CHAPTER 3

Concepts of Anticancer Treatment and Pharmacogenomics in Cancer Treatments

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Abstract: Pharmacogenomics is considered to be the extension of the rapidly growing field of pharmacogenetics. Its aim is to determine the genetic roles for inter-individual variations in drug response. It has been applied to various existing chemotherapy treatments in an attempt to detect genetic factors that play a significant role in optimal chemotherapy drug selection, dosage, and duration of use. In addition, pharmacogenomics studies aim to clarify, predict, and detect safety, toxicity, and/or efficacy of chemotherapy. Moreover, it can be used in predict patients’ response to chemotherapy and to personalize chemotherapy treatment, thereby tailoring a patient’s treatment strategy on the basis of his or her genetic map. Therefore, pharmacogenomics will significantly improve the work of researchers, pharmacists, and physicians working on the discovery, synthesis, and development of novel chemotherapeutic treatments that depend on pharmacogenomic science and/or techniques.

Keywords: Cancer, cancer pharmacogenomics, chemotherapy, hematological tumors, personalizing chemotherapy treatment, pharmacogenetics, pharmacogenomics, solid tumors.

CANCER BACKGROUND

During this century, cancer has become one of the major causes of death and the mortality rate of cancer is expected to increase from the deaths caused by heart diseases. Many researchers have begun to use the term “lifetime risk for cancer” which refers to the time during which cancer will develop and progress and/or the time that the patient will die because of cancer. Cancer is not only a disease; it is a group involving about 100 related diseases. Cancer is characterized by two points. Firstly, cancer cells grow uncontrollably, and secondly the cancer cells metastasize migrating from the original site to different parts of the body. There

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are two types of tumors: malignant and benign cancer, the first type “is made up of cells that grow out of control, and can be spread all over the body, and can only be treated with chemotherapy or gene therapy. While, the second type, is a mass of cells can often be removed with surgery or radiation as it is localized, and in most cases they do not come back”. Cancer can attack any individual and the rate of its occurrence increases as the individual ages [1-5]. “There are many problems (i.e., side effects) associated with cancer diseases, whether solid or hematological, such as nausea, vomiting, diarrhea, constipation, hypercalcemia, pain, loss of appetite, anemia, fatigue, cachexia, leucopenia, neutropenia and thrombocytopenia. However, the major problems are nausea and vomiting, neutropenia, anemia, thrombocytopenia and hypercalcemia”. Hence cancer is a major disease that affects quality of life [3, 6-9].

**CHEMOTHERAPY TREATMENT BACKGROUND**

“Chemotherapy has been developed during World War II out of the chemical weapons program of the United States of America. Since then chemotherapy has become one of the most important and significant treatments of cancer” [3, 10-13]. It works by eradicating the cancer cells, which are characterized by their high multiplication and growth rate. It also kills all the cancer cells that had broken off from the main tumor and spread to the blood or lymphatic system or any other part of the body. Chemotherapy kills either by “a direct effect on deoxyribonucleic acid (DNA) i.e., leads to disruption of DNA function, or interfere with the availability of normal purine, or pyrimidine nucleotide precursors or by covalent binding to nucleophilic groups on various cell constituents i.e., alkylation of DNA, or effecting on the factors involved in mitosis by the inhibition of its synthesis, production, or use” [3, 10-13]. Chemotherapy drugs may lead to a complete cure for some types of cancers; they may also suppress the growth of others, or may prevent their spread to other parts of the body. Many types of new therapies have emerged over the past 20 years. Some of them were straightforward, effective, and safe and some have many side effects. “However, when comparing chemotherapy with other types of treatments, it remains on a potentially high risk because of the side effects that are difficult to manage. Chemotherapy requires the involvement of various clinical professionals during the various stages of administration and results in significant patient care to overcome the side effects” [3, 10, 14-19].
CHEMOTHERAPY DISCOVERY AND DEVELOPMENT

During this century, both the discovery and development of cancer treatments are considered competitive issues because not only are many famous pharmaceutical companies doing such research but also several small companies. Moreover, some non-governmental and non-profit government organizations - for example: the National Cancer Institute (NCI), the European Organization for Research and Cancer Treatment (EORTC), and the British Cancer Research Campaign (CRC), are all making efforts in this field. The main is to produce a novel anticancer treatment therapy [20, 21].

Nevertheless, the discovery of new anticancer treatments can take place through detecting a new cytotoxic material or compound. But until now, development and progress in cancer treatment are restricted by detecting the unique biochemical aspects specific to tumor disease. These biochemical aspects can be used to selectively target tumor cells [12].

In the past hundred years, there has been significant progress in the field of molecular sciences, wherein genomics and proteomics have led to the production of various effective and novel drug targets. All of them led to significant alteration in the pattern of anticancer drug research and action strategies, i.e., molecularly targeted therapeutics [21-24].

In spite of all these recent technological developments, the discovery and synthesis of anticancer treatments remain a challenge for scientists and researchers. Because of these various challenges, difficulties and revelations can be found and/or expected at each step of the anticancer drug development process [21, 25].

The process of discovering and developing new anticancer treatments includes the following stages:

A. Acquisition of a potential compound: This step can be approached by either synthesis of a new chemical compound or by extracting one from natural sources such as plants, herbs, the marine world, venoms and toxins, or microbes. The cornerstone for this stage is the development of specific analytical processes in order to emphasize and detect the identity and purity of these compounds and to specify their stability under various circumstances that include real-life and harsh storage-conditions. Moreover, this step also includes the identification of the physiochemical properties of
the extracted or synthesized compound. These properties include the solid-state form, the melting point, the solubility, and the stability [21].

B. Drug screening and pre-clinical pharmacology: This step will mainly focus on the identification of drug potential activity, stability, toxicity, degradation pathway, metabolic routes, and many other points. This can be done through comparing the drug’s structure to that of existing compounds in the database [21, 26]. Pre-clinical screening includes testing drug anti-tumor activity by using cell culture models, followed by evaluation of its efficacy and toxicity in animal models.

C. Clinical development: This step includes various phases. Phase I involves identification of drug toxicity and the maximum tolerated dose (MTD) among human volunteers. Phase II focuses on the detection of efficacy and dosages, carried out among patients of the selected tumor type. Then comes phase III, which includes comparing the results between groups of people who received the new anticancer treatment with those who received the standard chemotherapy treatment i.e., which group has better survival rates or lower incidence of side effects [21, 26-29].

**IS ANTICANCER DRUG THERAPY DEVELOPMENT HEADING IN THE CORRECT DIRECTION?**

Since 2009 till date, all the results show a slowing down in the process of developing new anticancer therapies, because only a few anticancer agents have been approved, and the majority of these agents were either antibodies or do not belong to new directions in anticancer drug development [30].

Moreover, during this century, economic reality has meant that the drug (s) developed are characterized by their safety, effectiveness, and suitability for the largest patient populations. Drug companies must recoup the cost of development by sufficient profits [31].

As a result of the abundant availability of highly improved pharmacogenomics and pharmacogenetic facilities, economic realities have become more fragmented. Moreover, these technologies i.e., pharmacogenomics and pharmacogenetic technologies will lead to the production of drugs to use on a limited number of patients, i.e., orphan drugs [31].
In this situation, we are obliged to re-check whether the strategies and techniques we follow will lead to the development of new, effective and economic anticancer therapies [30, 31].

**PHARMACOGENETICS**

The branch of science that specifically focuses on understanding how the unique genetic composition of each human playing significant roles in varying both the pharmacokinetic and pharmacodynamic response of each patient towards a specific drug [31, 32].

In another definition, it is the branch of science that examines the mutual effect of how a drug behavior varies in response to human genome. These behaviors include various factors such as genetic (transcriptional, translation, polymorphisms) and epigenetic (environmental) significantly related to the drug’s pharmacological efficacy and toxicity.

Besides that, “pharmacogenomics is also referred to as toxogenomics, which is a branch of science considered to be more mature than pharmacogenetics and pharmacogenomics, because it includes various factors in its possibilities for alteration of drug action. These factors are genetics, pharmacology, and biochemistry”. While, “pharmacogenetic science only focuses on the impact of genetic variation on the drug’s pharmacological action, pharmacogenomics extends pharmacogenetics by focusing on various genetic factors and environmental variations in explaining alteration in drug action” [33, 34]. Therefore, the understanding of these complex interactions and detection for significant role played by genes are developed via analysis of gene interrogation algorithms.

This process, i.e., pharmacogenomics has given a positive motivation to the application of this effective branch of science as a means of personalizing chemotherapy or treatment to a group of population or individual [34]. Recently, the remarkable progress of molecular genetics and the expanding development of genomic technologies have made it possible matter to detect the impact of a patient’s genetic variation on pharmacological drug efficacy [31, 35-41].

**PHARMACOGENOMICS**

Pharmacogenomics is considered to be either the recent offspring of pharmacogenetics or an extension of pharmacogenetics. It is the branch of science that works hard to detect genetic variants that significantly affect drug response,
in order to tailor a patient’s therapy based on his or her genetic map. Besides that, researchers in this science are working on gaining a better understanding of the complicated relationship that exists between drug and gene, because there is a chance that genes do not only affect drug action, but drugs may affect gene function too [33, 42]. In fact, clinical trials can provide significant, though limited, information related to the average response of drug therapies at a standard doses in relatively small and specific populations. When applying a drug at the same dose to a large patient population, results show variations in therapeutic response among patients; for example, a group of patients shows a significant therapeutic response, while other groups show either no therapeutic response or develop serious adverse drug reactions (ADRs) [33, 42]. These variations can lead to significantly expensive and potentially life-threatening consequences. Therefore, these days, detecting reasons for and/or overcoming these variations is an urgent matter. Moreover, significant variations in drug efficacy, response and adverse drug reactions among patients are considered to be the cornerstone of determining the clinical use, regulation, or withdrawal from market of clinical drugs and a bottleneck in the development of new therapeutic agents [33, 42].

