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Pharmacogenomics in Cancer

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ABSTRACT

The science of one's genetic background and its impact on disease susceptibility and drug response has well established its place in clinics. As many drugs that are currently available in the market are "one size fits all," but they don't respond the same way for everyone. These inter-individual differences of drug response can be due to different age, drug-drug interaction, gender, inherited variations in drug disposition or through gene and drug target gene. The impact of Genetic study is mostly observed in the current arena of clinical oncology compared to any other chronic diseases due to several reasons: Toxicity, Critical time & narrow therapeutic index. "Pharmacogenomics" is the whole genome application of Pharmacogenetics, where genomic information is used to study the single gene interactions with drugs by studying the patient's genetic profile. Their biomarkers hold great promise for the individualization in cancer therapy by selecting the most appropriate medication thereby, applying the optimal dose for each individual patient according to precise markers assisted in screening tests by reducing the toxicity of chemotherapy. Two major aspects considered by researchers while studying the response of a drug in an individual are: how much of a drug is needed to reach its target in the body, and how well the target cells or genes respond to the drug. Overall, the current review summarizes the role of Pharmacogenomics in cancers mainly focusing on Colorectal, Osteosarcoma & Breast Cancer and the advances made in their treatment.

Keywords: *Cancer, Pharmacogenomics, Drug Response, Toxicity, Biomarkers.*

1. INTRODUCTION

Cancer is a global issue majorly affecting 82% of developing countries and thereby causing more than eight million deaths annually [1]. It's a multifactorial disorder involving complex alterations in the genome of the body. Considering severe complications of cancer, there is a crucial need to search treatment modalities for cancer [2]. However, treatment in Cancer has witnessed major advances over the past decade due to the recent revolution in medical interventions [3]. The success in any of the cancer treatment depends upon the type of cancer, tumor locality, and its stage of progression. The various conventional treatment modalities reported to treat and manage cancer: Surgery, radiation-based therapy, and systemic treatment (chemotherapy, targeted therapy, hormonal therapy, and immunotherapy, stem cell therapies & Dendritic cell-based immunotherapy) [4]. However, chemotherapy had been considered as an important therapeutic option for different malignancies, especially for the primary, advanced and metastatic tumours [5]. Chemotherapy acts to bring about changes in the tumor cells by halting tumor progression (killing off their ability to divide) and thereby enforcing apoptosis. This therapy also targets the normal growing cells, which could result in a variety of side effects depending on the dosage such as vomiting, hair loss, fatigue, nausea, etc. Figure 1 depicts the various other side effects. Also, using the chemotherapy treatment vigorously, the patients become immunocompromised; which can cause complicated infections and consequently death [6].

Resistance to this therapy is due to the variety of factors including individual variations in patients such as age, gender, etc.; genetic differences in tumours; insensitivity to drug-induced apoptosis [7]. Therefore, diseases like cancer where cost and the toxicity of chemotherapy are high, and the time is very critical, the pharmacogenomics offers a valuable tool to select an appropriate drug or dose for a particular patient. Pharmacogenomics helps us reduce the toxicity of chemotherapy by selecting the right drug and its dose for a given patient based on his drug response profile [8,9]. Pharmacogenomics is outlined as study of genes and the way

they have an effect on a private response to the administered medication. It's a branch with a combination of each medical specialty yet as genetic science for development of effective doses and safe medications tailored as per individual patient's genetic makeup.

