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Mercaptopurine Therapy and *TPMT* Genotype

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Introduction

Mercaptopurine is an immunosuppressant and antineoplastic agent that belongs to the drug class of thiopurines. It is used in combination with other drugs to treat acute lymphoblastic leukemia, which is the most common form of cancer in children (1). In addition, off-label uses include the treatment of inflammatory bowel disease (IBD).

Mercaptopurine is a prodrug that must first be activated to form thioguanine nucleotides (TGNs), the major active metabolites. Thiopurine S-methyltransferase (TPMT) inactivates mercaptopurine, leaving less parent drug available to form TGNs.

An adverse effect of mercaptopurine therapy is bone marrow suppression, which can occur in any patient, is dose-dependent, and may be reversed by reducing the dose of mercaptopurine. However, patients who carry two nonfunctional *TPMT* alleles universally experience life-threatening myelosuppression when treated with mercaptopurine, due to high levels of TGNs. Patients who carry one nonfunctional *TPMT* allele may also be unable to tolerate conventional doses of mercaptopurine (2, 3).

The FDA-approved drug label for mercaptopurine states that heterozygous patients with low or intermediate TPMT activity accumulate higher concentrations of active TGNs than people with normal TPMT activity and are more likely to experience mercaptopurine toxicity; and that TPMT genotyping or phenotyping (red blood cell TPMT activity) can identify patients who are homozygous deficient or have low or intermediate TPMT activity (1).

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published dosing recommendations for *TPMT* genotype-based mercaptopurine dosing. These recommendations include:

Start with reduced doses of mercaptopurine for patients with one nonfunctional *TPMT* allele, or drastically reduced doses for patients with malignancy and two nonfunctional alleles; adjust dose based on degree of myelosuppression and disease-specific guidelines. Consider alternative nonthiopurine immunosuppressant therapy for patients with nonmalignant conditions and two nonfunctional alleles (see Table 1) (2-4).

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Table 1. *TPMT* phenotypes and the therapeutic recommendations for mercaptopurine therapy, adapted from CPIC

Phenotype	Phenotype details	*TPMT* Genotype	Examples of diplotypes	Therapeutic recommendations for mercaptopurine (MP)
Homozygous wild-type ("normal")	High enzyme activity. Found in ~86-–97% of patients.	Two or more functional *TPMT* alleles	**1/*1*	Start with normal starting dose (e.g., 75 mg/m^2/d or 1.5 mg/kg/d) and adjust doses of MP (and of any other myelosuppressive therapy) without any special emphasis on MP compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment.
Heterozygous	Intermediate enzyme activity. Found in ~3-–14% of patients.	One functional *TPMT* allele plus one nonfunctional *TPMT* allele	**1/*2* **1/*3A* **1/*3B* **1/*3C* **1/*4*	Start with reduced doses (start at 30–70% of full dose: e.g., at 50 mg/m^2/d or 0.75 mg/kg/d) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In those who require a dosage reduction based on myelosuppression, the median dose may be ~40% lower (44 mg/m2) than that tolerated in wild-type patients (75 mg/ m^2). In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing MP over other agents.
Homozygous variant	Low or deficient enzyme activity. Found in ~1 in 178 to 1~3736 patients.	Two nonfunctional *TPMT* alleles	**3A/*3A* **2/*3A* **3C/*3A* **3C/*4* **3C/*2* **3A/*4*	For malignancy, start with drastically reduced doses (reduce daily dose by 10-fold and reduce frequency to thrice weekly instead of daily, e.g., 10 mg/m^2/d given just 3 days/week) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing MP over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.

MP: Mercaptopurine
The strength of therapeutic recommendations is "strong" for all phenotypes.
Table is adapted from Relling M.V. et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. Clinical pharmacology and therapeutics. 2011;89(3):387–91 (2, 3).

Drug Class: Thiopurines

Thiopurines are used as anticancer agents and as immunosuppressants in inflammatory bowel disease, rheumatoid arthritis, and other autoimmune conditions. Three thiopurines are used clinically: thioguanine, mercaptopurine, and azathioprine (a prodrug for mercaptopurine). All three agents have similar effects but are typically used for different indications. Thioguanine is most commonly used in the treatment of myeloid leukemias, mercaptopurine is used for lymphoid malignancies, and mercaptopurine and azathioprine are used for immune conditions.

Thiopurines are either activated to form TGNs (the major active metabolite) or deactivated by TPMT. Individuals who carry two non-functional *TPMT* alleles ("*TPMT* homozygotes") universally experience life-threatening bone marrow suppression because of high levels of TGNs when treated with conventional doses.

Individuals who carry one non-functional *TPMT* allele ("*TPMT* heterozygotes") may also be unable to tolerate conventional doses of thiopurines due to increased levels of TGNs.

