Published in final edited form as:

Pediatr Blood Cancer. 2011 December 15; 57(7): 1247. doi:10.1002/pbc.23249.

Pharmacogenetics, Cost of Genotyping and Guidelines for Individualizing Therapy with Mercaptopurine in Pediatric Acute Lymphoblastic Leukemia

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Keywords

pharmacogenetics; mercaptopurine; acute lymphoblastic leukemia; guidelines; therapy personalization

To the Editor

We read with interest the paper by Donnan et al. [1], reporting that screening for thiopurine-S-methyl-transferase (TPMT) status prior to the administration of mercaptopurine for the treatment of pediatric acute lymphoblastic leukemia (ALL) is not cost-effective.

We feel that for TPMT status and its clinical relation to mercaptopurine administration, the measure of effectiveness should not be limited to prolonged survival, but rather to reduction in toxicity without altering efficacy. As mentioned by Donnan et al., there are previous studies showing that TPMT genotyping is cost effective, even when considering only patients with TPMT homozygous variant genotypes as those who benefit from the genotyping assay and survival as the endpoint [2,3].

We understand the interest in applying economical models to evaluate and choose the optimal therapy for patients. However, in reference to evaluating the cost of acquiring genetic information, with the dawn of high-throughput genotyping approaches for clinical use, the cost of obtaining robust and reliable genotypes has been decreasing and it is now possible to obtain high-throughput genotyping of multiple genes for ~\$1/gene [4]. One would think that the potentially severe nature of mercaptopurine toxicity (which can be fatal [5]) and the risk of sub-therapeutic treatment (e.g., leukemia relapse) would make the consequences of inadequate dosing too compelling to ignore established pharmacogenetic data when treating a child with ALL. Moreover, it should not be forgotten that genotyping results are permanent for a patient and need be acquired only once in a lifetime. Any potential risks to the patient of including genetic test results in the medical record have been minimized by the adoption of genetic nondiscrimination laws [6]. The real issue then will be how to translate useful pharmacogenetic information to the clinical setting and how to encourage and educate clinicians to do so. [7,8] This will require overcoming some of the barriers to implementing individualized medicine such as fragmentation of health-care systems, low use of electronic medical records, and health care systems that do not reward prevention of a disease or adverse events and therefore lack of interest in preemptive

approaches [9]. In this perspective, for the clinical implementation of pharmacogenetics, the development of solid and accepted guidelines seems to be of key relevance [9]. For mercaptopurine in leukemia these guidelines are currently available and comprise for patients with a variant TPMT allele starting with reduced doses (30–70% of full dose given daily for patients heterozygous for TPMT, or 10% of full dose given three times a week for patients homozygous for TPMT) and increased monitoring of hematologic efficacy and toxicity [10,11]. These robust molecular diagnostics should be embraced by clinicians in order to reduce toxicity and provide better treatment with mercaptopurine for their patients. The methods are at hand to move medicine closer to science than art.

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