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Review

Pharmacogenetics of cancer chemotherapy

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Abstract

Significant heterogeneity in the efficacy and toxicity of chemotherapeutic agents is observed within cancer populations. Pharmacogenetics (PGx) is the study of inheritance in interindividual variation in drug disposition. The allure of pharmacogenetics, in the treatment of cancer patients, comes from the potential for individualisation of cancer therapy, minimizing toxicity, while maximizing efficacy. In this review we will focus on the current and potential clinical applications of pharmacogenetics in cancer therapy by citing relevant examples and discussing the possible approaches which may be used to establish a reliable, reproducible and cost-effective test for clinically relevant genetic polymorphisms, using easily accessible biological samples (e.g., blood and tumour samples). Ideally, routine management of patients would include analysis of their single nucleotide polymorphism linkage disequilibrium (SNP-LD) profile prior to treatment, allowing stratification of patients into treatment groups, thus individualising their therapy. In order to achieve this ambition, a combination of different approaches (candidate gene, genome-wide and pathway driven) will be required from scientists and clinician scientists, as well as an increased understanding and incorporation of pharmacogenetic aims and endpoints into current and future clinical trials.
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Keywords: Pharmacogenetics; Single nucleotide polymorphins; Candidate gene; Genome-wide; Pathway driven; Association studies; Cancer therapy; Toxicity

Contents

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1. Introduction

Significant heterogeneity in the efficacy and toxicity of chemotherapeutic agents is observed within cancer populations [1,2]. A wide variety of factors may influence drug disposition and response including age, ethnic origin, sex, diet, tumour biology, organ function and differences in drug pharmacokinetics and pharmacodynamics secondary to genetic polymorphisms in drug metabolising enzymes, transporters or drug targets.

Pharmacogenetics (PGx) is the study of inheritance in interindividual variation in drug disposition. The phrase pharmacogenetics was coined by Vogel [3] in 1959, although as early as 1932, Synder [4] (phenylcarbothiamide) and 1956, Hughes [5] (isoniazid — fast and slow acetylators) had both documented a clinical phenotype for interindividual variation in drug metabolism [6]. The term pharmacogenomics, which is often used interchangeably with pharmacogenetics, was first used in the literature in 1997, and encompasses the advances in genomic science that include the completion of the Human Genome Project. Developments in this field have also been greatly facilitated by rapid progress in molecular technology, in particular, high throughput DNA sequencing, microarrays and genotyping [7].

Why has pharmacogenetics become such a "high profile" field in recent years? The allure of pharmacogenetics, in the treatment of cancer patients, comes from the potential for individualisation of cancer therapy, minimizing toxicity, while maximizing efficacy. The final outcome being the ability to modify treatment to achieve optimal therapy for each individual patient. It is hoped that pharmacogenetics will allow stratification of individuals into therapeutic response groups according to their genotype, thus permitting greater treatment precision.

In this review we will focus on the current and potential clinical applications of pharmacogenetics in cancer therapy by citing relevant examples and discussing the possible approaches which may be used to establish a reliable, reproducible and cost-effective test for clinically relevant genetic polymorphisms using easily accessible biological samples (e.g., blood and tumour samples).

2. Clinical utility of PGx tests

The determinants of the clinical utility of a PGx test, one that for example, identifies an adverse drug reaction (ADR) are complex. It is dependent upon the test performance (sensitivity and specificity), the prevalence of the ADR, the severity of the ADR, and the management implications of the test result. For example, if we assume that a specific treatment would be used for all patients in the absence of a test, the purpose of the test would be to identify a group of patients for major dose modification (reduction or exclusion). However, inappropriate major dose modification would be harmful. The sensitivity of the test determines what proportion of patients would benefit from dose modification. A low sensitivity would not necessarily limit the clinical utility of the test, as those who would benefit from dose modification and test positive get the benefit, but those who test negative will be treated the same as they would have been in the absence of a test. On the other hand, test specificity is very important, as patients where dose modification is inappropriate (harmful) is given by (1 — specificity). In this setting, common variants with modest effects are therefore unlikely to prove useful, as they have low specificity. On the other hand, uncommon genetic variants (minor allele frequency (MAF) $<5\%$) with large effects, such as the rare alleles of thiopurine-*S*-methyltransferase (TPMT), are likely to be useful. A variant carried by 2% of the population that increases the risk of a serious adverse event by 30-fold has almost 100% specificity and 40% sensitivity. Testing for such a variant could reduce serious adverse events by 40% without any unnecessary and harmful dose modification.

Thus, rare variants with big effects may be more useful than common variants with small effect clinically. Common variants may provide important general insights.

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