Pharmacogenomics: Current Trends and Future Perspectives

Azra Ibrahimović(✉), Dalida Adilović, Lamija Brković, Nedžla Bučo, Amra Hadžagić, and Lana Popović

Students of Faculty of Pharmacy, University of Sarajevo, Sarajevo, Bosnia and Herzegovina
azraibrahimovic@ffsa.unsa.ba

Abstract. Pharmacogenetic research provides molecular diagnostic tools that can be used to optimize drug selection and dosage for individual patients. Many clinical trials of oncology drugs are now taken into consideration of pharmacogenomics, germline studies, or acquired genetic factors that determine drug response and toxicity. However, there is a lack of agreement on actual practice on where pharmacogenomic studies should be included in the oncological clinical course of drug development. This paper discusses the recent growth of pharmacogenomics in oncology clinical trials, especially in early-stage studies and several critical issues facing the incorporation of pharmacogenomics into the early development of oncology drugs.

Keywords: Pharmacogenomics · Pgx · Pharmacogenetics · Personalized medicine · Oncology medicine

1 Introduction

The modern way of life, globalization and digitalization have brought with them new improvements in the way of treating diseases. One of them is certainly pharmacogenomics, a branch of pharmacology that involves knowing the genome of each person who requires therapy. The goal of pharmacogenomics is to understand how an individual's genome determines the action of drugs in the body and the occurrence of frequent side effects. In short, pharmacogenomics assists the physician in prescribing the best possible therapy as well as drug dose, while reducing the risk of side effects and overdose as well as in preventing side effects caused by drug interactions.

The aim of this paper is to explain personalized medicine and benefits of this way of treatment, and importance of PGx methods in drug prescription for each individual patient. Finally, this paper focuses on current clinical practice of oncology pharmacogenomics and cancer drug development, as well as future prospectives of this method.

2 Pharmacogenomics in Individualized Cancer Therapy

One of the main components of personalized medicine, personalized care, is focused on the variable response to drugs in the forms of lack of response and adverse reaction,

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and the incentive to properly use medications. In view of these findings, the hypothesis proposed that one of the key causes was different genetic backgrounds among individuals, although environmental factors may also lead to various drug reactions. The discipline of pharmacogenetics has arisen as a branch of pharmacology to classify genetic variants from candidate genes linked to drug metabolism, transport or molecular targets/pathways in order to provide a deeper understanding of the relationship between human genetics and drug response. The word pharmacogenetics has progressively developed into pharmacogenomics since entering the postgenomic period in the new century as genome-wide integrative research has been increasingly used. In certain scenarios today, the two words are simply synonymous. Pharmacogenetics and pharmacogenomics are universally referred to as PGx.

So far, PGx consideration or package-insert labeling has been recommended by the US FDA for more than 120 drugs with relationships to more than 50 genes. These medications are widely used to treat cancers and respiratory infections and psychiatric disorders. It is clear that for the following reasons, PGx anti-cancer agents are one of the most actively researched fields. Next, chemotherapeutics are sometimes more severe and often more severe because of the limited therapeutic indices. Second, two related but separate genomic structures (tumor and germline genomes) that are specific to anticancer therapy need to be investigated to enhance drug effectiveness and minimize toxicity. Third, the pipelines for the production of anticancer agents have been very successful, contributing to many more drugs being put on the market or undergoing clinical trial assessments. In addition, if the package-insert label stipulates the use the beneficial effects of PGx may also be applied to Phase IV postmarketing trials.

2.1 Characterization of Heritability for Anticancer Agents

Generally speaking, either natural causes or environmental factors may be linked to the multiple opioid reactions [1]. It will also be important and essential to determine whether and how much genetics plays a role in variable drug responses before performing PGx discovery research. Heritability analyses may be used for this purpose to qualify and measure whether the drug reaction is a heritable trait. Either in twins or in large pedigrees, conventional heritability research is done. Measures of heritability will vary from 0 to 1, with nearly 0 showing that it is less likely to be a heritable trait, while nearly 1 suggests that genetics is responsible for most phenotypic variations.

It is impossible for anticancer agents to conduct heritability tests in humans, because the application of chemotherapy medications to noncancer relatives is illegal [2]. Study approach has also been based on conducting heritability experiments using resources obtained from human beings. Lymphoblastoid cell lines originating from large pedigrees, for example, have been used to study cisplatin and cytotoxicity caused by 5-fluorouracil (5-FU). More recently, Peters et al. performed a study of heritability among 29 Anticancer drugs approved by the FDA that use a total of 125 lymphoblastoid cell lines from 14 broad Caucasian pedigrees. At different therapy doses, cytotoxicity was calculated for each drug. For these 29 drugs, they found heritability ranging from 0.06 to 0.64, indicating the differing functions of genetics in the cellular reaction to anticancer agents. Nineteen out of 29 medications reported a median heritability of more than 0.3, indicating that biology contributed for more than 30% of the total variance in cytotoxicity,

which justified more PGx studies to classify genetic variations leading to these heritable characteristics [3].

