



**The Hospital for Sick Children
Technology Assessment at Sick Kids (TASK)**

**HEALTH TECHNOLOGY ASSESSMENT OF
THIOPURINE METHYLTRANSFERASE TESTING FOR
GUIDING 6-MERCAPTOPURINE DOSES IN
PEDIATRIC PATIENTS WITH ACUTE
LYMPHOBLASTIC LEUKEMIA**

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REPORT HIGHLIGHTS

The Report Highlights consists of a summary of the full report with the same name and should be evaluated in conjunction with the full report and its appendices. Full documents are available for download at the website:

<http://lab.research.sickkids.ca/task/reports-theses/>

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Conflicts of Interest

The authors declare that they do not have any conflicts of interest.

Introduction

Leukemia is the most common form of cancer in the pediatric population, accounting for 25% of all childhood cancer diagnoses.

Acute lymphoblastic leukemia (ALL) accounts for 75% of these leukemia diagnoses.¹

The treatment plan for childhood leukemia involves a multi-drug regimen over four phases, lasting two to three years. The goal is to first put the patient into clinical remission, then to target the cells that are clinically undetectable and then finally to maintain the patient in remission.² During the final phase of therapy (the maintenance phase), an immunosuppressive agent called 6-mercaptopurine (6-MP) is used. The risk of certain adverse drug events (ADE) as a result of 6-MP-treatment are influenced by genetic variations within the population in the enzyme responsible for metabolizing 6-MP, thiopurine methyltransferase (TPMT).

Currently, TPMT enzyme deficiency may be detected using a laboratory phenotype test (enzymatic assay) that gives a metabolite activity reading. Pharmacogenomics offers the promise of personalizing medication dosing via a genotype test that detects the presence of mutations in the gene(s) producing the TPMT enzyme. There is no evidence available that compares the cost-effectiveness of genotype and phenotype testing for preventing ADEs.

Key Messages

- Acute lymphoblastic leukemia (ALL) is a common childhood cancer; treatment includes 6-mercaptopurine (6-MP, an immunosuppressant).
- Patients receiving 6-MP may experience adverse drug events (ADEs). Individuals with mutations in the gene encoding thiopurine methyltransferase (TPMT), which metabolizes 6-MP, are exposed to higher doses and are therefore at higher risk for ADEs such as myelosuppression.
- Current treatment protocols advise weight-based dosing and genotyping for TPMT only if ADEs occur.
- A cost-effectiveness analysis (CEA) comparing weight-based dosing, phenotyping, and genotyping found weight-based dosing to be the least expensive strategy. Costs of phenotyping and genotyping were similar.
- The CEA did not detect differences in effectiveness (measured in life-months) between the three strategies, likely because the mutation is rare and the only ADE considered was myelosuppression.

Adverse treatment effects with 6-mercaptopurine

One of the more severe and common ADEs following treatment with 6-MP is myelosuppression (or bone marrow suppression), characterized by a decrease in all the blood components. When there is a drop in the neutrophil (white blood cell) count (neutropenia), the patient is at an increased risk of infection, which can be fatal in the ALL population. If a patient presents with a fever and a low neutrophil count (febrile neutropenia), the patient is immediately treated with intravenous antimicrobials. Myelosuppression is a dose-related effect and substantial dose reductions may be required in patients experiencing ADEs.

Methods of detecting , thiopurine methyltransferase deficiency

Weight-based dosing is the standard of care and is based on the patient's size. No detection of TPMT activity is conducted prior to dosing. If a patient experiences an ADE, genotyping is performed. **Genotyping** detects polymorphism in the DNA encoding TPMT. 6-MP is metabolized by TPMT. **Phenotyping (enzymatic assay)** measures the activity of the enzyme in the blood. A variety of phenotyping and genotyping laboratory testing technologies exist. Neither test has perfect sensitivity or specificity.

Rationale

Given the interest in personalized medicine that uses pharmacogenomics to guide dosing, and given the high cost of genetic testing and the importance of preventing serious ADEs, understanding the incremental cost-effectiveness of genotype and phenotype testing compared to standard care (weight-based dosing) would be valuable to guide therapy and allocation decision-making.

Objectives

The *primary objective* was to review the literature systematically to determine the accuracy of the TPMT phenotype and genotype tests. The *secondary objective* was to determine the incremental cost of TPMT genotyping and phenotyping compared to weight-based dosing strategies per life-month saved.

Target population

The target population was pediatric patients with ALL being treated with 6-MP.

Methods

Systematic literature review

The peer-reviewed literature (Pubmed, Embase, Cochrane databases) and grey literature were searched for studies of the accuracy of TPMT technologies. Studies were included if they evaluated either a TPMT genotype or phenotype test in comparison to a gold standard and expressed results in terms of sensitivity and specificity or positive and negative predictive value. Studies were excluded if they were in a language other than English or evaluated any subject other than humans. The quality of the identified studies was assessed using a modified Critical Appraisal Skills Program (CASP) tool.

Cost-effectiveness analysis

A cost-effectiveness analysis (CEA) was carried out from the health care system perspective. This analysis was performed on a hypothetical cohort of pediatric patients with ALL receiving 6-MP for the maintenance phase of therapy. The time horizon was set at three months to coincide with the period of identifying and treating myelosuppression caused by TPMT deficiencies at the start of 6-MP treatment.

Interventions

A decision analytic model was created to compare three potential test & treat strategies for 6-MP dosing: genotype testing with dose reductions for those testing positive, phenotype testing with dose reductions for those testing positive, no testing (standard weight-based dosing).

Measure of Effectiveness

Myelosuppression was the only ADE evaluated. Effectiveness was measured in terms of survival and expressed as life-months.

Costing

Costs included direct health care costs for testing, drugs, patient monitoring, physician services and inpatient care for serious cases of myelosuppression.