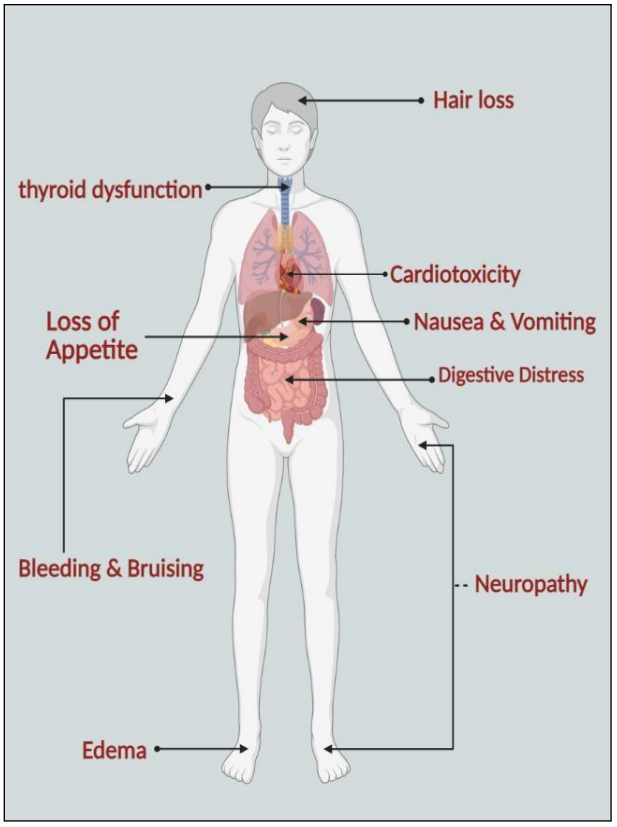

Fig-1 Adverse Effect of Chemotherapy

2. WORKING OF PHARMACOGENOMICS

The cytochrome P450 belongs to a family of enzymes found within the body which synthesize and metabolize various molecules and chemicals present within the cell, including the active part of most of the drugs. Common changes in genes, called polymorphisms which determine the activity of cytochrome P450 enzymes, will affect activity of enzymes. This is usually seen in the breakdown or metabolism of drugs. If the drug is metabolized slowly by CP450, the drug remains active longer and a lower dose is required to urge the specified impact whereas normal doses might cause toxicity. 70% of the drug metabolism method within the body is carried out by cytochrome P450 enzymes, particularly CYP2C9, CYP2C19 & CYP2D6. Except this there are many other genes outside of the cytochrome-p450 system that affect drug metabolism thereby affecting the patient's response to medications [10].

Response of drugs depends on various factors like how you are administering the drug and where the drug is acting in your body. Once the drug is taken, your body has to break it down and send it to metabolism. In this process, our deoxyribonucleic acid will have an effect on multiple steps and this will influence the reply to the drug. Some samples of these interactions are as follows:

2.1 Drug receptor

Some medication has to attach to proteins on the surface of cells referred to as receptors so as to bind properly. DNA determines what variety of receptors, which might have an effect on your response to the drug. Hence accordingly the drug dosage is determined.

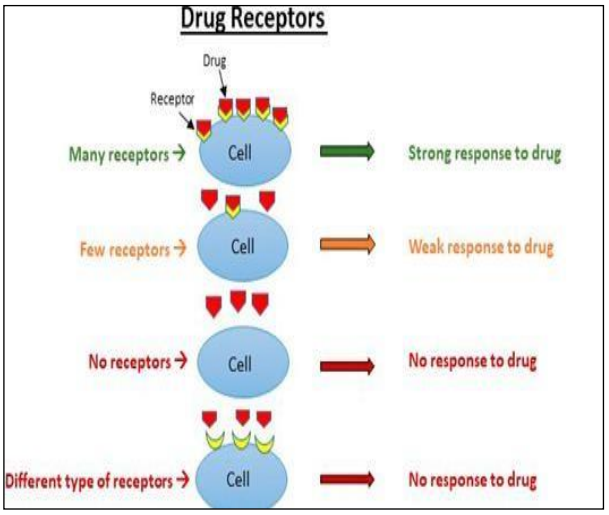

Fig-2.1 Receptor Mechanism

2.2 Drug Uptake

Some medications are actively taken into the tissues and cells for them to act. DNA will have an effect on uptake of sure medication. Decreased uptake will mean that the drug doesn't work furthermore and might cause it to make up in different elements of your body, which may cause issues.

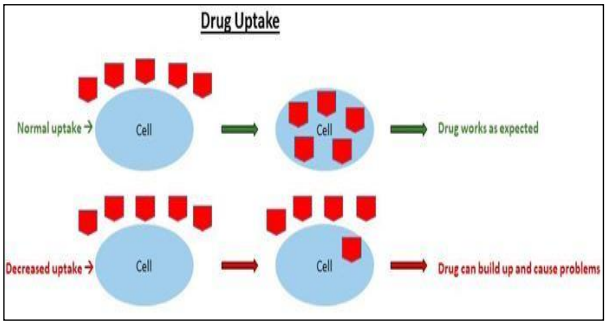

Fig-2.2 Drug Uptake Mechanism

2.3 Drug Breakdown

DNA will have an effect on how quickly our body breaks down a drug. If the drug in your body breaks down too quickly than a normal person, then it gets eliminated quickly and you may want a higher dose of the drug or a unique drug. If your body breaks the drug down a lot of slowly, you may want less of the drug.

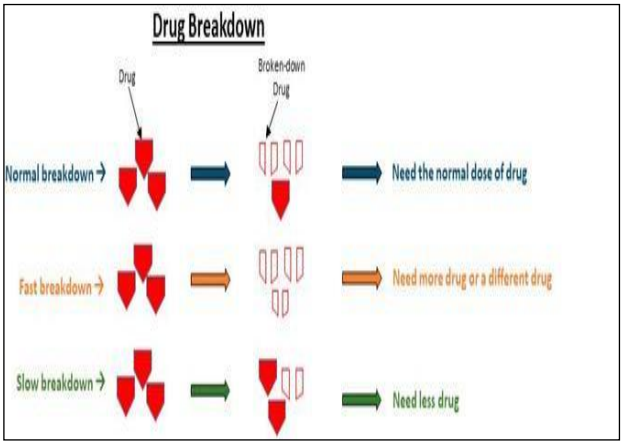

Fig-2.3 Drug Breakdown Mechanism

2.4 Targeted Drug Development

Pharmacogenomics approaches to drug development target the underlying downside rather than merely treating symptoms. Some diseases are caused by specific changes (mutations)

during a sequence. A similar sequence will have differing kinds of mutations that havecompletely different effects. Some mutations might lead to a protein that doesn't work properly, whereas others might mean that the protein isn't created. Medicine is created and supported; however, the mutation affects the proteins and these medicines can solely work for a particular sort of mutation [11].