Drug: Mercaptopurine

Mercaptopurine is a neoplastic agent and an immunosuppressive agent that is used in the treatment of acute lymphoblastic leukemia (ALL) as part of a combination regimen. ALL is the most common form of cancer in children, accounting for approximately 30% of childhood malignancies with a peak incidence occurring at 3 to 5 years of age (5).

An off-label use of mercaptopurine is in the treatment of inflammatory bowel disease (IBD). Along with the closely related azathioprine (which is metabolized to mercaptopurine), mercaptopurine is used as an "immunomodulator" and as a "steroid-sparing agent" in the treatment of Crohn's disease and ulcerative colitis.

Mercaptopurine is a slow-acting drug and for IBD, it typically takes at least three months of therapy before a therapeutic effect is observed. Therefore, mercaptopurine is used for the induction and maintenance of IBD remission rather than as a monotherapy for acute relapses (6). Because the discontinuation of mercaptopurine is associated with a high rate of relapse of IBD, mercaptopurine is usually continued long-term if there are no adverse effects (7, 8).

The use of mercaptopurine or the related drug azathioprine, has been associated with a 4-fold increased risk of developing lymphoma, which does not persist after discontinuation of therapy (9, 10).

Like all thiopurines, mercaptopurine is a purine analogue, and acts as an antimetabolite by interfering with nucleic acid synthesis and inhibiting purine metabolism. Activation of mercaptopurine occurs via HPRT1 (hypoxanthine phosphoribosyltransferase) followed by a series of reactions to form TGNs. The cytotoxicity of mercaptopurine is due, in part, to the incorporation of TGNs into DNA.

Inactivation of mercaptopurine occurs via two different pathways, via methylation (by TPMT) or via oxidation (by xanthine oxidase). TPMT activity is highly variable in patients because of genetic polymorphism in the *TPMT* gene.

One of the most frequent adverse reactions to mercaptopurine is myelosuppression, which can occur in any patient, and can usually be reversed by decreasing the dose of mercaptopurine. However, all patients who carry two nonfunctional *TPMT* alleles (approximately 0.3%) experience life-threatening myelosuppression after starting treatment with conventional doses of mercaptopurine, due to high levels of TGNs.

Individuals who are heterozygous for nonfunctional *TPMT* alleles (approximately 10%) are at a significantly higher risk for toxicity than individuals with two functional alleles. However, some of these individuals, approximately 40–70%, can tolerate the full dose of mercaptopurine. This may be because heterozygous-deficient individuals have lower concentrations of less active metabolites, such as MeMPN (methylmercaptopurine nucleotides), than homozygous-deficient individuals (2, 3).

Approximately 90% of individuals have normal TPMT activity with two functional alleles; however, all individuals receiving mercaptopurine require close monitoring (2, 3, 11, 12). One study reports that in patients with IBD receiving thiopurine therapy, TPMT polymorphisms are associated with the overall incidence of adverse reactions and with bone marrow toxicity, but not with other adverse reactions, such as liver damage and pancreatitis. Therefore, although determining *TPMT* genotype is helpful before initiating therapy, regular blood tests to monitor for side effects are needed during therapy (1, 13).

The other mercaptopurine inactivation pathway is via oxidation, which is catalyzed by xanthine oxidase. If this pathway is inhibited, for example, in patients taking allopurinol (an inhibitor of xanthine oxidase), the decreased break down of mercaptopurine can lead to mercaptopurine toxicity (1). However, some studies have found that

the co-administration of allopurinol, with a reduced dose of mercaptopurine (or azathioprine), can help optimize the treatment response in patients with IBD (14, 15).

Gene: *TPMT*

The *TPMT* gene encodes one of the important enzymes of phase II metabolism, thiopurine S-methyltransferase. TPMT is one of the main enzymes involved in the metabolism of thiopurines, such as mercaptopurine. TPMT activity is inherited as a co-dominant trait, as the *TPMT* gene is highly polymorphic with over 40 reported variant alleles (16-19).

The wild-type *TPMT*1* allele is associated with normal enzyme activity. Individuals who are homozygous for *TPMT*1* (TPMT normal metabolizers) are more likely to have a typical response to mercaptopurine and a lower risk of myelosuppression. This accounts for the majority of patients (~86–97%) (2, 3).

Individuals who are TPMT poor (approximately 0.3%) or intermediate (approximately 3–14%) metabolizers carry variant *TPMT* alleles that encode reduced or absent enzyme activity. Three variant *TPMT* alleles account for over 90% of the reduced or absent activity *TPMT* alleles (20, 21):

- *TPMT*2* (c.238G>C)
- *TPMT*3A* (c.460G>A and c.719A>G)
- *TPMT*3B* (c.460G>A)
- *TPMT*3C* (c.719A>G)

The frequency of *TPMT* alleles varies among different populations. In the United States, the most common low-activity allele in the Caucasian population is *TPMT*3A* (~5%). This allele is also found in individuals who originate from India and Pakistan, but less frequently (16, 20).

