

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Incorporating Biomarkers Into Drug Labeling



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H&O What initially spurred your interest in the subject of incorporating biomarkers into drug labeling?

MR The investigation of biomarkers of all kinds that may be associated with drug efficacy and/or side effects has been going on for years. However, a recent controversy has brought this issue to the fore. In 2009, a study by Ross and colleagues was published in *Nature Genetics* linking variants in 2 genes encoding drug-metabolizing enzymes—thiopurine methyltransferase and catechol-O-methyltransferase—with ototoxicity among children taking cisplatin. This finding led to a change in the labeling for this drug in 2011. This was surprising to many, as there had been no prior studies linking such enzymes to the pharmacokinetics or pharmacodynamics of cisplatin. In general, the US Food and Drug Administration (FDA) errs on the side of conservatism, and awaits definitive evidence before approving a label change.

In 2012, I learned about 2 additional studies, which were eventually published in 2013 in *Clinical Pharmacology and Therapeutics*. The first was a putative replication study by Pussegoda and colleagues at the University of British Columbia in Vancouver—the same institution that was involved with the 2009 paper. The second study, from Yang and colleagues at St Jude Children's Research Hospital in Memphis, Tennessee, failed to replicate the original study. I also subsequently became aware that the data from the original 2009 *Nature Genetics* publication had changed, as detailed in a published thesis from the University of British Columbia by Pussegoda.

H&O How did you research the issues raised by these papers and the label change?

MR I reviewed all the publications by the authors of the original study regarding cisplatin ototoxicity. This included patent filings dating back to 2006 that had not been disclosed by the authors, and which included statistical analyses that had not been published in journal form. I also discovered a 2012 paper by Dionne and colleagues in *The Pharmacogenomics Journal* touting the cost-effectiveness of the authors' putative test to predict cisplatin ototoxicity.

H&O What aspects of the data caused concern?

MR The major issue was the difference in the chemotherapy regimen between the cases and controls in the original data set. Specifically, the original *Nature Genetics* publication noted a nonsignificant difference in the use of vincristine, which had been part of the treatment for 9 of the case patients and none of the control patients, resulting in a P value of .055. The data in the published thesis (and subsequent *Clinical Pharmacology and Therapeutics* paper) noted vincristine use in 54 cases and 10 controls, a highly significant difference ($P=4.1 \times 10^{-5}$), essentially invalidating the original case-control design.

H&O Were the data in the 2009 *Nature Genetics* paper corrected?

MR No. Although the putative replication study was published in *Clinical Pharmacology and Therapeutics*

in 2013 and references a 2013 corrigendum in *Nature Genetics*, the corrigendum does not correct the data in the 2009 paper. This *Nature Genetics* corrigendum only notes that the original paper provided the wrong unit of time for the treatment duration (weeks, rather than correct duration of months).

H&O Does the second study acknowledge the differences in concomitant medication in the first study?

MR Yes, the second study (published in 2013 in *Clinical Pharmacology and Therapeutics*) does include the full data on the use of vincristine in the first study, and the authors highlight this addition in the paper.

H&O Did you contact the FDA regarding your concern about the label change?

MR I did. Although the individual who was responsible for making the change is no longer at the FDA, the current leadership at the FDA Office of Clinical Pharmacology has been very interested in my concerns.

H&O Does the drug label still indicate that children should be genotyped before taking cisplatin?

MR That is the implication. There is no specific requirement that all children be genotyped, but the data included in the current label imply that genotyping should be done.

H&O In light of the assertion that the original study was not rigorous enough, what would make for a reliable study on potential biomarkers such as these?

MR The first critical element is that the genotyping has to be done correctly. A similar scenario arose with studies of the association of *CYP2D6* variants with tamoxifen response, which have been inconsistently replicated. It now appears that this replication failure is due to errors in genotyping.

Phenotyping can be even more complex. If the phenotype is cisplatin-induced hearing loss, then that trait has to be controlled for completely. Any other drug that could be contributing to hearing loss needs to be excluded from the data analysis. The 2009 study regarding this toxicity did not adequately control for the use of other ototoxic drugs.