2.5 Current situation of Pharmacogenomics

It is presently viewed as a vital space for research projects, because the promise of targeting medicine consistent with the particular genetic makeup of every patient has tangible edges in application, if ready to be enforced properly. At this time in time, we have a tendency to area units commencing to perceive additional concerning variation within the human ordering, however the particular applications of however we can manipulate these discoveries to our advantage are still current. Most analysisso far has centered on the potential of variations within the single ester polymorphisms (SNPs) to work out individual drug response, and there's already an intensive in public on the market information on the subject. However, pharmacogenomics continues to be a promising resolution and isn't widely employed in practice. Instead, medicine is usually prescribed on a general basis, consistent with the peak and weight of the individual, instead of their ordering. Pharmacogenomics is applied to many areas of medication, as well as pain management, cardiology, oncology, and medical specialty. It gives Tailored treatments to satisfy patients' unique genetic predisposition, by giving them optimum dosage. An area might also exist in medical specialty, within which pharmacogenomics is wont to verify the reason for death in drug-related deaths wherever no findings emerge from the victimization autopsy.

2.6 Pharmacogenomics v/s current treatment

Surgery still remains the vital mode for treating the tumor at primary level, whereas adjuvant
chemotherapy plays an essential role in the control of subclinical metastatic disease. When in some patients complete surgical excision is impossible, the additionof radiation therapy may allow local tumor control. High-dose methotrexate, doxorubicin, cisplatin, and ifosfamide /etoposide still remain the most effective chemotherapy agents currently used for osteosarcoma patients [12], evacizumab (Avastin) and ramucirumab (Cyramza) are used widely for large intestine cancer. But introduction of pharmacogenomics is having a revolutionizing effect in treatment of cancer.

Pharmacogenomics plays two major roles in precision medicine. First, it guides and helps pharmaceutical companies in drug discovery and development. Second, it guides physicians in selecting the proper drug for patients supported by their genetic make-up, in avoiding ADR, and in maximizing drug efficacy by prescribing the appropriate dose. Genetic variations relevant to drugdevelopment include:

- genes concerned with the drug's pharmacokinetics (absorption, distribution,metabolism and excretion)
- genes coding for drug targets, intended or unintended and other pathways related with thedrug's pharmacological effect
- genes which will be susceptible to toxicities like immune reactions
- genes that predispose disease susceptibility or progression [13].

The individual's drug profile is affected by all these factors. Pharmacogenomics gradually can reduce health care cost by decreases in:

- the adverse drug reactions and failed drugtrials;
- the time taken to get a drug in market;
- the time duration patients are on medication;
- the quantity of medications patients must take to find an effective therapy;
- the consequence of a disease on the body (through early detection) [14].

2.7 Benefits of Pharmacogenomics are two-fold:

With a specific probability, we will be able to predict the risk of cancer for a given individual. This sort of pre-symptomatic diagnosis can prevent cancer mortality to a great extent by adopting frequent screening for the suspected cancer risk and catching it at the very early stage. BRCA1 and BRCA2 are excellent examples where women with positive cancer biomarkers are often vigilant and prone cancer before it can spread; In many cases, pharmacogenetic tests can help the oncologist to find a better treatment regimen with minimum toxicity. Both these benefits have become part of cancer study and management [15].

3. PHARMACOGENOMICS IN CANCER

Fluoropyrimidines, such as 5-Fluorouracil (5-FU), capecitabine and tegafur, are used extensively in the treatment of various cancers. Dihydropyramidine dehydrogenase (DPD) is involved in the 5-FU metabolism by converting 80% inactive metabolites and thus it is responsible for its elimination. It is encoded by the DPYD gene. Because of the great variety for DPD between individuals, different effects from treatment with 5-FU have been observed – efficacy, resistance andtoxicity.

Another enzyme that is involved in the drug's metabolism pathway is thymidylate synthetase. TS is related with thymidine synthesis and 5-FU inhibits it. The gene encoding for TS is TYMS. Two different alleles have been observed for this gene – with a 2- repeat sequence (TSER*2) and with a 3-repeat sequence (TSER*3). When a patient with colorectal carcinoma is treated with 5-FU, patients with TSER*3 shows better than patients with TSER*2 polymorphism.