Analysis

A decision analysis comparing the three options was conducted with base case estimates. To address uncertainty in some of the parameter estimates, univariate sensitivity analyses were conducted for select variables and a probabilistic sensitivity analysis (PSA) was conducted using Monte Carlo simulation. Mean and incremental costs and their 95% confidence intervals (CIs) were estimated from the PSA.

Results

Systematic literature review

Seventeen studies were identified that met the inclusion criteria. Both TPMT phenotype and genotype technologies were considered accurate though there is no gold standard (see full report³). Additionally, included studies were of low methodological quality according to the CASP tool. The sensitivity and specificity of the genotype test ranged from 55-100% and 94-100%, respectively. The sensitivity and specificity of the phenotype test ranged from 92-100% and 86-98%, respectively.

Cost-effectiveness analysis

Neither of the interventions showed a benefit in survival compared to weight-based dosing, as measured by life-months. It is likely that no difference in effectiveness was detected between the test strategies because death following myelosuppression is an extremely rare occurrence. Also, the homozygous TPMT mutation is so rare that approximately 300 children must be screened before one with a deficiency will be detected. Both testing strategies (genotyping and phenotyping) were more costly compared to standard weight-based dosing. In the base case analysis. The costs per child of the weight-based dosing, phenotyping and genotyping strategies were \$654, \$1,020, and \$1,090, respectively. As there were no differences in effectiveness, only incremental costs were calculated. The incremental cost between the phenotyping and weight-based dosing strategies was \$366, between the genotyping and weight-based dosing strategies was \$436, and between the genotyping and phenotyping strategies was \$70.

Sensitivity analyses

These findings were not altered in the PSA, which found that the mean costs per child of the weight-based, phenotyping and genotyping strategies were \$669 (95% CI \$547, 791), \$967 (95% CI \$721, 1,213), and \$946 (95% CI \$659, 1,233), respectively. The PSA demonstrated that the cost differences between the phenotyping and genotyping tests are small. The univariate sensitivity analysis showed that the incremental costs between strategies may be affected by changes in the price of the genotyping and phenotyping tests.

Table 1: Results of the Probabilistic Sensitivity Analysis

Strategy	Mean cost	Lower 95% CI	Upper 95% CI
Weight-based dosing	\$669	\$547	\$791
Phenotype testing	\$967	\$721	\$1,213
Genotype testing	\$946	\$659	\$1,233

Table 2: Incremental Costs in Probabilistic Sensitivity Analysis

	Phenotype minus Weight-based	Genotype minus Weight-based	Genotype minus Phenotype
Mean Costs	\$298	\$277	-\$21
Lower 95% CI	\$116	\$73	-\$343
Upper 95% CI	\$480	\$481	\$301
Per cent of simulations where intervention is more costly (%)	99.79	99.48	56.08
Upper 95% CI contrasted with Lower 95% CI	\$666	\$686	\$512
Lower 95% CI contrasted with Upper 95% CI	-\$70	-\$132	-\$554

Discussion

This systematic review and cost-effectiveness analysis found that using TPMT phenotype or genotype tests prior to the first dose of 6-MP therapy did not prove to be cost-effective compared to standard weight-based dosing. This assessment highlights a number of important issues and gaps in the literature.

With respect to the TPMT tests, it was found that the phenotype tests identified more positive results compared to the genotype tests because they detected all deficiencies in the enzyme, not only those influenced by TPMT gene mutations. Genotype tests were accurate; however, they were limited by the number of mutations the test was designed to detect. As a result, neither test could be considered the gold standard.

No difference in life-months was detected between the three strategies. Since there was no difference in effectiveness between the three arms of the decision tree, it was not possible to calculate incremental cost-effectiveness ratios. The reduction in the occurrence of febrile neutropenia is but one outcome that could be used to determine the benefits of TPMT testing. Other ADEs such as liver toxicity and other efficacy outcomes such as long-term survival, rate of relapse and development of secondary malignancy were not evaluated as there is presently very little available evidence on the incidence and impact on survival for these outcomes.

The analysis showed that there would be an additional cost to offering either the phenotype test or genotype test prior to dosing 6-MP over the standard of care as described in the Children's Oncology Group protocols.⁴ Thus these alternatives were not cost-effective to reduce the mortality and morbidity associated with 6-MP-induced neutropenia. The impact of dose reducing patients who received false positive test results was also not considered; it is possible that these patients will be under-dosed, potentially compromising their treatment.

Four previous economic evaluations have examined the assessment of TPMT activity prior to 6-MP dosing to prevent ADEs, however only one evaluated a pediatric ALL population.⁵⁻⁸ These evaluations have mainly concluded that the TPMT technologies were cost-effective, however many differences existed in the models used in those studies compared to the current study.

The study was limited by the data available through the systematic review. As studies in languages other than English were not included, it is possible that relevant studies were not identified. The assessment of quality-adjusted life-months or life-years was not possible due to a lack of data.

Conclusions

At this time there is insufficient evidence to recommend the use of phenotype or genotype testing prior to 6-MP therapy to guide initial doses in pediatric ALL patients. Institutions that follow the Children's Oncology Group guidelines should not be affected by the results of this assessment. Institutions who routinely screen for TPMT status prior to the first dose of 6-MP should review their current practice. Currently the costs of these tests in the pediatric ALL population are funded by the health care system. The opportunity costs of using such tests outside clinical guidelines need to be taken into consideration. Policies should outline which clinical scenarios are eligible for publicly funded TPMT testing. Health care organizations will need to be prepared for a potential increase in public pressure for such tests as their availability becomes more widely known. Health technology assessment agencies can play a role in disseminating health economic evidence to inform decision making with respect to pediatric TPMT technologies.

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