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Thioguanine Therapy and *TPMT* and *NUDT15* Genotype

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Introduction

Thioguanine (brand name Tabloid) is used to treat acute nonlymphocytic leukemias, such as acute myeloid leukemia (AML). Thioguanine is an analogue of the nucleic acid guanine and belongs to the drug class of thiopurines.

Thioguanine is a prodrug that must first be activated to form thioguanine nucleotides (TGNs), the major active metabolites. The active metabolites are metabolized and inactivated by the enzyme thiopurine methyltransferase (TPMT) and the enzyme nudix hydrolase 15 (NUDT15). Individuals with reduced activity of either enzyme are exposed to higher levels of thioguanine and have a higher risk of toxicity side effects, including severe bone marrow suppression (myelosuppression).

The FDA-approved drug label states that testing for TPMT and NUDT15 deficiency should be considered in individuals who experience severe bone marrow toxicities or repeated episodes of myelosuppression. The label also includes dosing recommendations for when *TPMT* or *NUDT15*, or both, genotypes are known. For individuals with a pharmacogenetic deficiency in either enzyme, the initial dose of thioguanine should be reduced, and individuals who have a deficiency in both enzymes may require more substantial dose reductions. The label notes that individuals with a complete deficiency of either enzyme often continue to require a lower dose, which is 10% or less than the standard thioguanine dose (Table 1) (1).

Dosing recommendations for thioguanine based on *TPMT* and *NUDT15* genotype have also been published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG). Both the CPIC and DPWG guidelines recommend substantial dose reductions for individuals who have low or deficient enzyme activity, including considering an alternative drug to thioguanine, particularly when treating a non-malignant condition (Table 2, Table 3) (2-4).

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Table 1. FDA Drug Label Dosage and Administration of Thioguanine (2020)

Enzyme	Dosage and administration
TPMT NUDT15	• Individuals with homozygous deficiency of either thiopurine S-methyl transferase (TPMT) or nucleotide diphosphatase (NUDT15) enzyme typically require 10% or less of the standard thioguanine dosage. • Reduce initial dosage in individuals who are known to have homozygous* TPMT or NUDT15 deficiency. • Most individuals with heterozygous TPMT or NUDT15 deficiency tolerate recommended thioguanine doses, but some require dose reduction based on toxicities. • Individuals who are heterozygous for both TPMT and NUDT15 deficiency may require more substantial dosage reductions. • Reduce the dosage based on tolerability.

* This also applies to compound heterozygous TPMT or NUDT15 deficiency, as multiple no function alleles exist. See Tables 4 and 5. This FDA table is adapted (1).

Table 2. CPIC Recommended Dosing of Thioguanine by *TPMT* Phenotype (2018 Update)

Phenotype	Implications for thioguanine phenotypic measures	Dosing recommendations for thioguanine	Classification of recommendations[b]
TPMT normal metabolizer	Lower concentrations of TGN metabolites; but note that TGN after thioguanine are 5–10 × higher than TGN after mercaptopurine or azathioprine. Normal risk of thiopurine-related leukopenia, neutropenia, myelosuppression.	Start with the normal starting dose[a] (e.g., 40–60 mg/m^2/day) and adjust doses of thioguanine and of other myelosuppressive therapy without any special emphasis on thioguanine. Allow 2 weeks to reach steady state after each dose adjustment.	Strong
TPMT intermediate metabolizer OR TPMT possible intermediate metabolizer	Moderate to high concentrations of TGN metabolites; but note that TGN after thioguanine are 5–10 × higher than TGN after mercaptopurine or azathioprine. Increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression.	Start with reduced doses (50–80% of normal dose) if normal starting dose[a] is ≥ 40–60 mg/m^2/day (e.g., 20–48 mg/ m^2/day) and adjust doses of thioguanine based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. If myelosuppression occurs, and depending on other therapy, emphasis should be on reducing thioguanine over other agents.	Moderate
TPMT poor metabolizer	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease. Greatly increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression.	Start with drastically reduced doses (reduce daily dose[a] by 10-fold and dose 3 times weekly instead of daily) and 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. If myelosuppression occurs, emphasis should be on reducing thioguanine over other agents. For non-malignant conditions, consider alternative nonthiopurine immunosuppressant therapy.	Strong

TGN, thioguanine nucleotides; TPMT, thiopurine methyltransferase.
[a]Normal starting doses vary by race/ethnicity and treatment regimens. If the standard dose is below the normal recommended dose, a dose reduction might not be recommended for intermediate metabolizers.
[b] Rating scheme described in Supplemental Material (2).
This CPIC table is adapted from (2).
Note, CPIC have also published recommendations for thiopurine dosing when the status of both TPMT and NUDT15 is known. Please see (2).

