see ARTICLE page 387, March 2011 issue

Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing: 2013 Update

MV Relling[1], EE Gardner[2], WJ Sandborn[3], K Schmiegelow[4,5], C-H Pui[6], SW Yee[7], CM Stein[8], M Carrillo[9], WE Evans[1], JK Hicks[1], M Schwab[10,11] and TE Klein[9]

The Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Thiopurine Methyltransferase Genotype and Thiopurine Dosing was originally published in March 2011. We reviewed recent literature and concluded that although relevant new evidence has been generated, none of the evidence would change the primary dosing recommendations in the original guideline; therefore, the original publication remains clinically current. Up-to-date information on thiopurine methyltransferase (*TPMT*) gene alleles and nomenclature can be found at PharmGKB (http://www.pharmgkb.org).

The CPIC of the Pharmacogenomics Research Network (http://www.pgrn.org) and the Pharmacogenomics Knowledge Base (PharmGKB, http://www.pharmgkb.org) provides peer-reviewed, updated, evidence-based, freely accessible guidelines for the translation of genetic laboratory tests into actionable prescribing recommendations for specific drugs.[1] CPIC guidelines undergo continuous peer review, and information pertaining to gene-specific alleles and nomenclature is updated periodically on the PharmGKB website. Furthermore, approximately every 2 years, each published guideline and associated Supplementary Data online are reviewed and updated accordingly.

The first guideline to be reviewed is the CPIC Guideline for Thiopurine Methyltransferase Genotype and Thiopurine Dosing originally published in March 2011.[2] We have done a focused review of the literature between June 2010 and November 2012 on *TPMT* genotype and thiopurine use (see **Supplementary Data, Tables S1–S5,** and **Figure S1** online). At this time, there is no new evidence that would change our original recommendations in the published guideline; therefore, the original guideline publication remains current.

Since the first CPIC guideline was published, the CPIC Steering Committee has recommended that authors address dosing in pediatrics or, at a minimum, comment that there is not enough supporting evidence to allow therapeutic recommendations in pediatrics. As thiopurines are a staple of childhood acute lymphoblastic leukemia and inflammatory bowel disease treatment regimens, much of the evidence (summarized in **Supplementary Table S5** online) used to support the original dosing recommendation was generated in children. Furthermore, the dosing recommendations in Table 2 of the main guideline are presented in units of mg/m^2 and mg/kg. Therefore, our original guideline dosing recommendations can be used in both the adult and pediatric populations.

Although we are not modifying the original main guideline, we have updated the **Supplementary Data** online to include additional studies that further support our original recommendations (see **Supplementary Table S5** online and the Other Considerations subsection of the **Supplementary Data** online).[3–5] In addition, we have added information for additional variant alleles not included in the original guideline (see **Supplementary Tables S1 and S2** online).

Up-to-date information on *TPMT* gene alleles and nomenclature can be found at PharmGKB (http://www.pharmgkb.org).

[1]Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; [2]Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [3]Division of Gastroenterology, University of California San Diego, La Jolla, California, USA; [4]Institute of Gynaecology, Obstetrics and Paediatrics, University of Copenhagen, Copenhagen, Denmark; [5]Department of Paediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen, Denmark; [6]Department of Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; [7]Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, California, USA; [8]Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; [9]Department of Genetics, Stanford University School of Medicine, Stanford, California, USA; [10]Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany; [11]Department of Clinical Pharmacology, Institute of Experimental and Clinical Pharmacology and Toxicology, University Hospital, Tuebingen, Germany. Correspondence: MV Relling (cpic@pharmgkb.org)

Received 12 November 2012; accepted 3 January 2013; advance online publication 20 February 2013. doi:10.1038/clpt.2013.4

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

DISCLAIMER

CPIC's guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making, as well as to identify questions and settings for further research. New evidence may have emerged since the time a guideline was submitted for publication, which may or may not affect that guideline. The health-care provider is responsible to check for updates to guidelines or subsequently published data. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the complete responsibility of the health-care provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the informed and consenting patient. CPIC assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of CPIC's guidelines, or for any errors or omissions.

CONFLICT OF INTEREST

M.V.R. and W.E.E. receive income from St. Jude for licensing patent rights for TPMT and GGH polymorphisms. They also receive funding for investigator-initiated research on the pharmacology of asparaginase from Sigma-Tau Pharmaceuticals.

1. Relling, M.V. & Klein, T.E. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin. Pharmacol. Ther.* **89**, 464–467 (2011).
2. Relling, M.V. *et al.* Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. *Clin. Pharmacol. Ther.* **89**, 387–391 (2011).
3. Krynetski, E. & Evans, W.E. Drug methylation in cancer therapy: lessons from the TPMT polymorphism. *Oncogene* **22**, 7403–7413 (2003).
4. González-Lama, Y. *et al.* Thiopurine methyl-transferase activity and azathioprine metabolite concentrations do not predict clinical outcome in thiopurine-treated inflammatory bowel disease patients. *Aliment. Pharmacol. Ther.* **34**, 544–554 (2011).
5. Adam de Beaumais, T. *et al.* Determinants of mercaptopurine toxicity in paediatric acute lymphoblastic leukemia maintenance therapy. *Br J Clin Pharmacol* **71**, 575–584 (2011).