Thiopurine S-Methyltransferase (TPMT): Pharmacogenetic Competency

Updated on 6/2015
Approximately 10% of patients have a (an) _____ TPMT phenotype.

a) Normal/high function
b) Intermediate function
c) Low/absent function
d) Ultra-rapid function
Which one of the following is NOT currently a recognized TPMT phenotype?

a) Normal/high function
b) Intermediate function
c) Low/absent function
d) Ultra-rapid function
In patients with high or normal TPMT function, how much time is needed to reach steady state after each dose adjustment?

a) 5 days 

b) 1 week 

c) 2 weeks 

d) 4-6 weeks
Which of the following mercaptopurine dosing adjustments is correct for a leukemia patient with low or absent TPMT function?

a) Reduce the dose by 90% and give daily
b) Reduce the dose by 50% and give daily
c) Reduce the dose by 50% and give three times a week
d) Reduce the dose by 90% and give three times a week
What is the predicted TPMT phenotype for a patient with a *TPMT* genotype of *1/*2?

a) Normal/high function  
b) Intermediate function  
c) Low/absent function  
d) Ultra-rapid function
Objectives

• Upon completion of this competency, participants will be able to:
  – Recognize the different *TPMT* allele variants
  – Recognize the different TPMT phenotypes
  – Assign the correct phenotype based upon the allele variants
  – Make therapeutic recommendations for thiopurines based on a patient's predicted TPMT phenotype
A 12-year-old patient was receiving azathioprine for autoimmune liver disease.

He presented to the hospital for a workup of pediatric leukemia because of a CBC that revealed severe myelosuppression.

Upon further work up, it was revealed that the patient had a TPMT genotype of *2/*2.

Given that genotyping revealed that the patient had deficient TPMT function, azathioprine was discontinued. He was switched to another myelosuppressive agent.

Blood counts slowly returned to normal after discontinuation of the azathioprine.
TPMT Pharmacogenetics
Azathioprine (Aza), mercaptopurine (MP), and thioguanine (TG) are all prodrugs inactivated by TPMT.

TPMT catabolizes MP and TG to inactive methyl-metabolites.

This leaves less parent drug available for metabolism to active thioguanine nucleotide (TGN) metabolites.

There is an inverse relationship between TPMT function and TGN metabolites.

TPMT Function

• There are three ways to assess TPMT status
  – *TPMT* genotype (from DNA)
  – TPMT function or phenotype (using RBCs)
  – Thiopurine metabolites (TGN and MMPN in RBCs)
• This competency will focus on *TPMT* genotype

RBC: Red Blood Cell
MMPN: 6-methylmercaptopurine ribonucleotide
TPMT Allele Variants

- Genetic variations in the *TPMT* gene may lead to changes in metabolic activity of the TPMT enzyme.
- The following table summarizes the most common TPMT allele variants and likely TPMT enzyme activity:

<table>
<thead>
<tr>
<th>Functional status</th>
<th>Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional/ normal activity/ wild-type</td>
<td>*1, *24</td>
</tr>
</tbody>
</table>

There are three TPMT phenotypes
- Normal or high function
- Intermediate function
- Low or absent function

The assignment of likely TPMT phenotype is based on genotype

Phenotype (activity and metabolites) may be combined with genotype for patients receiving thiopurines
Normal (or high) function

- Approximately 90% of patients
- An individual carrying two or more functional (*1) alleles
- Example diplotype: *1/*1

TPMT Phenotypes

**Intermediate function**

- Approximately 10% of patients
- Note: *1/*8 is classified as having possible intermediate TPMT function

• Low or absent function
  – Approximately 1 in 400 patients

TPMT Phenotypes

- **High (normal) function**: 90%
- **Intermediate function**: 10%
- **Low or absent function**: 0.3%

* The exact percent of each phenotype group varies by ethnicity
TPMT Phenotypes

• In rare cases, patients may be wild-type by genotype and show intermediate function by TPMT phenotype testing requiring an additional phenotype terminology

• These patients are assigned a “possible intermediate function” phenotype
Gene-Based Dosing Recommendations
Mercaptopurine
• High or normal TPMT function
  – Initiate normal starting doses
  – Allow 2 weeks to reach steady state after each dose adjustment