Table 3. CPIC Recommended Dosing of Thioguanine by *NUDT15* Phenotype (2018 Upate)

Phenotype	Implications for thiopurine phenotypic measures	Dosing recommendations for thioguanine	Classification of recommendations[b]
NUDT15 normal metabolizer	Normal risk of thiopurine-related leukopenia, neutropenia, myelosuppression	Start with the normal starting dose[a] (40–60 mg/m^2/day). Adjust doses of thioguanine and of other myelosuppressive therapy without any special emphasis on thioguanine. Allow 2 weeks to reach steady state after each dose adjustment.	Strong
NUDT15 intermediate metabolizer OR NUDT15 possible intermediate metabolizer	Increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression	Start with reduced doses (50–80% of normal dose) if normal starting dose[a] is ≥40–60 mg/m^2/day (e.g., 20–48 mg/m^2/day) and adjust doses of thioguanine based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. If myelosuppression occurs, and depending on other therapy, emphasis should be on reducing thioguanine over other agents.	Strong
NUDT15 poor metabolizer	Greatly increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression	Reduce doses to 25% of normal dose[a] and 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. In setting of myelosuppression, emphasis should be on reducing thioguanine over other agents. For non-malignant conditions, consider alternative nonthiopurine immunosuppressant therapy.	Strong

[a] Normal starting doses vary by race/ethnicity and treatment regimens. If the standard dose is below the normal recommended dose, dose reduction might not be recommended for intermediate metabolizers.
[b] Rating scheme described in Supplemental Material.
This CPIC table is adapted from (2).
Note, CPIC have also published recommendations for thiopurine dosing when the status of both thiopurine methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15) is known. Please see (2).

Drug Class: Thiopurines

Thiopurines are used as anticancer agents and as immunosuppressants in inflammatory bowel disease (IBD), rheumatoid arthritis, and other autoimmune conditions. Three thiopurines are used clinically: thioguanine, mercaptopurine, and azathioprine (a prodrug for mercaptopurine).

All 3 agents have similar effects but are typically used for different indications. Thioguanine is most commonly used to treat myeloid leukemias, mercaptopurine is used for lymphoid malignancies, and mercaptopurine and azathioprine are used for immune conditions.

There is increasing evidence that DNA testing for *NUDT15* and *TPMT* before initiating thiopurine therapy is clinically useful. In Europeans and Africans, inherited TPMT deficiency is the primary genetic cause of thiopurine intolerance, whereas for Asians, risk alleles in *NUDT15* explains most thiopurine-related myelosuppression (1, 5).

Drug: Thioguanine

Thioguanine is an anti-neoplastic agent used to treat AML. Acute myeloid leukemia 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.

Acute myeloid leukemia 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.

When thioguanine is used as part of a combination chemotherapy for AML, treatment more frequently induces remission and a longer duration of remission compared with using thioguanine alone. However, because of the high risk of liver toxicity, thioguanine is not recommended for long-term use. Younger individuals with AML tend to have a better response to thioguanine than older individuals (1).

Like all thiopurines, thioguanine is a purine analogue, and acts as an antimetabolite. Thioguanine is metabolized by 2 main pathways: bioactivation by hypoxanthine phosphoribosyltransferase and metabolized to form the major active metabolite (TGNs) or metabolized to an inactive metabolite by TPMT-mediated methylation or by NUDT15-mediated dephosphorylation of deoxythioguanine nucleotides.

The cytotoxicity of thioguanine is due, in part, to the incorporation of TGNs into DNA. In addition to inhibiting de novo purine synthesis, thioguanine also inhibits purine nucleotide interconversions (1).

The most frequent adverse reaction to thioguanine is myelosuppression, which typically can be reversed by decreasing the dose of thioguanine. However, individuals who have 2 nonfunctional *TPMT* alleles experience life-threatening myelosuppression after starting treatment with conventional doses of thioguanine. Similarly, individuals that have nonfunctional *NUDT15* alleles are at risk of thioguanine-induced myelosuppression.

