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Review

On the use of pharmacogenetics in cancer treatment and clinical trials

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Abstract There are an increasing number of studies devoted to the identification of associations between anticancer drug efficacy and toxicity and common polymorphisms present in the patients' genome. However, many articles presenting the results of such studies do not bring the simple and necessary background information allowing the evaluation of the relevance of the study, its significance and its potential importance for patients' treatment. This position paper first addresses clinical oncologists with the aim of giving them the basic knowledge on pharmacogenetics and on the potential use of gene polymorphisms as predictive biomarkers in routine and clinical research. A secondary objective is to give molecular biologists some recommendations on how to conceive protocols and how to publish their results when they develop pharmacogenetic studies appended to clinical trials or with autonomous goals.

1. Introduction

The efficacy of anticancer drugs, including both 'classical' chemotherapy and targeted therapy, is highly variable among individuals: the best protocols, applied to sensitive cancers, barely provide more than 50% responses, except for certain tumours such as paediatric leukaemias or testicular cancer. This means that 50% of patients will receive a heavy, toxic and often expensive treatment without any benefit. This variability can be assigned to numerous host-related factors: age, sex, hepatic and renal functions, comorbidities and co-medications, etc. The prescription of anticancer drugs is thus often adapted as a function of patients' features. In addition, this variability is also dependent upon the structure and expression of tumour genes which play a role in drug response: target enzymes, proteins involved in DNA repair or cell signalling, oncogene or tumour suppressor gene products. The oncologist can

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rely upon numerous prognostic factors, extracted either from clinical data (tumour size, node invasion, performance status) or from pathological data (histoprognostic grading), but these factors, which are very useful to take therapeutic decisions, are often not predictive and not helpful for the choice of the best drug or the best drug combination, for a given patient, in order to achieve the highest probability of response. Using the individual genetic characteristics, such as gene polymorphisms, may help to predict drug efficacy and toxicity.

Gene polymorphisms consist of minor changes in DNA sequence: substitutions, deletions and insertions, repeats, gene copy number variations and sometimes more important rearrangements. They can modify the structure, expression, stability and activity of the proteins encoded by these genes. Pharmacogenetics intends to identify relationships between gene polymorphisms and drug activity (in terms of both efficacy and toxicity), with the aim of proposing a rational individual drug prescription. Personalisation of treatments is a requirement, which must take into account the individual patients' features as well as the particular tumours' features, which are of now of general use for the prescription of targeted therapies. The terms pharmacogenetics and pharmacogenomics tend to be used interchangeably, and a precise, consensus definition of either term remains equivocal. Pharmacogenetics focuses on the association of one gene or several genes with drug activity, while pharmacogenomics considers the whole genome, through the broader application of new genomic technologies. However, in oncology pharmacogenetics is often considered as concerning the individual patient's features and pharmacogenomics as those of the tumour.

2. Gene polymorphisms

2.1. Mutations and polymorphisms

Errors occurring during DNA replication or lesions induced by mutagenic agents may lead to the replacement of a nucleotide by another one (*substitution*), to the loss of a nucleotide (*deletion*) or to the addition of a nucleotide (*insertion*). When they occur within the coding sequence of a gene, the protein originating from this gene may bear a structural alteration which may lead to its instability, a decrease or increase in its activity or the loss of its functionality. Mutations can be classified as *synonymous* or *silent* when there is no change of the amino-acid encoded, *missense* when there is a replacement of the amino-acid by another one and non-sense when they lead to a truncated protein, because of the occurrence of a stop codon or of the alteration of a splicing site, giving rise to a truncated protein. Insertions and deletions alter the reading frame, therefore change the complete downstream sequence of the protein, and are generally non-sense mutations. When mutations occur within the gene regulatory regions, especially in the 3′ and 5′ untranslated regions (UTR), or in intronic sequences, they can lead to alterations in protein expression, which are generally less deleterious than mutations affecting protein sequence. Table 1 presents the main genome alterations.

The frequency of gene polymorphisms is not identical for all genes; while it is generally higher in introns than in exons. They lead to minor phenotypic variations and explain the individual differences, from eye's colour or visage shape to disease susceptibility or drug sensitivity: this is why they present a major interest for the clinician and the pharmacologist. Numerous polymorphisms involve only one nucleotide, by substitution, insertion or deletion: they are called *Single nucleotide polymorphisms* or SNPs. However, some polymorphisms are more complex: they concern the number of minisatellite or microsatellite repeats, often called VNTR (*Variable number of tandem repeats*), or even the number of copies of a gene (CNV, *Copy number variations*), which play a major role in the level of the mRNA and the protein produced.

Mutations by substitutions and SNPs are thus biochemically identical (replacement of a nucleotide by another one) but they have a different meaning: mutations are rare and deleterious events while SNPs are common and non-deleterious events. By convention, SNPs have an allele frequency higher than 1%, which corresponds to a proportion of 0.01% variant homozygous subjects. Like mutations, SNPs occurring within coding sequences may be silent, lead to a change in protein sequence or to a truncated protein. Similarly, in non-coding regions, SNPs may lead to alterations in the level of the protein encoded and, therefore, to important phenotypic variations.

The majority of the polymorphic genes are those whose function is not indispensable for the life of the cell or the organism. A polymorphism within a gene involved in cell reproduction, for instance, would lead to the rapid extinction of the cells that harbour this polymorphism and would be rapidly eliminated by natural selection. In contrast, genes involved in the metabolism of xenobiotics, drugs included or those involved in DNA repair, are often polymorphic because these polymorphisms have no major consequence upon cell viability and do not give rise to natural selection outside some special situations such as contact with xenobiotics or DNA damaging agents; as a consequence, they are not eliminated from the genome. In addition, one can consider that polymorphisms occurring within these genes allow some flexibility in front of environmental variations of xenobiotic exposure.

2.2. Nomenclature

It is sometimes difficult to find its way within the nomenclature of polymorphisms, because of the