International Journal of Pharmacy and Pharmaceutical Science
www.pharmacyjournal.org
Online ISSN: 2664-7230; Print ISSN: 2664-7222; Impact Factor: RJIF 5.44
Received: 02-09-2019; Accepted: 09-10-2019; Published: 18-10-2019
Volume 1; Issue 2; 2019; Page No. 31-33

Pharmacogenomic strategies in personalizing anticancer therapy

[1] Xiaochen Tang
[1] Engineering Research Center of Natural Medicine Active Molecule Research & Development, Liaoning Province, China

DOI: https://doi.org/10.33545/26647222.2019.v1.i2a.95

Abstract
Pharmacogenomics holds transformative potential for personalizing anticancer therapy, tailoring treatments based on genetic profiles to optimize efficacy and minimize adverse effects. This review explores the integration of pharmacogenomic strategies into cancer treatment, highlighting the impact of genetic markers on drug metabolism and therapy outcomes. Key pharmacogenomic markers such as Cytochrome P450 enzymes, TPMT, UGT1A1, KRAS, BRAF, and HER2 are examined to demonstrate their influence on the pharmacokinetics and pharmacodynamics of anticancer drugs. The review also addresses the challenges and opportunities in implementing pharmacogenomic testing in clinical settings, including issues related to genetic diversity, ethical considerations, and the economic implications of personalized medicine. Ultimately, this paper aims to underscore the importance of pharmacogenomic data in refining anticancer therapies, fostering a move towards more individualized treatment plans that promise improved patient outcomes.

Keywords: Pharmacogenomics, anticancer therapy, personalized medicine

Introduction
Cancer continues to be a leading cause of morbidity and mortality worldwide, with diverse types that vary significantly in their pathophysiology and response to treatment. Traditional approaches to cancer therapy often adopt a one-size-fits-all model, which does not account for individual differences in drug metabolism and response, potentially leading to suboptimal treatment outcomes and severe side effects. The advent of pharmacogenomics offers a promising avenue to overcome these limitations by utilizing genetic information to guide drug selection and dosage, aiming to enhance treatment efficacy and safety. Pharmacogenomics, the study of how genes affect a person's response to drugs, integrates genetic science with pharmacology to develop effective, safe medications and doses tailored to a person's genetic makeup. In the realm of oncology, this approach is particularly pertinent due to the high stakes of treatment and the significant variability in responses to anticancer medications. Genetic variations can influence the absorption, distribution, metabolism, and excretion of drugs, profoundly affecting their performance and tolerability. The pharmacogenomic strategies include identifying genetic variants that predict response to medications, such as polymorphisms in metabolizing enzymes like Cytochrome P450, or in drug targets like HER2. For instance, polymorphisms in enzymes such as TPMT or UGT1A1 can predict severe toxicity in response to standard doses of certain chemotherapy drugs, guiding dose adjustments to mitigate risk. Similarly, mutations in genes like KRAS or BRAF can inform the use or avoidance of specific targeted therapies that are only effective in the absence of such mutations.

Main Objective
The primary objective of this review is to articulate the role of pharmacogenomic strategies in personalizing anticancer therapy.

Literature Review: Fujita & Sasaki, 2007 [5], Variations in enzymes like thiopurine S-methyltransferase (TPMT) and UDP-glucuronosyltransferase 1A1 (UGT1A1) can significantly affect the metabolism of anticancer drugs like 6-mercaptopurine and irinotecan, influencing both efficacy and toxicity. This highlights the importance of pharmacogenomic testing for individualizing doses and treatment plans. Rodríguez-Antona & Taron, 2015 [1], Personalized medicine is enhanced by understanding both the molecular characteristics of the tumor and the genetic background of the patient. This comprehensive approach aids in predicting drug efficacy and toxicity, utilizing high-throughput technologies to identify new pharmacogenomic markers and druggable molecules. Schwab & Schaeffeler, 2012, with advances in genomic technologies, integrating diverse genomic data is critical for tailoring cancer treatment more precisely. This integration involves not only genetic but also environmental and phenotypic factors, improving the prediction and management of drug responses and adverse effects. Sadee & Dai, 2005, Despite the potential benefits, the integration of pharmacogenomic data into clinical practice faces challenges including the complexity of genomic data and the need for extensive validation. Overcoming these barriers is essential for the widespread application of personalized cancer therapy.

