples. To test for *NUDT15 c.415C>T* (rs116855232) polymorphism, the *NUDT15* gene was first amplified using an Agilent Surecycler 8800 (Agilent Technologies Inc., Santa Clara, CA, USA) in a polymerase chain reaction (PCR) using a primer set from a previous study (17). The primers were as follows: NUDT15-F (forward primer): 5'-GGAGCTTTTCTG GGGACTGT-3' and NUDT15-R (reverse primer): 5'-GCTGAAA GAGTGGGGGATAC-3'. The PCR amplification was performed using MyTaq HS Red Mix (Bioline, London, UK) with an annealing temperature of 60˚C. Electrophoresis was performed using a 2 μl sample amplicon with 1% TBE agarose gel to evaluate the PCR band quality. Following amplification, direct Sanger DNA sequencing was conducted using the same primer set (Figure 2A and B). To confirm the results, 10 random samples were re-examined using the same reverse primer and a different forward primer (5'-GAAAGGA GAAGTGGATGTGAC-3'). We used Primer Blast tool from NCBI (https://www.ncbi.nlm.nih.gov/tools/primer-blast/index.cgi?) to test for our primer specificity and binding site (Supplemental Data 1).

Statistical analysis. SPSS 20 software (IBM, Armonk, NY, USA) was used for statistical analysis. The normality of data distribution was evaluated by the Kolmogorov–Smirnov test. The association between *NUDT15 c.415C>T* genotype and hematotoxicity was analyzed using the chi-square test or Fisher's exact test, as appropriate.

Results

Patient characteristics and prevalence of hematotoxicity. A total of 101 patients with ALL were included in our study. Baseline characteristics are shown in Table I. All subjects were Indonesian and the median age at study participation was 6.17 years. The proportion of male patients was 52.5%, and those with high-risk disease constituted 54.5% of the study population. About 98% of the patients had a normal to obese nutritional status, and 99% had a normal serum albumin level.

The prevalence of hematotoxicity was 70.3% (Table I). The majority of hematotoxicity was of grade 1 (Table II). The prevalence of neutropenia, anemia, and thrombocytopenia was 50.5%, 44.5%, and 6%, respectively. Nine patients (8.9%) presented with grade 3 to 4 neutropenia (absolute neutrophil count <1,000 cells/mm^3).

NUDT15 c.145>T genotyping and hematotoxicity. Genomic DNA amplification was followed by Sanger DNA sequencing using the primer set from a previous study (17), as mentioned in Patients and Methods. To our surprise, all 101 DNA samples were homozygous for the *NUDT15 c.415C>T* variant (Figure 2C), as confirmed by the chromatogram. Driven by our own skepticism, we rechecked all the procedure and found no errors. Additionally, to confirm the results obtained, 10 random samples were re-examined using a new set of primers (Figure 2A and B) and the same mutation was observed in all cases (Supplemental Data 2 and 3). However, in relation to this 'all cases' result, we found no

