

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Interethnic Differences in Drug Metabolism

Boon Cher Goh, MD

Senior Consultant

Department of Hematology-Oncology

National University Health System

Singapore

H&O How is ethnicity defined for the purposes of drug development?

BG Currently, the primary guidance on ethnicity comes from the US Food and Drug Administration (FDA), which issued guidelines for the pharmaceutical industry in September 2005. These guidelines direct drug manufacturers to utilize criteria developed by the federal Office of Management and Budget that state that race and ethnicity should include five categories: American Indian or Alaska native, Asian, Black or African American, native Hawaiian or other Pacific islander, and white or Latino. The FDA prefers that submitted data use these five categories. However, there was very little scientific input into the development of these classifications, and there certainly is no proof that genetic structure, determines these ethnic classifications. Nevertheless, drug development must proceed from these guidelines. The FDA does advise, however, that if the populations in whom an agent is under investigation, particularly outside the United States, do not fit these five categories, more details should be supplied with regard to ethnic or racial groupings.

H&O What hypotheses have been proposed regarding interethnic differences in drug metabolism?

BG There are data from the cardiovascular field showing that interethnic differences in drug efficacy and toxicity do exist. Together with data emerging in other settings,

the community now has a basis for studying interethnic differences in drug pharmacology. One hypothesis that has been proposed to explain these differences involves heritable genetic polymorphisms that affect the function of drug-metabolizing enzymes or transporters. These polymorphisms are anticipated to have the effect of modifying a drug's pharmacokinetics along its pathway of disposition. There are some examples, in addition, of genetic polymorphisms of the target of the drug's action, which can alter the effect even if the overall exposure among different ethnic groups remains the same.

Another hypothesis to explain interethnic differences includes commonly occurring diseases in particular populations. For example, liver disease due to the incidence of hepatitis B and C in the Southeast Asian population has been proposed as problematic for drug studies. Furthermore, dietary influences may affect drug interactions, and the possibility of environmental influences cannot be excluded. Social and cultural practices, which may include the use of herbal medications and concomitant traditional or alternative therapies that influence the pharmacokinetics of certain agents, must be taken into account. These hypotheses are under investigation today.

H&O How can drug assays be used to study interethnic differences in drug metabolism?

BG For a drug assay to serve as a probe for interethnic differences, a great deal must be understood about the drug in terms of its pathway of disposition. Some drugs are metabolized predominantly by a single pathway

along a well-characterized enzyme that can be used to study interethnic differences. For example, midazolam, which is predominantly metabolized by the CYP3A4 pathway, could be used to study interethnic differences in this pathway. This approach offers one way to study interethnic differences in a mechanistic manner. Other approaches include comparing pharmacokinetic and pharmacodynamic information for a particular agent (eg, an anticancer agent) between two population groups concurrently to assess whether there are ethnic differences, after correction for obvious covariables such as body weight and body surface area. Such an assessment would enable detection of differences between populations; candidate genes along the pathways of disposition can then be studied in a rigorous scientific manner to understand causes of this ethnic variability.

H&O Once an interethnic difference in drug metabolism has been successfully identified, what would be the next step?

BG There are a few ways to use this information. First, if the interethnic differences are known and can be clearly described, the next step would be to use this information to adjust the starting dose for safety reasons. As an example, for anticancer drugs with narrow therapeutic windows, such knowledge would be of great importance for avoiding excessive toxicity. Secondly, this information can be used to guide further elucidation of genetic influences, to find the mechanisms, and to assess whether these mechanisms can affect other drugs that are metabolized in the same way or undergo the same kind of transport mechanism. Finally, although it is controversial, this knowledge can be used to develop drugs that are specific to a particular ethnic group. In the cardiovascular field, isosorbide dinitrate/hydralazine (BiDil, NitroMed) was developed as an adjunct to standard therapy for African American patients with cardiac failure in order to improve survival, on the basis of a large phase III study, the African American Heart Failure Trial.

H&O How does a clinician identify a patient as a candidate to receive a drug specifically approved for one racial or ethnic group?

BG A potential drawback of using these types of definitions of ethnicity or race is precisely the fact that simple labels may not be entirely accurate in identifying groups. In fact, more work needs to be done in defining what is meant by one particular group name and how different each group is from the others. Currently, clinicians must depend on patient self-identification as belonging to a particular ethnic group, as was the case with the develop-

ment of isosorbide dinitrate/hydralazine. In the future, it would be useful to improve accuracy through the study of genetic differences between different population groups around the world. Through these efforts, relevant genetic factors that influence drug pharmacology could be identified and utilized for individualized treatment and dosing regardless of ethnicity or race.

H&O Acknowledging that the FDA's ethnic categories are rough and can encompass large geographic regions, what is known about intra-ethnic differences in drug metabolism?