Pharmacogenomic Markers in Cancer Therapy
Pharmacogenomic markers are genetic variations that influence an individual's response to drugs, including the efficacy and toxicity of medications. In cancer therapy, these markers are crucial for tailoring treatments to the genetic profile of an individual patient, potentially enhancing the effectiveness of treatment while minimizing adverse effects. Here, we detail some of the key pharmacogenomic markers that play significant roles in cancer treatment.

1. **Cytochrome P450 Enzymes (CYPs)**
   Cytochrome P450 enzymes (CYPs) are crucial in the metabolism of anticancer drugs, affecting both the efficacy and toxicity of treatments. This group of

enzymes, primarily located in the liver and found also in other tissues like intestines and kidneys, catalyzes the oxidation of organic substances, playing a pivotal role in drug metabolism and detoxification. One of the most studied in cancer therapy is CYP2D6, known for metabolizing tamoxifen, a standard treatment for estrogen receptor-positive breast cancer. The enzyme's genetic variability significantly influences therapeutic outcomes, as it exists in over 100 different alleles that range from poor to ultra-rapid metabolism. Patients with poor metabolizer variants may experience suboptimal activation of tamoxifen, leading to less effective treatment, while ultra-rapid metabolizers may process the drug too quickly, reducing its availability and efficacy. Another important set of enzymes, CYP3A4 and CYP3A5, metabolize a broad spectrum of chemotherapeutic agents, including cyclophosphamide, docetaxel, and vincristine. Variants in these genes can drastically alter the metabolism rates, impacting how drugs are cleared from the body. This variation can necessitate adjustments in dosing to achieve optimal drug concentrations for effective treatment without excessive toxicity. CYP2C8 also plays a significant role in the metabolism of paclitaxel, used in treating ovarian, breast, lung, and pancreatic cancers. Variations in the CYP2C8 gene can lead to different metabolic rates of paclitaxel, significantly affecting its effectiveness and the occurrence of side effects.

2. **Thiopurine S-methyltransferase (TPMT)**

Thiopurine S-methyltransferase (TPMT) plays a crucial role in cancer therapy, particularly in the treatment of acute lymphoblastic leukemia (ALL). TPMT is an enzyme that metabolizes thiopurines, such as 6-mercaptopurine (6-MP) and azathioprine, which are used to treat leukemia and other autoimmune disorders. The activity of TPMT in the body varies widely among individuals due to genetic polymorphisms, leading to significant differences in drug tolerance and treatment outcomes. Genetic variations in the TPMT gene can lead to three distinct levels of enzyme activity: high, intermediate, or very low. Patients with high or intermediate enzyme activity can typically tolerate standard doses of thiopurines. However, those with low or absent TPMT activity, which occurs in approximately 0.3% of the population, are at a high risk of severe myelosuppression when treated with standard doses of thiopurines. This adverse effect results from the accumulation of active thioguanine nucleotides, which can cause toxic effects on the bone marrow, leading to life-threatening infections, bleeding, and anemia. Due to the critical implications of TPMT activity on patient safety and treatment efficacy, preemptive genetic testing for TPMT polymorphisms is recommended before initiating therapy with thiopurines. Identifying patients with reduced TPMT activity allows clinicians to adjust drug doses or choose alternative treatments, thereby reducing the risk of severe toxicity and improving therapeutic outcomes. In clinical practice, patients identified as having low or absent TPMT activity are typically prescribed significantly reduced doses of thiopurines, or alternative non-thiopurine drugs are used. This tailored approach based on TPMT status is a prime example of personalized medicine in oncology, demonstrating how genetic information can guide treatment decisions to maximize efficacy and minimize harm.