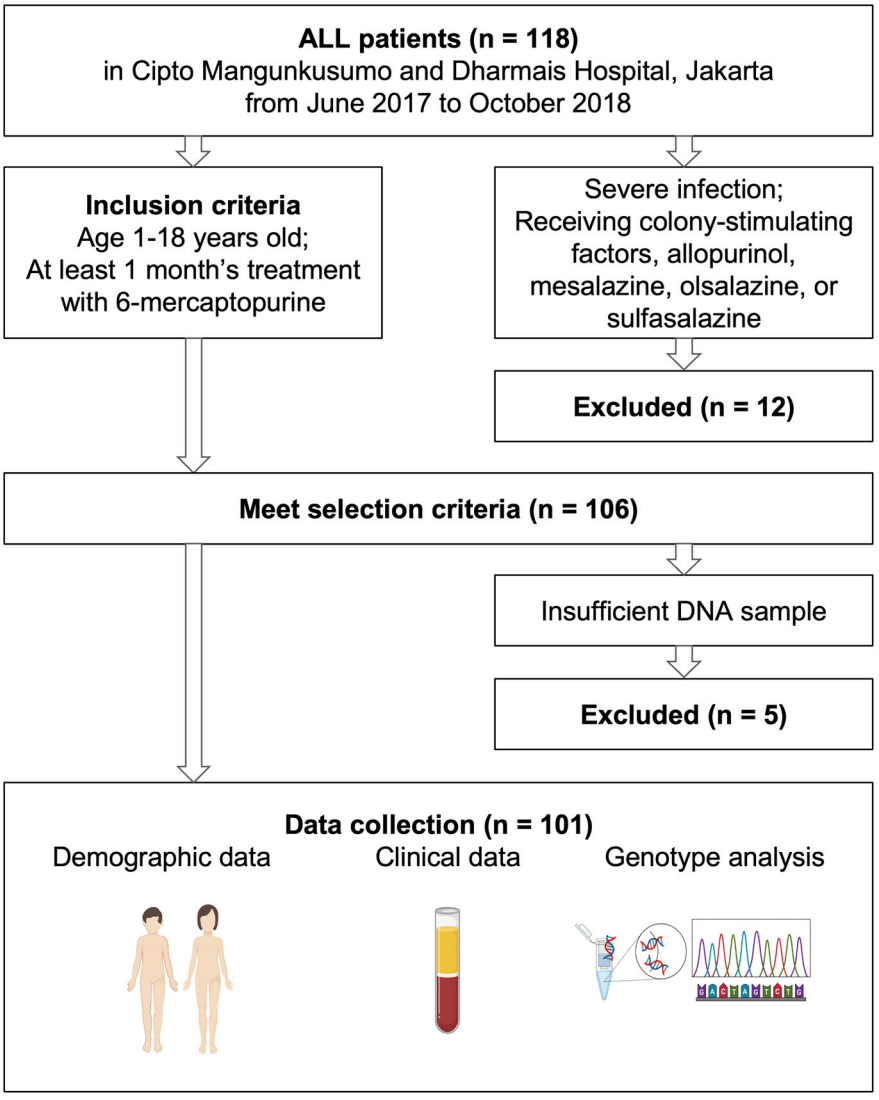

Figure 1. *Patient selection and study design. A total of 101 pediatric patients with acute lymphoblastic leukemia from June 2017 to October 2018 who met the selection criteria were recruited from two different cancer centers in Jakarta in this study. After obtaining written informed consent from parents or legal guardians of the patients, we recorded the demographic data and collected clinical data, as well as peripheral blood for hematological and genotype analysis (Sanger sequencing).*

association between *NUDT15 c.415C>T* genotype and hematotoxicity (Table III).

Discussion

As a backbone regimen in maintenance phase therapy of pediatric ALL, 6-MP has severe myelosuppression as a side-effect, which increases the risk of life-threatening infections, resulting in treatment discontinuation and a high risk of relapse (1). The *TPMT* polymorphism plays a role in 6-MP hematotoxicity, but not in Asian populations, include Indonesian, due to the low frequency of mutant *TPMT* allele (8, 13). The *NUDT15* gene polymorphism increases the risk of 6-MP hematotoxicity by affecting thiopurine metabolism, leading to more DNA strand breaks and apoptosis (20). There are several variants of *NUDT15,* the most common variant related to 6-MP intolerance is *NUDT15 c.415C>T* (9, 12, 15). The *NUDT15 c.415C>T* variant causes a missense mutation at residue Arg139, resulting in an arginine-to-cysteine change (p.Arg139Cys). This residue is in the α helix a2 at the base of the NUDT15 substrate-binding pocket. The alteration of arginine to cysteine in this location might introduce a disulfide bond resulting in structural perturbation and NUDT15–TGTP binding interference (21, 22). Wild-type NUDT15 efficiently

