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Cancer Treatment and Pharmacogenomics

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ABSTRACT

In cancer, we cannot pick and trial medicines, we only choose medicines after doing genetic studies. Because due to metabolic deficiency, a drug can be toxic to someone. Just like the deficiency of glucose-6-phosphate dehydrogenase. In normal cases, its deficiency is not noticeable because its function is performed by any other enzyme in the body. But if a person with this deficiency takes anti-malarian or some kind of food, RBCs start to lyse, this can result in many complications like kidney failure. Also, this is the only pathway in humans to remove oxidative damage in red blood cells. If oxidative stress occurs in RBCs, oxidation of haemoglobin occurs which results in its functional loss and it attaches with the cell membrane or in the worst cases RBC lyse.

Keywords: Cancer, Pharmacology, RBCs, Toxic, Human.

INTRODUCTION

The combination of genomics (study of genetic makeover) and pharmacology (study of how a certain drug works) is known as pharmacogenomics. It involves the study of how a person`s response to a specific kind of drug can be altered by genes. By studying pharmacogenomics, we can safely give the best medication to the patient depending upon its genetic makeup [1-2]. The term pharmacogenomics was created in 1950 [3].

Concept about pharmacogenomics

First of all, we need to understand how medicine works. It goes into the cells and the cells can either give them out against the concentration gradient or can metabolize them. Most of the drugs are usually metabolizable which are metabolized in the liver and are then secreted. So, the metabolism rate differs in every person. This can be overcome by the use of pharmacogenomics which gives us an understanding about the concentration of a drug for a particular patient respective to its genetic makeup.

Importance of pharmacogenomics

The variation in the effect of drugs can be studied with the help of pharmacogenomics. The metabolism rate of every person differs due to genetic differences. This can be the result of high drug concentration

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for people with faster metabolism and low concentration for slow metabolizers because if they are given a higher dose it may cause severe effects. This is quite important to know for a doctor for prescribing antidepressants or chemotherapeutics [2].

In a protein, which interacts with the drug genetic variation can be present, so the drug`s impact can be changed because of this. Examples of these kinds of drugs include anti-psychotics and drugs for the cure of asthma. Thus, the importance of study of pharmacogenomics lays in the fact that drug selection, amount of dosage for different patients and little to no harmful effects of a medication can be improved [2].

Pharmacogenomics and cancer treatment

In cancer, we cannot pick and trial medicines, we only choose medicines after doing genetic studies. Because due to metabolic deficiency, a drug can be toxic to someone. Just like the deficiency of glucose-6-phosphate dehydrogenase. In normal cases, its deficiency is not noticeable because its function is performed by any other enzyme in the body. But if a person with this deficiency takes anti-malarian or some kind of food, RBCs start to lyse, this can result in many complications like kidney failure. Also, this is the only pathway in humans to remove oxidative damage in red blood cells. If oxidative stress occurs in RBCs, oxidation of haemoglobin occurs which results in its functional loss and it attaches with the cell membrane or in the worst cases RBC lyse [3].

Now, if we talk about the potency of a drug then a gram of medicine can be more potent than 50 grams of medicine.

Pharmacogenomics in cancer treatment is now used a lot for getting the maximum efficacy of a drug and at the same time minimizing its harmful effects. Cancer pharmacogenomics can be a great tool for identifying whether a drug can be toxic to a patient or if it can benefit the patient. The **differences between cancer pharmacogenomics and other diseases pharmacogenomics** are that for cancer drug testing, both germline genome (for inter-individual genetic alternations) and somatic genome (of the tumor for studying any changes that have occurred due to the tumor) are studied. For drug trials involving cancers, there is also a shortage of healthy volunteers willing for tests to be conducted on them [3].

How genes influence response to a medication

- Variation in the drug target.
- Variations in pharmacokinetics

Cytochrome P450 and cancer

Cytochrome P450 are the enzymes which are able to metabolize a lot of drugs (xenobiotics). They are also involved in the metabolic activation of cancer which is caused by the activation of pre-carcinogens. Also, the treatment of cancer has been possible because of these enzymes as they have the ability to activate as well as inactivate certain anti-cancer therapeutics. Cytochrome P450 is polymorphic, so researchers are studying the risk of different types of cancer because of different CYP alleles but some studies showed that cytochromes which are responsible for cancer formation are not polymorphic. But it has also been seen that the variability among individuals to metabolize a particular type of drug is because of polymorphic alleles which have variable functions [4].

The impact of pharmacogenomics on clinical practice

The following are the anti-cancer drugs for which clinical trials are very important to find out that whether a person is suitable for therapy or not;

- Tyrosine kinase inhibitors like imatinib and trastuzumab,
- Retinoic acid

Role of tyrosine kinase in cancer formation

The effect and function of tyrosine kinase in normal cells is regulated for metabolism, growth, differentiation. But their functions are transformed in cancer cells due to overexpression and mutations which lead to a malignant tumor. The activation of oncogenes can be stopped by the use of certain tyrosine kinase inhibitors [5].

There are different approaches for tyrosine kinase inhibition like,

- Monoclonal antibodies
- Small molecule inhibitors
- Heat shock proteins
- Antisense and peptide drugs
- Immuno-conjugates

Also, tyrosine kinase inhibitors can be used for angiogenesis (which is the cause of cancer cell proliferation and growth) [5].

