

Mercaptopurine Therapy and *TPMT* Genotype

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Mercaptopurine is an immunosuppressant and antineoplastic agent that belongs to the drug class thiopurines. It is used in combination with other drugs for the maintenance therapy of acute lymphatic leukemia (^{1,2}).

Thiopurine S-methyltransferase (*TPMT*) is involved in the metabolism of all thiopurines and is one of the main enzymes that inactivates mercaptopurine. In all patients receiving mercaptopurine, there is a risk of bone marrow suppression. This adverse effect is dose-dependent and may be reversed by reducing the dose of mercaptopurine. However, individuals who inherit two nonfunctional *TPMT* alleles universally experience life-threatening myelosuppression (^{3,4}).

The FDA advises that *TPMT* genotyping or phenotyping can identify individuals who are homozygous for nonfunctional *TPMT* alleles or have low or intermediate *TPMT* activity (¹). The Clinical Pharmacokinetics Implementation Consortium (CPIC) has made recommendations on the dosing of mercaptopurine based on an individual's *TPMT* phenotype (see Table 1) (⁴).

Table 1.

TPMT phenotypes and the therapeutic recommendations for mercaptopurine therapy

Phenotype	Phenotype details	Genotype	Examples of diplotypes	Therapeutic recommendations for mercaptopurine
Homozygous wild-type ("normal")	High enzyme activity. Found in ~86–97% of patients.	Two or more functional alleles	*1/*1	Start with normal starting dose. Adjust doses of mercaptopurine along with concomitant medications. Allow 2 weeks to reach steady state after each dose adjustment.
Heterozygous	Intermediate enzyme activity. Found in ~3–14% of patients.	One functional allele plus one nonfunctional allele	*1/*2 *1/*3A *1/*3B *1/*3C *1/*4	Start with reduced doses (30–70% of the full dose). Adjust doses of mercaptopurine depending on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment.

Phenotype	Phenotype details	Genotype	Examples of diplotypes	Therapeutic recommendations for mercaptopurine
Homozygous variant	Low or deficient enzyme activity. Found in ~1 in 178 to 1~3736 patients.	Two nonfunctional alleles	*3A/*3A *2/*3A *3C/*3A *3C/*4 *3C/*2 *3A/*4	Consider alternative agents for nonmalignant conditions. For malignancy, start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) Adjust doses of mercaptopurine based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment.

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 (4).

Drug: Mercaptopurine

Thiopurines are antimetabolites—as purine analogues, they exert their immunosuppressive effects partly by blocking purine synthesis. Three thiopurines are used clinically: azathioprine, mercaptopurine, and thioguanine. All are prodrugs that give rise to the major active metabolites, thioguanine nucleotides (TGNs).

Activation of mercaptopurine occurs via the enzyme 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.

Mercaptopurine is inactivated by two different pathways, one being catalyzed by TPMT. Individuals who inherit two nonfunctional *TPMT* alleles (~1 in 178 to 1 in 3,736) experience life-threatening myelosuppression, due to high levels of TGNs, if they receive conventional doses of mercaptopurine (4).

Individuals who are heterozygous for nonfunctional *TPMT* alleles (~3–14%) are at a significantly higher risk for toxicity than individuals with two functional alleles. However, some of these individuals, ~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 (4).

Another mercaptopurine inactivation pathway is oxidation, which is catalyzed by xanthine dehydrogenase, XDH (also known as xanthine oxidase). If this pathway is inhibited, catabolism of mercaptopurine is reduced leading to mercaptopurine toxicity. Therefore, a lower dose of mercaptopurine is required in patients taking the XDH inhibitor, allopurinol (1).

Gene: *TPMT*

The *TPMT* gene encodes one of the main enzymes involved in the metabolism of thiopurines, such as mercaptopurine. TPMT activity is inherited as a monogenic, co-dominant trait.

TPMT is highly polymorphic—more than 25 variants are known^(5, 6). The wild-type allele *TPMT*1* is associated with normal enzyme activity. Individuals who are homozygous for *TPMT*1* have a phenotypically normal response to mercaptopurine and a lower risk of myelosuppression. This accounts for the majority of patients (~86–97%)⁽⁴⁾.

The following nonfunctioning alleles are associated with reduced levels of TPMT activity⁽⁷⁾:

- *TPMT*2* (238G>C)
- *TPMT*3A* (contains two SNPs, **3B* and **3C*)
- *TPMT*3B* (460G>A)
- *TPMT*3C* (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^(5, 7, 8).

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^(3, 5).

Genetic Testing

Genetic testing is available for several *TPMT* variant alleles. Most commonly *TPMT*2*, **3A*, and **3C* are tested for, which account for >90% of inactivating alleles. Rare or previously undiscovered variants will not be detected by variant-specific genotyping methods⁽⁴⁾.

Phenotype testing is also available. For example, the TPMT activity in red blood cells can be measured directly. However, the results will not be accurate in patients who have received recent blood transfusions⁽¹⁾. Measures of mercaptopurine metabolites (TGN and MeMPN) are also available.

Therapeutic Recommendations based on Genotype

This section contains excerpted¹ information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

Statement from the US Food and Drug Administration (FDA): Individuals who are homozygous for an inherited defect in the *TPMT* 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 deficiency 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

mercaptapurine 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⁾.

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: ⁽⁴⁾.

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.

Nomenclature

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

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

Acknowledgments

The Pharmacogenomics Knowledgebase: <http://www.pharmgkb.org>

The Clinical Pharmacogenetics Implementation Consortium: <http://www.pharmgkb.org/page/cpic>

References

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Tests in GTR by Condition

[Mercaptopurine response](#)

Tests in GTR by Gene

[TPMT gene](#)