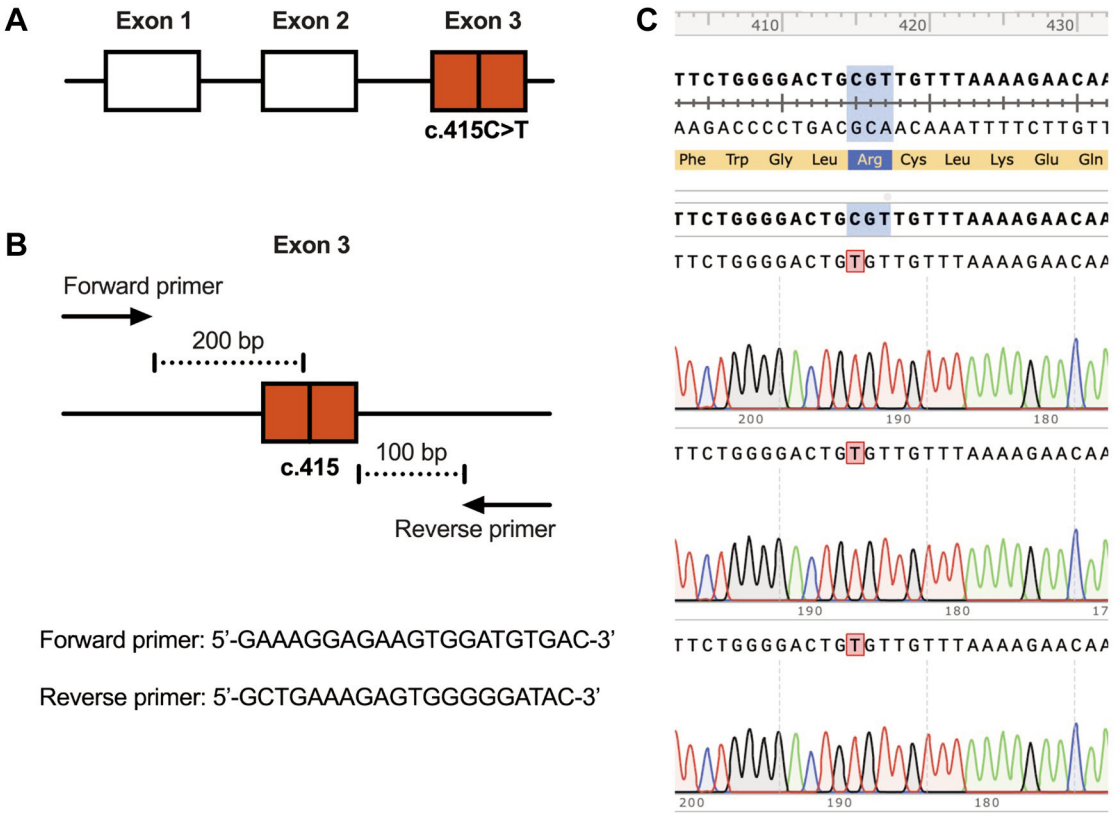

Figure 2. *Nudix hydrolase 15 (NUDT15) genotyping. (A) NUDT15 gene polymorphism. (B) Primer design used to confirm the result of NUDT15 c.415C>T genotyping. (C) Sequence of genomic polymerase chain reaction products in representative samples. c.415C>T homozygous variant in exon 3.*

converts the cytotoxic thiopurine active metabolite, TGTP, to the non-toxic monophosphate metabolite. In contrast, mutated NUDT15 showed 74.4% to 100% loss of enzymatic activity (21). Patients heterozygous for the *NUDT15 c.415C>T* variant showed intermediate NUDT15 enzymatic activity (intermediate metabolizers), and those homozygous for the variant showed low enzymatic activity (poor metabolizers) (13, 21). Moriyama *et al*. found that patients with the low-activity NUDT15 had the highest level of DNA-TG in white blood cells, followed by the intermediate activity group, and the lowest DNA-TG level was found in patients with wild-type *NUDT15*. The lack of functional NUDT15 directly resulted in more robust conversion of thioguanine to DNA-TG, and therefore elevated the risk of toxicity (23).

In this study, all patients were homozygous for the *c.415C>T* variant, potentially contributing to the high prevalence of hematotoxicity (70.3%) observed. The frequency of *NUDT15* polymorphism is indeed higher in Asian populations compared to Caucasians and Africans (15), but does not reach 100%. The frequency of *NUDT15 c.415C>T* in Asian pediatric patients with ALL was 12.6% in Thailand (17); 11.6%, 13.2% and 15.7% in China (14, 24, 25); 13.6% in Korea (26); 12% and 16% in Japan (9, 27); 9.5% and 9.8% in India (28, 29); and was very low in Europe (0.2%) and not observed in Africa (15). Our remarkable finding, where all our population had the polymorphism is not the sole revelation of this type. Hidayat *et al*. reported that 96% of a stroke patient population in Indonesia had *CYP2C19* allele *17 mutation, a polymorphism associated with clopidogrel sensitivity (30), while in Asian (31) and Caucasian (32) populations, the frequency is only 15.18% and 21%, respectively. These results underscore the association of polymorphism with ethnicity. Another possible explanation comes from patient variability. For example, *CYP2D6* polymorphism with poor metabolizer phenotype was found only 1.1% in healthy individuals (33) but at 48.8% in patients with breast cancer (34). Thus, study subject variability and disease state are important determinants of the variability in polymorphism prevalence. Groups of patients tend to have a higher tendency towards mutation compared to healthy individuals in a population. In our current study, the population was paediatric patients with ALL receiving

Table I. *Patients' characteristics (n=101).*

Characteristic		Value
Age (years)	Median (min-max)	6.17 (2.42-17.83)
Sex, n (%)	Male	53 (52.5)
	Female	48 (47.5)
Risk stratification, n (%)	High risk	55 (54.5)
	Standard risk	46 (45.5)
Nutritional status, n (%)	Underweight	2 (2)
	Normal/obese	99 (98)
BMI (kg/m^2)	Median (min-max)	17.01 (12.94-28.04)
Albumin (g/dl)	Mean±SD	4.53±0.34
	Normal, n (%)	100 (99)
	<3.5 g/dl, n (%)	1 (1)
Duration of maintenance therapy (weeks)	Median (min-max)	40 (19-106)
Hb level (g/dl)	Median (min-max)	11.6 (8.2-14.6)
White blood cells (cells/µl)	Median (min-max)	4,440 (1,150-10,900)
ANC (cells/µl)	Median (min-max)	2,427 (450-8,268)
Platelets (×10^3/µl)	Mean±SD	328.613±107.974
Hematotoxicity, n (%)	Yes	71 (70.3)
	No	30 (29.7)

ANC: Absolute neutrophil count; BMI: body mass index; Hb: hemoglobin; SD: standard deviation.