• Intermediate TPMT function
  – Start at 30-70% of the normal starting dose
  – Adjust dose based on myelosuppression and disease-specific guidelines
  – Allow 2-4 weeks to reach steady state after each dose adjustment
  – Eventually, up to 65% of patients with intermediate TPMT function may tolerate full doses of mercaptopurine

Mercaptopurine

- Low or absent TPMT function
  - For non-malignant conditions, consider alternative non-thiopurine immunosuppressants
  - For malignant conditions, reduce the daily dose by 90% and reduce the frequency to 3 times per week instead of daily
  - Allow 4-6 weeks to reach steady state after each dose adjustment

Azathioprine
Azathioprine

• High or normal TPMT function
  – Initiate normal starting doses and adjust based on disease-specific guidelines
  – Allow 2 weeks to reach steady state after each dose adjustment

• Intermediate TPMT function
  – Consider starting at 30-70% of target dose if “full doses” are to be used
  – Titrate doses based on tolerance
  – Allow 2-4 weeks to reach steady state after each dose adjustment

• Low or absent TPMT function
  – For non-malignant conditions, consider alternative non-thiopurine immunosuppressants
  – For malignant conditions, reduce the daily dose by 90% and reduce the frequency to 3 times per week instead of daily
  – Allow 4-6 weeks to reach steady state after each dose adjustment

Thioguanine
Thioguanine

- High or normal TPMT function
  - Initiate normal starting doses
  - Allow 2 weeks to reach steady state after each dose adjustment

- Intermediate TPMT function
  - Start at 30-50% of the normal starting dose
  - Adjust dose based on myelosuppression and disease-specific guidelines
  - Allow 2-4 weeks to reach steady state after each dose adjustment
  - Eventually, up to 65% of patients with intermediate TPMT function may tolerate full doses of thioguanine

Thioguanine

- Low or absent TPMT function
  - For non-malignant conditions, consider alternative non-thiopurine immunosuppressants
  - For malignant conditions, reduce the daily dose by 90% and reduce the frequency to 3 times per week instead of daily
  - Allow 4-6 weeks to reach steady state after each dose adjustment

For More Information...

• For more information about TPMT and thiopurine dosing click here.

• For more information about pharmacogenetics visit the following website: www.pharmgkb.org

• For more pharmacogenetic service implementation resources visit the following website: www.stjude.org/pg4kds/implement
Question # 1

Approximately 10% of patients have a (an) _______ TPMT phenotype.

a) Normal/high function
b) Intermediate function
c) Low/absent function
d) Ultra-rapid function

Correct answer: b
Which one of the following is NOT currently a recognized TPMT phenotype?

a) Normal/high function
b) Intermediate function
c) Low/absent function
d) Ultra-rapid function

Correct answer: d
In patients with high or normal TPMT function, how much time is needed to reach steady state after each dose adjustment?

a) 5 days
b) 1 week
c) 2 weeks
d) 4-6 weeks

Correct answer: c
Which of the following mercaptopurine dosing adjustments is correct for a leukemia patient with low or absent TPMT function?

a) Reduce the dose by 90% and give daily
b) Reduce the dose by 50% and give daily
c) Reduce the dose by 50% and give three times a week
d) Reduce the dose by 90% and give three times a week

Correct answer: d
Question # 5

What is the predicted TPMT phenotype for a patient with a *TPMT* genotype of *1/*2?

a) Normal/high function
b) Intermediate function
c) Low/absent function
d) Ultra-rapid function

Correct answer: b
The information in this competency, including but not limited to any text, graphics or images, is for informational and educational purposes only. Although reasonable efforts have been made to ensure that the information provided is current, complete and, where appropriate, based on scientific evidence, St. Jude Children's Research Hospital makes no assurances as to whether the provided information will at all times be current or complete. St. Jude Children's Research Hospital, in offering this document, is not providing medical advice or offering a consultative opinion, and is not establishing a treatment relationship with any given individual. You, therefore, should not substitute information contained herein for your own professional judgment, nor should you rely on information provided herein in rendering a diagnosis or choosing a course of treatment for a particular individual.