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

EXECUTIVE SUMMARY

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

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CONFLICTS OF INTEREST

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

Executive Summary

Introduction

Leukemia is the most common form of cancer in the pediatric population, accounting for 25.3% of all childhood cancer diagnoses. Acute lymphoblastic leukemia (ALL) accounts for 75% of these leukemia diagnoses.

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 finally to maintain the patient in remission. During the final maintenance phase of therapy, an immunosuppressive agent called 6-mercaptopurine (6-MP) is used. The risks 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). The most serious dose dependant ADE over the short-term is myelosuppression, or more specifically, febrile neutropenia. Myelosuppression is bone marrow suppression characterized by a decrease in all the blood components, including red blood cells (anemia), white blood cells (leukopenia) and platelets (thrombocytopenia). If a patient presents with a fever (a sign of infection) and a low neutrophil count (febrile neutropenia), the patient requires hospitalization and immediate treatment with intravenous antimicrobials. Long-term dose dependant side effects include hepatotoxicity and secondary malignancy.

There are currently two methods of detecting TPMT enzyme deficiency: a phenotype test (enzymatic assay) that gives a metabolite activity reading and a genotype test that detects the presence of mutations in the genes responsible for producing the TPMT enzyme. Given the high cost of genetic testing and the importance of preventing serious ADEs, understanding the incremental cost-effectiveness of either form of testing compared to standard care (no testing) would be valuable to guide therapy.

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 standard weight-based dosing strategies per life-month saved.

Methods

Systematic Review

A systematic review of the literature was conducted to assess the accuracy of the TPMT technologies. Studies were included if they evaluated either a TPMT genotype or TPMT phenotype technology in comparison to a gold standard and showed results on the accuracy of the two tests, using either sensitivity and specificity or positive/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 to compare three testing strategies for 6-MP dosing: genotype-based, phenotype-based and no testing (standard dosing based on weight and height). This analysis was performed on a hypothetical cohort of pediatric patients with ALL and receiving 6-MP for the maintenance phase of therapy. Costs included direct health care costs for testing, drugs, patient monitoring, physician services, and inpatient care for serious adverse events. The time horizon was set at three months to coincide with the period of identifying and treating myelosuppression at the start of 6-MP treatment. Myelosuppression was the only adverse drug effect evaluated. Given the short time horizon, the measure of effectiveness was life-months. To address uncertainty in some of the parameter estimates, univariate sensitivity analyses were conducted for variables of interest and a probabilistic sensitivity analysis (PSA) was conducted using Monte Carlo simulations. Mean costs and their 95% confidence intervals (CIs) were estimated from the PSA.

Results

Systematic 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. 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 standard dosing, as measured by life months. It is likely that no difference in effectiveness between the test strategies was detected because death following myelosuppression is an extremely rare occurrence and was the only outcome measure evaluated. 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 standard dosing, phenotyping and genotyping strategies were $654, $1,020, and $1,090, respectively. As there were no differences in effectiveness, incremental costs were calculated instead of incremental cost-effectiveness ratios. The incremental cost between the phenotyping and standard dosing strategies was $366; between the genotyping and standard dosing strategies was $436; and between the genotyping and phenotyping strategies was $70.

These conclusions were not altered in the PSA, which found that the mean costs per child of the standard, 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 likely negligible. The univariate sensitivity analysis showed that the incremental costs between the strategies may be affected by changes in the price of the genotyping and phenotyping tests. If one of the tests was cheaper, it would become the more attractive strategy.

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 an ICER. The reduction in the occurrence of neutropenia is only one outcome measure that could be used to determine the benefits of TPMT testing. Future research should

consider other ADEs such as liver toxicity, as well as efficacy outcomes such as long-term survival, rate of relapse and development of secondary malignancy. However, there is presently very little available evidence on the incidence and impact on survival for these outcomes. As a result, they could not be considered in this study.

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. 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 the false positives who are dose reduced 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. 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 COG guidelines should not be affected by the results of this assessment. Institutions who have adopted the screening 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.