Methylenetetrahydrofolate reductase is an enzyme which is involved with 5-FU and methotrexate (MTX) pathways. It is important for the metabolism of folate and methionine and eventually leads to synthesis and methylation of DNA. Studies have found that the T allele is related to higher total homocysteine than the C allele particularly in individuals with lower plasma folate. In studies of pediatric acute lymphoblastic leukemia patients treated with methotrexate, the T allele was related with a lower probability of event free survival but wasn't a risk factor for toxicity or seizures. Some studies have shown that the T allele could also beprotective compared to the C allele in disease incidence (colorectal neoplasms, breast neoplasms).

It has been found that in patients with bladder cancer, high ERCC1 levels are associated with worse outcomes.But in non-small cell lung carcinoma, polymorphism in exon 4 shows better survival rate due to the decreased activity of ERCC1. Both ERCC1 and ERCC2 genes are important in the DNA repair system and, therefore, are involved in nucleotide excision repair pathway.

The ABCB1 gene encodes for a P-glycoprotein. Overexpression of glycoprotein is observed in cells that are resistant to specific anticancer regimens. There are two synonymous SNPs and one seem to be linked in MDR1*2

haplotype. This haplotype leads to upregulation of P-glycoprotein which ultimately increases the activity of the drug transporter and reduces SN-38 clearance. Tamoxifen is one of the most widely used drugs for hormone-dependent breast cancer treatment. Some medicines are known as selective ER modulators as they inhibit estrogen binding to the ERs, reducing or excluding estrogen-driven proliferation of ER+ tumors. Its pharmacological activity is dependent on the hepatic enzyme cytochrome, which converts tamoxifen to its active metabolite endoxifen. It is observed that patients with reduced CYP2D6 activity either as a result of their genotype, or because of intake of other medicines, inhibiting CYP2D6 which produces less endoxifen, which then leads to less therapeutic benefit [16].

Below mentioned are some of the cancers where pharmacogenomics is used in various ways.

4. COLORECTUM CANCER

Colorectal cancer is a cancer that starts within the colon (large intestine) or rectum. Each of those organs square measure within the lower portion of your gastrointestinal system. The rectum is located at the tip of the colon. Most colon cancers begin as a growth on the inner lining of the colon or rectal. This growth area unit is known as polyps. Some kinds of polyps will develop into cancer over time (usually several years), however not all polyps become cancer. The prospect of a polyp turning into cancer depends on the kind of polyp it's. There are a unit differing types of polyps [17].

Types of cancer within the colon and rectum

Most large intestine cancers area unit adenocarcinomas. These cancers begin in cells that create mucous secretion to lubricate the within the colon and rectum. Some subtypes of adenocarcinoma, like seal ring and glycoprotein, might have a worse outlook than alternative subtypes of glandular cancer.

Other many common kinds of tumors may also begin within the colon and rectum. These include:

i. Carcinoid tumors: These begin from special hormone-making cells within the intestine.
ii. Gastrointestinal stromal tumors (GISTs) begin from special cells within the wall of the colon known as the opening cells of Cajal. Some area unit benign (not cancer). These tumors are often found in a place within the GI tract, however don't seem to be common within the colon.
iii. Lymphoma's area unit cancers of immune system cells. They principally begin in lymph nodes; however, they will conjointly begin within the colon, rectum, or alternative organs.
iv. Sarcomas will begin in blood vessels, muscle layers, or alternative connective tissues within the wall of the colon and rectum. It is rare to find cancer in sarcomas of the colon or rectum [18].

4.1 Pharmacogenomic Biomarker

i. RAS

EGFR signaling pathway plays an important role within the regulation of cellular responses to growth signals and its constituent activation is one amongst the most actors promoting CRC growth and proliferation through the KRAS/RAF/MAPK and therefore the PI3K/AKT/mTOR axes. KRAS is a little GTPase member of the RAS protein family, and corporeal cistron mutations will cause its constituent activation leading to freelance cell proliferation and survival [19]. The identification of KRAS DNA as a pair of (codons twelve and 13) mutations as a negative prognostication marker of response to anti-EGFRs described the turning purpose of biomarker choice for anti-EGFR treatment.

ii. BARF

The serine/threonine protein enzyme BRAF is associated with the EGFR-mediated signaling pathway that is well-known to be involved as an oncogenic driver in CRC. Mutations in BRAF will be found in about 8%-10% of CRCs, about 80% involve the substitution of glutamic acid for essential amino acid at residue 600 among the protein enzyme domain (V600E). BRAF constituent activation ensuing from V600E mutation promotes signaling transduction through the MEK-ERK-MAP enzyme pathway even in absence of RAS-mediated signals [20].