Another adverse effect of thioguanine treatment when used in treating AML is hyperuricemia, which frequently occurs because of the rapid lysis of tumor cells. Liver toxicity associated with vascular endothelial damage has been reported when thioguanine is used for maintenance therapy in acute lymphoblastic leukemia (ALL) as an alternative to mercaptopurine, or for long-term continuous therapy as an immunomodulator. 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 esophageal varices). For this reason, the long-term use of thioguanine is not recommended (1).

Gene: *TPMT*

The *TPMT* gene encodes thiopurine S-methyltransferase, which is historically classified as a phase II metabolism enzyme. Importantly, TPMT is one of the main enzymes involved in the metabolism of thiopurines, including thioguanine.

The *TPMT* gene is highly polymorphic, with over 40 reported variant star (*) alleles (6-8). The *TPMT*1* allele is associated with normal enzyme activity (wild type).

The *TPMT*1* is considered the wild-type allele when no variants are detected and is associated with normal enzyme activity and the “normal metabolizer” phenotype. Individuals who are normal metabolizers are more likely to have a typical response to thioguanine and a low risk of myelosuppression; however, all individuals receiving thioguanine require close monitoring (9-12).

Most individuals are TPMT normal metabolizers (~86–97%). Three variant *TPMT* alleles account for over 90% of the reduced or absent activity *TPMT* alleles (9, 10, 13):

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

Individuals who are TPMT poor metabolizers (~0.3% of individuals of European or African ancestry) have 2 no function *TPMT* alleles (Table 4). When treated with thioguanine, these individuals will universally experience life-threatening bone marrow suppression because of high levels of TGNs (1).

Individuals who are TPMT intermediate metabolizers (approximately 3–14% of the general population) are heterozygous for one no function *TPMT* allele. When treated with thioguanine, these individuals may also be unable to tolerate conventional doses of thiopurines due to increased levels of TGNs and are at an increased risk of moderate to severe bone marrow suppression.

Table 4. Assignment of likely *TPMT* Phenotype based on Genotype (CPIC, 2018)

Likely phenotype[a]	Genotype	Examples of diplotype
Normal metabolizer	An individual with 2 normal function alleles	*1/*1
Intermediate metabolizer	An individual with one normal function allele PLUS one no function allele	*1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4
Possible intermediate metabolizer	An individual with one uncertain/unknown function allele PLUS one no function allele	*2/*8, *3A/*7
Poor metabolizer	An individual with 2 no function alleles	*3A/*3A, *2/*3A, *3A/*3C, *3C/*4,*2/*3C, *3A/*4
Indeterminate	An individual with 2 uncertain/unknown function alleles OR one normal function allele plus one uncertain allele function allele	*6/*8 *1/*8

TPMT, thiopurine methyltransferase; NUDT15, Nudix (Nucleoside Diphosphate Linked Moiety X)-Type Motif 15
[a] See TPMT and NUDT15 Frequency Table and Diplotype-Phenotype Table (2). for estimates of phenotype frequencies among different ethnic/geographic groups and for a more comprehensive list of predicted metabolizer phenotypes.
This CPIC table is adapted from (2).

The frequency of *TPMT* variant alleles vary among different ethnic 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 (6).

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 (6, 14).

Gene: *NUDT15*

The *NUDT15* gene encodes an enzyme that belongs to the nudix hydrolase superfamily. Members of this superfamily catalyze the hydrolysis of nucleoside diphosphates, which are created as a result of oxidative damage (e.g., from treatment with drugs such as thiopurines).

Nudix hydrolase 15 is directly involved in the metabolism of thiopurines, as it catalyzes the conversion of active metabolites (TdGTP) to less toxic metabolites (TdGMP) and in doing so, prevents the incorporation of toxic metabolites into DNA (15).

In individuals with reduced or absent NUDT15 activity (intermediate or poor metabolizers, Table 5), the reduction in NUDT15-mediated degradation of TdGTP results in more TdGTP available for incorporation into DNA, leading to increased DNA damage and cell death. These individuals subsequently have increased sensitivity to thiopurines at standard doses, including an increased risk of severe myelosuppression (16).

Similar to *TPMT*, the *NUDT15* gene is polymorphic, as the PharmVar Consortium has catalogued 21 variant alleles. However, most variants are rare, and the clinical significance of many *NUDT15* star (*) alleles is unclear.

