

Pharmacogenetics for Oncology Practice

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Pharmacogenetics (PG) refers to the hereditary basis of drug response and has held the promise of pharmacotherapy that is individualised both in the selection and dosing of medications, the potential of which is enticing for clinicians like oncologists faced with prescribing drugs that have unpredictable side effects and narrow therapeutic windows. The aim of PG in clinical care is to direct drug and dosing decisions that can render higher efficacy and improved safety to their use. The basis of PG is that interindividual variability of anticancer treatment is partially related to genetics, either germline or somatic. The pace of PG discoveries and associations with drug therapy has accelerated in recent years as a consequence of technological improvements in genomic tools that can de-encrypt genetic material in massively parallel fashion at falling costs and advances in bioinformatics that evaluate massive dimensions of genomic and clinical data. More recently, apart from structural polymorphisms that associate with drug response, other common genetic lesions that can potentially influence phenotype include copy number variations, gene translocation and fusion and epigenetic modulation. In somatic tissues, gene expression profiles have added to the list of predictors studied for drug treatment.

There are 2 main approaches to PG discovery; candidate gene approach and genome-wide approach. In the candidate gene approach, variants in genes that are biologically involved in the pathway of disposition and action of the drug are correlated to the drug pharmacokinetics (PK) and pharmacodynamics (PD). However, the impact of each gene variant may not be dramatic, and the overall drug PK and PD is more likely the aggregate of interactive, smaller gene effects. In the genome-wide approach, a non-biased approach is used to associate whole genome scan of known single nucleotide polymorphisms (SNPs) or haplotypes against drug phenotype, and to validate positive correlations on an independent data set. As with other genome-wide association studies (GWAS), statistical corrections for multiple comparisons are necessary to avoid false positives, and the genes discovered usually are not intuitive.¹ Both strategies are important and have their limitations, drawbacks and strengths, but both need

to be validated on independent datasets before clinical application.

At the cellular level, the state of a particular gene or genes would determine the level of protein expression and function, and in the case of target proteins may determine the interaction with therapeutic drugs. Allelic variants of drug metabolising enzymes, membrane influx and efflux transporters can impact on pharmacokinetic processes of clearance and distribution and result in variability in exposure to same doses of drug and therefore variable toxicity and efficacy. Examples include UGT1A1 polymorphisms and irinotecan induced toxicity,² thiopurine methyl transferase polymorphisms and toxicity from 6 mercaptopurine or azathioprine,³ and dihydropyrimidine dehydrogenase polymorphisms associated with 5 fluorouracil induced toxicity.⁴ Several of the articles in this special edition of the Annals will expand on these aspects.

Of great interest is the fact that whole genome and candidate gene sequencing of somatic tissue has yielded significant insight into oncogenic driver mutations in tumours that are susceptible to inhibition by small molecules or monoclonal antibodies, a state termed “oncogenic addiction”. Inhibition of these signalling pathways is effective in inhibiting tumour growth, inducing apoptosis, and in some cases with lasting remissions like imatinib in bcr-abl positive chronic myeloid leukaemia and c-kit positive gastrointestinal stromal tumours (GIST). Detection of overexpression of receptor tyrosine kinases like HER2/neu through gene amplification in breast cancer has been successfully exploited by development of the therapeutic monoclonal antibody trastuzumab, resulting in improved treatment and prognosis. Furthermore, we are learning that overexpression of the same receptor in different cancers may indicate application of the same therapeutic strategy, as in the case of HER2/neu in gastric cancer. More recently, gene translocations detected by fluorescent in-situ hybridisation have been shown to be relevant as well to oncogene signalling, as in the case of the EML4-ALK translocation in about 3% to 5% of non-small cell lung cancer, that results in ALK kinase signalling of cell growth and proliferation.⁵ This translocation has significant

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therapeutic relevance, as an ALK kinase inhibitor, crizotinib, has shown remarkable therapeutic effect in patients with EML4-ALK translocation. Similarly, the V600E mutation in BRAF kinase is found in 50% of melanoma, 10% of colorectal carcinoma, and can be inhibited successfully in melanoma by a specific BRAF inhibitor, PLX-4032.⁶ O6-methylguanine–DNA methyltransferase (MGMT) promoter silencing by methylation and its association with better outcome from alkylating agents like temozolomide in glioblastoma therapy is a pharmacogenetic example involving an epigenetic mechanism.⁷

To successfully apply pharmacogenomic tests in clinical practice, assays should be reproducible and validated through large scale studies with adequate samples sizes, preferably in a prospective, randomised study, and demonstrate sensitivity and specificity for predicting outcome. Conditions for positive and negative results should be standardised between laboratories. Physicians who order these tests should understand the implications and limitations of these tests in clinical decision making. In general, a PG test is no different from a routine laboratory test, and the information obtained should be used according to accepted evidence-based recommendations. Gene variants that have a large effect on the outcome, and are frequent in the relevant (ethnic) population are likely to have a large impact on outcome, and will be easily adopted clinically. Examples include HER2/neu testing for determining use of trastuzumab, K-ras testing in colorectal cancer to determine use of epidermal growth factor receptor (EGFR) inhibitors cetuximab and panitumumab, and detection of activating EGFR mutations in lung adenocarcinoma to determine the first line treatment with EGFR tyrosine kinase inhibitors. Given the potential for these tests to change practice, clinicians should be mindful of the need to obtain sufficient tumour tissue during diagnosis of the conditions; fine needle aspirates may not yield suitable material for PG testing. On the other hand, smaller gene effects, especially in the absence of other known genes that have similar influence on drug effects, or gene variants that are relatively rare in the population, requires due considerations including but not limited to cost effectiveness and risks involved in obtaining tissue samples.

An important aspect in successful introduction of PG tests to routine clinical practice involves education of the physicians, patients, as well as third party health payers. Clinical pharmacologists, pharmacists and possibly clinical geneticists should consider incorporation of PG information and counselling services within drug information services to communicate relevance and recommendations of PG tests and their results according to best available evidence. To be successful, PG should be developed in the curriculum of medical education. Given ethnic variability

of genetic alleles in different populations, a regional database would be important to interrogate and iteratively validate pharmacogenomic associations for the East Asian population.

At the United States National Cancer Institute, a review panel has made recommendations to assemble an expert panel to advise and evaluate evidence and formulate research questions, to integrate sample and data collection in clinical trials, to encourage research to better understand drug pharmacology, and to study the clinical effectiveness and pharmacoeconomics of applying PG to clinical practice.⁸ There should be a similar effort in Singapore, where there is keen interest in pharmacogenomics research, good genomic capabilities, progressive establishment of an islandwide fully computerised database of patient information from the primary to tertiary care, and the availability of multiple ethnic populations that allow cross ethnic comparisons of drug effects. The benefits of these efforts are expected to be immediately obvious: a high level expert panel would be able to advise the government on priorities in deployment of PG in clinical practice on the basis of current evidence, and save costs as well as toxicities by avoidance of ineffective treatment. Researchers should be encouraged to cooperate in PG studies in group trials and share datasets to optimise statistical power for validating PG discoveries. Only with these motivations will we be successful in applying the full potential of PG in oncology clinical practice.

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