In East Asian, African-American, and some African populations, the most common variant is *TPMT*3C* (~2%), although *TPMT*8* may be more common in African populations than previously thought (~2%). In general, *TPMT*2* occurs much less commonly, and *TPMT*3B* occurs rarely (16, 22).

Genetic Testing

Genetic testing is available for several *TPMT* variant alleles, which most commonly includes *TPMT*2*, **3A*, and **3C* as they account for >90% of inactivating alleles. Of note, rare and/or previously undiscovered variants will not be detected by variant-specific genotyping methods (2, 3, 23-26).

TPMT phenotype enzyme activity testing is also available by measuring TPMT activity in red blood cells directly (11). In adult patients taking mercaptopurine as an immunosuppressive agent, there is strong evidence of a near 100% concordance between phenotype and genotype testing. Inflammatory disease processes do not interfere with the accuracy of TPMT activity measurements if the blood sample is taken under standard conditions (e.g., not within two months of a blood transfusion).

However, in patients with leukemia, the concordance between TPMT phenotype and genotype is poor (27). By the time of diagnosis, red cell TPMT activity is typically greatly reduced because of atypical hematopoiesis. Therefore, phenotype testing may wrongly identify an individual as having a TPMT deficiency, e.g., a patient who has two functional copies of the *TPMT* gene (homozygous wild-type) may be determined as having only one functional copy and one nonfunctional variant (*TPMT* heterozygous); and a patient who is *TPMT* heterozygous may be wrongly determined to be *TPMT* homozygous (two copies of nonfunctional *TPMT* variants). In addition, during the course of chemotherapy, *TPMT* phenotype testing may reveal excessively high TPMT activity. This is thought to be due to an excess of young red blood cells with their associated higher level

of TPMT enzyme activity. Therefore, to avoid an incorrect TPMT status, genotype testing is recommended for patients with leukemia (27).

Finally, one study reported that *TPMT* genotyping was more reliable than phenotyping in identifying patients at risk of adverse reactions from thiopurine treatment (28), and several studies reported that the *TPMT* genotype is a better indicator than TPMT activity for predicting TGN accumulation or treatment outcome (12, 29-31).

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2015 Statement from the US Food and Drug Administration (FDA): Individuals who are homozygous for an inherited defect in the TPMT (thiopurine-S-methyltransferase) gene are unusually sensitive to the myelosuppressive effects of mercaptopurine and prone to developing rapid bone marrow suppression following the initiation of treatment. Laboratory tests are available, both genotypic and phenotypic, to determine the TPMT status. Substantial dose reductions are generally required for homozygous-TPMT deficient patients (two non-functional alleles) to avoid the development of life threatening bone marrow suppression. Although heterozygous patients with intermediate TPMT activity may have increased mercaptopurine toxicity, this is variable, and the majority of patients tolerate normal doses of mercaptopurine. If a patient has clinical or laboratory evidence of severe toxicity, particularly myelosuppression, TPMT testing should be considered. In patients who exhibit excessive myelosuppression due to 6-mercaptopurine, it may be possible to adjust the mercaptopurine dose and administer the usual dosage of other myelosuppressive chemotherapy as required for treatment.

Please review the complete therapeutic recommendations that are located here: (1).

2013 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC): Testing for *TPMT* status is recommended prior to starting mercaptopurine therapy so that the starting dosages can be adjusted accordingly—see Table 1 for dosing recommendations. In homozygous variant individuals, consider an alternative agent for nonmalignant conditions and drastically reduce doses in malignant conditions. In heterozygous individuals, depending on the disease being treated, starting doses should be reduced. In both patient groups, a longer period of time should be left after each dose adjustment to allow for a steady state to be reached.

Please review the complete therapeutic recommendations that are located here: (2, 3).

Nomenclature

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*TPMT*2*	238G>C Ala80Pro	NM_000367.2:c.238G>C	NP_000358.1:p.Ala80Pro	rs1800462
*TPMT*3A*	This allele contains two variants in cis: c.460G>A and c.719A>G			
*TPMT*3B*	460G>A Ala154Thr	NM_000367.2:c.460G>A	NP_000358.1:p.Ala154Thr	rs1800460
*TPMT*3C*	719A>G Tyr240Cys	NM_000367.2:c.719A>G	NP_000358.1:p.Tyr240Cys	rs1142345

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labelled all formulations containing the generic drug.

The TPMT Nomenclature Committee defines the nomenclature and numbering of novel TPMT variants: http://www.imh.liu.se/tpmtalleles

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

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