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Review Article

Personalized Treatment of 6-Mercaptopurine in Thai Children with Acute Lymphoblastic Leukemia

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ABSTRACT

Thanks to its ability to inhibit deoxyribonucleic acid synthesis, 6-mercaptopurine (6-MP), is one of the indispensable medications for acute lymphoblastic leukemia (ALL) patients. Nevertheless, some patients may succumb to myelotoxicity, leading to treatment disruption or even life-threatening events. Owing to the advances in pharmacogenomics, the genetic polymorphism of genes regulating purine synthesis has been identified and physicians can adjust the dose of 6-MP according to each polymorphism. Such polymorphisms genetically vary among ethnicities. In this article, 2 genetic polymorphisms, namely thiopurine methyltransferase and Nudix (nucleoside diphosphate linked moiety X) type motif 15, are clinically discussed, with a special focus on the clinical studies in Thai children with ALL.

Keywords: 6-mercaptopurine; acute lymphoblastic leukemia; TPMT

INTRODUCTION

The treatment outcome for pediatric acute lymphoblastic leukemia patients (ALL) has drastically improved over the past 10 years, with event-free survival now of 90.0%.[1] The major factors appear not to be due to the discovery of new drugs but rather a result of more effective supportive care and individualized treatment, e.g., the escalation of treatment intensity according to the measurement of the minimal residual disease and personalized dosing in chemotherapy, such as methotrexate (MTX) and 6-mercaptopurine (6-MP).[2]

The treatment schedule for ALL consists of several phases of treatment, namely an induction phase, consolidation phase, delayed intensification phase, and main-

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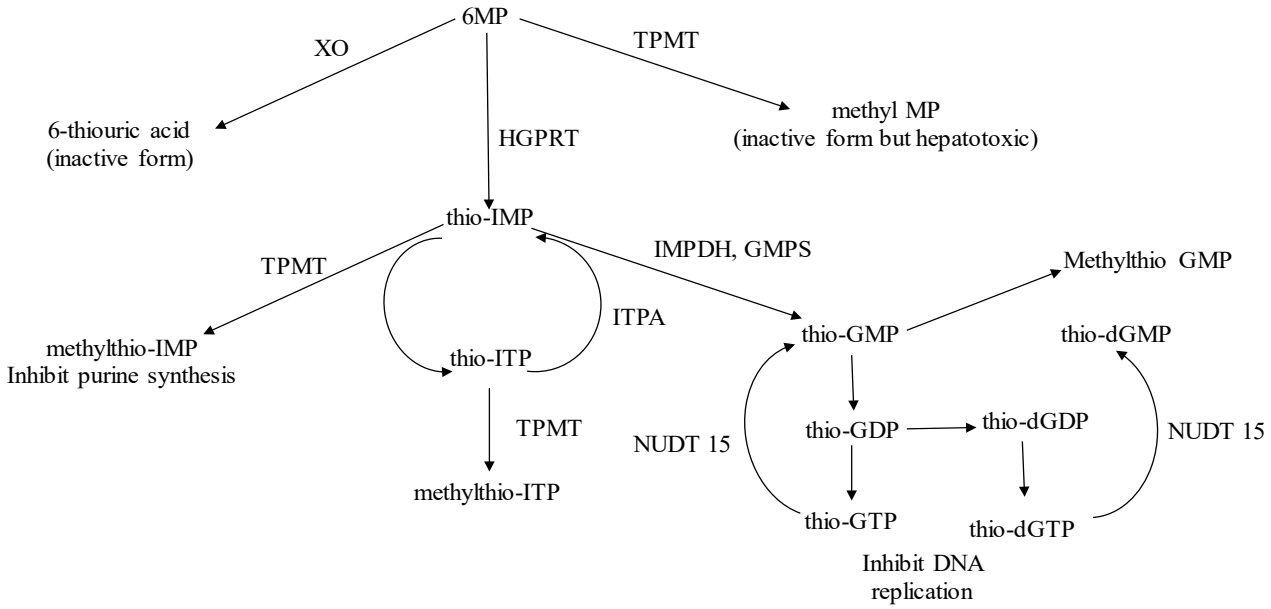
tenance phase, aimed at eliminating the leukemic cells and maintaining the remission, with an approximate total duration of treatment of 3 years in boys and 2 years in girls. The maintenance phase, the longest phase of treatment for ALL, requires a daily dose of 6-MP, a purine analog, and a weekly dose of MTX as a mainstay therapy. A mechanistic study revealed that the inhibition of purine synthesis seems to be more pivotal to eliminate leukemic stem cells.[3] As per the aforementioned reason, 6-MP appears to be one of the most essential medications for ALL. Patients with poor adherence to 6-MP during the maintenance phase are at risk of relapse.[4] Furthermore, measurement of the 6-thioguanine (6-TGN) metabolite of 6-MP is favorably correlated with the adherence to treatment[5] and ultimately is reflected in relapse-free survival.[6] The serial monitoring of the 6-TGN level has been used in some clinical practices to improve the risk of relapse. Unfortunately, no laboratory study has yet been done in Thailand. The other parameter that is well correlated with 6-TGN is the absolute neutrophil count (ANC). The Nordic Society of Pediatric Hematology and Oncology ALL study demonstrated that those with an average ANC of less than 2,000/mm^3 had better event-free survival than those who with a higher ANC.[7] Taken together, it is prudent for ALL patients that their dose of 6-MP and MTX should be adjusted to maintain their ANC between 500−1,500/mm^3.