THE MAIN AIMS OF PHARMACOGENOMICS

The First Aim: Personalizing Medicine

Many scientists and researchers believe that adverse drug reactions and/or therapy failure will be erased by the introduction of personalized medicine, i.e., the administration of a medication will be based mainly on a patient’s genes. This can be attained by determining the genetic variations that can alter drug action. The predominant occurring genetic variations are single-nucleotide polymorphisms (SNPs), and the average of their incidence is 1 per 1000 bases. Thus, they cause genetic variation of many human proteins [33, 43, 44]. These SNPs play a critical role in personalized medicine studies because they make a significant difference between individuals. So by correlating SNPs and drug response data, researchers will be able to predict drug efficacy and toxicity within acceptable limits for each individual [33, 45]. In addition, biomarkers can also play a role in personalizing medicine, but, as a result of their variety, their study or identification requires various kinds of investigation [42, 46, 47].

The Second Aim: Drugs Affecting Gene Expression

Gene expression mainly depends on the amount of RNA produced by DNA conversion, so any variation in the amount of RNA, will result in significant
functional variation of the gene, translated in terms of genes expression. The
discovery of gene expression has changed our concepts related to genetics,
because recently it has become obvious that gene interaction may mean that one
gene affects the expression and functions of other genes [48, 49].

Moreover, various other factors such as hormones, disease, food, or drugs, can
also play major roles in altering gene expression. Therefore, researchers do not
know whether the drug action is the result of the drug affecting a protein or gene,
so this point can be explained or clarified by using gene expression changes [33,
50].

The Third Aim: Detection of New Targets for Future Drugs

The main causes of common diseases include the combined action of several
genes and/or environmental factors. Therefore, genomic methods that focus on
various genes can significantly help in detecting a gene that is mainly related to a
disease. A researcher can design or synthesize a chemical that can target or attack
that gene or its protein products. Later on this chemical can be used as a drug that
may help to overcome the disease. This type of research is classified or called a
search for “druggable targets”. Therefore, it becomes obvious that genomic
studies can significantly lead to novel medical therapies [33].

Because the set of genes responsible for a specific disease may vary from human
to human, druggable targets will not be exactly the same in various subjects. As a
result of that, this hypothesis is not classical pharmacogenetics, but it can explain
why a given drug may cure the disease among some people but not in others. So
genomic studies that can predict which person can benefit from the drug are a part
of personalized medicine [33].

By comparing genes in the presence and in the absence of a disease, researchers
can detect which genes are affected by the disease or which genes play a vital role
in causing the disease. Also, in exceptional cases, researchers can compare gene
expression among people before and after the onset of the disease, or by
comparing groups of healthy and diseased people to detect variations in gene
expression that are not related to the disease [33].

Therefore, pharmacogenomics is the branch of science that focuses on the ways
genetics and pharmacology can interact, to solve some difficulties, and to produce
and use various facts to improve medicine and thereby to help all human beings.
CANCER PHARMACOGENOMICS

The main aim of cancer pharmacogenomics is to make full use of patients’ genetic profiles to predict and clarify cancer patients’ responses towards chemotherapy, detect chemotherapy toxicity and discover and develop a novel anticancer treatment(s). This approach has the potential to revolutionize the use of various types of chemotherapeutics treatments, because oncology is considered as one of the most challenging fields of medicine. Despite the encouraging results obtained from the application of pharmacogenomics in oncology, personalizing cancer therapy is still exclusive to a limited number of drugs based on specific genes. Moreover, the results of some medical studies have shown negative correlation between clinical outcomes and the genotyping of cancer patients [51, 52]. Therefore, improvements within pharmacogenomic analyzing techniques have become obligatory for the personalization of cancer chemotherapy and discovering new therapies [51].

GENERAL CONSIDERATION IN CANCER PHARMACOGENOMICS

Pharmacokinetics in Cancer Pharmacogenomic Drug Metabolism

Pharmacokinetic is the disposition of drugs in human body, *i.e.*, drug transport and metabolism, so any change(s) that takes place in these activities will mainly cause an alteration in drug action. Therefore, pharmacokinetic consideration in pharmacogenomics is valuable because it can help in understanding the relationship between genetic polymorphism and alteration in drug action, *i.e.*, incidence of adverse drug reactions. Moreover, pharmacokinetic importance comes from its significant role in drug inactivation, excretion, and activation of pro-drugs (*e.g.*, the metabolism of cyclophosphamide to its active metabolite 4-hydroxycyclophosphamide) [53].

There are various enzymes that take part in the metabolism of chemotherapy drugs. These enzymes can result either in the activation (toxication) or deactivation (detoxication) of the chemotherapy drug. “Broadly, drug-metabolizing enzymes are divided into two categories: Phase I (functionalizing) enzymes and Phase II (conjugating) enzymes” [53-56].

**Phase I Enzymes**

“One of these major and most potent families of metabolic enzymes is the cytochrome P450 (CYP 450). CYP is the most vital enzymatic system concerned
with drug metabolism. Approximately 65% of common drugs used are metabolized by cytochrome P450 enzymes and half of them are mediated by the CYP3A subfamily” [54]. “The CYP3A subfamily consists of four members: CYP3A4, CYP3A5, CYP3A7 and CYP3A47, and represents about 30% of the total CYP in the human liver. The most superior subfamily among the four types that plays the major role in metabolism of more than 60% of all drugs used in humans is CYP3A4” [54]. “Miscellaneous CYP3A4 alleles in the population may partake in interindividual variability in CYP3A4 activity” [54]. As a result of that the metabolic profile for various CYP3A4 alleles has been classified into multiple classes of poor, intermediate, extensive, and ultra-rapid metabolizers. Moreover, these different genetic polymorphisms play a significant role in cancer pharmacogenomics [53].

Unlike other CYPs, CYP2D6 is not inducible; as a result, the main factor that alters enzyme expression and the activity of this enzyme is genetic polymorphism. To date there are more than 63 functional variants, i.e., alleles, that have been identified for CYP2D6. Therefore it is considered to be the most highly polymorphic enzyme. “These variants lead to abolished, decreased, normal, or ultra-rapid CYP2D6 enzyme activity. Both CYP2D6*4 (splicing defect) and CYP2D6*5 (gene deletion) are the most important null alleles, while, CYP2D6*10, *17 and *41 work on to severely reduce CYP2D6 enzyme activity. On other hand, ultra-rapid enzyme activity is mainly caused by the duplication or multiplication of active CYP2D6 genes” [34, 55, 56].

Both CYP2C9 and CYP2C19 genes are considered to be the most homologous at nucleotide level. Both “CYP2C9*2 and *3 are considered to be the most common nonsynonymous CYP2C9 polymorphisms that cause significant alteration in CYP2C9 enzyme affinity for clearing various substrates. While, for CYP2C19 enzyme, CYP2C19*2 and *3 are considered as the most null alleles, genetic polymorphisms in CYP2C19 have a significant effect on pharmacokinetics and/or action of various classes of drugs, specifically proton pump inhibitors (omeprazole) and barbiturates” [34, 56].

**Phase II Enzymes**

Among this group, the most important phase II enzymes that are highly suggested to suffer from genetic polymorphism are “uridine diphosphate glucuronosyl-transferase (UGT), sulfotransferase (SULT), and glutathione methyltransferase (TPMT)” [56]. Genetic variations that take place in these enzymes will mainly cause
differential susceptibility to diseases like cancers and directly affect pharmacokinetics and the clinical outcome of substrate drugs [34, 57-60].

Pharmacodynamics in Cancer Pharmacogenomics-Drug Targets

In order for a drug to exert its pharmacological action, it has to be bound to a specific molecular component of a cell, i.e., drug target. When the drug molecule binds to its binding site found on the cell, this will mainly lead to educe the required therapeutic action from the targeted cell. The majority of drugs targets are proteins i.e., genes, so any genetic polymorphism that takes place within these genes will lead considerably to an alteration or variation in the efficacy of drug action.

Therefore the application of these approaches, i.e., pharmacodynamics in cancer pharmacogenomics among cancer patients treated with chemotherapy, will significantly enhance our understanding of how genetic variations that have taken place in the specified drug target gene will lead to different drug action between individuals [53, 61].

An example of the application of pharmacodynamics in cancer pharmacogenomics includes the genetic variation in thymidylate synthase (TYMS), which might affect the action of 5-FU and/or methotrexate [62, 63]. Various studies, have failed to explain the variation in drug action mainly based on or caused by specific gene variation. But several meaningful and unexpected results obtained from genome-wide association studies (GWAS) related with individual differences in drug action. These studies focus on the association between variation in drug action with genetic variation without selecting a specific gene or genes. Thus, it is not necessary for associated studies that focus on detecting variation in drug action based on genetic variation to follow the sensibility of the unexpected pharmacodynamics considerations in cancer pharmacodynamics studies [53].

Drug Transports Pumps (Drug Efflux Pumps)

These transport pumps transport the drug molecules across the cell membrane, i.e., the transfer of molecules into (uptakes pumps) and out (efflux pumps). Moreover these pumps play a major in pharmacokinetics and/or the pharmacodynamics of cancer pharmacogenomics, since these pumps control the transfer of various molecules, ranging from sodium ions (small molecules) to docetaxel anticancer treatment (large molecules) [53, 63]. There are more than
200 transporters found in various cell types. These pumps are classified into various families depending on their activity and the similarity of encoded proteins. Among these families, efflux pumps play the most critical role in cancer therapies, because these pumps remove chemotherapy from the inside of the cancer cell, preventing chemotherapy treatments from reaching their targets. As a result, drug efflux pumps play a critical role regarding pharmacodynamic and pharmacokinetic consideration in cancer pharmacogenomics. The most important examples of these efflux pumps directly related with chemotherapy treatments actions are mitoxantrone resistance protein (MXR) and P-glycoprotein or multidrug resistance protein (MDR 1) [53, 63].