The first *NUDT15* variant associated with thiopurine toxicity is p.R139C (rs116855232), which is present in both the *NUDT15*2* and *NUDT15*3* haplotypes. This amino acid change results in an unstable protein with almost no enzymatic activity. (16)

The FDA drug label for thioguanine cites one study of 1028 children with ALL, wherein the tolerated maintenance dose of the related drug, mercaptopurine, varied greatly, depending on the degree of TPMT, or NUDT15, or both, deficiency. Individuals who were heterozygous deficient for only one gene tolerated between 50-90% of the planned dosage. However, the tolerated dosage dropped to 30-50% of the planned dosage for individuals who were heterozygous deficient for both TPMT and NUDT15. Individuals who had bi-allelic deficiency of either TPMT or NUDT15 only tolerated 5–10% of the planned mercaptopurine dosage. (1, 15)

Deficiency of NUDT15 is rare among individuals with European or African ancestry (found in less than 1%); however, NUDT15 deficiency is more common among individuals with East Asian ancestry (e.g., Korea, China, Japan, Vietnam) (~2%) (2, 17, 18).

Table 5. Assignment of likely *NUDT15* Phenotype based on Genotype (CPIC, 2018)

Likely phenotype[a]	Genotype	Examples of diplotype
Normal metabolizer	An individual with 2 normal function alleles	*1/*1
Intermediate metabolizer	An individual with one normal function allele PLUS one no function allele	*1/*2, *1/*3
Possible intermediate metabolizer	An individual with one uncertain/unknown function allele PLUS one no function allele	*2/*5, *3/*6
Poor metabolizer	An individual with 2 no function alleles	*2/*2, *2/*3, *3/*3
Indeterminate	An individual with 2 uncertain function alleles OR one normal function allele plus one uncertain function allele	*1/*4, *1/*5 *4/*5, *5/*6

TPMT, thiopurine methyltransferase; NUDT15, Nudix (Nucleoside Diphosphate Linked Moiety X)-Type Motif 15
[a] See TPMT and NUDT15 Frequency Table and Diplotype-Phenotype Table (2) for estimates of phenotype frequencies among different ethnic/geographic groups and for a more comprehensive list of predicted metabolizer phenotypes.
This CPIC table is adapted from (2).

Linking Gene Variation with Treatment Response

Genetic variation in the *TPMT* and *NUDT15* genes strongly influences the safety of thiopurine therapy, specifically, influencing the risk of treatment-related bone marrow suppression (19).

Thiopurine methyltransferase deficiency is the primary genetic cause of thiopurine intolerance in Europeans and Africans, and NUDT15 deficiency is a more common cause in Asians and Hispanics.

The clinical impact of variant *NUDT15* alleles was discovered more recently than for *TPMT*, and there is less evidence available to guide dose adjustments. However, there is one clinical trial in progress that addresses azathioprine (a thiopurine) dosing guided by the status of both TPMT and NUDT15, for the treatment of IBD (17, 20, 21).

Currently, *TPMT* and *NUDT15* testing is not required by the FDA before starting treatment with any thiopurine (azathioprine, mercaptopurine, or thioguanine); however, both genes were listed in the recently published FDA Association tables as pharmacogenetic associations with data supporting therapeutic management recommendations (22). Consequently, routine genotyping for *TPMT* and *NUDT15* polymorphisms has not been universally adopted (23).

Genetic Testing

The NIH Genetic Testing Registry, GTR, displays genetic tests that are available for the thioguanine drug response, and the genes *TPMT* and *NUDT15*. The genes may be tested separately, or together, as part of a test panel that evaluates the drug response to thiopurines.

As with many commercial tests, only the most common variants are usually tested (e.g., for *TPMT*, the **2*, **3A*, and **3C* allele, which accounts for more than 90% of known inactivating alleles). This means that rare, or previously undiscovered variants, or both, will not be detected by variant-specific genotyping methods (9, 10, 24-27).

It is important to note that for *TPMT*3A*, 2 variants, c.460G>A and c.719A>G, are in *cis*. The variant, c.460G>A by itself is *TPMT*3B* and c.719A>G by itself is *TPMT*3C*. Most clinical laboratories are unable to phase the 2 variants. In most cases, especially if the individual is of European ancestry, the laboratory will assume the 2 variants are in *cis*, though the possibility of the variants being in *trans* cannot be ruled out.

Phenotype testing is also available for *TPMT*. Phenotype tests directly measure TPMT enzyme activity in red blood cells. In adult individuals 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 2 months of a blood transfusion) (11).