3. **UDP-Glucuronosyltransferase 1A1 (UGT1A1)**

UDP-Glucuronosyltransferase 1A1 (UGT1A1) is an enzyme involved in the metabolism of bilirubin and many drugs, including the chemotherapeutic agent irinotecan, used in the treatment of colorectal and other cancers. UGT1A1's primary function is to convert lipophilic substances into water-soluble excretable metabolites through glucuronidation, a process critical for the body's ability to eliminate these substances safely. Genetic polymorphisms in the UGT1A1 gene can significantly affect the enzyme's activity. The most well-known variant, UGT1A128, involves a repetition in the TATA box of the gene promoter, leading to reduced expression of UGT1A1. Individuals who are homozygous for this variant (having two copies of UGT1A128) exhibit significantly lower enzyme activity compared to those with the wild-type sequence. As a result, these individuals have reduced capacity to glucuronidate and thereby detoxify drugs like irinotecan. Irinotecan is metabolized by UGT1A1 to form an inactive metabolite, which is then excreted. In patients with decreased UGT1A1 activity, irinotecan's active metabolite, SN-38, accumulates in the body, significantly increasing the risk of severe side effects such as neutropenia and severe diarrhea. This accumulation poses a substantial threat to the patient's health and can limit the effectiveness of the cancer treatment by forcing dose reductions or treatment discontinuation. Given the implications of UGT1A1 genetic variants on treatment safety, genetic testing for UGT1A128 is recommended prior to initiating irinotecan therapy. Identifying patients with the homozygous UGT1A128 genotype allows oncologists to adjust irinotecan dosing accordingly. Typically, these patients receive a reduced initial dose to mitigate the risk of severe toxicity. This proactive approach enhances treatment safety and improves the overall management of cancer therapy, reflecting a shift towards more personalized medical care in oncology.

4. **KRAS and BRAF**

KRAS and BRAF are genes involved in the regulation of cell division, growth, and repair. Mutations in these genes are significant in cancer biology because they often lead to uncontrolled cell growth, a hallmark of cancer. These genes encode proteins that are part of the RAS/MAPK signaling pathway, which is critical for the transmission of signals from cell surface receptors to the nucleus, influencing cell growth and survival. KRAS mutations are prevalent in various cancers, including colorectal cancer (CRC), non-small cell lung cancer (NSCLC), and pancreatic cancer. About 40% of CRC cases have KRAS mutations. The presence of a KRAS mutation in CRC is a strong predictor of resistance to anti-EGFR (epidermal growth factor receptor) antibody therapies such as cetuximab and panitumumab. These therapies are effective in blocking the growth signals in cells that do not have mutated KRAS, thereby inhibiting tumor growth. However, if the KRAS gene is mutated, it continuously signals the cancer cells to grow, even in the presence of these drugs. Thus, testing for KRAS mutations is crucial before initiating treatment with anti-EGFR therapies to

ensure that only patients likely to benefit from these treatments receive them. BRAF is another key player in the same pathway as KRAS. The most common BRAF mutation, V600E, results in an amino acid substitution at position 600 in BRAF, from a valine (V) to a glutamic acid (E), leading to increased kinase activity. This mutation is particularly significant in melanoma, where it occurs in about 50% of tumors. It is also found in about 10% of CRCs and is associated with a poor prognosis. BRAF inhibitors, such as vemurafenib and dabrafenib, have been developed to target this mutation. These drugs have dramatically improved outcomes for melanoma patients with the BRAF V600E mutation, showcasing the benefits of targeted therapy. The effectiveness of targeting KRAS and BRAF mutations highlights the importance of molecular profiling in cancer treatment. Identifying the mutational status of these genes helps personalize therapy, ensuring patients receive the most effective treatments based on their tumor genetics. This not only spares patients from unnecessary side effects of ineffective treatments but also significantly improves therapeutic outcomes. As understanding of these pathways deepens, more sophisticated treatments are being developed to target different components of the signalling cascade, promising further advances in personalized cancer therapy.