The third requirement for a proper biomarker study is proper statistical analysis. A rigorous analysis requires appropriate correction for multiple testing, appropriate

concern that any findings are not the result of chance, and appropriate replication studies conducted before any labeling changes are made. A complete replication may not be warranted in order to publish initial findings, but the study should be well beyond the point of hypothesis.

H&O Did the authors of the original study disclose any personal financial conflicts of interest?

MR The authors did not disclose their patent filings, even though they have been aggressively prosecuted, and even though they published on the societal economic value of their proposed diagnostic test.

H&O What are the potential harmful implications of the label change?

MR If a parent reads the drug label and worries that his or her child will have hearing loss as a result of cisplatin treatment, then the child may be genetically tested for the variants. This could then result in children not receiving cisplatin, which is an effective drug for the treatment of many pediatric malignancies.

H&O But if there is a chance that these variants are associated with a higher risk of hearing loss, is it not reasonable to be cautious?

MR The evidence, when analyzed today, does not suggest that there is any increased risk of hearing loss for children with the variants listed in the cisplatin label.

H&O With biomarker studies becoming increasingly common, is there a need for clearer guidelines on what warrants a drug label change?

MR It would be useful to have some debate on criteria for incorporating biomarker information in a drug label, if the biomarker is not reviewed by the FDA as a companion diagnostic. Some might advocate that all potentially useful information should be included; others might advocate for a more conservative approach to avoid the risk of withholding important drugs such as cisplatin.

H&O Could you discuss the approach you are taking with pharmacogenomic research?

MR Our group continues to look for biomarkers that are predictive of anticancer drug response (both efficacy and toxicity). However, we are also making major efforts in implementation of pharmacogenomics—making it useful for the practice of medicine. We are conducting a pilot study called The 1200 Patients Project, in which enrolled

patients can benefit from their physicians having pharmacogenomic information before they need the drug. We are delivering such information to physicians as “virtual consults,” based only on peer-reviewed literature.

For example, there is an HLA type that is associated with hypersensitivity to abacavir, an HIV medication. Patients with this HLA type should be treated with a different drug. As another example, the amount of pain relief a person receives from codeine is associated with *CYP2D6* genotype.

There are also national efforts (independent of the FDA) to create guidelines for pharmacogenomic implementation. One such effort is the Clinical Pharmacogenomics Implementation Consortium led by Dr Mary Relling at St Jude Children’s Research Hospital and supported as part of the National Institutes of Health Pharmacogenomics Research Network. But soon there will be data on hundreds (if not thousands) of drugs. We will need to find a scalable way to provide the information to physicians and ensure that this information is reliable.

Suggested Reading

Dionne F, Mitton C, Rassekh R, et al. Economic impact of a genetic test for cisplatin-induced ototoxicity. *Pharmacogenomics J*. 2012;12(3):205-213.

O’Donnell PH, Bush A, Spitz J, et al. The 1200 patients project: creating a new medical model system for clinical implementation of pharmacogenomics. *Clin Pharmacol Ther*. 2012;92(4):446-449.

Pussegoda K, Ross CJ, Visscher H, et al; CPNDS Consortium. Replication of TPMT and ABCC3 genetic variants highly associated with cisplatin-induced hearing loss in children. *Clin Pharmacol Ther*. 2013;94(2):243-251.

Ratain MJ, Cox NJ, Henderson TO. Challenges in interpreting the evidence for genetic predictors of ototoxicity. *Clin Pharmacol Ther*. 2013;94(6):631-635.

Ratain MJ, Nakamura Y, Cox NJ. CYP2D6 genotype and tamoxifen activity: understanding interstudy variability in methodological quality. *Clin Pharmacol Ther*. 2013;94(2):185-187.

Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin Pharmacol Ther*. 2011;89(3):464-467.

Ross CJ, Katzov-Eckert H, Dubé MP, et al; CPNDS Consortium. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. *Nat Genet*. 2009;41(12):1345-1349.

Yang JJ, Lim JY, Huang J, Bass J, et al. The role of inherited TPMT and COMT genetic variation in cisplatin-induced ototoxicity in children with cancer. *Clin Pharmacol Ther*. 2013;94(2):252-259.