iii. Microsatellite Instability

MMR may be an extremely preserved polymer repair mechanism that ensures genomic integrity by correcting impaired or unmatched bases that have at large the proofreading activity of polymer polymerases throughout polymer replication and recombination, moreover as repairing some kinds of polymer harm. The loss of MMR proteins activity results in associate degree accumulation of polymer replication errors, a development referred to as MSI, characterized by high frequency of frameshift mutations in microsatellite polymer that interprets into a high corporeal modification burden in MMR- deficient (MMR-D) cells (mutator phenotype). The prevalence of MSI in CRC depends on the stage of the sickness. About 2 hundredth of CRCs in stage I-II, twelve-tone music in stage III and 4%-5% in stage IV, are deficient in one or additional polymer MMR proteins, with one-quarter of those ensuing from kill syndrome (LS), associate degree chromosome dominant condition characterized by germline mutations in genes committal to writing for MMR proteins (i.e., MLH1, MSH2, MSH6, PMS2 or EPCAM). The overwhelming majority (circa 80%-90%) of stray MSI cases are due to hypermethylation of the MLH1 cistron promoter, related to a high CpG island methylation constitution (CIMP+) and concerning half-hour harbor a BRAF V600E mutation. The remaining cases of stray MSI will be explained chiefly by the presence of multiple corporeal mutations within the MMR genes while not associate degree diagnosable germline MMR mutation ("double somatic" MSI cases), found to be related to a better frequency of corporeal mutations in PIK3CA [21].

iv. Dihydropyramidine dehydrogenase

Fluoropyrimidine analog 5-FU and its pro-drug capecitabine represent the backbone of therapy treatment for body part cancer [22].

The mechanism of action of those medicine relies on thymidylate synthase (TYMS) inhibition through the formation of a ternary advanced between the active matter 5-fluoro-2-deoxyuridine-5- monophosphate (5-FdUMP), TYMS and 5,10 methylenetetrahydrofolates, resulting in the suppression of polymer synthesis [23]. The rate- limiting accelerator for 5-FU biological process is that the accelerator Dihydropyramidine dehydrogenase (DPD), accountable for the inactivation of quite eightieth of the administered dose of 5-FU [24].

v. Fluoropyrimidines

5-FU is regenerated to the active matter, FdUMP (fluorodeoxyuridylate), by the enzymes, nucleoside phosphorylase (TP) and nucleoside enzyme intracellularly [25]. FdUMP binds and inhibits TS within the presence of five,10- methylenetetrahydrofolate (MTHF). Inhibition of TS leads to the build-up of deoxyuridylate (dUMP), that then gets misincorporated into polymer within the style of deoxyuridine triphosphate (dUTP), ensuing finally in inhibition of polymer synthesis and performance [26-28].

vi. Capecitabine

Capecitabine is generally employed as monotherapy, or together with alternative medicine in adjuvant and advanced treatment. Capecitabine undergoes metabolism by carboxylesterase a pair of nucleoside deaminase and TP to be remodeled to 5-FU [27-30].

vii. Irinotecan

Irinotecan, a topoisomerase I substance, is another key drug within the therapy treatment of mCRC, which may be used as a monotherapy or together with 5-FU and/or alternative agents in several treatment lines [23]. It is a pro-drug that is metabolized to its active type, SN-38, via carboxylation. SN-38 biological process and excretion are afterward hooked in to conversion to its inactive type, SN-38G, operated by internal organ UDP-Glucuronosyltrasferases (UGT) like UGT1A1 [31]. It can be a hemisynthetic analog of the natural product, camptothecin, ready to inhibit topoisomerase I, a polymer helicase (cutting enzyme).

viii. EGFR inhibitors

Cetuximab is a chimerical (fusion of human/mouse protein) immunoglobulin-G1 protein, targeting the extracellular domain of the EGFR (ErbB1). This agent was primarily used for treatment of irinotecan refractory CRC, but recently it is verified for treatment of alternative solid tumors, that additionally specific the EGFR [28, 32-34].

ix. VEGFR inhibitors

Bevacizumab is a humanized antibody against VEGF- A, and so binds to the VEGF receptors.

It is proved that bevacizumab is effective in varied solid tumors, and significantly in advanced CRC, in conjunction with cytotoxic therapy. It is seen that ontogenesis plays an important role in cancer progression and metastases, and it's been shown that VEGF is overexpressed in advanced CRC tumors and associated with advanced stages and probably poor survival [35,36]. There's no proof to date that the expression standing of VEGF is expounded to bevacizumab effectiveness [28, 37].

5. OSTEOSARCOMA

Osteosarcoma, also called bone cancer, begins from the cells that form bones. Osteosarcoma mostly occurs in the long bones — mostly in the legs, but sometimes the arms — but it can start in any bone and rarely soft tissue outside the bone can also be affected. Osteosarcomas are divided as high grade, intermediate grade, or low grade based on how cells appear under microscope.