5. **HER2/neu**

HER2/neu, also known as ERBB2, is a gene that plays a critical role in the development of certain types of cancer, most notably breast cancer. The HER2 gene encodes a protein receptor on the surface of cells, which is part of the human epidermal growth factor receptor (HER) family. This family of receptors is involved in the signaling pathways that regulate cell growth, survival, and differentiation. HER2 is unique among the HER family members because it has no known natural ligand, meaning it is activated in a ligand-independent manner. When overexpressed, the HER2 protein leads to the activation of several signal transduction pathways, including the PI3K/Akt and MAPK pathways, which drive cell proliferation and survival. HER2 overexpression is found in approximately 20-30% of invasive breast cancers and is associated with aggressive disease, high recurrence rates, and reduced survival. The clinical significance of HER2 in breast cancer was recognized in the late 1980s, leading to the development of targeted therapies specifically designed to inhibit HER2 signaling. The most famous of these therapies is trastuzumab (Herceptin), a monoclonal antibody that binds to the HER2 protein on the surface of cancer cells, blocking its ability to signal and marking the cells for destruction by the immune system. Trastuzumab has been shown to significantly improve survival rates in HER2-positive breast cancer patients, especially when used in combination with chemotherapy. Further advances in targeted therapy for HER2-positive breast cancer have led to the development of additional drugs, including pertuzumab, which also targets the HER2 receptor but at a different site than trastuzumab, allowing for dual inhibition of HER2 signaling. Another significant advancement is the development of antibody-drug conjugates such as ado-trastuzumab emtansine (Kadcyla), which combines the HER2-targeting capabilities of trastuzumab with a potent cytotoxic drug, allowing for the direct delivery of chemotherapy to HER2-overexpressing cells. HER2 status is also crucial in the management of other cancers, such as stomach cancer, where HER2 positivity is associated with a worse prognosis. Like in breast cancer, trastuzumab has been adapted to treat HER2-positive gastric cancer, further illustrating the importance of HER2 as a molecular target across different types of cancer.

Conclusion

The integration of pharmacogenomics into the field of oncology represents a significant advancement in personalized medicine, offering a pathway to more effective and safer cancer treatment by tailoring therapies to the genetic makeup of individual patients. As demonstrated throughout this review, key pharmacogenomic markers such as Cytochrome P450 enzymes, TPMT, UGT1A1, KRAS, BRAF, and HER2 have critical implications for the metabolism, efficacy, and safety of anticancer drugs. These markers can guide the selection and dosing of chemotherapeutics and targeted agents, potentially transforming treatment outcomes by reducing adverse effects and improving efficacy. The implementation of pharmacogenomic strategies in clinical practice faces several challenges. These include the variability in genetic testing resources across healthcare settings, the need for enhanced education and awareness among healthcare providers, and the ethical and economic considerations of personalized medicine. Despite these challenges, the benefits of pharmacogenomics are increasingly recognized, driving more widespread adoption and integration into clinical guidelines.

References

1. Rodríguez-Antona C, Taron M. Pharmacogenomic biomarkers for personalized cancer treatment. Journal of internal medicine. 2015 Feb;277(2):201-217.
2. Weng L, Zhang L, Peng Y, Huang RS. Pharmacogenetics and pharmacogenomics: a bridge to individualized cancer therapy. Pharmacogenomics. 2013 Feb;14(3):315-324.
3. Bignucolo A, De Mattia E, Cecchin E, Roncato R, Toffoli G. Pharmacogenomics of targeted agents for personalization of colorectal cancer treatment. International journal of molecular sciences. 2017 Jul 14;18(7):1522.
4. Huang RS, Ratain MJ. Pharmacogenetics and pharmacogenomics of anticancer agents. CA: A cancer journal for clinicians. 2009 Jan;59(1):42-55.
5. Fujita KI, Sasaki Y. Pharmacogenomics in drug-metabolizing enzymes catalyzing anticancer drugs for personalized cancer chemotherapy. Current drug metabolism. 2007 Aug 1;8(6):554-562.
6. De Mattia E, Cecchin E, Toffoli G. Pharmacogenomics of intrinsic and acquired pharmacoresistance in colorectal cancer: toward targeted personalized therapy. Drug Resistance Updates. 2015 May 1;20:39-70.
7. Jeibouei S, Akbari ME, Kalbasi A, Aref AR, Ajoudanian M, Rezvani A, *et al*. Personalized medicine in breast cancer: Pharmacogenomics approaches. Pharmacogenomics and personalized medicine. 2019 May 27:59-73.