**Mitoxantrone Resistance Protein (MXR)**

This MXR or ABCG2 protein is considered to be a member of the G subfamily of ATP-binding cassette. It can also be considered to be the breast cancer resistance protein. Its major function is to act as a basic physiological barrier protecting tissues against the toxicity of the environment and/or clinically administrated treatments. Besides that, it works as an efflux transporter that plays a critical role in conferring resistance to some vital classes of chemotherapeutic treatments such as anthracyclines, anthracenediones, and camptothecins. This protein has been considered as a cornerstone of therapeutic resistance in acute myelogenous leukemia and breast cancer. Moreover, various forms of MXR have been detected. Further clinical and genetic studies are required to determine the crucial role these MXR various forms play on the pharmacological effect of chemotherapy treatments [64-66].

**Multiple Drug Resistance 1 (P-Glycoprotein)**

The most vital point that limits the pharmacological benefit of chemotherapeutic therapies in treating cancer is the development of cancer cell resistance. These resistances can take place through various mechanisms and ways. One of most critical ways is genetic mutation in P-glycoprotein.

P-glycoprotein is one of the ABC transporter proteins consisting of two homologous parts. Each part is mainly composed of six trans-membrane domains and an ATP-binding domain. Both are separated by a flexible linker region. Examples of the drugs that might be pumped from cells by this protein are anthracyclines, calcium channel blockers, digoxin, vinca alkaloids, and paclitaxel.
The first time this protein was detected in a cancer cell was as an overexpressed protein and is considered as another cornerstone in cancer cells’ resistance to chemotherapy treatments [65, 67].

Various genetic mutations related to this protein have been detected, but only few will have a significant effect on P-glycoprotein pump efflux action. The deletion of the central core of the linker region of this protein will mainly produce mutant protein, which is nearly identical to wild protein but is not functional for transport and/or drug-stimulate ATPase activity [65, 68, 69]. Other mutations that significantly affect P-protein expression are C3435T and the homozygous T form of glycoprotein. This will mainly lead to a direct effect on drug plasma protein levels. Therefore, P-glycoprotein genetic variations have a significant effect on the pharmacokinetic properties of administered drugs. Even so, until today, modification or alteration of chemotherapy treatment regimens based on P-glycoprotein genetic variation has yet to be successful [53, 65, 70].

INCIDENCE OF GENETIC VARIATION IN THE MIDDLE OF CANCER PROGRESSION

Hematological Tumors

This group of malignancies affects the blood-forming cells. They vary significantly from solid tumors in various aspects, specifically the chemotherapy regimens used to treat them. Several of those malignancies are characterized by the movement of gene fragments from one chromosomal location to another. This gene movement or translocation plays a critical role in the progress and maintenance of these cancer phenotypes. Moreover, these genes translocations have been significantly related with the incidence of crucial cancer disease [71]. In various cases, the gene product related with these gene movements has been used as a therapeutic target. Examples of these cancers are as follows:

**Acute Lymphoblastic Leukemia (ALL)**

This type of cancer is predominantly found among children. Various genetic alterations have been used as biomarkers for disease prognosis. “These gene translocations were detected cytogenetically. Examples of these genes translocations are t(12; 21)(p13; q22), t(1; 19)(q23; p13), t(9; 22)(q34; q11), t(4; 11)(q21; q23), t(8; 14)(q24; q32) and t(11; 14)(p13; q11)” [71]. Some of these gene translocations are associated with a good prognosis; others are related with a negative prognosis. Moreover, the identification of some of these genetic
variations is a complicated process, and some of those ALL patients suffer from chemotherapy treatment failure or chemotherapy crucial side effects, or may show cancer disease relapse [71].

As a result of application of pharmacogenomic techniques in the last four decades in the development of 6-mercaptopurine and methotrexate chemotherapy treatment, a significant progress in ALL treatment has been noticed. Just like the genetic variations in thiopurine S-methyltransferase (TMPT) and thymidylate synthesis (TYMS), which will be clarified later in this chapter, will play a significant role in the incidence of 6-mercaptopurine and methotrexate crucial side effects among cancer patients carrying less active variants of these genes [53].

**Acute Myeloid Leukemia (AML)**

This cancer is more common than ALL and is predominantly found among adults rather than children. It classified as a heterogeneous group of leukemia. The clonal transformation of hematopoietic precursors is considered to be the main risk factor responsible for AML incidence. This transformation takes place via two major mechanisms that multiply genetic polymorphism and the earning of chromosomal rearrangements *i.e.*, gene deletion or duplication or inversion or translocation [72]. Other prognostic factors for AML besides cytogenetic considerations are the patient’s former history, age and dysplastic features.

Just like other types of leukemia, the incidence of AML is associated with genetic mutations; almost a third of the AML patients carry genetic polymorphisms in their fms-like tyrosine kinase 3 (*FLT3*) gene. These mutations will mainly include both internal tandem duplications and point mutations that lead to a consecutively active receptor. When these mutations are present among AML patients, the chance of AML relapses with the use of conventional chemotherapies will be high. As a consequence both FLT3 inhibitors and antibodies have been designed and developed in clinical trials for AML treatment [73].

Other AML subtype such as acute promyelocytic leukemia (APL) is cytogenetically classified based on even reciprocal translocation between the non-homologous chromosomes 15 and 17. This process will mainly lead to fusion between two genes: the promyelocytic leukemia gene and the retinoic acid receptor alpha gene. Clinically, it has been found that the complete remission rate for APL has been significantly increased from when all-trans retinoic acid (ATRA) was applied as the treatment of APL because this treatment works as a
differentiation agent. However, genetic variation in CYP2D6 enzyme that plays a major role in retinoic acid metabolism, probably has a direct influence in relapse after ATRA treatment [74].

**Chronic Lymphocytic Leukemia (CLL)**

This type of leukemia is considered to be the predominant type found among adults over 65 years of age. It is a blood cancer that affects B-lymphocytes. The main characteristic associated with CLL is the accumulation of CD5-positive monoclonal B cells in different places: the peripheral blood, primary and secondary lymphoid tissues and bone marrow. Clinically, for an accurate diagnosis of CLL, more than $5 \times 10^9/L$ monoclonal CD5-positive B lymphocytes must be detected in peripheral blood, and these monoclonal lymphocytosis cells must last for at least three months [75, 76]. Karyotypic investigations clarified the association of various genetic mutations with CLL incidence, such as 11q22-q23 deletions. “Trisomy 12q13 occurs in 15% of CLL cases. 6q21 deletions, del17p13 is found in 5-10% of CLL cases”. The most common genetic mutation is 13q14 deletions found in 50-60% of cases. These genetic mutations will significantly confer resistance to chemotherapy and/or lose their therapeutic targets [53, 75-77].

**Chronic Myelogenous Leukemia (CML)**

It represents the first type of leukemia that had been described in 1845 by Edinburgh. Clinically CML is a myeloproliferative neoplasm that is created in pluripotent hematopoietic stem cells. These hematopoietic stem cells are characterized by their high proliferation rate and failure of apoptosis process (prolong life span) [78, 79]. The signs and symptoms of CML patients include anemia, splenomegaly and leukocytosis [78]. This disease is cytogenetically classified by a reciprocal chromosomal translocation between chromosomes 9 and 22. This process mainly includes fusion of “Abelson murine leukemia viral oncogene homolog 1 ABL proto-oncogene from chromosome 9 with the breakpoint cluster region BCR of chromosome 22”, i.e., BCR-ABL oncogenic fusion gene [53, 80, 81]. The result of this chromosomal translocation or fusion process is known as the Philadelphia (Ph) chromosome [53, 80, 81]. Besides that, this chromosomal translocation will significantly alter the regulation of ABL expression and this will mainly lead to oncogenic character. Moreover, the ABL is protein which is characterized by its tyrosine kinase ability that alters cell cycle regulation. A great advancement in CML treatment took place with the discovery
of a selective tyrosine kinase inhibitor, i.e., imatinib. This success combined with the use of imatinib treatment has motivated researchers to discover other tyrosine kinase inhibitors used for cancer treatment, including selective, specific, and advanced agents for the treatment of CML. Therefore, imatinib is considered as an example of rational drug design [82, 83].

**Solid Tumors**

**Breast Cancer**

Today breast cancer represents a critical challenge and is one of the most predominant forms of cancer with an incidence of more than 1,000,000 new cases and 370,000 deaths per year in the whole world. Ten percent of these breast cancer patients suffer from genetic mutation in both *BRCA1* and *BRA2*, but the likelihood of breast cancer incidence with *BRCA1* mutation carriers is higher compared to *BRCA2* mutation carriers [53, 84, 85]. Moreover, women in their forties and carrying a *BRCA* mutation have a 20% greater chance of developing breast cancer than those who do not carry a *BRCA* mutation. This chance will increase as their age increases. The risk increases to 37% by age 50 years old, 55% by the age of 60 years old, and so on [85]. The risk of breast cancer in a woman’s lifetime is 1 in 8 individuals, while for those who carry *BRCA1* and *BRA2* mutation the lifetime risk is 45-80% [85].

Besides that, *BRCA1* mutation carriers more often show negative estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) compared to their other coequal. While, *BRCA2* mutation carriers only show more ER positive than their coequal, but no variations in their PR and HER2 positivity levels have been found to compare with their other counterparts [85].

