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Thioguanine Therapy and *TPMT* Genotype

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Introduction

Thioguanine is an antineoplastic agent that belongs to the drug class of thiopurines. It is used in the treatment of acute myeloid leukemia (1).

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

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

The FDA-approved drug label for thioguanine states that there are individuals with an inherited deficiency of the thiopurine methyltransferase (TPMT) enzyme who may be unusually sensitive to the myelosuppressive effects of thioguanine and prone to developing rapid bone marrow suppression following treatment initiation. 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.

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

Start with reduced doses of thioguanine 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 thioguanine therapy, adapted from CPIC

Phenotype	Phenotype details	*TPMT* Genotype	Examples of diplotypes	Therapeutic recommendations for thioguanine (TG)
Homozygous wild-type ("normal")	High enzyme activity. Found in approximately 86–97% of patients.	Two or more functional *TPMT* alleles	**1/*1*	Start with normal starting dose. Adjust doses of TG and of other myelosuppressive therapy without any special emphasis on TG. Allow 2 weeks to reach steady state after each dose adjustment.
Heterozygous	Intermediate enzyme activity. Found in approximately 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 (reduce by 30–50%) and adjust doses of TG based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing TG over other agents.
Homozygous variant	Low or deficient enzyme activity. Found in approximately 1 in 178 to 1~3736 patients.	Two nonfunctional *TPMT* alleles	**3A/*3A* **2/*3A* **3C/*3A* **3C/*4* **3C/*2* **3A/*4*	Start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of TG 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 TG over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.

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 (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: Thioguanine

Thioguanine is a neoplastic agent used in the treatment of acute myeloid leukemia (AML). AML is the most common acute leukemia in adults, accounting for approximately 80% of cases, and the incidence increases with age. It is a less common cause of acute leukemia in children accounting for less than 10% of cases.

AML is characterized by a proliferation of the myeloid lineage of blood cells, causing an accumulation of abnormal and immature cells in the blood, bone marrow, and sometimes other tissues. This causes a disruption in the production of normal red blood cells, platelets, and mature granulocytes, leading to anemia, bleeding, and an increased risk of infection.

Combination chemotherapy for AML, which includes thioguanine, more frequently induces remission and a longer duration of remission than using thioguanine alone, but because of the high risk of liver toxicity, thioguanine is not recommended for long-term use. Younger patients with AML tend to have a better response to thioguanine than older patients (1).

Like all thiopurines, thioguanine is a purine analogue, and acts as an antimetabolite. Thioguanine is metabolized by two main pathways—it is either activated by HPRT1 (hypoxanthine phosphoribosyltransferase) and metabolized to form TGNs, or deactivated by TPMT. 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).

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

Individuals who are heterozygous for nonfunctional *TPMT* alleles (approximately 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 (2, 3, 5, 6).

The FDA-approved drug label for thioguanine states that substantial dosage reductions may be required to avoid the development of life-threatening bone marrow suppression in patients with an inherited deficiency of TPMT. A concern among oncologists may be that a reduced dose of thioguanine will have less anti-tumor efficacy. However, CPIC recommendations (table 1) state that "dose adjustments based on *TPMT* genotype have reduced thiopurine-induced adverse effects without compromising desired antitumor and immunosuppressive therapeutic effects in several clinical settings".

Another adverse effect of thioguanine treatment is hyperuricemia, which frequently occurs because of the rapid lysis of tumor cells. In addition, liver toxicity associated with vascular endothelial damage has been reported when thioguanine is used for maintenance, or for similar long-term continuous therapy. Liver toxicity usually presents as the clinical syndrome of hepatic veno-occlusive disease (hyperbilirubinemia, tender hepatomegaly, weight gain due to fluid retention, and ascites) or with signs of portal hypertension (splenomegaly, thrombocytopenia, and oesophageal varices). For this reason, the long-term use of thioguanine is not recommended (1).

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 thioguanine. TPMT

activity is inherited as a co-dominant trait, as the *TPMT* gene is highly polymorphic with over 40 reported variant alleles (7-10).

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 thioguanine 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 (11, 12):

- *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 (7, 13).

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 (7, 14).

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, 15-18).

TPMT phenotype enzyme activity testing is also available by measuring TPMT activity in red blood cells directly (5). In adult patients taking thioguanine 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 (19). 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 (19).

Finally, one study reported that *TPMT* genotyping was more reliable than phenotyping in identifying patients at risk of adverse reactions from thiopurine treatment (20), and several studies reported that the *TPMT* genotype is a better indicator than TPMT activity for predicting TGN accumulation or treatment outcome (6, 21-23).

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.

2013 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).

2013 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: (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

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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[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 labeled all formulations containing the generic drug.

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

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

Version History

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