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ANTI-TUMOUR TREATMENT

An overview of the relations between polymorphisms in drug metabolising enzymes and drug transporters and survival after cancer drug treatment

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Summary A wide interindividual variability in survival after cancer treatment is observed. This is attributable to many factors, including tumour and patient related factors. Genetic polymorphisms in drug metabolising enzymes and drug transporters may be one of these factors. Drug metabolising enzymes are responsible for the activation, inactivation and detoxification of many chemotherapeutic agents. Deficiencies in these enzymes may result in altered exposure (both extracellular and intracellular) to the chemotherapeutic agents, thereby influencing the efficacy of treatment. Drug transporters are important in the uptake and excretion of chemotherapeutic agents. Polymorphisms in drug transporter genes may influence the bioavailability and disposition of these agents.

Studies have shown that variability in survival can (partly) be explained by polymorphisms in genes encoding drug metabolising enzymes and drug transporters. This review will discuss the role of genetic polymorphisms in drug metabolising enzymes and drug transporters in relation to survival after cancer treatment.

The most important polymorphisms shown to influence survival after cancer treatment are polymorphisms in the genes encoding the phase II detoxification enzymes glutathione-S-transferases (GSTs). It appears that *GSTM1* null and *GSTT1* null have a clear association with longer overall survival in patients with different malignancies who are treated with substrates for

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these GSTs (mostly alkylating agents and platinum compounds). Genetic polymorphisms in *GSTP1* and *GSTA1* are also associated with an increased overall survival in patients with different malignancies.

Most of the current data on the relation between treatment response and pharmacogenetics is derived from retrospective and exploratory studies. Prospective studies will be necessary.

Introduction

Differences in drug response among patients after cancer treatment are common. This variability in drug response is partly due to variability in pharmacokinetics. Factors responsible for this variability include ethnicity, age, gender, diet, smoking, alcohol consumption, renal and liver function, concomitant disease and co-medication. In many cases however, genetic factors are shown to have an even greater influence on drug disposition. It is estimated that genetic variability accounts for 20—95% of the variability in therapeutic response and toxic effects.[1] These differences in genetic factors, for instance observed in genes encoding drug metabolising enzymes and drug transporters, can influence the pharmacokinetic and pharmacodynamic profile of anti-cancer drugs, leading to differences in response and development of severe toxicities.

Genetic variation in the human genome is a common phenomenon and approximately 1 out of 1000 basepairs differs between any two individuals.[2] Most of these variations are single nucleotide polymorphisms (SNPs). These single nucleotide differences account for >90% of the genetic variation. Insertions and deletions, tandem repeats and microsatellites account for the remaining 10%.[3] The number of polymorphisms identified in genes encoding drug metabolising enzymes and drug transporters is rapidly increasing, probably leading to a better understanding of the observed variation in efficacy and toxicity of anti-cancer drugs in patients.

Drugs are metabolised by drug metabolising enzymes and drug transporters play a role in the disposition of drug in the body. These can be classified into three main categories. The first category consists of phase I enzymes. These include reductases, oxidases and hydrolases. The cytochrome P450 enzymes (CYPs) belong to this category. Most drugs are metabolised by CYPs either as a route to detoxification or as an activation pathway for an inactive prodrug. The second category is called phase II enzymes. These enzymes usually conjugate phase I products, but can also conjugate other reactive intermediates or the parent compound, with various endogenous moieties such as glucuronic acid, glutathione or sulphate. These enzymes also contribute to the intracellular metabolism of many substrates. The phase II enzymes include UDP-glucuronosyltransferases (UGTs), glutathione-S-transferases (GSTs), and sulfotransferases (SULTs).[4] The last category consists of drug transporters. These transporters are membrane-bound proteins that control drug uptake and excretion. Drug transporters greatly influence the bioavailability and disposition of drugs. Examples of genes that encode these transporters are *MDR1* (*ABCB1*), which encodes P-glycoprotein, and *ABCG2*, which encodes breast cancer resistance protein (BCRP).[5]

Polymorphisms in genes encoding drug metabolising enzymes may decrease the intracellular enzyme concentration, lead to a dysfunctional protein, or may structurally alter the enzyme with consequent changes in enzyme function. Polymorphisms in drug transporter genes can influence the uptake and excretion capability of the protein. Together this may alter the pharmacokinetic and pharmacodynamic profile of a drug. Therefore, polymorphisms in genes encoding proteins involved in drug metabolism and disposition may be important for treatment response after cancer treatment. Especially the influence of polymorphisms on survival after cancer treatment is important since this is the ultimate outcome measure.

This review will focus on the influence of genetic polymorphisms in phase I and II enzymes and drug transporters on survival after cancer treatment. A review of the literature of studies reporting significant relations between survival and polymorphisms in drug metabolising enzymes and drug transporters is provided. Furthermore, the clinical relevance of these polymorphisms in predicting outcome is discussed.

Methods

A literature search was carried out using PubMed for publications concerning the influence of polymorphisms in drug metabolising enzymes and drug transporters on survival. Furthermore, reference lists of publications were screened on other relevant studies. Studies that reported significant relations were included in this review, limiting results to human research published in English.

Phase I enzymes

Cytochrome P450

CYP enzymes are important in the biosynthesis and degradation of endogenous compounds such as steroids, lipids and vitamins. They metabolise many drugs as well as chemicals present in the diet and environment. The CYP enzymes are responsible for the metabolism of over 90% of clinically prescribed drugs. CYPs reduce or alter the pharmacologic activity of many drugs and facilitate their elimination. Three families of encoded proteins, CYP1, CYP2, and CYP3 contribute mainly to the metabolism of drugs.[6]

Individual CYP enzymes each have unique substrate specificity. However, considerable overlap may be present. Thus, drugs may be metabolised by a single CYP enzyme or a variety of CYP enzymes may contribute.

The liver is the major site of CYP mediated metabolism, but the CYP enzymes are also expressed in the enterocytes in the epithelium of the small intestine, kidney and lung.