There are two ways to classify different types of osteosarcomas. It can either be primary (occurring as a result of an abnormality in bone development) or secondary (occurring as a result of another condition). Secondary osteosarcomas are usually considered higher- grade malignancies than primary osteosarcomas.

From there, it is determined whether osteosarcoma should be classified based on its location or appearance:

(a) Intramedullary osteosarcoma – These osteosarcomas develop in the medullary cavity of a long bone, such as the femur.

(b) Juxtacortical osteosarcoma – These osteosarcomas develop on the outer surface of the bones or the periosteum (the dense layer of connective tissue that covers the bones).

(c) Extra skeletal osteosarcoma – These tumors arise in soft tissues and are not attached to bone; they often arise at a site of prior radiationtherapy.

5.1 Causes of osteosarcoma

The large majority of cases are the result of sporadic mutations, but loss of tumor suppressor function is commonly identified in OS and represents a critical step in its pathogenesis [38-40]. Li–Fraumeni syndrome (LFS) is the most common syndrome resulting in pediatric sarcomas and involves a germline mutation of the TP53 gene.

Retinoblastoma is another condition commonly identified to cause OS. Recq helicases are members of a conserved family of proteins that unwind double-stranded DNA before replication. Loss of recq helicases is an inheritable risk factor for OS [41].

Pharmacogenomic Markers related to Treatment Response.

i. TP53 and Its Regulators MDM2 & MDM4

The MDM2 gene, is an important regulator of the TP53 protein stability and degradation, has been found to be amplified and overexpressed in a relevant number of HGOS. Another major inhibitor of TP53 is MDM4, which encodes for a protein like MDM2, which binds to TP53, inhibiting its activity [42].

ii. DNA Repair-Related Genes

The altered activity of factors involved in the repair of drug-induced DNA damages can significantly affect either the resistance or sensitivity to DNA targeting drugs, including those used in HGOS chemotherapy. Several polymorphisms affecting DNA repair genes tend to variably correlate with treatment response and/or survival in HGOS. The CC genotype of the ERCC1 rs11615 polymorphism showed good response to cisplatin-based chemotherapy and hence, better survival when compared to TT genotype. Patients carrying the C allele of the ERCC1 rs3212986 polymorphism were described to have better event-free survival [43-46].

iii. Genes Involved in Drug Metabolism

Prodrugs which are activated by several drug metabolizing enzymes (dmes), are responsible for their biotransformation in both tumor and normal cells. Hence, dmes can significantly influence the tumor response to chemotherapy and also the susceptibility of normal tissues to treatment-related toxicities. Pharmacogenetic and pharmacogenomic analyses of dmes in tumor patients may thus prove useful in recommending or giving chemotherapeutic drugs according to patients' genetic characteristics. For example, gene variations causing impairment in dme function can decrease the therapeutic effect of pharmacologically inactive prodrugs, which require bioactivation to become effective, but are also associated with a lower induction of toxicity in normal cells. Also, regarding dmes involved in drug detoxification, gene alterations is associated with an impaired enzyme activity which cannot only determine an increased therapeutic effectiveness, but also tells us higher risk for collateral toxicity.

Different polymorphisms of the GSTP1 gene have been reported to be associated with a variable enzyme ability to metabolize anticancer agents and, for some of them, evidence of a possible clinical impact in HGOS has been reported. Cyps play a crucial role in determining drug effectiveness and collateral toxicity as they are involved in anticancer drugs detoxification and prodrugs activation. Since these enzymes show a relevant genetic variability, differences in treatment response and susceptibility to chemotherapy-associated toxicities can be observed [47].

iv. Genes Involved in Drug Transport

Several first- and second-line HGOS chemotherapeutic drugs are substrates of ATP Binding Cassette transporters and polymorphisms affecting members of this family have been indicated as candidate biomarkers for a possible clinical translation. The TT genotype of the ABCB1 rs1128503 polymorphism was related to good chemotherapy and G allele was associated with worse survival of ABCC5 rs939338 Polymorphism.

vii. Polymorphisms of Genes Involved in Antifolate Drugs Metabolism

The GG genotype of the dihydrofolate reductase (DHFR) gene, the main target of MTX, was seen to have higher chances of developing metastasis during follow-up. A MTX membrane transporter showed that patients with the allele G had better survival and lower predisposition to develop metastases. A folate cycle enzyme, involved in de novo purine synthesis, is related with good histological response after preoperative chemotherapy. Enzyme which catalyzes the hydrolysis of folylpoly-gamma-glutamates and anti- folylpoly-gamma-glutamates influencing the overall effectiveness of MTX, was found to be associated with poor survival [48].

viii. Gene Polymorphisms Associated withToxicities

High-dose methotrexate is observed to often causes bone marrow suppression and liver and renal toxicities, whereas anthracycline-induced cardiotoxicity and cisplatin-induced ototoxicity have been reported [47].

ix. Personalized treatment through tissueengineering

The tissue engineering (TE) depends on the use of biomaterials, cells, and biomolecules, alone or in combination, to provide specific approaches to repair and regenerate damaged tissues or organs [49]. Tissue Engineering is coupled with personalized medicine through cell engineering, cell therapy, and genetic manipulation procedures. It is emerging as a promising and life changing method in anti-cancer therapy.

