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Mini Review

The Era of Pharmacogenomics

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Abstract

The sequencing of the complete human genome led to a before and after in medicine and, specifically, in oncological treatments. Nowadays, we are getting closer to what we call personalized medicine, where it is necessary to know the individual biochemical mechanisms of each patient. The future predicts a precision medicine based on markers of toxicity and pharmacogenomics.

Keywords: Pharmacogenomics; Biomarkers; Precision Medicine; Personalized Medicine

Abbreviations

6-MP: 6-Mercaptopurine; ABCB1: ATP-Binding Cassette Bus-Family B Member 1; ABBC4: ATP-Binding Cassette Sub-Family C Member 4; EGFR: Epidermal Growth Factor Receptor; IGSR: International Genome Sample Resource; ITPA: Inosine Triphosphate Pyrophosphatase; NTRK: Neurotrophic Receptor Tyrosine Kinase; TPMT: Thiopurine S-Methyltransferase.

Introduction

In the 60s, Yanase indicated for the first time the fact that different patients presented a different biochemistry, specifically in their response to anesthesia [1]. However, it was not until 2003, with the complete sequencing of the human genome that a series of changes occurred in the approach to diseases based on genomics [2]. The HapMap project, a catalog of common genetic variants of human DNA and of free access, was the next step [3]. In turn, it was quickly overshadowed by the current project 1000 Genomes of the IGSR where we can find not only variants in human DNA, but other information such as its frequencies and correlations in samples of populations from different parts of the world [4].

Biomarkers, pharmacogenomics and precision medicine

Currently, the use of biomarkers, pharmacogenomics and even the use of precision medicine seems even necessary in practically any pathology to obtain effective results in their treatment. Understanding that the response to medications is an individual response that depends on genetic and environmental factors, in addition to the interaction between them, is crucial nowadays to understand both the development of the disease and, mainly, its response to treatment [5].

However, before the complete sequencing of the genome, Jennings already conducted studies to show that the differences found in the metabolism of anticonvulsants were due to a specific polymorphism [6]. Other studies, also in the 1980s, studied the differences that patients presented in the metabolism of S conjugates of cysteine, related to the metabolism of many drugs, showing differences in the percentage of metabolites excreted between individuals [7]. These differences were related to an autosomal recessive inheritance, although environmental factors could not be ruled out [8]. However, T. J. Pallasch in his 1988 review, where he treated the different factors that could affect the metabolism of drugs [9], related these differences observed among patients with factors such as sex, body weight or age (factors that we now know can affect genetic through epigenetic processes). Other studies focused on adverse drug reactions due to hereditary differences in methylating enzymes [10].

The first study in which it was applied directly in carcinogenesis process was from Vetticaden (1989). In this study, polymorphism

directly associated with cytochrome P-450 variants, involved in drug metabolism was analyzed [11]. The conclusion was that certain variants are related to a higher incidence of cancer, mainly lung cancer [12]. But it was not until 2003, after the complete sequencing of the human genome when a pharmacogenomics application study was conducted in the treatment of cancer with 6-MP, which indicated a genetic deficiency of autosomal recessive inheritance in the activity of the thiopurine S- methyltransferase that made them more susceptible to drug toxicity [13].

Personalized Medicine in Oncology: past and future

Thanks to these early studies, patients now have access to important advances in the optimization of pharmacological treatment depending on the metabolic characteristics of the individual or the genetic characteristics of the tumor. Some examples of this in clinical practice are the study of the genotype of TPMT, ITPA, ABCC4 and ABCB1 related to the toxicity to mercaptopurine [14], analysis of genetic variants in the promoter region of the thymidylate synthase gene and its relationship with the response to treatment with 5-Fluoracil [15] or previous study of polymorphisms of the UDP-glucuronosyl transferase 1A1 gene in the treatment with inhibitors of EGFR receptors [16], among other examples.

Therefore, nowadays before performing a treatment with chemotherapy, it is necessary to study the genotype of the patient, so that the study of specific genotypes helps the clinician to make therapeutic decisions. For example, we know that mutations in the KRAS gene produce a low response to panitumumab or cetuximab in patients with colon cancer that patients suffering from lung cancer with mutations in the EGFR gene respond efficiently to treatment with Tarceva, among many others. An exhaustive study on this was carried out by Ong in 2012 [17]. The latest example is FDA's approval in 2018 of larotrectinib, indicated for any solid tumor with gene fusion of the receptor tyrosine kinase (NTRK) without known resistance mutation [18].

However, in the pharmacological response several genes usually intervene, so that more studies are needed in order to identify a greater number of regulatory genes for response to drugs and their interactions. This is being carried out successfully thanks to the development of bioinformatics and microarray technology, mainly in acute leukemia, B-cell lymphomas or breast cancer [19].

Conclusion

The personalization of oncological treatments thanks to pharmacogenetics analysis will continue to improve. It will increase the number of studies and clinical trials that relate the genetics of the individual and the tumor with the response to treatment and, with it, the number of clinical guidelines that use this information.

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Conflict of Interest

I declare no financial interest or conflict of interests exists.

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