However, the FDA recommends considering all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes. This is because some co-administered drugs can influence measurement of TPMT activity in blood, and blood from recent transfusions will misrepresent an individual's actual TPMT activity.

In individuals with leukemia, the concordance between *TPMT* phenotype and genotype is poor. 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., an individual who has 2 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 an individual who is *TPMT* heterozygous may be wrongly determined to be *TPMT* homozygous (2 copies of nonfunctional *TPMT* variants) (28).

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 individuals with leukemia (28).

Finally, one study reported that *TPMT* genotyping was more reliable than phenotyping in identifying individuals at risk of adverse reactions from thiopurine treatment, 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.

2020 Statement from the US Food and Drug Administration (FDA):

Thioguanine, known chemically as 2-amino-1,7-dihydro-6H-purine-6-thione, is an analogue of the nucleic acid constituent guanine, and is closely related structurally and functionally to mercaptopurine.

[…]

Metabolism and Genetic Polymorphism

Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the planned dosage) was as follows: heterozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30- 50%; homozygous for either TPMT or NUDT15, 5-10%.

Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the *TPMT* gene and have little or no TPMT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The *TPMT*2*, *TPMT*3A*, and *TPMT*3C* alleles account for about 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the *NUDT15* gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of *NUDT15* (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function *NUDT15* alleles have been observed.

Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood, and blood from recent transfusions will misrepresent a patient's actual TPMT activity.

[…]

Warnings

[…]

Evaluate patients with repeated severe myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and *NUDT15* genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions. Bone marrow suppression could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine, or sulphasalazine.

[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. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

[…]

Laboratory Tests

Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression.

[…]

Drug Interactions

[…]

As there is in vitro evidence that aminosalicylate derivatives (e.g., olsalazine, mesalazine, or sulphasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent thioguanine therapy.

Dosage and Administration

[…]

Patients with homozygous deficiency of either TPMT or NUDT15 enzyme typically require 10% or less of the standard thioguanine dosage. Reduce initial dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended thioguanine doses, but some require dose reduction based on toxicities. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions. Reduce the dosage based on tolerability.

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

2018 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

TPMT recommendation

If starting doses are already high (e.g., 75 mg/m^2 of mercaptopurine), as is true in some ALL treatment regimens, lower than normal starting doses should be considered in TPMT intermediate metabolizers and markedly reduced doses (10-fold reduction) should be used in TPMT poor metabolizers. This approach has decreased the risk of acute toxicity without compromising relapse rate in ALL. Even at these markedly reduced dosages, erythrocyte TGN concentrations in TPMT poor metabolizers remain well above those tolerated and achieved by the majority of patients (who are TPMT normal metabolizers).

In some nonmalignant conditions, alternative agents may be chosen for TPMT intermediate or poor metabolizers rather than reduced doses of thiopurines; if thiopurines are used, full starting doses are recommended for TPMT normal metabolizers, reduced doses (30–80% of target dose) in TPMT intermediate metabolizers, and substantially reduced doses (or use of an alternative agent) in TPMT poor metabolizers.

Some of the clinical data upon which dosing recommendations are based rely on measures of TPMT phenotype rather than genotype; however, because TPMT genotype is strongly linked to TPMT phenotype, these recommendations apply regardless of the method used to assess TPMT status.

NUDT15 recommendation

Similar to TPMT, tolerated mercaptopurine dosage is also correlated with the number of nonfunctional alleles of the NUDT15 gene. In fact, the degree of thiopurine intolerance (e.g., for mercaptopurine) is largely comparable between carriers of TPMT vs. NUDT15 decreased function alleles, there remains a paucity of multi-ethnic studies examining both TPMT and NUDT15 variants.

Therefore, our NUDT15 recommendations parallel those for TPMT. For NUDT15 normal metabolizers (NUDT15*1/*1), starting doses do not need to be altered. For NUDT15 intermediate metabolizers (e.g., NUDT15*1/*3), reduced starting doses should be considered to minimize toxicity, particularly if the starting doses are high (e.g., 75 mg/m^2/day for mercaptopurine). For NUDT15 poor metabolizers (e.g., NUDT15*3/*3), substantially reduced doses (e.g.,10 mg/m^2/day of mercaptopurine) or the use of an alternative agent should be considered.