Byrski et al. (2010) found that the rate of pathologic complete response (pCR) of breast cancer patients who carry the *BRCA1* mutation to neoadjuvant chemotherapy varies according to the type of chemotherapy regimen used. Their results show that pCR for breast cancer patients who are treated with doxorubicin and docetaxel (AT) or cyclophosphamide, methotrexate, and fluorouracil (CMF) is low. While the pCR value found to be moderate for those who received both doxorubicin and cyclophosphamide (AC), or fluorouracil, doxorubicin, and cyclophosphamide (FAC). The pCR rate was high for those patients treated with cisplatin [86].
Genetic variation among breast cancer patients was found to play a critical role in disease pathogenesis. For example, HER2 (ErbB2) protein over-expression in breast cancer leads to a poor prognosis. Therefore, it has become necessary to detect the ErbB2 level to optimize therapies for breast cancer using monoclonal antibody therapies, e.g., trastuzumab [53]. Even so, the majority of oncologists do not utilize genetic mutation status BRCA1 and BRA2 mutation to guide chemotherapy, since a lot of emerging data confirm that breast cancer mutation carriers will show more varied pharmacological responses to specific chemotherapy than non-mutations carriers. Besides, selection and optimization of chemotherapy treatment for women with BRCA mutation is considered a critical matter [53, 86-88].

**Colorectal Cancer**

Colorectal cancer is considered to be the most widely found cancer type in the whole world with approximately 1.2 million new cases diagnosed yearly, and mortality rate is over 600,000 cases per year (about 8-9% of all cancer deaths). Besides, it is the fourth most widespread type of cancer among men and the third among women [89, 90]. Moreover, colorectal cancer is becoming a critical problem in many countries in Asia such as China, Japan, Korea and Singapore, but the highest rate of its incidence still in the western world in highly developing countries such as USA, Canada, Australia, UK, and some European countries [89, 90].

Genetic mutations associated with the progress of colorectal cancer have been widely studied, such as the mutations in the Kirsten rat sarcoma viral oncogene homolog (KRAS) gene, which is found in 40% of primary stages of colorectal cancer progression. The presence of an active mutation, *i.e.*, the KRAS gene among colorectal cancer patients, can be significantly correlated with an alteration in the pharmacological action of Epidermal Growth Factor Receptor (EGFR) antibody therapies such as cetuximab and Panitumumab. These EGFR-antibodies have been used effectively in the treatment of advanced colorectal cancer [53, 91-93].

Lievre and his colleagues conducted a study in the United States in which eighty-nine patients suffering from advanced colorectal cancer (CRC) were treated with cetuximab after failure with ironotican-based chemotherapy. Twenty-four of them carry the KRAS gene mutation, and 65 were non-mutated. The results clarify that mutated patients, *i.e.*, the 24 patients, showed negative response, *i.e.*, lack of
response to EGRF antibody therapy (cetuximab) and poor progression-free survival (PFS), and overall survival (OS), whereas 40% of the 65 non-mutated showed a significant pharmacological response after the administration of cetuximab. They responded and showed significantly longer progression-free survival (PFS), and overall survival (OS) than mutated patients [94].

These results, besides the results obtained from previous studies oblige researchers, clinicians and physicians to consider KRAS gene mutation in selecting treatment for advanced colorectal cancers [53, 91, 94].

Prostate Cancer

There are two major types of prostate cancer, familial and sporadic. Clinically it is a heterogeneous disease. Every year more than 900,000 cases are diagnosed. Although, it is frequently found as an indolent disease, it is still considered the sixth predominant cause of male cancer death around the world (responsible for 29% of all male cancer deaths 250,000 deaths per year), the second in the United States and the third in the European Union. This cancer disease targets a lot of men in the West but its incidence is very low among men in Japan and China [95-98]. Prostate cancer responses to applied therapy will significantly vary depend on its status, i.e., whether it is localized or has metastasized. In case of metastasized disease, 70 to 80% of the patients respond initially to androgen-deprivation therapy, but in later advance stages prostate cancer converts to hormone refractory and becomes very aggressive, which will mainly lead to a poor prognosis. Localized prostate cancer, can be treated by various therapies and ways [97].

The primary risk factors that are significantly associated with prostate cancer incidence are age, family history of prostate cancer, ethnicity, and genetic mutations that are considered to be the major causes for prostate cancer incidence [98, 99]. Moreover, it has been found that prostate cancer is frequently aggregate with other types of tumors, specifically breast and ovarian cancers. Various genetic mutations that are considered major risk factors in breast and ovarian cancer incidence such as BRCA1, BRCA2, CHEK2 and BRIP1, have subsequently been shown to increase the risk of prostate cancer incidence as well [98, 100].

Prostate cancer and various other solid cancer diseases are originated from a heterogeneous population, which is characterized by different genetic mutations. As a result, each cancer cell responds differently to a specific chemotherapy treatment. Therefore, multi-chemotherapy treatments were applied specifically to
prostate cancer patients to overcome this critical problem, *i.e.*, to target cancer cells via various pharmacological actions. In spite of that, this combination of chemotherapy treatment faces a limitation as a result of clonal evolution, *i.e.*, develops resistance to chemotherapy. Additionally, the application of this combination of chemotherapy will mainly lead to various genetic polymorphisms and activate mutations in transcription factor which force cancer cells to elevate their metastasis potential through activation of epithelial cell proliferating process into invasive mesenchymal cells [101].

All these findings obligate the researchers to develop a new chemotherapy treatment for prostate cancer patients.

**IMPORTANCE OF FOCUSING ON CANCER PATIENTS GENE EXPRESSION PROFILE**

Focusing on cancer patients, gene expression profile will significantly help in determining abnormal or mutated gene that play a critical role in the incidence of cancer. Moreover, the determination of cancers mRNA expression by using microarray analysis technique will significant help in profiling cancers genes, detecting cancers subgroups, determining and understanding of various and abnormal mRNA expression taken place in cancer cells. Obtain information will mainly lead to understand the pathological basis of cancer diseases and will facilitate the identification of novel chemotherapy therapeutic targets, and in optimizing cancer therapy. The profiling abnormal genes expressed in breast cancer disease are considered as the most appropriate clinical examples for using gene profile expression for specifying target therapy [53].

**APPLICATION OF PHARMACOGENOMICS IN THE DEVELOPMENT OF CHEMOTHERAPY AGENTS**

Development of cancer treatment is considered as one of the most promising fields in which pharmacogenomics analysis is applied, this will take place through detecting genetic markers which will significantly help in predicting patients’ responses towards chemotherapy treatment. Besides, the identification of these genetic markers, will not only lead to accelerating chemotherapy drug approval, but also will mainly help in overcoming post-approval critical side effects [61]. Therefore, progress and advances in application of pharmacogenomic technologies (genotyping and/or proteomics) in clinical studies will significantly assist in reducing trial duration and patients sample size required in reaching ‘proof of concept’ [61].
PROMISES AND PROOFS OF PHARMACOGENOMICS IN THE SUCCESS OF CHEMOTHERAPY

Genetic polymorphism which includes insertion, deletion and single nucleotide polymorphism (SNPs) all can cause variation within amino acid sequence of either RNA splicing and/or encoded protein and/or gene transcription and/or drug-metabolizing enzymes [31, 32]. As a consequence of these genetic polymorphisms, a significant variation will take place in expression level and/or activity of encoded protein (i.e., phenotype). As well this genetic variation is considered to be the main cause of various drugs responses [31, 32]. With the application of pharmacogenomic approaches among cancer patients this may lead to a great revolution in determining chemotherapy treatment action, response and outcomes [51].

As in the cases that follow:

Pyrimidine Analogs 5-Flourouracil (5-FU)

The detection of genetic polymorphism (such as deletion, insertion, and/or exon skipping) in the dihydropyrimidine dehydrogenase (DPD) gene, which will cause DPD-deficiency phenotype and is associated with side effects, the most detected DPD SNPs that are associated with grade 3 and 4 toxicity are “IVS14 + 1G>A, 2846 A>T, 1679 T>G and 85 T>C. The DPD activity in patients who are classified as having a heterozygous IVS14 + 1 G>A allele will reduce to half. As a result, they suffer from severe 5-FU toxicity. While the DPD activity of cancer patients who are classified as homozygous for the IVS14 + 1 G>A allele is completely lacking”. As a result 5-FU toxicity will be ranged from life-threatening to fatal [34, 102-104]. Moreover, it has been found that massive production of oratate phosphoribosyltransferase (OPRT) enzyme and OPRT mRNA is mainly associated with improvement in 5-FU response among cancer patients suffering from metastatic colorectal cancer [34].

Besides, not only genetic polymorphism in 5-FU metabolizing enzymes can lead to alteration in clinical outcome of patients treated with 5-FU, but also a genetic variation in the drug target i.e., thymidylate synthase (TS) is also associated with variations in 5-FU pharmacokinetics response and toxicity [34, 105].

Therefore, detection of variation within genes involved in 5-FU pharmacokinetics such as metabolic activation (e.g., OPRT), detoxification (e.g., DPD), and target interaction (e.g., TS), will help in the efficacy and safety of 5-FU treatment.
Moreover, success in its anticancer action will be significant when tailoring 5-FU based chemotherapy for individual patients [34] (Fig. 1A, B) and (Fig. 2A, B).

![Chemical structure of 5-Flourouracil](image)

Fig. (1A). Chemical structure of 5-Flourouracil [106, 107].