Examples of anti-cancer drugs

IMATINIB

The pharmacogenomics of imatinib

A tyrosine kinase inhibitor, IM (imatinib mesylate) is one

of the first therapeutic to be used in clinics. Particularly, it is used for the treatment of chronic myeloid leukemia. It can also be used to treat cancer caused by tyrosine kinase as it has the ability to inactivate it. Some patients develop resistance to the drug while others show harmful side effects. The pharmacokinetics of this drug can be affected due to certain enzymes and transporters [6].

In some cancer patients, there is a chromosomal rearrangement. For example, if there is a gene ABL in one chromosome and BCR in the other. BCR is the breakpoint cluster region whereas ABL is the tyrosine kinase. Then the fusion of these will result in the formation of a fusion protein known as Philadelphia chromosome. The expression of this fusion protein causes cancer. This fusion protein is mostly found in leukemia cancer types. So, IM is used to treat this which results in the inhibition of the tyrosine kinase activity of fusion protein (BCR-ABL). IM will occupy the ATP-binding site of ABL kinase, this will help in the conformation of protein by preventing it to convert into an active molecule and the apoptosis of the cell is therefore caused by IM [6].

There are 3 main approaches to study the response of different patients to this treatment:

- The first one is the normal peripheral blood count from normal spleen which is otherwise known as complete hematological remission.
- The second one is the absence of Philadelphia chromosome in bone marrow which is otherwise known as complete cytogenetic response (CCyR).
- Major molecular response (MMR), is a 1000-fold reduction in fusion protein transcript levels in relation to a standard line.

Despite the usefulness of IM in the treatment of leukemia, some patients show zero response to the drug (e.g. there was not any achievement in CCyR at 18th month in about 25 % of the patients). Also, some patients developed resistance against the drug even though they performed very well in the first dosages (about 25%) [6].

Not only dosage errors could result in resistance, but there are also various other factors responsible for this, like:

- Alternations in the fusion protein
- Downstream pathways which are independent of the ABL-BCR fusion.
- The pharmacokinetic factors of the drug; like, absorption, distribution, metabolism and excretion) [6].

Fluorescence in situ hybridization is a technique that is used to determine the effects of imatinib on a patient.

In a normal interphase nucleus, there are isolates of ABL and BCR genes whereas the interphase nucleus of leukemia patients also contains the fusion of both of the genes.

TRASTUZUMAB

In breast cancers, HER2 (human epidermal growth factor receptor 2), which is a tyrosine kinase is overly expressed in ranges from about 25-30% breast cancers. It may be due to the amplification of gene.

TRASTUZUMAB is a humanized IgG1 monoclonal antibody used for human treatments. It is used to treat cancers where HER2 is overexpressed. It is given by intravenous infusion on a week or 3 week schedule [7].

The tests used for its study that whether it is suitable for a person or not include immunohistochemistry, FISH, and PCR based tests.

Recent studies have also proved it to be suitable for the treatment of HER2+ advanced gastric cancer. This type of drug is given in combination with chemotherapy. If the woman is post-menopausal then this drug should be given in combination with an aromatase inhibitor [7].

5-FLUOROURACIL

5-FU is used widely for the treatment of colorectal cancer. It is an anti-metabolite drug. It is thymidylate synthase (TS) inhibitor. It works by incorporating its metabolites into DNA and RNA. The anticancer activity of this drug can be increased with various methods like combination with leucovorin and methotrexate. The sensitivity of a tumor to the treatment against 5-FU can be determined with the help of certain molecular biomarkers and the expression levels of cancer causing TS enzyme. DNA microarray is widely used for the identification of new biomarkers in therapeutics and development of suitable drug combinations. The microarray of the genes which are responsive to the drug is done [8].

The other classes of chemotherapy agents (candidate genes) include thiopurines, irinotecan, platinum agents.

Economic evaluation of tests related to pharmacogenetics

After the complete sequencing of human genome, different tests have been conducted for treatment on the basis of genetic makeup which is an achievable goal. One of the important goal of pharmacogenomics is to deliver “personalized medicine” to patients considering the health

and safety of patient based on his genetic makeover.

Pharmacogenetics tests have the ability to;

- Observe the goal of outcome of medication
- Titrate the medication dose according to the metabolism of patients
- Observe the undesirable response to the medication
- Inform the novel therapeutics development [9].

Advantages of pharmacogenomics in cancer treatment

- The study of cancer pharmacogenomics will help in the identification of patients which can have a toxic side effect of the drug so that doctors must not give that drug to the patient. Also, it will tell us that the patient will benefit from certain type of drugs [3].
- It will also help in the determination of the metabolism rate of the patient so that doctors can be sure what concentration of the drug is suitable for the patient [3]. So, it helps in the understanding of individualized cancer therapy [3].

Disadvantages of cancer pharmacogenomics

- Development of drug resistance in patients [3].
- Side effects may sometimes be life threatening [3].
- Normal tissues can also get damaged due to modest tumor specificity of the drugs [3].

CONCLUSION

The treatment of cancer involves various chemotherapeutic agents which have a different levels of toxicities, so to revolutionize the treatment of cancer pharmacogenomics is the best study to be performed in order to prescribe a medication to the patient. Sometimes a single gene plays a role in the overall response to a drug, but pharmacogenomics covers the determination of the whole human genome for the therapy of cancer. Thus, this topic can be concluded as:

Pharmacogenomics is one of the best way to save a patient from the toxic side effects of an anti-cancer drug by understanding metabolic rate through genetic study of the patient. This method is useful unless or until the patient develops resistance against the drug, in that condition another drug is prescribed which again needs the use of pharmacogenomics for its prescription [3].

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