Table II. *Hematotoxicity data.*

	Hematotoxicity, n (%)		Grade, n (%)*			
Hematology	No	Yes	1	2	3	4
Hb	56 (55.4)	45 (44.5)	36 (35.6)	9 (8.9)	0	0
ANC	50 (49.5)	51 (50.5)	30 (29.7)	12 (11.9)	7 (6.9)	2 (2)
Thrombocytes	95 (94)	6 (6)	4 (4)	0	0	2 (2)

ANC: Absolute neutrophil count; Hb: hemoglobin. *According to Common Terminology Criteria for Adverse Events v.3 (19).

anticancer therapy: mercaptopurine, vincristine, and methotrexate. Mercaptopurine metabolite is known to cause DNA mismatch repair (35). Vincristine and methotrexate are both genotoxic, causing DNA damage (36, 37). These medications may be related to the higher mutant allele frequency in our study population. However, further study to investigate the frequency of *NUDT15 c.415C>T* allele in healthy children in Indonesia is required.

The *NUDT15 c.415C>T* variant was associated with increased risk of leukopenia, early-onset leukopenia, and neutropenia during 6-MP therapy in a cohort study of pediatric patients with ALL in Japan (9), Thailand (16, 17), China (25, 38), and Korea (39, 40). In our study, 51 patients (50.5%) experienced neutropenia during 6-MP therapy, nine of them (8.9%) had grade 3-4 neutropenia or an absolute neutrophil count <1,000 cells/mm^3. Although it is impossible to infer a direct association between *NUDT15 c.415C>T* variant and hematotoxicity due to the absolute number of mutations in our population, we cannot ignore the fact that our population had a pretty high hematotoxicity rate following 6-MP administration. Since to our knowledge this is the first cross-sectional study of *NUDT15* polymorphism in Indonesia, we strongly recommend that further cohort

Table III. *Association between hematotoxicity and nudix hydrolase 15 (NUDT15) c.415C>T genotype.*

Variable		Hematotoxicity		*p*-Value[a]
		Yes (grade 1-4) (n=71)	No (n=30)	
NUDT15 genotype	Wild-type	0	0	1.000
	c.415C>T	71	30	

[a]Fisher's exact test.

study is needed to confirm the frequency of NUDT *c.415C>T* variant in other populations in Indonesia and its association with 6-MP hematotoxicity.

In this study, pediatric patients with *NUDT15 c.415C>T* variant showed lower tolerance to 6-MP therapy for ALL. Liang *et al*. found that pediatric patients with ALL heterozygous for the *NUDT15 c.415C>T* variant were able to tolerate an average dose of 30.7 mg/m^2 per day of 6-MP, whereas homozygous patients were only able to endure an average dose of 9.4 mg/m^2 (14). In line with that, Tanaka *et al*. found that pediatric patients with ALL who were heterozygous or homozygous for the *c.415C>T* variant tolerated average doses of 29.3 and 8.8 mg/m^2 per day of 6-MP, respectively (9). The Clinical Pharmacogenetics Implementation Consortium recommends a substantially reduced starting dose of 10 mg 6-MP/m^2/day for *NUDT15* poor metabolizers (homozygous for the variant allele) (13). In our study, all patients were homozygous for *NUDT15 c.415C>T* and received 50 mg/m^2/day of 6-MP as a starting dose. Based on our results, adjustment of the initial 6-MP dose is strongly recommended for paediatric patients with ALL to lower the risk of hematotoxicity.

Conclusion

The frequency of *NUDT15 c.415C>T* genotype polymorphism in our population was 100%. In the present study, we did not find an association between *NUDT15* c.415C>T genotype polymorphism and hematotoxicity. Our results lead us to recommend testing for the genotype of *NUDT15* for 6-MP initial dose adjustment to avoid hematotoxicity in paediatric patients with ALL in Indonesia. However, we recommend that further cohort study is needed to confirm the frequency of *NUDT15* variant in other populations in Indonesia as well as to understand the consequences of reducing the initial dose of 6-MP on patient's survival.

Supplementary Material

Available at: https://drive.google.com/file/d/1Edn79DH14IyWfPsASBCX5BQ0LxGhxpI7/view?pli=1

Conflicts of Interest

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

All the Authors listed in this article have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content; and final approval of the version to be published.

Acknowledgements

The Authors would like to thank DRPM Indonesia University for the research grant PUTI Q2, number: NKB-1225/UN2.RST/HKP.05.00/2022.

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Received March 8, 2024
Revised April 22, 2024
Accepted April 25, 2024