![5-Flourouracil metabolisms pathway](image)

Fig. (1B). 5-Flourouracil metabolisms pathway “5-Flourouracil (5-FU; see structure) is converted to three main active metabolites: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP) and fluorouridine triphosphate (FUTP). The main mechanism of 5-FU activation is conversion to fluorouridine monophosphate (FUMP), either directly by orotate phosphoribosyltransferase (OPRT) with phosphoribosyl pyrophosphate (PRPP) as the cofactor, or indirectly via fluorouridine (FUR) through the sequential action of uridine phosphorylase (UP) and uridine kinase (UK). FUMP is then phosphorylated to fluorouridine diphosphate (FUDP), which can be either further phosphorylated to the active metabolite fluorouridine triphosphate (FUTP), or converted to fluorodeoxyuridine diphosphate (FdUDP) by ribonucleotide reductase (RR). In turn, FdUDP can either be phosphorylated or dephosphorylated to generate the active metabolites FdUTP and FdUMP, respectively. An alternative activation pathway involves the thymidine phosphorylase catalysed conversion of 5-FU to fluorodeoxyuridine (FUDR), which is then phosphorylated by thymidine kinase (TK) to FdUMP. Dihydropyrimidine dehydrogenase (DPD)-mediated conversion of 5-FU to dihydrofluorouracil (DHFU) is the rate-limiting step of 5-FU catabolism in normal and tumor cells. Up to 80% of administered 5-FU is broken down by DPD in the liver” [106].
DPD deficiency mechanism of action: Variations in *DPYD* can lead to DPD insufficiency. This results in an inability to inactivate 5-FU leading to increased levels of active drug in the system that can result in greater toxicity.

TS deficiency mechanism of action: Variations in *TYMS* can lead to altered TS expression *i.e.*, lower TS enzyme level. This result in an inability to inactivate 5-FU leading to increased levels of active drug in the system that can result in greater toxicity” [108].

**Topoisomerase I Inhibitors (Irinotecan)**

Irinotecan, a semisynthetic derivative of camptothecin, is water soluble, a plant alkaloid isolated from *Camptotheca acuminata*. It mainly used in the treatment of metastatic colorectal cancer, either in combination therapy with 5-FU and leucovorin (FOLFIRI) or as a single therapy. To produce its pharmacological activity, “it first must be metabolized to 7-ethyl-10-hydroxycamptothecin (SN-38) by human carboxylesterase 1 and 2. Later on SN-38 will detoxified by UGT1A1” [34, 109-111]. Besides that, irinotecan undergoes CYP3A4 mediate oxidation to form the “inactive metabolites 7-ethyl-10-(4-N-(5-aminopentanoic acid)-1-piperidon) carbonyloxycamptothecin (APC), and 7-ethyl-10-(4-amino-1-piperidon) carbonyloxycamptothecin” [34, 112, 113]. Clinically and pharmaco-logically, irinotecan shows inter-individual variations in its pharmacokinetic, efficacy, and toxicity. All this is a result of genetic polymorphism in metabolic enzymes and/or transporters involved in irinotecan metabolism [114]. The main reason for these hematological...
and gastrointestinal side effects is the genetic polymorphism that takes place within UGT1A1*28 metabolizing enzyme. This mutation is characterized by the presence of an additional TA repeat in the TATA sequence of the UGT1A1 promoter [(TA)$_7$ TAA instead of (TA)$_6$ TAA]. This is significantly associated with SN-38 glucuronidation and a greater incidence of irinotecan gastrointestinal and hematologic toxicity [34, 115, 116]. Another genetic polymorphism that is significantly associated with irinotecan toxicity is UGT1A1*6, which is found in about 12% of the East Asian population [34, 117]. Moreover, this mutation plays a critical role in incidence of irinotecan and cisplatin toxicity among Korean non-small cell lung cancer patients [110]. While, two promoter mutations UGT1A1 -3263T>G and -3156G>A are strongly associated with UGT1A128, which is predominantly found in Caucasians, but less frequently among African-American and Asians, this mutation strongly correlates with the incidence of severe (grade 4) neutropenia and diarrhea [116, 118] (Fig. 3A, B). Besides UGT1A1, genetic polymorphism in drug transporters such as ABCB1 (3435C>T) is found to be associated with high plasma concentration of irinotecan among the Chinese population. Moreover, mutation in ABCB1 (1236C>T) is found to be correlated with a high AUC level of irinotecan and SN-38 among Chinese population but leads to lower AUC of SN-38 among the Caucasian population [114, 119]. Significant association between irinotecan chemotherapy treatment with ABCB1 mutations remains to be clarified more [34]. As mentioned before, “UGT1A1*28 plays a significant role in irinotecan gastrointestinal and hematological toxicity. Therefore, the initial dose of irinotecan should be reduced specifically for homozygous for the UGT1A1*28 allele” [34]. Moreover, further studies focusing on genetic polymorphism within other genes involved in irinotecan metabolism correlated with cancer patient outcomes are required and necessary to overcome crucial side effects associated with this chemotherapy [34, 104, 120]. So here many pharmacogenomic studies will play a major role in developing irinotecan action and overcoming its critical side effects.

![Irinotecan chemical structure](image)

**Fig. (3A).** Irinotecan chemical structure [121-123].
“IRI uptake and transport into the liver is facilitated by: OATP1B1 (SLCO1B1), ABCB1, MRP1 (ABCC1), MRP2 (ABCC2), and MXR (ABCG2). Specifically, ABCB1 is present on the bile membrane and is responsible for the secretion of IRI and its metabolites into the liver. IRI is metabolized in the liver and converted to SN-38, the active metabolite and Topoisomerase I inhibitor, by carboxylesterases (CES) mediated hydrolysis. CES1 and CES2 have a low affinity for IRI, resulting in a small percentage of IRI converted to active SN-38 (<3%). SN-38 targets Topoisomerase I, inhibiting DNA replication in cancer cells and leading to cell death. SN-38 is then glucoronized to SN-38 glucoronic acid and detoxified in the liver via conjugation by the UGT1A1 family, which releases SN-38G into the intestines for elimination. Approximately 70% of SN-38 becomes SN-38G, which has 1/100 of the antitumor activity and is virtually inactive. In the intestinal lumen, bacterial beta-glucuronidases can reverse the reaction and transform inactive SN-38G back into the active form SN-38. This is a factor contributing to varied toxicity, specifically dose limiting diarrhea” [121-124].
**Purine Analogs (6-Mercaptopurine and 6-Thioguanine)**

The use of thiopurines analogs in treating acute lymphoblastic leukemia leads to a significant increase in the survival rates of leukemic patients. Moreover, both 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG) are found to be very effective in treating colitis, psoriasis and rheumatoid arthritis [53, 125-127].

These analogs are considered to be inactive pro-drugs and they will exert their cytotoxic activities after metabolism to thioguanine nucleotide (TG), which will be incorporated into DNA and RNA. This will mainly lead to DNA destruction and cytotoxicity.

There are two major metabolic pathways for the inactivation of these analogs. The first pathway includes oxidation of these two drugs to thiouric acid. This takes place through the action of an enzyme called xanthine oxidase. While the second pathway is the more important pathway, catalyzes or activates by thiopurine methyltransferase (TPMT), which will mainly leads to conversion of 6-MP and 6-TG to inactive S-methyl derivatives [125, 127, 128] (Fig. 4A, B). Many pharmacogenomic studies have been focused on the TPMT genetic polymorphism as a result of its vital role in individualize therapy. Although, various TPMT mutations have been detected, but only three of these variants (TPMT *2, *3A and *3C) were found to have a significant clinical impact [86, 89]. These mutations were found to be associated with severe toxicity as a result of reducing mercaptopurine and thioguanine clearance among patients carrying these TPMT mutations. Therefore, researchers and physicians need to detect other TPMT mutations for therapeutic considerations among specific ethnic groups [126, 129].
Fig. (4B). (6-mercaptopurine and 6-thioguanine metabolic pathway) “The thiopurine drugs are purine antimetabolites widely used in the treatment of acute lymphoblastic leukemia, autoimmune disorders (e.g., Crohn’s disease and Rheumatoid Arthritis) and of organ transplant recipients. As inactive prodrugs, 6-mercaptopurine (6-MP), 6-thioguanine (6-TG) and azathioprine (AZA) require intracellular activation, catalyzed by multiple enzymes, to exert cytotoxicity. The first step in AZA activation is the release of 6-MP, which involves glutathione transferases and non-enzymatic conversion. Transport of 6-MP into the cell involves SLC28A2, SLC28A3, SLC29A1 and SLC29A2. After uptake, 6-MP is converted into thioinosine monophosphate (TIMP) by hypoxanthine guanine phosphoribosyl transferase (HPRT1), with 5-phospho-D-ribose-1-pyrophosphate (PRPP) as the phosphoribosyl donor. In a similar way, 6-TG can be converted into thioguanosine monophosphate (TGMP). TIMP can be converted into TGMP in two steps: first, thioxanthosine monophosphate (TXMP) is formed by inositol monophosphate dehydrogenase (IMPDH); second, TGMP is formed by guanosine monophosphate synthetase (GMPS). Subsequently, TGMP can be converted into thioguanine nucleotide diphosphates (TGDP) and triphosphates (TGTP). Cytotoxic effects of thiopurine drugs are achieved through incorporation of thio-deoxyguanosine triphosphate (TdGTP) into DNA and of thioguanosine triphosphate (TGTP) into RNA, by inhibition of de novo purine synthesis by methylmercaptopurine nucleotides (MeMPR) and by inhibition of Rac1 (this inhibition induces apoptosis in activated T cells). The TdGTP incorporation inhibits the function of several enzymes involved in DNA replication and repair, and induces DNA damage such as single strand-breaks, DNA-protein cross-links and chromatid exchanges. The pathway that leads to synthesis of active metabolites is in competition with inactivation pathways catalyzed by xanthine oxidase (XDH) or the polymorphic thiopurine methyltransferase (TPMT)” [126].
Folic Acid Antimetabolites (Methotrexate)

This class of chemotherapy (antimetabolites) is considered to be the first class for the treatment of various types of cancers such as breast, head and neck, gastrointestinal, lung, and acute lymphoblastic leukemia (ALL). They act by inhibiting the transfer of folic acid to tetrahydrofolate (by opposing dihydrofolate reductase enzyme action). This will arrest cell cycle and impede the synthesis or production of DNA, RNA, and protein (Fig. 5A, B). Few genetic variations in dihydrofolate reductase enzyme have been detected. These variations have a direct relationship with the alteration of anti-metabolites drug, pharmacokinetics and pharmacodynamics activities.