8. BREAST CANCER

Breast cancer is a metastatic cancer which originates from ductal hyperproliferation, commonly from the inner lining of milk ducts or the lobules and transfers to other distant organs such as the bone, liver, lung and brain, thereby accounting for incurability. It mostly occurs in women and the number of cases is 100 times higher than that in men [50].

There are classified into three main histologic types of breast cancer:

(a) Estrogen-dependent breast cancers which expresses Estradiol receptor (ER) and treated with various drugs that target the ER pathway;
(b) BC with Over expressing of human epidermal growth factor receptor 2 (HER2) and treated with anti-HER2 drug, trastuzumab which is a monoclonal antibody;
(c) The "Triple negative" breast cancers which lack the expression of the ER, PGR, and HER2. TNBC still doesn't have any targeted therapies and is considered to have a high metastatic potential, and a bad prognosis [51].

8.1. Genomics of Breast Cancer: "Who is at risk"?

Both family and personal histories can influence a woman's risk of developing breast cancer. The known risk factors for breast cancer: alcohol consumption, body mass index (BMI), height, mammographic density, breast cancer in a first-degree relative, menopause (age at onset), smoking, and type 2 diabetes mellitus (T2DM), reproductive and hormonal factors explain only a portion of the variability in breast cancer risk [52]. A Lot of genes are identified in relation to breast cancer. Hereditary breast cancer is linked to genetic mutations where BRCA1, BRCA2, PALB2, TP53, CDH1, and PTEN are genes that may undergo mutations associated with cumulative breast cancer risk. The first major gene associated with hereditary breast cancer was BRCA1 and BRCA2 which are antioncogenes, located on chromosome 17q21 and 13q12, respectively. Mutation in either of these two genes increases an individual's risk for breast cancer across their lifespan. Females with mutations in BRCA1 or BRCA2 have 50%–85% risk of breast cancer. Males with BRCA1 mutation have an increased risk of breast cancer, though to a lesser degree than carriers of BRCA2 who have an estimated 5%–10% lifetime risk [53]. Heterogeneity in clinical, pathological, and molecular characteristics makes breast cancer a challenging disease to manage and therapy failure due to unexpected outcomes [54]. A pharmacogenomics approach provides care and treatment by identifying all the genetic variations in tumor cells. It helps the clinician to select the appropriate therapeutic regimens to overcome resistance [55]. Here is a case study when pharmacogenomics was used in breast cancer. A woman in her 60's, on a date with her Husband, started experiencing palpitations, dizziness, swelling around breast & sweating and they were very severe enough that she was rushed to the emergencyt rooms.

Interestingly, a year prior to that she had a similar symptom but they were milder. That time she had alsogone to the emergence room but they were unable to find out and send her Home. Again, after two days she experiences those same symptoms and likes the same thing they send her back.

But this time being the third recurrence the symptoms were more severe and she was hospitalized for four days and they ran a bunch of tests and were still unable to come up with any answers for her symptoms. So, she went to the local care provider where she was treated for 9 days but no one could find anything to explain hersymptoms. That was the time when the Pharmacogenetics test was used in BC [56]. Currently, only three individual biomarkers such as estrogen receptor (ER), progesterone receptor (PGR), and HER2/ErbB2, are utilized to guide treatment in BC patients. Where, Aromatase inhibitors (AI) have been demonstrated to be an effective alternative for endocrine treatment in postmenopausal women. In the following sections, we summarize the role of pharmacogenomics (PGx) as Currently, only three individual biomarkers such as estrogen receptor (ER), progesterone receptor (PGR), and HER2/ErbB2, are utilized to guide treatment in BC patients. Where, Aromatase inhibitors (AI) have been demonstrated to be an effective alternative for endocrine treatment in postmenopausal women. In the following sections, we summarize the role of pharmacogenomics (PGx) as Biomarkers in BC for adverse events of individual chemotherapeutic agents or combination regimens [57].

i. Estrogen Receptors (ER) Biomarkers

Among various treatments for breast cancer, there is no better example of a targeted treatment than tamoxifen. Tamoxifen a selective estrogen receptor modulator (SERM) is used for treatment & prevention of ER- positive BC [58]. It exerts its effects by binding to the ER's thereby modulating estrogen-induced transcription. It is metabolized in liver by several cytochrome P450 systems to its primary N-demethylated metabolite, and other potent antiestrogenic metabolites including 4- hydroxytamoxifen and Endoxifen (4-hydroxy-N-desmethyl-tamoxifen). Till now, over 40 individual alleles of

CYP2D6 have been identified. The inactivation of tamoxifen and its metabolites is mediated by the enzymes UGTs (UDP glucuronosyltransferase) [59]. The most active UGT is UGT2B7 which is found in the gastrointestinal tract and breast tissue [60].