The interindividual variation in enzymes involved in the purine metabolism multi-step pathway also plays an important role in the difference in 6-MP degradation resulting in treatment-related toxicities and outcome. 6-MP is metabolized by three major pathways as follows (Figure 1).[3, 8]

1. Metabolized by xanthine oxidase and thiopurine methyltransferase (TPMT) to 6-thiouric acid and 6-



dGDP=deoxyguanosine diphosphate; dGMP=deoxyguanosine monophosphate; dGTP=dexyguanosine triphosphate; GDP=guanosine diphosphate; GMP=guanosine monophosphate; GMPS=guanosine monophosphate synthetase; GTP=guanosine triphosphate; HGPRT=hypoxanthine guanine phosphoribosyl transferase; IMP=inosine monophosphate; IMPDH=inosine monophosphate dehydrogenase; ITP=inosine triphosphate; ITPA=inosine triphosphate pyrophosphatases; MP=mercaptopurine; NUDT15=Nudix Hydrolase 15; TMP=thymidine monophosphate; TPMT=thiopurine methyltransferase; XO=xanthine oxidase

Figure 1 Mercaptopurine metabolism pathway

methylmercaptopurine (6-MMP), respectively, which are inactive forms. However, some studies have demonstrated that 6-MMP may account for hepatotoxicity in those receiving 6-MP.

2. Metabolized by hypoxanthine guanine phophoribosyltransferase (HGPRT) and subsequently metabolized by multi-step enzymes to thio-guanosine triphosphate (thio-GTP) and thiodeoxyguanosine triphosphate (thio-dGTP). Both thio-GTP and thio-dGTP are active metabolites inhibiting deoxyribonucleic acid (DNA) replication. The thioguanine metabolite has also demonstrated an anti-inflammatory effect by downregulating the genes involved in the tumor necrosis factor pathway and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which, however, may be beyond the scope of this article.

3. After being metabolized by HGPRT, thioinosine monophosphate (thioIMP), the intermediated substance, is subsequently metabolized by TPMT to methylthioinosine monophosphate (methyl-thioIMP), which interferes with de novo purine synthesis and ultimately enhances the inhibitory effect to DNA replication of thio-GTP and thio-dGTP. However, similar to 6-MMP, methyl-thioIMP may cause hepatotoxicity.

