Available online at www.sciencedirect.com

SCIENCE DIRECT®

Pharmacology & Therapeutics 107 (2005) 155 – 176

Pharmacology & Therapeutics

www.elsevier.com/locate/pharmthera

Pharmacogenetics for individualized cancer chemotherapy

Thomas Efferth*, Manfred Volm

German Cancer Research Center, M070, Im Neuenheimer Feld 282, 69120 Heidelberg, Germany

Abstract

The same doses of medication cause considerable heterogeneity in efficacy and toxicity across human populations. Genetic factors are thought to represent important determinants of drug efficacy and toxicity. Pharmacogenetics focuses on the prediction of the response of tumor and normal tissue to standard therapy by genetic profiling and, thereby, to select the most appropriate medication at optimal doses for each individual patient. In the present review, we discuss the relevance of single nucleotide polymorphisms (SNP) in genes, whose gene products act upstream of the actual drug target sites, that is, drug transporters and drug metabolizing phase I and II enzymes, or downstream of them, that is, apoptosis-regulating genes and chemokines. SNPs in relevant genes, which encode for proteins that interact with anticancer drugs, were also considered, that is, enzymes of DNA biosynthesis and metabolism, DNA repair enzymes, and proteins of the mitotic spindle. A significant body of evidence supports the concept of predicting drug efficacy and toxicity by SNP genotyping. As the efficacy of cancer chemotherapy, as well as the drug-related toxicity in normal tissues is multifactorial in nature, sophisticated approaches such as genome-wide linkage analyses and integrate drug pathway profiling may improve the predictive power compared with genotyping of single genes. The implementation of pharmacogenetics into clinical routine diagnostics including genotype-based recommendations for treatment decisions and risk assessment for practitioners represents a challenge for the future.

Keywords: Cancer drug resistance; Single nucleotide polymorphisms; Toxicity

Abbreviations: ABC transporter, ATP-binding cassette transporter; BCRP, breast cancer-related protein; CDA, cytidine deaminase; CYP, cytochrome P450 monoxigenase; DPYD, dihydropyrimidine dehydrogenase; ER, estrogen receptor; ERCC1/2, excision repair cross-complementing gene 1/2; G6PD, glucose-6-phosphate dehydrogenase; GST, glutathione S-transferase; hCNT, human concentrative nucleoside transporter; hENT, human equilibrative nucleoside transporter; IL, interleukin; MDR1, multidrug resistance 1 gene; MGMT, O^6-methylguanine-DNA methyltransferase; MRP, multidrug resistance-related protein; MTHFR, 5,10-methylenetetrahydrofolate reductase; NQO, NADH quinone oxidase; RFC, reduced folate carrier; SNP, single nucleotide polymorphism; TNF, tumor necrosis factor; TPMT, thiopurine *S*-methyltransferase; TS, thymidylate synthase; TSER, thymidylate synthase 5′ promotor enhancer region; UGT, UDP-glucuronosyltransferase; XRCC1, X-ray cross complementation group 1.

Contents

* Corresponding author. Tel.: +49 6221 423426; fax: +49 6221 653195.
E-mail address: thomas.efferth@web.de (T. Efferth).

0163-7258/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2005.02.005

1. The concept: The right drug for the right patient

1.1. Pharmacogenetics and the human genome

It is a well-known clinical observation that the same doses of medication cause considerable heterogeneity in efficacy and toxicity across human populations (Evans & Relling, 1999; Fagerlund & Braaten, 2001). This heterogeneity can lead to unpredictable life-threatening or even lethal adverse effects in small groups of patients (Rothenberg et al., 2001; Sargent et al., 2001). The interindividual variability in drug response cannot satisfactorily be explained by factors such as renal and liver function, patients' age and comorbidity, life style, or comedication and compliance of patients. Therefore, genetic factors are important determinants for drug efficacy and toxicity. The identification of these genetic factors is the goal of pharmacogenetics.

The draft sequence of the human genome published in the year 2001 (Lander et al., 2001; Venter et al., 2001) has shown that there is a large extent of genetic variation. Very recently, a highly accurate genome sequence with few unknown gaps and an error rate of 1 event per 100 000 bases has been released (International Human Genome Consortium, 2004). While the number of coding DNA regions was estimated to 30 000 to 40 000 in the draft sequence, the number of genes was now down-scaled to 20 000 to 25 000 protein-coding genes. This precise genome sequence could serve as reliable basis for pharmacogenetic research in the years to come. It is to be expected that the number of drug targets will increase dramatically.

The term "pharmacogenetics" was coined in the 1950s, as it became evident that there is an inherited basis for differences in the disposition and effects of drugs and xenobiotics (Vogel, 1959). In these initial observational studies, it was recognized that antimalarial drugs and certain foods (soy beans) cause hemolytic crises in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD deficiency is the most frequent enzymopathy worldwide, with an estimated 400 million affected patients. Although single base alterations in the *G6PD* gene are by far the most common reason for reduced enzyme activity (over 140 different variants), other rare alterations such as splice site mutations have also been discovered (Beutler & Vulliamy, 2002; Efferth et al., 2004a).

Pharmacogenetics focuses on the prediction of drug efficacy and toxicity based on a patient's or tumor's genetic profile with routinely applicable genetic tests and easily accessible test samples, that is, tumor biopsies or peripheral blood. Pharmacogenetic biomarkers hold great promise for the individualization of therapeutic intervention to select the most appropriate medication and to apply the optimal dose for each individual patient according to precise marker-assisted screening tests. The hope is to stratify individual patients based on their probability to response to a particular customized therapy.

The pharmaceutical industry has high expectations for patient-tailored drug selection and individual dose adaptation (Kirkwood & Hockett, 2002). Drug development is a time- and cost-consuming process. The development of candidate compounds could be terminated sooner, if severe toxicity could be predicted with higher accuracy. Although the number of candidate drugs in the developmental pipeline may be decreased by pharmacogenetic and toxicogenetic approaches, the long-term benefit of the applications of these concepts has significant clinical benefits.

1.2. Problems of cancer therapy

The major obstacles of cancer chemotherapy are the development of drug resistance and the severe side effects. Due to the modest tumor specificity of many anticancer drugs, normal tissues are also damaged. This prevents the application of sufficient high doses to eradicate less sensitive tumor cell populations. Thereby, tumors develop drug resistance that leads to treatment failure and fatal consequences for patients. Novel strategies to broaden the narrow therapeutic range by separating the effective dose and toxic dose would be of great benefit for the improvement of cancer chemotherapy.