Several evidences indicated that most of the tamoxifen therapeutic effects in breast cancer are mediated by its metabolites (4-hydroxytamoxifen & endoxifen), by exhibiting greater affinity for the ER, and higher potency in suppressing cell proliferation compared to tamoxifen. A SNP in CYP2D6 or one any other CYP Enzymes may influence the concentration of each tamoxifen metabolite. Tamoxifen reduces the recurrenceof breast cancer in women by 50% [61].

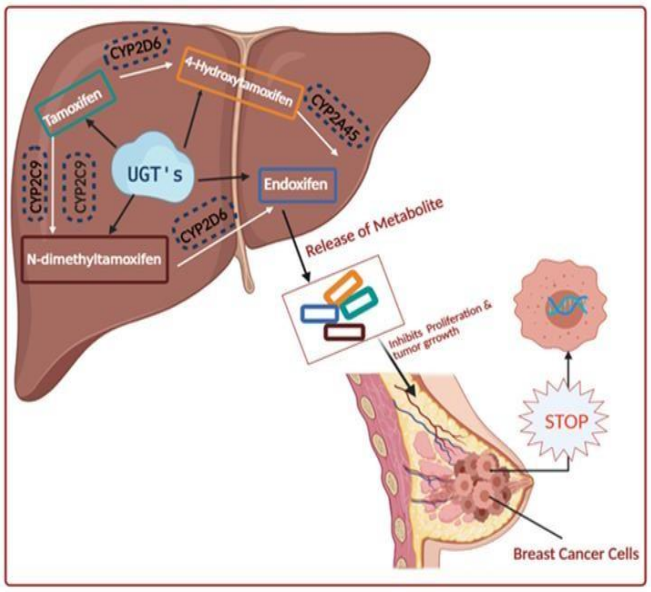

Fig-8.1 Tamoxifen Mechanism

ii. Progesterone Receptor (PGR)

Aromatase inhibitors (AIs) is a class of endocrine drugs used in the treatment of early and advanced breast cancer in postmenopausal women [62]. AIs exert its effect by blocking the enzyme aromatase, which turns the hormone androgen into small amounts of estrogen in the body, which means that less estrogen is available to stimulate the growth of cancer cells. They are considered to be more effective than tamoxifen in postmenopausal women [63].

iii. HER2/ErbB2 Receptors

Trastuzumab is a therapeutic humanized monoclonal antibody that binds to the HER2 receptor and suppresses cell proliferation that is driven by overexpression of the HER2 protein [64]. It can be used as a first line treatment in combination with paclitaxel, or as a single agent in the second line treatment of patients who have failed prior chemotherapy. The combination of trastuzumab with chemotherapy (paclitaxel) had led to reduction in recurrence of breast cancer in HER2 overexpressing or amplified tumors ("HER2-positive") when used in the adjuvant setting [65]. Trastuzumab efficacy is believed to be, in large part, due to engagement of Fc gamma receptors on immune effector cells, enable immune effector cells, such as macrophages, natural killer cells, to bind to the Fc portion of IgG antibodiesthat are attached to invading antigens. Despite extreme enhancement in the outcomes of trastuzumab, not all women having HER2-positive cancer will benefit equally from adjuvant trastuzumab[66].

9. CONCLUSION

Surgery, chemotherapy, and radiation therapy are still most widely used methods to treat cancer. But major problems are a side effect of these drugs. All these drugs have low specificity and affect healthy cells and tissues and cause heavy damage to the person's body. Also, the body develops resistance to these drugs and hence, higher dosage is administered. This can be fatal or cause serious disorder in patients. Progress in pharmacogenetics is seen to have a revolutionizing effect in cancer therapy. By studying a patient's genetic makeup, it can help in deciding perfect chemotherapy regimens and drug dosage with maximum effect with minimal toxicity risk. Various genotyping methods can be used to make decisions regarding treatment strategies. Future developments in some key areas can play an important role to decide the overall influence of pharmacogenetics data on therapy. By gaining knowledge of genome wide techniques and by incorporating a metabolic pathway approach, we can enhance candidate gene-based approach. Before clinical implementation, proof from controlled clinical trials is required. Although many different studies have been conducted so far in pharmacogenomics, there is still a long way to go in order customized medicine to be applied into everyday practice.

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