The Hospital for Sick Children

Technology Assessment at Sick Kids (TASK)

EXECUTIVE SUMMARY

THIOPURINE S-METHYLTRANSFERASE TESTING FOR AVERTING DRUG TOXICITY IN PATIENTS RECEIVING THIOPURINES: A META-ANALYSIS OF DIAGNOSTIC TEST ACCURACY

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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Introduction

Thiopurine S-methyltransferase (TPMT) is an enzyme that metabolizes thiopurine drugs. The absence or a deficiency in TPMT activity can significantly increase the risk of an adverse drug event (ADE) in persons receiving thiopurine therapy as they are unable to properly metabolize the drug. Unless thiopurine drugs are avoided or doses are reduced in these patients, they are at greater risk for life-threatening bone marrow toxicity and liver toxicity, which may lead to myelosuppression, anemia, bleeding, leukopenia, infection and death. There are two approaches to testing for TPMT deficiency. Phenotype tests that measure levels of TPMT enzyme activity *in vitro* are common. Alternatively, genotype tests are available that detects the presence of variants in the genes responsible for expressing the TPMT enzyme. It remains uncertain whether an enzyme activity (phenotype) or genotype diagnostic test is the most appropriate strategy for clinical practice. Numerous studies have been performed to assess the accuracy of both types of diagnostic tests, however meta-analyses that summarize all available evidence have been limited to due to the technical challenges with pooling diagnostic test accuracy (DTA) results and the lack of a gold reference standard.

Objectives

The aim of this study was to meta-analyze the sensitivity and specificity of phenotype and genotype TPMT testing reported in the literature. The specific objecitves were:

1. To perform meta-analyses of two methods of evaluating TMPT enzyme activity: a) identifying patients with deficient or absent TPMT enzyme activity (patients that are homozygous for TPMT mutations) versus the rest of the population and b) identifying patients that have either low or intermediate TPMT enzyme activity (patients that are homozygous or heterozygous for TPMT mutations) versus the rest of the population.

2. To perform a DTA meta-analysis that accounts for the imperfect reference standard provided by genotype testing.

Methods

A comprehensive systematic review and critical appraisal of all published studies of TPMT test accuracy were conducted in the first phase of this research. Two different testing approaches were considered: 1) tests identifying patients with deficient or absent TPMT enzyme activity (patients that are homozygous for TPMT mutations) versus the rest of the population and 2) test identifying patients that have either low or intermediate TPMT enzyme activity (patients that are homozygous or heterozygous for TPMT mutations) versus the rest of the population. The meta-analysis was performed using a hierarchical summary receiver operating characteristic (HSROC) approach. A latent class meta-analysis method that allowed for heterogeneity in cut-point definition in phenotype TPMT testing while also allowing for an imperfect reference standard was used to meta-analyze the sensitivity and specificity data for the two approaches.

Results

When identifying patients with deficient or absent TPMT enzyme activity (patients that are homozygous for TPMT mutations), the latent class model resulted in a pooled sensitivity and specificity of phenotype testing of 75.9% (95% credible Interval [CrI], 58.3% to 87.0%) and 98.9% (95% CrI, 96.3% to 100%), respectively. The latent class meta-analysis also provided pooled sensitivity and specificity of the genotype tests. For genotype tests evaluating only the most common TPMT*2 and TPMT*3 polymorphisms, the pooled sensitivity and specificity was 90.4% (95% CrI, 79.1% to 99.4%) and 100.0% (95% CrI, 99.9% to 100%), respectively. For genotype tests evaluating TPMT*2, TPMT*3 and more polymorphisms, the pooled sensitivity and specificity was 80.7% (95% CrI, 41.7% to 99.4%) and 99.9% (95% CrI, 99.7% to 100%), respectively.

When testing individuals to detect deficient or intermediate TPMT activity (homozygous or heterozygous TPMT mutations) versus the remainder of the population, the pooled sensitivity and specificity of phenotype testing was 91.3% (95% CrI, 86.4% to 95.5%) and 92.6% (95% CrI, 86.5% to 96.6%), respectively. For genotype tests evaluating TPMT*3 mutations only, the pooled sensitivity and specificity was 66.8% (95% CrI, 51.1% to 94.6%) and 99.9% (95% CrI, 99.5% to 100%), respectively. For genotype tests evaluating TPMT*2 and TPMT*3 only, the pooled sensitivity and specificity was 88.9% (95% CrI, 81.6% to 97.5%) and 99.2% (95% CrI, 98.4% to 99.9%), respectively. For genotype tests evaluating TPMT*2, TPMT*3, and more polymorphisms, the pooled sensitivity and specificity was 93.5% (95% CrI, 84.9% to 99.3%) and 99.9% (95% CrI, 99.7% to 100%), respectively.

Conclusions

The pooled estimates of sensitivity suggest that genotype testing has higher sensitivity than phenotype testing as long as both TPMT*2 and TPMT*3 polymorphisms are tested. However, due to the large 95% CrIs around sensitivity estimates the results are not statistically significant. Both tests have been shown to have high specificity, valuable for ruling in the presence of TPMT deficiency. This meta-analysis cannot conclude that one test is superior to the other. Although more complex than standard meta-analysis techniques, the latent class HSROC approach is straight-forward to implement and interpret. Therefore, this report supports existing recommendations to perform HSROC or bivariate methods for DTA meta-analyses.