The incidence of DHFR gene mutations that confer resistance to methotrexate, after exposure of cell lines culture to methotrexate chemotherapy was significantly detected in the laboratory setting. But these mutations have not been linked to use of methotrexate in the clinical setting [53, 132-134].

However, until now the relation between genetic variation in DHFR enzyme activity and/or DHFR enzyme levels with alteration of folic acid antimetabolites action in cancer treatment has not been well clarified.

Moreover, genetic variations in thymidylate synthase (TYMS) also play a significant role in the pharmacogenomics of folic acid antimetabolites in cancer treatment. Therefore, genotyping of TYMS plays an important role in individualizing methotrexate treatment for cancer patients [135, 136].

![Methotrexate chemical structure](137)
Fig. (5B). (Methotrexate metabolic pathway) “Methotrexate exerts its anti-inflammatory actions through a number of cellular mechanisms. Competitive inhibition of dihydrofolate reductase diminishes the de novo synthesis of purines and pyrimidines by preventing the regeneration from dihydrofolate of tetrahydrofolate, which is essential for the generation of folate cofactors required for purine and pyrimidine synthesis. Reduction of the levels of methyl donors, such as tetrahydrofolate and methyltetrahydrofolate, by the inhibition of dihydrofolate reductase results in the inhibition of the generation of lymphotoxic polyamines through methionine and SAM. Inhibition of AICAR transformylase results in an increase in intracellular AICAR levels. This increase has potent inhibitory effects on AMP deaminase and adenosine deaminase, which are involved in the catabolism of AMP and adenosine to IMP and inosine, respectively. The consequent accumulation of adenosine confers anti-inflammatory effects. Levels of AICARriboside, a metabolite of AICAR, also accumulate and inhibit adenosine deaminase. Abbreviations: AICAR, aminomimidazolecarboxamidoribonucleotide; AICARriboside, aminomimidazolecarboxamidoribonucleoside; AMP, adenosine monophosphate; FPGS, folyl polyglutamate synthase; IMP, inosine monophosphate; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine” [138].
Selective Estrogen Receptor Modulators (Tamoxifen)

Tamoxifen belongs to the selective estrogen receptor modulators (SERMs) class of drugs used for breast cancer treatment, *i.e.*, antagonist in estrogen receptor positive breast cancer. Among breast cancer patients who express alpha estrogen receptor, this receptor will play a critical role in stimulating breast cancer growth, specifically in the presence of estrogen. About 75% of women with newly diagnosed breast cancer will express steroid hormone receptors, and the treatment highly recommended for these patients is endocrine therapy. Even with the presence of various types of endocrine therapy, tamoxifen remains the standard treatment recommended for premenopausal women [34, 139-141]. Furthermore, tamoxifen is also recommended for postmenopausal women for 2-3 years, followed by an aromatase inhibitor for a total of 5 years. In long term following clinical studies (for 15 years), it has been found that administration of tamoxifen as adjuvant therapy next to anthracycline-based chemotherapy will significantly minimize the recurrence rate by 50% and the mortality rate by a third. The pharmacological action of tamoxifen is gained from the interaction of the tamoxifen itself, *i.e.*, main drug and its most potent metabolites [4-hydroxytamoxifen, 4-hydroxy-N-desmethyl tamoxifen (endoxifen) and N-desmethyl tamoxifen] with the ER in both breast and non-breast tissues (Fig. 6A, B). This interaction causes a significant alteration of the ER, and leads to the inhibition of the estrogen effect in breast cancer tissues by competing with the hormone at the receptor binding sites, *i.e.*, antagonizing the effect of estrogen. Tamoxifen will pass through various stages of liver metabolism. These stages are N-oxidation, N-demethylation, and hydroxylation. N-desmethyl tamoxifen metabolite, pharmacologically is found to be equipotent as its major drug tamoxifen and it produced by CYP3A4 and/or CYP3A5 enzymes. While the 4-hydroxytamoxifen metabolite is produced by the action of several CYP450 enzymes, it is characterized by its high affinity for the ER, *i.e.*, 100-fold affinity more than

![Tamoxifen](image_url)

*Fig. (6A). Tamoxifen chemical structure [147].*
Tamoxifen metabolic pathway

"Tamoxifen is extensively metabolized predominantly by the cytochrome P450 (CYP) system to several primary and secondary metabolites, some of which exhibit more antiestrogenic effects in breast cancer cells than tamoxifen itself. Tamoxifen metabolism mostly occurs via two pathways, 4-hydroxylation and N-demethylation, both of which result in the very potent secondary metabolite, endoxifen. Originally, the 4-hydroxylation path, which is catalyzed by multiple CYPs including CYP2D6, was given much attention because the immediately resulting metabolite, 4-hydroxytamoxifen, had been shown to be approximately 30- to 100-fold more potent as an antiestrogen than tamoxifen. However, this pathway only contributes approximately 7% of tamoxifen metabolism. N-demethylation to N-desmethyaltamoxifen, catalyzed primarily by CYP3A4 and CYP3A5, contributes approximately 92% of tamoxifen metabolism. N-desmethyaltamoxifen is further oxidized to a number of metabolites that appear important to tamoxifen activity, the most important being endoxifen. Endoxifen, first identified in human bile, is formed from N-desmethyaltamoxifen through hydroxylation by CYP2D6, and from 4-hydroxy-tamoxifen through demethylation by CYP3A4. While 4-hydroxytamoxifen and endoxifen have similar potencies in terms of antiestrogenic activity, endoxifen plasma concentrations in those receiving tamoxifen therapy is, on average, over ten-fold higher than that of 4-hydroxytamoxifen with large interpatient variability. In addition to the estrogen receptor inhibition exhibited by endoxifen, it also uniquely targets ERα (coded for by ESR1 gene) for proteasomal degradation. Endoxifen alone causes a decrease in ERα protein levels while the other metabolites of tamoxifen merely stabilize them. Because of this added effect, endoxifen is likely to be the primary metabolite responsible for the success seen in tamoxifen treatment" [148].
tamoxifen and 30 to 100 times more potent than tamoxifen in preventing estrogen-dependent proliferation. But 4-hydroxy-tamoxifen metabolite is yielded in a small quantity compared to its parent drug tamoxifen. Endoxifen, the third metabolite of tamoxifen, pharmacologically is found to be potent as 4-hydroxytamoxifen in inhibiting estrogen-mediated proliferation, but its plasma concentration is found to be six to twelve-folds higher than 4-hydroxy-tamoxifen concentration. Therefore, endoxifen is found to be responsible for the majority of parent drug associated anticancer activity. The major enzyme responsible for the generation of this endoxifen metabolite is CYP2D6, so any genetic variations of this enzyme this will significantly alter the outcome in tamoxifen treated patients [34, 56, 142-146]. One of the predominant genetic variations that reduces CYP2D6 enzyme activity in metabolizing tamoxifen to 4-hydroxy-tamoxifen is CYP2D6*4. This variation is present in 17 to 21% of the Caucasian population. Individuals either homozygous or heterozygous for this mutation are considered poor metabolizers, and, according to the U.S. Food and Drug Administration, breast cancer patients who carry the CYP2D6*4 mutation (poor metabolizers) might be at high risk for recurrence of breast cancer if treated with tamoxifen [53, 70]. Therefore, the FDA recommended that the tamoxifen package should include an alert warning health provider about that point. However, the 2009 breast cancer guidelines produced by the National Comprehensive Cancer Network of National Institutes of Health, do not include any such recommendation [34].

Further studies focusing on postmenopausal and premenopausal women to detect the relationship between CYP2D6 genetic variations and the effectiveness and success of tamoxifen therapy are highly recommended.

**Taxanes (Paclitaxel and Docetaxel)**

This class of chemotherapy produces its anti-tumor activity via promoting and stabilizing the assembly of microtubule formation by inhibiting depolymerization. Paclitaxel is a plant derivative first discovered and isolated in 1967 from the bark of the Pacific yew tree. Docetaxel is a semi-synthetic drug similar to, or an analog of, paclitaxel that is extracted from the European yew tree. This class of anti-tumor drug has a wide band efficacy for the treatment of various types or classes of tumors. Docetaxel is mainly metabolized by the cytochrome P-450 enzyme, specifically by CYP3A4. This enzyme will convert docetaxel to its inactive form
(hydroxelated form) (Fig. 7A, B). Therefore, any alteration or mutation that leads to an increase in CYP3A4 activity will cause a significant reduction in the therapeutic efficacy of docetaxel. On the other hand, reduction or inhibition of CYP3A4 enzyme activity (for example: after using ketoconazole) will mainly lead to a reduction in docetaxel clearance [111, 149, 150].

Although, numerous CYP3A4 variants have been detected, until now there is a lack of information that supports or confirms that these genetic variations affect docetaxel pharmacological activity in cancer treatment. Therefore, advanced studies that focus on clarifying the association between variations in paclitaxel and/or docetaxel pharmacokinetics with CYP3A4 haplotypes are highly recommended [151].