The genetic polymorphism of genes involved in purine metabolism resulting in the decreased activity of enzymes such as *TPMT* may lead to the risk of myelotoxicity and secondary malignancy.[9,10] As previously discussed, TPMT metabolizes 6-MP to an inactive metabolite; therefore, those with a low activity of TPMT and having more residual substrate, which is subsequently converted to the active form, might be at risk of neutropenia. TPMT activity can be indirectly assessed by genotyping polymorphism of *TPMT*, an encoding gene. Patients harboring the homozygous *TPMT* polymorphism require a dose reduction of 90.0%. Those with a heterozygous type may need a dose reduction of 30.0−80.0% if the initial dose is more than 75 mg/m^2, while those receiving a dose less than 75 mg/m^2 may not initially require a dose reduction.[11] However, the prevalence of *TPMT* polymorphism varies among ethnicities[12] and the prevalence in Asian populations appears to be lower than that in Europeans.[13] In Thailand *TPMT*3C* is the most common, with an allele frequency of 0.05.[14, 15]

The Nudix (nucleoside diphosphate linked moiety X)-type motif 15 (NUDT15) is another hydrolytic enzyme that changes 6-MP, both thio-GTP and thio-dGTP, as the active forms, to thio-GMP and thio-dGMP, as the inactive forms, respectively. Similar to those with *TPMT* polymorphism, those with NUDT15 require a dose reduction to prevent neutropenia. Compared to *TPMT, NUDT15* polymorphism seems to be more prevalent in Asian populations.[16] *NUDT15 c.415C>T* is a polymorphism first identified in 2014 and found to be associated with the risk of excessive leukopenia.[17] The allele frequency of *NUDT15*

Table 1 Dosing recommendation for 6-MP followed by NUDT15 phenotype[11,22,23]

NUDT15 Phenotype	Diplotypes	Dosing recommendations (At normal dose 75 mg/m^2/day or 1.5 mg/kg/day)	Patients follow up protocol
Normal metabolizer	**1/*1*	Use normal starting dose	At least 2 weeks
Intermediate metabolizer or Possible intermediate metabolizer	**1/*2, *1/*3* (Intermediate) **2/*5, *3/*6* (Possible intermediate)	30.0–80.0% of normal dose	2-4 weeks
Poor metabolizer	**2/*2, *2/*3, *3/*3*	Initiate dose at 10 mg/m^2/day	4-6 weeks

c.415C>T of Thai children with ALL was reported to be about 5.0−12.6% and to be strongly correlated with neutropenia, and those harboring such polymorphism require dose reduction.[18-20] Other polymorphisms of *NUDT15* have recently been identified, such as c.52G > A and c.36_37 insGGAGTC, and found to be associated with neutropenia.[21]

From the aforementioned studies, dose adjustment for those harboring such polymorphism is warranted to prevent severe neutropenia-related complications and treatment interruption. The recent guideline suggests a dose reduction of 30.0−80.0% for those having an intermediate metabolizer (or carrying one non-functional allele) of *NUDT15* treated with 75 mg/m^2 of 6-MP and an initial 10 mg/m^2 of 6-MP for those having a poor metabolizer (or carrying two non-functional allele) of *NUDT15*[11] (Table 1). Notably, a few Thai patients with homozygous *NUDT15*[18, 20] needed a reduction dose of 6-MP of 40.0−50.0%, less than the recent guideline of 80.0−90.0%. Therefore, Thai patients with homozygous *NUDT15* may require an increment of the dose if they receive the dose at 10 mg/m^2 but their neutrophil count cannot reach the target of 500−1500/mm^3.

CONCLUSION

In conclusion, the evaluation of *TPMT* and *NUDT15* before the initiation of 6-MP appears to be indispensable to prevent the risk of myelotoxicity. Further studies in other *NUDT15* polymorphisms and other candidate genes to completely justify the risk of thiopurine-related toxicities in Thai populations is warranted to better personalize the treatment.

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