CORRESPONDENCE

Genetic Markers of Cisplatin-Induced Hearing Loss in Children

To the Editor: Thank you for the opportunity to reply to Dr Ratain’s interview.¹ We have addressed Dr Ratain’s comments about our research in a recently accepted commentary to *Clinical Pharmacology and Therapeutics* that is summarized and referenced here. In addition, we propose additional references to include in Dr Ratain’s suggested reading list.

Dr Ratain commented that our findings were “surprising to many, as there had been no prior studies linking such enzymes to the pharmacokinetics or pharmacodynamics of cisplatin.” Indeed these were novel findings, but in addition to our observed replication of the thiopurine methyltransferase (TPMT) associations in 3 independent pediatric cohorts, cisplatin-TPMT interactions have now also been recently reported at the genetic and metabolomic level. In vitro, cisplatin significantly increases the expression of TPMT and metabolic genes clustered around the key methyl donor substrate for TPMT, S-adenosyl-methionine.² Moreover, functional TPMT variants have been significantly associated with progression-free survival in cisplatin-treated ovarian cancer patients.³ In addition to our findings, together these reports provide additional evidence for the role of TPMT in cisplatin response.

As we have noted,⁴ Dr Ratain had no criticism of Yang and colleagues,⁵ whereas we identified numerous reasons why no statistically significant results were found in this study.⁶ In fact, we noted a strong trend of association, in line with our findings, in their second treatment-matched cohort. In that cohort, the association of ototoxicity with functional *TPMT* variants could not have been stronger with an odds ratio approaching infinity, but these results were limited by an insufficient sample size to achieve reasonable statistical power.

As we noted,⁴ the revised US Food and Drug Administration (FDA) cisplatin label highlights the observed association with *TPMT* variants and hearing loss in children, but does not recommend genotyping before cisplatin use in children. The FDA is very specific in their choice of language and recommendations. The drug label specifically states:

Certain genetic variants in the thiopurine S-methyltransferase (TPMT) gene are associated with increased risk of ototoxicity in children administered conventional doses of

Cisplatin (see CLINICAL PHARMACOLOGY). Children who do not have one of these TPMT gene variants remain at risk for ototoxicity. All pediatric patients receiving Cisplatin should have audiometric testing at baseline, prior to each subsequent dose, of drug and for several years post therapy.

In regard to potential conflict of interest, we have commented⁴ that our federal grant funding specifically encouraged intellectual property protection, recognizing, as we do, this important part in the process for the translation of research. We agree that the disclosure of patents should be included in conflict of interest statements. To clarify, our patent and applications are not licensed to any commercial entity. In regard to perceived conflict of interest, we sought patents on behalf of the entire team of researchers and clinicians who contributed to this research to provide the best chance that these findings will be successfully implemented to improve drug safety. Although we perceived no financial conflict of interest, we agree that patent applications could be perceived as a conflict.

In regard to the updated clinical data in our 2013 publication,⁷ we identified—as described in our previous response to Dr Ratain⁴—additional patients from the initial study who received vincristine. We described this update in the subsequent publication, and also conducted analyses that showed the additional data did not affect the observed genetic associations.^{4,7}

In addition to the additional references noted above that also link TPMT and cisplatin response,^{2,3} Lanvers-Kaminsky and colleagues also recently examined the association of cisplatin-induced ototoxicity with TPMT.⁸ While their results did not reach statistical significance, their results do show similar trends in line with our findings.⁹ Importantly, for these analyses, it is also critical to account for confounding factors such as concomitant medications, cranial irradiation, concomitant otoprotectants, length of follow-up, and ancestry.⁹ The authors also did not examine the functional variants in TPMT. Most importantly, the interpretation of these findings was severely limited by the small sample size and limited statistical power, similar to the limitations of Yang and colleagues.⁵

All science involves validation and replication, and the strongest validation of these associations will come from replication in additional, similarly treated, pediatric patient cohorts. Importantly, such studies should be sufficiently powered and account for confounding clinical factors.

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Disclosures

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- Carleton BC, Ross CJ, Bhavsar AP, et al. Response to "Evaluation of pharmacogenetic markers to predict the risk of cisplatin-induced ototoxicity" [letter; published online April 22, 2014]. *Clin Pharmacol Ther.* doi:10.1038/clpt.2014.90.