A cost effectiveness analysis of thiopurine methyltransferase testing for guiding 6-mercaptopurine dosing in children with acute lymphoblastic leukemia
Donnan JR, Ungar WJ, Mathews M, Hancock-Howard RL, Rahman P

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
This study assessed the cost-effectiveness of thiopurine methyltransferase genotyping to guide the dose of six-mercaptopurine for children with acute lymphoblastic leukaemia, compared with enzymatic testing or standard weight-based dosing. The authors concluded that neither genotyping nor enzymatic testing, before administering six-mercaptopurine, was cost-effective, compared with standard dosing. The methods were valid and transparent, which enhances the validity of the authors’ conclusions.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
The objective was to assess the cost-effectiveness of thiopurine methyltransferase genotyping to guide the dose of six-mercaptopurine for children with acute lymphoblastic leukaemia, compared with enzymatic testing and standard weight-based dosing.

Interventions
The three strategies were genotype testing, enzymatic testing, and no testing (standard dosing, based on weight and body surface area). With standard dosing, the genotype was tested if a severe adverse event, defined as myelosuppression, occurred. After genetic testing, the dose was reduced for children with homozygous mutations. Enzymatic testing was by biochemical assay of the enzyme thiopurine methyltransferase in the blood, and the dose was reduced for children who were assumed to be homozygous based on their enzyme levels.

Location/setting
Canada/out-patient setting.

Methods
Analytical approach:
The analysis was based on a decision-tree model, with a three-month time horizon. The authors stated that the analysis was carried out from the perspective of the health care system.

Effectiveness data:
A systematic search of the literature was undertaken to identify the relevant sources of evidence. The grey literature was searched and experts were consulted. The quality of the selected studies was assessed using a modified Critical Appraisal Skills Programme tool. The key input was the accuracy of testing, and the midpoints of the reported estimates were used.

Monetary benefit and utility valuations:
Not considered.

Measure of benefit:
Survival, measured in life-months gained, was the summary benefit measure.

Cost data:
The economic analysis included the costs of the laboratory tests, medications, physician services, pharmacy services, and in-patient care. The patterns of resource consumption were based on routine dosages and the normal use of health services. The costs of tests were from the US Mayo Clinic prices. Physician fees and the costs of laboratory monitoring were from the Ontario Health Insurance Plan. The cost of in-patient stay was from the Ontario Case Costing Initiative database. All costs were in Canadian dollars (CAD) and the price year was 2008.

Analysis of uncertainty:
One-way sensitivity analyses were carried out on selected inputs, using published or calculated ranges of values. A probabilistic analysis was performed by varying all the uncertain inputs simultaneously in a Monte Carlo simulation. Threshold analyses were carried out to determine the cost of each test, at which the strategy was cost neutral, compared with standard dosing.

Results
The expected survival was 2.9997 months for all three strategies, which were equally effective. The projected costs were CAD 654 with standard dosing, CAD 1,020 with enzymatic testing, and CAD 1,090 with genotype testing.

These base-case results were robust and were only affected by changes in the price of each test. At CAD 39 for the enzymatic test and CAD 12 for the genotype test, each strategy was cost neutral compared with standard dosing.

The probabilistic analysis showed that standard dosing was less expensive than either testing strategy in more than 99% of simulations.

Authors' conclusions
The authors concluded that screening for thiopurine methyltransferase mutations, using either genotyping or enzymatic laboratory tests, before administering six-mercaptopurine was not cost-effective, compared with standard dosing.

CRD commentary
Interventions:
The rationale for the selection of the comparators was clear as the two available testing strategies were compared against the standard approach (weight-based dosing).

Effectiveness/benefits:
A valid method was used to identify the relevant sources of evidence; a review was conducted, searching several databases and the grey literature. Most of the selected studies were not of high quality. Meta-analysis could not be used to pool the evidence from multiple sources because of the heterogeneity between these studies. Extensive sensitivity analysis was conducted to assess the uncertainty in several clinical parameters. Survival was a valid benefit measure, given the impact of the disease on life expectancy. The authors acknowledged that quality-adjusted life expectancy would have been more appropriate, but no valid utility values for children with acute lymphoblastic leukaemia were found.

Costs:
The cost categories and data sources appear to have been appropriate for the perspective adopted. Standard Canadian sources were used for all the model parameters and these were generally justified by the authors. The unit costs were reported for all items, but limited information on the resource quantities was given. Reflation exercises for other time periods will be possible as the price year was reported. Variations in the costs were appropriately considered in the sensitivity analyses and the results were clearly reported.

Analysis and results:
The results were clearly reported. A synthesis of the costs and benefits was not required as the three strategies were equally effective. The cost differences were analysed using an incremental approach. The authors justified their selection of a short time horizon, which corresponded to the period in which intolerance to six-mercaptopurine, due to thiopurine methyltransferase deficiency, would be evident. A longer time horizon would have included mortality, mainly due to cancer. The only adverse event considered was myelosuppression as this was the main risk for these children, but other events could occur. Valid approaches were used to investigate the uncertainty. The authors
compared their results with those of a previous economic evaluation and explained the reasons for different findings. These results should be transferable to settings with similar epidemiology and costs.

Concluding remarks:
The methods were valid and transparent, which enhances the validity of the authors’ conclusions.

Funding
Funding received from the Atlantic Canada Opportunities Agency, the provincial government of Newfoundland and Labrador, the Memorial University of Newfoundland, the Ontario Ministry of Health and Long-term Care, and the Newfoundland and Labrador Centre for Health Information.

Bibliographic details

PubMedID
21344614

DOI
10.1002/pbc.22936

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
6-Mercaptopurine /administration & dosage /adverse effects; Antimetabolites, Antineoplastic /administration & dosage /adverse effects; Bone Marrow Diseases /chemically induced /prevention & control; Child, Preschool; Clinical Enzyme Tests /economics; Cost-Benefit Analysis; Decision Trees; Drug Dosage Calculations; Genetic Testing /economics; Genotype; Humans; Methyltransferases /deficiency /genetics; Models, Econometric; Ontario; Precursor Cell Lymphoblastic Leukemia-Lymphoma /drug therapy /enzymology /genetics; Sensitivity and Specificity; Survival Analysis

AccessionNumber
22011001091

Date bibliographic record published
24/08/2011

Date abstract record published
16/11/2011