![Chemical structures of Paclitaxel and Docetaxel](image)

**a-Paclitaxel**

**b-Docetaxel**

**Fig. (7A).** Paclitaxel and Docetaxel chemical structure [152, 153].
While paclitaxel and docetaxel share many common structural features, their pharmacology and pharmacokinetics differ somewhat. Consequently, in some patients, solid tumors with resistance to paclitaxel have been shown to be sensitive to docetaxel. The pharmacokinetics of taxanes are complex and are complicated by their different formulations. Both taxanes are primarily metabolized in the liver and their primary route of elimination of the parent drug and hydroxylated metabolite is through biliary excretion via feces. Both paclitaxel and docetaxel are metabolized by CYP3A4. Paclitaxel is also metabolized by CYP2C8, while docetaxel is also metabolized by CYP3A5. Moreover, both paclitaxel and docetaxel are substrates for the ATP binding cassette multidrug transporters ABCB1, ABCG2, ABCC1 and ABCC2" [150].
**Platinum Agents**

This class of chemotherapy treatment includes cisplatin, carboplatin, and oxaliplatin, and was first synthesized in the nineteenth century. But they were not used as anticancer treatments until the 1970s. Their main mechanism of action is by forming crosslink of DNA and mono-adduct to prevent cell replication and lead to apoptosis. These platinum analogs were developed mainly to overcome both cancer cell resistance and toxicity. These chemotherapeutics agents have been found very effective for the treatment of various types of cancers such as breast, lung, ovarian, colorectal, bladder, head and neck, and testicular cancer [34, 111, 154].

Cisplatin is considered to be the first member or generation of this group. It exerts its anticancer activity by binding specifically to the N-7 position of adenine and guanine of DNA. This will lead to crosslinks of DNA. Its use is characterized by crucial side effects neurotoxicity, nephrotoxicity, ototoxicity, and emetogenicity. While carboplatin is the second generation of platinum analogs, its chemical structure differs from cisplatin in the replacement of two chloride groups by a 1, 1-cyclobutane dicarboxylate group. Both cisplatin and carboplatin are similar in their efficacy, but carboplatin’s toxicity profile is more favorable [42, 154, 155]. That is the main reason to prefer using carboplatin instead of cisplatin. Then comes oxaliplatin, which belongs to the third generation of platinum compound. This drug is frequently used for metastatic colorectal cancer and various other cancers such as breast, melanoma, non-Hodgkin lymphoma, and head and neck cancer [154, 156, 157]. The most common side effects associated with oxaliplatin use are myelotoxicity, nausea, vomiting, diarrhea, paresthesia, and dysesthesias.

Major problems associated with platinum agent use are cancer cell resistance and/or the side effects, *i.e.*, toxicity. These side effects can play a major role in altering the clinical outcome of treatment resulting from chemotherapy treatment discontinuation or reduction. Genetic factors are considered to be the crucial factor in the incidence of these toxicities or side effects. Thus, the detection of genetic factors in cancer patients who suffer from platinum side effects is considered a major point [158]. The key to determine the mechanism through which chemotherapy can cause its toxic effect is the disposition or action of the chemotherapeutic agent. The key that regulates chemotherapy disposition is chemotherapy pharmacokinetic, *i.e.*, chemotherapy metabolism, absorption, distribution, and excretion. DNA repair proteins (ERCC1, ERCC2, and XRCC1) play a significant role in platinum chemotherapy resistance, clinical outcome, and toxicity (Fig. 8A, B). Dzagnidze *et al.* 2007; McWhinney *et al.* 2009 and Li *et al.*
2011 have hypothesized that there is a strong association between excision repair cross-complementation group 1 (ERCC1) and Nucleotide excision repair (NEG) proteins with clinical efficacy and outcome of platinum based chemotherapy drugs [34, 158, 159]. Therefore, genotyping these proteins will significantly help in detecting the clinical outcome of platinum based chemotherapy. But until today, there has not been an association proven or detected between ERCC1 genetic polymorphism and chemotherapy neurotoxicity [34, 158]. Therefore, future studies and efforts to elucidate the relationship between these DNA repair proteins and platinum chemotherapy resistance, clinical outcome and toxicity, leading to individualized therapy are highly recommended.

Fig. (8A). Platinum agents chemical structure [160-164].
Platinum compound

SLC31A1

ABCC2

ABCG2

ATP7A, ATP7B

MT1A, MT2A, MPO, GSTP1, GSTT1, SOD1, NQO1, GSTM1

Detoxification

POLH, POLM, POLB, REV3L

Platinum compound

Damage recognition

HMGB1

G

Mismatch repair

Translesional replication

Cell death

Excision repair

XRCC1, XRCC3, ERCC1, ERCC2, ERCC4, ERCC6, SWESNF, XPA

Fig. (8B). (Platinum Agents metabolic pathway) “Platinum (Pt)-containing drugs are currently used in the clinic for treating cancer. Platinum is the 78th element in the periodic table and has been used in medicine since the mid-1960’s. The major Pt-containing drugs are cisplatin, carboplatin, and oxaliplatin. Platinum-based drugs are now the largest class of drugs used to treat cancer. They destroy cancerous cells by interfering with the DNA, via inter- and intrastrand crosslinks, and DNA-protein crosslinks, thereby preventing cell division and growth” [165].
Alkylation Agents (Cyclophosphamide)

Cyclophosphamide (CPA) is a nitrogen mustard alkylating agent. It is one of the most widely used anticancer drugs in the treatment of hematological malignancies and a variety of solid tumors including breast cancer [110, 111, 114]. “CPA is often used in combination with other chemotherapeutic agents, such as CPA + anthracyclin (adriamycin, epirubicin) termed the CA regimen, or CPA + methotrexate and 5-fluorouracil (CMF), or CPA + adriamycin and 5-fluorouracil (CAF), or CPA + 5-fluorouracil (CF)” [101, 166, 167]. Clinically these cyclophosphamide based combination treatments have been determined to be efficient for breast cancer. However these combinations cause various “adverse drug reactions (ADRs), such as leukopenia/neutropenia, and gastrointestinal symptoms such as vomiting, anorexia and nausea” [101, 166, 167].

Cyclophosphamide “is a prodrug that requires metabolic activation to exert its effect. After CPA administration, the drug is metabolized to 4-hydroxycyclophosphamide (4-OH-CPA) by CYP2B6 and CYP3A4 in the liver” [167-170]. “The 4-OH-CPA interconverts rapidly with its tautomer, aldophosphamide and then degrades spontaneously to form phosphoramide mustard, which is a therapeutically active component (Fig. 9A, B). Both 4-OHCPA and aldophosphamide are detoxified by glutathione (GSH) conjugation catalyzed by multiple glutathione S-transferases (GSTA1, GSTM1, GSTP1 and GSTT1) and by aldehyde dehydrogenase (ALDH1A1 and ALDH3A1) to carboxycyclophosphamide” [170-172]. Therefore, hepatic metabolism is the primary route of cyclophosphamide metabolism and excretion. Moreover, it has been found that transporters such as ABCC2 and ABCC4 play a significant role in the transport of CPA and its metabolites [170-172]. The majority of the cyclophosphamide metabolizing enzymes and transporters are characterized by a wide range of genetic variations, which might cause a large interindividual variability in the plasma concentration of drugs and their pharmacological efficacy. “Furthermore, anticancer therapies are notoriously known to have a narrow therapeutic range; a higher concentration in the patient’s body causes toxicity and a lower concentration reduces the efficacy of the drugs” [167, 169, 173, 174]. Therefore, future studies to detect the role of genetic polymorphism with cyclophosphamide crucial toxicity and to enable individualized therapy are essential.
Cyclophosphamide toxicity profile is characterized by myelosuppression and urotoxicity. This diagram shows the genes involved in the biotransformation of CP and its metabolites and includes pathways of activation, deactivation and toxicity. Activation of CP to 4-hydroxycyclophosphamide is catalyzed by the hepatic cytochrome P450 (CYP) isozymes CYP2B6, 2C9 and 3A4 (with 2A6, 2C8 and 2C19 making more minor contributions). Competing with C-4 hydroxylation of CP is a minor (~10%) oxidative pathway that leads to N-dechloroethylation and the formation of the neurotoxic chloroacetaldehyde. CYP3A4 is primarily responsible for this undesirable side-chain oxidation with a minor contribution from CYP2B6. 4-Hydroxycyclophosphamide interconverts rapidly with its tautomer, aldophosphamide and it is likely that both of these metabolites passively diffuse out of hepatic cells, circulate, and then passively enter other cells. Aldophosphamide undergoes a spontaneous (non-enzymatic) elimination reaction to yield phosphoramid mustard (PM) and acrolein (associated with bladder toxicity). PM, which is generally believed to be the DNA crosslinking agent of clinical significance, is a circulating metabolite with its anionic form not entering cells very easily. Thus, the intracellular generation of PM from aldophosphamide is believed to be important to a therapeutic result. A major detoxification route is the oxidation of aldophosphamide to the inactive carboxycyclophosphamide by ALDH1A1 and, to a much lesser extent, by ALDH3A1 and ALDH5A1. Multiple CP metabolites can react with glutathione (GSH) resulting in the formation of various conjugates at different sites along the pathway [176].