As for TPMT, there is substantial variability in the tolerated thiopurine dosages within NUDT15 intermediate metabolizers, with a minority of individuals who do not seem to require significant dose reduction. Therefore, genotype-guided prescribing recommendations apply primarily to starting doses; subsequent dosing adjustments should be made based on close monitoring of clinical myelosuppression (or disease-specific guidelines). In contrast, a full dose of mercaptopurine poses a severe risk of prolonged hematopoietic toxicity in NUDT15 poor metabolizers and pre-emptive dose reductions are strongly recommended.

The NUDT15 poor metabolizer phenotype is observed at a frequency of about 1 in every 50 patients of East Asian descent, which is more common than the TPMT poor metabolizer phenotype in Europeans, and, thus, genotyping NUDT15 in the Asian populations may be of particular clinical importance. NUDT15 deficiency is also more prevalent in individuals of Hispanic ethnicity, particularly those with high levels of Native American genetic ancestry.

Please review the complete therapeutic recommendations, which include CPIC's recommended course of action if both TPMT and NUDT15 genotypes are known, located here: (2).

2019 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

TPMT Intermediate Metabolizer

The risk of serious adverse events such as myelosuppression is increased. The genetic variation increases the concentration of the active metabolites of thioguanine.

IMMUNOSUPPRESSION

- Start with 75% of the standard dose
- Adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and efficacy.

LEUKEMIA

- start with 75% of the standard thioguanine dose, or start with the standard dose and reduce to 75% if side effects necessitate a dose reduction
- It is not known whether dose reduction in advance results in the same efficacy as dose reduction based on toxicity.
  The initial dose should be adjusted based on toxicity (monitoring of the blood counts) and efficacy.

Note: more stringent dose reductions are necessary if the patient is also NUDT15 IM or NUDT15 PM.

TPMT Poor Metabolizer

The risk of serious, life-threatening adverse events such as myelosuppression is strongly increased. The genetic variation increases the concentration of the active metabolites of thioguanine.

- Choose an alternative or use 6-7% of the standard dose
  Any adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and effectiveness.
- If the dose is decreased: advise patients to seek medical attention when symptoms of myelosuppression (such as severe sore throat in combination with fever, regular nosebleeds and tendency to bruising) develop.

NUDT15 Intermediate Metabolizer

Grade ≥ 2 leukopenia occurs in an estimated 40% of these patients with standard therapy. The genetic variation increases the concentration of the fully activated metabolite of thioguanine.

IMMUNOSUPPRESSION

- start with 75% of the standard dose
- Adjustment of the initial dose should be performed based on toxicity (monitoring of the blood counts) and efficacy.
- Monitoring should be performed at an increased frequency.

LEUKEMIA

- start with 75% of the standard thioguanine dose or start with the standard dose and reduce to 75% if side effects necessitate a dose reduction
- It is not known whether dose reduction in advance results in the same efficacy as dose reduction based on toxicity.
- Adjustment of the initial dose should be performed based on toxicity (monitoring of the blood counts) and efficacy.
- Monitoring should be performed at an increased frequency.

Note: more stringent dose reductions are necessary if the patient is also TPMT IM.

NUDT15 Poor Metabolizer

Grade ≥ 2 leukopenia occurs in an estimated 95% of these patients with standard therapy. The genetic variation increases the concentration of the fully activated metabolite of thioguanine.

- avoid thioguanine
- if it is not possible to avoid thioguanine: use 10% of the standard dose and advise patients to seek medical attention when symptoms of myelosuppression (such as severe sore throat in combination with fever, regular nosebleeds and tendency to bruising) occur
- Any adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and efficacy.
- Monitoring should be performed at an increased frequency.

For more information about TPMT and NUDT15 phenotypes: see the general background information about TPMT and NUDT15 on the KNMP Knowledge Bank or on www.knmp.nl (search for TPMT or NUDT15).

Please review the complete therapeutic recommendations that are located here: (3, 4).

Nomenclature for Selected *TPMT* and *NUDT15* Alleles

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

Table continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*TPMT*3A*	This allele contains 2 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
*NUDT15*3*	p.R139C c.415C>T	NM_018283.4:c.415C>T	NP_060753.1:p.Arg139Cys	rs116855232

Note: the p.R139C variant of nudix hydrolase 15 (*NUDT15)* is present on the *NUDT15*2* and *NUDT15*3* alleles.
The TPMT Nomenclature Committee defines the nomenclature and numbering of novel thiopurine methyltransferase *(TPMT)* variants.
Nomenclature for *NUDT15* is available from the Pharmacogene Variation (PharmVar) Consortium.
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS)

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