3 Methods Used in Study PGx

3.1 Genetic Variants

In oncology, genetic modifications, all of which are targets of PGx studies, can be present either in the germline genome as germline alterations or in the tumor genome as somatic mutations. Any observable and heritable variance in the lineage of germ cells, such as genetic polymorphisms in genes that encode drug-metabolizing enzymes, is a germline variation; whereas somatic mutations are unintended modifications that can trigger cancer in a genomic sequence of DNA. Although drug efficacy and toxicity could theoretically be predicted by germline variants, somatic mutations are also used to refine chemotherapy agent selection to improve efficacy. SNPs, nucleotide addition, deletion, tandem repeat, copy number variation and chromosomal translocation are the genetic variations usually tested in PGx. Furthermore, gene expression in PGx is also widely examined for significance in tumorigenesis and reaction to chemotherapy. This term has now been formally adopted by the new FDA description of pharmacogenomics. The SNP is currently the most commonly studied genetic variant, thanks to the rapid technical advancement in the speed, coverage, precision and reduced cost of acquiring SNP genotypes. Their future practical importance also lies in the interest in researching SNPs. These variants may subsequently affect the transcription of genes, translation of genes and splicing of RNA, as well as cell stability of RNA. In a population in which each individual has his or her particular genetic make-up, all of which could contribute to variable drug responses.

3.2 PGx Discovery for Optimizing Anticancer Agents Usage

Advances in PGx have steadily begun to unveil the mystery of interindividual variations in drug responses in the past decade. A substantial number of the advances in the field of anticancer treatment have been made at present. A literature search on PGx in cancer therapy revealed a steady rise in publications in the past 10 years, in line with this pattern. In 2011, the publication figure is almost 2.5 times that of 10 years earlier. Ses PGx studies of anticancer agents have revealed several genetic variants for their possible role in tailoring individualized chemotherapy, or have pointed to certain unique chromosome loci. To date, the drug labels for 30 FDA-approved anticancer agents contain PGx data for 24 biomarkers. Such biomarkers include variations of genes, functional defects, changes in speech, chromosomal anomalies and others. Notice that some of these PGx markers, while others are tumor specific, are germline variants. Ses markers were interpreted differently in multiple parts of the FDA-approved drug labeling on the basis of the extent of support for clinical evidence.

Both PGx markers used in the drug box inserts are thus, of importance. Medical intervention should be taken for such markers suggested as ‘mandatory’ or ‘recommended’. With the accumulation of extra research data, these recommendations can change/evolve.

Improved effectiveness or decreased toxicity have been found when integrating these PGx markers into directing cancer chemotherapy. In addition, numerous credible studies have shown pharmaco-economic benefits.

4 Current Progress and Future Perspectives

The main goal of clinical medicine is to increase the therapeutic effect of drugs and decrease their toxicity level [4]. Pharmacogenomics is included more and more in drug development, because it allows targeting drugs in specific location, in individual patients. Currently, a lot of PGx studies are based on SNP, which, in the future, will provide drug prescription personalised for each patient [1]. Pharmacogenomic treatment approach in clinical practice is still not fully utilized, since there is not enough effective information about the benefits of this way of treatment. It is important to know, that besides the genome profile of individual patient, there are more thing to consider when defining convinient therapy, such as patients' age, gender, weight and also drug interactions.

In past years, a great progress has been made in the field of tumor biology, but also tumor development and response to treatment. Current gene-based PGx approaches face a lot of difficulties, since there is not enough reliable information about tumor drug response, as well as normal tissue toxicity, although there was considerable success where single genes play a big role in overall drug response [5, 6]. Ideally, a genome-wide studies should provide much better results and are the future of pharmacogenomic analysis [7]. Latest genome-wide studies show that new biomarkers are needed for possible future drug targets. Moreover, it is important that all new discoveries are later implemented in clinical practice and drug development.

In the end, pharmacogenomic approach to cancer treatment has full potential for personalising therapy for each patient, regarding optimal drug doses that will fully benefit individual patients as well as minimize the risk of toxicity. There is still a lot of economical, legal, ethical and clinical issues with pharmacogenomic approach to treatment, which need to be solved before PGx is completely incorporated in clinical practice [8]. Also, with technology development in the future, all researches will develope even more and the money needed to invest for those researches will be less with time.

5 Conclusion

Pharmacogenomics determines how your genes affect your body's response to drugs. This way of testing can help your doctor choose the right medicine for you as well as help the amount of medicine to suit your needs. Good communication between doctor and patient is extremely important, and the doctor will be able to determine your potential response to the drug based on gender, weight, age, diet, other medications and environmental factors, such as long-term exposure to cigarette smoke. Remember, your genetic code can also have a big impact on the reaction to a particular drug and its amount. In fact, genetic factors can affect up to 95% of the way you respond to medications.

In the future, large clinical trials will be needed to collect more information about the effectivnes of PGx treatment approach, but to this day a lot of positive effects are shown. One of the priorities for more and more clinicians to prepare and learn about

PGx testing and analyzing, since personalized medicine is indeed the future of health care. Finally, pharmacogenomics show great potential of revolutionzing personalized medicine, including cancer therapy, with the ability of increasing therapy efficiacy, and decreasing toxicity levels.

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