**Fig. (9A).** Cyclophosphamide chemical structure [175].

**Fig. (9B).** *(Cyclophosphamide metabolic pathway)* “Cyclophosphamide toxicity profile is characterized by myelosuppression and urotoxicity. This diagram shows the genes involved in the biotransformation of CP and its metabolites and includes pathways of activation, deactivation and toxicity. Activation of CP to 4-hydroxycyclophosphamide is catalyzed by the hepatic cytochrome P450 (CYP) isozymes CYP2B6, 2C9 and 3A4 (with 2A6, 2C8 and 2C19 making more minor contributions). Competing with C-4 hydroxylation of CP is a minor (~10%) oxidative pathway that leads to N-dechloroethylation and the formation of the neurotoxic chloroacetaldehyde. CYP3A4 is primarily responsible for this undesirable side-chain oxidation with a minor contribution from CYP2B6. 4-Hydroxycyclophosphamide interconverts rapidly with its tautomer, aldophosphamide and it is likely that both of these metabolites passively diffuse out of hepatic cells, circulate, and then passively enter other cells. Aldophosphamide undergoes a spontaneous (non-enzymatic) elimination reaction to yield phosphoramid mustard (PM) and acrolein (associated with bladder toxicity). PM, which is generally believed to be the DNA crosslinking agent of clinical significance, is a circulating metabolite with its anionic form not entering cells very easily. Thus, the intracellular generation of PM from aldophosphamide is believed to be important to a therapeutic result. A major detoxification route is the oxidation of aldophosphamide to the inactive carboxycyclophosphamide by ALDH1A1 and, to a much lesser extent, by ALDH3A1 and ALDH5A1. Multiple CP metabolites can react with glutathione (GSH) resulting in the formation of various conjugates at different sites along the pathway” [176].
APPLICATION OF PHARMACOGENOMICS STUDIES IN PREDICTING AND/OR OVERCOMING CHEMOTHERAPY SIDE EFFECTS

The main goals of applying pharmacogenomic techniques and facilities are to detect the pathways involved in the metabolism of chemotherapeutic agents, the safety starting doses for each chemotherapeutic treatment and the therapeutic response. Moreover, pharmacogenomics will play a significant role in the identification of patients at increased risk of toxicity or low likelihood of response. All these will potentially help in developing and producing highly effective chemotherapeutic agents [104, 177]. In case of acute lymphoblastic leukemia (ALL) patients, the incidence of genetic polymorphism in the metabolizing enzyme (thiopurine methyltransferase) is mainly associated with myelosuppression after administration of 6-mercaptopurine (6-MP) and/or 6-thioguanine (6-TG) chemotherapy treatment. Therefore, these clinical data indicate that genetic evaluation for thiopurine methyltransferase (TPMT) concentration is recommended, not only for detecting 6-MP crucial side effects, i.e., toxicity but also to help in predicting patients’ response towards this chemotherapy [105]. As a consequence the U.S. Food and Drug Administration (FDA) has promoted a test for genetic variation as an important recommendation, i.e., 6-MP dose should be modified based on TPMT genetic evaluation [35, 178, 179].

All these are examples for the benefits of the application of pharmacogenomics to evaluate, regulate, develop and detect the most efficient way to use chemotherapy treatments. Also, it will help in discovering new chemotherapeutics treatments, and overcoming, palliating or reducing the incidence and/or severity of side effects that frequently associated with their use.

PERSONALIZING CHEMOTHERAPY TREATMENT

Cancer diseases vary significantly from other diseases in their pathological feature of unlimited growth. Besides that they are marked by multiplying of genes and multiple by stages [180-182]. Also as a result, their chemotherapy sensitivity is diverse, i.e., each tumor tissue shows sensitivity to different chemotherapy treatments. Therefore, the majority of cancer patients is not homogeneous and should not receive or use standardized chemotherapy treatment [181-183]. Until today there is no single or combination of chemotherapeutics drugs that is classified as the optimal treatment for tumors of all origins. Therefore developing
and detecting highly sensitive chemotherapy regimens is no less vital and/or less valuable than synthesis of new anticancer treatments [181].

Thus the term “Individualized Cancer Therapy” (ICT) was created to capture this vital requirement of improving chemotherapy treatment quality. This will accomplished mainly through following various sequence of systematic procedures in clinics to specify and use well matched anticancer drugs and averting inappropriate chemotherapeutics drugs [35, 181].

A-Personalizing Breast Cancer Treatment

During the past decade, discoveries have played significant roles in developing our understanding of the molecular mechanisms related to breast cancer progression. Moreover, new discoveries correlated with the central role of genetic polymorphisms help in the early detection, diagnosis and treatment of breast cancer [184, 185]. Additionally, recent developments in DNA analysis technologies have been used as a cornerstone in the biological evaluation, classification and therapeutic planning of breast cancer patients.

Therefore, the two main bases for developing novel approaches for the prevention and management of breast cancer are the further understanding of molecular biology and gene expression signatures. The earliest and best examples of breast cancer targeted therapies were produced and developed after progress has taken place in cancer molecular biology, which are trastuzumab (humanized anti-HER2 monoclonal antibody) and tamoxifen (estrogen receptor target therapy). These two drugs have inspired researchers to develop and/or discover other selective and effective anticancer target in breast cancer, through the utilization of pharmacogenomics techniques [185].

B-Personalizing Bladder Cancer Treatment

During this century, the majority of bladder cancer patients are treated with a similar combination of platinum based chemotherapy, frequently gemcitabine + cisplatin (GC). But only half of those patients show a positive response to chemotherapy. Recently, great efforts are ongoing to clarify the molecular biology of bladder cancer disease in order to improve clinical outcomes. Besides, it is recommended to focus on cancer biomarkers that play a significant role not only in detecting high risk bladder cancer patients, but also in specifying those who will obtain the maximum benefit from using it. Therefore, studies that focus on personalizing chemotherapy for bladder cancer patients, i.e., based on
pharmacogenomic techniques, will help in developing chemotherapy that will improve clinical outcomes and reduce side effects [186].

C-Personalizing Colon Cancer Treatment

Personalized medicine is considered to be the most important part of supportive and palliative care for colon cancer patients, since colon cancer is the second leading cause of death in United States and the fourth leading cause of death around the world [187, 188]. In the past three decades there has been a significant improvement in clarifying and understanding the molecular origins of this cancer. Moreover, significant progress has been observed in the fields of genomic and proteomic data, both leading to the discovery of novel personalize chemotherapy treatment for those who suffer from either primary or advanced colon cancer [187].

PERSONALIZING ANTICANCER THERAPY BASED ON TUMOR ONCOGENIC PATHWAY MARKERS

DNA microarray-based gene expression signature technique has been proven in various studies as an efficient technique in personalizing anticancer treatment. Because, it can significantly detect both tumor cell outcomes and gene expression signature after receiving chemotherapy, these outcomes can significantly specify the patterns of pathway deregulation among tumor cells and their sensitivity towards chemotherapy treatments used. Therefore, these facts can significantly help in personalizing cancer therapies [35, 189, 190].

DISCOVERIES IN MOLECULAR TARGETED THERAPIES USED FOR CANCER TREATMENT

A-Induction of Apoptosis and Inhibition of Anti-Apoptosis

Apoptosis is a mechanism of programmed cell suicide that includes various and complicated signaling pathways. This process plays a critical role during two phases, the embryogenesis phase and the immunology phase. Therefore, any disruption or disturbance in this biological process will mainly lead to prolongation in cell life and this will promote carcinogenesis [191, 192].

Clinically, it has been assumed that the apoptosis process controls the pharmacological actions of chemotherapeutic drugs and ionizing radiation in tumor treatment. Therefore, the discovery and the development of molecular
target anticancer treatment, i.e., the trigger apoptosis agent(s), will significantly help in overcoming this problem. This can take place through two signaling mechanisms. One is stimulation and release of caspases, which are mitochondrial pro-apoptotic proteins. This mechanism is also called intrinsic pathway. The second mechanism, extrinsic pathway, includes stimulating expression of pro-apoptotic receptors on cancer cells, these receptors include Fas and/or tumor necrosis factor (TNF)-related apoptosis inducing ligands receptors [21, 193].

The synthesis and development of chemotherapeutic treatments that stimulate apoptotic pathway should be considered as a novel therapeutic method. Moreover researchers need to understand the molecular mechanism that controls the apoptosis signaling mechanisms that are stimulated or induced by chemotherapeutic treatments, because the mechanisms of apoptosis are more various than researchers have previously expected. Further, diverse forms of cell death have been proposed recently. Therefore, detecting these mechanisms will significantly help in individualizing the tumors and improving the chemotherapeutics treatments’ effectiveness based on the genetic polymorphism [194-196].

B-Anti-Metastatic Treatment

The most critical problems in cancer chemotherapy are neoplasm metastasis and multi-chemotherapy drug resistances. Treatment of neoplasm metastases is still considered the most complicated and important matter, since more than 90% of cancer deaths are mainly caused by metastases [197]. Clinically most chemotherapeutic treatments have been used for the treatment of primary stages, while anti-metastatic treatments are frequently used as an assistance therapy [197, 198]. As a result, the cancer patient’s survival has not significantly improved. Therefore, researchers should focus on the development of effective and selective anti-metastatic treatments based on clinical outcomes and patients’ genetic variations [181, 199].

PHARMACIST AND PHARMACOGENOMICS ROLE IN PERSONALIZING CHEMOTHERAPY TREATMENT

Over several years, pharmacists have worked hard to detect and determine the proper dose of the vast majority of pharmacological agents for their patients depending on their body weight. Response towards drugs varies from one individual to another, and their response is extremely unpredictable and can vary
from little or no therapeutic benefit to crucial and/or troubling adverse drug reactions.

Therefore, in the case of cancer treatment, pharmacogenomics can play an important role in guiding pharmacist and clinicians to detect and to distinguish cancer patients who are highly susceptible to suffering from chemotherapy side effects at standard chemotherapy doses. This will show the importance of the application of pharmacogenomics cancer treatment, because the majority of chemotherapy treatments are characterized by narrow therapeutic index and with a wide band of critical side effects [200].

Thus, the lack in studies that focus on personalizing treatment and/or expectation of patients’ responds specifically in cancer treatment leads to significant negative effect on the contemporary health care system.

CONCLUSION

Therefore, the application of comprehensive pharmacogenomic testing of cancer patients is necessary, since recently it has had a significant role in developing and discovering new chemotherapeutic treatments. Moreover, it will play a major role in detecting and predicting chemotherapeutic toxicity and response. Therefore, the main point in this field is to use cancer patients’ genetic map as the cornerstone in making decisions regarding chemotherapy treatment guidelines and scheduling, in order to gain their maximum clinical benefits with the fewest adverse effects.

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CONFLICT OF INTEREST

The author confirms that this chapter contents have no conflict of interest.

REFERENCES


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[79] Roche-Lestienne C, Soenen-Cornu V, Grardel-Duflos N, et al. Several types of mutations of the Abl gene can be found in chronic myeloid leukemia patients resistant to STI571, and they can pre-exist to the onset of treatment. Blood 2002; 100(3): 1014-8.


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