The applications of pharmacogenetics to prescribing: what is currently practicable?

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Both during the human genome project[1] and since its completion interest in pharmacogenetics has increased significantly, evidenced by an increasing number of publications and interest from industry and healthcare systems. Drugs are increasingly prescribed on the basis of genetic (or phenotypic) tests. This article highlights areas in which pharmacogenetics currently plays a role in prescribing (or likely to do so in the near future). Definitions of pharmacogenetics and other relevant terms are given in Table 1.

Pharmacogenetic tests

Pharmacogenetic tests can be based on phenotype or genotype. Although genotypic tests are usually easier and cheaper, phenotypic tests are more widely used because not all the genotypes that contribute to a phenotype have been defined. Genotypic tests may detect single nucleotide polymorphisms (substitution of one base by another) or more structural variants such as insertions/deletions or copy number polymorphisms. Those variations that determine the level of expression of an mRNA species are also being used, especially in cancers.

Genotypic or phenotypic tests can be used to guide drug choice and/or dosage regimen. A test may predict how efficacious or safe the drug is likely to be. This is relatively straightforward when there is an alternative drug that may be more effective or safe in an individual. Individualising drug dosages, however, is much more difficult.

Determining drug choice

Cancer therapy

Personalised therapy is more advanced in cancer than in any other therapeutic area (Table 2). The best example is trastuzumab, which improves disease-free and overall survival in breast cancer in patients with HER2 gene amplification or overexpression on breast cancer cells.[2] This adverse prognostic factor, a somatic change, occurs in 20% of breast cancers. In patients with colorectal cancer, the proto-oncogene KRAS acts as a downstream signal transducer of epidermal growth factor receptor (EGFR).[3] Responses to EGFR inhibitory monoclonal antibodies, panitumumab and cetuximab, are better in patients with the wild-type KRAS gene.[4] Testing for the KRAS gene is now a routine part of the care of patients with metastatic colorectal cancer and is mentioned both in the Summary of Product Characteristics (SPCs) of panitumumab and cetuximab and in National Institute for Health and Clinical Excellence guidance.

Abacavir

Abacavir, an HIV-1 reverse transcriptase inhibitor, causes a hypersensitivity reaction (skin rash, fever, gastrointestinal and respiratory effects) in about 5% of patients and is associated with an HLA allele, HLA-B*5701. Pre-prescription genotyping prevents abacavir hypersensitivity and is cost-effective.[5] In Europe, screening for HLA-B*5701 is now mandatory before prescribing abacavir.

Carbamazepine

Severe immune-mediated adverse effects can be caused by carbamazepine, including Stevens–Johnson syndrome and toxic epidermal necrolysis. In Han Chinese patients this is associated with HLA-B*1502.[6] The association is phenotype-specific and does not predispose to carbamazepine-induced hypersensitivity syndrome. The SPC recommends testing for HLA-B*1502 in Chinese and Thai patients before using carbamazepine. However, the positive predictive value is low because the reaction is rare.

Glucose-6-phosphate dehydrogenase deficiency

The most common enzyme deficiency worldwide is glucose-6-phosphate dehydrogenase (G6PD) deficiency, with many (>300) allelic variants.[7] It is associated with acute haemolysis on exposure to oxidising drugs such as primaquine, chlorproguanil-dapsone, sulfonamides

Table 1. Some relevant definitions.

Pharmacogenomics*	The study of variations of DNA and RNA characteristics as related to drug response
Pharmacogenetics*	The study of variations in DNA sequence as related to drug response
Genomic biomarker*	A measurable DNA and/or RNA characteristic that is an indicator of a normal biological or a pathogenic process and/or a response to therapeutic or other interventions
Personalised medicine**	The application of genomic and molecular data to improve the delivery of healthcare, facilitate the discovery and clinical testing of new products, and help determine individual predisposition to a particular disease or condition

*Definitions adapted from *Note for guidance on definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample categories* (EMEA/CHMP/ICH/437986/2006).

**Definition adapted from the US Genomics and Personalised Medicines Act 2007.

Table 2. Examples of the use of pharmacogenetics in cancer therapy.

Drug	Genomic marker	Disease	Comments
Trastuzumab	HER2 receptor expression	Breast cancer	Efficacy marker in 20% of cases
Cetuximab or panitumumab	KRAS mutation	Colorectal cancer	More effective with wild-type KRAS
Tamoxifen	CYP2D6	Breast cancer	Reduced efficacy in poor CYP2D6 metabolisers
Imatinib	BCR-ABL translocation	CML	Also used in treatment of Philadelphia chromosome-positive ALL and GI stromal tumours
Irinotecan	UGT1A1 polymorphism	Colorectal cancer	Increased risk of neutropenia and diarrhoea in patients with UGT1A1*28 polymorphism
Mercaptopurine (and azathioprine)	TPMT	ALL	Increased risk of severe leukopenia with homozygote variant and heterozygous individuals
Fluorouracil	DHPDH	Colorectal cancer	Increased toxicity in patients with variant forms of the enzyme

ALL = acute lymphoblastic leukaemia; CML = chronic myeloid leukaemia; DHPDH = dihydropyrimidine dehydrogenase; GI = gastrointestinal; TPMT = thiopurine methyltransferase; UGT = uridine diphosphate-glucuronosyl-transferase.

and sulfones, nitrofurantoin, nalidixic acid, quinine, flutamide and methylthioninium chloride. Phenotypic tests for G6PD deficiency are recommended before using drugs such as primaquine, but it is not known how often this is done. Testing for G6PD deficiency is also recommended before using rasburicase, a recombinant urate oxidase enzyme used in preventing hyperuricaemia in patients at high risk of tumor lysis syndrome.[8]

Determining drug dosage regimens

Dosage regimens are currently determined on the basis of population data. This 'one-dose-fits-all' approach leads to variability in drug response, in terms of both efficacy and toxicity. In some cases, dosage depends, at least partly, on genetic factors.