BG If researchers use the FDA's recommended ethnic categories, people in the Indian subcontinent and Southeast Asia are grouped together under the term "Asian." My colleagues and I have used the population of Singapore for research in this regard; this country includes three main ethnic groups: Southern Indian, Southern Chinese, and native Malay. We have shown that there are differences among these groups in terms of anticancer drug pharmacology. Therefore, I believe the generalization that considers members of these three groups all as "Asian" is too broad. Within this large group, there are subgroups with varying genetic structures. On the basis of allelic frequencies of several drug-metabolizing enzymes, the Southern Indian population has a genetic structure more similar to that of the Western population than to that of the Southeast Asian population.

H&O What were the findings of the research on the pharmacology of anticancer agents in Singapore?

BG Several years ago, a Singaporean study of a combination of docetaxel (Taxotere, Sanofi-Aventis) and carboplatin in patients with metastatic non-small cell lung cancer, which enrolled predominantly Southern Chinese patients, used a similar protocol as another study from Sydney, Australia, which enrolled a predominantly white population. We found that the Chinese population experienced greater hematologic toxicity compared to the white population and required dose adjustment. The mean nadir neutrophil counts were lower in the Singaporean population than in the Australian population. On the other hand, the response rate appeared to be higher in the Singaporean population compared to the Australian population. This study, however, was small and non-randomized and can be used only for the generation of hypotheses for future research.

A second Singaporean study consisting of patients with breast cancer treated with standard doxorubicin or docetaxel showed differences between the Indian, Chi-

nese, and Malay patients in terms of the Chinese patients experiencing more hematologic toxicity on doxorubicin compared to the Indian patients. Third, a recent study of a prodrug of 5-fluorouracil (5-FU) called S-1, under development by the Japanese manufacturer Taiho, compared its pharmacokinetics and pharmacodynamics in Southeast Asian and white patients. This drug has three components and fairly complicated pharmacology. We showed that there were some differences in terms of the pharmacokinetics of 5-FU and the constituents of S-1 among Singaporean Chinese and American whites. This study was presented at the 2008 annual meeting of the American Society of Clinical Oncology. Taken together, these studies have highlighted differences in the pharmacology of common anticancer agents.

H&O In future research, what sort of trial design should be used in order to better understand interethnic differences in drug metabolism in the setting of cancer?

BG I believe it is necessary to use a common protocol for two different ethnic populations. The definition of ethnicity should be stated clearly in the protocol, and other characteristics of the study population should be controlled (eg, organ function, performance status, etc.). During the study, the pharmacokinetic assays should be analyzed at a central laboratory simultaneously. The collection of toxicity data should be standardized among the study groups. One important point would be to look at sample size differences. We could define a difference that interests us and define the sample size for the two populations that we hope to observe. With this sort of central control and standardization of format and conduct of a study, it should be feasible to distinguish interethnic differences in a more robust manner than has been previously possible.

It is important to note that cooperative groups within the United States and elsewhere should work together to ensure that sufficient ethnic representation is present in clinical trials conducted across different parts of the world. With greater cooperation, it would be possible to generate a great deal of information on interethnic differences and begin to study how this understanding can lead to individualization of therapy. The very important point of studying interethnic differences is not simply to describe them, classify groups, and treat patients differently, but rather to uncover the genetic influences or other mechanisms in place, with the eventual goal of treating the patient with individualized therapy. Describing broad differences between two groups is only a starting point. The goal is to improve safety and efficacy based on an understanding of drug metabolism in individual patients.

Suggested Readings

Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med*. 2004;351:2049-2057.

Fan L, Goh BC, Wong CI, et al. Genotype of human carbonyl reductase CBR3 correlates with doxorubicin disposition and toxicity. *Pharmacogenet Genomics*. 2008;18:621-629.

Millward MJ, Boyer MJ, Lehnert M, et al. Docetaxel and carboplatin is an active regimen in advanced non-small-cell lung cancer: a phase II study in Caucasian and Asian patients. *Ann Oncol*. 2003;14:449-454.

Goh BC, Soo RA, Lim S, et al. Inter-ethnic variability of S-1 pharmacokinetics (PK) and correlation with CYP2A6 phenotyping. *J Clin Oncol*. 2008;26(15S pt 1):Abstract 2507.

Hor SY, Lee SC, Wong CI, et al. PXR, CAR and HNF4alpha genotypes and their association with pharmacokinetics and pharmacodynamics of docetaxel and doxorubicin in Asian patients. *Pharmacogenomics J*. 2008;8:139-146.

Goh BC, Lee SC, Wang LZ, et al. Explaining inter-individual variability of docetaxel pharmacokinetics and pharmacodynamics in Asians through phenotyping and genotyping strategies. *J Clin Oncol*. 2002;20:3683-3690.

Lee SC, Ng SS, Oldenburg J, et al. Interethnic variability of warfarin maintenance requirement is explained by VKORC1 genotype in an Asian population. *Clin Pharmacol Ther*. 2006;79:197-205.