Thioguanine Therapy and *TPMT* Genotype

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Thioguanine is an antineoplastic antimetabolite that belongs to the drug class thiopurines. It is used in the treatment of acute myeloid leukemia ([1, 2]).

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

The FDA advises that testing for *TPMT* deficiency is available, and that substantial dosage reductions of thioguanine may be required to avoid the development of life-threatening bone marrow suppression in patients with *TPMT* deficiency ([1]). The Clinical Pharmacokinetics Implementation Consortium (CPIC) has made recommendations on the dosing of thioguanine based on an individual's *TMPT* phenotype (see Table 1) ([4]).

Table 1.

TPMT phenotypes and the therapeutic recommendations for thioguanine therapy

Phenotype	Phenotype details	Genotype	Examples of diplotypes	Therapeutic recommendations for thioguanine
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 thioguanine 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 (30–50% of the full dose). Adjust doses of thioguanine depending on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment.
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 thioguanine 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 “moderate” for heterozygous individuals, and “strong” for the other 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: Thioguanine

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 thioguanine occurs via the enzyme HPRT1 (hypoxanthine phosphoribosyltransferase) followed by a series of reactions to form TGNs. The cytotoxicity of thioguanine is due, in part, to the incorporation of TGNs into DNA. In addition to inhibiting de novo purine synthesis, thioguanine may also inhibit purine nucleotide interconversions ([1]).

Thioguanine is directly inactivated by TPMT. Individuals who inherit two nonfunctional *TPMT* alleles (~1 in 178 to 1 in 3,736) experience life-threatening myelosuppression after starting treatment with conventional doses of thioguanine ([4]).

Individuals who are heterozygous for nonfunctional *TPMT* alleles (~3–14%) are at an increased risk of moderate to severe bone marrow suppression, whereas individuals who are homozygous for wild-type *TPMT* alleles have a lower risk of bone marrow suppression. However, all individuals receiving thioguanine require close monitoring. ([4]).

Gene: *TPMT*

The *TPMT* gene encodes one of the main enzymes involved in the metabolism of thiopurines, such as thioguanine. 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 thioguanine 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 TMPT 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 thioguanine metabolites (TGN) are also available.

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.

Statement from the US Food and Drug Administration (FDA): There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effects of thioguanine and prone to developing rapid bone marrow suppression following the initiation of treatment. Substantial dosage reductions may be required to avoid the development of life-threatening bone marrow suppression in these patients. Prescribers should be aware that some laboratories offer testing for TPMT deficiency. Since bone marrow suppression may be associated with factors other than TPMT deficiency, TPMT testing may not identify all patients at risk for severe toxicity. Therefore, close monitoring of clinical and hematologic parameters is important. Bone marrow suppression could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine, or sulphasalazine.

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 thioguanine 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, the 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	
*TPMT*2*	238G>C Ala80Pro	NM_000367.2:c.238G>C	NP_000358.1:p.Ala80Pro	rs1800462
*TPMT*3A*	This allele contains two SNPs, *TPMT*3B* and *TPMT*3C*			

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*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

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

Thioguanine response

Tests in GTR by Gene

TPMT gene