Mercaptopurine

Mercaptopurine and its pro-drug azathioprine are metabolised by thiopurine methyl transferase (TPMT) which is trimodally distributed. About 10% of the population are heterozygotes, while the enzyme is absent in one in 300.[9] Both genotyping and phenotyping can iden-tify heterozygotes and homozygous variants, but the phenotypic test in erythrocytes is more widely used. In homozygotes, agranulocytosis can be avoided by reducing the dose of mercaptopurine or azathioprine. The usefulness of dosage reduction in heterozygotes is less clear and white cell count monitoring has been alleged to be as effective. It is currently recommended that all patients should be tested for TPMT activity before starting azathioprine.[10]

Irinotecan

Irinotecan is converted to an active metabolite, SN38. This is glucuronidated by UGT1A1, the activity of which is determined by a two base-pair insertion (TA) in the promoter region. Individuals with seven TA repeats (*28 allele) have reduced enzyme activity and higher rates of severe neutropenia and diarrhoea than those with the wild-type allele (UGT1A1*1).[11] In the USA there is an FDA-approved test for UGT1A1 genotyping, but it is little used because specific dosing instructions are not included.

Warfarin

There is a 40-fold interindividual variation in dosage requirements of warfarin. Together with age and weight, variations

Key Points

Genetic factors can affect the way individuals respond to drugs in terms of efficacy and toxicity

The contribution to drug response is most likely to be multifactorial and multigenic

Genetic factors can be used to guide drug choice and/or dosage regimen

The best examples of gene-guided therapies currently are the expression of the HER2 receptor as a determinant of the efficacy of trastuzumab, and predisposition to abacavir hypersensitivity by HLA-B*5701

There is a need to test the clinical validity and clinical utility of any pharmacogenetic markers that are developed

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in two genes, CYP2C9 (which metabolises S-warfarin) and VKORC1 (pharmacological target: vitamin K epoxide reductase), account for 50% of the variance in dosage requirements.[12] Dosing algorithms incorporating genetic and clinical factors have been developed[13] but, although testing is mentioned on the label in the USA, as for irinotecan there is no dosage guidance. Routine use is not currently recommended. Randomised controlled trials are underway.

Conclusions

Genotype-guided prescribing is now routine in a few cases and should increase in coming years. It will probably be most useful for drugs with a narrow therapeutic index in the management of cancers and in drug safety. A House of Lords report has highlighted the need to develop this field.[14] It will be crucial to test the clinical validity and usefulness of any pharmacogenetic markers that are developed.

Acknowledgments

References

1 Meyer UA. Pharmacogenetics – five decades of therapeutic lessons from genetic diversity. *Nat Rev Genet* 2004;5:669–76.

2 Smith I, Procter M, Gelber RD *et al.* 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007;369:29–36.

3 Walther A, Johnstone E, Swanton C *et al.* Genetic prognostic and predictive markers in colorectal cancer. *Nat Rev Cancer* 2009;9:489–99.

4 Jimeno A, Messersmith WA, Hirsch FR, Franklin WA, Eckhardt SG. KRAS mutations and susceptibility to cetuximab and panitumumab in colorectal cancer. *Cancer J* 2009;15:110–3.

5 Waters LJ, Mandalia S, Gazzard B, Nelson M. Prospective HLA-B*5701 screening and abacavir hypersensitivity: a single centre experience. *AIDS* 2007;21:2533–4.

6 Chung WH, Hung SI, Hong HS *et al.* Medical genetics: a marker for Stevens–Johnson syndrome. *Nature* 2004;428:486.

7 Beutler E. G6PD deficiency. *Blood* 1994;84:3613–36.

8 Browning LA, Kruse JA. Hemolysis and methemoglobinemia secondary to rasburicase administration. *Ann Pharmacother* 2005;39:1932–5.

9 McLeod HL, Krynetski EY, Relling MV, Evans WE. Genetic polymorphism of thiopurine methyltransferase and its clinical relevance for childhood acute lymphoblastic leukaemia. *Leukaemia* 2000;14:567–72.

10 (No authors listed.) TPMT testing before azathioprine therapy? *Drug Ther Bull* 2009;47:9–12.

11 Liu CY, Chen PM, Chiou TJ *et al.* UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. *Cancer* 2008;112:1932–40.

12 Takeuchi F, McGinnis R, Bourgeois S *et al.* A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. *PLoS Genet* 2009;5:e1000433.

13 Garcia D, Regan S, Crowther M, Hughes RA, Hylek EM. Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. *Chest* 2005;127:2049–56.

14 House of Lords Science and Technology Committee. 2nd Report of Session 2008–09. HL Paper 107-I. *Genomic medicine*. London: The Stationery Office Limited, 2009. www.publications.parliament.uk/pa/ld200809/ldselect/ldsctech/107/107i.pdf (last accessed 31 July 2009).

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Erratum

Fogo A, du Vivier A. The cutaneous manifestations of haematological malignancy. *Clin Med* 2009;4:366–70.

Please note figure 3 on page 368 of the August issue of *Clinical Medicine* was reproduced incorrectly. This was due to an technical error which occurred during the typesetting process.

The correct version of figure 3 is reproduced below.

Fig 3. Pyoderma gangrenosum. An 'infection' developed at the site of the Hickman line and at other venous access sites in this patient. It was debrided until a haematologist made the correct diagnosis and a biopsy was performed. The lesions responded dramatically to steroids.